pISSN 2005-9531
eISSN 2586-7024
www.kosinmedj.org

KMJ KOSIN MEDICAL JOURNAL

# KMJ

## KOSIN MEDICAL JOURNAL

Vol. 41 No. 1, March 2026

KOSIN UNIVERSITY
COLLEGE OF MEDICINE

Vol. 41 No. 1, March 2026

Pages 1-90

KOSIN UNIVERSITY
COLLEGE OF MEDICINE

KMJ

kosinmedj.org

pISSN 2005-9531
eISSN 2586-7024

KOSIN MEDICAL JOURNAL

Vol. 41 No. 1, March 2026

## Aims and scope

*The Kosin Medical Journal* (Kosin Med J, KMJ, pISSN 2005-9531, eISSN 2586-7024, https://www.kosinmedj.org), the official publication of Kosin University College of Medicine, is a peer-reviewed and open access journal of research in all medical fields, including medicine, medical science, medical ethics, medical policy, and medical education. Its regional focus is Korea, but it welcomes submissions from researchers all over the world.

The KMJ aims to communicate new medical information to medical personnel, and to facilitate the development of medicine, medical science, medical ethics, medical policy, and medical education, as well as the propagation of medical knowledge by publishing high-quality, evidence-based articles.

The KMJ publishes editorials, review articles, original articles, and case reports. All manuscripts should be creative, informative, and helpful for the diagnosis and treatment of medical diseases and the communication of valuable information about all fields of medicine, medical science, medical ethics, medical policy, and medical education.

The first volume was published in Korean in February 1985. The KMJ has been published in English since 2016. A total of 1,165 papers were published by 2021. Since 2022, the KMJ has been published four times a year, on March 31, June 30, September 30, and December 31.

KMJ is indexed, tracked, and covered by National Research Foundation of Korea (NRF), KoreaMed, KoreaMed Synapse, Google Scholar, Index Copernicus International, Directory of Open Access Journals (DOAJ), Korean Medical Citation Index, and DOI/Crossref.

## Open access

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

**Publisher** Kosin University College of Medicine
**Editor-in-Chief** Won Moon, MD, PhD

**Editorial office**
#262, Gamcheon-ro, Seo-gu, Busan 49267, Korea
Tel: +82-51-990-3088 Fax: +82-51-241-5458 E-mail: office@kosinmedj.org

**Printing office**
M2PI
#805, 26 Sangwon 1-gil, Seongdong-gu, Seoul 04779, Korea
Tel: +82-2-6966-4930 Fax: +82-2-6966-4945 E-mail: support@m2-pi.com

Published on March 31, 2026

© 2026 Kosin University College of Medicine
This paper meets the requirements of KS X ISO 9706, ISO 9706-1994 and ANSI/NISO Z39. 48-1992 (Permanence of paper).

# Editorial board

KMJ
KOSIN MEDICAL JOURNAL

## Editor-in-Chief

Won Moon, MD, PhD
*Kosin University College of Medicine, Korea*

## Associate Editors

Hee-Jae Cha, PhD
*Kosin University College of Medicine, Korea*

Rok Seon Choung, MD, PhD
*Mayo Clinic Rochester, USA*

Hyunyong Hwang, MD, PhD
*Kosin University College of Medicine, Korea*

Sung Eun Kim, MD, PhD
*Kosin University College of Medicine, Korea*

Hyoung Shin Lee, MD, PhD
*Kosin University College of Medicine, Korea*

Ir Vin Oh, MD
*Yale University, USA*

Chi Eun Oh, MD, PhD
*Kosin University Gospel Hospital, Korea*

Kwang Il Seo, MD, PhD
*Kosin University College of Medicine, Korea*

## Editorial Board

Juan Aguilar, MD
*Hospital Universitario Fundación Valle del Lili, Colombia*

Ji Cheol Bae, MD, PhD
*Samsung Changwon Hospital, Korea*

Byung Hyo Cha, MD, MSc
*Sheikh Khalifa Specialty Hospital, UAE*

Alfred Kow Wei Chieh
*National University Hospital, Singapore*

Youngil Choi, MD, PhD
*Kosin University College of Medicine, Korea*

Jin Hyuk Choi, MD, PhD
*Kosin University College of Medicine, Korea*

Gye Won Han, PhD
*USC Michelson Center, USA*

Satoshi Higuchi, MD, PhD
*Tokyo Women's Medical University, Japan*

Sung Ho Hong, MD
*Corewell Health East, USA*

Ji Hun Kang, MD, MS
*Kosin University College of Medicine, Korea*

Seul Gi Hyeon, MD
*Agape Christian Hospital, Mongolia*

Sung Il Im, MD, PhD
*Kosin University College of Medicine, Korea*

Min Soo Jang, MD, PhD
*Kosin University College of Medicine, Korea*

Seri Jeong, MD, PhD
*Kangnam Sacred Heart Hospital, Hallym University College of Medicine, Korea*

Hee Kang, MD, PhD
*Kosin University College of Medicine, Korea*

Dong-Won Kang, MD, PhD
*University of Zimbabwe Faculty of Medicine and Health Sciences, Zimbabwe*

Myong-Hwan Karm, MD, PhD
*Seoul National University School of Dentistry, Korea*

Eun Seok Kim, MD, MSc, PhD
*London School of Hygiene and Tropical Medicine, UK*

Hyun Min Mike Kim, MD
*VA Southern Nevada Healthcare System, USA*

Jason Kim, PhD
*University of Massachusetts Chan Medical School, USA*

Jeong Tae Kim, DVM, PhD
*Jeju National University School of Medicine, Korea*

Chang Zoo Kim, MD
*Kosin University College of Medicine, Korea*

Kwang-Youn A. Kim, PhD
*Northwestern University Feinberg School of Medicine, USA*

Sejin Kim, PhD
*Dong-A University College of Medicine, Korea*

Hyung Jin Kim, MD, PhD
*Sungkyunkwan University School of Medicine, Korea*

Won Yong Lee, MD
*Guthrie Clinic, Geisinger School of Medicine, USA*

Ho Sup Lee, MD, PhD
*Kosin University College of Medicine, Korea*

James Weiquan Li, MD, PhD
*Changi General Hospital, Singapore*

Hyun Joon Park, MD
*Pyeongtaek St.Mary's Hospital, Korea*

Hyung Seok Park, MD, PhD
*Yonsei University, Korea*

Musheer Shafqat, MBBS, MRCS, FCPS, MCCEE
*Bach Christian Hospital, Pakistan*

Jae Won Shim, PhD
*Kosin University College of Medicine, Korea*

Su Min Shin, MD, PhD
*Ewha Womans University, Korea*

Seung Yong Shin, MD, PhD
*Chung-Ang University, School of Medicine, Korea*

Jae-Gook Shin, MD, PhD
*Inje University College of Medicine, Inje University Busan Paik Hospital, Korea*

Kuk Hui Son, MD, PhD
*Gachon University Gil Medical Center, Korea*

Kyoung Seob Song, PhD
*Kosin University College of Medicine, Korea*

Napadon Tangjaturonrasme, MD
*Chulalongkorn University, Thailand*

Vimalraj Velayutham, MD, PhD
*MIOT Hospital, India*

Arzu Velioglu, MD
*Marmara University, School of Medicine, Turkey*

Aleksandr Voskoboinik, MBBS (Hons), FRACP, PhD
*Alfred Health Care, Australia*

Brian J. Wentworth, MD
*MSc University of Virginia, USA*

Jeong Ha Wie, MD, PhD
*The Catholic University of Korea, Korea*

Che-Wei Wu, MD, PhD
*Kaohsiung Medical University Hospital, Taiwan*

Jin Seo Yang, MD, PhD
*Hallym University, Korea*

Young-Ran Yoon, MD, PhD
*Kyungpook National University School of Medicine, Korea*

# Editorial board

KMJ
KOSIN MEDICAL JOURNAL

## Statistical Editor

Jin Mi Kim, PhD
*Pusan National University HospitalBiomedical Research Institute, Korea*

## Ethics Editor

Gwang Ha Kim, MD, PhD
*Pusan National University College of Medicine, Korea*

## English Editor

Linda Sohn, MD, MPH, CMD
*UCLA School of Medicine, USA*

## Managing Editors

Hye Kyung An
*Kosin University College of Medicine, Korea*

Hyo Won Jung
*Kosin University College of Medicine, Korea*

## Manuscript Editor

Hayoung Kim
*InfoLumi, Korea*

## Layout Editor

Eun Mi Jeong
*M2PI, Korea*

## Website and Jats xml file producer

Min Young Choi
*M2PI, Korea*

# Contents

KMJ
KOSIN MEDICAL JOURNAL

Vol. 41 No. 1, March 2026

## Editorial

1 Dynamic changes in liver regeneration after major hepatectomy: the association between volumetric recovery and functional adaptation

*Chan Woo Cho*

## Review articles

3 The onco-bariatric paradigm: a tri-phasic metabolic obesity framework for synergizing glucagon-like peptide-1 receptor agonists and metabolic bariatric surgery

*Dong Jin Park, Yoonhong Kim, Dongjae Jeon, Young Suk Park, Kyung Won Seo, Ki Hyun Kim*

9 Bowel preparation for colonoscopy in special populations: a practical and risk-stratified approach

*Myung-Hun Lee, Won Moon, Kyoungwon Jung, Jae Hyun Kim, Sung Eun Kim, Moo In Park, Seun Ja Park*

19 Chemoimmunotherapy and targeted therapy in biliary tract cancer: current evidence and future directions

*Jae Jun Heo, Jung Wook Lee*

26 Gout in the era of multimorbidity: pathogenesis, systemic comorbidities, and evolving therapeutic strategies

*Phillip J Kim, Jihun Kang, Jesang Yu, Geun-Tae Kim, Yunkyung Kim*

## Original articles

37 Real-world survival outcomes of sequential treatment strategy for newly diagnosed advanced high-grade serous ovarian cancer

*Eun Taeg Kim, Sun Young Ma, Tae Kyoung Kang, Tae Hwa Lee, Dong Hwi Kim, Won Gyu Kim*

46 Association of allergen sensitization and air pollution in childhood asthma and allergic rhinitis: a single-center study

*Sunbok Suh, Hyungsu Kim*

58 Predictors and patterns of early liver regeneration after major hepatectomy

*Seoyeong Ku, Garam Lee, Hyung Hwan Moon, Hyungjune Ku, Won Jong Yang, Junho Song, Suyeon Kim, Chol Min Kang, Amy Choi, Dong Hyeon Gim, Young Il Choi, Dong Hoon Shin, Namkee Oh, Jinsoo Rhu*

67 Trends in participation and abnormal screening results in the National Health Screening Program for Infants and Children in South Korea, 2010–2023

*Ji Sook Kim*

© 2026 Kosin University College of Medicine

# Contents

KMJ
KOSIN MEDICAL JOURNAL

Vol. 41 No. 1, March 2026

## Case reports

81 Two-stage transurethral cystolithotripsy of a giant neobladder stone: a case report
*Sin Woo Lee, Seung-Kwon Choi*

85 Locally recurrent primary adrenal leiomyosarcoma discovered incidentally 7 years after initial surgery: a case report
*Myungsoo Im, Doohwa Kim, Soree Ryang, Bo Hyun Kim*

© 2026 Kosin University College of Medicine

Editorial

Kosin Medical Journal 2026;41(1):1-2
pISSN: 2005-9531 • eISSN: 2586-7024
https://doi.org/10.7180/kmj.26.160

KMJ
KOSIN MEDICAL JOURNAL

# Dynamic changes in liver regeneration after major hepatectomy: the association between volumetric recovery and functional adaptation

**Chan Woo Cho**

*Department of Surgery, Yeungnam University College of Medicine, Daegu, Korea*

See "Predictors and patterns of early liver regeneration after major hepatectomy" by Seoyeong Ku, Garam Lee, Hyung Hwan Moon, Hyungjune Ku, Won Jong Yang, Junho Song, et al.

Major hepatectomy remains a cornerstone in the treatment of primary and secondary hepatic malignancies. Despite technical refinements and advances in perioperative management, post-hepatectomy liver failure remains the most serious postoperative complication [1,2]. The key determinant of this risk is the regenerative capacity of the future liver remnant (FLR). Although volumetric thresholds, such as the FLR-to-standard liver volume (SLV) ratio, have long guided surgical planning, the dynamic pattern of postoperative regeneration and its relationship to functional recovery remain incompletely understood [3,4].

This study provides a detailed volumetric and biochemical analysis of liver regeneration following anatomical hemihepatectomy [5]. In a cohort of 50 patients, the authors demonstrate that the FLR/SLV ratio is the strongest independent predictor of early regeneration, with excellent discriminative performance (area under the curve, 0.922). Smaller remnants (FLR/SLV <50%) exhibited accelerated and sustained hypertrophy, whereas larger remnants (FLR/SLV ≥50%) showed slower growth that plateaued after reaching approximately 90% of SLV. These findings support a fundamental biological principle: the regenerative stimulus is proportional to the extent of resection [6]. Increased portal inflow and hepatocyte workload after major resection promote compensatory hypertrophy. The observation that regeneration decelerates near 90% of SLV suggests a physiological ceiling effect, indicating that hepatic regeneration is tightly regulated rather than unlimited [7].

However, the most thought-provoking aspect of this study extends beyond volumetric kinetics. The divergent trajectory of spleen volume between groups provides important insight into postoperative functional adaptation. Although spleen enlargement was observed early in all patients, only those with FLR/SLV ≥50% demonstrated a reduction toward baseline by 3 months. In contrast, patients with smaller remnants maintained persistent splenomegaly despite substantial volumetric regeneration.

This dissociation indicates that volumetric recovery does not necessarily correspond to functional recovery. Persistent splenic enlargement may reflect sustained portal hypertension, altered splanchnic hemodynamics, or incomplete restoration of hepatic functional reserve [8,9]. In this context, the observation that the high-regeneration group exhibited lower postoperative day 1 high-sensitivity C-reactive protein levels and higher bilirubin concentrations further suggests that syn-

**Received:** February 23, 2026; **Accepted:** March 10, 2026
**Corresponding Author:** Chan Woo Cho, MD, PhD
Department of Surgery, Yeungnam University College of Medicine, 170 Hyeonchung-ro, Nam-gu, Daegu 42415, Korea
Tel: +82-53-620-3580 Fax: +82-53-624-1213 E-mail: cwcho@ynu.ac.kr

© 2026 Kosin University College of Medicine
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

thetic and excretory function may lag behind structural expansion. Collectively, these findings suggest that rapid hypertrophy of a small remnant may represent a compensatory stress response rather than complete physiological normalization.

From a practical standpoint, these findings have meaningful implications for perioperative management. A lower FLR/SLV ratio predicts rapid hypertrophy but may also correspond to a period of transient functional vulnerability. Surgeons should therefore interpret early volumetric expansion with caution, recognizing that functional recovery may not occur synchronously with structural growth. Persistent postoperative splenomegaly may serve as an adjunct marker of delayed physiological normalization and may warrant closer monitoring in selected patients.

This study challenges the traditional reliance on liver volume alone as a surrogate marker of postoperative safety. While the FLR/SLV ratio remains a robust predictor of regenerative kinetics, spleen volume dynamics provide complementary insight into functional adaptation. The combined assessment of FLR/SLV and spleen volume dynamics may refine perioperative risk stratification and help identify patients at risk for delayed recovery despite apparently adequate volumetric growth.

Several limitations—including the retrospective design, relatively small sample size, and absence of direct functional imaging or long-term laboratory follow-up—temper the strength of the conclusions. Nonetheless, this study provides valuable clinical insight into how volumetric reserve, regenerative kinetics, and spleen dynamics interact after major hepatectomy.

In summary, the 50% FLR/SLV threshold represents a clinically meaningful reference point for stratifying regenerative behavior without implying an absolute safety cutoff. Patients with FLR/SLV <50% demonstrate faster and more dynamic hypertrophy, reflecting strong compensatory stimuli. However, persistent spleen enlargement in this group suggests that volumetric recovery may not fully reflect complete functional adaptation. By integrating liver and spleen dynamics, this study provides a clearer understanding of postoperative regeneration. It highlights the relationship between structural restoration and physiological recovery and offers practical guidance for surgical planning and risk assessment.

## Article information

**Conflicts of interest**
No potential conflict of interest relevant to this article was reported.

**Funding**
None.

**Author contributions**
All the work was done by Chan Woo Cho.

**ORCID**
Chan Woo Cho, https://orcid.org/0000-0002-3546-8442

## References

1. Rahbari NN, Garden OJ, Padbury R, Brooke-Smith M, Crawford M, Adam R, et al. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). Surgery 2011;149:713–24.
2. Kauffmann R, Fong Y. Post-hepatectomy liver failure. Hepatobiliary Surg Nutr 2014;3:238–46.
3. Vauthey JN, Chaoui A, Do KA, Bilimoria MM, Fenstermacher MJ, Charnsangavej C, et al. Standardized measurement of the future liver remnant prior to extended liver resection: methodology and clinical associations. Surgery 2000;127:512–9.
4. Shoup M, Gonen M, D'Angelica M, Jarnagin WR, DeMatteo RP, Schwartz LH, et al. Volumetric analysis predicts hepatic dysfunction in patients undergoing major liver resection. J Gastrointest Surg 2003;7:325–30.
5. Ku S, Lee G, Moon HH, Ku H, Yang WJ, Song J, et al. Predictors and patterns of early liver regeneration after major hepatectomy. Kosin Med J 2026;41:59-67.
6. Michalopoulos GK. Liver regeneration. J Cell Physiol 2007;213:286–300.
7. Yagi S, Hirata M, Miyachi Y, Uemoto S. Liver regeneration after hepatectomy and partial liver transplantation. Int J Mol Sci 2020;21:8414.
8. Bae JS, Lee DH, Yoo J, Yi NJ, Lee KW, Suh KS, et al. Association between spleen volume and the post-hepatectomy liver failure and overall survival of patients with hepatocellular carcinoma after resection. Eur Radiol 2021;31:2461–71.
9. Ito T, Tanemura A, Kuramitsu T, Murase T, Kaluba B, Noguchi D, et al. Spleen volume is a predictor of posthepatectomy liver failure and short-term mortality for hepatocellular carcinoma. Langenbecks Arch Surg 2023;408:297.

**Review article**

Kosin Medical Journal 2026;41(1):3-8
pISSN: 2005-9531 • eISSN: 2586-7024
https://doi.org/10.7180/kmj.26.154

KMJ
KOSIN MEDICAL JOURNAL

# The onco-bariatric paradigm: a tri-phasic metabolic obesity framework for synergizing glucagon-like peptide-1 receptor agonists and metabolic bariatric surgery

**Dong Jin Park[1,*], Yoonhong Kim[2,*], Dongjae Jeon[3], Young Suk Park[3], Kyung Won Seo[2], Ki Hyun Kim[2]**

[1]*Department of Surgery, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, Korea*
[2]*Department of Surgery, Kosin University Gospel Hospital, Kosin University College of Medicine, Busan, Korea*
[3]*Department of Surgery, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea*

Obesity is a chronic, progressive neuroendocrine disease that warrants a shift toward an “onco-bariatric” treatment paradigm. This study introduces the tri-phasic metabolic obesity (TPMO) framework, which integrates glucagon-like peptide-1 receptor agonists (GLP-1 RAs) with metabolic bariatric surgery (MBS). Recent clinical and economic evidence—including findings from the Indiana multicenter study and the Highmark Health analysis—was reviewed to evaluate the effectiveness of the TPMO model in improving surgical and metabolic outcomes. The TPMO framework streamlines the patient journey through three synergistic phases. In the neoadjuvant phase, a 4–8-week course of GLP-1 RAs reduces liver volume and visceral fat, thereby improving surgical access, provided that treatment is discontinued 1 week before surgery to mitigate aspiration risk. During the core surgery phase, MBS provides a definitive metabolic reset and remains the most cost-effective treatment, yielding an average savings of $11,689 per patient over 2 years compared with medication alone. In the adjuvant phase, pharmacotherapy—used by 17.2% of post-bariatric patients—counteracts metabolic adaptation and supports sustained weight loss, while a high-protein intake (≥1.2 g/kg/day) is essential for preserving lean body mass. The TPMO framework represents a precision-based, synergistic standard of care designed to promote durable, cost-effective long-term metabolic health within the onco-bariatric paradigm.

**Keywords:** Anti-obesity agents; Bariatric surgery; Combined modality therapy; Glucagon-like peptide-1 receptor agonists; Precision medicine

## Introduction

Obesity is now recognized not just as a cosmetic issue or a result of willpower failure, but as a complex, chronic, progressive neuroendocrine disease marked by systemic inflammation and dysregulation of homeostasis. Given its chronic and relapsing nature, the medical community advocates for a fundamental shift in approach—adopting an "onco-bariatric" model that treats obesity with the same rigorous, staged strategies used for malignant tumors. The World Health Organization and the International Federation for the Surgery of Obesity and Metabolic Disorders

**Received:** February 12, 2026; **Accepted:** March 9, 2026
**Corresponding Author:** Ki Hyun Kim, MD, PhD
Department of Surgery, Kosin University Gospel Hospital, Kosin University College of Medicine, 262 Gamcheon-ro, Seo-gu, Busan 49267, Korea
Tel: +82-51-990-6782 Fax: +82-51-246-6093 E-mail: linus.kkh@gmail.com

*These authors contributed equally to this work as first authors.

© 2026 Kosin University College of Medicine
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

have consistently emphasized the biological foundations of obesity, urging for aggressive clinical intervention [1]. For decades, metabolic bariatric surgery (MBS) has been the gold standard for achieving remission of type 2 diabetes and preventing cardiovascular events [2]. However, the therapeutic landscape has changed significantly with the introduction of next-generation incretin-based therapies, including semaglutide and tirzepatide [3].

The initial rise in glucagon-like peptide-1 (GLP-1) prescriptions was accompanied by a temporary decrease in surgical volumes. However, real-world data has revealed notable challenges associated with relying solely on pharmacotherapy, such as rapid weight regain after discontinuation and considerable long-term economic costs [4]. As a result, the medical community is shifting towards an oncology model for obesity treatment, which involves using neoadjuvant therapy to improve surgical conditions and adjuvant therapy to enhance long-term outcomes [5]. To implement this paradigm, we introduce the tri-phasic metabolic obesity (TPMO) framework—a strategic clinical protocol aimed at optimizing the synergy between glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and surgical intervention. This collaborative approach marks a transition toward more personalized and comprehensive obesity care. By incorporating recent insights into metabolic pathways along with strategic clinical protocols, we can advance from one-size-fits-all solutions to true precision obesity medicine, promoting lasting metabolic health [6,7]. As shown in Fig. 1 and summarized in Table 1, the TPMO framework follows a structured progression: the neoadjuvant phase focuses on surgical optimization, the surgery (core) phase aims for a definitive metabolic reset, and the adjuvant phase is designed for long-term maintenance to prevent metabolic adaptation.

## Pathophysiological synergy: complementarity of surgery and pharmacotherapy

This synergy forms the biological foundation of the TPMO framework, where surgery and pharmacotherapy act as reciprocal stabilizers of metabolic homeostasis. Successful treatment of obesity depends on normalizing the gut-brain axis. In patients with severe obesity, the incretin effect is

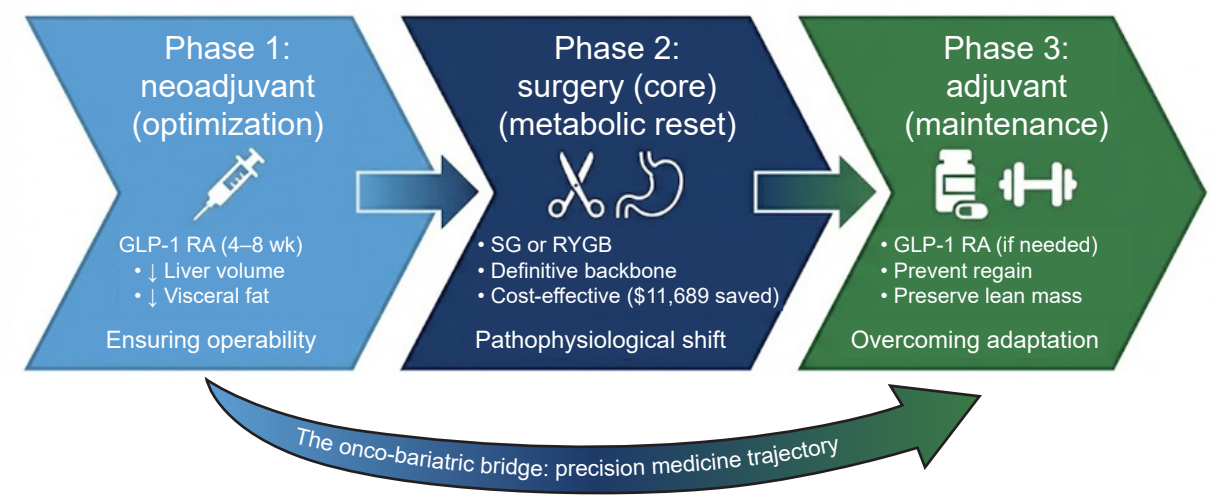


**Fig. 1.** The tri-phasic metabolic obesity framework: a staged approach to synergizing glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and metabolic surgery. The model operationalizes the onco-bariatric paradigm by synchronizing pharmacological and surgical interventions across three distinct clinical phases. Phase 1 (optimization): preoperative GLP-1 RA therapy for 4–8 weeks to reduce liver volume and visceral fat. A 1-week discontinuation ("hard stop") is required to ensure anesthesia safety. Phase 2 (core): metabolic surgery serves as the definitive backbone for metabolic reset and demonstrates superior cost-effectiveness ($11,689 mean savings over 2 years). Phase 3 (maintenance): adjuvant pharmacotherapy counteracts metabolic adaptation and helps prevent weight regain. Emphasis is placed on preserving muscle mass through high-protein intake (≥1.2 g/kg/day) and resistance training. GLP-1 RA, glucagon-like peptide-1 receptor agonist; SG, sleeve gastrectomy; RYGB, Roux-en-Y gastric bypass.

**Table 1.** The tri-phasic metabolic obesity, framework: goals, interventions, and evidence

| Phase | Clinical goal | Primary intervention | Key evidence & rationale |
|---|---|---|---|
| Phase 1: neoadjuvant | Surgical optimization and ensuring operability | GLP-1 RA (4–8 weeks) | ↓ Liver volume and visceral fat for better access. Strict 1-week hard stop to prevent aspiration |
| Phase 2: core surgery | Definitive metabolic reset and disease remission | Metabolic bariatric surgery (SG or RYGB) | Superior cost-effectiveness ($11,689 saved over 2 years). Immediate insulin resistance resolution |
| Phase 3: adjuvant | Long-term maintenance and preventing adaptation | GLP-1 RA+medical nutrition therapy | Counteracting metabolic adaptation and weight regain. Focus on lean body mass preservation (≥1.2 g/kg/day protein) |

GLP-1 RA, glucagon-like peptide-1 receptor agonist; SG, sleeve gastrectomy; RYGB, Roux-en-Y gastric bypass.

often diminished, while ghrelin levels remain abnormally elevated, resulting in persistent hunger [8].

Pharmacological agents such as GLP-1 RAs and dual glucose-dependent insulinotropic polypeptide/GLP-1 agonists bypass these defects by directly stimulating the hypothalamic satiety centers and enhancing insulin sensitivity [9,10]. Concurrently, surgical procedures such as sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB) fundamentally alter anatomy to induce a hormonal cliff by removing the ghrelin-producing fundus. Additionally, these surgeries activate the ileal brake through rapid nutrient transit, resulting in a significant release of endogenous GLP-1 and peptide YY (PYY) [11-13]. This core surgical intervention facilitates a fundamental metabolic reset that is challenging to achieve through pharmacotherapy alone. While MBS induces exaggerated postprandial hormonal surges that exceed the pharmacological range of current GLP-1 RAs [13], adjunct pharmacotherapy can stabilize appetite control and address the suboptimal weight loss observed in the late postoperative phase [14]. This relationship mirrors the synergy between surgery and systemic therapy in oncology, where one modality targets macro-level disease (anatomical and hormonal reset) while the other addresses micro-level adaptations (homeostatic resistance). This biological complementarity underpins the integrated TPMO treatment model, ensuring a more robust and durable therapeutic outcome.

## Phase 1: metabolic neoadjuvancy and surgical optimization

The first stage of the TPMO framework, metabolic neoadjuvancy, prioritizes preoperative optimization to enhance surgical safety and ease. This phase mirrors the concept of neoadjuvant chemotherapy in oncology, where treatment is given before the main procedure to improve surgical feasibility. In particular, the enlarged left lobe of the liver in patients with metabolic dysfunction-associated steatotic liver disease poses a significant technical challenge during laparoscopic surgery. A 4–8 week course of GLP-1 RAs during this neoadjuvant phase effectively reduces liver volume and visceral fat [15]. This optimization improves surgical access to the hiatus and decreases the risk of iatrogenic liver traction injuries, especially in super-obese individuals (body mass index >50 kg/m$^2$) [16]. However, the role of neoadjuvant pharmacotherapy should be critically evaluated as a means of establishing technical operability rather than as a direct biological preventative for clinical complications. The Indiana multicenter study (AbuHasan et al. [17]), which analyzed 2,169 patients, found that preoperative GLP-1 use did not lead to a statistically significant reduction in 30-day readmission rates or emergency department visits. These findings suggest that while neoadjuvant therapy significantly enhances the surgical environment, it should not be regarded as a magic bullet for reducing complications such as anastomotic leaks. Moreover, within the TPMO model, patient safety remains the highest priority, particularly concerning anesthesia-related risks. Delayed gastric emptying associated with GLP-1 RAs elevates the risk of pulmonary aspiration during induction. Therefore, adherence to the 2024 American Society of Anesthesiologists consensus, which strongly recommends a 1-week hard stop protocol for weekly GLP-1 formulations prior to surgery [18], is a nonnegotiable requirement. This rigorous safety standard ensures that the metabolic benefits of neoadjuvant optimization are not undermined by preventable perioperative risks.

## Phase 2: surgery (core)–the definitive metabolic reset and economic advantage

In the core stage of the TPMO framework, MBS serves as the essential backbone of the entire treatment pathway. While pharmacotherapy plays a crucial supportive role, surgery offers a fundamental metabolic reset through anatomical changes that medication alone cannot achieve. Procedures like SG and RYGB create a hormonal cliff by removing the ghrelin-producing gastric fundus, which triggers a significant release of endogenous GLP-1 and PYY through the ileal brake mechanism.

Despite the recent advancements in pharmacological treatments, surgery remains the most cost-effective solution for chronic obesity. A landmark study by Barrett et al. [19], published in JAMA Surgery, utilized data from Highmark Health to directly compare the economic outcomes of MBS and GLP-1 pharmacotherapy. The analysis showed that over 2 years, the surgical cohort saved an average of about $11,689 per patient compared to the medication-only group. Although surgery incurs higher initial costs, monthly maintenance expenses decreased significantly in the second year to $1,154, while costs for continuous pharmacotherapy remained high at $2,448. Beyond economic metrics, the metabolic remission achieved during the surgery (core) phase is both deeper and more durable. MBS leads to an immediate resolution of insulin resistance that occurs independently of weight loss [20], effectively breaking the pathophysiological connection between metabolic syndrome and various malignancies [21]. Within the onco-bariatric paradigm, this phase represents the primary resection or definitive treatment that establishes a new physiological set point, serving as the foundation for all subsequent adjuvant therapies [22].

## Phase 3: metabolic adjuvancy–overcoming homeostatic resistance

The final stage of the TPMO framework, metabolic adjuvancy, is crucial for preventing weight regain and maintaining the new set point established by surgery. In the onco-bariatric paradigm, this phase is similar to adjuvant chemotherapy in oncology, which aims to eliminate residual micrometastases and prevent disease recurrence. In obesity management, adjuvant pharmacotherapy focuses on addressing metabolic adaptation, a complex physiological response to weight loss that results in a significant decrease in resting metabolic rate [23]. Weight recurrence is considered not a failure of patient willpower, but rather a biological drive that necessitates ongoing metabolic modulation. Recent real-world evidence, including an analysis of Johns Hopkins data by Kim et al. [24], shows that around 17.2% (or 1 in 7) of post-bariatric patients ultimately need GLP-1 RA therapy to address weight recurrence.

This indicates that adjuvant pharmacotherapy is becoming a clinical standard for stabilizing the hormonal environment after the core surgical reset. The importance of this ongoing management was highlighted by the SURMOUNT-4 randomized clinical trial (continued treatment with tirzepatide for maintenance of weight reduction in adults with obesity), which showed significant weight regain after the discontinuation of tirzepatide. This confirms that obesity is a chronic, progressive condition that necessitates long-term intervention [25]. However, the combined catabolic effects of surgery and potent incretin mimetics increase the risk of sarcopenia. Research indicates that a substantial portion of weight lost with GLP-1 RAs can be attributed to a reduction in lean body mass [26]. Consequently, TPMO adjuvant protocols must rigorously mandate high-protein medical nutrition therapy (≥1.2 g/kg/day) and supervised resistance training to preserve muscle mass and metabolic health [27]. Furthermore, clinicians must implement precise dosing strategies that consider the altered pharmacokinetics and drug absorption rates observed after gastrectomy [28].

## Conclusions

The era of considering bariatric surgery and pharmacotherapy as competing options has ended. Current evidence supports a unified, precision-based approach that encompasses the entire patient journey. This onco-bariatric paradigm, implemented through the TPMO framework, ensures that each treatment modality is strategically aligned to achieve the best outcomes. In this model, neoadjuvant therapy is strategically used to reduce liver volume and improve surgical safety, as long as preoperative withdrawal windows are closely followed to reduce the risk of anesthesia-related aspiration [29]. Metabolic surgery remains the cornerstone

of this framework due to its exceptional cost-effectiveness and the significant metabolic remission it achieves. Consequently, adjuvant pharmacotherapy should be actively employed to address homeostatic metabolic adaptation, with a strong emphasis on preserving lean mass through medical nutrition and resistance training. This integrated, multimodal approach represents the future standard of care. The next frontier in obesity management lies in developing artificial intelligence (AI)-driven, deep-phenotyping algorithms that can predict individual therapeutic responses. By identifying the specific biological and behavioral phenotypes that benefit most from this synergy, we can finally fulfill the promise of personalized, long-term metabolic health, moving beyond one-size-fits-all interventions to achieve true precision medicine [30,31].

## Article information

**Conflicts of interest**
No other potential conflicts of interest relevant to this article were reported.

**Funding**
None.

**Author contributions**
Conceptualization: KWS, KHK. Data curation: DJP, YK, DJ. Formal analysis: DJP, YK, DJ, YSP. Methodology: DJP, YK, DJ. Project administration: KHK. Validation: DJP, YK, DJ, YSP. Writing-original draft: DJP, YK, DJ. Writing-review & editing: YSP, KWS, KHK. All authors read and approved the final manuscript.

**ORCID**
Dong Jin Park, https://orcid.org/0000-0001-7820-9179
Yoonhong Kim, https://orcid.org/0000-0003-1611-5390
Dongjae Jeon, https://orcid.org/0009-0000-6736-1191
Young Suk Park, https://orcid.org/0000-0002-6352-9759
Kyung Won Seo, https://orcid.org/0000-0002-5771-3832
Ki Hyun Kim, https://orcid.org/0000-0002-8296-3307

## References

1. World Health Organization. WHO acceleration plan to stop obesity [Internet]. World Health Organization; 2023 [cited 2026 Mar 13]. https://www.who.int/publications/i/item/9789240075634
2. Mingrone G, Panunzi S, De Gaetano A, Guidone C, Iaconelli A, Capristo E, et al. Metabolic surgery versus conventional medical therapy in patients with type 2 diabetes: 10-year follow-up of an open-label, single-centre, randomised controlled trial. Lancet 2021;397:293–304.
3. Lin K, Mehrotra A, Tsai TC. Metabolic bariatric surgery in the era of GLP-1 receptor agonists for obesity management. JAMA Netw Open 2024;7:e2441380.
4. Rubino F, Puhl RM, Cummings DE, Eckel RH, Ryan DH, Mechanick JI, et al. Joint international consensus statement for ending stigma of obesity. Nat Med 2020;26:485–97.
5. Sher T, McGee M, DuCoin C, Sujka J, Docimo S. Adjuvant and neo-adjuvant anti-obesity medications and bariatric surgery: a scoping review. Curr Obes Rep 2024;13:377–402.
6. Lee JY. Exploring the nexus between obesity, metabolic syndrome, and colorectal cancer. KMJ 2024;39:18–25.
7. Yu S, Lee SS, Hwang H. The ethics of using artificial intelligence in medical research. KMJ 2024;39:229–37.
8. Cummings DE, Weigle DS, Frayo RS, Breen PA, Ma MK, Dellinger EP, et al. Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery. N Engl J Med 2002;346:1623–30.
9. Holst JJ. The physiology of glucagon-like peptide 1. Physiol Rev 2007;87:1409–39.
10. Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S, Connery L, Alves B, et al. Tirzepatide once weekly for the treatment of obesity. N Engl J Med 2022;387:205–16.
11. Vincent RP, le Roux CW. Changes in gut hormones after bariatric surgery. Clin Endocrinol (Oxf) 2008;69:173–9.
12. Schauer PR, Kashyap SR, Wolski K, Brethauer SA, Kirwan JP, Pothier CE, et al. Bariatric surgery versus intensive medical therapy in obese patients with diabetes. N Engl J Med 2012;366:1567–76.
13. le Roux CW, Aylwin SJ, Batterham RL, Borg CM, Coyle F, Prasad V, et al. Gut hormone profiles following bariatric surgery favor an anorectic state, facilitate weight loss, and improve metabolic parameters. Ann Surg 2006;243:108–14.
14. Stanford FC, Alfaris N, Gomez G, Ricks ET, Shukla AP, Corey KE, et al. The utility of weight loss medications after bariatric surgery for weight regain or inadequate weight loss: a multi-center study. Surg Obes Relat Dis 2017;13:491–500.
15. Edholm D, Kullberg J, Haenni A, Karlsson FA, Ahlstrom A, Hedberg J, et al. Preoperative 4-week low-calorie diet reduces liver volume and intrahepatic fat, and facilitates laparoscopic gastric bypass in morbidly obese. Obes Surg 2011;21:345–50.

16. Colles SL, Dixon JB, Marks P, Strauss BJ, O'Brien PE. Preoperative weight loss with a very-low-energy diet: quantitation of changes in liver and abdominal fat by serial imaging. Am J Clin Nutr 2006;84:304–11.
17. AbuHasan Q, Funk LM, Holl JL, Draucker C, Grannis S, Bilimoria KY, et al. Preoperative glucagon-like peptide-1 receptor agonist utilization and association with bariatric surgery outcomes. Obes Surg 2025;35:556–60.
18. Ushakumari DS, Sladen RN. ASA consensus-based guidance on preoperative management of patients on glucagon-like peptide-1 receptor agonists. Anesthesiology 2024;140:346–8.
19. Barrett TS, Hafermann JO, Richards S, LeJeune K, Eid GM. Obesity treatment with bariatric surgery vs GLP-1 receptor agonists. JAMA Surg 2025;160:1232–9.
20. Guidone C, Manco M, Valera-Mora E, Iaconelli A, Gniuli D, Mari A, et al. Mechanisms of recovery from type 2 diabetes after malabsorptive bariatric surgery. Diabetes 2006;55:2025–31.
21. Aminian A, Wilson R, Al-Kurd A, Tu C, Milinovich A, Kroh M, et al. Association of bariatric surgery with cancer risk and mortality in adults with obesity. JAMA 2022;327:2423–33.
22. Schauer PR, Bhatt DL, Kirwan JP, Wolski K, Aminian A, Brethauer SA, et al. Bariatric surgery versus intensive medical therapy for diabetes: 5-year outcomes. N Engl J Med 2017;376:641–51.
23. Maclean PS, Bergouignan A, Cornier MA, Jackman MR. Biology's response to dieting: the impetus for weight regain. Am J Physiol Regul Integr Comp Physiol 2011;301:R581–600.
24. Kim M, Schweitzer MA, Kim JS, Alexander GC, Mehta HB. Use of glucagon-like peptide-1 agonists among individuals undergoing bariatric surgery in the US. JAMA Surg 2025;160:1058–66.
25. Aronne LJ, Sattar N, Horn DB, Bays HE, Wharton S, Lin WY, et al. Continued treatment with tirzepatide for maintenance of weight reduction in adults with obesity: the SURMOUNT-4 randomized clinical trial. JAMA 2024;331:38–48.
26. Sargeant JA, Henson J, King JA, Yates T, Khunti K, Davies MJ. A review of the effects of glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter 2 inhibitors on lean body mass in humans. Endocrinol Metab (Seoul) 2019;34:247–62.
27. Parrott J, Frank L, Rabena R, Craggs-Dino L, Isom KA, Greiman L. American society for metabolic and bariatric surgery integrated health nutritional guidelines for the surgical weight loss patient 2016 update: micronutrients. Surg Obes Relat Dis 2017;13:727–41.
28. Darwich AS, Pade D, Ammori BJ, Jamei M, Ashcroft DM, Rostami-Hodjegan A. A mechanistic pharmacokinetic model to assess modified oral drug bioavailability post bariatric surgery in morbidly obese patients: interplay between CYP3A gut wall metabolism, permeability and dissolution. J Pharm Pharmacol 2012;64:1008–24.
29. American Society of Anesthesiologists. American Society of Anesthesiologists consensus-based guidance on preoperative management of patients (adults and children) on glucagon-like peptide-1 (GLP-1) receptor agonists [Internet]. American Society of Anesthesiologists; 2023 [cited 2026 Mar 13]. https://www.asahq.org/about-asa/newsroom/news-releases/2023/06/american-society-of-anesthesiologists-consensus-based-guidance-on-preoperative
30. Sacoto D, Hurtado MD, Acosta A. Precision medicine and obesity. Handb Exp Pharmacol 2022;274:467–85.
31. Bektas M, Reiber BM, Pereira JC, Burchell GL, van der Peet DL. Artificial intelligence in bariatric surgery: current status and future perspectives. Obes Surg 2022;32:2772–83.

**Review article**

Kosin Medical Journal 2026;41(1):9-18
pISSN: 2005-9531 • eISSN: 2586-7024
https://doi.org/10.7180/kmj.26.156

KMJ
KOSIN MEDICAL JOURNAL

# Bowel preparation for colonoscopy in special populations: a practical and risk-stratified approach

**Myung-Hun Lee, Won Moon, Kyoungwon Jung, Jae Hyun Kim, Sung Eun Kim, Moo In Park, Seun Ja Park**

*Department of Internal Medicine, Kosin University Gospel Hospital, Kosin University College of Medicine, Busan, Korea*

Bowel preparation is a key determinant of colonoscopy quality; however, inadequate cleansing remains common among patients with overlapping clinical and logistical barriers. In routine practice, preparation failure may prolong procedures, reduce diagnostic confidence, and necessitate early repeat colonoscopy. We review major society guidelines and selected studies addressing bowel preparation in inflammatory bowel disease (IBD), chronic kidney disease (CKD), older adults, chronic constipation, and hospitalized patients. Across these settings, the most consistently supported measures include split-dose administration, completion of the final dose close to the time of colonoscopy in accordance with local fasting and sedation policies, and structured patient instructions reinforced through follow-up communication. A standardized assessment of preparation quality is recommended to support quality improvement and appropriate follow-up. Risk stratification can help identify patients who may benefit from intensified preparation pathways, including those with prior inadequate preparation, severe constipation, frailty, or inpatient status. Safety considerations are particularly important in CKD, in which oral sodium phosphate should be avoided and magnesium-containing agents used cautiously; polyethylene glycol-based solutions are generally preferred. In IBD, regimen selection should also consider endoscopic interpretability because sodium phosphate preparations have been associated with preparation-related mucosal abnormalities that may confound the assessment of subtle inflammatory findings. Among hospitalized patients, system-level barriers often predominate, and protocolized pathways may improve workflow and patient comfort while maintaining cleansing effectiveness. We propose a practical, risk-stratified approach to regimen selection, timing, rescue strategies, and safety monitoring that can be implemented in high-volume clinical practice.

**Keywords:** Chronic renal insufficiency; Colonoscopy; Constipation; Inflammatory bowel diseases; Inpatients

## Introduction

Bowel preparation is an unavoidable part of colonoscopy practice. Clinicians are repeatedly required to select a regimen in routine care—often within limited consultation time, with variable patient understanding, and with an expanding range of preparation options. When cleansing is inadequate, mucosal visualization is compromised, the examination may be prolonged, diagnostic confidence may be reduced, and repeat colonoscopy is frequently required. Major society guidelines therefore emphasize modifiable measures such as split-dose administration, completing the final dose close to the procedure, and structured patient instruction to improve preparation adequacy and tolerability. In addition, guidelines recommend that preparation quality be documented using standardized descriptors or

**Received:** February 10, 2026; **Revised:** March 10, 2026; **Accepted:** March 13, 2026
**Corresponding Author:** Won Moon, MD, PhD
Department of Internal Medicine, Kosin University Gospel Hospital, Kosin University College of Medicine, 262 Gamcheon-ro, Seo-gu, Busan 49267, Korea
Tel: +82-51-990-6103 Fax: +82-51-990-3049 E-mail: moonone70@hanmail.net

© 2026 Kosin University College of Medicine
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

validated scoring systems to support quality monitoring and follow-up planning [1-3].

In everyday practice, however, bowel preparation is rarely a simple choice of "which product to prescribe." Patients with inflammatory bowel disease (IBD), chronic kidney disease (CKD), advanced age, chronic constipation, or those undergoing inpatient colonoscopy often present with overlapping risk factors for inadequate preparation and incomplete intake. Evidence syntheses in "hard-to-prepare" patients summarize consistent clinical and setting-related correlates of suboptimal cleansing, including constipation, comorbidity burden, medication exposure, and inpatient status [4]. Safety considerations also differ by population; oral sodium phosphate has well-described renal safety concerns in susceptible individuals and is generally discouraged in patients with kidney disease [1-3,5]. For hospitalized patients, barriers are frequently system-related, and randomized data suggest that protocolized pathways can improve comfort while maintaining cleansing effectiveness [6]. Recent clinical updates also emphasize protocolization and workflow alignment as practical levers in high-risk settings [7].

These challenges are also encountered in high-volume practice settings, including many Korean centers, where bowel preparation is commonly prescribed during brief outpatient visits and procedure schedules (early-morning or add-on inpatient cases) can make regimen timing and adherence difficult. Regional practice perspectives and safety considerations have also been discussed in the Korean literature [8].

Accordingly, this review summarizes major society guidelines and selected studies relevant to bowel preparation in IBD, CKD, older adults, chronic constipation, and hospitalized patients, and we suggest a practical, risk-stratified approach to regimen selection, timing, and safety monitoring in routine practice (Tables 1, 2, Fig. 1) [1-8].

In this review, "special populations" refers to patients who require bowel preparation strategies beyond routine outpatients for one of the following reasons: (1) safety vulnerability to fluid/electrolyte shifts (e.g., advanced CKD, frailty/advanced age, limited intake), (2) high risk of inadequate cleansing due to clinical or system barriers (e.g., severe constipation, inpatient status, prior inadequate preparation), and/or (3) condition-specific interpretability concerns, as in IBD where subtle mucosal assessment is central. These categories often overlap in real-world practice.

## General principles

**1. Regimen timing: split dose as the default**

Preparation adequacy should be assessed and documented in a standardized manner, using validated scoring systems when feasible, to support quality improvement and appropriate surveillance intervals [1-3]. In practice, "inadequate preparation" refers to cleansing that does not allow reliable mucosal assessment and may preclude assignment of standard screening or surveillance intervals [1-3].

Regimen timing is a major determinant of bowel cleansing quality and often explains failure even when an appropriate agent is prescribed. Current guidelines consistently recommend split-dose administration for most patients because it improves overall cleansing—particularly in the proximal colon—and is generally better tolerated than single, day-before dosing [1-3]. This approach is most effective when the interval between completion of the final dose and colonoscopy is kept short, while still observing institutional fasting and sedation policies [1-3]. For afternoon colonoscopy, same-day regimens may be considered when split dosing is impractical, provided that safety requirements are met and the patient can tolerate intake [1-3]. Clinicians should anticipate common reasons for incomplete intake (nausea, early satiety, anxiety, competing medications) and address them proactively, because partial consumption is a frequent cause of inadequate preparation in high-risk groups [4,5].

**2. Diet and patient instruction: consistently modifiable drivers**

Dietary measures and patient instruction remain the most consistently modifiable components of bowel preparation. Although specific diet protocols vary across institutions, guidelines generally support restricting solid residue before colonoscopy and providing clear, standardized instructions regarding permitted intake, timing of preparation, and management of common symptoms [1-3]. Evidence syntheses and clinical updates also emphasize reinforcement strategies (e.g., reminders and caregiver engagement when appropriate), particularly in older adults and hospitalized patients [4,5]. Practical details—such as coordinating the

**Table 1.** Risk factors for inadequate bowel preparation and practical implications

| Risk factors | Practical implications in practice |
|---|---|
| Prior inadequate bowel preparation | Use intensified regimen, earlier special diet, clearer instructions; consider preprocedure check and low threshold for rescue or early rescheduling. |
| Chronic constipation or infrequent bowel movements, baseline laxative use | Consider earlier low-residue diet, split-dose PEG-based regimen, and adjunct laxatives (e.g., bisacodyl) when appropriate; provide reinforcement and reminders. |
| High comorbidity burden (e.g., diabetes, neurologic disease), limited mobility | Expect slower transit and adherence barriers; simplify instructions, engage caregiver, and consider supervised pathways if needed. |
| Exposure to medication that impairs motility (e.g., opioids, anticholinergics, tricyclics, iron/calcium) | Review medications and anticipate reduced efficacy; consider intensified regimens and symptom control for nausea. |
| Older age, frailty, cognitive impairment | Prioritize safety and completion; use predictable agents (often PEG), hydration plan, caregiver support, and fall-risk precautions. |
| CKD or electrolyte vulnerability | Avoid oral sodium phosphate; use caution with magnesium-containing agents; consider selective labs in advanced CKD or frailty. |
| Inpatient status, acute illness, competing tests/scheduling constraints | Use protocolized inpatient order sets with nursing monitoring of intake/output; coordinate timing with procedure schedule. |
| Poor health literacy, language barriers, limited social support | Use standardized written instructions, teach-back, reminders (text message/phone), and involve family/caregiver. |
| Short lead time to colonoscopy, early-morning procedures | Ensure true split dose when feasible; provide clear timing schedule; consider same-day regimen for afternoon cases when appropriate and safe. |

PEG, polyethylene glycol; CKD, chronic kidney disease.

**Table 2.** Suggested bowel preparation strategies for special populations

| Population | Preferred agents | Timing and diet | Special considerations | Monitoring and rescue |
|---|---|---|---|---|
| Inflammatory bowel disease | PEG-based solutions as first-line | Split dose; emphasize completion; standard low-residue diet per institutional policy | Interpret subtle lesions with awareness of prep-related mucosal changes (especially after sodium phosphate); prioritize visualization for activity assessment/surveillance | Early recognition of incomplete intake; low threshold for intensified or repeat preparation when visualization is critical |
| CKD | PEG-based solutions preferred; avoid sodium phosphate | Split dose; hydration plan | Use caution with magnesium-containing agents (advanced CKD); review diuretics/RAAS blockers; avoid dehydration | Consider selective electrolytes/renal function monitoring in advanced CKD or frailty; favor PEG-based rescue |
| Older adults | PEG-based regimens with predictable safety; consider low-volume PEG in selected patients | Split dose; simplify instructions; consider supervised preparation if there are adherence barriers | Assess frailty, mobility, cognition; caregiver engagement; fall-risk precautions | Hydration plan and medication review; early assessment for rescue or rescheduling if inadequate |
| Chronic constipation/hard-to-prepare outpatients | PEG-based regimens; consider higher-volume or adjuncts | Earlier dietary modification; split dose; reinforced education | Ask about prior inadequate preparation; consider adjunct laxatives (e.g., bisacodyl) when appropriate | Preprocedure effluent assessment; rescue strategy or early repeat colonoscopy if inadequate |
| Hospitalized patients | PEG-based regimens commonly used within protocolized pathways | Split dose aligned to schedule; standardized orders and diet | Address nausea/pain, opioid exposure; nursing documentation of intake/output and stool quality | Protocol-driven early assessment; presedation rescue or rescheduling to avoid low-yield procedures |

PEG, polyethylene glycol; CKD, chronic kidney disease; RAAS, renin–angiotensin–aldosterone system.

timing of regular medications and ensuring access to clear liquids—often determine whether the prescribed regimen is actually completed.

### 3. Risk stratification

Risk stratification is useful because the likelihood of inadequate preparation is not evenly distributed. Reviews focusing on hard-to-prepare patients summarize a consistent set of clinical and contextual features linked to suboptimal cleansing, including constipation, comorbidity burden, medication exposures, and inpatient setting [4]. Risk factors and practical implications are summarized in Table 1. For

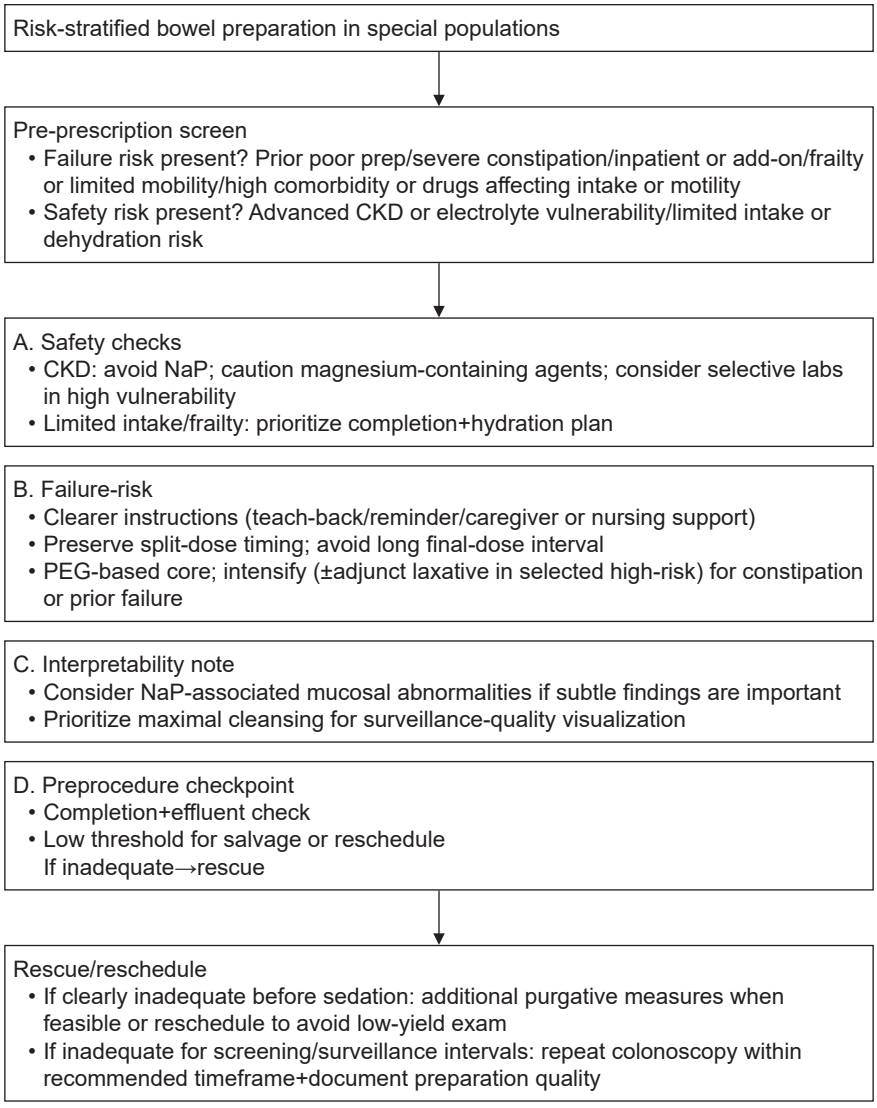


**Fig. 1.** Practical, risk-stratified workflow for bowel preparation in special populations. Patients are assessed for failure risk and safety vulnerability before prescription; split-dose with standardized instructions is the default strategy. High-risk patients follow an intensified pathway (reinforced support, preserved timing, and a PEG-based core regimen with safety checks), with an inflammatory bowel disease interpretability note and a preprocedure checkpoint to guide salvage/rescheduling and appropriate follow-up when preparation is inadequate. CKD, chronic kidney disease; NaP, oral sodium phosphate; PEG, polyethylene glycol.

patients with one or more high-risk features—particularly a prior history of inadequate preparation, severe constipation, frailty, or inpatient status—guidelines and evidence syntheses support adopting "high-risk pathways," such as intensified regimens, closer follow-up before the procedure, and a lower threshold for rescue strategies when preparation is clearly incomplete [1-5].

**4. Choice of agent and safety considerations**

Agent selection should balance cleansing efficacy, tolerability, and patient-specific safety risks. Society guidelines generally position polyethylene glycol (PEG)-based solutions as a conservative option across a wide range of patients because of their iso-osmotic profile and favorable safety record [1-3]. Low-volume PEG-based regimens may improve tolerability and completion rates in selected patients; however, success remains anchored in adequate dose

completion and appropriate timing [1-3]. Real-world data suggest that low-volume PEG strategies can achieve acceptable preparation quality in outpatient practice, but patient selection and adherence remain important [9]. In regions where access to 4-L PEG is limited (including South Korea), locally available low-volume PEG-based formulations (e.g., 2-L PEG with/without ascorbate or other PEG regimens) represent acceptable alternatives when split dosing, full completion, and a short final-dose-to-colonoscopy interval are preserved.

Importantly, PEG-based regimens are not entirely without risk. A case report described a 75-year-old female patient who developed acute severe hyponatremia with generalized tonic-clonic seizure after ingestion of a PEG-electrolyte solution, with thiazide exposure noted as a potential contributor [7]. Although such events appear uncommon, the report highlights a practical point: in patients at risk for hyponatremia (e.g., older adults, those receiving thiazides or other agents associated with hyponatremia, patients with limited physiologic reserve, or those with prior hyponatremia), bowel preparation should be accompanied by medication review and clear hydration guidance. In highly vulnerable patients, clinicians may consider emphasizing electrolyte-containing fluids rather than excessive hypotonic "free water," and selective serum electrolyte assessment can be considered when clinical concern is high or symptoms occur [7].

Hyperosmotic preparations require more caution in patients vulnerable to fluid and electrolyte disturbances. Oral sodium phosphate, in particular, is associated with acute phosphate nephropathy and should be avoided in patients with kidney disease and other high-risk settings [1-3,6]. Practical selection under special conditions has been summarized in the literature and can help guide individualized decisions in routine care [10].

## Bowel preparation in special populations

### 1. Inflammatory bowel disease

*1) Clinical context*

In IBD, bowel preparation influences more than procedural completion. Cleansing quality affects the reliability of mucosal assessment for inflammatory activity and supports surveillance examinations in which subtle lesions matter [9,10]. Suboptimal preparation can obscure mild inflammatory changes and reduce confidence in endoscopic interpretation [9,10]. Because many patients undergo repeated colonoscopies over time, regimens that provide consistent cleansing while maintaining interpretability are preferred [11,12].

*2) Preparation-related mucosal abnormalities and interpretability*

Several bowel preparations have been reported to induce transient mucosal changes that may complicate interpretation. In particular, colonic mucosal abnormalities have been described after oral sodium phosphate, raising concern for potential diagnostic confusion when subtle mucosal findings guide decisions [13]. This issue is also emphasized in IBD-focused discussions of bowel preparation [11,12]. In practice, avoiding agents that may introduce interpretive uncertainty is reasonable when endoscopic assessment is expected to influence treatment decisions or surveillance planning.

*3) Regimen selection in inflammatory bowel disease*

PEG-based solutions are generally a practical first choice in IBD because they are recommended in major guidelines and have a long-standing safety profile in routine practice [1-3,11,12]. Observational IBD cohorts have identified patient- and setting-related factors associated with inadequate preparation, reinforcing the importance of timing, completion, and patient-level barriers [12,14]. In clinically stable patients, low-volume options may be considered to improve completion when tolerability is the primary barrier, while maintaining strict attention to timing and completion [5,12,14].

In patients with limited oral intake, frailty, or higher dehydration risk—including those with active symptoms—clinicians should prioritize safety and the likelihood of completing the full dose. Practical measures include simplifying stepwise instructions, planning hydration, and considering symptom control (e.g., antiemetics when nausea is anticipated) to support completion [7,9,10]. When high-quality visualization is critical (e.g., suspected subtle lesions or surveillance examinations), it is reasonable to prioritize cleansing adequacy over minimal volume and to adopt intensified strategies when high-risk features are present [1-5].

*4) Practical recommendations for inflammatory bowel disease*

- Use PEG-based split-dose regimens as a practical first-line approach in most IBD patients [1-3,11,12].
- Avoid oral sodium phosphate when interpretability is important, and consider preparation-related mucosal abnormalities when subtle findings are present [11-13].
- In limited intake, frailty, or dehydration risk, emphasize completion and safety (hydration plan and symptom control when appropriate) [5,11,12].
- For examinations requiring high-quality visualization, use an intensified pathway when high-risk features for inadequate preparation are present [1-5].

**2. Chronic kidney disease**

*1) Clinical context*

In CKD, the choice of bowel preparation is primarily driven by safety. Patients with reduced renal reserve are more vulnerable to clinically meaningful electrolyte shifts and volume depletion, and these risks may be amplified by diuretics or renin–angiotensin system blockers [5,10]. In advanced CKD (commonly including stage 4–5) or in patients with poor oral intake, conservative planning focused on hydration and completion is often necessary.

*2) Major safety concerns: phosphate and magnesium loading*

The most established safety concern is the association between oral sodium phosphate and acute phosphate nephropathy [6]. Accordingly, major guidelines discourage sodium phosphate in patients with kidney disease and other high-risk settings [1-3,6]. Magnesium-containing preparations warrant additional caution in advanced CKD due to impaired excretion and the risk of hypermagnesemia, consistent with general guidance on safety-oriented regimen selection [1-3,5,10]

*3) Regimen selection in chronic kidney disease*

PEG-based solutions are generally preferred in CKD because they are iso-osmotic and are less likely to produce clinically relevant electrolyte shifts when taken as recommended [1-3,5,10]. In advanced CKD, frailty, or limited intake, the regimen should be selected with attention to dose completion and hydration planning. Selective laboratory monitoring (electrolytes and renal function) may be considered when clinical vulnerability is high or when dehydration risk is expected to be difficult to mitigate [5,10].

*4) Practical recommendations for chronic kidney disease*

- Avoid oral sodium phosphate in CKD because of the risk of acute phosphate nephropathy [6].
- Prefer PEG-based regimens and emphasize split-dose timing and completion [1-3].
- Use caution with magnesium-containing agents, particularly in advanced CKD [1-3,5,10].
- In advanced CKD or frailty/limited intake, plan hydration and consider selective laboratory monitoring when clinically indicated [5,10].

**3. Older adults**

*1) Clinical context*

Older adults are a heterogeneous group in whom preparation failure often reflects both physiologic and practical factors. Reduced mobility, slower transit, comorbidity burden, and polypharmacy increase the likelihood of inadequate cleansing and incomplete intake [15]. Safety is central because limited physiologic reserve increases vulnerability to dehydration and electrolyte disturbances [5,10,15].

*2) Efficacy and tolerability considerations*

Reviews focusing on elderly patients emphasize that regimen success is strongly influenced by timing, completion, and patient support, and that low-volume strategies may be appropriate for selected patients to improve completion [5,15]. A recent study comparing in-hospital versus at-home administration in elderly outpatients supports a tailored approach when adherence barriers are prominent [16]. Real-world data on low-volume PEG strategies also suggest that acceptable preparation quality can be achieved in outpatient practice, although patient selection and adherence remain important [9].

*3) Safety considerations: frailty, hydration, and medication review*

In older adults, adverse events often reflect a mismatch between regimen demands and patient capacity. Frailty, baseline low intake, and diuretic use increase dehydration risk; cognitive impairment may reduce adherence and increase fall risk during frequent toileting [15]. When safety concerns are prominent, it is reasonable to prioritize regimens with predictable safety profiles (often PEG-based)

and to involve caregivers to support timing and completion [1-3,5,15]. In selected patients with substantial adherence or safety concerns, supervised preparation may be more appropriate than unsupervised home preparation [15,16].

*4) Practical recommendations for older adults*

- Use split-dose timing as the default and prioritize completion and timing [1-3].
- Consider low-volume options in selected older adults to improve completion, while individualizing for frailty and comorbidity [5,9,15].
- Perform medication review and provide a hydration plan; engage caregivers when appropriate [5,15].
- Consider supervised pathways when adherence barriers or safety concerns are substantial [15,16].

**4. Chronic constipation (and "hard-to-prepare" outpatients)**

*1) Clinical context*

Constipation is frequently discussed as a practical marker of "hard-to-prepare" patients and is commonly listed among factors associated with inadequate cleansing [4,17]. In practice, constipation may be under-recognized unless specifically assessed, and patients may present with prior inadequate preparation or prolonged stool retention [17].

*2) Practical approach and intensified strategies*

Guidelines and reviews recommend intensified strategies for patients with constipation or prior inadequate preparation, including split-dose timing, PEG-based regimens, earlier dietary modification, and reinforced instruction [1-5,17]. A practical approach begins with proactive identification (bowel frequency, baseline laxative use, history of prior poor preparation) and early planning for adherence and completion [17].

As part of intensified pathways, adjunctive agents are sometimes used in selected high-risk patients. Bisacodyl is not routinely recommended for average-risk patients in major society guidelines, but it is commonly incorporated into intensified regimens for severe constipation or prior inadequate preparation. Clinicians should counsel patients about cramping and monitor for dehydration from diarrhea in vulnerable patients, and avoid use when bowel obstruction is suspected.

Constipation is also a common indication for colonoscopy referral. Available data suggest that constipation alone may not be associated with higher rates of significant findings, and concomitant alarm features or additional indications remain important in clinical decision-making; however, this review focuses on preparation strategy rather than indication assessment [18,19].

Practical tools for constipation assessment and management in Asia may help standardize evaluation and communication in primary care and referral pathways [20].

*3) Practical recommendations for constipation*

- Screen proactively for constipation and ask about prior inadequate preparation [4,17].
- Use a high-risk pathway when severe constipation or prior failure is present: earlier dietary modification, split-dose timing, PEG-based core regimen, and reinforced instructions [1-5,17].
- Keep indication assessment in context; constipation alone should be interpreted with accompanying symptoms and risk factors (briefly noted) [18,19].
- Use structured assessment tools where helpful [20].

**5. Hospitalized patients**

*1) Clinical context*

Inpatients represent a distinct high-risk group. Preparation failure is commonly driven by acute illness, reduced mobility, opioid exposure, nausea, competing diagnostic tests, and limited autonomy [4,5]. Inadequate preparation may lead to delays and repeat procedures, with implications for resource utilization [5].

*2) Evidence for system-focused interventions*

A randomized controlled trial in hospitalized patients aged ≥50 years supports protocolized regimens incorporating dietary measures and adjunct strategies to maintain cleansing effectiveness and improve comfort, reinforcing the value of structured pathways in ward practice [8]. Clinical updates similarly emphasize protocolization, monitoring of intake/output, and coordination with scheduling to preserve effective timing [5].

*3) Practical approach: protocolized pathway*

A practical inpatient pathway should address both regimen prescription and system barriers. Core elements include:

- Standardized order set: specifying agent, split-dose tim-

ing, diet, and symptom control [5,8].
- Nursing checklist: for dose administration and documentation of completion [5,8].
- Monitoring of intake/output and stool/effluent quality: with escalation criteria when preparation is clearly incomplete [5,8].
- Symptom control plan (e.g., nausea management; coordination of analgesics when feasible): because nausea and pain commonly limit completion [5].
- Scheduling coordination: to preserve effective timing and reduce repeated delays [5].

When preparation is clearly inadequate, early recognition allows rescue strategies or rescheduling decisions before proceeding with a low-yield examination [1-3,5].

*4) Practical recommendations for hospitalized patients*
- Recognize inpatient status as a hard-to-prepare setting and plan accordingly [4,5].
- Prioritize protocolized pathways rather than ad hoc regimen changes [5,8].
- Address barriers to completion with symptom control and monitoring of intake/output and stool quality [5,8].
- Use early assessment to guide rescue strategies or rescheduling when preparation is inadequate [1-3,5].

## Rescue strategies and safety monitoring

Even with careful planning, inadequate preparation is encountered in routine practice. A practical approach begins with early recognition, ideally before sedation. Guidelines emphasize that bedside assessment of completion and effluent quality, together with patient history, can help identify a high likelihood of inadequate cleansing and justify additional measures before proceeding [1-3]. Such preprocedure salvage is particularly relevant in high-risk settings where incomplete intake is common [4,5].

When inadequacy is recognized during colonoscopy, salvage options may be considered, including intensified washing/suctioning and adjunctive measures; recommendations are generally framed as context-dependent rather than as a single preferred approach [1-3,5]. In special populations, safety considerations should remain central. In CKD or in patients vulnerable to electrolyte disturbances, strategies that increase phosphate or magnesium exposure should be avoided when possible, and PEG-based approaches are generally preferred when feasible [1-3,5,6]. In selected older adults or medically vulnerable patients, symptoms suggestive of dysnatremia during preparation should prompt clinical reassessment and consideration of serum electrolyte measurement [7].

If preparation remains inadequate to support standard screening or surveillance intervals, early repeat colonoscopy is recommended. European Society of Gastrointestinal Endoscopy recommends repeating colonoscopy within 1 year after inadequate preparation, unless clinically contraindicated [2]. The US Multi-Society Task Force similarly recommends completing a repeat colonoscopy within 12 months after an inadequate examination for screening or surveillance, with earlier repetition in selected higher-risk indications [1]. Documentation of preparation quality and explicit follow-up plans are therefore important components of quality and patient safety [1,2,5].

## Conclusions

Bowel preparation remains a key determinant of colonoscopy performance, and inadequate cleansing continues to occur disproportionately in special populations. Across patient groups, the most consistently supported strategies include split-dose timing, completion of the final dose close to the procedure, and structured patient instruction with reinforcement [1-3]. Standardized documentation of preparation quality supports quality improvement and appropriate follow-up after an inadequate examination [1-3].

In special populations, regimen selection should balance cleansing efficacy with patient-specific safety risks. In IBD, clinicians should prioritize reliable mucosal visualization and interpretability and consider preparation-related mucosal abnormalities associated with sodium phosphate when subtle findings matter, with PEG-based regimens serving as a conservative first-line option in most cases [1-3,11-14]. In CKD, avoidance of oral sodium phosphate and careful consideration of electrolyte risks are important, and PEG-based regimens are usually favored when safety is a priority [1-3,5]. However, PEG-based solutions are not entirely risk-free; severe hyponatremia with seizure has been reported after PEG-electrolyte bowel preparation in an older patient, highlighting the need for medication review and individualized hydration guidance in selected high-risk settings [7]. In older adults, planning should incorporate

frailty, comorbidity, polypharmacy, mobility, hydration status, and dysnatremia risk; low-volume strategies may be suitable for selected patients but should not supersede safety and completion [5,7,9,15,16]. Chronic constipation is a common marker of hard-to-prepare patients and often warrants intensified strategies with reinforced instruction and timing optimization [1-5,17]. For hospitalized patients, system-level barriers frequently predominate, and protocolized pathways and multidisciplinary coordination are important levers for improving adequacy and comfort [5,8].

Given the heterogeneity of evidence in high-risk groups and real-world constraints, we suggest a practical, risk-stratified approach to regimen selection, timing, education, and safety monitoring, with structured recognition and management of inadequate preparation and timely repeat colonoscopy when needed [1,2,5].

## Article information

### Conflicts of interest

Won Moon is the Editor-in-Chief and Sung Eun Kim is an editorial board member of the journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

### Funding

None.

### Author contributions

Conceptualization: MHL, WM. Data curation: MHL, WM. Investigation: MHL, WM. Methodology: WM. Project administration: WM. Resources: MHL. Supervision: WM. Validation: KJ, JHK, SEK, MIP, SJP. Visualization: MHL. Writing-original draft: MHL, WM. Writing-review & editing: all authors. All authors read and approved the final manuscript.

### ORCID

Myung-Hun Lee, https://orcid.org/0009-0002-2545-2057
Won Moon, https://orcid.org/0000-0002-3963-8680
Kyoungwon Jung, https://orcid.org/0000-0002-5324-7803
Jae Hyun Kim, https://orcid.org/0000-0002-4272-8003
Sung Eun Kim, https://orcid.org/0000-0002-1835-4830
Moo In Park, https://orcid.org/0000-0003-2071-6957
Seun Ja Park, https://orcid.org/0000-0003-3217-5115

## References

1. Jacobson BC, Anderson JC, Burke CA, Dominitz JA, Gross SA, May FP, et al. Optimizing bowel preparation quality for colonoscopy: consensus recommendations by the US multi-society task force on colorectal cancer. Am J Gastroenterol 2025;120:738–64.
2. Hassan C, East J, Radaelli F, Spada C, Benamouzig R, Bisschops R, et al. Bowel preparation for colonoscopy: European Society of Gastrointestinal Endoscopy (ESGE) guideline. Update 2019. Endoscopy 2019;51:775–94.
3. Saltzman JR, Cash BD, Pasha SF, Early DS, Muthusamy VR, Khashab MA, et al. Bowel preparation before colonoscopy. Gastrointest Endosc 2015;81:781–94.
4. Shahini E, Sinagra E, Vitello A, Ranaldo R, Contaldo A, Facciorusso A, et al. Factors affecting the quality of bowel preparation for colonoscopy in hard-to-prepare patients: evidence from the literature. World J Gastroenterol 2023;29:1685–707.
5. Maida M, Grieme AD, Wu Y, Vitello A, Bonomo F, Maida CD, et al. Clinical updates in bowel preparation for colonoscopy. Best Pract Res Clin Gastroenterol 2026;80:102046.
6. Markowitz GS, Stokes MB, Radhakrishnan J, D'Agati VD. Acute phosphate nephropathy following oral sodium phosphate bowel purgative: an underrecognized cause of chronic renal failure. J Am Soc Nephrol 2005;16:3389–96.
7. Lee MH, Lee BH, Oh SK, Seo JY, Kim HJ, Seo BJ. Acute severe hyponatremia with seizure following polyethylene glycol-based bowel preparation for colonoscopy. Kosin Med J 2012;27:173–6.
8. He Y, Liu Q, Chen YW, Cui LJ, Cao K, Guo ZH. Bowel preparation protocol for hospitalized patients ages 50 years or older: a randomized controlled trial. World J Gastrointest Endosc 2024;16:18–28.
9. Scalvini D, Lenti MV, Maimaris S, Lusetti F, Alimenti E, Fazzino E, et al. Superior bowel preparation quality for colonoscopy with 1L-PEG compared to 2L-PEG and picosulphate: data from a large real-world retrospective outpatient cohort. Dig Liver Dis 2024;56:1906–13.
10. Moon W. Optimal and safe bowel preparation for colonoscopy. Clin Endosc 2013;46:219–23.
11. Lightner AL. Bowel preparation in inflammatory bowel disease: a necessary evil? Crohns Colitis 360 2020;2:otaa078.
12. Gravina AG, Pellegrino R, Romeo M, Palladino G, Cipullo M, Iadanza G, et al. Quality of bowel preparation in patients with inflammatory bowel disease undergoing colonoscopy: what fac-

tors to consider? World J Gastrointest Endosc 2023;15:133–45.
13. Zwas FR, Cirillo NW, el-Serag HB, Eisen RN. Colonic mucosal abnormalities associated with oral sodium phosphate solution. Gastrointest Endosc 1996;43:463–6.
14. Negreanu L, Voiosu T, State M, Mateescu RB. Quality of colonoscopy preparation in patients with inflammatory bowel disease: retrospective analysis of 348 colonoscopies. J Int Med Res 2020;48:300060520903654.
15. Ho SB, Hovsepians R, Gupta S. Optimal bowel cleansing for colonoscopy in the elderly patient. Drugs Aging 2017;34:163–72.
16. Yamaguchi D, Gondo K, Nomura T, Mizuta Y, Fukami S, Ishida S, et al. Comparison of in-hospital and at-home administration of bowel preparation agents before outpatient colonoscopy in elderly patients. JGH Open 2025;9:e70303.
17. Popovic DD, Filipovic B. Constipation and colonoscopy. World J Gastrointest Endosc 2024;16:244–9.
18. Abu Baker F, Mari A, Taher R, Nicola D, Gal O, Zeina AR. The yield of colonoscopy in the evaluation of constipation: an age-based analysis of outcome. J Clin Med 2024;13:2910.
19. Gupta M, Holub J, Knigge K, Eisen G. Constipation is not associated with an increased rate of findings on colonoscopy: results from a national endoscopy consortium. Endoscopy 2010;42:208–12.
20. Gwee KA, Ghoshal UC, Gonlachanvit S, Chua AS, Myung SJ, Rajindrajith S, et al. Primary care management of chronic constipation in Asia: the ANMA chronic constipation tool. J Neurogastroenterol Motil 2013;19:149–60.

**Review article**

Kosin Medical Journal 2026;41(1):19-25
pISSN: 2005-9531 • eISSN: 2586-7024
https://doi.org/10.7180/kmj.26.157

KMJ
KOSIN MEDICAL JOURNAL

# Chemoimmunotherapy and targeted therapy in biliary tract cancer: current evidence and future directions

**Jae Jun Heo, Jung Wook Lee**

*Department of Internal Medicine, Kosin University Gospel Hospital, Kosin University College of Medicine, Busan, Korea*

Biliary tract cancer (BTC) is an uncommon, heterogeneous malignancy with increasing incidence and mortality. Most patients present with advanced disease, which limits curative treatment options and contributes to a poor prognosis. Recent advances in molecular profiling and immuno-oncology have substantially reshaped the therapeutic landscape of BTC by providing deeper insight into its molecular and immunological features. In particular, the incorporation of immune checkpoint inhibitors, such as durvalumab and pembrolizumab, into first-line gemcitabine-cisplatin therapy has demonstrated clinically meaningful survival benefits. Phase III trials, including TOPAZ-1 and KEYNOTE-966, reported significant improvements in overall survival and progression-free survival compared with gemcitabine-cisplatin alone, establishing chemoimmunotherapy as a new standard of care for advanced BTC. The advent of targeted therapies has further expanded treatment options. Agents directed against fibroblast growth factor receptor 2 (*FGFR2*) fusions, isocitrate dehydrogenase 1 (*IDH1*) mutations, and human epidermal growth factor receptor 2 (HER2) overexpression have enabled precision-based approaches for patients harboring actionable molecular alterations. These developments highlight the critical role of comprehensive molecular profiling in guiding individualized treatment strategies. Despite these advances, important challenges remain, largely because of the relative rarity of BTC and the inherent limitations of small, heterogeneous study populations. Future research should prioritize large-scale, multicenter, prospective trials to optimize therapeutic sequencing and combination strategies. Furthermore, the routine integration of next-generation sequencing into clinical practice is essential to fully realize the potential of molecularly tailored therapies. This review summarizes the latest evidence on immunotherapy and targeted therapy for BTC and discusses their clinical implications for improving patient outcomes.

**Keywords:** Biliary tract neoplasms; Immune checkpoint inhibitors; Immunotherapy; Molecular targeted therapy

## Introduction

The incidence of and mortality rates for biliary tract cancer (BTC) have steadily increased over the past two decades [1,2]. BTC encompasses intrahepatic cholangiocarcinoma, perihilar cholangiocarcinoma, distal extrahepatic cholangiocarcinoma, and gallbladder cancer, each of which is characterized by distinct anatomical and molecular features relative to other malignancies. Most patients present with unresectable advanced-stage disease at the time of diagnosis, resulting in limited therapeutic options and a poor overall prognosis [1-3]. However, recent advances in genomic analysis and related translational research have progressively elucidated the molecular mechanisms underlying BTC. Concurrent developments in immunological and molecular approaches have led to meaningful changes in diagnostic and therapeutic strategies [1]. In particular, growing insights into the immunological characteristics of

**Received:** February 18, 2026; **Revised:** March 12, 2026; **Accepted:** March 13, 2026
**Corresponding Author:** Jung Wook Lee, MD, PhD
Department of Internal Medicine, Kosin University Gospel Hospital, Kosin University College of Medicine, 262 Gamcheon-ro, Seo-gu, Busan 49267, Korea
Tel: +82-51-990-6711 Fax: +82-51-990-3005 E-mail: teaterry@hanmail.net

© 2026 Kosin University College of Medicine
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

BTC have redefined this disease as a tumor entity with a unique tumor microenvironment, underscoring the importance of understanding this microenvironment for the development and clinical application of immunotherapeutic agents [2].

In addition, emerging evidence regarding the heterogeneity and functional roles of cancer-associated fibroblasts, along with advances in circulating tumor DNA analysis, has expanded the potential applications of these approaches to early diagnosis and assessment of treatment response [2]. From a therapeutic perspective, agents targeting isocitrate dehydrogenase 1 (*IDH1*) mutations and fibroblast growth factor receptor 2 (*FGFR2*) fusions are used in clinical practice, and their indications continue to broaden. Furthermore, the combination of durvalumab or pembrolizumab with gemcitabine and cisplatin has demonstrated improved survival, thereby shifting the paradigm in first-line treatment for advanced BTC.

In this review, we summarize the most recent evidence regarding immunotherapy and targeted therapy for BTC to provide practical guidance for the development of treatment strategies in real-world practice.

## Main subjects

In the clinical management of BTC, the role of systemic therapy is expanding beyond advanced-stage disease into the perioperative setting. For patients with resectable BTC, adjuvant capecitabine currently remains the standard of care based on the BILCAP trial, which demonstrated a significant survival benefit compared to observation. Although chemoimmunotherapy and targeted agents have not yet been established as standard adjuvant or neoadjuvant treatments, their clinical success in advanced settings has catalyzed investigations into their efficacy in earlier stages. Notably, induction therapy using these novel agents is being actively explored to improve resectability and long-term outcomes, potentially shifting the treatment paradigm across all stages of the disease.

### 1. Advances in targeted therapy for biliary tract cancer

Despite the recent increase in its incidence, BTC remains a malignancy with a poor prognosis and a 5-year survival rate of approximately 20%, largely due to challenges in early diagnosis and limited therapeutic options [2]. Over the past decade, the standard first-line treatment for unresectable advanced BTC has been a combination of gemcitabine and cisplatin; however, the reported median overall survival (OS) with this regimen remains less than 12 months, underscoring the ongoing need for improved therapeutic outcomes [4].

Molecular profiling studies using next-generation sequencing (NGS) have demonstrated that various anatomical subtypes of BTC possess distinct molecular characteristics that extend beyond mere differences in anatomical location [1].

Among intrahepatic cholangiocarcinomas, the mass-forming small duct-type subtype is characterized by a relatively high frequency of *IDH1/2* mutations (10%–30%) and *FGFR2* fusions (10%–20%). In contrast, the large duct subtype, which exhibits infiltrative growth along the bile ducts, is characterized by Kirsten rat sarcoma virus oncogene homolog (*KRAS*; 15%–30%) and tumor protein p53 (TP53) mutations (10%–40%) [2].

In perihilar cholangiocarcinoma, distal cholangiocarcinoma, and gallbladder cancer, *KRAS* mutations are observed at a high frequency (30%–50%), and erb-b2 receptor tyrosine kinase 2 (ERBB2) amplification (15%–20%) is also relatively more common than in intrahepatic cholangiocarcinoma. In contrast, *IDH1/2* mutations and *FGFR2* fusions are exceedingly rare in these subtypes, occurring in less than 1% of the cases [2,5].

This molecular heterogeneity not only underscores the importance of NGS-based genomic profiling at diagnosis but also supports the need for subtype-specific, precision-based therapeutic strategies. Indeed, according to a multicenter retrospective study conducted in Austria and published in 2023, among 159 patients with BTC harboring targetable molecular alterations, those who received targeted therapy after first-line treatment (n=36) demonstrated a significantly longer OS of 22.3 months compared with 17.5 months in those treated with cytotoxic chemotherapy (n=43) [3].

Although the currently available targeted therapeutic options for BTC remain limited, these findings indicate that targeted therapy is no longer merely a future possibility but has already emerged as an important treatment strategy in real-world clinical practice.

**2. *IDH* mutation**

*IDH* mutations convert α-ketoglutarate to 2-hydroxyglutarate (2-HG), leading to its intracellular accumulation. Elevated 2-HG functions as an oncometabolite that contributes to tumorigenesis. Based on this mechanism, *IDH* mutations are considered promising therapeutic targets for BTCs [6].

Ivosidenib, a mutant *IDH1* inhibitor, significantly improved progression-free survival (PFS) in the phase III ClarIDHy trial, which enrolled 185 patients with previously treated BTC. In that study, median PFS was significantly longer in the ivosidenib group than in the placebo group (2.7 months vs. 1.4 months). However, no statistically significant difference in OS was observed [7]. Regarding the safety profile, common adverse events included fatigue and gastrointestinal symptoms such as nausea; notably, the approximately 7% incidence of corrected QT prolongation necessitates regular monitoring of electrocardiograms and electrolytes. To date, no additional IDH mutation-targeted inhibitors have been approved for use in the United States beyond ivosidenib.

**3. *FGFR2* fusions and rearrangements**

*FGFR2* fusions and rearrangements were first reported in BTC in 2013 and are currently considered among the most clinically actionable and targetable alterations.

Pemigatinib, a competitive inhibitor of *FGFR1, FGFR2,* and *FGFR3* was the first *FGFR* inhibitor to receive regulatory approval for this indication. In the single-arm, phase II FIGHT-202 study of patients who had received at least one prior line of systemic therapy, 107 patients with *FGFR2* fusions or rearrangements achieved an objective response rate of 35.5% and a disease control rate of 82%, with a median OS of 21.1 months [8]. In contrast, no meaningful therapeutic response was observed in patients harboring other *FGF/FGFR* alterations. Consequently, pemigatinib is currently approved only for patients with confirmed *FGFR2* fusions or rearrangement.

The most common adverse event associated with pemigatinib treatment is hyperphosphatemia (approximately 60% of cases), which typically occurs during the early treatment phase. Other reported adverse events include arthralgia, stomatitis, nail disorders, hyponatremia, abdominal pain, fatigue, pyrexia, cholangitis, and pleural effusion [9].

Futibatinib, another *FGFR* inhibitor, has also been approved for the treatment of BTC based on data from a single-arm phase II study of patients with *FGFR2* rearrangements, demonstrating an objective response rate of 42% and a median OS of 21.7 months [10]. Currently, both pemigatinib and futibatinib are approved for use as second-line or later therapies. However, phase III trials comparing these agents with conventional first-line standard regimens of gemcitabine and cisplatin are ongoing. The trials in question are NCT03656536 for pemigatinib and NCT04093362 for futibatinib.

Preclinical studies exploring mechanisms of resistance to *FGFR2*-targeted therapy may open new therapeutic avenues for the management of BTC.

**4. Human epidermal growth factor receptor 2 overexpression or gene amplification**

As noted above, *IDH1/2* mutations and *FGFR2* fusions have been predominantly identified in intrahepatic cholangiocarcinoma and are exceedingly rare in extrahepatic cholangiocarcinoma. In contrast, human epidermal growth factor receptor 2 (HER2; ERBB2) overexpression or amplification is common in extrahepatic cholangiocarcinoma and gallbladder cancer.

Clinical trials targeting HER2 have primarily enrolled patients who experienced disease progression after gemcitabine plus cisplatin therapy. In the phase IIa MyPathway basket study, the combination of trastuzumab and pertuzumab resulted in an objective response rate of 23% among 39 patients, with a median OS of 11 months [11].

A multicenter phase II study conducted in Korea evaluated trastuzumab in combination with 5-fluorouracil-leucovorin-oxaliplatin (FOLFOX) in 34 patients. The reported outcomes included an objective response rate of 29.4%, median PFS of 5.1 months, and median OS of 10.7 months [12].

Additionally, the phase II HERIZON-BTC-01 study evaluated zanidatamab, a bispecific antibody targeting two distinct HER2 epitopes. Among the 80 treated patients, the objective response rate was 41.3%. The median PFS and OS were 5.5 months and 9 months, respectively, demonstrating encouraging efficacy [13].

Major adverse events associated with HER2-targeted therapy include elevated liver function test results, diarrhea, infusion-related hypersensitivity reactions, and cardiotoxicity. Although the incidence of cardiotoxicity was

relatively low (less than 3%), it may have significant clinical consequences. Therefore, baseline assessment of cardiac function before treatment initiation and regular cardiac monitoring during therapy are essential.

**5. Other targetable genes**

Therapies targeting relatively rare, actionable genetic alterations in BTCs are largely tumor-agnostic agents developed independently of a specific cancer type. These agents have received regulatory approval based on basket trials that enrolled patients with advanced solid tumors, and demonstrated meaningful clinical efficacy in a subset of patients with BTC.

B-type rapidly accelerated fibrosarcoma (*BRAF*) V600E mutations are observed primarily in intrahepatic cholangiocarcinoma and have been identified in approximately 5% of all BTCs. Combination therapy with the *BRAF* inhibitor dabrafenib and the mitogen-activated protein kinase kinase (MEK) inhibitor trametinib demonstrated a clinically meaningful benefit in the BTC cohort, with an objective response rate of 47% and a median PFS of 9 months [14]. The combination of dabrafenib and trametinib was generally manageable, with pyrexia, fatigue, nausea, and rash being the most frequently reported treatment-related adverse events.

Neurotrophic tyrosine receptor kinase (*NTRK*) fusions are exceedingly rare in BTCs, occurring in approximately 0.7% of cases. The TRK inhibitors larotrectinib and entrectinib received tumor-agnostic approval after demonstrating high response rates of 75% and 57%, respectively, in clinical trials involving patients with various solid tumors [15,16].

Rearranged during transfection (*RET*) fusions are extremely uncommon and have been identified in less than 0.2% of all BTCs. In a phase I/II study of the *RET* inhibitor pralsetinib, two of three patients with metastatic BTC achieved partial responses, and one patient had stable disease [17,18]. Another *RET* inhibitor, selpercatinib, was evaluated in a study that included a variety of solid tumors. Among the 45 participants enrolled, two had BTC, and an overall response rate of 44% was reported for the entire study population [19].

Taken together, tumor-agnostic targeted therapies may represent an important therapeutic option for patients with BTC harboring rare, actionable genomic alterations. However, further well-designed studies are warranted to establish the optimal treatment strategies for this molecularly defined population.

**6. Recent advances in immunotherapy for biliary tract cancer**

The tumor microenvironment of BTC is characterized by immunosuppressive features. Compared to normal tissues, cytotoxic T lymphocytes and natural killer cells are decreased, while regulatory T cells tend to increase [20]. Additionally, the expression of immune checkpoint molecules, such programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), is upregulated [20]. The presence of various immunosuppressive cell populations also contributes to marked intratumoral transcriptomic heterogeneity. These characteristics promote tumor growth, immune evasion, and resistance to anticancer therapies [21], which may explain the generally low response rates observed with immune checkpoint inhibitor [21,22].

To overcome these limitations, combination strategies that incorporate immune checkpoint inhibitors and cytotoxic chemotherapy have been actively investigated. In the pivotal phase III TOPAZ-1 trial, the addition of the PD-L1 inhibitor durvalumab to gemcitabine-cisplatin demonstrated superiority over gemcitabine-cisplatin alone. In the updated analysis, the median OS in the combination group was 12.9 months (95% confidence interval [CI], 11.6–14.1), compared with 11.3 months (95% CI, 10.1–12.5) in the control group [23]. The 24-month OS rates were 23.6% and 11.5% (95% CI, 18.7–28.9; 7.6–16.2) in the combination group and control group, respectively. PFS and objective response rates were also significantly improved. No significant difference in treatment-related toxicity was observed between the two groups [23]. These findings demonstrate that durvalumab combination therapy provides a clinically significant long-term survival benefit and is currently considered an important first-line standard of care for advanced BTC.

Pembrolizumab, a PD-1 inhibitor, also demonstrated efficacy in the first-line setting in the phase III KEYNOTE-966 trial. Although pembrolizumab is primarily used as salvage therapy in patients with mismatch repair deficiency or high microsatellite instability, the KEYNOTE-966 trial showed that its combination with pembrolizumab, gemcitabine, – and cisplatin resulted in superior survival outcomes

compared to chemotherapy alone [22,24]. The median OS was 12.7 months (95% CI, 11.5–13.6) in the combination group versus 10.9 months (95% CI, 9.9–11.6) in the control group, with a hazard ratio of 0.83 (95% CI, 0.72–0.95). Treatment-related toxicity did not differ significantly between the two groups [22,24].

Beyond combinations with cytotoxic chemotherapy, immune checkpoint inhibitors have also been explored in combination with targeted agents. In patients with BTC who had progressed on prior therapy, the combination of the tyrosine kinase inhibitor lenvatinib and pembrolizumab demonstrated response rates of 10%–25% and median OS ranging from 8.6 to 11 months [25]. This regimen may represent a potential therapeutic option in the context of limited alternatives following failure of first-line treatment.

However, because BTC is a relatively uncommon malignancy, many clinical studies have been limited to small cohorts or single-center studies. Therefore, large-scale, multicenter prospective studies are essential to establish immunotherapy as a more definitive standard of care for this disease. Furthermore, ongoing efforts are required to expand the current indications and develop treatment strategies applicable to a broader patient population.

## Conclusions

Since the introduction of gemcitabine plus cisplatin in 2010, progress in the treatment of BTC remained limited for an extended period. However, recent advances in novel therapeutic strategies, particularly those involving immunotherapy and targeted agents, have marked a significant turning point in disease management (Fig. 1) Combination regimens that integrate immune checkpoint inhibitors and cytotoxic chemotherapy have helped overcome the limita-

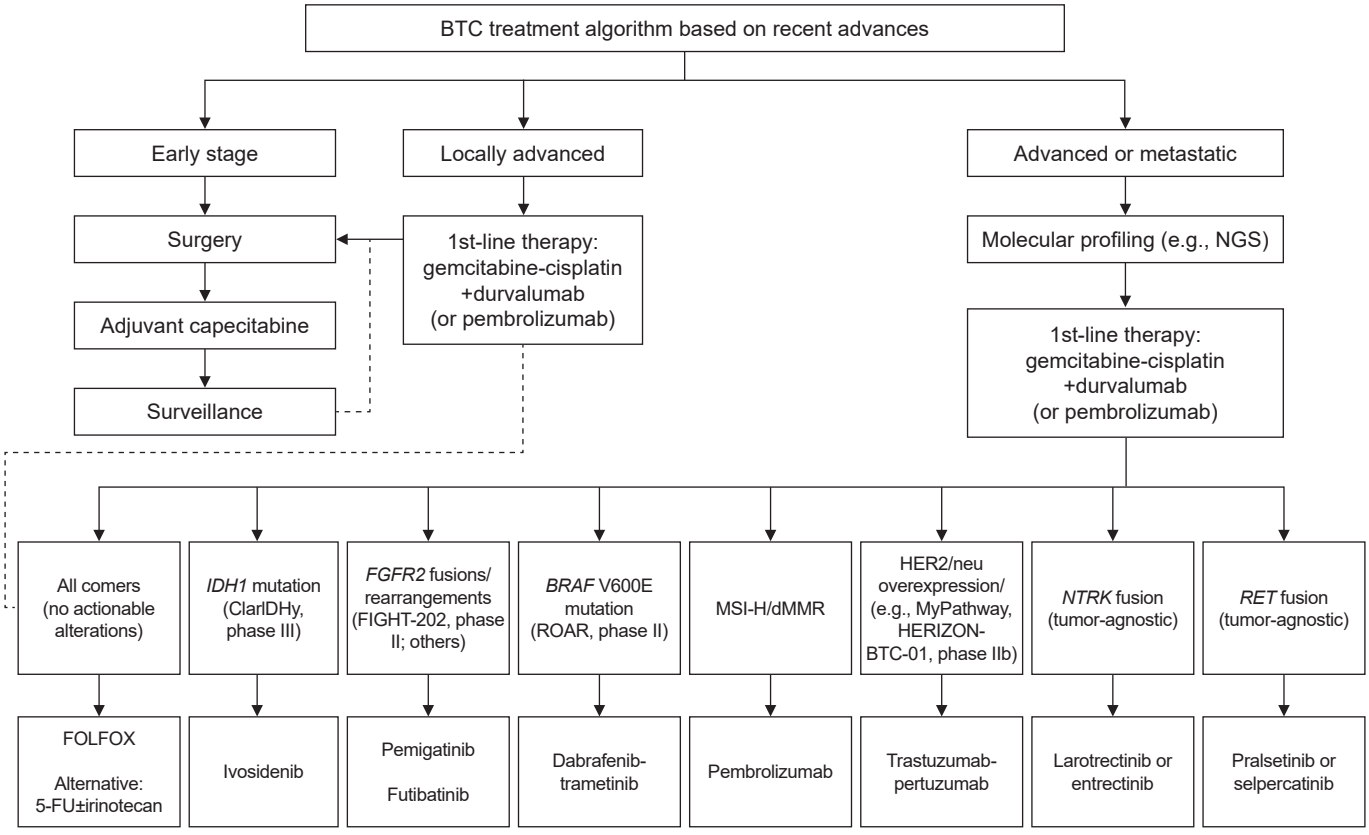


**Fig. 1.** Treatment algorithm for biliary tract cancer (BTC). NGS, next-generation sequencing; *IDH1*, isocitrate dehydrogenase 1; *FGFR2*, fibroblast growth factor receptor 2; *BRAF*, b-type rapidly accelerated fibrosarcoma; MSI-H, microsatellite instability-high; dMMR, mismatch repair deficiency; HER2, human epidermal growth factor receptor 2; *NTRK*, neurotrophic tyrosine receptor kinase; *RET*, rearranged during transfection; FOLFOX, 5-fluorouracil-leucovorin-oxaliplatin; 5-FU, 5-fluorouracil.

tions of conventional first-line therapies, leading to meaningful improvements in survival outcomes. Furthermore, precision-based treatments targeting specific molecular alterations, such as *FGFR2* fusions, *IDH* mutations, and HER2 overexpression, have demonstrated clinically meaningful survival benefits in patients who have progressed after first-line therapy.

In the future, the application of targeted therapies is expected to expand into first-line settings. If optimal combination strategies that integrate cytotoxic chemotherapy, immunotherapy, and targeted agents can be established, further improvements in therapeutic efficacy may be achieved, with the potential to also minimize treatment-related toxicities.

## Article information

**Conflicts of interest**
No potential conflict of interest relevant to this article was reported.

**Funding**
None.

**Author contributions**
Conceptualization: JJH, JWL. Supervision: JWL. Visualization: JJH. Writing-original draft: JJH. Writing-review & editing: JJH, JWL. All authors have read and approved the final manuscript.

**ORCID**
Heo Jae Jun, https://orcid.org/0009-0006-3445-1231
Jung Wook Lee, https://orcid.org/0000-0003-4166-0315

## References

1. Ilyas SI, Affo S, Goyal L, Lamarca A, Sapisochin G, Yang JD, et al. Cholangiocarcinoma: novel biological insights and therapeutic strategies. Nat Rev Clin Oncol 2023;20:470–86.
2. Lee SH, Song SY. Recent advancement in diagnosis of biliary tract cancer through pathological and molecular classifications. Cancers (Basel) 2024;16:1761.
3. Doleschal B, Taghizadeh H, Webersinke G, Piringer G, Schreil G, Decker J, et al. Real world evidence reveals improved survival outcomes in biliary tract cancer through molecular matched targeted treatment. Sci Rep 2023;13:15421.
4. Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 2010;362:1273–81.
5. Normanno N, Martinelli E, Melisi D, Pinto C, Rimassa L, Santini D, et al. Role of molecular genetics in the clinical management of cholangiocarcinoma. ESMO Open 2022;7:100505.
6. Lu C, Thompson CB. Metabolic regulation of epigenetics. Cell Metab 2012;16:9–17.
7. Abou-Alfa GK, Macarulla T, Javle MM, Kelley RK, Lubner SJ, Adeva J, et al. Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol 2020;21:796–807.
8. Abou-Alfa GK, Sahai V, Hollebecque A, Vaccaro G, Melisi D, Al-Rajabi R, et al. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. Lancet Oncol 2020;21:671–84.
9. Cho SM, Esmail A, Raza A, Dacha S, Abdelrahim M. Timeline of FDA-approved targeted therapy for cholangiocarcinoma. Cancers (Basel) 2022;14:2641.
10. Goyal L, Meric-Bernstam F, Hollebecque A, Valle JW, Morizane C, Karasic TB, et al. Futibatinib for FGFR2-rearranged intrahepatic cholangiocarcinoma. N Engl J Med 2023;388:228–39.
11. Meric-Bernstam F, Hurwitz H, Raghav KP, McWilliams RR, Fakih M, VanderWalde A, et al. Pertuzumab plus trastuzumab for HER2-amplified metastatic colorectal cancer (MyPathway): an updated report from a multicentre, open-label, phase 2a, multiple basket study. Lancet Oncol 2019;20:518–30.
12. Lee CK, Chon HJ, Cheon J, Lee MA, Im HS, Jang JS, et al. Trastuzumab plus FOLFOX for HER2-positive biliary tract cancer refractory to gemcitabine and cisplatin: a multi-institutional phase 2 trial of the Korean Cancer Study Group (KCSG-HB19-14). Lancet Gastroenterol Hepatol 2023;8:56–65.
13. Harding JJ, Fan J, Oh DY, Choi HJ, Kim JW, Chang HM, et al. Zanidatamab for HER2-amplified, unresectable, locally advanced or metastatic biliary tract cancer (HERIZON-BTC-01): a multicentre, single-arm, phase 2b study. Lancet Oncol 2023;24:772–82.
14. Subbiah V, Lassen U, Elez E, Italiano A, Curigliano G, Javle M, et al. Dabrafenib plus trametinib in patients with BRAFV600E-mutated biliary tract cancer (ROAR): a phase 2, open-label, single-arm, multicentre basket trial. Lancet Oncol 2020;21:1234–43.
15. Drilon A, Laetsch TW, Kummar S, DuBois SG, Lassen UN, Demetri GD, et al. Efficacy of larotrectinib in TRK fusion-positive

cancers in adults and children. N Engl J Med 2018;378:731–9.
16. Doebele RC, Drilon A, Paz-Ares L, Siena S, Shaw AT, Farago AF, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. Lancet Oncol 2020;21:271–82.
17. Parimi V, Tolba K, Danziger N, Kuang Z, Sun D, Lin DI, et al. Genomic landscape of 891 RET fusions detected across diverse solid tumor types. NPJ Precis Oncol 2023;7:10.
18. Subbiah V, Cassier PA, Siena S, Garralda E, Paz-Ares L, Garrido P, et al. Pan-cancer efficacy of pralsetinib in patients with RET fusion-positive solid tumors from the phase 1/2 ARROW trial. Nat Med 2022;28:1640–5.
19. Subbiah V, Wolf J, Konda B, Kang H, Spira A, Weiss J, et al. Tumour-agnostic efficacy and safety of selpercatinib in patients with RET fusion-positive solid tumours other than lung or thyroid tumours (LIBRETTO-001): a phase 1/2, open-label, basket trial. Lancet Oncol 2022;23:1261–73.
20. Zhou G, Sprengers D, Mancham S, Erkens R, Boor PP, van Beek AA, et al. Reduction of immunosuppressive tumor microenvironment in cholangiocarcinoma by ex vivo targeting immune checkpoint molecules. J Hepatol 2019;71:753–62.
21. Loeuillard E, Yang J, Buckarma E, Wang J, Liu Y, Conboy C, et al. Targeting tumor-associated macrophages and granulocytic myeloid-derived suppressor cells augments PD-1 blockade in cholangiocarcinoma. J Clin Invest 2020;130:5380–96.
22. Kelley RK, Ueno M, Yoo C, Finn RS, Furuse J, Ren Z, et al. Pembrolizumab in combination with gemcitabine and cisplatin compared with gemcitabine and cisplatin alone for patients with advanced biliary tract cancer (KEYNOTE-966): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2023;401:1853–65.
23. Oh DY, He AR, Bouattour M, Okusaka T, Qin S, Chen LT, et al. Durvalumab or placebo plus gemcitabine and cisplatin in participants with advanced biliary tract cancer (TOPAZ-1): updated overall survival from a randomised phase 3 study. Lancet Gastroenterol Hepatol 2024;9:694–704.
24. Maio M, Ascierto PA, Manzyuk L, Motola-Kuba D, Penel N, Cassier PA, et al. Pembrolizumab in microsatellite instability high or mismatch repair deficient cancers: updated analysis from the phase II KEYNOTE-158 study. Ann Oncol 2022;33:929–38.
25. Lin J, Yang X, Long J, Zhao S, Mao J, Wang D, et al. Pembrolizumab combined with lenvatinib as non-first-line therapy in patients with refractory biliary tract carcinoma. Hepatobiliary Surg Nutr 2020;9:414–24.

**Review article**

Kosin Medical Journal 2026;41(1):26-36
pISSN: 2005-9531 • eISSN: 2586-7024
https://doi.org/10.7180/kmj.26.159

KMJ
KOSIN MEDICAL JOURNAL

# Gout in the era of multimorbidity: pathogenesis, systemic comorbidities, and evolving therapeutic strategies

**Phillip J Kim[1,*], Jihun Kang[1,2,*], Jesang Yu[3], Geun-Tae Kim[4,**], Yunkyung Kim[4,**]**

[1]*Department of Family Medicine, Saint Agnes Medical Center, Fresno, CA, USA*
[2]*Department of Family Medicine, Kosin University Gospel Hospital, Kosin University College of Medicine, Busan, Korea*
[3]*Department of Radiation Oncology, Kosin University Gospel Hospital, Kosin University College of Medicine, Busan, Korea*
[4]*Division of Rheumatology, Department of Internal Medicine, Kosin University Gospel Hospital, Kosin University College of Medicine, Busan, Korea*

Gout is the most prevalent inflammatory arthritis worldwide and represents a growing global health burden. It arises from hyperuricemia resulting from disordered purine metabolism, leading to monosodium urate (MSU) crystal deposition and recurrent inflammatory arthritis. Although hyperuricemia is the principal risk factor, genetic susceptibility, impaired urate transport, and emerging factors such as the gut microbiota also contribute to disease development. Acute flares are mediated by MSU crystal-induced activation of the NLRP3 inflammasome and subsequent interleukin-1$\beta$ production, whereas chronic inflammation results in tophus formation and structural joint damage. Gout is closely associated with metabolic syndrome, chronic kidney disease, and cardiovascular disease, which contribute to persistently elevated mortality. Although advances in imaging and pharmacologic therapy have improved diagnosis and management, the real-world use of urate-lowering therapy remains suboptimal. Further research and sustained efforts by healthcare professionals are needed to improve long-term disease control.

**Keywords:** Drug therapy; Gout; Hyperuricemia; Metabolic diseases; Uric acid

## Introduction

Gout is the most common inflammatory arthritis, affecting approximately 55 million people worldwide [1]. It is caused by dysregulation of purine metabolism, which contributes to elevated uric acid concentrations, crystal formation, and subsequent phagocytosis by leukocytes, resulting in recurrent inflammation of the joints and periarticular tissues [2]. Gout has been shown to be associated with a substantially increased disease burden and mortality compared with the

**Received:** February 20, 2026; **Revised:** March 7, 2026; **Accepted:** March 10, 2026
**Corresponding Author:** Geun-Tae Kim, MD, PhD
Division of Rheumatology, Department of Internal Medicine, Kosin University Gospel Hospital, Kosin University College of Medicine, 262 Gamcheon-ro, Seo-gu, Busan 49267, Korea
Tel: +82-51-990-6154 Fax: +82-51-990-3005 Email: gtah@hanmail.net

**Corresponding Author:** Yunkyung Kim, MD, PhD
Division of Rheumatology, Department of Internal Medicine, Kosin University Gospel Hospital, Kosin University College of Medicine, 262 Gamcheon-ro, Seo-gu, Busan 49267, Korea
Tel: +82-51-990-6154 Fax: +82-51-990-3005 Email: efmsungmo@hanmail.net

*These authors contributed equally to this work as first authors.
**These authors contributed equally to this work as corresponding authors.

© 2026 Kosin University College of Medicine
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

general population [3]. These findings indicate that gout is not merely a joint disease but a chronic inflammatory metabolic disorder with significant socioeconomic impact.

The concept of multimorbidity, defined as the coexistence of two or more chronic conditions within an individual, has emerged as an important concept in chronic disease management [4]. Patients with gout frequently present with multiple comorbid conditions, including chronic kidney disease (CKD), diabetes mellitus and cardiovascular disease [5]. The high prevalence of comorbid conditions in patients with gout adds complexity to disease management and may adversely affect clinical outcomes. These comorbidities share common metabolic and inflammatory pathways with hyperuricemia and may mutually exacerbate disease progression [6]. Understanding the patterns and clinical implications of multimorbidity in gout may help improve risk stratification and guide more comprehensive management strategies.

## Epidemiology of gout

The global prevalence of gout ranges from 0.68% to 3.90% and has been steadily increasing [1]. Data from the Global Burden of Disease study indicate that gout prevalence has risen by approximately 22.5% over the past 30 years [7]. Data from the National Health and Nutrition Examination Survey (NHANES) 2007–2016 indicate that approximately 20% of US adults have hyperuricemia, and the prevalence of gout has risen to 5.1%, compared with 3.9% in earlier reports [8]. In Korea, three epidemiologic studies using Health Insurance Review and Assessment Service data reported a gout prevalence ranging from 0.4% to 2.0% [9]. The number of patients with gout has exceeded 500,000, and cumulative healthcare expenditures over 5 years have surpassed US $3.5 billion [10]. Notably, the number of younger patients with gout has increased markedly, likely due to the higher prevalence of hyperuricemia in younger populations [11].

## Risk factors for gout

### 1. Hyperuricemia

Hyperuricemia is the primary risk factor for gout, and the risk of gout increases in a dose-dependent manner with rising serum urate levels. Compared with individuals with baseline serum urate levels below 6 mg/dL, a pooled analysis of four cohort studies has shown that the risk of incident gout increased by approximately 15–30-fold in those with serum urate levels of 8.0–9.9 mg/dL, and by nearly 40-fold in those with levels exceeding 10 mg/dL [12]. Nevertheless, more than half of individuals with hyperuricemia never develop clinical gout, suggesting that additional factors beyond hyperuricemia, such as genetic predisposition, smoking, and physical activities, contribute to gout pathogenesis [13].

Hyperuricemia results from an imbalance between uric acid production and excretion, with reduced renal urate excretion being the most common mechanism. This condition is closely associated with the use of medications such as diuretics, aspirin, and cyclosporine, as well as comorbid conditions including CKD, obesity, and metabolic syndrome [14-16]. In contrast, increased uric acid production is associated with purine-rich dietary intake (e.g., red meat and alcohol) and conditions characterized by increased cell turnover, such as hematologic malignancies [17].

### 2. Genetic predispositions

Genetic variation represents one of the most important risk factors for the development of hyperuricemia and gout [17]. A meta-analysis demonstrated that dietary factors account for only approximately 1% of the variance in serum urate levels, whereas genetic factors explain up to 23.9% of the variation [17]. Genetic variants in urate transporter genes are strongly associated with interindividual differences in serum urate concentrations [18]. In addition to well-established urate transporter genes such as *SLC2A9* and *ABCG2*, a recent genome-wide association study including approximately 120,000 patients with gout identified 377 genetic loci, including *NLRP3* and *IL1R1*, which are implicated in the inflammatory pathogenesis of gout [19].

### 3. Gut microbiota

The gut microorganisms also play essential roles in the regulation of the immune system. Dysbiosis of the gut microbiota has been associated with various diseases and inflammation [20]. More recently, the gut microbiota has emerged as a novel contributing factor in gout pathogenesis. Several studies have reported that patients with gout exhibit reduced gut microbial diversity and a microbial composition distinct from that of healthy controls. These alterations,

along with microbial metabolites, may influence purine metabolism and uric acid homeostasis, leading to the onset of gout [21,22].

## Inflammatory pathways in the pathogenesis of gout

Approximately one-third of the body urate pool is derived from dietary sources, whereas two-thirds originate from endogenous production, primarily through nucleic acid degradation (Fig. 1) [23]. After ingestion of purine-containing foods, purines are metabolized in the liver, leading to increased serum urate levels. Approximately 90% of filtered urate is reabsorbed, with only 10% excreted; of total urate elimination, about two-thirds occurs via the kidneys and the remaining one-third through the intestine. Increased urate production or impaired urate excretion results in hyperuricemia, which can ultimately lead to the development of gout.

Acute gout flares result from monosodium urate (MSU) crystal-induced activation of innate immune responses [24]. MSU crystals interact with synovial macrophage receptors, such as Toll-like receptors, or are phagocytosed by monocytes and macrophages. These processes activate the NLRP3 inflammasome, leading to the maturation of interleukin-1$\beta$ (IL-1$\beta$), which subsequently promotes the production and release of proinflammatory cytokines, including tumor necrosis factor and interleukin-6 (IL-6). This inflammatory cascade is further amplified through the activation of neutrophils and mast cells, resulting in an acute gout flare [25,26].

With disease progression, tophi formation and structural

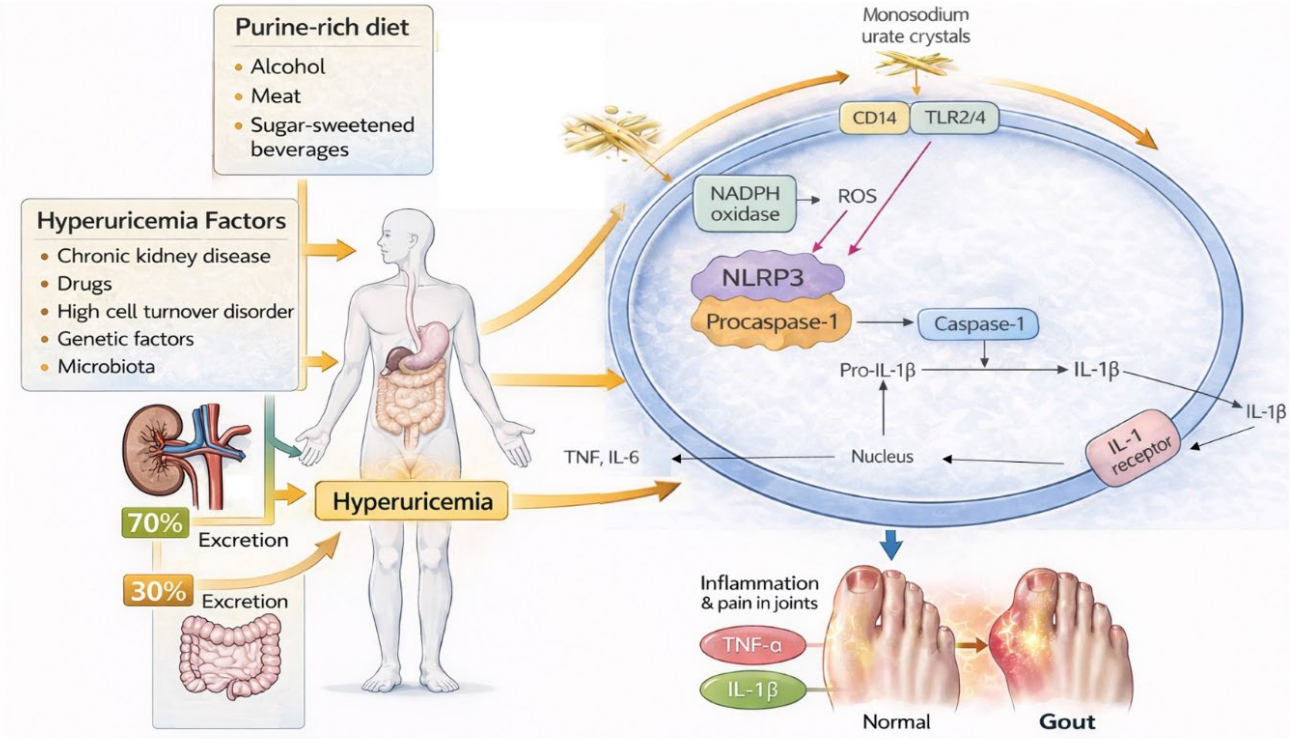


**Fig. 1.** Pathogenesis of gout. Purine-rich diets and other hyperuricemia-promoting factors increase serum urate levels. Approximately 70% of urate is excreted by the kidneys and 30% by the intestine, and impaired excretion leads to hyperuricemia. Monosodium urate crystals deposit in joints and activate the NLRP3 inflammasome, leading to caspase-1–mediated interleukin-1β (IL-1β) production and the release of proinflammatory cytokines (e.g., tumor necrosis factor-α [TNF-α], interleukin-6 [IL-6]). These processes result in the acute joint inflammation and pain characteristic of gout. CD14, cluster of differentiation 14; TLR2/4, Toll-like receptor 2/4; NADPH, nicotinamide adenine dinucleotide phosphate; ROS, reactive oxygen species; NLRP3, NOD-like receptor protein 3. Schematic illustration of monosodium urate crystal-induced NLRP3 inflammasome activation, created with reference to previous studies (Busso & So, 2010; Liu-Bryan, 2010).

joint damage may occur [27]. Tophi are commonly found in joints, bones, cartilage, tendons, and subcutaneous tissues. Although primarily composed of MSU crystals, tophi exhibit a structure resembling chronic granulomas, surrounded by inflammatory cells and connective tissue [24]. Tophi are closely associated with structural joint damage [28], as MSU crystals and activated macrophages promote inflammation and osteoclast activation, leading to increased bone resorption and subsequent bone erosion [29,30].

## Comorbidities and pharmacologic implications

Approximately half of patients with gout meet the World Health Organization criteria for metabolic syndrome [31]. An increased risk of type 2 diabetes mellitus has been observed among patients with gout. A US-based study indicated that 26% of patients with gout had diabetes, with the prevalence rising to 33% among those with higher serum urate levels [32]. In addition, 75% of patients with gout have hypertension [1], along with an elevated risk of cardiovascular diseases, including coronary artery disease, heart failure and peripheral vascular disease, is approximately twofold higher compared with the general population [33,34]. CKD is also closely associated with gout. A recent meta-analysis demonstrated that when serum urate levels were stratified into quartiles, individuals in the third and fourth quartiles had a 1.5–2-fold increased risk of incident CKD compared with individuals in the lowest quartile [35]. However, large randomized controlled trials, including the Febuxostat versus Allopurinol Streamlined Trial (FEATHER), Controlled Trial of Slowing of Kidney Disease Progression From the Inhibition of Xanthine Oxidase (CKD-FIX), Preventing Early Renal Loss in Diabetes (PERL) studies, showed that although urate-lowering therapy effectively reduced serum urate levels, evidence for improvement in renal function or reduction in mortality remains insufficient [36-38].

The development of these comorbidities has been linked to gout-related inflammation. Uric acid can directly stimulate the renin–angiotensin–aldosterone system [39], and impair endothelial function through oxidative stress and nitric oxide dysregulation [40]. In addition, urate crystal-induced inflammation has been associated with an increased risk of cardiovascular disease and diabetes [41,42]. Notably, studies using dual-energy computed tomography (DECT) have shown that a greater volume of MSU crystal deposition is associated with conditions such as chronic heart failure, type 2 diabetes, and hypertension [43].

In patients with gout and concomitant hypertension, the use of urate-lowering antihypertensive agents, particularly angiotensin receptor blockers, is preferred over diuretics. In those with coexisting dyslipidemia, treatment with statins may provide additional benefit [44].

In patients with a history of myocardial infarction, low-dose colchicine (0.5 mg daily) was associated with a reduced risk of ischemic cardiovascular events compared with placebo, leading to approval by the US Food and Drug Administration (FDA) for primary and secondary prevention of cardiovascular disease [45,46]. Although IL-1 inhibitors, such as canakinumab, have demonstrated efficacy in reducing cardiovascular events, their use for cardiovascular risk management remains limited [47]. The effects of allopurinol and febuxostat on the progression of cardiovascular disease, diabetes, and CKD remain controversial [48,49].

In a cohort study of patients with concomitant gout and type 2 diabetes, treatment with sodium–glucose cotransporter 2 inhibitors (SGLT2i) was associated with a 19% reduction in gout flares and a 29% lower mortality rate compared with nonusers [50]. These findings indicate that SGLT2i may represent a promising therapeutic option for patients with gout and diabetes by mitigating comorbidity risk while simultaneously reducing the overall burden of gout [51].

## Diagnosis criteria and modalities for gout

In general, gout is diagnosed when clinical symptoms become apparent [52]. The 2015 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) gout classification criteria specify a history of at least one episode of swelling, pain, or tenderness involving a peripheral joint or bursa as an entry requirement for gout classification [53]. The gold standard for definitive diagnosis is identification of needle-shaped MSU crystals under polarized light microscopy following arthrocentesis of the affected joint [54]. However, in routine clinical practice, the use of joint aspiration is limited by the availability of trained

**Table 1.** Pharmacological treatment of acute gout flares

| Drug | Representative agents | Dose | Key precautions | Adverse effects |
|---|---|---|---|---|
| Colchicine | Colchicine | 1.2 mg at onset, followed by 0.6 mg 1 hr later; then 0.6 mg once or twice daily if needed | Avoid or reduce the dose in severe renal impairment (CrCl <30 mL/min) or Child–Pugh class C; avoid strong CYP3A4 or P-gp inhibitors | Diarrhea, nausea, vomiting, abdominal pain; myopathy, bone marrow suppression |
| NSAIDs | Naproxen, ibuprofen, celecoxib | Full antiinflammatory dose for 3–5 days (e.g., naproxen 500 mg twice daily; celecoxib 200 mg twice daily) | Avoid in advanced CKD, peptic ulcer disease, heart failure, or concurrent anticoagulant/antiplatelet use | Gastrointestinal bleeding, acute kidney injury, hypertension, cardiovascular events |
| Systemic glucocorticoid | Prednisone, prednisolone | 0.5 mg/kg/day or 30–35 mg/day for 3–5 days | Caution in diabetes, infection, osteoporosis, heart failure | Hyperglycemia, fluid retention, hypertension, mood changes, infection |
| Intraarticular glucocorticoid | Triamcinolone, methylprednisolone | Single intraarticular injection (e.g., knee 20–40 mg triamcinolone) | Appropriate for mono- or oligoarticular gout; septic arthritis must be excluded prior to injection | Post-injection flare, local infection (rare) |
| IL-1 inhibitors | Anakinra, canakinumab | Anakinra 100 mg daily for 3 days; canakinumab 150 mg single subcutaneous dose | Reserved for refractory cases or contraindications to standard therapy; it is necessary to screen for infection, high cost | Injection site reactions, infection risk |

CrCl, creatinine clearance; CYP3A4, cytochrome P450 3A4; P-gp, P-glycoprotein; NSAIDs, nonsteroidal antiinflammatory drugs; CKD, chronic kidney disease; IL-1, interleukin-1.

personnel and appropriate equipment. Data from several European countries indicate that only 18%–32% of cases are definitively diagnosed as gout in rheumatology clinics, and the proportion is likely even lower in primary care settings [55,56].

Imaging modalities can aid in the diagnosis of gout. Plain radiographs are often normal at the time of initial diagnosis but may reveal soft tissue tophi and, in advanced disease, characteristic gouty bone erosions [57]. An enhanced understanding of crystal-induced arthritis has led to greater recognition of the diagnostic utility of musculoskeletal ultrasonography and DECT. On ultrasonography, MSU crystal deposition on the cartilage surface may produce the double contour sign, and hyperechoic aggregates within the joint space may appear as a snowstorm pattern [58]. DECT allows visualization of urate deposition, typically displayed as green-colored tophaceous deposits [59]. Both the double contour sign on ultrasonography and DECT have demonstrated high sensitivity and specificity (74%–90%), whereas the diagnostic accuracy of tophi detection alone is somewhat lower [60]. A key limitation is that urate crystal deposition may not be detectable in early disease, resulting in variability in diagnostic sensitivity depending on disease duration [61]. Therefore, continued efforts are needed to improve the early detection of crystal deposition in gout.

## Treatment framework and emerging therapies

Treatment of gout can be broadly divided into acute flare management and urate-lowering therapy (ULT). Antiinflammatory agents used for the treatment of acute gout flares include colchicine, nonsteroidal antiinflammatory drugs, and glucocorticoids. In patients with monoarticular involvement, such as the knee, who are unable to tolerate oral medications, intraarticular corticosteroid injection may be considered, provided that septic arthritis has been excluded. Clinicians should be familiar with the adverse effects and precautions associated with each therapeutic agent (Table 1) [62]. Canakinumab, an IL-1 antagonist, has been approved by the FDA for the treatment of gout flares; however, its clinical use remains limited due to its high cost [63,64].

During an acute gout flare, patients are advised to minimize joint movement and rest, and local ice application

may help alleviate symptoms. Pharmacologic treatment should be started as early as possible, preferably within 24 hours of symptom onset, as early intervention is associated with more rapid symptom improvement. Both the 2020 ACR guidelines and the 2024 Korean College of Rheumatology guidelines support the initiation of urate-lowering therapy during an acute flare, noting that patients may be more motivated to adhere to ULT when symptoms are present [62,65].

ULT reduces serum urate levels, decreases recurrent gout flares, promotes resolution of tophi, and prevents progression to more severe forms of gout [66]. Pharmacologic options include xanthine oxidase inhibitors, such as allopurinol and febuxostat, which inhibit uric acid production, and uricosuric agents including probenecid and benzbromarone, which reduce serum urate by enhancing renal uric acid excretion [67]. Benzbromarone is currently not available in Korea. Allopurinol and febuxostat are considered first-line treatment options. Allopurinol is primarily excreted by the kidneys and accordingly requires dose modification in patients with CKD; and carries the highest risk of severe cutaneous adverse reactions (SCARs) among available agents [68]. In Korea, the prevalence of the *HLA-B*58:01* allele, which is strongly associated with allopurinol-induced SCARs, is relatively high. Consequently, *HLA-B*58:01* genotyping, which is reimbursed by the national health insurance system, should be performed prior to initiating allopurinol therapy [69]. In contrast, febuxostat is less affected by renal function and has potent urate-lowering efficacy, leading to its widespread use in Korea. Although a black box warning regarding increased cardiovascular risk was issued following the Cardiovascular Safety of Febuxostat and Allopurinol in Participants with Gout and Cardiovascular Comorbidities (CARES) trial [70], subsequent evidence from the Febuxostat Versus Allopurinol Streamlined Trial (FAST) study did not demonstrate an increased cardiovascular risk with febuxostat use [71]. ULT should be initiated at a low dose, with titration every 2–4 weeks until the target serum urate level is achieved, and a uricosuric agent may be added if adequate control is not achieved with monotherapy [44]. Allopurinol is typically initiated at 100 mg daily, or 50 mg daily in patients with CKD, whereas febuxostat is commonly started at 40 mg daily. To prevent acute gout flares during ULT initiation, low-dose antiinflammatory prophylaxis may be co-administered for approximately 6 months [72]. Alternatively, gradual up-titration of febuxostat starting at 10 mg has been shown to provide flare prevention efficacy comparable to that of colchicine prophylaxis [73].

According to the ACR guidelines, ULT is indicated in patients with frequent gout flares (≥2 per year), the presence of tophi, or radiographic evidence of erosive disease [44]. In addition, ULT may be beneficial even after a first gout flare in patients with a serum urate level ≥9 mg/dL, a history of urolithiasis, or CKD stage 3 or higher. Both the ACR and EULAR recommend a treat-to-target strategy, with a target serum urate target of <6 mg/dL in patients without tophi and <5 mg/dL in those with frequent flares or tophaceous gout [44,74].

Among emerging therapies, agents targeting the NLRP3 inflammasome, which plays a central role in the pathogenesis of gout, are currently under clinical investigation. Dapansutrile, an oral NLRP3 inhibitor, has demonstrated effective analgesic and antiinflammatory effects with no significant safety concerns reported to date [75]. Dotinurad is a selective urate reabsorption inhibitor that reduces serum urate levels through selective inhibition of *URAT1* in the renal proximal tubules. In two randomized controlled trials, dotinurad has demonstrated noninferiority to febuxostat and benzbromarone in reducing serum urate levels [76,77]. Dotinurad was approved in Japan in 2020, and approval in other countries may follow. Beyond gout, its potential use has been suggested in conditions such as metabolic syndrome, CKD, and cardiovascular disease [78,79].

Pegloticase, a recombinant uricase, is indicated for refractory chronic gout, particularly in patients with tophaceous disease who are unresponsive to or have contraindications to xanthine oxidase inhibitors. It is currently approved by the FDA for this indication [52]. Due to the potential for infusion reactions and anaphylaxis, premedication and close monitoring of serum urate levels prior to each infusion are required. To minimize the risk of infusion-related reactions, the FDA has recently approved the concomitant use of methotrexate with pegloticase [80,81].

## Long-term prognosis and therapeutic optimization in gout

When mortality rates among patients with gout were compared between an early cohort (1988–1994) and a later

cohort (2007–2016) using data from NHANES, mortality remained similar in both periods (hazard ratios, 1.20 [1.03–1.40] and 1.19 [1.04–1.37], respectively) [3]. While survival outcomes in diseases such as rheumatoid arthritis and systemic lupus erythematosus have improved over recent decades [82,83], mortality associated with gout has not shown comparable improvement. The persistently high mortality in gout is likely related to suboptimal implementation of current therapies and insufficient long-term disease management. Between 2007 and 2016, only 35.5% of patients with gout in the US were treated with ULT, indicating that fewer than one-third of eligible patients were treated [84]. Moreover, a meta-analysis demonstrated that adherence to ULT was poor, with an estimated adherence rate of approximately 46% [85]. Because ULT is intended for long-term use over many years rather than short-term treatment, multiple factors contribute to difficulties in maintaining therapy. One important factor is the perception that gout is a condition that requires medication only during painful episodes, leading patients to discontinue treatment during asymptomatic periods [86]. In addition, some patients intentionally stop therapy to assess whether they can manage without treatment or as an expression of resistance to chronic medication use [87]. Poor adherence contributes substantially to increased healthcare costs and unfavorable clinical outcomes. Patients should be educated that gout is a chronic metabolic disease and that sustained ULT can dissolve urate crystals and improve long-term clinical outcomes [88]. Regular monitoring of serum urate levels and imaging findings is also essential to encourage continued adherence to therapy [89]. Indeed, several studies have reported that intensive care delivered by specially trained nurse educators significantly improved gout flare frequency, tophus burden, and treatment adherence [90]. Continuous efforts to optimize gout management and further research in this field are therefore needed.

## Conclusions

Gout is an increasingly prevalent inflammatory metabolic disease driven by hyperuricemia. Beyond joint involvement, it is strongly associated with major comorbidities, contributing to increased morbidity and mortality. Although effective diagnostic tools and urate-lowering therapies are available, suboptimal treatment implementation and poor adherence remain significant challenges. Early diagnosis, a treat-to-target strategy, and sustained patient education are essential to reduce the long-term burden of gout.

## Article information

**Conflicts of interest**
Jihun Kang is an editorial board member of the journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

**Acknowledgments**
Hyeong Taek Woo (Keimyung University, Daegu, Korea) provided statistical support.

**Funding**
None.

**Author contributions**
Conceptualization: PJK, JK, GTK, YK. Investigation: PJK, JK, GTK, YK. Supervision: JY, GTK, YK. Validation: PJK, JY. Visualization: YK. Writing-original draft: PJK, JK. Writing-review & editing: GTK, YK. All authors have read and approved the final manuscript.

**ORCID**
Phillip J Kim, https://orcid.org/0009-0000-5323-3439
Jihun Kang, https://orcid.org/0000-0002-2263-9054
Jesang Yu, https://orcid.org/0000-0002-0469-2660
Geun-Tae Kim, https://orcid.org/0000-0001-9765-3558
Yunkyung Kim, https://orcid.org/0000-0003-0393-7264

## References

1. Dehlin M, Jacobsson L, Roddy E. Global epidemiology of gout: prevalence, incidence, treatment patterns and risk factors. Nat Rev Rheumatol 2020;16:380–90.
2. Zhang S, Wang Y, Cheng J, Huangfu N, Zhao R, Xu Z, et al. Hyperuricemia and cardiovascular disease. Curr Pharm Des 2019;25:700–9.
3. McCormick N, Lin K, Yokose C, Lu N, Zhang Y, Choi HK. Unclosing premature mortality gap among patients with gout in the US general population, independent of serum urate and

atherosclerotic cardiovascular risk factors. Arthritis Care Res (Hoboken) 2024;76:691–702.
4. Singh JA, Gaffo A. Gout epidemiology and comorbidities. Semin Arthritis Rheum 2020;50:S11–6.
5. Pillinger MH, Goldfarb DS, Keenan RT. Gout and its comorbidities. Bull NYU Hosp Jt Dis 2010;68:199–203.
6. Du L, Zong Y, Li H, Wang Q, Xie L, Yang B, et al. Hyperuricemia and its related diseases: mechanisms and advances in therapy. Signal Transduct Target Ther 2024;9:212.
7. Punjwani S, Jani C, Liu W, Kakoullis L, Salciccioli I, Al Omari O, et al. Burden of gout among different WHO regions, 1990-2019: estimates from the global burden of disease study. Sci Rep 2024;14:15953.
8. Yokose C, McCormick N, Lu N, Tanikella S, Lin K, Joshi AD, et al. Trends in prevalence of gout among US Asian adults, 2011-2018. JAMA Netw Open 2023;6:e239501.
9. Ahn JK. Epidemiology and treatment-related concerns of gout and hyperuricemia in Korean. J Rheum Dis 2023;30:88–98.
10. Health Insurance Review & Assessment Service. Medical care expenditure statistical indicators for the first half of 2023 [Internet]. Health Insurance Review & Assessment Service; 2023 [cited 2026 Mar 27]. https://www.hira.or.kr/bbsDummy.do?pgmid=HIRAA020045010000&brdScnBltNo=4&brdBltNo=2400&pageIndex=1&pageIndex2=1
11. Kim Y, Kang J, Kim GT. Prevalence of hyperuricemia and its associated factors in the general Korean population: an analysis of a population-based nationally representative sample. Clin Rheumatol 2018;37:2529–38.
12. Dalbeth N, Phipps-Green A, Frampton C, Neogi T, Taylor WJ, Merriman TR. Relationship between serum urate concentration and clinically evident incident gout: an individual participant data analysis. Ann Rheum Dis 2018;77:1048–52.
13. Reginato AM, Mount DB, Yang I, Choi HK. The genetics of hyperuricaemia and gout. Nat Rev Rheumatol 2012;8:610–21.
14. Lyngdoh T, Vuistiner P, Marques-Vidal P, Rousson V, Waeber G, Vollenweider P, et al. Serum uric acid and adiposity: deciphering causality using a bidirectional Mendelian randomization approach. PLoS One 2012;7:e39321.
15. Choi HK, McCormick N, Lu N, Rai SK, Yokose C, Zhang Y. Population impact attributable to modifiable risk factors for hyperuricemia. Arthritis Rheumatol 2020;72:157–65.
16. Bruderer S, Bodmer M, Jick SS, Meier CR. Use of diuretics and risk of incident gout: a population-based case-control study. Arthritis Rheumatol 2014;66:185–96.
17. Major TJ, Topless RK, Dalbeth N, Merriman TR. Evaluation of the diet wide contribution to serum urate levels: meta-analysis of population based cohorts. BMJ 2018;363:k3951.
18. Tin A, Marten J, Halperin Kuhns VL, Li Y, Wuttke M, Kirsten H, et al. Target genes, variants, tissues and transcriptional pathways influencing human serum urate levels. Nat Genet 2019;51:1459–74.
19. Major TJ, Takei R, Matsuo H, Leask MP, Sumpter NA, Topless RK, et al. A genome-wide association analysis reveals new pathogenic pathways in gout. Nat Genet 2024;56:2392–406.
20. Park YE, Kim JH. Revolutionizing gut health: exploring the role of gut microbiota and the potential of microbiome-based therapies in lower gastrointestinal diseases. Kosin Med J 2023;38:98–106.
21. Xing SC, Meng DM, Chen Y, Jiang G, Liu XS, Li N, et al. Study on the diversity of Bacteroides and Clostridium in patients with primary gout. Cell Biochem Biophys 2015;71:707–15.
22. Mendez-Salazar EO, Vazquez-Mellado J, Casimiro-Soriguer CS, Dopazo J, Cubuk C, Zamudio-Cuevas Y, et al. Taxonomic variations in the gut microbiome of gout patients with and without tophi might have a functional impact on urate metabolism. Mol Med 2021;27:50.
23. Mandal AK, Mount DB. The molecular physiology of uric acid homeostasis. Annu Rev Physiol 2015;77:323–45.
24. Ahn EY, So MW. The pathogenesis of gout. J Rheum Dis 2025;32:8–16.
25. Bauernfeind FG, Horvath G, Stutz A, Alnemri ES, MacDonald K, Speert D, et al. Cutting edge: NF-kappaB activating pattern recognition and cytokine receptors license NLRP3 inflammasome activation by regulating NLRP3 expression. J Immunol 2009;183:787–91.
26. Martinon F, Petrilli V, Mayor A, Tardivel A, Tschopp J. Gout-associated uric acid crystals activate the NALP3 inflammasome. Nature 2006;440:237–41.
27. Dalbeth N, Gosling AL, Gaffo A, Abhishek A. Gout. Lancet 2021;397:1843–55.
28. Dalbeth N, Clark B, Gregory K, Gamble G, Sheehan T, Doyle A, et al. Mechanisms of bone erosion in gout: a quantitative analysis using plain radiography and computed tomography. Ann Rheum Dis 2009;68:1290–5.
29. Dalbeth N, Smith T, Nicolson B, Clark B, Callon K, Naot D, et al. Enhanced osteoclastogenesis in patients with tophaceous gout: urate crystals promote osteoclast development through interactions with stromal cells. Arthritis Rheum 2008;58:1854–65.
30. Chhana A, Callon KE, Pool B, Naot D, Watson M, Gamble GD, et al. Monosodium urate monohydrate crystals inhibit osteoblast

viability and function: implications for development of bone erosion in gout. Ann Rheum Dis 2011;70:1684–91.
31. Yoo HG, Lee SI, Chae HJ, Park SJ, Lee YC, Yoo WH. Prevalence of insulin resistance and metabolic syndrome in patients with gouty arthritis. Rheumatol Int 2011;31:485–91.
32. Zhu Y, Pandya BJ, Choi HK. Comorbidities of gout and hyperuricemia in the US general population: NHANES 2007-2008. Am J Med 2012;125:679–87.
33. Bardin T, Richette P. Impact of comorbidities on gout and hyperuricaemia: an update on prevalence and treatment options. BMC Med 2017;15:123.
34. Krishnan E. Gout and the risk for incident heart failure and systolic dysfunction. BMJ Open 2012;2:e000282.
35. Goncalves DL, Moreira TR, da Silva LS. A systematic review and meta-analysis of the association between uric acid levels and chronic kidney disease. Sci Rep 2022;12:6251.
36. Kimura K, Hosoya T, Uchida S, Inaba M, Makino H, Maruyama S, et al. Febuxostat therapy for patients with stage 3 CKD and asymptomatic hyperuricemia: a randomized trial. Am J Kidney Dis 2018;72:798–810.
37. Badve SV, Pascoe EM, Tiku A, Boudville N, Brown FG, Cass A, et al. Effects of allopurinol on the progression of chronic kidney disease. N Engl J Med 2020;382:2504–13.
38. Afkarian M, Polsky S, Parsa A, Aronson R, Caramori ML, Cherney DZ, et al. Preventing early renal loss in diabetes (PERL) study: a randomized double-blinded trial of allopurinol-rationale, design, and baseline data. Diabetes Care 2019;42:1454–63.
39. Mene P, Punzo G. Uric acid: bystander or culprit in hypertension and progressive renal disease? J Hypertens 2008;26:2085–92.
40. Khosla UM, Zharikov S, Finch JL, Nakagawa T, Roncal C, Mu W, et al. Hyperuricemia induces endothelial dysfunction. Kidney Int 2005;67:1739–42.
41. Bardin T, Richette P. Definition of hyperuricemia and gouty conditions. Curr Opin Rheumatol 2014;26:186–91.
42. Rho YH, Lu N, Peloquin CE, Man A, Zhu Y, Zhang Y, et al. Independent impact of gout on the risk of diabetes mellitus among women and men: a population-based, BMI-matched cohort study. Ann Rheum Dis 2016;75:91–5.
43. Pascart T, Ramon A, Ottaviani S, Legrand J, Ducoulombier V, Houvenagel E, et al. Association of specific comorbidities with monosodium urate crystal deposition in urate-lowering therapy-naive gout patients: a cross-sectional dual-energy computed tomography study. J Clin Med 2020;9:1295.
44. FitzGerald JD, Dalbeth N, Mikuls T, Brignardello-Petersen R, Guyatt G, Abeles AM, et al. 2020 American College of Rheumatology guideline for the management of gout. Arthritis Care Res (Hoboken) 2020;72:744–60.
45. AGEPHA Pharma. U.S. FDA approves first anti-inflammatory drug for cardiovascular disease [Internet]. AGEPHA Pharma; 2023 [cited 2026 Mar 16]. https://us.agephapharma.com/blog/2023/06/20/us-fda-approves-first-anti-inflammatory-drug-for-cardiovascular-disease/
46. Nidorf SM, Fiolet AT, Mosterd A, Eikelboom JW, Schut A, Opstal TS, et al. Colchicine in patients with chronic coronary disease. N Engl J Med 2020;383:1838–47.
47. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med 2017;377:1119–31.
48. Jung I, Lee DY, Chung SM, Park SY, Yu JH, Moon JS, et al. Impact of chronic kidney disease and gout on end-stage renal disease in type 2 diabetes: population-based cohort study. Endocrinol Metab (Seoul) 2024;39:748–57.
49. Casanova AG, Morales AI, Vicente-Vicente L, Lopez-Hernandez FJ. Effect of uric acid reduction on chronic kidney disease: systematic review and meta-analysis. Front Pharmacol 2024;15:1373258.
50. Wei J, Choi HK, Dalbeth N, Li X, Li C, Zeng C, et al. Gout flares and mortality after sodium-glucose cotransporter-2 inhibitor treatment for gout and type 2 diabetes. JAMA Netw Open 2023;6:e2330885.
51. McCormick N, Yokose C, Lu N, Wexler DJ, Avina-Zubieta JA, De Vera MA, et al. Sodium-glucose cotransporter-2 inhibitors vs sulfonylureas for gout prevention among patients with type 2 diabetes receiving metformin. JAMA Intern Med 2024;184:650–60.
52. Sivera F, Andres M, Dalbeth N. A glance into the future of gout. Ther Adv Musculoskelet Dis 2022;14:1759720X221114098.
53. Neogi T, Jansen TL, Dalbeth N, Fransen J, Schumacher HR, Berendsen D, et al. 2015 Gout classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2015;74:1789–98.
54. Sivera F, Andres M, Carmona L, Kydd AS, Moi J, Seth R, et al. Multinational evidence-based recommendations for the diagnosis and management of gout: integrating systematic literature review and expert opinion of a broad panel of rheumatologists in the 3e initiative. Ann Rheum Dis 2014;73:328–35.
55. Roddy E, Packham J, Obrenovic K, Rivett A, Ledingham JM. Management of gout by UK rheumatologists: a British Society for Rheumatology national audit. Rheumatology (Oxford) 2018;57:826–30.
56. Perez Ruiz F, Sanchez-Piedra CA, Sanchez-Costa JT, Andres M,

Diaz-Torne C, Jimenez-Palop M, et al. Improvement in diagnosis and treat-to-target management of hyperuricemia in gout: results from the GEMA-2 transversal study on practice. Rheumatol Ther 2018;5:243–53.
57. Sivera F, Andres M, Falzon L, van der Heijde DM, Carmona L. Diagnostic value of clinical, laboratory, and imaging findings in patients with a clinical suspicion of gout: a systematic literature review. J Rheumatol Suppl 2014;92:3–8.
58. Ogdie A, Taylor WJ, Neogi T, Fransen J, Jansen TL, Schumacher HR, et al. Performance of ultrasound in the diagnosis of gout in a multicenter study: comparison with monosodium urate monohydrate crystal analysis as the gold standard. Arthritis Rheumatol 2017;69:429–38.
59. Choi HK, Burns LC, Shojania K, Koenig N, Reid G, Abufayyah M, et al. Dual energy CT in gout: a prospective validation study. Ann Rheum Dis 2012;71:1466–71.
60. Stewart S, Su I, Gamble GD, Dalbeth N. Diagnostic value of different imaging features for patients with suspected gout: a network meta-analysis. Semin Arthritis Rheum 2021;51:1251–7.
61. Zhang B, Yang M, Wang H. Diagnostic value of ultrasound versus dual-energy computed tomography in patients with different stages of acute gouty arthritis. Clin Rheumatol 2020;39:1649–53.
62. FitzGerald JD, Dalbeth N, Mikuls T, Brignardello-Petersen R, Guyatt G, Abeles AM, et al. 2020 American College of Rheumatology guideline for the management of gout. Arthritis Rheumatol 2020;72:879–95.
63. Schlesinger N, Alten RE, Bardin T, Schumacher HR, Bloch M, Gimona A, et al. Canakinumab for acute gouty arthritis in patients with limited treatment options: results from two randomised, multicentre, active-controlled, double-blind trials and their initial extensions. Ann Rheum Dis 2012;71:1839–48.
64. U.S. Food and Drug Administration. ILARIS® (canakinumab) injection, for subcutaneous use [Internet]. U.S. Food and Drug Administration; 2024 [cited 2026 Mar 16]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125319s110lbl.pdf
65. Lee JJ, Lee JS, Chung MK, Ahn JK, Choi HJ, Hong SJ, et al. Korean guidelines for the management of gout. J Rheum Dis 2023;30:141–50.
66. FitzGerald JD. Gout. Ann Intern Med 2025;178:ITC33–48.
67. Li S, Yang H, Guo Y, Wei F, Yang X, Li D, et al. Comparative efficacy and safety of urate-lowering therapy for the treatment of hyperuricemia: a systematic review and network meta-analysis. Sci Rep 2016;6:33082.
68. Park HJ, Yun J, Kang DY, Park JW, Koh YI, Kim S, et al. Unique clinical characteristics and prognosis of allopurinol-induced severe cutaneous adverse reactions. J Allergy Clin Immunol Pract 2019;7:2739–49.
69. Yu KH, Yu CY, Fang YF. Diagnostic utility of HLA-B*5801 screening in severe allopurinol hypersensitivity syndrome: an updated systematic review and meta-analysis. Int J Rheum Dis 2017;20:1057–71.
70. White WB, Saag KG, Becker MA, Borer JS, Gorelick PB, Whelton A, et al. Cardiovascular safety of febuxostat or allopurinol in patients with gout. N Engl J Med 2018;378:1200–10.
71. Mackenzie IS, Ford I, Nuki G, Hallas J, Hawkey CJ, Webster J, et al. Long-term cardiovascular safety of febuxostat compared with allopurinol in patients with gout (FAST): a multicentre, prospective, randomised, open-label, non-inferiority trial. Lancet 2020;396:1745–57.
72. Borstad GC, Bryant LR, Abel MP, Scroggie DA, Harris MD, Alloway JA. Colchicine for prophylaxis of acute flares when initiating allopurinol for chronic gouty arthritis. J Rheumatol 2004;31:2429–32.
73. Yamanaka H, Tamaki S, Ide Y, Kim H, Inoue K, Sugimoto M, et al. Stepwise dose increase of febuxostat is comparable with colchicine prophylaxis for the prevention of gout flares during the initial phase of urate-lowering therapy: results from FORTUNE-1, a prospective, multicentre randomised study. Ann Rheum Dis 2018;77:270–6.
74. Richette P, Doherty M, Pascual E, Barskova V, Becce F; Castaneda-Sanabria J; et al. 2016 Updated EULAR evidence-based recommendations for the management of gout. Ann Rheum Dis 2017;76:29–42.
75. Kluck V, Jansen TL, Janssen M, Comarniceanu A, Efde M, Tengesdal IW, et al. Dapansutrile, an oral selective NLRP3 inflammasome inhibitor, for treatment of gout flares: an open-label, dose-adaptive, proof-of-concept, phase 2a trial. Lancet Rheumatol 2020;2:e270–80.
76. Hosoya T, Furuno K, Kanda S. A non-inferiority study of the novel selective urate reabsorption inhibitor dotinurad versus febuxostat in hyperuricemic patients with or without gout. Clin Exp Nephrol 2020;24:71–9.
77. Hosoya T, Sano T, Sasaki T, Fushimi M, Ohashi T. Dotinurad versus benzbromarone in Japanese hyperuricemic patient with or without gout: a randomized, double-blind, parallel-group, phase 3 study. Clin Exp Nephrol 2020;24:62–70.
78. Kaufmann D, Chaiyakunapruk N, Schlesinger N. Optimizing gout treatment: a comprehensive review of current and emerging uricosurics. Joint Bone Spine 2025;92:105826.

79. Yanai H, Adachi H, Hakoshima M, Iida S, Katsuyama H. A possible therapeutic application of the selective inhibitor of urate transporter 1, dotinurad, for metabolic syndrome, chronic kidney disease, and cardiovascular disease. Cells 2024;13:450.
80. Botson JK, Saag K, Peterson J, Parikh N, Ong S, La D, et al. A randomized, placebo-controlled study of methotrexate to increase response rates in patients with uncontrolled gout receiving pegloticase: primary efficacy and safety findings. Arthritis Rheumatol 2023;75:293–304.
81. Botson J, Obermeyer K, LaMoreaux B, Padnick-Silver L, Verma S, Weinblatt ME, et al. Quality of life and clinical gout assessments during pegloticase with and without methotrexate co-therapy: MIRROR randomized controlled trial exploratory findings. Rheumatol Adv Pract 2024;8:rkae145.
82. Zhang Y, Lu N, Peloquin C, Dubreuil M, Neogi T, Avina-Zubieta JA, et al. Improved survival in rheumatoid arthritis: a general population-based cohort study. Ann Rheum Dis 2017;76:408–13.
83. Yen EY, Shaheen M, Woo JM, Mercer N, Li N, McCurdy DK, et al. 46-Year trends in systemic lupus erythematosus mortality in the United States, 1968 to 2013: a nationwide population-based study. Ann Intern Med 2017;167:777–85.
84. Chen-Xu M, Yokose C, Rai SK, Pillinger MH, Choi HK. Contemporary prevalence of gout and hyperuricemia in the United States and decadal trends: the national health and nutrition examination survey, 2007-2016. Arthritis Rheumatol 2019;71:991–9.
85. Scheepers LE, van Onna M, Stehouwer CD, Singh JA, Arts IC, Boonen A. Medication adherence among patients with gout: a systematic review and meta-analysis. Semin Arthritis Rheum 2018;47:689–702.
86. Oderda GM, Shiozawa A, Walsh M, Hess K, Brixner DI, Feehan M, et al. Physician adherence to ACR gout treatment guidelines: perception versus practice. Postgrad Med 2014;126:257–67.
87. Weinman J, Graham S, Canfield M, Kleinstauber M, Perera AI, Dalbeth N, et al. The Intentional Non-Adherence Scale (INAS): initial development and validation. J Psychosom Res 2018;115:110–6.
88. Abhishek A, Doherty M. Education and non-pharmacological approaches for gout. Rheumatology (Oxford) 2018;57:i51–8.
89. Bourke S, Taylor WJ, Doyle AJ, Gott M, Dalbeth N. The patient experience of musculoskeletal imaging tests for investigation of inflammatory arthritis: a mixed-methods study. Clin Rheumatol 2018;37:2261–8.
90. Fuller A, Jenkins W, Doherty M, Abhishek A. Nurse-led care is preferred over GP-led care of gout and improves gout outcomes: results of Nottingham Gout Treatment Trial follow-up study. Rheumatology (Oxford) 2020;59:575–9.

Original article

Kosin Medical Journal 2026;41(1):37-45
pISSN: 2005-9531 • eISSN: 2586-7024
https://doi.org/10.7180/kmj.25.130

KMJ
KOSIN MEDICAL JOURNAL

# Real-world survival outcomes of sequential treatment strategy for newly diagnosed advanced high-grade serous ovarian cancer

**Eun Taeg Kim[1], Sun Young Ma[2], Tae Kyoung Kang[1], Tae Hwa Lee[1], Dong Hwi Kim[3], Won Gyu Kim[1]**

[1]*Department of Obstetrics and Gynecology, Kosin University Gospel Hospital, Kosin University College of Medicine, Busan, Korea*
[2]*Department of Radiation Oncology, Kosin University Gospel Hospital, Kosin University College of Medicine, Busan, Korea*
[3]*Mirae-i Women's Hospital, Busan, Korea*

**Background:** Various strategies are being explored to improve outcomes in advanced ovarian cancer. This study evaluated the survival outcomes of a sequential treatment strategy comprising dose-dense weekly chemotherapy, selective adjuvant radiotherapy, and poly(ADP-ribose) polymerase (PARP) inhibitor maintenance following primary debulking surgery.

**Methods:** We retrospectively reviewed 12 patients with newly diagnosed advanced high-grade serous ovarian cancer (HGSOC) who underwent a sequential treatment strategy (debulking surgery followed by dose-dense chemotherapy, selective adjuvant radiotherapy, and PARP inhibitor maintenance) at Kosin University Gospel Hospital between December 2019 and March 2023. Survival outcomes were analyzed using the Kaplan-Meier method, and treatment-related adverse effects were evaluated.

**Results:** All 12 patients achieved complete remission after the sequential treatment strategy. At the cutoff date (June 20, 2025), all patients were alive, with a median follow-up duration of 48.1 months (range, 28.7–66.5 months). The median progression-free survival (PFS) was 43.8 months. Acute toxicities, including bone marrow suppression and alopecia, were transient and manageable. Peripheral neuropathy and extremity edema were observed as persistent late toxicities.

**Conclusions:** This study highlights promising outcomes with a multimodal sequential treatment strategy in newly diagnosed advanced HGSOC. All patients remained alive at the time of analysis, and the median PFS reached 43.8 months, suggesting a potential benefit of this sequential approach compared with conventional treatment strategies. Prospective studies are warranted to validate these findings.

**Keywords:** Adjuvant radiotherapy; Cytoreduction surgical procedures; Ovarian neoplasms; Poly(ADP-ribose) polymerase inhibitors; Survival analysis

## Introduction

Ovarian cancer is one of the most lethal gynecologic malignancies [1], largely due to its asymptomatic progression and lack of effective early detection methods. Approximately 75% of patients are diagnosed at an advanced stage, and most cases are the high-grade serous ovarian cancer (HGSOC) subtype, which accounts for about 70% of epithelial ovar-

**Received:** September 5, 2025; **Revised:** December 1, 2025; **Accepted:** December 2, 2025
**Corresponding Author:** Won Gyu Kim, MD, PhD
Department of Obstetrics and Gynecology, Kosin University Gospel Hospital, Kosin University College of Medicine, 262 Gamcheon-ro, Seo-gu, Busan 49267, Korea
Tel: +82-51-990-6227 Fax: +82-51-244-6939 E-mail: kimwongyu203@naver.com

© 2026 Kosin University College of Medicine
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ian cancers [2]. Although initial responses to standard treatment—optimal cytoreductive surgery followed by paclitaxel-platinum chemotherapy—are generally favorable, recurrence within 3 years is common and often fatal [3].

To improve long-term outcomes, several modifications and additions to standard first-line therapy have been investigated. Dose-dense weekly paclitaxel-based chemotherapy demonstrated significantly improved survival compared to the standard 3-weekly paclitaxel regimen in Japanese patients, as shown in the Japanese Gynecologic Oncology Group (JGOG) 3016 trial [4]. However, similar survival benefits were not observed in subsequent Western trials (Multicentre Italian Trials in Ovarian Cancer [MITO]-7, International Collaborative Ovarian Neoplasm [ICON]8, and Gynecologic Oncology Group [GOG]-262) [5-7]. Several factors may explain these discrepancies. Firstly, pharmacogenomic differences between East Asian and Western populations have been documented in the context of paclitaxel metabolism and toxicity profiles. For example, ethnic variability in *CYP2C8* and *ABCB1* polymorphisms—key enzymes and transporters involved in paclitaxel clearance—has been documented [8]. *CYP2C8* variants that reduce paclitaxel metabolism are more common in Western populations than in East Asians [9], while *ABCB1* polymorphisms affecting drug efflux have been associated with altered paclitaxel exposure in Japanese patients [8]. Secondly, population-specific differences may underlie the inconsistent outcomes observed across trials [10]. The proportion of East Asian patients in these Western trials was low, limiting the generalizability of the findings to Asian populations [6]. Given the close genetic similarities between Korean and Japanese populations [11], this background provided a rationale for exploring the potential relevance of the dose-dense regimen in Korean clinical settings.

In certain cases, such as unresectable metastatic lymph nodes, local radiotherapy may serve as an effective treatment modality [12-14]. Advances in radiation planning and imaging, such as positron emission tomography-computed tomography (PET-CT), allow more precise targeting of disease sites. Adjuvant radiotherapy prior to poly(ADP-ribose) polymerase (PARP) inhibitor maintenance may contribute to improved locoregional control, particularly in patients with microscopic residual disease [15].

PARP inhibitors have emerged as a key component of maintenance therapy, especially in patients with pathogenic or likely pathogenic *BRCA* mutations or homologous recombination deficiency (HRD) [16,17]. Their integration into first-line treatment has demonstrated improved survival across multiple clinical trials, establishing them as standard of care in selected patients [18,19].

This study aims to evaluate the real-world outcomes of a sequential first-line treatment strategy involving cytoreductive surgery, followed by dose-dense weekly paclitaxel-carboplatin chemotherapy, selective adjuvant radiotherapy for unresectable nodal disease, and PARP inhibitor maintenance therapy in patients with newly diagnosed advanced HGSOC.

## Methods

**Ethical statements:** The Institutional Review Board (IRB) of Kosin University Gospel Hospital (IRB No. 2025-06-030) determined that this study was exempt from formal review. Because the analysis was retrospective and relied exclusively on deidentified clinical data, the requirement for informed consent was waived.

### 1. Patients

In this retrospective study, we reviewed the medical records of 12 patients with advanced HGSOC who received dose-dense weekly paclitaxel-carboplatin chemotherapy, selective adjuvant radiotherapy, and PARP inhibitor maintenance therapy following cytoreductive surgery at Kosin University Gospel Hospital (Busan, Korea) between December 2019 and March 2023. Patient characteristics are summarized in Table 1.

Among the 12 patients, 11 underwent primary debulking surgery (PDS) followed by nine cycles of dose-dense weekly paclitaxel (80 mg/m$^2$) and three weekly carboplatin (area under the curve [AUC] 6) chemotherapy. One patient received six cycles of neoadjuvant chemotherapy consisting of weekly paclitaxel (80 mg/m$^2$) and 3-weekly carboplatin (AUC 6) prior to interval debulking surgery (IDS), followed by six additional cycles of the same dose-dense regimen. Chemotherapy schedules were adjusted based on hematologic parameters. Treatment was delayed or dose was reduced if the absolute neutrophil count (ANC) dropped below 500/μL or platelet count was less than 80,000/μL. Therapy continued as scheduled when ANC ≥1,000/μL and platelets ≥100,000/μL unless contraindicated.

**Table 1.** Baseline clinicopathologic characteristics, treatment details, and outcomes of patients

| Patient | Age (yr) | FIGO stage | Optimal surgery (residual tumor <1 cm) | *BRCA* status | Site of distant metastasis | Chemotherapy dosage | | Target of adjuvant RTx | Maintenance therapy | Recurrence (site) | Salvage treatment | PFS (mo) | Follow-up duration (mo) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Delivered dose intensity (%) | Reduced dose intensity (%) | | | | | | |
| 1 | 41 | IIIC | Yes | *BRCA2* mutation | - | 900 | 0 | - | Niraparib | - | - | - | 65.0 |
| 2 | 55 | IVB | No | *BRCA2* mutation | Neck, para-aortic | 900 | 0 | Neck, para-aortic LN | Olaparib | - | - | - | 62.1 |
| 3 | 53 | IVB | No | *BRCA* wild-type | Neck, para-aortic, right parasternal LN | 900 | 0 | Neck, para-aortic, right parasternal LN | Niraparib | Right axillar LN, right diaphragm | OP, CTx | 46.3 | 65.2 |
| 4 | 56 | IVB | Yes | *BRCA* wild-type | Colon | 820 | 80 | - | Niraparib | - | - | - | 66.5 |
| 5 | 51 | IVB | No | *BRCA1* mutation | Neck, para-aortic | 900 | 0 | Neck, para-aortic LN | Niraparib | Left inguinal LN, left obtulator LN | RTx, CTx | 56.9 | 60.7 |
| 6 | 53 | IVB | No | *BRCA1* mutation | Both SCN, mediastinal LN, rectum | 900 | 0 | - | Olaparib | Brain (right frontal) | RTx, CTx | 42.4 | 50.2 |
| 7 | 55 | IVB | Yes | *BRCA2* mutation | Right axillary LN | 900 | 0 | - | Olaparib | - | - | - | 47.2 |
| 8 | 57 | IVB | No | *BRCA* wild-type | Neck, para-aortic | 900 | 0 | Neck, para-aortic LN | Niraparib | - | - | - | 40.1 |
| 9 | 54 | IIIC | Yes | *BRCA1* mutation | - | 720 | 180 | - | Niraparib | - | - | - | 28.7 |
| 10 | 63 | IVB | No | *BRCA* wild-type | Para-aortic, parasternal, mediastinal LN | 720 | 180 | - | Niraparib | Left neck LN, both SCN, retrocaval LN | CTx | 25.1 | 29.3 |
| 11 | 73 | IVB | No | *BRCA* wild-type | Left neck, para-aortic | 1080 | 120 | Left neck, para-aortic LN | Niraparib | - | - | - | 35.2 |
| 12 | 73 | IIIC | Yes | *BRCA* wild-type | - | 720 | 180 | - | Niraparib | - | - | - | 27.1 |

This table presents individual patient data including baseline characteristics. All patients were diagnosed with high-grade serous ovarian carcinoma (HGSOC) and received dose-dense weekly paclitaxel-carboplatin chemotherapy. All patients initially achieved complete response to chemotherapy, and no deaths were observed during the follow-up period.
FIGO, International Federation of Gynecology and Obstetrics; RTx, radiation therapy; PFS, progression-free survival; LN, lymph node; OP, operation; CTx, chemotherapy; SCN, supraclavicular lymph node.

Genomic DNA was extracted from peripheral blood leukocytes. *BRCA1* (22 exons) and *BRCA2* (26 exons) genes were analyzed using Sanger sequencing. Variant classification was based on the 2015 American College of Medical Genetics and Genomics/Association for Molecular Pathology guidelines. Pathogenic and likely pathogenic variants were classified as "mutation-positive," while patients without such variants were classified as "wild-type." Variants of uncertain significance were not detected in our cohort.

**2. Selective adjuvant radiotherapy**

All patients underwent PET-CT before surgery to evaluate lymph node metastasis. For patients with International Federation of Gynecology and Obstetrics (FIGO) stage IVB disease and suspected unresectable lymph node metastasis, fine-needle aspiration (FNA) was performed to confirm involvement. Based on preoperative imaging, radiotherapy was considered for lymph nodes larger than 1 cm confined to a limited anatomical region.

The decision to administer selective adjuvant radiotherapy was made by a multidisciplinary team, including a gynecologic oncologist, medical oncologist, and gynecologic oncology radiologist, following completion of chemotherapy and prior to PARP inhibitor maintenance. Among the nine patients with stage IVB disease, eight had distant lymph node metastases, and one had colon metastasis. Initial adjuvant radiotherapy was administered to five patients, targeting metastatic lymph nodes. In patients with FIGO stage IVB disease with distant lymph node metastases, we considered selective adjuvant radiotherapy based on the location and size of metastatic lymph nodes.

Radiotherapy was primarily directed to high-risk lesions such as the upper para-aortic lymph nodes (above the inferior mesenteric artery) and neck (cervical or supraclavicular) nodes greater than 1 cm in diameter, as identified through PET-CT or FNA biopsy. The clinical target volume encompassed the entire metastatic nodal lesion. A total dose of 45.0–50.4 Gy was delivered in 25–28 fractions of 1.8 Gy per fraction. Radiotherapy was delivered following debulking surgery and chemotherapy but prior to initiation of PARP inhibitor maintenance. PARP inhibitor maintenance therapy was started after completion of chemotherapy, with or without selective adjuvant radiotherapy (Table 1).

**3. Surveillance and endpoints**

Patients were monitored by three weekly cancer antigen 125 levels and imaging (magnetic resonance imaging, ultrasound, or computed tomography) every 3 months. Primary endpoints were progression-free survival (PFS), overall survival (OS), and recurrence. PFS was defined as the time from diagnosis to radiologically confirmed recurrence. OS was defined as the time from diagnosis to death from any cause.

## Results

Twelve patients with advanced HGSOC were included in this study (Table 1). The median age at diagnosis was 55 years (range, 41–73 years). Nine patients had FIGO stage IVB disease and three had stage IIIC. *BRCA* mutations were identified in six patients (50.0%)—three with *BRCA1* and three with *BRCA2* mutations—while the remaining six patients were *BRCA* wild-type. All patients underwent cytoreductive surgery: 11 received PDS and one underwent IDS after neoadjuvant chemotherapy. The residual tumor size was >1 cm in seven patients (58.3%) and ≤1 cm in five patients (41.7%). Patients were followed for a median of 48.1 months (range, 28.7–66.5 months).

All patients received dose-dense weekly paclitaxel-carboplatin chemotherapy. Chemotherapy dosage was summarized using delivered dose intensity (DDI) and reduced dose intensity (RDI) across all patients. A total of seven patients (58.3%) completed nine cycles of dose-dense chemotherapy without dose reduction, achieving a DDI of 900% and RDI of 0%. The remaining five patients (41.7%) required dose modifications, with DDI ranging from 720% to 1,080% and corresponding RDI values from 80% to 180%, reflecting individualized adjustments based on clinical tolerance or hematologic toxicity. Targeted therapy with PARP inhibitors was initiated in all cases: niraparib in nine patients and olaparib in three. Among the nine patients with stage IVB disease, five received selective adjuvant radiotherapy targeting distant lymph node metastases (e.g., supraclavicular or para-aortic lymph nodes) after chemotherapy and prior to maintenance therapy (Table 1).

During follow-up, four patients (33.3%) experienced recurrence (Table 1). All had FIGO stage IVB disease, residual tumor >1 cm and *BRCA1* mutations were identified in two patients. Two had also received selective adjuvant radiotherapy. Notably, all recurrences occurred outside the

irradiated fields. The median PFS among the four recurrent patients was 43 months. Salvage treatments included surgery (n=1), radiotherapy (n=2), and chemotherapy (n=4). At final follow-up, all four recurrent patients were alive and had achieved a no-evidence-of-disease (NED) state (Table 1).

Table 2 provides information on the prevalence of treatment-related adverse events, each graded according to the Common Terminology Criteria for Adverse Events (CTCAE) 5.0. Bone marrow suppression was the most common toxicity during dose-dense chemotherapy, with neutropenia observed in 75.0% of patients (grade 3 in 41.7%), thrombocytopenia in 91.7% (grade 1–2 in 91.7%, no grade ≥3), and anemia in 58.3% (grade 3 in 16.7%). During PARP inhibitor therapy, hematologic toxicity was minimal, with only mild neutropenia (16.7%), thrombocytopenia (33.3%), and anemia (16.7%) observed. Among all chemotherapy cycles, any-grade treatment-emergent adverse events neutropenia, thrombocytopenia, and anemia were reported in 29.9%, 23.5%, and 23.5% of events, respectively. These were primarily attributed to chemotherapy and managed effectively using supportive agents such as granulocyte colony-stimulating factor (G-CSF; filgrastim) and granulocyte-macrophage colony-stimulating factor (GM-CSF). Alopecia (CTCAE grade 1-2) occurred in all patients receiving chemotherapy but was fully reversible after completion of chemotherapy.

Chronic adverse effects were peripheral neuropathy and extremity edema. Peripheral neuropathy occurred in 83.3% of patients following dose-dense chemotherapy, although all cases were grade 1–2. No patient experienced grade 3 or higher neuropathy. Limb edema was reported in 33.3% of patients after surgery and in 20.0% of patients following radiotherapy. All cases were mild (grade 1–2) (Table 2).

The median follow-up duration was 48.1 months (range, 28.7–66.5 months) (Table 1). All patients achieved complete remission after first-line sequential treatment, and no deaths were reported at the time of data cutoff (June 20, 2025). Five patients survived more than 5 years, and eight more than 3 years. The median OS was not reached.

The median PFS was 43.8 months, and the upper limit of the 95% confidence interval (CI) was not reached (Fig. 1). Compared to PFS values from previous dose-dense chemotherapy trials (Table 3), this result is notably favorable. However, due to the small sample size and relatively limited number of events and short follow-up period, statistical significance could not be determined.

## Discussion

Optimal cytoreductive surgery remains the most critical prognostic factor in advanced ovarian cancer. Two surgical approaches are commonly used: PDS and IDS, both of which aim to achieve maximal cytoreduction [20]. While complete cytoreduction (no visible residual disease) is ideal, it is often unachievable in advanced-stage cases. Studies have shown that reducing residual disease to less than 1 cm is associated with a significant survival benefit. When optimal cytoreduction is not feasible, neoadjuvant chemother-

**Table 2.** Treatment-emergent adverse events associated with the sequential treatment strategy

| Adverse event | Treatment modality (n=12) | Grade 1–2 | Grade 3 | Grade 4 | Total |
|---|---|---|---|---|---|
| Neutropenia | Dose-dense CTx | 5 | 4 | 0 | 9 (75.0) |
| | PARPi | 4 | 0 | 0 | 4 (33.3) |
| Thrombocytopenia | Dose-dense CTx | 8 | 3 | 0 | 11 (91.7) |
| | PARPi | 3 | 1 | 0 | 4 (33.3) |
| Anemia | Dose-dense CTx | 5 | 2 | 0 | 7 (58.3) |
| | PARPi | 2 | 0 | 0 | 2 (16.7) |
| Peripheral neuropathy | Dose-dense CTx | 8 | 2 | 0 | 10 (83.3) |
| Edema (leg, arm) | Debulking surgery (leg) | 4 | 0 | 0 | 4 (33.3) |
| | Radiotherapy (arm) (n=5) | 1 | 0 | 0 | 1 (20.0) |
| Alopecia | Dose-dense CTx | 12 | 0 | 0 | 12 (100.0) |

A total of 27 cycles per patient for 11 patients and 36 cycles per patient for one patient=333 cycles, any-grade neutropenia, thrombocytopenia, and anemia occurred in 29.9%, 23.5%, and 23.5% of all recorded events, respectively.
CTx, chemotherapy; PARPi, poly(ADP-ribose) polymerase inhibitors.

apy followed by IDS is a viable alternative. Recent studies have demonstrated that IDS after neoadjuvant chemotherapy provides survival outcomes comparable to PDS and may offer a survival advantage in advanced-stage disease [21-23]. In our study, all 12 operations were performed by a single gynecologic oncologic surgeon with the assistance of general and urologic surgeons to ensure maximal cytoreduction. Eleven patients underwent PDS, and one received IDS. Efforts were made to reduce the residual tumor burden to ≤1 cm, in line with optimal cytoreductive goals.

Second, dose-dense weekly paclitaxel chemotherapy has been explored as an alternative to the conventional three weekly regimen in first-line treatment. While the efficacy of 3-week paclitaxel and platinum chemotherapy following cytoreductive surgery is well established, its limitations have led to the exploration of dose-dense regimens. The JGOG 3016 trial conducted in Japan compared the conventional regimen (three weekly paclitaxel 180 mg/m$^2$+carboplatin AUC 6) with a dose-dense regimen (weekly paclitaxel 80 mg/m$^2$+three weekly carboplatin AUC 6) in patients with FIGO stage II–IV epithelial ovarian, primary peritoneal, or fallopian tube cancer [4]. Interpretation of these findings suggests that dose-dense paclitaxel therapy improves long-term survival in Japanese patients with epithelial ovarian cancer, particularly in those with extensive residual disease and serous histology. However, no benefit was observed in patients with clear cell carcinoma or mucinous carcinoma. Hematologic toxicity was a major concern in most patients receiving dose-dense therapy. Genetic and pharmacogenomic differences may influence treatment efficacy, underscoring the need for further investigation. Subsequent trials in Western populations, including the MITO-7 and ICON8 studies in Europe and the GOG-262 study in the United States, failed to confirm consistent survival benefits of weekly dose-dense paclitaxel in non-Japanese women with stage II–IV disease [5-7]. Neither MITO-7 nor ICON8 found significant difference in PFS between the weekly and conventional arms. In GOG-262, overall PFS was also not significantly different between groups; however, among patients not receiving bevacizumab (n=112), weekly paclitaxel was associated with a 4-month improvement in PFS (hazard ratio [HR], 0.62; 95% CI, 0.40–0.95; $p$=0.03) [10-12]. These discrepancies may reflect ethnic pharmacogenomic

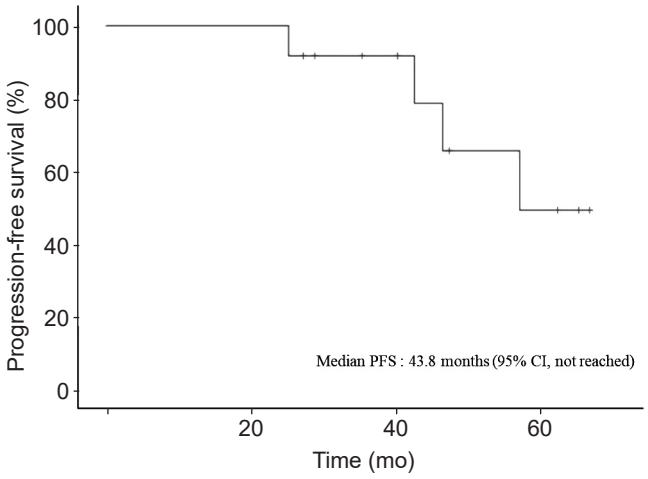


**Fig. 1.** Progression-free survival (PFS) of patients receiving the sequential treatment strategy. CI, confidence interval.

**Table 3.** PFS in dose-dense chemotherapy trials for advanced epithelial ovarian cancer

| Trial | PFS (mo) | | |
|---|---|---|---|
| | Weekly d-d paclitaxel and 3-weekly carboplatin | 3-Weekly paclitaxel and 3-weekly carboplatin | Weekly paclitaxel and weekly carboplatin |
| JGOG 3016 (n=637) | 28.2 (n=312) (HR, 0.76; CI, 0.62–0.91; $p$=0.0037) | 17.5 (n=319) | NA |
| MITO-7 (n=810) | NA | 17.3 (n=404) | 18.3 (n=406) (HR, 0.96; 95% CI, 0.80–1.16; $p$=0.66) |
| ICON 8 (n=1,566) | 20.8 (n=523) ($p$=0.35) | 17.7 (n=522) | 21.0 (n=521) ($p$=0.51) |
| GOG 262+3 weekly bevacizumab (n=692) | 14.7 (n=346) (HR, 0.89; 95% CI, 0.74–1.06; $p$=0.18) | 14.0 (n=346) | NA |
| Our institution (n=12)+selective adjuvant RTx+adjuvant PARPi | 43.8 (n=12) (not reached) | NA | NA |

PFS, progression-free survival; d-d, dose-dense; JGOG, Japanese Gynecologic Oncology Group; HR, hazard ratio; CI, confidence interval; NA, not available; MITO, Multicentre Italian Trials in Ovarian Cancer; ICON, International Collaborative Ovarian Neoplasm; GOG, Gynecologic Oncology Group; RTx, radiation therapy; PARPi, poly(ADP-ribose) polymerase inhibitors.

differences and suggest that weekly dose-dense paclitaxel treatment could be a potentially viable first-line option in East Asian populations. Based on this evidence, our institution adopted the dose-dense weekly paclitaxel-carboplatin regimen for 12 patients with advanced HGSOC. The main treatment-related toxicities were bone marrow suppression, alopecia, and peripheral neuropathy. Hematologic toxicity, particularly leukopenia, was effectively managed with proactive use of hematopoietic growth factors such as G-CSF and GM-CSF. These agents stimulate hematopoietic stem cells and enhance neutrophil production, preventing severe neutropenia and reducing the risk of sepsis. Regarding peripheral neuropathy, eight patients (66.7%) experienced grade 1–2 symptoms, which were tolerable and did not require pharmacologic intervention. Two patients (grade 3) reported persistent neuropathy requiring pharmacologic management.

A variety of targeted therapies is being developed to improve survival and response rates in patients with advanced ovarian cancer. Among these, PARP inhibitors have been extensively studied. Clinical trials have demonstrated that PARP inhibitors significantly improve survival outcomes and treatment response [16,17,24], and they are now established as standard maintenance therapy for patients with advanced ovarian cancer [25,26]. The recognition of *BRCA1* and *BRCA2* mutations and HRD as key molecular vulnerabilities has served as the foundation for introducing PARP inhibitors into frontline treatment [27]. Analyses from The Cancer Genome Atlas reveal that HRD occurs in roughly 50% of epithelial ovarian cancer, underscoring its clinical relevance for targeted therapies [28]. PARP inhibition leads to the accumulation of DNA damage, and cells with *BRCA* mutations or HRD are unable to repair these lesions, ultimately leading to cell death—a phenomenon known as synthetic lethality [29]. The PARP inhibitors olaparib, niraparib, and rucaparib are currently approved and have demonstrated efficacy in both frontline and recurrent ovarian cancer settings. Maintenance therapy with these agents has been shown in key clinical trials to markedly prolong PFS. For patients with *BRCA*-mutated advanced ovarian cancer, the SOLO1 study reported that olaparib reduced the risk of progression or death by about 70% compared with placebo (HR, 0.30; 95% CI, 0.23–0.41). In the PRIMA trial, niraparib extended PFS in the overall population regardless of biomarker status, with an HR of 0.62 (95% CI, 0.50–0.76) versus placebo. PARP inhibitors are considered manageable in terms of safety, even though a modest rise in serious adverse events has been observed. Common adverse effects include anemia, neutropenia, fatigue, vomiting, and nausea, typically mild to moderate in severity. The risk of myelodysplastic syndrome and acute myeloid leukemia appears low and is observed primarily in recurrent disease [26]. Further study is warranted to monitor long-term safety, including myelosuppression and secondary malignancies [30]. In the present study, PARP inhibitors included niraparib in nine patients and olaparib in three. *BRCA* mutations were detected in six of the 12 patients. Among the four recurrent patients, *BRCA* mutations were present in two. PARP inhibitor-related side effects were minimal and tolerable in our cohort.

Complete tumor resection is often unfeasible, especially in cases with lymph node metastases that are unresectable during PDS. In such situations, adjuvant therapies including chemotherapy, targeted therapy, and radiotherapy should be considered. Adjuvant radiotherapy can serve as an alternative to surgical resection for distant metastatic lymph nodes that are unresectable, such as upper para-aortic, intrathoracic, and cervical lymph nodes [12,14,15]. Advances in radiotherapy techniques allow precise targeting of metastatic lymph nodes while sparing uninvolved tissue, potentially preventing locoregional recurrence [14,31]. Selective adjuvant radiotherapy before PARP inhibitor maintenance may help reduce recurrence. PET-CT is essential for accurate identification of metastatic lymph nodes. From a molecular perspective, even when complete response is observed on imaging, microscopic residual disease may persist, supporting the rationale for radiotherapy [13,14]. At our institution, five of nine patients with stage IVB disease received initial adjuvant radiotherapy targeting metastatic lymph nodes. Among these, two experienced recurrence—but all recurrences occurred outside the irradiated fields. These findings suggest potential efficacy of adjuvant radiotherapy for unresectable nodal metastases and support its possible role as a future standard modality. Current advanced radiotherapy allows effective disease control while sparing healthy tissue. All four patients who experienced recurrence are currently alive and in a NED state following second-line treatment. Salvage therapy included surgery (n=1), radiotherapy (n=2), and chemotherapy (n=1), with ongoing systemic therapy.

This study has several limitations. First, as a retrospective, single-institution study, it is subject to inherent bias, including selection and information biases. Second, the small sample size of only 12 patients may limit generalizability. Third, the median follow-up less than 48.1 months may be insufficient to capture long-term outcomes and late complications. Last, the absence of a control group restricts causal inference. Despite these limitations, this study offers valuable insights. Expanding the cohort and increasing the sample size could produce statistically robust results.

A sequential treatment strategy combining optimal cytoreductive surgery, dose-dense chemotherapy, selective radiotherapy, and PARP inhibitor maintenance resulted in favorable outcomes in advanced HGSOC. All patients achieved complete remission, with a median PFS of 43.8 months and no in-field recurrences. While limited by sample size and follow-up duration, these preliminary findings suggest the potential value of this approach and merit further prospective validation.

## Article information

### Conflicts of interest

No potential conflict of interest relevant to this article was reported.

### Funding

This study was supported by a grant from Kosin University College of Medicine (2025).

### Author contributions

Conceptualization: ETK, WGK. Data curation: ETK, SYM, WGK. Formal analysis: ETK, WGK. Funding acquisition: ETK. Investigation: SYM. Methodology: ETK, WGK. Project administration: ETK, WGK. Resources: WGK, DHK. Software: ETK. Supervision: TKK, THL. Validation: WGK. Visualization: ETK. Writing-original draft: ETK, WGK. Writing-review & editing: all authors. All authors have read and approved the final manuscript.

### ORCID

Eun Taeg Kim, https://orcid.org/0000-0002-2754-2657
Sun Young Ma, https://orcid.org/0000-0002-4288-1139
Tae Kyoung Kang, https://orcid.org/0009-0006-2940-0974
Tae Hwa Lee, https://orcid.org/0000-0002-1912-9694
Dong Hwi Kim, https://orcid.org/0009-0008-7172-0888
Won Gyu Kim, https://orcid.org/0009-0008-6991-9054

## References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2024;74:229–63.
2. Torre LA, Trabert B, DeSantis CE, Miller KD, Samimi G, Runowicz CD, et al. Ovarian cancer statistics, 2018. CA Cancer J Clin 2018;68:284–96.
3. Mahmood RD, Morgan RD, Edmondson RJ, Clamp AR, Jayson GC. First-line management of advanced high-grade serous ovarian cancer. Curr Oncol Rep 2020;22:64.
4. Katsumata N, Yasuda M, Isonishi S, Takahashi F, Michimae H, Kimura E, et al. Long-term results of dose-dense paclitaxel and carboplatin versus conventional paclitaxel and carboplatin for treatment of advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (JGOG 3016): a randomised, controlled, open-label trial. Lancet Oncol 2013;14:1020–6.
5. Chan JK, Brady MF, Penson RT, Huang H, Birrer MJ, Walker JL, et al. Weekly vs. every-3-week paclitaxel and carboplatin for ovarian cancer. N Engl J Med 2016;374:738–48.
6. Clamp AR, James EC, McNeish IA, Dean A, Kim JW, O'Donnell DM, et al. Weekly dose-dense chemotherapy in first-line epithelial ovarian, fallopian tube, or primary peritoneal carcinoma treatment (ICON8): primary progression free survival analysis results from a GCIG phase 3 randomised controlled trial. Lancet 2019;394:2084–95.
7. Pignata S, Scambia G, Katsaros D, Gallo C, Pujade-Lauraine E, De Placido S, et al. Carboplatin plus paclitaxel once a week versus every 3 weeks in patients with advanced ovarian cancer (MITO-7): a randomised, multicentre, open-label, phase 3 trial. Lancet Oncol 2014;15:396–405.
8. Yamaguchi H, Hishinuma T, Endo N, Tsukamoto H, Kishikawa Y, Sato M, et al. Genetic variation in ABCB1 influences paclitaxel pharmacokinetics in Japanese patients with ovarian cancer. Int J Gynecol Cancer 2006;16:979–85.
9. Dai D, Zeldin DC, Blaisdell JA, Chanas B, Coulter SJ, Ghanayem BI, et al. Polymorphisms in human CYP2C8 decrease metabolism of the anticancer drug paclitaxel and arachidonic acid. Pharmacogenetics 2001;11:597–607.
10. Marchetti C, De Felice F, Musella A, Palaia I, Monti M, Musio D, et al. Weekly versus three weeks chemotherapy for advanced

ovarian cancer: a meta-analysis. Oncotarget 2016;7:58709–15.
11. Kim J, Mizuno F, Matsushita T, Matsushita M, Aoto S, Ishiya K, et al. Genetic analysis of a Yayoi individual from the Doigahama site provides insights into the origins of immigrants to the Japanese Archipelago. J Hum Genet 2025;70:47–57.
12. Hata M, Miyagi E, Koike I, Numazaki R, Asai-Sato M, Kasuya T, et al. Radiation therapy for para-aortic lymph node metastasis from uterine cervical cancer. Anticancer Res 2015;35:4849–54.
13. Macchia G, Titone F, Restaino S, Arcieri M, Pellecchia G, Andreetta C, et al. Is it time to reassess the role of radiotherapy treatment in ovarian cancer? Healthcare (Basel) 2023;11:2413.
14. Shaikh T, Churilla TM, Mantia-Smaldone GM, Chu C, Rubin SC, Anderson PR. The role of adjuvant radiation in lymph node positive endometrial adenocarcinoma. Gynecol Oncol 2016;141:434–9.
15. Kim ET, Oh SY, Ma SY, Lee TH, Kim WG. Selective adjuvant radiation therapy for distant lymph node metastasis in patients with stage 4B epithelial ovarian cancer: a case series. KMJ 2023;38:293–9.
16. Gonzalez-Martin A, Pothuri B, Vergote I, DePont Christensen R, Graybill W, Mirza MR, et al. Niraparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med 2019;381:2391–402.
17. Moore K, Colombo N, Scambia G, Kim BG, Oaknin A, Friedlander M, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med 2018;379:2495–505.
18. DiSilvestro P, Banerjee S, Colombo N, Scambia G, Kim BG, Oaknin A, et al. Overall survival with maintenance olaparib at a 7-year follow-up in patients with newly diagnosed advanced ovarian cancer and a BRCA mutation: the SOLO1/GOG 3004 trial. J Clin Oncol 2023;41:609–17.
19. Monk BJ, Barretina-Ginesta MP, Pothuri B, Vergote I, Graybill W, Mirza MR, et al. Niraparib first-line maintenance therapy in patients with newly diagnosed advanced ovarian cancer: final overall survival results from the PRIMA/ENGOT-OV26/GOG-3012 trial. Ann Oncol 2024;35:981–92.
20. Chang SJ, Hodeib M, Chang J, Bristow RE. Survival impact of complete cytoreduction to no gross residual disease for advanced-stage ovarian cancer: a meta-analysis. Gynecol Oncol 2013;130:493–8.
21. Fago-Olsen CL, Ottesen B, Kehlet H, Antonsen SL, Christensen IJ, Markauskas A, et al. Does neoadjuvant chemotherapy impair long-term survival for ovarian cancer patients?: a nationwide Danish study. Gynecol Oncol 2014;132:292–8.
22. Mueller JJ, Zhou QC, Iasonos A, O'Cearbhaill RE, Alvi FA, El Haraki A, et al. Neoadjuvant chemotherapy and primary debulking surgery utilization for advanced-stage ovarian cancer at a comprehensive cancer center. Gynecol Oncol 2016;140:436–42.
23. Vergote I, Trope CG, Amant F, Kristensen GB, Ehlen T, Johnson N, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N Engl J Med 2010;363:943–53.
24. Monk BJ, Parkinson C, Lim MC, O'Malley DM, Oaknin A, Wilson MK, et al. A randomized, phase III trial to evaluate rucaparib monotherapy as maintenance treatment in patients with newly diagnosed ovarian cancer (ATHENA-MONO/GOG-3020/ENGOT-ov45). J Clin Oncol 2022;40:3952–64.
25. Baradacs I, Teutsch B, Varadi A, Bila A, Vincze A, Hegyi P, et al. PARP inhibitor era in ovarian cancer treatment: a systematic review and meta-analysis of randomized controlled trials. J Ovarian Res 2024;17:53.
26. Hao J, Liu Y, Zhang T, He J, Zhao H, An R, et al. Efficacy and safety of PARP inhibitors in the treatment of advanced ovarian cancer: an updated systematic review and meta-analysis of randomized controlled trials. Crit Rev Oncol Hematol 2021;157:103145.
27. Ray-Coquard I, Pautier P, Pignata S, Perol D, Gonzalez-Martin A, Berger R, et al. Olaparib plus bevacizumab as first-line maintenance in ovarian cancer. N Engl J Med 2019;381:2416–28.
28. Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. Nature 2011;474:609–15.
29. Farmer H, McCabe N, Lord CJ, Tutt AN, Johnson DA, Richardson TB, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature 2005;434:917–21.
30. Morice PM, Leary A, Dolladille C, Chretien B, Poulain L, Gonzalez-Martin A, et al. Myelodysplastic syndrome and acute myeloid leukaemia in patients treated with PARP inhibitors: a safety meta-analysis of randomised controlled trials and a retrospective study of the WHO pharmacovigilance database. Lancet Haematol 2021;8:e122–34.
31. Rutten MJ, van de Vrie R, Bruining A, Spijkerboer AM, Mol BW, Kenter GG, et al. Predicting surgical outcome in patients with International Federation of Gynecology and Obstetrics stage III or IV ovarian cancer using computed tomography: a systematic review of prediction models. Int J Gynecol Cancer 2015;25:407–15.

Original article

Kosin Medical Journal 2026;41(1):46-57
pISSN: 2005-9531 • eISSN: 2586-7024
https://doi.org/10.7180/kmj.25.132

KMJ
KOSIN MEDICAL JOURNAL

# Association of allergen sensitization and air pollution in childhood asthma and allergic rhinitis: a single-center study

**Sunbok Suh, Hyungsu Kim**

*Department of Pediatrics, Busan Medical Center, Busan, Korea*

**Background:** Ambient air pollution has been linked to the increasing prevalence of allergic diseases in children. Exposure to air pollution increases the incidence of asthma and allergic rhinitis and is also known to be associated with inhalant allergen sensitization.
**Methods:** From 2011 to 2024, we retrospectively analyzed the medical records of 313 children in Busan, Korea, with asthma and allergic rhinitis who underwent allergen testing for house dust mites (*Dermatophagoides pteronyssinus*, *D. farinae*), animal dander, tree pollen, grass pollen, weed pollen, mold (Alternaria alternata), and cockroach. Ambient air pollutant concentrations of $O_3$, $SO_2$, CO, $NO_2$, particulate matter (PM) ≤10 μm ($PM_{10}$) and PM ≤2.5 μm ($PM_{2.5}$) were obtained from measurement sites located near the residences of the study subjects.
**Results:** Among the 313 subjects, 94 had asthma, 137 had allergic rhinitis, and 82 had combined asthma and allergic rhinitis. In children who experienced allergic rhinitis symptoms, changes in $PM_{10}$, $PM_{2.5}$, maximum $SO_2$ concentration, and maximum $NO_2$ concentration showed positive correlations (correlation coefficients, 0.60, 0.56, 0.64, and 0.49, respectively). In cases of allergic rhinitis accompanied by inhalant allergen sensitization, changes in $PM_{10}$, $PM_{2.5}$, CO, $NO_2$, maximum $SO_2$ concentration, maximum CO concentration, and maximum $NO_2$ concentration also showed positive correlations (correlation coefficients, 0.64, 0.60, 0.56, 0.49, 0.52, 0.71, and 0.60, respectively).
**Conclusions:** In this study, several air pollutants were associated with allergic rhinitis symptoms in children residing in Busan, and a broader range of air pollutants was associated with allergic rhinitis accompanied by inhalant allergen sensitization.

**Keywords:** Air pollution; Allergic rhinitis; Asthma; Child; Hypersensitivity

## Introduction

Air pollution is increasing worldwide due to urbanization and industrialization. As a result, the prevalence rate of allergic diseases, including asthma and allergic rhinitis, are increasing, and the association of air pollution is constantly being suggested and are emerging as a social and environmental problem [1,2]. Air pollutants related to allergic diseases can be divided into indoor and outdoor, and indoor pollutants include particulate matter (PM), molds, and house dust mites, while outdoor pollutants include $O_3$, $SO_2$, CO, $NO_2$, PM ≤10 μm ($PM_{10}$), and fine PM ≤2.5 μm ($PM_{2.5}$), which are representative air pollutants. It has been recently hypothesized that these air pollutants accumulate oxidative

**Received:** October 9, 2025; **Revised:** December 1, 2025; **Accepted:** December 16, 2025
**Corresponding Author:** Hyungsu Kim, MD
Department of Pediatrics, Busan Medical Center, 359 World cup-daero, Yeonje-gu, Busan 47527, Korea
Tel: +82-51-607-2216 Fax: +82-51-507-3001 E-mail: h660216@hanmail.net

© 2026 Kosin University College of Medicine
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

stress in tissues and induce tissue inflammation and cell death, ultimately causing allergic diseases. It is also known that this oxidative stress causes immunological changes, leading to changes in Th2 and Th17 inflammation, and that air pollutants act as adjuvants of immunity, producing immunoglobulin E (IgE) and Th2 cytokines, thereby increasing allergen sensitization [3,4]. Additionally, exposure to air pollutants is known to increase the risk of allergen sensitization as well as the induction of allergic diseases. However, there are research results that suggest that air pollutants may contribute to the development of allergic diseases through mechanisms other than allergen sensitization, such as greater effects in nonatopic individuals or reports of increased incidence of allergic diseases unrelated to inhalant allergen sensitization [5,6].

In children, the lungs are not yet fully developed, so they are easily damaged and recover incompletely. In addition, since they generally breathe through their mouths, the rate of air pollutants filtered through the nose is low. Since the respiratory rate is high relative to body weight, more exposure is made to the lungs, and since the immune system is immature, respiratory infections easily occur, and these damages can progress to asthma [7,8]. Although numerous reports have reported the association between air pollutants and allergic diseases [9-11], there are not many studies that objectively evaluated the association between air pollutants, allergic diseases and allergen sensitization in children.

Busan is the second largest city in South Korea and has both fixed and mobile sources of air pollution, such as automobile exhaust fumes, small and medium-sized factories in the industrial complex in the western Busan area, and many ships in the northern and new ports. In addition, the climate has both warm and humid oceanic climate and humid continental climate characteristics [12].

This study investigated the sensitization rate of inhalant allergens and local air pollutants concentrations in the Busan city, analyzed trends, and identified the children's air pollution exposure based on the results of daily average and peak air pollutants concentrations measured at measuring stations near their residences. Furthermore, the association between air pollutants concentrations and asthma, allergic rhinitis, and the coexistence of these two conditions was examined, and the impact of coexisting inhalant allergen sensitization was assessed.

## Methods

**Ethical statements:** This study was approved by the Busan Medical Center Institutional Review Board (IRB No. 2025-01-002). The requirements for patient consent were waived because this study was a retrospective chart review study in which there are minimal risks to subjects.

### 1. Subjects

This study retrospectively analyzed children under 18 years of age who visited the Department of Pediatrics, Busan Medical Center, from January 2011 to December 2024, were treated for asthma and allergic rhinitis in the outpatient or emergency room, and underwent allergen-specific IgE testing (ImmunoCAP; Thermo Fisher Scientific). Age groups were divided into preschool (age 7 years and younger) and school-age (age 8 years and older). In order to conduct a relatively accurate assessment of exposure to air pollution in selecting the subject children, the subject children were children living within a 2 km radius of 32 air pollution measurement stations of the Busan Metropolitan City Health and Environment Research Institute. And the subject children were children who lived within 3 years prior to the diagnosis of asthma and allergic rhinitis and for 1 year after the diagnosis.

### 2. Serum allergen-specific immunoglobulin E test

Serum allergen-specific IgE was measured using the ImmunoCAP assay. The ImmunoCAP assay analyzed the results of eight major inhalant allergens: house dust mites (*Dermatophagoides pteronyssinus* [Dp], *D. farinae* [Df]), cat dander, tree pollen, grass pollen, weed pollen, mold (*Alternaria alternata*), and cockroach. In distinguishing between indoor and outdoor allergens, indoor allergens included house dust mites, cat epithelium, cockroach, outdoor antigens included tree pollen, grass pollen, weed pollen and molds were considered common allergens. Sensitization was defined as an antibody level of 0.35 kUA/L or higher for each inhalant allergen using the ImmunoCAP assay.

### 3. Diagnosis and diagnostic criteria for asthma and allergic rhinitis

We collected and analyzed information on the diagnoses of the children through the medical records. These diagnoses were assigned by pediatricians while treating the children,

in accordance with the International Classification of Diseases (11th revision, Clinical Modification). Asthma was defined as a case in which the patient had typical asthma symptoms (wheezing, dyspnea, chronic cough, etc.) and the forced expiratory volume in 1 second ($FEV_1$) increased by 12% or more in a bronchodilator response test or the concentration causing a 20% decrease in $FEV_1$ was 16 mg/mL or less in a methacholine provocation test [13]. In cases where bronchodilator response testing and bronchial provocation testing could not be performed, asthma was defined as a diagnosis of asthma or recurrent wheezing by a physician with two or more typical asthma symptoms or a response to bronchodilator inhalation therapy [14]. Acute asthma exacerbation was defined as a case in which hospitalization or an emergency room visit was made due to asthma symptoms. Allergic rhinitis was defined as prevalence of symptoms when characteristic clinical symptoms such as recurrent rhinorrhea, nasal congestion, sneezing, conjunctival injection, and itching were present in the medical history, and allergic rhinitis was diagnosed when a positive reaction to one or more inhalant allergens was confirmed in the ImmunoCAP test [15].

#### 4. The concentration of air pollutants

The average daily concentration and maximum daily concentration of each air pollutant on the day of diagnosis and treatment of asthma and allergic rhinitis in the subject children were identified. Data on air pollutant concentrations were collected from the Busan Metropolitan City Health and Environment Research Institute, using the values from the monitoring stations closest to the subject's residence [16]. Pollutants included $PM_{10}$ (PM with a median aerodynamic diameter less than or equal to 10 μm in diameter, $\mu g/m^3$), $PM_{2.5}$ (PM<2.5 μm, $\mu g/m^3$), $SO_2$ (ppm), $NO_2$ (ppm), $O_3$ (ppm), and CO (ppm). The measurement methods used were beta-ray absorption for $PM_{10}$ ($\mu g/m^3$), ion chromatography for $PM_{2.5}$ ($\mu g/m^3$), ultraviolet fluorescence for $SO_2$ (ppm), chemiluminescence for $NO_2$ (ppm), ultraviolet photometry for $O_3$ (ppm), and nondispersive infrared for CO (ppm).

#### 5. Statistical analysis

Categorical variables were expressed as frequency (%), and continuous data were expressed as mean and standard deviation. Statistical analysis was performed using IBM SPSS ver. 25.0 (IBM Corp.), and *p*-value less than 0.05 was considered statistically significant. The prevalence of asthma, allergic rhinitis and allergen sensitization was calculated by year. Comparison of allergen sensitization by age group was performed using a paired sample t-test, and differences in air pollution concentrations by season were analyzed using a one-way analysis of variance. Comparisons between indoor and outdoor allergen sensitization in asthma and allergic rhinitis were performed using cross tabulation analysis. Changes in inhalant allergen sensitization rates and air pollution concentrations by year were analyzed using linear regression analysis. The correlations between the prevalence of asthma, allergic rhinitis, and combined cases of asthma plus allergic rhinitis and air pollution, as well as the presence or absence of inhalant allergen sensitization in asthma and allergic rhinitis, were tested using Spearman correlation coefficient.

Logistic regression analysis was performed to determine air pollutants odds ratio (OR) of each allergic diseases (allergic rhinitis, asthma, allergic rhinitis with asthma, allergic rhinitis with aeroallergen sensitization, asthma with aeroallergen sensitization). The OR and 95% confidence interval (CI) were calculated. All ORs were statistically processed as results according to the increase in the interquartile range of air pollution concentration. A model was used that adjusted for confounding variables such as age, sex, season.

## Results

#### 1. Characteristics of the subjects

A total of 313 patients were analyzed, of which 192 (60.4%) were male. Allergic rhinitis was the most common disease, with 137 patients (44%), followed by asthma 94 patients (30%), and combined asthma and allergic rhinitis 82 patients (26%). The mean age was 9.96±4.78 years. The preschool age group comprised 97 patients (30.5%) and the school-age group comprised 216 patients (67.9%). In the preschool group, allergic rhinitis was the predominant disease, with 49 patients (50.5%) having allergic rhinitis and 29 patients (29.9%) having combined asthma and allergic rhinitis. In the school-age group, allergic rhinitis was the predominant disease, with 88 patients (40.7%) having allergic rhinitis and 75 patients (34.7%) having asthma. In bronchial asthma, allergic rhinitis, and combined asthma and allergic rhinitis, the indoor allergen sensitization rate was higher

than the outdoor allergen sensitization rate (27.7%, 38.5% and 33.8% vs. 75.0%, 25.0%, and 0%). Asthma showed the highest rate of outdoor allergen sensitization (75.0%), while allergic rhinitis showed the highest rate of indoor allergen sensitization (38.5%), but the difference was not statistically significant ($p$=0.199). In cases where indoor and outdoor sensitization were concurrent, the sensitization rates for asthma and allergic rhinitis were similar (25% and 29%) (Table 1). During the study period, the number of sensitized patients, prevalence rate of allergic rhinitis and bronchial asthma tended to increase, and the age also tended to increase (Table 2).

### 2. Changes in allergen sensitization by age and year

The highest sensitization rate across all patients was to house dust mites, with Dp at 58% and Df at 61%. The next highest sensitization rate was to animal danders, at 21.4%, followed by tree pollen at 20.8%, cockroach at 9.2%, weed pollen at 7.3%, grass pollen at 6.4%, and mold at 3.5%. Next, we analyzed changes in sensitization rates between 2011 and 2024. Among indoor allergens, sensitization rates for Dp increased from 23.8% to 57%, and for animal danders and mold increased from 4.7%, 0% to 23.8%, 1.6%, respectively. Cockroach remained unchanged at 4.7% and 4.7% ($p$>0.05). Outdoor allergens increased from 4.7% to 25.3% for tree pollen, from 0% to 3.1% for grass pollen, and from 0% to 7.9% for weed pollen ($p$>0.05) (Fig. 1A). Looking at

**Table 1.** Characteristics of subjects

| Variable | BA (n=94) | AR[a] (n=137) | BA+AR (n=82) |
|---|---|---|---|
| Mean age (yr) | 9.40±5.18 | 11.47±4.34 | 9.17±4.16 |
| Sex (male:female) | 51:43 | 91:46 | 50:32 |
| Age (yr) | | | |
| 0–7 | 19 (19.6) | 49 (50.5) | 29 (29.9) |
| 8–18 | 75 (34.7) | 88 (40.7) | 53 (24.5) |
| Aeroallergen sensitization | | | |
| Outdoor allergen[b] | 6 (75.0) | 2 (25.0) | 0 |
| Indoor allergen[c] | 36 (27.7) | 50 (38.5) | 44 (33.8) |
| Mixed allergen | 25 (36.2) | 29 (42.0) | 15 (21.7) |

Values are presented as mean±standard deviation or number (%). Percentages represent the proportion within each row.
BA, bronchial asthma only; AR, allergic rhinitis only; BA+AR, coexisting asthma and allergic rhinitis.
[a]AR includes allergic rhinitis symptom within 12 months plus allergic rhinitis with aeroallergen sensitization.
[b]Outdoor allergens include tree pollen, grass pollen, weed pollen, molds.
[c]Indoor allergens include house dust mites, cat epithelium, cockroach, molds.

**Table 2.** Number and prevalence rate of childhood asthma and allergic rhinitis in each year

| Variable | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | 2021 | 2022 | 2023 | 2024 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No. of subjects | 21 | 8 | 11 | 21 | 17 | 22 | 11 | 20 | 32 | 5 | 17 | 19 | 39 | 70 |
| No. of sensitizations | 5 | 4 | 10 | 13 | 12 | 16 | 5 | 15 | 23 | 4 | 15 | 16 | 28 | 48 |
| Age (yr), mean±SD | 6.29±4.75 | 6.25±4.2 | 8.09±6.02 | 5.57±4.33 | 9.71±4.71 | 11.27±4.93 | 10.73±3.95 | 9.85±5.14 | 10.0±4.72 | 9.8±2.77 | 12.65±3.24 | 10.42±3.85 | 10.87±5.19 | 11.38±3.81 |
| BA (%) | 19 | 25 | 45 | 10 | 41 | 32 | 9 | 30 | 25 | 20 | 35 | 42 | 36 | 75 |
| BA+AR (%) | 33 | 50 | 27 | 14 | 29 | 36 | 36 | 40 | 22 | 40 | 18 | 11 | 15 | 44 |
| AR (%) | 48 | 25 | 27 | 76 | 29 | 32 | 55 | 30 | 53 | 40 | 47 | 47 | 49 | 81 |

SD, standard deviation; BA, bronchial asthma only; AR, allergic rhinitis only; BA+AR, coexisting asthma and allergic rhinitis.

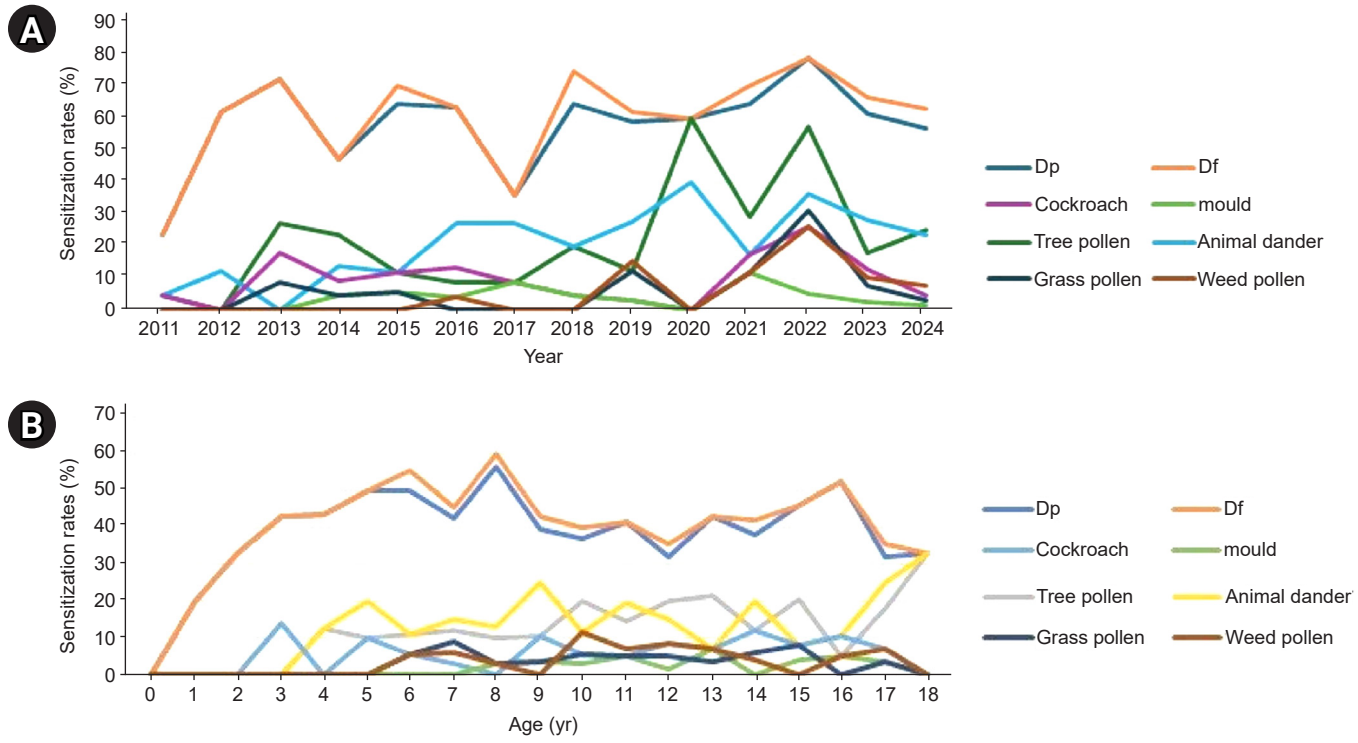


**Fig. 1.** (A) Changes of allergen sensitization rates from 2011 to 2024 in children with asthma and allergic rhinitis. (B) Changes in allergen sensitization rate according to age in children with asthma and allergic rhinitis. Linear regression analysis showed no significant ($p$>0.05). Dp, *Dermatophagoides pteronyssinus*; Df, *D. farinae*.

the changes in allergen sensitization by age, tree pollen increased from 5.7% in preschool children to 17% in school-age children, animal danders increased from 7.4% in preschool children to 17.2% in school-age children, mold increased from 0% in preschool children to 3.3% in school-age children, and weed allergen increased from 1.4% in preschool children to 4.9% in school-age children ($p$<0.05) (Fig. 1B).

### 3. Annual changes in the concentrations of the air pollutants

Examining the changes in daily average concentrations of air pollutants in Busan from 2011 to 2024, $O_3$ concentrations increased by 30% from 0.021 ppm in 2011 to 0.03 ppm in 2024 ($p$=0.477). $NO_2$, $SO_2$, and CO concentrations decreased by 33%, 60%, and 33%, respectively, from 0.031 ppm, 0.0071 ppm, and 0.524 ppm in 2011 to 0.017 ppm, 0.0028 ppm, and 0.328 ppm in 2024 ($p$=0.93, $p$=0.025, $p$=0.72). The changes in the maximum daily average concentration of air pollutants for $O_3$, $NO_2$ increased by 19%, 34%, respectively, from 0.072 ppm, 0.055 ppm in 2011 to 0.088 ppm, 0.083 ppm in 2024 ($p$=0.08, $p$=0.02). But, the changes in the maximum daily average concentration of air pollutants for $SO_2$, CO decreased by 58%, 33%, respectively, from 0.026 ppm, 1.325 ppm in 2011 to 0.011 ppm, 0.888 ppm in 2024 ($p$=0.94, $p$=0.34) (Fig. 2A). $PM_{10}$, $PM_{2.5}$, maximal $PM_{10}$, and maximal $PM_{2.5}$ showed a decrease of 44%, 47%, 48%, and 40% from 50 μg/m$^3$, 26 μg/m$^3$, 157.6 μg/m$^3$, and 68.2 μg/m$^3$ in 2011 to 28 μg/m$^3$, 14 μg/m$^3$, 83.2 μg/m$^3$, and 41 μg/m$^3$ in 2024, respectively ($p$>0.05) (Fig. 2B). When looking at changes in the concentration of air pollutants by season, it was confirmed that the concentration of air pollutants decreased in summer and fall, but the prevalence of diseases did not show a significant difference by season ($p$=0.21, $p$=0.19) (Fig. 3). Each air pollutant concentration satisfied the Busan regional environmental standards ($O_3$, 8-hour 0.06 ppm or less; $NO_2$, annual average 0.03 ppm or less; $SO_2$, annual average 0.01 ppm or less; CO, annual average 8 ppm or less; $PM_{10}$, annual average 50 μg/m$^3$ or less; $PM_{2.5}$, annual average 15 μg/m$^3$ or less). $PM_{2.5}$ was found to exceed the Busan

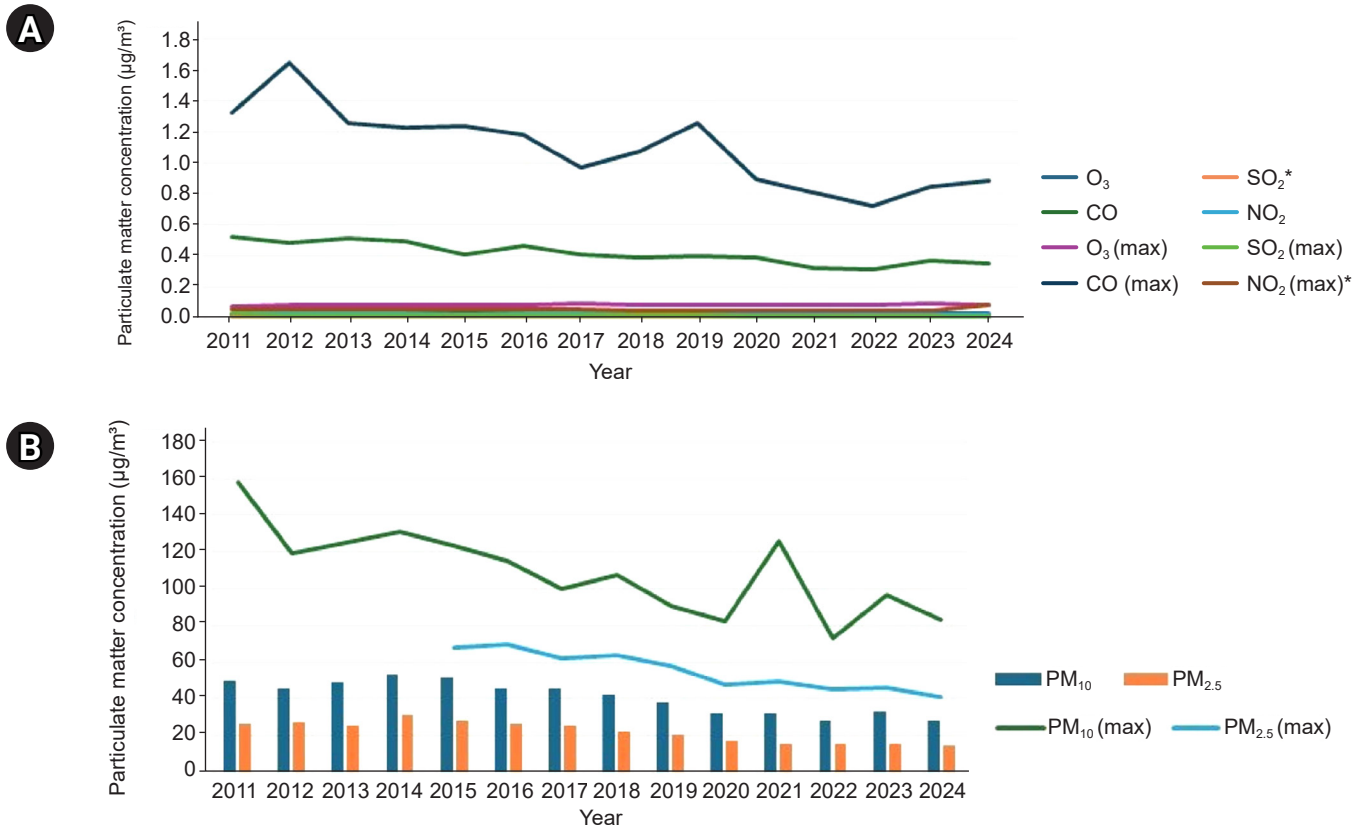


**Fig. 2.** (A) Variations in annual average and maximal concentrations of air pollutants during 2011–2024. (B) Variations in annual average and maximal concentrations of $PM_{10}$ and $PM_{2.5}$ during 2011–2024. Linear regression analysis showed statistical significance (*$p$<0.05). $PM_{10}$, particulate matter; $PM_{2.5}$, fine particulate matter.

regional environmental standards (annual average of 15 μg/m$^3$).

**4. Association between air pollutants, allergic diseases and allergen sensitization**

In cases of allergic rhinitis and asthma alone, no association was observed with changes in the concentration of air pollutants. However, in cases of combined asthma and allergic rhinitis, positive correlations were observed with daily average $SO_2$ and CO concentrations, with correlation coefficients of 0.72 and 0.64, respectively ($p$<0.05) (Fig. 4). The frequency of acute asthma exacerbations was positively correlated with maximal $SO_2$ and $NO_2$ concentrations, with correlation coefficients of 0.76 and 0.61, respectively ($p$<0.05) (Fig. 5).

The prevalence of allergic rhinitis symptoms and changes in $PM_{10}$, $PM_{2.5}$, maximal $NO_2$, and maximal $SO_2$ concentrations showed statistically significant positive correlations, with correlation coefficients of 0.60, 0.56, 0.49, and 0.64, respectively ($p$<0.05). In allergic rhinitis accompanied by inhalant allergen sensitization, statistically significant positive correlations were observed with $PM_{10}$, $PM_{2.5}$, $NO_2$, CO, maximal $SO_2$ concentration, maximal CO concentration, and maximal $NO_2$ concentration at 0.64, 0.60, 0.49, 0.56, 0.52, 0.71, and 0.60, respectively ($p$<0.05). In the case of asthma without inhalant allergen sensitization, a positive correlation was observed with maximal $NO_2$ concentration with a correlation coefficient of 0.71 ($p$<0.05) (Table 3).

In the logistic regression analysis, $PM_{2.5}$ maximal concentration was found to be associated with the prevalence of allergic rhinitis in this study (OR, 3.86; 95% CI, 1.33–11.23). In cases of asthma with allergic rhinitis, statistically significant association of CO maximal concentration was found (OR,1.57; 95% CI,1.09–2.27). And, in the analysis of the

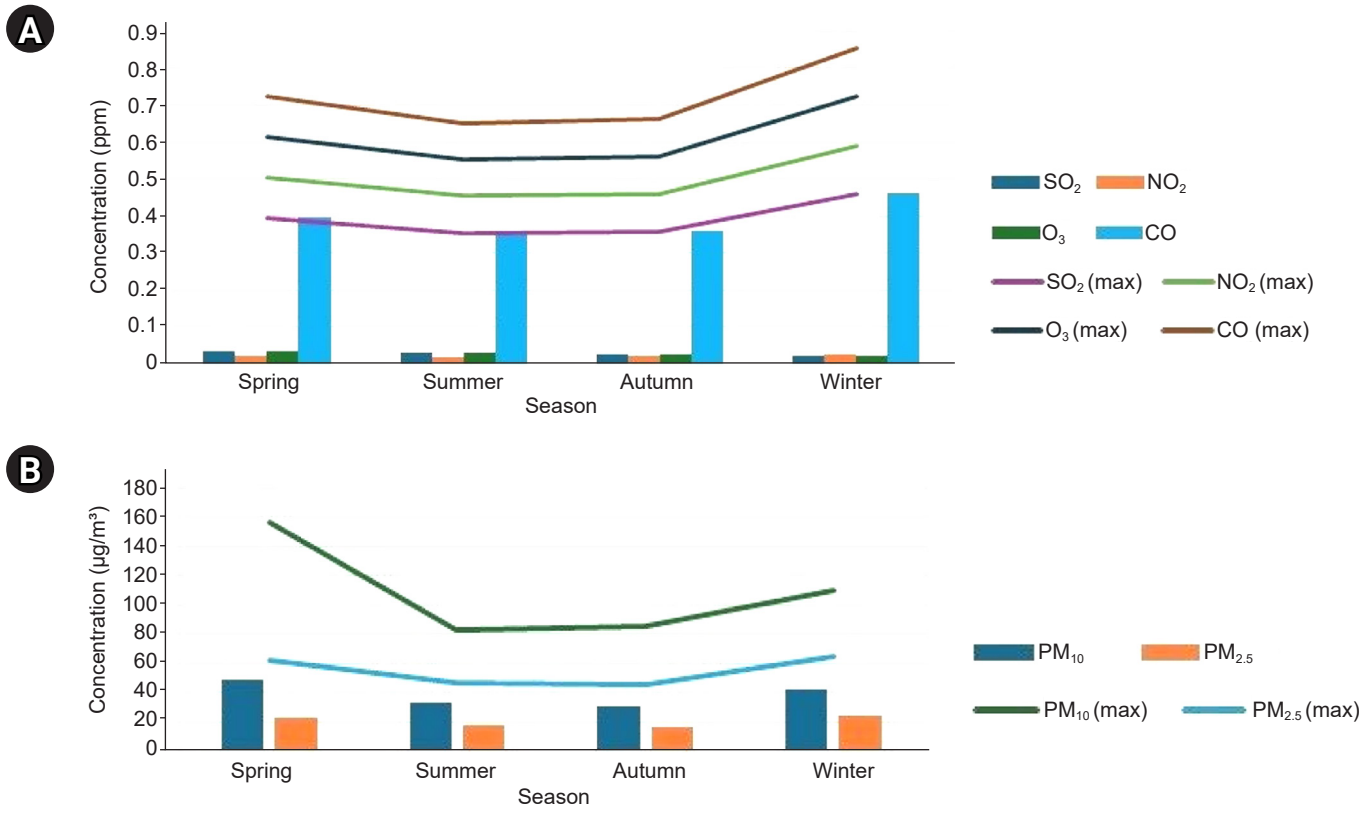


**Fig. 3.** (A, B) Seasonal trends in air pollutant concentrations in Busan. (C) The number of patients with allergic rhinitis and asthma according to season. Chi-square test showed no significant difference ($p$>0.05). $PM_{10}$, particulate matter; $PM_{2.5}$, fine particulate matter.

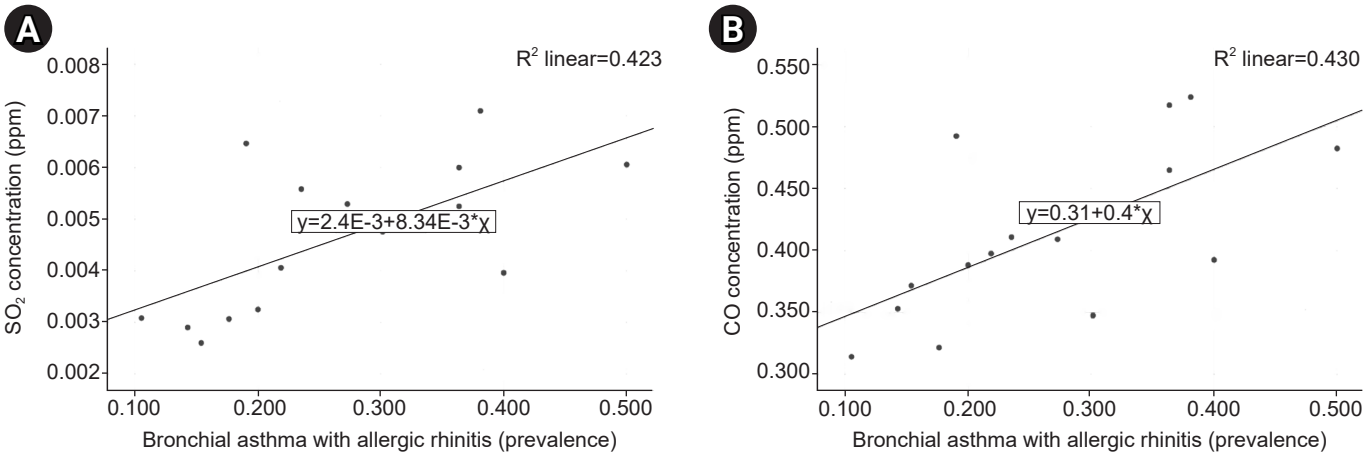


**Fig. 4.** Correlation between the prevalence of combined asthma and allergic rhinitis and air pollutant concentrations. (A) Correlation between maximal $SO_2$ concentration and the prevalence of bronchial asthma with allergic rhinitis ($r$=0.72, $p$<0.05). (B) CO concentration and the prevalence of bronchial asthma with allergic rhinitis ($r$=0.64, $p$<0.05). $r$, correlation coefficient.

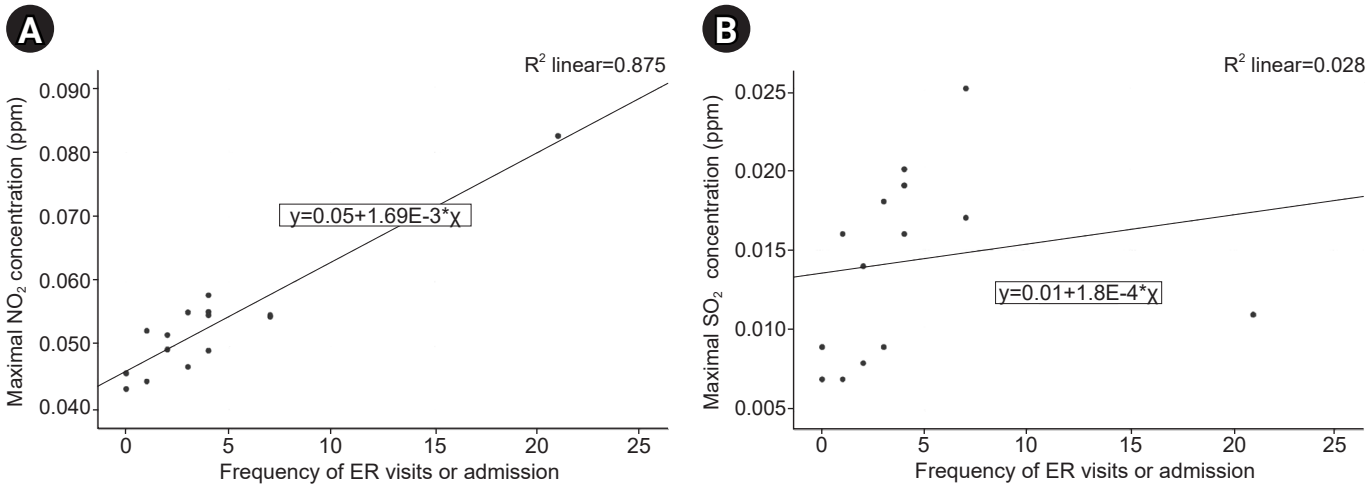


**Fig. 5.** Correlation between air pollutants concentration and frequency of asthma aggravation. (A) Correlation between maximal $NO_2$ concentration and the frequency of ER visits or admissions ($r$=0.76, $p$<0.05). (B) Correlation between maximal $SO_2$ concentration and the frequency of ER visits or admissions ($r$=0.61, $p$<0.05). ER, emergency room; $r$, correlation coefficient.

**Table 3.** Correlations of air pollution in asthma and allergic rhinitis with or without inhalant allergen sensitization

| Variable | Allergic rhinitis[a] (n=84) | | Allergic rhinitis with AAS (n=136) | | Asthma (n=52) | | Asthma with AAS (n=124) | |
|---|---|---|---|---|---|---|---|---|
| | *r* | *p*-value | *r* | *p*-value | *r* | p-value | *r* | *p*-value |
| $PM_{10}$ | 0.60 | 0.010[b] | 0.64 | 0.006[b] | 0.46 | 0.052 | −0.64 | 0.006 |
| $PM_{2.5}$ | 0.56 | 0.016[b] | 0.60 | 0.010[b] | 0.42 | 0.073 | −0.53 | 0.024 |
| CO | 0.46 | 0.052 | 0.56 | 0.016[b] | 0.38 | 0.102 | −0.64 | 0.006 |
| $NO_2$ | 0.46 | 0.052 | 0.49 | 0.036[b] | 0.38 | 0.102 | −0.49 | 0.036 |
| $SO_2$ (max) | 0.64 | 0.008[b] | 0.52 | 0.028[b] | 0.34 | 0.157 | −0.64 | 0.008 |
| CO (max) | 0.46 | 0.052 | 0.71 | 0.002[b] | 0.46 | 0.052 | −0.49 | 0.036 |
| $NO_2$ (max) | 0.49 | 0.036[b] | 0.60 | 0.010[b] | 0.71 | 0.002[b] | −0.46 | 0.052 |

AAS, aeroallergen sensitization; $r$, correlation coefficient; $PM_{10}$, particulate matter ≤10 μm; $PM_{2.5}$, fine particulate matter ≤2.5 μm.
[a]Allergic rhinitis with symptoms within 12 months.
[b]Indicates a statistically significant difference with $p$<0.05.

association between allergic rhinitis with aeroallergen sensitization and $O_3$ maximal concentration, a correlation was shown (OR, 2.25; 95% CI,1.08–4.70) (Table 4).

## Discussion

In allergic diseases, allergen sensitization is a critical factor in disease development, and identifying the causative allergen is crucial for the diagnosis and management of these conditions. This study investigated the sensitization rate to inhalant allergens in children and adolescents with asthma and allergic rhinitis treated at a single center in Busan over a 14-year period from 2011 to 2024, and examined the correlation between air pollutant concentrations in Busan and sensitization rates to inhalant allergens. House dust mites showed the highest sensitization rate throughout the study period and remained at a relatively stable level. This result differs from other studies that recently reported no further increase in the rate of house dust mite sensitization [17]. Allergens from tree pollen, animal dander, cockroach, grass pollen, and weed pollen showed relatively stable or increasing trends. House dust mites have been reported to maintain a consistently high sensitization rate but without further increase, possibly due to increased awareness of dust mites and improvements in living environments [18]. In this study, the persistently high sensitization rate to house dust mites is presumed to reflect the characteristics of our center, which treats many socially vulnerable patients from

**Table 4.** Association (odds ratios) between increments (per interquartile range) in air pollutants and allergic disease with or without aeroallergen sensitization

| Exposure variable | BA (n=94) | AR (n=137) | BA+AR (n=82) | BA+AAS (n=67) | AR+AAS (n=76) |
|---|---|---|---|---|---|
| $PM_{2.5}$ (maximal) | 0.25 (0.09–0.75) | 3.86 (1.33–11.23)[a] | 1.13 (0.39–3.35) | 0.82 (0.29–2.38) | 1.24 (0.45–3.44) |
| $C_0$ (maximal) | 0.93 (0.65–1.33) | 1.08 (0.75–1.54) | 1.57 (1.09–2.27)[a] | 1.09 (0.75–1.59) | 1.08 (0.74–1.57) |
| $O_3$ (maximal) | 1.12 (0.56–2.24) | 0.89 (0.45–1.79) | 1.04 (0.50–2.15) | 1.20 (0.59–2.48) | 2.25 (1.08–4.70)[a] |

Values are presented as odds ratio (95% confidence interval).
BA, bronchial asthma only; AR, allergic rhinitis only; BA+AR, coexisting asthma and allergic rhinitis; AAS, aeroallergen sensitization. $PM_{2.5}$, fine particulate matter ≤2.5 μm.
[a]Indicates a statistically significant difference with $p<0.05$.

poor living environments. In the case of companion animals, the increase in pet ownership and the social trend of not easily giving up animals with whom attachments have formed are considered contributing factors [18,19]. It was also confirmed that sensitization to tree, grass, and weed pollens is gradually increasing, as reported in other studies. This increase has been attributed to the extended flowering period of plants caused by global warming, which prolongs pollen suspension time, as well as to climate change induced variations in temperature and humidity that influence inhalant allergens such as pollen [20,21].

When examining changes in daily average and daily maximum concentrations of air pollutants in Busan from 2011 to 2024, $NO_2$, $SO_2$, CO, $PM_{10}$, $PM_{2.5}$, maximum $SO_2$, maximum CO, maximum $PM_{10}$ and maximum $PM_{2.5}$ all decreased, except for $O_3$, maximum $O_3$ and maximum $NO_2$ which increased [13]. Busan, as a representative port city in Korea, encompasses commercial, industrial, and residential areas, and ships have been identified as major sources of emissions not only of $SO_2$ but also of PM and nitrogen oxides. It is known that exhaust gases from ships in port cities affect air quality in both coastal and inland areas, and concentrations of $SO_2$ and $O_3$ in the coastal areas of Busan have been reported to be relatively high compared to other regions [22]. Therefore, in this study, higher concentrations of $SO_2$, $NO_2$, and $O_3$ in port cities compared with other regions were observed to be related to increases in daily average $SO_2$ levels in cases where combined asthma and allergic rhinitis were present. Additionally, a significant OR was confirmed between the prevalence of allergic rhinitis and changes in maximal $PM_{2.5}$ concentration in logistic regression analysis.

Air pollutants that influence allergen sensitization are known to manifest several years later in children, partly due to the impact of immature lungs exposed during infancy [23,24]. In addition, pollutant levels measured at the time of allergic disease diagnosis have been reported to be associated with the experience of allergic symptoms and the exacerbation of preexisting disease [25]. This study was a retrospective cross-sectional design that did not longitudinally observe children but rather aimed to examine the relationship between air pollutants, allergic disease, and allergen sensitization by identifying pollutant concentrations in residential areas at the time of diagnosis. Therefore, the effect of prior exposures to air pollutants on allergen sensitization could not be assessed.

Patel et al. [9] reported that in a cohort of US children aged 0–5 years followed for 5 years, serum total IgE concentrations were higher in groups exposed to traffic-related air pollution near major roads than in nonexposed groups. This can be interpreted as allergens bound to pollution-related particles being transported into the airways during allergic processes, leading to sensitization.

In addition, the finding that Th2 cytokine concentrations in nasal secretions increased 16-fold when exposed to pollen and diesel exhaust particles (DEP) simultaneously compared with pollen alone indicates that air pollutants act as cofactors in allergen sensitization and allergic inflammatory responses [10]. Morgenstern et al. [11] also suggested that traffic-related pollutants substantially increase the risk of atopic disease and allergic sensitization, with particularly strong effects in children living within 50 m of major roads. DEP is a fine particulate component of $PM_{10}$ and $PM_{2.5}$. Most DEP particles are small in diameter, remain suspended in the air for long periods, and contain CO, $NO_2$, polycyclic aromatic hydrocarbons, and other toxic substances along with PM, which are inhaled and deposited in the lungs [26]. To observe the effect of pollutant exposure on asthma and allergic rhinitis according to sensitization status, both sensitized and nonsensitized groups were analyzed. This study

found that $PM_{10}$, $PM_{2.5}$, and maximum concentrations of $SO_2$ and $NO_2$ were associated with the lifetime prevalence of allergic rhinitis symptoms. These results are consistent with previous findings that among CO, $NO_2$, $PM_{10}$, $PM_{2.5}$, and $SO_2$, $NO_2$ and $SO_2$ had the greatest impact on outpatient visits for allergic rhinitis [27]. Moreover, allergic rhinitis with inhalant allergen sensitization was associated with changes in a greater number of pollutants. In addition, a significant OR for changes in the highest concentration of $O_3$ was observed in allergic rhinitis with inhalant allergen sensitization in logistic regression analysis. This finding is consistent with prior studies [28-30] showing that greater exposure to air pollution contributes to the sensitization stage and thus influences the development of allergic diseases.

In this study, the comorbidity rate of asthma in allergic rhinitis was 37%, and the comorbidity rate of allergic rhinitis in bronchial asthma was 46%. These rates differ slightly from previous epidemiological studies reporting that approximately 40% of allergic rhinitis patients eventually develop asthma and that allergic rhinitis is present in 70%–80% of asthma patients [31]. In the analysis of the correlation between air pollutant changes and combined asthma and allergic rhinitis, an association was observed with daily average $SO_2$ and CO concentrations in children with both conditions. In addition, logistic regression analysis also confirmed a significant OR for changes in maximal CO concentration in cases of concurrent asthma and allergic rhinitis. This is consistent with prior findings that atopy indices and the degree of sensitization are more severe in children with comorbid allergic diseases compared with those with a single diagnosis [32]. Another population-based study also reported that patients with combined asthma and allergic rhinitis had a higher frequency and degree of sensitization than those with only one condition [33]. In our study, sensitization to inhalant allergens was observed in 61% of children with asthma or allergic rhinitis alone and in 74% of those with both, consistent with earlier reports and supporting the association of pollutant exposure with higher sensitization in comorbid cases. Furthermore, Riedel et al. [34] reported that prolonged $SO_2$ exposure, regardless of concentration, causes bronchoconstriction and airway hyperresponsiveness, and that long-term exposure to low concentrations enhances allergen-induced airway constriction. These reports support the association of combined allergic rhinitis and asthma with pollutant changes such as $SO_2$ and CO.

Among children with acute asthma exacerbations, correlations were also observed with maximum concentrations of $NO_2$ and $SO_2$. This is consistent with reports that short-term acute $SO_2$ exposure increases the risk of asthma attacks, hospitalization rates, and delayed adverse effects [35]. Fine particles containing nitrogen oxides, sulfur oxides, carbon oxides, O3, and metals have been reported to reduce lung function, and increases in hourly peak or daily average concentrations have been shown to reduce $FEV_1$ and increase airway inflammation [36]. This study demonstrated similar findings.

The limitations of this study are as follows. First, because the study population consisted of hospitalized and outpatient patients, the findings do not reflect the prevalence of allergic diseases and sensitization rates in the general pediatric population. Second, as a single-center regional study, it may not capture the relationship between allergic diseases and air pollution across broader areas. Third, only outdoor pollutant exposure was considered, without accounting for individual or indoor exposures. Fourth, diagnostic accuracy may have been limited by changes in pediatric specialists over the study period, potentially leading to over- or underestimation of allergic diseases and sensitization rates.

Studies examining associations between changes in air pollutant concentrations in specific regional contexts and the prevalence of childhood asthma, allergic rhinitis, and allergen sensitization remain scarce. Although not a birth cohort or longitudinal study, this investigation is significant in that it demonstrates the overall association. These findings are important because they may help children with allergic diseases better recognize and prevent the risks of air pollution exposure. Further research addressing various aspects of air pollution and allergic diseases is warranted.

## Article information

### Conflicts of interest

No potential conflict of interest relevant to this article was reported.

### Acknowledgments

We gratefully acknowledge the staff in the outpatient and ward departments of Busan Metropolitan City Medical

Center who treated children with allergic diseases, and to the Public Medical Research Institute who supported this research.

**Funding**

This work was supported by Public Medical Research Institute, Busan Medical Center.

**Author contributions**

Conceptualization: HK. Data curation: SS, HK. Software: HK. Validation: HK. Investigation: HK. Formal analysis: SS, HK. Methodology: SS, HK. Project administration: HK. Visualization: SS, HK. Writing-original draft: SS, HK. Writing-review & editing: HK. All authors read and approved the final manuscript.

**ORCID**

Sunbok Suh, https://orcid.org/0009-0002-9397-2206
Hyungsu Kim, https://orcid.org/0009-0004-8923-6454

## References

1. Kampa M, Castanas E. Human health effects of air pollution. Environ Pollut 2008;151:362–7.
2. Braback L, Forsberg B. Does traffic exhaust contribute to the development of asthma and allergic sensitization in children: findings from recent cohort studies. Environ Health 2009;8:17.
3. Naclerio R, Ansotegui IJ, Bousquet J, Canonica GW, D'Amato G, Rosario N, et al. International expert consensus on the management of allergic rhinitis (AR) aggravated by air pollutants: impact of air pollution on patients with AR: current knowledge and future strategies. World Allergy Organ J 2020;13:100106.
4. Hwang YH, Kim SW. PM(2.5) and pediatric asthma. Allergy Asthma Respir Dis 2019;7:116–21.
5. Gehring U, Wijga AH, Brauer M, Fischer P, de Jongste JC, Kerkhof M, et al. Traffic-related air pollution and the development of asthma and allergies during the first 8 years of life. Am J Respir Crit Care Med 2010;181:596–603.
6. Jeong SH, Kim JH, Son BK, Hong SC, Kim SY, Lee GH, et al. Comparison of air pollution and the prevalence of allergy-related diseases in Incheon and Jeju City. Korean J Pediatr 2011;54:501–6.
7. Bateson TF, Schwartz J. Children's response to air pollutants. J Toxicol Environ Health A 2008;71:238–43.
8. Miller MD, Marty MA. Impact of environmental chemicals on lung development. Environ Health Perspect 2010;118:1155–64.
9. Patel MM, Quinn JW, Jung KH, Hoepner L, Diaz D, Perzanowski M, et al. Traffic density and stationary sources of air pollution associated with wheeze, asthma, and immunoglobulin E from birth to age 5 years among New York City children. Environ Res 2011;111:1222–9.
10. Diaz-Sanchez D, Tsien A, Casillas A, Dotson AR, Saxon A. Enhanced nasal cytokine production in human beings after in vivo challenge with diesel exhaust particles. J Allergy Clin Immunol 1996;98:114–23.
11. Morgenstern V, Zutavern A, Cyrys J, Brockow I, Koletzko S, Kramer U, et al. Atopic diseases, allergic sensitization, and exposure to traffic-related air pollution in children. Am J Respir Crit Care Med 2008;177:1331–7.
12. Busan Metropolitan City Institute of Health & Environment. 2023 Busan Metropolitan City air quality assessment report [Internet]. Busan Metropolitan City Institute of Health & Environment; 2024 [cited 2025 Dec 10]. Available from: https://book.busan.go.kr/Viewer/L769S108GLDA
13. Global Initiative for Asthma. 2021 GINA report, global strategy for asthma management and prevention [Internet]. Global Initiative for Asthma; 2021 [cited 2025 Dec 10]. Available from: https://ginasthma.org
14. Choi YJ, Jang GC, Yang HJ, Kim HB, Yoo Y, Shin M, et al. The Korean Version of the Test for Respiratory and Asthma Control in Kids (TRACK): reliability and validity. J Korean Med Sci 2019;34:e25.
15. Brozek JL, Bousquet J, Agache I, Agarwal A, Bachert C, Bosnic-Anticevich S, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines-2016 revision. J Allergy Clin Immunol 2017;140:950–8.
16. Busan Metropolitan City Institute of Health & Environment. Air environment [Internet]. Busan Metropolitan City Institute of Health & Environment; 2025 [cited 2025 Dec 10]. Available from: https://www.busan.go.kr/ihe/environdata01
17. Jung JH, Kim GE, Park M, Kim SY, Kim MJ, Lee YJ, et al. Changes in allergen sensitization in children with allergic diseases in the 1980 to 2019. Allergy Asthma Respir Dis 2021;9:208–15.
18. Jung YH, Hwang KH, Yang SI, Lee E, Kim KH, Kim MJ, et al. Changes of aeroallergen sensitization in children with asthma or allergic rhinitis from a tertiary referral hospital in Seoul over 10 years. Allergy Asthma Respir Dis 2014;2:97–102.
19. Chan SK, Leung DY. Dog and cat allergies: current state of diagnostic approaches and challenges. Allergy Asthma Immunol Res 2018;10:97–105.

20. Frenguelli G. Interactions between climatic changes and allergenic plants. Monaldi Arch Chest Dis 2002;57:141–3.
21. Oh JW, Lee HB, Kang IJ, Kim SW, Park KS, Kook MH, et al. The revised edition of Korean calendar for allergenic pollens. Allergy Asthma Immunol Res 2012;4:5–11.
22. Kim DH, Son YS. Spatial-temporal variations in air pollution in Busan metropolitan city (2010- 2018). J Korean Soc Atmos Environ 2020;36:309–28.
23. Wright RJ, Brunst KJ. Programming of respiratory health in childhood: influence of outdoor air pollution. Curr Opin Pediatr 2013;25:232–9.
24. Codispoti CD, LeMasters GK, Levin L, Reponen T, Ryan PH, Biagini Myers JM, et al. Traffic pollution is associated with early childhood aeroallergen sensitization. Ann Allergy Asthma Immunol 2015;114:126–33.
25. Mann JK, Balmes JR, Bruckner TA, Mortimer KM, Margolis HG, Pratt B, et al. Short-term effects of air pollution on wheeze in asthmatic children in Fresno, California. Environ Health Perspect 2010;118:1497–502.
26. Lee JH, Lee YK, Lee JY, Lee SB, Kim SH, Bae GN, et al. Cytotoxicity of diesel exhaust particles from various vehicles toward macrophage cells. Environ Health Toxicol 2010;25:111–20.
27. Wang J, Lu M, An Z, Jiang J, Li J, Wang Y, et al. Associations between air pollution and outpatient visits for allergic rhinitis in Xinxiang, China. Environ Sci Pollut Res Int 2020;27:23565–74.
28. Kanoh T, Suzuki T, Ishimori M, Ikeda S, Ohasawa M, Ohkuni H, et al. Adjuvant activities of pyrene, anthracene, fluoranthene and benzo(a)pyrene in production of anti-IgE antibody to Japanese cedar pollen allergen in mice. J Clin Lab Immunol 1996;48:133–47.
29. Perzanowski MS, Chew GL, Divjan A, Jung KH, Ridder R, Tang D, et al. Early-life cockroach allergen and polycyclic aromatic hydrocarbon exposures predict cockroach sensitization among inner-city children. J Allergy Clin Immunol 2013;131:886–93.
30. Yoo Y. Air pollution and childhood allergic disease. Allergy Asthma Respir Dis 2016;4:248–56.
31. Chawes BL, Bonnelykke K, Kreiner-Moller E, Bisgaard H. Children with allergic and nonallergic rhinitis have a similar risk of asthma. J Allergy Clin Immunol 2010;126:567–73.
32. Boulet LP, Turcotte H, Laprise C, Lavertu C, Bedard PM, Lavoie A, et al. Comparative degree and type of sensitization to common indoor and outdoor allergens in subjects with allergic rhinitis and/or asthma. Clin Exp Allergy 1997;27:52–9.
33. Siroux V, Ballardini N, Soler M, Lupinek C, Boudier A, Pin I, et al. The asthma-rhinitis multimorbidity is associated with IgE polysensitization in adolescents and adults. Allergy 2018;73:1447–58.
34. Riedel F, Kramer M, Scheibenbogen C, Rieger CH. Effects of $SO_2$ exposure on allergic sensitization in the guinea pig. J Allergy Clin Immunol 1988;82:527–34.
35. Jo EJ, Lee WS, Jo HY, Kim CH, Eom JS, Mok JH, et al. Effects of particulate matter on respiratory disease and the impact of meteorological factors in Busan, Korea. Respir Med 2017;124:79–87.
36. O'Connor GT, Neas L, Vaughn B, Kattan M, Mitchell H, Crain EF, et al. Acute respiratory health effects of air pollution on children with asthma in US inner cities. J Allergy Clin Immunol 2008;121:1133–9.

Original article

Kosin Medical Journal 2026;41(1):58-66
pISSN: 2005-9531 • eISSN: 2586-7024
https://doi.org/10.7180/kmj.26.147

KMJ
KOSIN MEDICAL JOURNAL

# Predictors and patterns of early liver regeneration after major hepatectomy

**Seoyeong Ku[1,2,*], Garam Lee[1,3,*], Hyung Hwan Moon[1,4], Hyungjune Ku[1], Won Jong Yang[5], Junho Song[6], Suyeon Kim[7], Chol Min Kang[8], Amy Choi[9], Dong Hyeon Gim[10], Young Il Choi[1,4], Dong Hoon Shin[1,4], Namkee Oh[11], Jinsoo Rhu[11]**

[1]*Chang Kee-Ryo Memorial Liver Institute, Kosin University Gospel Hospital, Kosin University College of Medicine, Busan, Korea*
[2]*Department of Horticulture, Life and Landscape Architecture, Seoul Women's University, Seoul, Korea*
[3]*College of Veterinary Medicine, Chonnam National University, Gwangju, Korea*
[4]*Division of Hepatobiliary-Pancreas and Transplantation, Department of Surgery, Kosin University Gospel Hospital, Kosin University College of Medicine, Busan, Korea*
[5]*H. Milton Stewart School of Industrial and Systems Engineering, Georgia Institute of Technology, Atlanta, GA, USA*
[6]*College of Medicine, Pennsylvania State University, Hershey, PA, USA*
[7]*Department of Information Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea*
[8]*Department of Applied Biomedical Engineering, The Johns Hopkins University, Baltimore, MD, USA*
[9]*Department of Neurosurgery, College of Medicine, Pennsylvania State University, Hershey, PA, USA*
[10]*College of Pharmacy, Yonsei University, Seoul, Korea*
[11]*Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea*

**Background:** Postoperative liver regeneration is essential for maintaining hepatic function. This study evaluated the rate, determinants, and volumetric patterns of early liver regeneration after hemihepatectomy.

**Methods:** A retrospective review was conducted of 50 patients who underwent right or left hemihepatectomy between April 2019 and March 2025. Liver and spleen volumes (SV) were assessed preoperatively, at postoperative day (POD) 1 week, and at POD 3 months. Early liver regeneration rate (LRR) was defined as the percentage increase in remnant liver volume at POD 1 week relative to the preoperative future liver remnant (FLR), and patients were categorized into low (<50%) and high (≥50%) LRR groups. Clinical, biochemical, and volumetric variables were compared, and predictors of regeneration were identified using multivariable analyses. Regeneration patterns were also examined according to whether the FLR/standard liver volume (SLV) ratio was <50% or ≥50%.

**Results:** FLR/SLV was the strongest independent predictor of rapid early liver regeneration ($p$<0.001). Remnants with FLR/SLV <50% exhibited rapid and sustained regeneration, whereas those with FLR/SLV ≥50% showed slower regrowth that plateaued after reaching approximately 90% of SLV. SV increased at POD 1 week in all patients; however, only the FLR/SLV ≥50% group showed a reduction by POD 3 months, whereas the <50% group maintained elevated volumes.

**Conclusions:** FLR/SLV reliably predicts early postoperative liver regeneration. Smaller remnants regenerate more rapidly, whereas persistent splenic enlargement suggests a sustained portal hemodynamic burden. Combined evaluation of FLR/SLV and SV may enhance perioperative risk assessment and surgical planning.

**Keywords:** Computed tomography; Hepatectomy; Liver failure; Liver regeneration; Spleen

**Received:** January 12, 2026; **Revised:** February 15, 2026; **Accepted:** March 10, 2026
**Corresponding Author:** Hyung Hwan Moon, MD
Division of Hepatobiliary-Pancreas and Transplantation, Department of Surgery, Kosin University Gospel Hospital, Kosin University College of Medicine, 262 Gamcheon-ro, Seo-gu, Busan 49267, Korea
Tel: +82-51-990-6462 Fax: +82-51-990-3005 E-mail: ras99m@kosin.ac.kr

*These authors contributed equally to this work as first authors.

© 2026 Kosin University College of Medicine
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

## Introduction

Major hepatectomy is a key treatment for primary and secondary hepatic malignancies, Despite advances in surgical technique and perioperative care, posthepatectomy liver failure (PHLF) remains a leading cause of postoperative morbidity and mortality. Because postoperative outcomes depend largely on the functional capacity of the remnant liver, identifying reliable predictors of safe resection and regenerative potential is a central issue in hepatobiliary surgery [1,2].

Liver regeneration is regulated by portal hemodynamics, shear stress, inflammatory cytokines, and growth factor signaling [3]. Prior studies, particularly in living donor liver transplantation, have shown that smaller remnants regenerate more rapidly due to increased hepatocyte workload and portal inflow [4,5]. These observations support the principle of compensatory hypertrophy, where the extent of resection is a key determinant of both the rate and magnitude of regeneration [6].

Among volumetric indices, future liver remnant (FLR)/standard liver volume (SLV) provides a standardized estimate of functional liver reserve. Lower FLR/SLV values have been associated with a higher risk of PHLF and impaired postoperative metabolic function [7]. However, it remains unclear how the extent of resection influences the pattern of liver regeneration over time, how long regeneration continues, and whether the regenerated volume corresponds to true functional recovery.

Spleen volume (SV) dynamics may also offer insight into postoperative physiology. Early splenic enlargement is common after hepatectomy and reflects portal congestion, but emerging evidence suggests that SV may additionally indicate hepatic functional reserve [8]. Increased SV or SV/body surface area (BSA) has been linked to PHLF, delayed recovery, and poorer long-term survival [9,10,11]. Persistent splenomegaly may therefore signal inadequate functional regeneration even when volumetric regeneration appears satisfactory. Yet, the relationship between SV trajectories and FLR/SLV-based liver regeneration has not been clearly defined.

Accordingly, this study aimed to identify the major factors influencing postoperative liver regeneration and to characterize how hepatic growth progresses over time after major hepatectomy. By integrating liver volumetry, SV changes, and early biochemical markers, we sought to clarify both the determinants and temporal patterns of liver regeneration in clinical practice.

## Methods

**Ethical statements:** This study was approved by the Institutional Review Board (IRB) of Kosin University Gospel Hospital (IRB No. 2024-08-029). The requirement for informed consent was waived as this study was retrospective in nature, relying solely on previously collected and anonymized data, in accordance with institutional and ethical guidelines.

### 1. Patient selection

We retrospectively reviewed all consecutive patients who underwent anatomical right or left hemihepatectomy at Kosin University Gospel Hospital between April 2019 and March 2025, identifying a total of 125 cases. Only anatomical right or left hemihepatectomies, defined as right or left hemihepatectomy performed for any indication, were considered eligible for this study. Patients were excluded if they had undergone nonstandard hepatic resections (n=23), such as central hepatectomy, right posterior sectionectomy, or other atypical procedures that did not meet the definition of major hemihepatectomy. Additional exclusions were applied to patients in whom accurate volumetric assessment could not be ensured (n=15), including those with a history of previous liver resection (n=6) and those who underwent combined or extended procedures, such as wedge resection performed concurrently with hemihepatectomy (n=9). Patients with a prior history of liver surgery, splenectomy, or incomplete preoperative and postoperative imaging were excluded. Finally, patients without essential postoperative imaging required for liver regeneration analysis were excluded (n=37), as volumetry at postoperative day (POD) 1 week and POD 3 months was mandatory for inclusion. After applying all exclusion criteria, 50 patients remained and constituted the final study cohort.

### 2. Volumetric measurement and liver regeneration calculation

A three-dimensional (3D) residual U-Net model, previously validated for hepatic segmentation was employed for automated extraction of the FLR [12,13]. The network, implemented in TensorFlow ver. 1.14 (Google LLC) with

residual and skip connections, was trained using the Adam optimizer (learning rate=0.0001) and the Dice similarity coefficient as the loss metric. Data augmentation (3D rotation and scaling) was applied to improve robustness. Preoperative SV and regenerated liver volume (RV) at POD 1 week and POD 3 months were obtained using 3D Slicer ver. 5.6.2 (Brigham and Women's Hospital) with the Total Segmentator module for automatic segmentation [14].

FLR, SLV, total functional liver volume (TFLV), and SV were measured in cubic centimeters ($cm^3$). All segmentations were reviewed and manually corrected by an experienced hepatobiliary surgeon to ensure accuracy.

LRR was calculated using the following formula:

$$\text{LRR}\ (\%) = \frac{(\text{Remnant liver volume at POD 1 week} - \text{FLR})}{\text{FLR}} \times 100$$

**3. Grouping according to liver regeneration rate**

Patients were grouped by their POD 1-week liver regeneration rate (LRR) into two groups: low-regeneration group (LRR <50%) and a high-regeneration group (LRR ≥50%).

**4. Clinical and laboratory parameters**

Demographic and clinical data were collected from electronic medical records, including age, sex, body mass index (BMI), comorbidities (hypertension, diabetes mellitus, viral hepatitis, alcoholism), and American Society of Anesthesiologists (ASA) classification. Preoperative laboratory parameters included total bilirubin (TB), aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, prothrombin time-international normalized ratio (PT-INR), platelet count, and fibrosis markers including AST-to-platelet ratio index (APRI), albumin-bilirubin (ALBI), model for end-stage liver disease (MELD), fibrosis-4 index (FIB-4), platelet-albumin-bilirubin (PALBI), and Child-Turcotte-Pugh (CTP) score. Postoperative variables measured on POD 1 included TB, AST, ALT, creatinine, and high-sensitivity C-reactive protein (HS-CRP). These data were compared between the low and high-LRR groups to identify factors associated with rapid early liver regeneration.

**5. Statistical analysis**

Continuous variables were expressed as median (range) and compared using the Mann-Whitney *U*-test, whereas categorical variables were compared using the chi-square or Fisher exact test. Variables with $p<0.10$ in univariate analysis were entered into a multivariate linear regression model to determine independent predictors of rapid early liver regeneration (POD 1-week LRR). Receiver operating characteristic (ROC) curve analysis was performed separately after dichotomizing POD 1-week LRR at 50% (≥50% vs. <50%) to evaluate the discriminative ability of individual volumetric indices. The area under the curve (AUC) was calculated to quantify predictive performance. All statistical analyses were conducted using Python (ver. 3.11.8) A two-sided $p<0.05$ was considered statistically significant.

## Results

**1. Comparison of baseline characteristics between low- and high-POD 1-week LRR groups**

Among 50 patients, baseline characteristics were largely comparable between the low (<50%) and high (≥50%) POD 1-week LRR groups (Table 1). Age, sex, BMI, comorbidities (hypertension, diabetes mellitus), and underlying diagnoses showed no significant differences (all $p>0.05$). Alcohol intake, ASA classification, and surgical approach (open, laparoscopic, robotic, hybrid) were also similar.

A notable between-group difference was observed in the type of hepatectomy: right hepatectomy was significantly more frequent in the high-LRR group (86.7% vs. 30.0%), whereas left hepatectomy predominated in the low-LRR group ($p<0.001$). The high-LRR group demonstrated significantly greater estimated blood loss ($p=0.023$), which may be attributable to a larger extent of hepatic resection in this group. Among laboratory indices, only APRI was significantly higher in the high-LRR group (0.4 vs. 0.3, $p=0.033$), whereas ALBI, MELD, FIB-4, PALBI, and CTP scores did not differ significantly.

**2. Pre- and postoperative laboratory findings between low- and high-POD 1-week LRR groups**

Preoperative laboratory variables were largely comparable between the low- and high-LRR groups (Table 2). Preoperative white blood cell (WBC) count, neutrophil count, platelet count, PT-INR, bilirubin, protein, and AST showed no significant differences (all $p>0.05$). However, preoperative ALT was higher in the high-LRR group than in the low-LRR group (29.0 vs. 20.0 IU/L, $p=0.009$).

At POD 1, most hematologic parameters—including

**Table 1.** Comparison of baseline variables between the low- and high-POD 1-week LRR groups

| Variable | Low (<50%) (n=20) | High (≥50%) (n=30) | *p*-value |
|---|---|---|---|
| Age (yr) | 58.5 (44.0 to 77.0) | 63.0 (45.0 to 78.0) | 0.159 |
| Sex (male/female) | 17/3 | 28/2 | 0.377 |
| Body mass index (kg/m$^2$) | 24.6 (18.7 to 32.1) | 26.0 (18.5 to 30.3) | 0.201 |
| Hypertension | 8 (40.0) | 12 (40.0) | 1.000 |
| Diabetes mellitus | 15 (75.0) | 19 (63.3) | 0.538 |
| Diagnosis | | | 0.580 |
| Donor | 1 (5.0) | 1 (3.3) | |
| Colorectal metastasis | 1 (5.0) | 3 (10.0) | |
| HCC | 12 (60.0) | 14 (46.7) | |
| ICC | 4 (20.0) | 11 (36.7) | |
| Other | 2 (10.0) | 1 (3.3) | |
| Alcoholism | 14 (70.0) | 27 (90.0) | 0.130 |
| ASA (I/II/III) | 12 (60.0)/8 (40.0)/0 (0) | 21 (70.0)/9 (30.0)/0 (0) | 0.548 |
| MIS (open/lap/robot/hybrid) | 8 (40.0)/10 (50.0)/1 (5.0)/1 (5.0) | 11 (36.7)/18 (60.0)/0 (0)/1 (3.3) | 0.608 |
| Rt/Lt hepatectomy | 6 (30.0)/14 (70.0) | 26 (86.7)/4 (13.3) | <0.001 |
| Operative time (min) | 320 (115 to 705) | 270 (165 to 805) | 0.820 |
| Estimated blood loss (mL) | 350 (50 to 1,000) | 500 (100 to 3,200) | 0.023 |
| APRI | 0.3 (0.1 to 0.8) | 0.4 (0.1 to 1.0) | 0.033 |
| ALBI | −3.1 (−3.4 to −2.2) | −2.9 (−3.5 to −2.3) | 0.586 |
| MELD | 4.4 (1.1 to 8.7) | 4.4 (1.5 to 10.7) | 0.843 |
| Fibrosis-4 index | 1.5 (0.7 to 5.2) | 2.0 (0.7 to 3.6) | 0.201 |
| PALBI score | −2.7 (−3.2 to −1.9) | −2.6 (−3.2 to −2.1) | 0.851 |
| CTP score | 5.0 (5.0 to 6.0) | 5.0 (5.0 to 6.0) | 0.999 |
| ISGLS B/C grade PHLF | 2 (10) | 7 (23) | 0.285 |

Values are presented as median (range) or number (%).
POD, postoperative day; LRR, liver regeneration rate; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; ASA, American Society of Anesthesiologists physical status classification; MIS, minimally invasive surgery; Rt/Lt, right or left; APRI, aspartate aminotransferase-to-platelet ratio index; ALBI, albumin-bilirubin grade; MELD, model for end-stage liver disease; PALBI, platelet-albumin-bilirubin score; CTP, Child-Turcotte-Pugh score; ISGLS, the International Study Group for Liver Surgery; PHLF, posthepatectomy liver failure.

WBC, neutrophil count, and platelet count—were similar between groups. In contrast, several liver function markers differed significantly. The high-LRR group demonstrated higher PT-INR ($p$=0.023), higher TB ($p$<0.001), higher AST ($p$=0.025), and higher ALT ($p$=0.039) than the low-LRR group, whereas POD 1 HS-CRP was lower in the high-LRR group ($p$=0.020). Serum creatinine was also modestly higher in the high-LRR group ($p$=0.041).

### 3. Comparison of volumetric variables between low- and high-POD 1-week LRR groups

Volumetric analysis demonstrated significant differences in resection-related parameters between the two groups (Table 3). Preoperative SV, TFLV, and SLV were comparable between the low and high-LRR groups (all $p$>0.05).

In contrast, FLR volume was markedly lower in the high-LRR group (430.3 mL vs. 901.3 mL, $p$<0.001). Similarly, both FLR/SLV (36.3% vs. 70.4%, $p$<0.001) and FLR/SV (3.1 vs. 5.2, $p$=0.001) were significantly lower in the high-LRR group.

### 4. Multivariate linear regression analysis for factors associated with rapid early liver regeneration (POD 1-week LRR)

Table 4 presents the results of the multivariate linear regression analysis evaluating predictors of rapid early liver regeneration, as assessed by POD 1-week LRR. Among the variables included, FLR/SLV emerged as the only independent predictor significantly associated with LRR ($\beta$, −1.369; 95% confidence interval, −1.96 to −1.15; $p$<0.001), whereas FLR/SV, APRI, preoperative ALT and bleeding were not significant after adjustment. Variance inflation factor (VIF) analysis demonstrated no evidence of significant multicol-

**Table 2.** Comparison of preoperative and POD 1 laboratory data between the low- and high-POD 1-week LRR groups

| Variable | Low (<50%) (n=20) | High (≥50%) (n=30) | *p*-value |
|---|---|---|---|
| Preoperative | | | |
| WBC | 6.26 (2.97–9.52) | 6.22 (3.71–10.37) | 0.850 |
| Neutrophil | 3.65 (1.57–5.88) | 3.51 (1.28–7.09) | 0.528 |
| Platelet | 227.5 (120.0–372.0) | 213.5 (101.0–349.0) | 0.195 |
| PT-INR | 1.0 (0.9–1.2) | 1.0 (0.9–1.5) | 0.222 |
| TB | 0.58 (0.30–0.84) | 0.57 (0.36–2.04) | 0.526 |
| Protein | 7.2 (6.5–8.0) | 7.4 (6.3–8.0) | 0.736 |
| AST | 27.0 (15.0–46.0) | 32.0 (14.0–133.0) | 0.113 |
| ALT | 20.0 (7.0–46.0) | 29.0 (8.0–140.0) | 0.009 |
| POD 1 | | | |
| WBC | 11.94 (4.95–24.98) | 12.73 (6.06–21.66) | 0.475 |
| Neutrophil | 9.23 (4.20–15.77) | 10.90 (4.53–19.49) | 0.092 |
| Platelet | 200.0 (89.0–366.0) | 160.5 (97.0–318.0) | 0.064 |
| PT-INR | 1.3 (1.1–1.5) | 1.4 (1.1–2.3) | 0.023 |
| TB | 1.0 (0.7–4.0) | 1.8 (0.8–4.8) | <0.001 |
| AST | 233.0 (95.0–2,000) | 367.5 (154.0–994.0) | 0.025 |
| ALT | 164.0 (38.0–754.0) | 327.5 (36.0–892.0) | 0.039 |
| Cr | 0.8 (0.4–1.4) | 0.9 (0.5–2.3) | 0.041 |
| HS-CRP | 5.0 (1.2–11.5) | 3.6 (0.9–8.0) | 0.020 |

Values are presented as median (range).
POD, postoperative day; LRR, liver regeneration rate; WBC, white blood cell count; PT-INR, prothrombin time-international normalized ratio; TB, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Cr, creatinine; HS-CRP, high-sensitivity C-reactive protein.

**Table 3.** Comparison of volumetric variables between the low- and high-POD 1-week LRR groups

| Variable | Low (<50%) (n=20) | High (≥50%) (n=30) | *p*-value |
|---|---|---|---|
| SV (mL) | 184.7 (48.5–369.3) | 148.2 (52.1–275.4) | 0.378 |
| TFLV (mL) | 1217.9 (820.1–1,724.7) | 1079.2 (871.8–1,689.4) | 0.157 |
| SLV (mL) | 1231.2 (987.3–1,601.0) | 1264.1 (1,000.0–1,423.0) | 0.134 |
| FLR (mL) | 901.3 (498.4–1,393.7) | 430.3 (229.2–840.9) | <0.001 |
| FLR/SLV (%) | 70.4 (44.2–114.1) | 36.3 (18.2–67.6) | <0.001 |
| FLR/SV (%) | 5.2 (2.3–12.7) | 3.1 (0.8–11.4) | 0.001 |

Values are presented as median (range).
POD, postoperative day; LRR, liver regeneration rate; SV, spleen volume; TFLV, total functional liver volume; SLV, standard liver volume; FLR, future liver remnant volume; FLR/SLV, ratio of future liver remnant to standard liver volume; FLR/SV, ratio of future liver remnant to spleen volume.

**Table 4.** Multivariable linear regression analysis of factors associated with early liver regeneration (POD 1-week LRR)

| Variable | β | *p*-value |
|---|---|---|
| FLR/SLV (%) | −1.369 (−1.783 to −0.956) | <0.001 |
| FLR/SV (%) | 0.298 (−2.882 to 3.478) | 0.851 |
| APRI | −9.772 (−53.214 to 33.669) | 0.653 |
| Preoperative ALT | 0.301 (−0.082 to 0.683) | 0.121 |
| EBL | 0.014 (−0.001 to 0.029) | 0.064 |

Values are presented as β coefficients (95% confidence intervals).
POD, postoperative day; LRR, liver regeneration rate; FLR/SLV, ratio of future liver remnant to standard liver volume; FLR/SV, ratio of future liver remnant to spleen volume; APRI, aspartate aminotransferase-to-platelet ratio index; ALT, alanine aminotransferase; EBL, estimated blood loss.

linearity among the variables included in the model (all VIF values<2.0). ROC curve analysis further confirmed the strong predictive performance of volumetric indices. Inverted FLR/SLV demonstrated the highest discriminative ability for predicting rapid early liver regeneration (AUC, 0.922), followed by inverted FLR (AUC, 0.888). In comparison, inverted FLR/SV (AUC, 0.767) and inverted right/left classification (AUC, 0.783) showed moderate predictive power (Supplementary Fig. 1).

### 5. Liver regeneration by timepoint FLR/SLV ≥50% vs. FLR/SLV <50% groups

Liver regeneration patterns differed markedly according to the FLR/SLV ratio. As shown in Fig. 1, patients with smaller remnant livers (FLR/SLV <50%) showed a significantly greater increase in RV/SLV from the immediate postoperative period to POD 1 week ($p$<0.001). In contrast, regeneration in the FLR/SLV ≥50% exhibited a more modest increase during the same period.

The most rapid phase of regeneration occurred during the first postoperative week, after which the rate of growth declined. Patients with FLR/SLV <50% continued to exhibit regeneration up to POD 3 months, whereas those with FLR/SLV ≥50% demonstrated little additional growth beyond the first week. Across groups, remnant liver volume approached approximately 90% of the SLV by 3 months, at which point volumetric expansion appeared to plateau.

### 6. Spleen volume by timepoint in FLR/SLV ≥50% vs. FLR/SLV <50% groups

SV increased after hepatectomy in both groups, showing the expected early postoperative splenic congestion (Fig. 2). In patients with FLR/SLV ≥50%, SV tended to decrease between POD 1 week and POD 3 months ($p$=0.030). In contrast, patients with FLR/SLV <50% showed an increase in spleen size at POD 1 week, and no significant reduction was observed by POD 3 months ($p$=0.626).

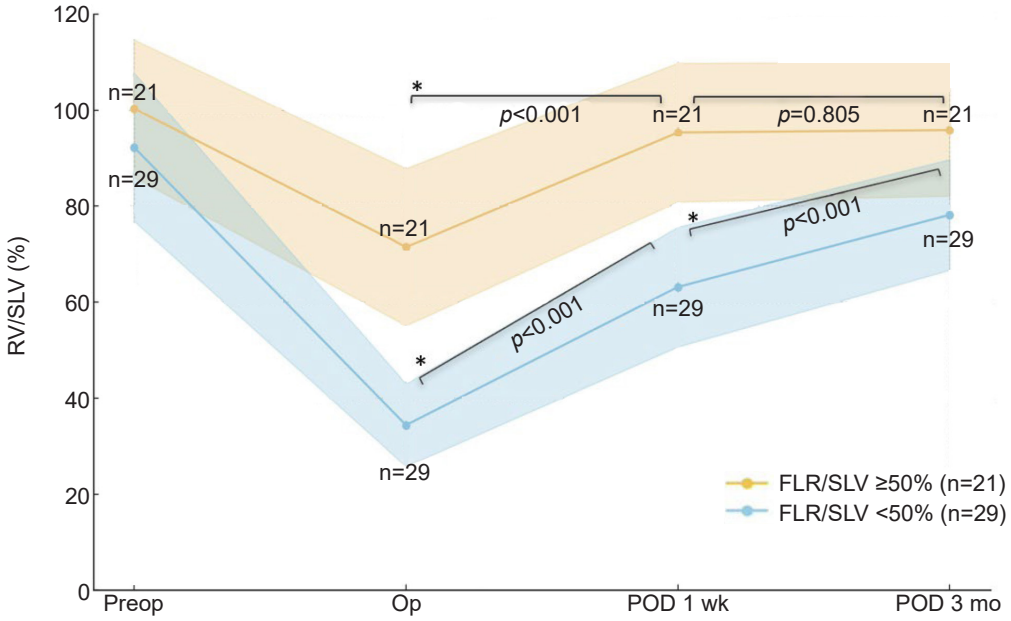


**Fig. 1.** Comparison of liver volume (RV/SLV) over time in the FLR/SLV <50% vs. ≥50% groups. Asterisks (*) indicate a statistically significant difference between consecutive time points ($p$<0.05). FLR/SLV, ratio of future liver remnant to standard liver volume; RV/SLV, ratio of regenerated liver volume to standard liver volume; preop, preoperative period; op, operation; POD, postoperative day.

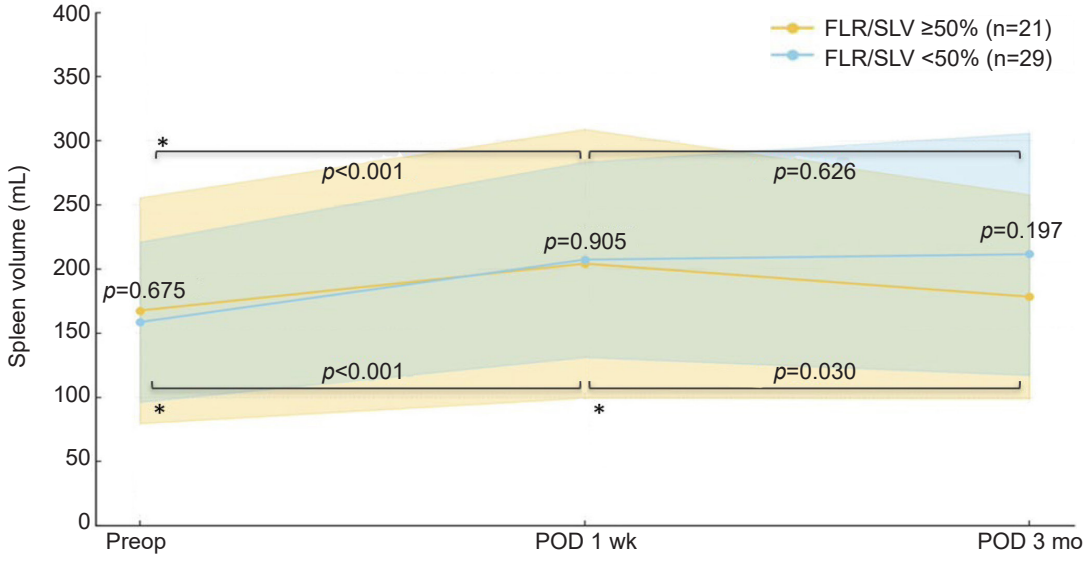


**Fig. 2.** Comparison of spleen volume over time in the FLR/SLV <50% vs. ≥50% groups. Asterisks (*) indicate a statistically significant difference between consecutive time points ($p$<0.05). FLR/SLV, ratio of future liver remnant to standard liver volume; preop, preoperative period; POD, postoperative day.

## Discussion

This study demonstrates that the FLR/SLV is a major determinant of postoperative rapid early liver regeneration after major hepatectomy. Patients with an FLR/SLV <50% showed faster overall regenerative gain, whereas growth slowed once the liver reached approximately 90% of SLV, indicating a physiological upper limit of regeneration.

After hepatectomy, SV increased compared with the preoperative state in both groups. Interestingly, in patients with FLR/SLV <50%, the spleen remained enlarged over time, whereas in those with FLR/SLV ≥50%, SV gradually returned toward baseline. Assuming that SV reflects hepatic functional reserve, our findings suggest that limited liver resection allows hepatic function to return to preoperative levels, whereas extensive resection is more likely to result in sustained functional impairment despite volumetric regeneration.

Previous research has consistently emphasized that the remnant liver volume and its functional capacity are major determinants of postoperative liver regeneration and clinical outcomes. Yoon et al. [4] demonstrated that in right-lobe living liver donors, those with a remnant liver volume of ≤35% had a POD 7 regeneration rate of 79.9%, compared with 50.3% in donors with a remnant volume >35%, indicating that smaller remnants regenerate more rapidly. Wang et al. [15] reported that RLV/body weight, RLV/TLV ratio, and postoperative bilirubin and albumin levels predicted regeneration in living liver donors, with left-lobe remnants showing faster hypertrophy. They also showed that liver volume typically reaches 80% of baseline within 1 month and nearly 90% by 6–12 months, reinforcing the dominant role of remnant volume [15].

These findings align closely with our results, in which FLR/SLV emerged as the strongest predictor of rapid early liver regeneration. Our study suggests that the relative extent of resection is the critical determinant of both regenerative speed and magnitude. This is consistent with hepatic physiology, whereby increased hepatocyte workload proportionally stimulates compensatory proliferation [16].

Kauffmann and Fong identified resection of more than 50% of liver volume and leaving less than 25% functional remnant as major surgical risk factors for PHLF, along with systemic risk factors such as diabetes, cirrhosis, malnutrition, hyperbilirubinemia, and renal dysfunction [17]. Thus, the association between lower FLR/SLV and accelerated regeneration underscores its clinical relevance: FLR/SLV reflects both regenerative potential and vulnerability to PHLF and may help balance oncologic radicality against postoperative safety.

Growing evidence suggests that postoperative splenomegaly may reflect alterations in portal hemodynamics and the underlying hepatic functional reserve. Bae et al. [10] demonstrated that SV/BSA was significantly larger in patients who developed PHLF and that SV/BSA predicted PHLF (AUC 0.663), independently influencing overall survival (hazard ratio, 3.935). Chen et al. [18] reported that splenomegaly in living donor liver transplant recipients may persist long term, and failure of regression may be associated with abnormal portal hemodynamics or graft dysfunction. Furthermore, Wang et al. [19] identified preoperative SV as an independent predictor of FLR growth after major hepatectomy, supporting the link between spleen size and regenerative dynamics.

In our cohort, although patients with FLR/SLV ≥50% and <50% achieved comparable remnant liver volumes at 3 months, postoperative spleen behavior differed between groups. Persistent splenomegaly was observed in the <50% group, whereas SV in the ≥50% group gradually approached baseline levels. This divergence may reflect differences in postoperative portal flow redistribution and sustained hemodynamic burden, particularly in patients undergoing larger resections.

Taken together, these findings suggest that SV may function as an imaging biomarker reflecting portal hypertension, fibrosis-related vascular remodeling, and overall hemodynamic stress imposed on the remnant liver. Persistent postoperative splenomegaly may therefore represent a state of latent liver vulnerability—an adaptive yet potentially strained physiologic condition—rather than incomplete regeneration per se. These observations require further validation through prospective studies incorporating longitudinal functional liver assessments.

Patients in the high-LRR group, who underwent more extensive resection, showed lower POD 1 HS-CRP levels, suggesting reduced acute-phase synthetic capacity of the remnant liver. Because CRP is synthesized exclusively by hepatocytes, a blunted early CRP response has been associated with impaired functional reserve and increased risk of postoperative liver dysfunction [20,21].

Conversely, higher POD 1 TB in this group likely reflects impaired bilirubin clearance after major resection. The extent of hepatectomy correlates with early postoperative bilirubin elevation [22], and inadequate bile excretion may delay the regenerative process [23]. Thus, despite volumetric hypertrophy, functional recovery—particularly in bile handling and acute-phase protein synthesis—lags behind liver regeneration, especially after extensive resection.

This study has several limitations. First, its relatively small sample size may introduce selection bias and limit generalizability. Second, postoperative imaging was not perfomed according to a strict protocol, with timing varying from 4–8 days for the 1-week scan and 2–4 months for the 3-month scan, potentially affecting volumetric accuracy. Third, laboratory data at 1 week and 3 months were unavailable, precluding direct assessment of functional recovery in parallel with volumetric changes. Fourth, imaging or functional assessment for baseline cirrhosis was not included, limiting evaluation of fibrosis-related regenerative differences. Lastly, follow-up beyond 3 months was unavailable, preventing assessment of long-term regeneration or functional recovery.

Despite these limitations, this study provides valuable insights into postoperative liver regeneration. By evaluating changes in liver and SV alongside early biochemical markers, it helps clarify the distinct patterns of volumetric regeneration and functional recovery according to the extent of hepatic resection.

FLR/SLV was the strongest predictor of postoperative liver regeneration, with smaller remnants showing faster early hypertrophy. SV dynamics differed according to FLR/SLV, and persistent postoperative splenomegaly may reflect sustained portal hemodynamic burden rather than incomplete volumetric regeneration per se. Combined assessment of FLR/SLV and SV patterns may improve risk stratification and enhance the evaluation of postoperative regenerative and recovery dynamics.

Future studies should explore whether postoperative SV changes represent a reversible adaptive response or a surrogate marker of latent hepatic vulnerability, and clarify the temporal trajectory and clinical implications of persistent splenomegaly.

## Supplementary material

Supplementary materials are available at https://doi.org/10.7180/kmj.26.147

## Article information

**Conflicts of interest**

No potential conflict of interest relevant to this article was reported.

**Funding**

This study was supported by a grant from Kosin University College of Medicine (2025).

**Author contributions**

Conceptualization: SK, GL, HHM. Data curation: GL, HK, WJY, NO, JR. Formal analysis: SK, HHM. Funding acquisition: HHM. Investigation: SK, GL, HK, SYK, YIC, DHS, NO, JR. Methodology: HHM, HK, JS, AC, DHG, CMK. Supervision: HHM. Visualization: SK, HHM. Writing-original draft: SK, HHM, HK. Writing-review and editing: SK, GL, HHM, WJY, JS, SYK, CMK, AC, DHG, NO, JR. All authors read and approved the final manuscript.

**ORCID**

Seoyeong Ku, https://orcid.org/0009-0002-8959-6981
Garam Lee, https://orcid.org/0000-0002-9941-8540
Hyung Hwan Moon, https://orcid.org/0000-0002-4212-4568
Hyungjune Ku, https://orcid.org/0000-0002-9804-6183
Won Jong Yang, https://orcid.org/0009-0001-1153-9170
Junho Song, https://orcid.org/0000-0003-0898-8749
Suyeon Kim, https://orcid.org/0009-0004-5260-5105
Chol Min Kang, https://orcid.org/0000-0001-6321-0003
Amy Choi, https://orcid.org/0009-0007-4836-5614
Dong Hyeon Gim, https://orcid.org/0009-0005-1157-8160
Young Il Choi, https://orcid.org/0000-0002-9630-6287
Dong Hoon Shin, https://orcid.org/0000-0001-6602-3393
Namkee Oh, https://orcid.org/0000-0002-6594-8973
Jinsoo Rhu, https://orcid.org/0000-0001-9809-8525

## References

1. Ibis C, Asenov Y, Akin M, Azamat IF, Sivrikoz N, Gurtekin B. Fac-

tors affecting liver regeneration in living donors after hepatectomy. Med Sci Monit 2017;23:5986–93.
2. Park HJ, Seo KI, Kim SJ, Lee SU, Yun BC, Han BH, et al. Effectiveness of albumin-bilirubin score as a predictor of post-hepatectomy liver failure in patients with hepatocellular carcinoma. Korean J Gastroenterol 2021;77:115–22.
3. Bohm F, Kohler UA, Speicher T, Werner S. Regulation of liver regeneration by growth factors and cytokines. EMBO Mol Med 2010;2:294–305.
4. Yoon YC, Park JH, Hong TH, You YK, Kim DG. Liver regeneration and factors influencing liver regeneration in donors and recipients of adult living donor liver transplantation using right lobe graft. J Korean Soc Transplant 2011;25:87–94.
5. Moon HH. Refractory ascites with intrahepatic portal thrombosis after living donor liver transplantation successfully treated by splenic artery embolization and apixaban (case report). Kosin Med J 2021;36:187–92.
6. Korchilava B, Khachidze T, Megrelishvili N, Svanadze L, Kakabadze M, Tsomaia K, et al. Liver regeneration after partial hepatectomy: triggers and mechanisms. World J Hepatol 2025;17:107378.
7. Kim HJ, Kim CY, Hur YH, Koh YS, Kim JC, Cho CK, et al. Comparison of remnant to total functional liver volume ratio and remnant to standard liver volume ratio as a predictor of postoperative liver function after liver resection. Korean J Hepatobiliary Pancreat Surg 2013;17:143–51.
8. Yu Q, Xu C, Li Q, Ding Z, Lv Y, Liu C, et al. Spleen volume-based non-invasive tool for predicting hepatic decompensation in people with compensated cirrhosis (CHESS1701). JHEP Rep 2022;4:100575.
9. Ito T, Tanemura A, Kuramitsu T, Murase T, Kaluba B, Noguchi D, et al. Spleen volume is a predictor of posthepatectomy liver failure and short-term mortality for hepatocellular carcinoma. Langenbecks Arch Surg 2023;408:297.
10. Bae JS, Lee DH, Yoo J, Yi NJ, Lee KW, Suh KS, et al. Association between spleen volume and the post-hepatectomy liver failure and overall survival of patients with hepatocellular carcinoma after resection. Eur Radiol 2021;31:2461–71.
11. Kim S, Ku HJ, Moon HH, Song SH, Choi YI, Shin DH, et al. Predictors of post-hepatectomy liver failure in Klatskin tumors: The role of preoperative glucose, future liver remnant to spleen ratio, and early bilirubin monitoring. Diagnostics (Basel) 2024;14:2716.
12. Oh N, Kim JH, Rhu J, Jeong WK, Choi GS, Kim JM, et al. Automated 3D liver segmentation from hepatobiliary phase MRI for enhanced preoperative planning. Sci Rep 2023;13:17605.
13. Oh N, Kim JH, Rhu J, Jeong WK, Choi GS, Kim J, et al. Comprehensive deep learning-based assessment of living liver donor CT angiography: from vascular segmentation to volumetric analysis. Int J Surg 2024;110:6551–7.
14. Oh N, Kim JH, Rhu J, Jeong WK, Choi GS, Kim JM, et al. 3D auto-segmentation of biliary structure of living liver donors using magnetic resonance cholangiopancreatography for enhanced preoperative planning. Int J Surg 2024;110:1975–82.
15. Wang WC, Wu TH, Hung HC, Lee JC, Cheng CH, Wang YC, et al. Liver regeneration of living donor after liver donation for transplantation: disparity in the left and right remnant liver. Medicine (Baltimore) 2024;103:e37632.
16. Michalopoulos GK, Bhushan B. Liver regeneration: biological and pathological mechanisms and implications. Nat Rev Gastroenterol Hepatol 2021;18:40–55.
17. Kauffmann R, Fong Y. Post-hepatectomy liver failure. Hepatobiliary Surg Nutr 2014;3:238–46.
18. Chen TY, Chen CL, Huang TL, Tsang LL, Wang CC, Liu YW, et al. Spleen volume and platelet count changes among donors after living donor liver transplantation. Hepatogastroenterology 2008;55:1211–5.
19. Wang W, Qin Z, Wang JL, Zhang L, Xu BH, Zhu H, et al. Spleen volume after stage-I associated liver partition and portal vein ligation for staged hepatectomy predicts future liver remnant. Langenbecks Arch Surg 2025;410:128.
20. Rahman SH, Evans J, Toogood GJ, Lodge PA, Prasad KR. Prognostic utility of postoperative C-reactive protein for posthepatectomy liver failure. Arch Surg 2008;143:247–53.
21. Yagi S, Hirata M, Miyachi Y, Uemoto S. Liver regeneration after hepatectomy and partial liver transplantation. Int J Mol Sci 2020;21:8414.
22. Gong WF, Zhong JH, Lu Z, Zhang QM, Zhang ZY, Chen CZ, et al. Evaluation of liver regeneration and post-hepatectomy liver failure after hemihepatectomy in patients with hepatocellular carcinoma. Biosci Rep 2019;39:BSR20190088.
23. Otao R, Beppu T, Isiko T, Mima K, Okabe H, Hayashi H, et al. External biliary drainage and liver regeneration after major hepatectomy. Br J Surg 2012;99:1569–74.

Original article

Kosin Medical Journal 2026;41(1):67-80
pISSN: 2005-9531 • eISSN: 2586-7024
https://doi.org/10.7180/kmj.26.152

KMJ
KOSIN MEDICAL JOURNAL

# Trends in participation and abnormal screening results in the National Health Screening Program for Infants and Children in South Korea, 2010–2023

**Ji Sook Kim**

*Department of Pediatrics, Kyungpook National University School of Medicine, Daegu, Korea*

**Background:** The National Health Screening Program for Infants and Children (NHSPIC) provides nationwide early detection of developmental issues. However, evidence regarding long-term national trends and regional disparities remains limited. We examined 14-year variations in screening participation and abnormal screening results.

**Methods:** We analyzed nationally aggregated NHSPIC data from the Korean Statistical Information Service for the period 2010-2023. Outcomes included annual screening participation rates and the prevalence of any abnormal overall screening result. Abnormal results were defined as "Caution" or "Follow-up needed," based on integrated assessments of growth and nutrition, developmental screening, sensory function, and oral health. Temporal trends were assessed using joinpoint regression to estimate annual percent changes and to identify statistically significant change points. Regional risk ratios and risk differences were calculated using national estimates for reference.

**Results:** National screening participation increased from 50.0% in 2010 to 87.1% in 2021, followed by a decline to 76.7% in 2023. The prevalence of any abnormal overall screening result increased from 8.6% to 19.3%, largely driven by a nearly threefold increase in the "Follow-up needed" category, from 3.0% to 8.8%. Across 17 regions, participation rates ranged from 66.9% to 79.7%, and abnormal result prevalence ranged from 11.4% to 18.3%, indicating persistent geographic disparities.

**Conclusions:** Over a 14-year period, NHSPIC coverage expanded substantially but declined in recent years, while regional disparities persisted in both participation and abnormal screening results. These patterns underscore the need for targeted regional strategies to improve access, strengthen follow-up systems, and support equity-oriented monitoring of early childhood screening outcomes.

**Keywords:** Child health services; Health status disparities; Infant; Mass screening; Preschool child

## Introduction

Early childhood represents a critical period for growth and neurodevelopment, during which the timely identification of developmental delays and health problems can significantly influence lifelong outcomes [1]. Early intervention maximizes developmental potential and mitigates long-term burdens, making systematic health screening programs a fundamental component of public health policy worldwide [2]. Many high-income countries have incorporated structured screening into their preventive health strategies, including the United Kingdom's Healthy Child Programme, the United States' Bright Futures guidelines, and Japan's mandated health examinations under the Ma-

**Received:** January 27, 2026; **Revised:** February 3, 2026; **Accepted:** February 3, 2026
**Corresponding Author:** Ji Sook Kim, MD, PhD
Department of Pediatrics, Kyungpook National University School of Medicine, 90 Chilgokjungang-daero 136-gil, Buk-gu, Daegu 41405, Korea
Tel: +82-53-200-2750 Fax: +82-53-200-2168 E-mail: jisook.kim.neo@gmail.com

© 2026 Kosin University College of Medicine
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ternal and Child Health Law [3-6]. International evidence shows that participation rates and outcomes of pediatric screening programs vary widely across regions and socioeconomic groups, reflecting differences in access to care, health system organization, and parental awareness [7]. Recent societal shifts, including the coronavirus disease 2019 (COVID-19) pandemic, have further altered healthcare-seeking behaviors [8].

In South Korea, the National Health Screening Program for Infants and Children (NHSPIC) was introduced in November 2007 to address emerging health challenges, including the need for systematic growth monitoring and early identification of developmental disorders [9,10]. Administered by the National Health Insurance Service (NHIS), the NHSPIC provides comprehensive serial health examinations, comprising physical measurements, developmental screening, and oral health checks, free of charge to all eligible children. The program originally comprised seven screening rounds conducted at ages 4–6 months, 9–12 months, 18–24 months, 30–36 months, 42–48 months, 54–60 months, and 66–71 months. On January 1, 2021, the program was expanded to include a new screening round for newborns aged 14–35 days, bringing the total to eight rounds and aiming to detect neonatal abnormalities such as congenital conditions and breastfeeding problems at the earliest possible stage [11]. However, challenges remain regarding equitable access and the stability of screening outcomes over time. Regional disparities in healthcare utilization persist, attributed to uneven distribution of medical resources and varying socioeconomic conditions [12].

Although earlier evaluations focused mainly on the program's introductory phase, there is limited longitudinal evidence on how screening participation and abnormal screening results have evolved over more than a decade, particularly with respect to regional disparities. This study therefore analyzes temporal trends and regional variations in screening participation rates and the prevalence of abnormal screening results in South Korea from 2010 to 2023. Using nationwide aggregated data, we applied joinpoint regression analysis to identify significant temporal changes over the 14-year period. These findings provide empirical evidence on the program's long-term performance and can inform policy refinements to enhance equity in child health screening programs.

## Methods

**Ethical statements:** This study was approved by the Institutional Review Board (IRB) of Kyungpook National University Chilgok Hospital (IRB No. 2026-01-035). Patient consent was waived because this study was based on publicly available aggregated statistical data and did not involve individual-level identifiable information.

### 1. Data sources

Data from the NHSPIC were obtained from the Korean Statistical Information Service (KOSIS), the national statistical database that provides access to Korea's official statistics. We used aggregated indicators on infant and child health screening available through KOSIS, which are derived from the National Health Screening Statistical Yearbook published by the NHIS. The yearbook compiles nationwide administrative data from the NHSPIC. We extracted annual statistics for the period 2010–2023.

### 2. Study variables

The primary variable was the annual screening participation rate, defined as the proportion of eligible children who underwent screening in a given year. We further calculated age-specific participation rates for each screening round at the national level for the years 2012–2023. The secondary variable was the annual prevalence of any abnormal overall screening result, rather than abnormalities in individual test items. Operationally, an abnormal result was defined as the combined proportion of "Caution" and "Follow-up needed" classifications. These results are based on integrated assessments conducted at each screening round, including physical measurements, developmental screening with the Korean Developmental Screening Test for Infants and Children (K-DST), sensory function tests, and oral health examinations.

To ensure analytic consistency across years with varying reporting categories, we harmonized "Follow-up evaluation needed" and "Ongoing management needed" into a single "Follow-up needed" category (Supplementary Table 1). This category includes both children requiring further diagnostic evaluation and those with existing diagnoses requiring ongoing management. Because this harmonized "Follow-up needed" category encompasses both newly identified concerns and children already diagnosed and

under ongoing management, temporal increases in this category may overestimate trends in new-onset cases and are better interpreted as reflecting growing follow-up and care needs within the screening system.

Temporal patterns were evaluated using joinpoint regression analysis to identify significant changes in slope and to estimate annual percent changes (APCs) with 95% confidence intervals [13,14]. These analyses were performed at both national and regional levels. Furthermore, to account for the structural change in eligibility introduced in 2021, we conducted a sensitivity analysis excluding infants aged 14–35 days. For this analysis, participation rates were recalculated using criteria consistent with the pre-2021 period to assess whether the observed trends were robust to this definitional change. As additional stratified analysis beyond the primary and secondary outcomes, screening participation rates and the prevalence of any abnormality were calculated separately for each screening round group and region. The NHSPIC rounds were grouped based on the standard scheduled ages: round 1 (14–35 days; newborn), rounds 2–3 (4–6 and 9–12 months; infancy), rounds 4–5 (18–24 and 30–36 months; early toddlerhood), and rounds 6–8 (42–48, 54–60, and 66–71 months; late preschool). The screening rate was defined as the proportion of eligible children who underwent screening in each round group. Any abnormality was defined as the proportion of screened children classified as either "Caution" or "Follow-up needed" in the overall integrated screening assessment for that round group.

### 3. Statistical analysis

For descriptive regional comparisons, we calculated rate ratios (RRs) and risk differences (RDs), with corresponding 95% confidence intervals (CIs), using the national total (South Korea) as the reference. RRs were defined as the ratio of regional screening participation rates or prevalences of abnormal screening results to the corresponding national estimates. Ninety-five percent CIs for RRs were constructed assuming a log-normal distribution of the ratio measure, using standard large-sample approximations for rate ratios based on aggregated count data [15].

RDs were defined as the absolute difference (in percentage points) between regional and national estimates. Ninety-five percent CIs for RDs were calculated using normal approximations based on binomial variance estimates for independent proportions, taking advantage of the large-sample properties of the national dataset.

Temporal trends in screening participation rates and the prevalence of any abnormal screening result were evaluated using joinpoint regression analysis, which identifies time points at which a statistically significant change in the linear slope occurs and estimates the APC for each time segment [13,14].

All joinpoint analyses were conducted using the Joinpoint Regression Program ver. 5.4.0.0 (April 2025) developed by the Statistical Research and Applications Branch, Surveillance Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute. Joinpoint regression was performed using a grid search approach, with a minimum of 0 and a maximum of two joinpoints permitted and a minimum segment length of two observations before and after each joinpoint. We limited the maximum number of joinpoints to two to avoid overfitting given the 14 annual observations in each time series. The optimal model was selected using the weighted Bayesian Information Criterion.

APC estimates were calculated directly from the observed annual data used in this study rather than relying on presmoothed or model-derived values. APCs and corresponding 95% CIs were estimated using an empirical quantile method based on 5,001 resamples. For variance estimation, we specified the heteroscedastic error option with standard errors calculated from the data, and temporal correlation was addressed by fitting a first-order autocorrelation model estimated from the data, as implemented in the joinpoint software. Statistical significance of changes in trend and APC estimates was assessed using the default permutation test procedures provided by the program, with a two-sided $p$-value <0.05 considered statistically significant. Joinpoint analyses were performed for both outcomes at the national and regional levels to characterize geographic variation in temporal trends.

## Results

### 1. Screening participation rate: overall level and regional comparisons

Across 2010–2023, the national screening participation rate was 69.9% (27,778,863 of 39,743,828 eligible children), serving as the reference for regional comparisons (Table 1).

**Table 1.** Regional screening participation rates in the NHSPIC, South Korea, 2010–2023

| Region | Eligible population | Screened population | Screening rate (%) | Screening rate ratio (95% CI)[a] | Screening rate difference (95% CI)[a] |
|---|---|---|---|---|---|
| Total (South Korea) | 39,743,828 | 27,778,863 | 69.9 | Reference | Reference |
| Seoul | 7,490,678 | 5,188,441 | 69.3 | 0.99 (0.99 to 0.99) | –0.6 (–0.7 to –0.6) |
| Busan | 2,276,254 | 1,671,041 | 73.4 | 1.05 (1.05 to 1.05) | 3.5 (3.5 to 3.6) |
| Daegu | 1,725,449 | 1,160,160 | 67.2 | 0.96 (0.96 to 0.96) | –2.7 (–2.7 to –2.6) |
| Incheon | 2,275,049 | 1,623,260 | 71.4 | 1.02 (1.02 to 1.02) | 1.5 (1.4 to 1.5) |
| Gwangju | 1,158,429 | 775,529 | 66.9 | 0.96 (0.96 to 0.96) | –2.9 (–3.0 to –2.9) |
| Daejeon | 1,225,781 | 867,100 | 70.7 | 1.01 (1.01 to 1.01) | 0.8 (0.8 to 0.9) |
| Ulsan | 999,253 | 731,709 | 73.2 | 1.05 (1.05 to 1.05) | 3.3 (3.2 to 3.4) |
| Sejong[b] | 193,601 | 154,282 | 79.7 | 1.14 (1.14 to 1.14) | 9.8 (9.6 to 10.0) |
| Gyeonggi-do | 10,667,653 | 7,454,148 | 69.9 | 1.00 (1.00 to 1.00) | –0.0 (–0.0 to 0.0) |
| Gangwon-do | 1,033,123 | 725,382 | 70.2 | 1.00 (1.00 to 1.01) | 0.3 (0.2 to 0.4) |
| Chungcheongbuk-do | 1,229,336 | 866,902 | 70.5 | 1.01 (1.01 to 1.01) | 0.6 (0.5 to 0.7) |
| Chungcheongnam-do | 1,716,753 | 1,170,822 | 68.2 | 0.97 (0.97 to 0.98) | –1.7 (–1.8 to –1.6) |
| Jeollabuk-do | 1,280,112 | 858,958 | 67.1 | 0.96 (0.96 to 0.96) | –2.8 (–2.9 to –2.7) |
| Jeollanam-do | 1,340,071 | 911,701 | 68.0 | 0.97 (0.97 to 0.97) | –1.9 (–1.9 to –1.8) |
| Gyeongsangbuk-do | 1,946,238 | 1,351,758 | 69.5 | 0.99 (0.99 to 0.99) | –0.4 (–0.5 to –0.4) |
| Gyeongsangnam-do | 2,668,242 | 1,894,674 | 71.0 | 1.02 (1.02 to 1.02) | 1.1 (1.1 to 1.2) |
| Jeju-do | 513,376 | 372,996 | 72.7 | 1.04 (1.04 to 1.04) | 2.8 (2.6 to 2.9) |

NHSPIC, National Health Screening Program for Infants and Children; CI, confidence interval.
[a]Screening rate ratios, risk differences, and 95% CIs were calculated using South Korea as the reference. Due to the large national sample size, 95% CIs are very narrow and reflect high statistical precision rather than the magnitude of effect.
[b]Sejong is a special self-governing city established in 2012.

Substantial geographic variation in screening uptake was observed over the study period. Sejong exhibited the highest overall participation rate (79.7%; RR, 1.14; 95% CI, 1.14–1.14), corresponding to an absolute increase of 9.8 percentage points compared with the national average. Conversely, Gwangju (66.9%; RR, 0.96; 95% CI, 0.96–0.96), Jeollabuk-do (67.1%; RR, 0.96; 95% CI, 0.96–0.96), and Daegu (67.2%; RR, 0.96; 95% CI, 0.96–0.96) demonstrated participation rates below the national level, with absolute differences ranging from –2.7 to –2.8 percentage points. Other metropolitan areas showed mixed patterns, with Busan (73.4%; RR, 1.05; 3.5 percentage points) and Ulsan (73.2%; RR, 1.05; 3.3 percentage points) exceeding the national average, while Seoul (69.3%; RR, 0.99; –0.6 percentage points) closely approximated the national level. These findings indicate that regional disparities were evident not only in relative measures but also in absolute participation differences over the aggregated study period.

**2. Screening participation rate: temporal trends**

Year-specific participation rates and joinpoint trend estimates are presented in Table 2, with the national trajectory illustrated in Fig. 1. Nationally, screening participation increased from 50.0% in 2010 to a peak of 87.1% in 2021, followed by a decline to 76.7% in 2023. To account for the 2021 addition of neonatal screening (14–35 days), sensitivity analysis excluding this group was performed (Supplementary Table 2). This analysis showed a peak of 90.8% in 2021 followed by a significant decline to 79.9% in 2023 (APC, –5.7; $p<0.05$), confirming that the recent downward trend is robust regardless of the change in eligibility criteria. Joinpoint regression identified three distinct trend periods: a rapid early expansion from 2010 to 2013 (APC, 7.96%; $p<0.05$), sustained moderate growth from 2015 to 2020 (APC, 3.48%; $p<0.05$), and a significant decline from 2022 to 2023 (APC, –5.44%; $p<0.05$).

Regional trend patterns were heterogeneous, reflecting differential improvements in screening uptake across the country. While regional patterns varied, absolute differences (RD) provided additional insight into geographic disparities (Table 1). Most regions demonstrated similar triphasic patterns with varying magnitudes. For example,

**Table 2.** Screening participation rate (%) and joinpoint trends by region, South Korea, 2010–2023

| Region | Screening participation rate (%) | | | | | | | | | | | | | | Trend | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | 2021 | 2022 | 2023 | Trend 1 | | Trend 2 | | Trend 3 | |
| | | | | | | | | | | | | | | | Year | APC | Year | APC | Year | APC |
| Total (South Korea) | 50.0 | 53.8 | 55.4 | 63.7 | 69.8 | 69.5 | 71.9 | 72.1 | 74.5 | 77.6 | 83.0 | 87.1 | 80.7 | 76.7 | 2010–2013 | 7.96[a] | 2015–2020 | 3.48[a] | 2022–2023 | −5.44[a] |
| Busan | 55.2 | 58.4 | 61.3 | 69.2 | 73.9 | 73.2 | 74.3 | 75.2 | 77.8 | 80.2 | 84.9 | 88.1 | 82.5 | 77.8 | 2010–2013 | 6.92[a] | 2015–2020 | 2.79[a] | 2022–2023 | −5.51[a] |
| Chungcheongbuk-do | 49.3 | 52.0 | 55.8 | 63.5 | 68.7 | 70.9 | 73.0 | 74.1 | 75.9 | 78.6 | 85.3 | 88.8 | 82.1 | 77.4 | 2010–2013 | 8.58[a] | 2015–2020 | 3.83[a] | 2022–2023 | −6.27[a] |
| Chungcheongnam-do | 47.1 | 50.2 | 50.5 | 60.2 | 66.1 | 68.1 | 70.9 | 71.3 | 73.7 | 77.1 | 83.6 | 88.1 | 81.3 | 75.8 | 2010–2013 | 8.87[a] | 2015–2020 | 4.37[a] | 2022–2023 | −6.46[a] |
| Daegu | 46.7 | 51.1 | 49.4 | 59.8 | 66.1 | 65.7 | 68.9 | 69.9 | 71.8 | 74.8 | 81.8 | 88.4 | 81.1 | 77.5 | 2010–2020 | 5.23[a] | 2022–2023 | −5.71 | | |
| Daejeon | 48.8 | 55.8 | 56.9 | 64.3 | 71.6 | 72.3 | 73.8 | 73.4 | 75.6 | 77.9 | 82.9 | 87.6 | 81.7 | 78.0 | 2010–2013 | 8.85[a] | 2015–2020 | 3.00[a] | 2022–2023 | −4.47[a] |
| Gangwon-do | 48.2 | 51.4 | 54.5 | 62.5 | 71.8 | 70.4 | 73.6 | 73.7 | 77.1 | 80.9 | 85.5 | 87.6 | 80.4 | 76.7 | 2010–2013 | 10.13[a] | 2015–2020 | 3.40[a] | 2022–2023 | −6.43[a] |
| Gwangju | 43.7 | 47.6 | 50.8 | 60.8 | 66.3 | 68.7 | 70.3 | 71.6 | 72.9 | 74.8 | 81.2 | 87.3 | 79.9 | 74.8 | 2010–2013 | 10.75[a] | 2015–2020 | 3.93[a] | 2022–2023 | −6.39[a] |
| Gyeonggi-do | 51.6 | 54.8 | 56.5 | 64.4 | 69.5 | 68.2 | 70.8 | 70.7 | 73.8 | 77.4 | 82.8 | 86.5 | 80.7 | 77.3 | 2010–2020 | 4.23[a] | 2022–2023 | −5.42 | | |
| Gyeongsangbuk-do | 49.2 | 52.1 | 51.9 | 62.0 | 69.7 | 67.9 | 72.1 | 72.2 | 74.4 | 77.5 | 83.7 | 88.7 | 82.3 | 78.8 | 2010–2013 | 8.58[a] | 2015–2020 | 3.94[a] | 2022–2023 | −4.72[a] |
| Gyeongsangnam-do | 51.7 | 55.0 | 56.7 | 65.6 | 70.4 | 71.4 | 73.2 | 73.5 | 75.6 | 78.9 | 84.5 | 88.4 | 82.8 | 78.2 | 2010–2013 | 7.61[a] | 2015–2020 | 3.48[a] | 2022–2023 | −5.25[a] |
| Incheon | 52.4 | 55.5 | 58.3 | 65.0 | 72.2 | 71.1 | 74.4 | 73.2 | 75.3 | 79.4 | 83.0 | 86.4 | 80.4 | 77.0 | 2010–2013 | 7.85[a] | 2015–2020 | 2.87[a] | 2022–2023 | −4.98[a] |
| Jeju-do | 52.0 | 57.1 | 59.7 | 67.8 | 71.7 | 70.0 | 74.0 | 75.5 | 76.6 | 79.4 | 84.7 | 88.8 | 82.5 | 78.6 | 2010–2012 | 8.79[a] | 2014–2020 | 3.40[a] | 2022–2023 | −5.13[a] |
| Jeollabuk-do | 50.6 | 52.8 | 54.0 | 60.9 | 66.8 | 66.4 | 68.1 | 69.3 | 71.0 | 73.1 | 81.3 | 87.3 | 79.2 | 74.0 | 2010–2020 | 4.75[a] | 2022–2023 | −7.46[a] | | |
| Jeollanam-do | 47.2 | 49.9 | 53.2 | 61.9 | 68.2 | 67.7 | 70.4 | 70.0 | 73.0 | 75.7 | 83.2 | 88.2 | 80.7 | 73.7 | 2010–2020 | 5.07[a] | 2022–2023 | −8.39[a] | | |
| Seoul | 48.3 | 53.2 | 54.7 | 63.0 | 69.8 | 70.3 | 72.4 | 72.4 | 74.3 | 76.8 | 81.0 | 85.5 | 78.2 | 74.3 | 2010–2013 | 9.11[a] | 2015–2020 | 2.99[a] | 2022–2023 | −5.76[a] |
| Ulsan | 55.0 | 59.3 | 58.5 | 67.6 | 73.6 | 72.9 | 73.6 | 74.8 | 76.9 | 80.7 | 85.8 | 89.3 | 83.4 | 79.3 | 2010–2020 | 3.87[a] | 2022–2023 | −5.68[a] | | |

Screening participation rate was defined as the proportion of eligible children who received at least one screening examination in a given year.
APC, annual percent change.
[a] $p<0.05$

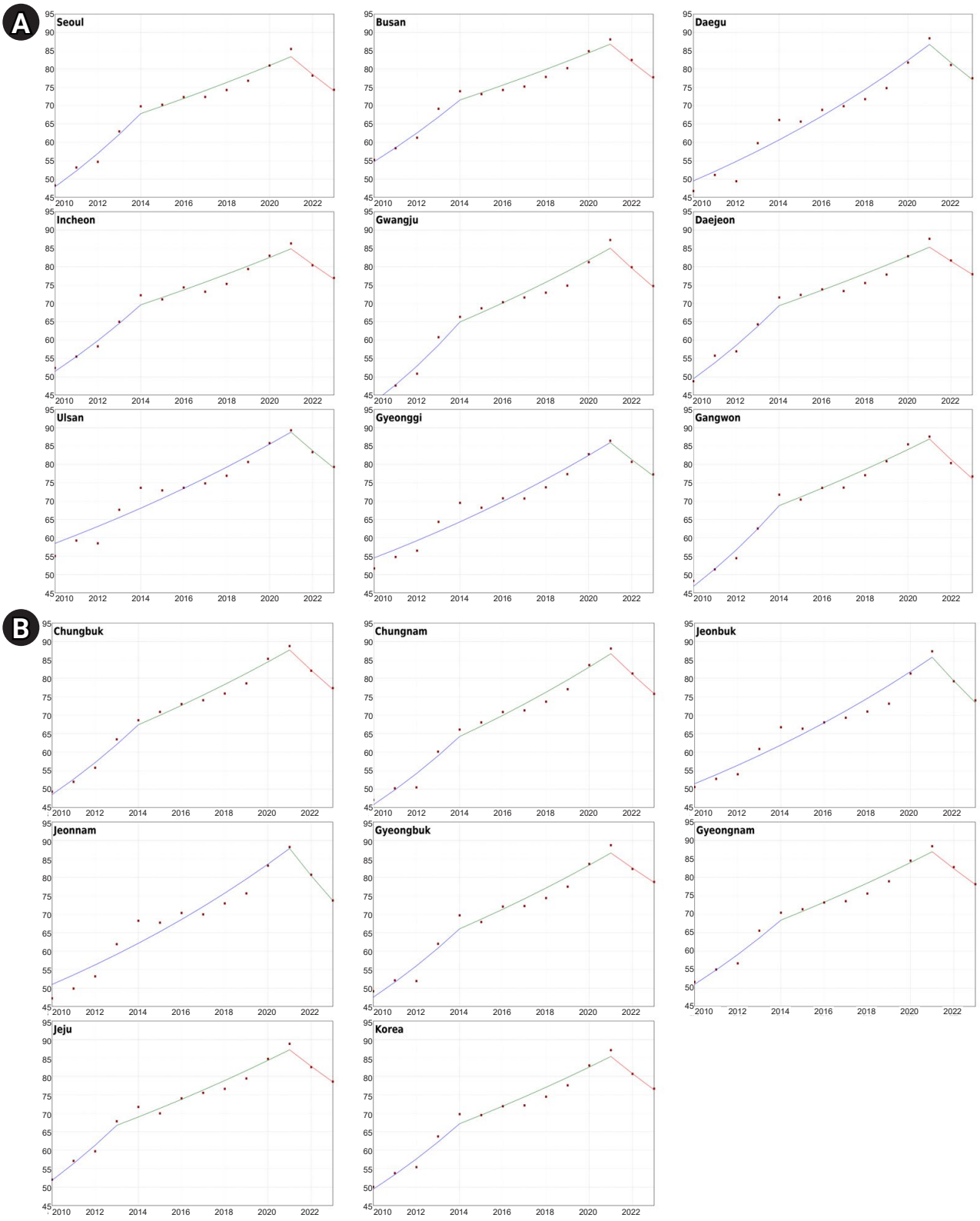


**Fig. 1.** Regional trends in infant and child health screening participation in South Korea, 2010–2023. (A) Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, Ulsan, Gyeonggi, and Gangwon; (B) Chungbuk, Chungnam, Jeonbuk, Jeonnam, Gyeongbuk, Gyeongnam, Jeju, and Korea.

Busan showed comparable phases with APCs of 6.92% (2010–2013), 2.79% (2015–2020), and –5.51% (2022–2023), all statistically significant. However, some regions exhibited distinct patterns. Daegu and Gyeonggi-do showed only two significant trend segments: a prolonged increasing phase from 2010 to 2020 (APC 5.23% and 4.23%, respectively), followed by a decline in 2022–2023 (APC –5.71% and –5.42%, respectively, though not statistically significant in Daegu). Notably, Ulsan demonstrated continuous growth throughout 2010–2020 (APC, 3.87%; $p<0.05$) with a subsequent decline in 2022–2023 (APC, –5.68%; $p<0.05$). The widespread decline in 2022–2023 observed across all regions suggests a common underlying factor, likely related to the ongoing effects of the COVID-19 pandemic. In addition, we analyzed nationwide participation rates by screening round (age group) from 2012 to 2023, which showed marked differences in temporal trends across age groups (Supplementary Table 3).

### 3. Prevalence of any abnormal screening result: overall level and regional comparisons

Table 3 summarizes the distribution of screening results aggregated over 2010–2023. Nationally, any abnormal result (defined as "Caution" or "Follow-up needed") accounted for 14.6% of examinees (4,049,349 of 27,778,862), indicating that approximately one in seven screened children was classified as having a finding warranting either Caution or Follow-up. These classifications are based on integrated assessments across growth, development (K-DST), sensory function, and oral health. Within the abnormal category, 8.5% were classified as "Caution" and 6.1% as "Follow-up needed." It is important to note that the abnormal category includes children with existing diagnoses receiving ongoing management, as detailed in the classification scheme in Supplementary Table 1.

Marked regional variation in the overall prevalence of abnormal results was observed. Gyeongsangbuk-do exhibited the highest prevalence (18.3%; RR, 1.27; 95% CI, 1.27–1.28), corresponding to an absolute increase of 3.7 percentage points compared with the national average. Similarly, Gyeongsangnam-do (17.0%; RR, 1.18; 95% CI, 1.18–1.18; 2.4 percentage points) and Daegu (16.3%; RR, 1.12; 95% CI, 1.12–1.13; 1.7 percentage points) demonstrated substantially higher prevalences of abnormal findings.

In contrast, several regions showed markedly lower prevalences than the national level, including Daejeon (11.4%; RR, 0.78; 95% CI, 0.78–0.78; –3.2 percentage points), Sejong (11.9%; RR, 0.82; 95% CI, 0.81–0.83; –2.7 percentage points), and Jeollanam-do (12.5%; RR, 0.85; 95% CI, 0.85–0.86; –2.1 percentage points). Other regions exhibited more modest absolute differences, generally within ±1 percentage point of the national prevalence.

Taken together, these findings indicate that regional disparities in abnormal screening results are evident not only in relative measures such as risk ratios, but also in absolute differences in prevalence, underscoring substantial geographic heterogeneity in screening outcomes beyond what would be expected from random variation alone.

### 4. Prevalence of any abnormal screening result: temporal trends

Trends in abnormal screening prevalence are presented in Table 4, with the national trajectory depicted in Fig. 2. At the national level, the prevalence increased from 8.6% in 2010 to 19.3% in 2023, representing more than a twofold increase over the study period.

When decomposed, the increase was more strongly driven by the "Follow-up needed" category (3.0% to 8.8%; Supplementary Table 4) than by the "Caution" category (5.6% to 10.7%) (Supplementary Table 5). Additional details on category definitions and harmonization across years are provided in Supplementary Table 1. Joinpoint analysis identified two significant trend periods: a rapid increase from 2010 to 2018 (APC, 11.03%; $p<0.05$), followed by relative stabilization from 2020 to 2023 (APC, 0.86%; not significant). This pattern indicates that abnormal screening prevalence increased most rapidly during the first half of the study period before plateauing in recent years.

Regional joinpoint estimates revealed heterogeneous trend patterns. Most regions demonstrated patterns similar to the national trend, with significant increases during the early-to-mid period followed by stabilization. However, the timing and magnitude of changes varied. For example, Busan showed a non-significant decline in 2010–2011 (APC, –10.02%), followed by a steep increase from 2013 to 2017 (APC, 17.73%; $p<0.05$), and modest continued growth from 2019 to 2023 (APC, 2.63%; not significant). Several regions, including Daegu, Gangwon-do, Gyeonggi-do, and Seoul, exhibited continuous increasing trends from 2010 through 2018–2021 before reaching a plateau or slight

**Table 3.** Regional distribution of infant and child health screening results from the NHSPIC, South Korea, 2010–2023

| Region | Examinee | Normal (%) | Caution (%) | Follow-up needed (%)[a] | Any abnormality (%) | Risk ratio (95% CI)[b] | Risk difference (95% CI)[b] |
|---|---|---|---|---|---|---|---|
| Total (South Korea) | 27,778,862 | 23,729,513 (85.4) | 2,348,068 (8.5) | 1,701,281 (6.1) | 4,049,349 (14.6) | Reference | Reference |
| Seoul | 5,188,442 | 4,424,035 (85.3) | 432,126 (8.3) | 332,281 (6.4) | 764,407 (14.7) | 1.01 (1.01 to 1.02) | 0.1 (0.05 to 0.15) |
| Busan | 1,671,040 | 1,412,820 (84.5) | 136,275 (8.2) | 121,945 (7.3) | 258,220 (15.5) | 1.06 (1.06 to 1.07) | 0.9 (0.85 to 0.95) |
| Daegu | 1,160,160 | 971,219 (83.7) | 117,556 (10.1) | 71,385 (6.2) | 188,941 (16.3) | 1.12 (1.12 to 1.13) | 1.7 (1.60 to 1.80) |
| Incheon | 1,623,259 | 1,402,129 (86.4) | 126,668 (7.8) | 94,462 (5.8) | 221,130 (13.6) | 0.93 (0.93 to 0.93) | −1.0 (−1.05 to −0.95) |
| Gwangju | 775,529 | 661,566 (85.3) | 67,113 (8.7) | 46,850 (6.0) | 113,963 (14.7) | 1.01 (1.00 to 1.01) | 0.1 (0.02 to 0.18) |
| Daejeon | 867,100 | 767,836 (88.6) | 55,222 (6.4) | 44,042 (5.1) | 99,264 (11.4) | 0.78 (0.78 to 0.78) | −3.2 (−3.30 to −3.10) |
| Ulsan | 731,709 | 627,269 (85.7) | 55,989 (7.7) | 48,451 (6.6) | 104,440 (14.3) | 0.98 (0.97 to 0.98) | −0.3 (−0.40 to −0.20) |
| Sejong[c] | 154,282 | 135,878 (88.1) | 9,754 (6.3) | 8,650 (5.6) | 18,404 (11.9) | 0.82 (0.81 to 0.83) | −2.7 (−2.90 to −2.50) |
| Gyeonggi-do | 7,454,150 | 6,403,070 (85.9) | 604,684 (8.1) | 446,396 (6.0) | 1,051,080 (14.1) | 0.96 (0.95 to 0.96) | −0.5 (−0.55 to −0.45) |
| Gangwon-do | 725,382 | 616,699 (85.0) | 59,903 (8.3) | 48,780 (6.7) | 108,683 (15.0) | 1.03 (1.02 to 1.03) | 0.4 (0.30 to 0.50) |
| Chungcheongbuk-do | 866,902 | 765,310 (88.3) | 59,392 (6.9) | 42,200 (4.9) | 101,592 (11.7) | 0.80 (0.79 to 0.80) | −2.9 (−3.00 to −2.80) |
| Chungcheongnam-do | 1,170,819 | 1,004,334 (85.8) | 104,151 (8.9) | 62,334 (5.3) | 166,485 (14.2) | 0.97 (0.97 to 0.98) | −0.4 (−0.45 to −0.35) |
| Jeollabuk-do | 858,958 | 748,017 (87.1) | 68,204 (7.9) | 42,737 (5.0) | 110,941 (12.9) | 0.88 (0.88 to 0.89) | −1.7 (−1.80 to −1.60) |
| Jeollanam-do | 911,701 | 797,566 (87.5) | 65,447 (7.2) | 48,688 (5.3) | 114,135 (12.5) | 0.85 (0.85 to 0.86) | −2.1 (−2.20 to −2.00) |
| Gyeongsangbuk-do | 1,351,758 | 1,104,641 (81.7) | 147,135 (10.9) | 99,982 (7.4) | 247,117 (18.3) | 1.27 (1.27 to 1.28) | 3.7 (3.60 to 3.80) |
| Gyeongsangnam-do | 1,894,675 | 1,572,551 (83.0) | 200,960 (10.6) | 121,164 (6.4) | 322,124 (17.0) | 1.18 (1.18 to 1.18) | 2.4 (2.30 to 2.50) |
| Jeju-do | 372,996 | 314,573 (84.3) | 37,489 (10.1) | 20,934 (5.6) | 58,423 (15.7) | 1.08 (1.07 to 1.08) | 1.1 (1.00 to 1.20) |

NHSPIC, National Health Screening Program for Infants and Children; CI, confidence interval.

[a]"Follow-up needed" includes children requiring further diagnostic evaluation as well as those already diagnosed with developmental problems or currently receiving treatment requiring ongoing management.

[b]Risk ratios, risk differences, and 95% CIs were calculated using South Korea as the reference. Due to the large national sample size, 95% CIs are very narrow and reflect high statistical precision rather than the magnitude of effect.

[c]Sejong is a special self-governing city established in 2012.

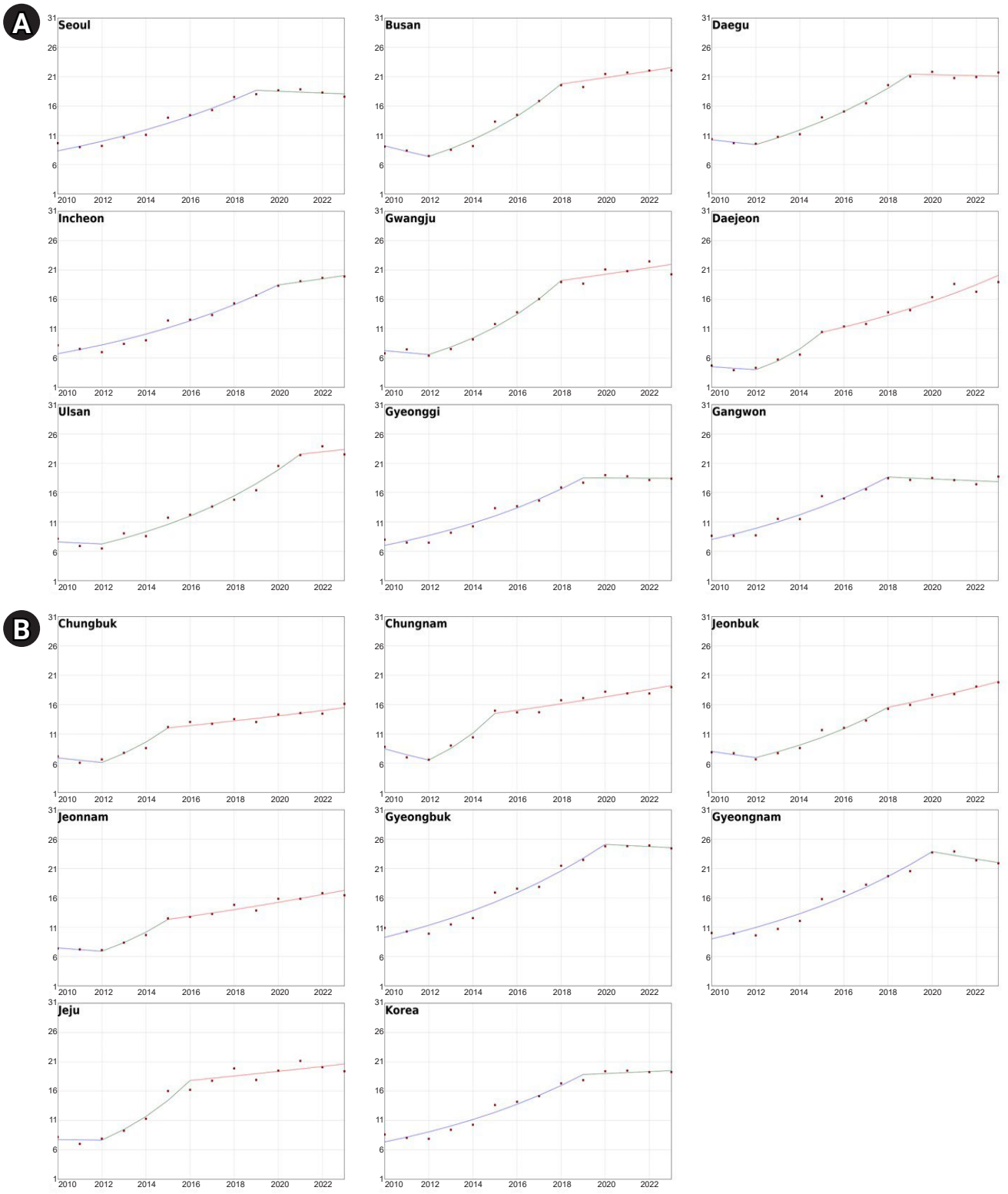


**Fig. 2.** Regional trends in abnormal infant and child health screening results in South Korea, 2010–2023. (A) Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, Ulsan, Gyeonggi, and Gangwon; (B) Chungbuk, Chungnam, Jeonbuk, Jeonnam, Gyeongbuk, Gyeongnam, Jeju, and Korea.

**Table 4.** Trends in the prevalence of any abnormal screening result (%) across regions in Korea, 2010 to 2023

| Region | Screening participation rate (%) | | | | | | | | | | | | | | Trend | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | 2021 | 2022 | 2023 | Trend 1 | | Trend 2 | | Trend 3 | |
| | | | | | | | | | | | | | | | Year | APC | Year | APC | Year | APC |
| Total (South Korea) | 8.6 | 8.1 | 7.9 | 9.4 | 10.3 | 13.6 | 14.2 | 15.2 | 17.3 | 17.9 | 19.4 | 19.5 | 19.2 | 19.3 | 2010–2018 | 11.03[a] | 2010–2018 | 0.86 | - | - |
| Busan | 9.1 | 8.4 | 7.5 | 8.5 | 9.2 | 13.3 | 14.5 | 16.9 | 19.6 | 19.2 | 21.4 | 21.7 | 22.0 | 22.1 | 2010–2011 | −10.02 | 2013–2017 | 17.73[a] | 2019–2023 | 2.63 |
| Chungcheongbuk-do | 7.2 | 6.1 | 6.7 | 7.8 | 8.6 | 12.2 | 13.0 | 12.7 | 13.5 | 13.0 | 14.3 | 14.6 | 14.4 | 16.1 | 2010–2011 | −5.82 | 2013–2014 | 24.91[a] | 2016–2023 | 3.28[a] |
| Chungcheongnam-do | 8.8 | 7.0 | 6.6 | 9.0 | 10.4 | 14.9 | 14.7 | 14.7 | 16.7 | 17.1 | 18.2 | 17.9 | 17.9 | 19.0 | 2010–2011 | −12.69 | 2013–2014 | 30.68[a] | 2016–2023 | 3.53[a] |
| Daegu | 10.4 | 9.7 | 9.6 | 10.7 | 11.2 | 14.1 | 15.1 | 16.5 | 19.6 | 21.0 | 21.8 | 20.8 | 20.9 | 21.7 | 2010–2011 | −4.11 | 2013–2018 | 12.37[a] | 2020–2023 | −0.13 |
| Daejeon | 4.7 | 3.9 | 4.3 | 5.8 | 6.6 | 10.4 | 11.4 | 11.8 | 13.8 | 14.2 | 16.4 | 18.6 | 17.3 | 18.9 | 2010–2011 | −6.08 | 2013–2014 | 37.46[a] | 2016–2023 | 8.49[a] |
| Gangwon-do | 8.7 | 8.7 | 8.7 | 11.5 | 11.5 | 15.4 | 15.0 | 16.6 | 18.5 | 18.2 | 18.5 | 18.1 | 17.4 | 18.7 | 2010–2017 | 10.91[a] | 2019–2023 | −0.60 | - | - |
| Gwangju | 6.8 | 7.5 | 6.4 | 7.5 | 9.2 | 11.8 | 13.8 | 16.1 | 18.9 | 18.7 | 21.1 | 20.8 | 22.5 | 20.3 | 2010–2011 | −4.12 | 2013–2017 | 19.58[a] | 2019–2023 | 2.49 |
| Gyeonggi-do | 8.0 | 7.5 | 7.5 | 9.2 | 10.2 | 13.3 | 13.7 | 14.6 | 16.9 | 17.7 | 19.0 | 18.8 | 18.2 | 18.4 | 2010–2018 | 11.52[a] | 2020–2023 | −0.18 | - | - |
| Gyeongsangbuk-do | 10.9 | 10.3 | 9.9 | 11.5 | 12.6 | 16.9 | 17.6 | 17.9 | 21.5 | 22.5 | 24.8 | 24.8 | 24.9 | 24.4 | 2010–2019 | 10.47[a] | 2021–2023 | −0.78 | - | - |
| Gyeongsangnam-do | 10 | 9.9 | 9.6 | 10.7 | 12.1 | 15.8 | 17.1 | 18.2 | 19.7 | 20.6 | 23.7 | 23.9 | 22.4 | 21.9 | 2010–2019 | 10.51[a] | 2021–2023 | −2.83 | - | - |
| Incheon | 8.2 | 7.5 | 7.0 | 8.4 | 9.0 | 12.4 | 12.5 | 13.3 | 15.3 | 16.7 | 18.3 | 19.1 | 19.6 | 19.9 | 2010–2019 | 10.64[a] | 2021–2023 | 2.79 | - | - |
| Jeju-do | 8.2 | 7.0 | 7.9 | 9.3 | 11.3 | 16.0 | 16.2 | 17.8 | 19.9 | 17.9 | 19.5 | 21.1 | 20.1 | 19.4 | 2010–2016 | 16.10[a] | 2018–2023 | 1.31 | - | - |
| Jeollabuk-do | 7.9 | 7.7 | 6.7 | 7.7 | 8.6 | 11.7 | 12.0 | 13.3 | 15.3 | 15.9 | 17.7 | 17.8 | 19.1 | 19.8 | 2010–2011 | −6.76 | 2013–2017 | 14.31[a] | 2019–2023 | 5.07[a] |
| Jeollanam-do | 7.4 | 7.2 | 7.1 | 8.4 | 9.7 | 12.5 | 12.8 | 13.3 | 14.8 | 13.8 | 15.8 | 15.8 | 16.8 | 16.4 | 2010–2011 | −3.46 | 2013–2014 | 21.46[a] | 2016–2023 | 4.19[a] |
| Seoul | 9.7 | 9.0 | 9.2 | 10.6 | 11.1 | 14 | 14.4 | 15.3 | 17.5 | 18.0 | 18.7 | 18.8 | 18.3 | 17.6 | 2010–2018 | 9.26[a] | 2020–2023 | −0.81 | - | - |
| Ulsan | 8.2 | 6.9 | 6.5 | 9.1 | 8.6 | 11.7 | 12.2 | 13.6 | 14.8 | 16.4 | 20.5 | 22.4 | 23.9 | 22.5 | 2010–2023 | 11.17[a] | - | - | - | - |

Blank cells indicate nonapplicable trend segments because the final selected model included no additional joinpoints for that region.
APC, annual percent change.
[a] $p<0.05$

decline. Ulsan uniquely showed a sustained significant increase throughout the entire study period (2010–2023; APC, 11.17%; $p<0.05$), with no evidence of deceleration. These heterogeneous patterns suggest that geographic differences in abnormal screening prevalence may reflect variations in screening practices, provider thresholds for classifying abnormalities, or actual differences in child health status.

Notably, the transition from the Korean Ages and Stages Questionnaires (K-ASQ) to the K-DST did not coincide with any clear joinpoints or abrupt level changes in the APC analysis, suggesting that the observed temporal trends in abnormal findings were not primarily driven by the change in developmental screening tools. Additional context regarding regional trends in Follow-up needed and Caution results is available in Supplementary Tables 4, 5.

### 5. Screening participation and any abnormality by screening round group

Table 5 shows that, at the national level, the prevalence of any abnormality was higher in later screening round groups (6.8% in round 1 and 17.4% in rounds 6–8). Screening participation rates varied by round group and region. Regional differences in any abnormality were observed within each round group, with the widest range in rounds 6–8 (13.8%–22.0%). When screening rounds were grouped into age bands, participation remained high and relatively stable in infancy rounds (4–12 months), whereas more pronounced recent declines were observed in early toddlerhood (18–36 months) and late preschool rounds (42–71 months), suggesting greater challenges in sustaining attendance at older ages (Supplementary Table 3).

## Discussion

This study provides a longitudinal national and regional assessment of the NHSPIC in South Korea from 2010 to 2023. Screening participation increased from 50.0% in 2010 to a peak of 87.1% in 2021 but declined to 76.7% by 2023, while abnormal screening prevalence more than doubled from 8.6% to 19.3%. Persistent geographic disparities in both participation (66.9%–79.7%) and abnormality prevalence (11.4%–18.3%) highlight the need for policy responses that

**Table 5.** Screening rates and prevalence of any abnormality by screening round group and region

| Variable | Newborn period (14–35 day) | | Infant period (4–6, 9–12 mo) | | Early toddler period (18–24, 30–36 mo) | | Late preschool period (42–48, 54–60, 66–71 mo) | |
|---|---|---|---|---|---|---|---|---|
| | Screening rate | Any abnormality | Screening rate | Any abnormality | Screening rate | Any abnormality | Screening rate | Any abnormality |
| Total (South Korea) | 48.8 | 6.8 | 74.5 | 11.1 | 76.3 | 14.5 | 63.7 | 17.4 |
| Busan | 49.2 | 9.0 | 76.5 | 12.7 | 79.6 | 15.6 | 68.4 | 17.4 |
| Chungcheongbuk-do | 47.7 | 4.0 | 71.2 | 8.6 | 75.0 | 12.0 | 68.1 | 13.8 |
| Chungcheongnam-do | 51.5 | 5.0 | 72.0 | 9.6 | 74.1 | 14.2 | 62.6 | 17.8 |
| Daegu | 65.7 | 8.9 | 74.4 | 12.9 | 74.3 | 16.3 | 58.3 | 19.2 |
| Daejeon | 62.0 | 9.8 | 74.9 | 7.9 | 77.0 | 11.3 | 64.4 | 14.1 |
| Gangwon-do | 39.4 | 4.8 | 72.6 | 11.7 | 75.3 | 14.7 | 66.8 | 17.7 |
| Gwangju | 63.7 | 8.2 | 69.6 | 11.3 | 73.3 | 14.3 | 61.4 | 17.7 |
| Gyeonggi-do | 44.4 | 6.6 | 76.1 | 10.7 | 76.9 | 14.0 | 62.5 | 17.1 |
| Gyeongsangbuk-do | 65.6 | 11.1 | 73.3 | 14.2 | 75.6 | 17.7 | 63.2 | 22.0 |
| Gyeongsangnam-do | 62.6 | 3.5 | 75.2 | 13.2 | 77.3 | 16.8 | 64.7 | 20.3 |
| Incheon | 47.0 | 9.3 | 75.5 | 10.6 | 78.2 | 13.8 | 65.2 | 15.8 |
| Jeju-do | 59.0 | 6.7 | 72.1 | 10.3 | 78.8 | 15.1 | 69.5 | 19.9 |
| Jeollabuk-do | 50.4 | 4.6 | 70.4 | 9.6 | 73.5 | 12.8 | 61.6 | 15.5 |
| Jeollanam-do | 49.9 | 2.2 | 65.8 | 9.6 | 73.9 | 12.7 | 66.2 | 14.5 |
| Seoul | 39.9 | 6.6 | 75.3 | 11.4 | 75.3 | 14.6 | 62.7 | 17.5 |
| Ulsan | 49.7 | 6.6 | 78.2 | 10.7 | 80.8 | 14.0 | 66.0 | 17.4 |

Values are presented as percentages (%).
Screening rate was calculated as the number of children who underwent screening in each period divided by the number of eligible children in that period. Any abnormality was defined as the proportion of screened children classified as either "Caution" or "Follow-up needed" in the overall integrated assessment for that period.

address equitable access to screening as well as follow-up care capacity.

Joinpoint regression identified three distinct phases in national participation trends (Table 2, Fig. 1). These comprised an early rapid increase, followed by sustained growth, and then a recent decline. Participation increased through 2020 despite pandemic-era disruptions in healthcare utilization, whereas the 2022–2023 decline occurred across most regions (Table 2), suggesting a shared system-level influence. However, our aggregated data cannot identify visit-level disruptions or individual reasons for non-attendance [16,17]. This recent downturn may indicate emerging access constraints in pediatric preventive care, emphasizing the need to monitor service capacity and outreach in parallel with coverage metrics. Regional variation in participation persisted, with Sejong consistently highest and Gwangju, Jeollabuk-do, and Daegu lowest, patterns that are unlikely to be explained by a simple urban–rural gradient and are plausibly related to differences in local healthcare infrastructure and implementation capacity [18-20].

The increase in abnormal screening prevalence requires careful interpretation (Table 4, Fig. 2). The rise was driven more by "Follow-up needed" (3.0% to 8.8%) (Supplementary Table 4) than "Caution" (5.6% to 10.7%) (Supplementary Table 5), and NHSPIC abnormal classifications include children already diagnosed and receiving ongoing management; therefore, increasing abnormality does not necessarily indicate a proportional rise in incident developmental disorders. Accordingly, increases in the Follow-up needed category over time are more likely to reflect accumulated follow-up and management demands rather than a proportional rise in the incidence of newly emerging conditions. These patterns are compatible with changes in tools and practices, including the introduction and dissemination of K-DST, and broader shifts in developmental contexts and risk profiles [9-11,21-27]. The relative stabilization of abnormal prevalence during 2020–2023 (APC, 0.86%; not significant) suggests the system may be approaching a new equilibrium after implementation changes.

International experiences mirror these temporal and regional shifts. Following the COVID-19 pandemic, several countries reported reduced pediatric primary-care contacts or avoidance of scheduled child health checkups, and persistent geographic/socioeconomic disparities in screening uptake have been widely documented [28,29]. In addition, studies using standardized developmental screening tools and workflows (e.g., ASQ-based approaches) have reported increased identification of developmental or socioemotional concerns in young children during the pandemic era, consistent with our observed rise in abnormal findings after the K-DST transition [30,31].

Regional disparities in abnormal prevalence were more pronounced than differences in participation (Table 3) and were also evident by screening round group, with the widest regional range in late preschool rounds (13.8%–22.0%) (Table 5). These differences may reflect both true variation in developmental risk and regional variation in implementation and classification thresholds [17]. Regions combining lower participation with higher abnormality prevalence may represent "double jeopardy" settings where barriers to screening coexist with higher clinical needs. In such settings, delayed detection and delayed linkage to services may compound developmental risk, making these regions high-yield targets for equity-focused interventions.

From a policy perspective, screening is only the first step: participation gains will have limited impact unless timely diagnostic evaluation and effective early intervention are accessible. Evidence supports benefits of early developmental interventions, particularly for high-risk infants, in improving cognitive and motor outcomes [32,33]; thus, strengthening referral pathways and regional service capacity is essential so that increased detection translates into meaningful improvements [9-11,21,34].

This study's strengths include nationwide coverage over 14 years (>28 million examinations) and the use of joinpoint regression to identify statistically supported inflection points in participation and abnormality trends. The analyses also provide a comprehensive description of regional disparities at both national and subnational levels, including additional stratification by screening round groups. Several limitations should be acknowledged. First, the use of aggregated administrative data precludes adjustment for individual-level sociodemographic and clinical factors and limits causal inference. Second, the dataset lacks linked information on diagnostic confirmation, service utilization, and long-term outcomes, preventing assessment of how changes in screening patterns translate into developmental trajectories. Third, because the abnormal category includes children already diagnosed and receiving ongoing manage-

ment, increases may partly reflect improved tracking and accumulated follow-up needs rather than incident conditions.

In conclusion, the NHSPIC achieved substantial expansion in screening coverage over the past decade, but the recent downturn in participation and persistent regional disparities highlight ongoing challenges. The more than twofold rise in abnormal screening prevalence—likely reflecting a combination of tool/practice changes and increasing follow-up needs—underscores the importance of strengthening referral and early intervention capacity so that detection leads to timely care. Targeted strategies to reduce regional gaps in both screening access and follow-up services will be essential to achieve equitable early childhood development.

## Supplementary material

Supplementary materials are available at https://doi.org/10.7180/kmj.26.152

## Article information

### Conflicts of interest

No potential conflict of interest relevant to this article was reported.

### Acknowledgments

Hyeong Taek Woo (Keimyung University, Daegu, Korea) provided statistical support.

### Funding

None.

### Author contributions

All the work was done by Ji Sook Kim.

### ORCID

Ji Sook Kim, https://orcid.org/0000-0002-0100-5845

## References

1. Shonkoff JP, Garner AS. The lifelong effects of early childhood adversity and toxic stress. Pediatrics 2012;129:e232–46.
2. Boyle CA, Boulet S, Schieve LA, Cohen RA, Blumberg SJ, Yeargin-Allsopp M, et al. Trends in the prevalence of developmental disabilities in US children, 1997-2008. Pediatrics 2011;127:1034–42.
3. Blair M, Macaulay C. The healthy child programme: how did we get here and where should we go? Paediatr Child Health 2014;24:118–23.
4. Hagan JF, Shaw JS, Duncan PM. Bright futures guidelines for health supervision of infants, children, and adolescents. 4th ed. American Academy of Pediatrics; 2017.
5. Takeuchi J, Sakagami Y, Perez RC. The mother and child health handbook in Japan as a health promotion tool: an overview of its history, contents, use, benefits, and global influence. Glob Pediatr Health 2016;3:2333794.X16649884.
6. Tomokawa S, Miyake K, Takahashi K, Tomokawa A, Kokudo S, Ueno M, et al. Health screening system to ensure children's health and development in Japan. Pediatr Int 2021;63:869–79.
7. Hirai AH, Kogan MD, Kandasamy V, Reuland C, Bethell C. Prevalence and variation of developmental screening and surveillance in early childhood. JAMA Pediatr 2018;172:857–66.
8. Moynihan R, Sanders S, Michaleff ZA, Scott AM, Clark J, To EJ, et al. Impact of COVID-19 pandemic on utilisation of healthcare services: a systematic review. BMJ Open 2021;11:e045343.
9. Kim D, Choe YJ, Durrani BA, Kim E, Byeon J, Eun BL. Korean Developmental Screening Test for infants and children (K-DST): development, applications, and implications for future early childhood development interventions. Clin Exp Pediatr 2023;66:288–93.
10. Chung HJ, Yang D, Kim GH, Kim SK, Kim SW, Kim YK, et al. Development of the Korean Developmental Screening Test for infants and children (K-DST). Clin Exp Pediatr 2020;63:438–46.
11. Kim E, Lee Y, Seo J, Ha J, Shin SM. Improvement of the screening program for infants and children in the national health screening system. Public Health Wkly Rep 2021;14:58–67.
12. Woo H, Kim JS. Regional disparities in the infant mortality rate in Korea between 2001 and 2021. J Korean Med Sci 2023;38:e367.
13. Kim HJ, Chen HS, Byrne J, Wheeler B, Feuer EJ. Twenty years since Joinpoint 1.0: two major enhancements, their justification, and impact. Stat Med 2022;41:3102–30.
14. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. Stat Med 2000;19:335–51.
15. Breslow NE, Day NE. Statistical methods in cancer research. Volume II: the design and analysis of cohort studies. IARC Sci Publ 1987;(82):1–406.
16. Noh JW, Koo JH, Heo MH, Lee JY. Massive closures of pediat-

ric clinics and an exodus of pediatricians in Korea during the COVID-19 pandemic: what career paths did closed-down pediatricians choose? J Korean Med Sci 2025;40:e71.
17. Rah SS, Jung M, Lee K, Kang H, Jang S, Park J, et al. Systematic review and meta-analysis: real-world accuracy of children's developmental screening tests. J Am Acad Child Adolesc Psychiatry 2023;62:1095–109.
18. Kang M, Choi YJ, Kim Y, You S, Kim Y, Fried C. Sustainability and resilience in the Republic of Korea health system. World Economic Forum; 2024.
19. Kim S. Worldwide national intervention of developmental screening programs in infant and early childhood. Clin Exp Pediatr 2022;65:10–20.
20. Rah SS, Hong SB, Yoon JY. Prevalence and incidence of developmental disorders in Korea: a nationwide population-based study. J Autism Dev Disord 2020;50:4504–11.
21. Jang CH, Kim SW, Jeon HR, Jung DW, Cho HE, Kim J, et al. Clinical usefulness of the Korean Developmental Screening Test (K-DST) for developmental delays. Ann Rehabil Med 2019;43:490–6.
22. Hessami K, Norooznezhad AH, Monteiro S, Barrozo ER, Abdolmaleki AS, Arian SE, et al. COVID-19 pandemic and infant neurodevelopmental impairment: a systematic review and meta-analysis. JAMA Netw Open 2022;5:e2238941.
23. O'Connor H, DiSalvo M, Gersten M, Boyden S, Uchida M. Effects of the COVID-19 pandemic on early child development: a systematic review & meta-analysis. J Dev Behav Pediatr 2025;46:e227–39.
24. Blencowe H, Lee AC, Cousens S, Bahalim A, Narwal R, Zhong N, et al. Preterm birth-associated neurodevelopmental impairment estimates at regional and global levels for 2010. Pediatr Res 2013;74 Suppl 1:17–34.
25. Durkin MS, Maenner MJ, Newschaffer CJ, Lee LC, Cunniff CM, Daniels JL, et al. Advanced parental age and the risk of autism spectrum disorder. Am J Epidemiol 2008;168:1268–76.
26. Hertz-Picciotto I. Commentary: diagnostic change and the increased prevalence of autism. Int J Epidemiol 2009;38:1239–41.
27. Shattuck PT. The contribution of diagnostic substitution to the growing administrative prevalence of autism in US special education. Pediatrics 2006;117:1028–37.
28. Foley KA, Maile EJ, Bottle A, Neale FK, Viner RM, Kenny SE, et al. Impact of COVID-19 on primary care contacts with children and young people in England: longitudinal trends study 2015-2020. Br J Gen Pract 2022;72:e464–71.
29. Ojio M, Maeda Y, Tabuchi T, Fujiwara T. The association between Types of COVID-19 information source and the avoidance of child health checkups in Japan: findings from the JACSIS 2021 study. Int J Environ Res Public Health 2022;19:9720.
30. Kuehn LM, Jones A, Helmkamp L, Knudtson M, Domek GJ, Allison MA. Socioemotional development of infants and toddlers during the COVID-19 pandemic. JAMA Pediatr 2024;178:151–9.
31. Felix G, Deavenport-Saman A, Stavros S, Farboodi N, Durazo-Arvizu R, Garcia J, et al. Standardizing and improving primary care-based electronic developmental screening for young children in federally qualified health center clinics. Matern Child Health J 2024;28:1716–25.
32. Hirve R, Adams C, Kelly CB, McAullay D, Hurt L, Edmond KM, et al. Effect of early childhood development interventions delivered by healthcare providers to improve cognitive outcomes in children at 0-36 months: a systematic review and meta-analysis. Arch Dis Child 2023;108:247–57.
33. Orton J, Doyle LW, Tripathi T, Boyd R, Anderson PJ, Spittle A. Early developmental intervention programmes provided post hospital discharge to prevent motor and cognitive impairment in preterm infants. Cochrane Database Syst Rev 2024;2:CD005495.
34. Shonkoff JP, Richter L, van der Gaag J, Bhutta ZA. An integrated scientific framework for child survival and early childhood development. Pediatrics 2012;129:e460–72.

Case report

Kosin Medical Journal 2026;41(1):81-84
pISSN: 2005-9531 • eISSN: 2586-7024
https://doi.org/10.7180/kmj.25.125

KMJ
KOSIN MEDICAL JOURNAL

# Two-stage transurethral cystolithotripsy of a giant neobladder stone: a case report

**Sin Woo Lee, Seung-Kwon Choi**

*Department of Urology, Seoul Medical Center, Seoul, Korea*

Giant neobladder stone (NS) is a rare complication in patients who have undergone orthotopic urinary diversion. Generally, patients with giant NS are treated with open or percutaneous cystolithotripsy to preserve urinary continence. We report the case of a 72-year-old male patient diagnosed with an 11.0-cm giant NS. The patient declined open surgery because of previous postoperative complications. After consultation, transurethral cystolithotripsy (TUCL) was selected as the treatment modality. However, the NS was impacted against the neobladder wall, and because of the hardness of the stone, complete fragmentation was difficult to achieve. Additional treatments were planned with extracorporeal shock wave lithotripsy and a second TUCL. One week after discharge, the patient was readmitted because of pain and hematuria. The second TUCL was performed after conservative management, and surgery required 5 hours to complete. The patient experienced transient urinary incontinence during the first postoperative week, which gradually improved. Both the NS and continence symptoms resolved completely after 3 months of follow-up. The operation time of TUCL for giant NS may be prolonged, and incomplete stone fragmentation can lead to complications, as demonstrated in this case. In our opinion, TUCL should be considered only in selected cases of NS.

**Keywords:** Case reports; Minimally invasive surgical procedures; Urinary bladder calculi; Urinary diversion

## Introduction

Bladder stone formation is a delayed complication in patients who have undergone radical cystectomy with continent urinary diversion. The etiology of neobladder stone (NS) formation is multifactorial and may involve urinary tract infection, urine retention, metabolic acidosis, and the presence of mucus or foreign bodies. The reported incidence of NS ranges from 0.5% to 7.0% [1]. Generally, giant bladder stones weighing more than 100 g are rare [2]. However, many patients with pouch stones remain asymptomatic and the risk factors contributing to stone formation are complex. Cases of giant NS have occasionally been reported. Previous studies suggest that patients with giant NS are typically treated with open cystolithotomy (OCL) or percutaneous cystolithotripsy (PCCL) to preserve urinary continence. In this report, we describe our experience performing transurethral cystolithotripsy (TUCL) in a patient with a giant NS.

## Case

**Ethical statements:** This study was approved by the Institutional Review Board (IRB) of Seoul Medical Center (IRB No. 2025-07-006) and the IRB approved a waiver of informed consent.

A 72-year-old male patient with a several-year history of

**Received:** August 5, 2025; **Revised:** November 14, 2025; **Accepted:** November 21, 2025
**Corresponding Author:** Sin Woo Lee, MD
Department of Urology, Seoul Medical Center, 156 Sinnae-ro, Jungnang-gu, Seoul 02053, Korea
Tel: +82-2-2276-8605 Fax: +82-2-2276-7800 E-mail: icinoo0923@seoulmc.or.kr

© 2026 Kosin University College of Medicine
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

lower abdominal discomfort and gross hematuria visited our urology clinic. Approximately 20 years earlier, he had undergone radical cystoprostatectomy with orthotopic neobladder reconstruction for invasive bladder carcinoma at another hospital. Following surgery, he experienced recurrent episodes of urinary retention, which required clean intermittent catheterization (CIC) 5 to 6 times daily. After 5 years, the patient was lost to follow-up. The patient experienced intermittent hematuria and abdominal discomfort, which were presumed to be related to urinary retention and CIC; thus, medical attention was not sought. We performed X-ray scan and cystoscopic examinations at the initial visit, and diagnosed an 11.0-cm bladder stone (Fig. 1A). The renal parameters and urine cytology results were normal. The pH of urine was 8.0 and *Escherichia coli* were isolated in the urine culture test.

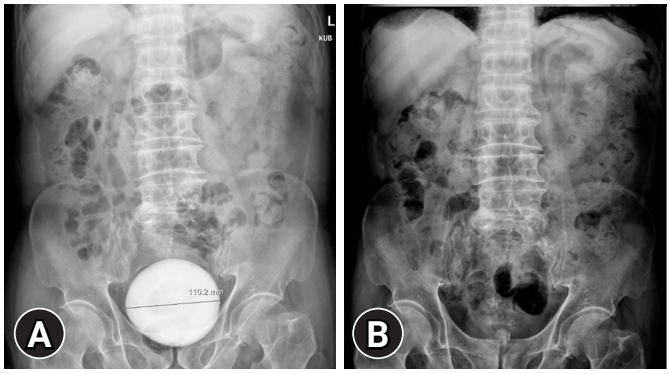


**Fig. 1.** X-ray scans: (A) preoperative, (B) after the second transurethral cystolithotripsy.

The patient experienced wound dehiscence following a previous cystectomy, and therefore did not prefer open surgery. We explained to the patient the possibility of staged operation starting with the first TUCL surgery. We performed the first TUCL surgery using a 24-Fr cystoscope with a 0° telescope (Richard Wolf GmbH) and Holmium:YAG laser machine (VersaPulse Power Suite 100 W, Lumenis) for stone fragmentation. The stone fragmentation was performed using a laser power ranging from 24 W (0.6 J at 40 Hz) to 25 W (0.5 J at 50 Hz) for about 1 hour and 40 minutes: however, the stone was extremely hard and could only be partially removed (20%–25%). The bladder stone was firmly impacted against the neobladder wall, limiting endoscopic maneuverability within the narrow space. Therefore, we decided to reoperate after pulverizing it. We planned to perform two to three sessions of extracorporeal shock wave lithotripsy (ESWL). However, the patient was readmitted to the emergency room due to gross hematuria and moderate degree of abdominal pain 1 week later. The emergency X-ray scan revealed that the lower portion of neobladder was compressed by a sharp margin of the previously operated bladder stone (Fig. 2A). Consequently, a computed tomography scan was performed to evaluate possible complications. Fortunately, no perforation or severe injury of neobladder pouch was detected (Fig. 2B and C).

We performed the second TUCL after 3 days of bed rest and conservative management. All remaining bladder

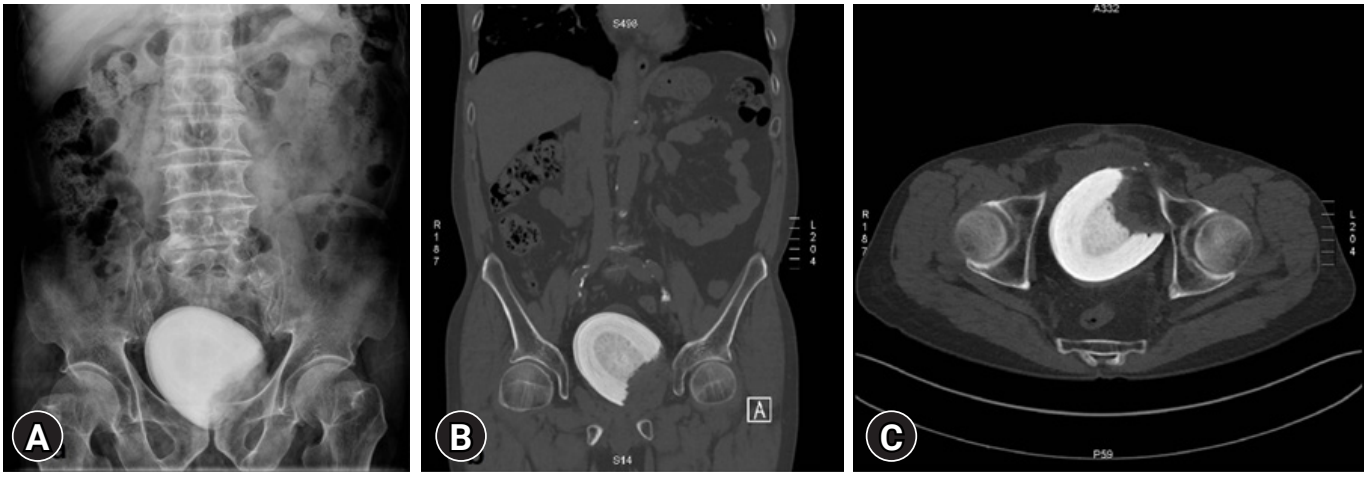


**Fig. 2.** Imaging after the first transurethral cystolithotripsy: (A) X-ray scan, (B, C) abdominal pelvic computed tomography scan.

stones were successfully removed after a 5-hour operation, with a total of 588 g of stone fragments retrieved (Fig. 3). All abdominal pain and discomfort completely resolved by postoperative day 1, and the patient was discharged 2 days after surgery. Transient urinary incontinence persisted for approximately 1 week, but gradually improved and resolved completely by the end of the 3-month postoperative follow-up. Follow-up X-ray imaging revealed no evidence of calcification (Fig. 1B). Stone culture confirmed *E. coli*, identical to that identified in the urine culture. Subsequent biochemical stone analysis revealed the presence of carbonates and phosphates on qualitative assay. Despite the 5-hour operation, no urethral strictures or recurrent bladder stones were observed during the 12-month follow-up period.

## Discussion

A recent meta-analysis comparing TUCL, PCCL, and OCL reported similar stone-free rates, short hospital stays, and rapid convalescence among these procedures [3]. However, TUCL may affect the continence mechanism in patients who have undergone orthotopic neobladder reconstruction. Excessive torque during TUCL increased the risk of damage to continence mechanism and also induced urethral strictures during long-term follow-up [4]. Nevertheless, another meta-analysis reported that the incidence of urethral strictures after TUCL was only 2.8%, showing no significant difference compared with that after transurethral resection of the prostate (2.2%–9.8%).

In our case, the patient was reluctant to undergo open surgery because of previous postoperative complications, including wound dehiscence and urinary retention, which had required CIC five to six times daily. Therefore, we performed cystoscopy to evaluate the urethra-neobladder junction and confirmed that endoscopic passage was possible without difficulty. A cystoscope with a 24-Fr external sheath (smaller than the standard 26-Fr instrument) was used. Stone fragmentation was achieved solely using a Holmium:YAG laser machine. The Foley catheter was removed as early as possible—on postoperative day 1 in both procedures. The patient experienced mild urinary incontinence for 1 week, which gradually resolved. No significant urethral stricture or incontinence was observed during the 12-month follow-up period.

In patients with neobladder, OCL operation increased the risk of side effects, such as postoperative scar formation, tissue adhesion and altered anatomy. Further, in cases of recurrent giant NS, performing OCL can be technically challenging [5]. PCCL surgery decreased the possibility of mesenteric vessel injury, despite the need for attention. In some cases, urine leakage from the wound or neobladder cystotomy repair site occurred, which required prolonged urethral catheterization until the urine leakage site healed [1,6]. However, in TUCL surgery, there is no concern about neobladder injury or urine leakage, and the urethral catheter can be removed within 1–2 days after surgery [7]. If the bladder stone was treated with ESWL, it was crushed without damaging the continence mechanism [8]. However, no ESWL treatment for cases involving giant NS have been

**Fig. 3.** Fragmented neobladder stone. (A) The first transurethral cystolithotripsy (TUCL); (B) second TUCL; (C) the stone, with an estimated weight of 588 g.

reported until now.

In patient with NS, usage of laser may increase the risk of mucosal injury to the neobladder and surrounding tissue; therefore, caution is required, especially when treating the stone surface. In our case, stone fragmentation was challenging because of the limited bladder space and firm adherence of the stone to the neobladder mucosa. Consequently, we discontinued the first TUCL and planned additional ESWL and second TUCL. However, the remaining large, incompletely fragmented stone—with sharp margins—caused abdominal pain and hematuria by compressing adjacent neobladder tissue. To prevent worsening of the condition, bed rest was recommended for 3 days, followed by prompt second operation. In patients with giant NS, incomplete stone fragmentation may increase the risk of complications or unexpected readmission, necessitating careful management.

In previous studies, TUCL cases of giant bladder stone were rarely reported. Kupajski and Tkocz [7] reported a case of giant NS treated with TUCL, although the procedure duration was not specified. For extremely hard stones such as in our case, the operation may exceed 5 hours. To our knowledge, there are no previous reports describing two-stage TUCL for giant NS.

In conclusion, TUCL for giant NS may be prolonged and incomplete stone fragmentation can lead to complications, as demonstrated in our case. Therefore, TUCL should be considered only in selected patients, such as those with a small stone burden or a prior history of OCL.

## Article information

**Conflicts of interest**

No potential conflict of interest relevant to this article was reported.

**Funding**

None.

**Author contributions**

Conceptualization: SWL. Data curation: SWL. Investigation: SKC. Project administration: SWL. Supervision: SKC. Validation: SWL. Visualization: SWL. Writing-original draft: SWL. Writing-review & editing: SWL, SKC. All authors read and approved the final manuscript.

**ORCID**

Sin Woo Lee, https://orcid.org/0000-0002-3050-6366
Seung-Kwon Choi, https://orcid.org/0000-0001-5854-8675

## References

1. Tiu A, Soloway MS. Giant neobladder stone. ANZ J Surg 2014;84:390–1.
2. Tahtali IN, Karatas T. Giant bladder stone: a case report and review of the literature. Turk J Urol 2014;40:189–91.
3. Donaldson JF, Ruhayel Y, Skolarikos A, MacLennan S, Yuan Y, Shepherd R, et al. Treatment of bladder stones in adults and children: a systematic review and meta-analysis on behalf of the European Association of Urology Urolithiasis Guideline Panel. Eur Urol 2019;76:352–67.
4. L'Esperance JO, Sung J, Marguet C, L'Esperance A, Albala DM. The surgical management of stones in patients with urinary diversions. Curr Opin Urol 2004;14:129–34.
5. Zhong W, Yang B, He F, Wang L, Swami S, Zeng G. Surgical management of urolithiasis in patients after urinary diversion. PLoS One 2014;9:e111371.
6. Tafuri A, Porcaro AB, Ashrafi AN, Cerruto MA, Amigoni N, Mariotto A, et al. Multiple stones in neobladder: case report and literature review. Urologia 2019;86:216–9.
7. Kupajski M, Tkocz MT. Use of endoscopic lithotripsy technique in the treatment of intestinal neobladder lithiasis performed by means of the VIP method. Wideochir Inne Tech Maloinwazyjne 2014;9:93–5.
8. Claus C, Jorion JI, Libon E. Continent urinary diversion and calculus. Acta Urol Belg 1997;65:33–7.

Case report

Kosin Medical Journal 2026;41(1):85-90
pISSN: 2005-9531 • eISSN: 2586-7024
https://doi.org/10.7180/kmj.25.129

KMJ
KOSIN MEDICAL JOURNAL

# Locally recurrent primary adrenal leiomyosarcoma discovered incidentally 7 years after initial surgery: a case report

**Myungsoo Im, Doohwa Kim, Soree Ryang, Bo Hyun Kim**

*Department of Endocrinology and Metabolism, Pusan National University Hospital, Pusan National University School of Medicine and Biomedical Research Institute, Busan, Korea*

Primary adrenal leiomyosarcoma (PAL) is an aggressive, rare tumor that is frequently diagnosed at an advanced stage. We report the case of a 65-year-old female patient with hypertension who presented with stabbing lower abdominal pain and unintentional weight loss. Abdominal computed tomography (CT) demonstrated a 10.4×8.2×8.1 cm heterogeneous left adrenal mass without biochemical evidence of hormonal hypersecretion. Retroperitoneal left adrenalectomy was performed without complications, and histopathological examination confirmed a moderately differentiated adrenal leiomyosarcoma. The patient was followed at the outpatient oncology clinic for 5 years with no evidence of recurrence. Seven years after the initial surgery, a newly detected left suprarenal mass was identified on imaging. Abdominal CT revealed a new, well-circumscribed 7.1×6.4×6.2 cm heterogeneous mass. Laparoscopic resection of the recurrent mass was performed. Pathological examination again revealed a moderately differentiated leiomyosarcoma with positive surgical margins but no lymphovascular invasion. Immunohistochemical staining was positive for smooth muscle actin, desmin, h-caldesmin, neuron-specific enolase, and synaptophysin, findings consistent with recurrent adrenal leiomyosarcoma. This case demonstrates that PAL can recur locally after prolonged disease-free intervals, underscoring the importance of extended surveillance, potentially beyond 10 years.

**Keywords:** Adrenocortical carcinoma; Case reports; Leiomyosarcoma; Recurrence

## Introduction

Primary adrenal leiomyosarcoma (PAL) is a high-grade mesenchymal tumor of smooth muscle wall origin, arising from the central adrenal vein or its branches; fewer than 50 cases have been documented globally [1,2]. PAL is extremely rare and is estimated to account for less than 0.1% of all adrenal tumors [3]. PAL is typically diagnosed either at an advanced stage or incidentally during postoperatively histopathological examination due to its non-specific clinical manifestations.

The primary treatment is complete surgical resection; however, recurrence rates remain high, occurring in approximately 40%–50% of cases [2,4,5]. While most recurrences develop within months to several years postoperatively, late recurrences, beyond 5 years of disease-free

**Received:** August 22, 2025; **Revised:** December 3, 2025; **Accepted:** January 10, 2026
**Corresponding Author:** Bo Hyun Kim, MD
Department of Endocrinology and Metabolism, Pusan National University Hospital, Pusan National University School of Medicine and Biomedical Research Institute, 179 Gudeok-ro, Seo-gu, Busan 49241, Korea
Tel: +82-51-240-7983 Fax: +82-51-254-3237 E-mail: pons71@pusan.ac.kr

© 2026 Kosin University College of Medicine
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

survival after prolonged disease-free intervals, are exceptionally rare [6]. We report a rare case of PAL recurring locally after 7 disease-free years following surgery, providing valuable insights into the disease's clinical behavior and recurrence patterns.

## Case

**Ethical statements:** The Institutional Review Board (IRB) of Pusan National University Hospital reviewed and approved this report (IRB No. 2401-013-135). Written informed consent was obtained from the patient for the publication of this case report and the use of clinical images.

A 65-year-old female patient with hypertension presented to our outpatient clinic for evaluation of a left adrenal mass. She reported 1 week of stabbing lower abdominal pain and unintentional 6-kg weight loss. Her past surgical history included right hemithyroidectomy for goiter and hysterectomy for severe dysmenorrhea. She was taking antihypertensive and lipid-lowering medications as part of her chronic disease management at the time of the initial evaluation.

Abdominal contrast-enhanced computed tomography (CT) revealed a 10.4×8.2×8.1 cm heterogeneous left adrenal mass (precontrast attenuation, 25 Hounsfield units [HUs]) abutting the splenic vein, left renal artery/vein, and aorta (Fig. 1A, 1B). A detailed endocrine workup was performed to assess for functional adrenal activity. Serum cortisol, plasma metanephrines, aldosterone, renin, and sex hormone levels were all within reference ranges, without biochemical evidence of hormonal hypersecretion. The patient underwent retroperitoneal left adrenalectomy and recovered without complications.

### 1. Initial pathology

Histopathologic examination demonstrated an ill-defined, yellow-white solid mass (11.0×8.0×5.6 cm) with approximately 30% necrosis. The mitotic index was 13/10 high-power fields (HPFs) in the most active areas. Immunohistochemistry showed tumor cells positivity for desmin, smooth muscle actin (SMA), h-caldesmin, and neuron-specific enolase (NSE), with negativity for S-100 protein, pancytokeratin, CDK4, MDM2, and c-kit. These findings supported the diagnosis of moderately differentiated adrenal leiomyosarcoma. The surgical resection margins were negative, and no lymphovascular invasion was identified.

### 2. Follow-up and recurrence

Adjuvant radiotherapy was not administered after the surgery, because the tumor had been completely removed with negative margin (R0 resection), and no residual disease was identified on postoperative imaging. The patient received follow-up at the outpatient oncology clinic for 5 years without evidence of recurrence (Fig. 1C). During the 5-year disease-free interval, surveillance consisted of annual abdominal CT scans and clinical assessments, all showing no evidence of recurrence. Seven years postoperatively, she was referred to endocrinology for evaluation of a

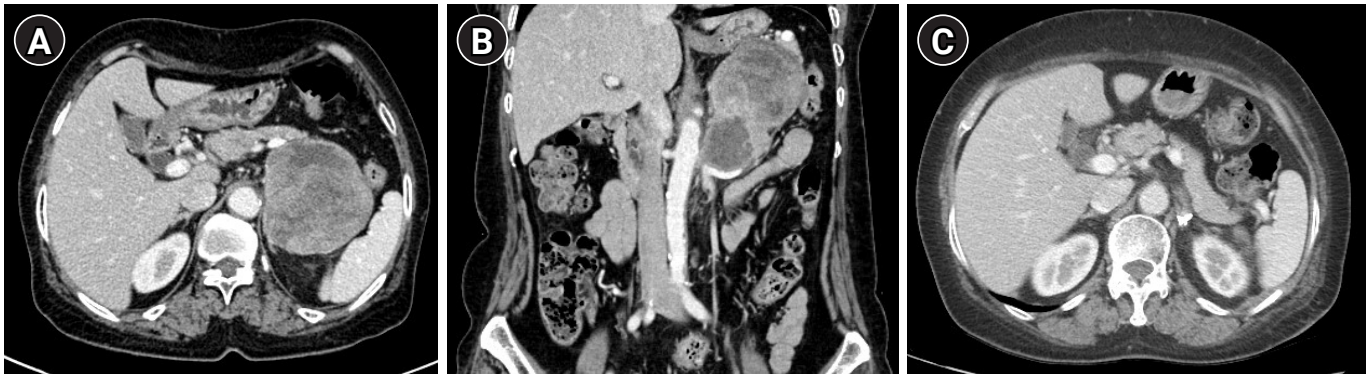


**Fig. 1.** Contrast-enhanced computed tomography (CT) of the abdomen and pelvis at initial diagnosis and at 5-year follow-up. (A) Axial view showing a heterogeneously enhancing mass (10.4×8.2×8.1 cm) in the left adrenal gland, abutting the splenic vein, left renal artery and vein, and the aorta. (B) Coronal view of the same mass. (C) Axial image from follow-up CT 5 years after surgery showing no evidence of recurrence.

newly detected left adrenal mass on abdominal ultrasound. Subsequent CT revealed a 7.1×6.4×6.2 heterogeneous left suprarenal mass (precontrast attenuation, 30 HU) (Fig. 2). The recurrent tumor was located in the left adrenal bed, abutting the upper pole of the left kidney and anterior surface of the aorta, consistent with a local recurrence rather than a new primary lesion. Biochemical evaluation showed decreased serum dehydroepiandrosterone sulfate levels (21.64 μg/dL; reference range, 30–333 μg/dL), with normal cortisol and adrenocorticotropic hormone levels. Given these findings, recurrent adrenal leiomyosarcoma was suspected, and the patient underwent laparoscopic resection of the recurrent mass.

### 3. Recurrent tumor pathology

Gross pathological examination revealed a firm, rubbery 9.2×7.7×3.9 cm mass (Fig. 3A) with a tan-white cut surface containing focal hemorrhage and necrosis (approximately 5% of tumor volume). Histologically, the tumor was hypercellular, composed of atypical spindle cells arranged in intersecting fascicles (Fig. 3B). Immunohistochemistry demonstrated diffuse desmin positive (Fig. 3C) and a mitotic rate of 5/10 HPFs in most active areas. Although surgical margins were involved, no lymphovascular invasion was

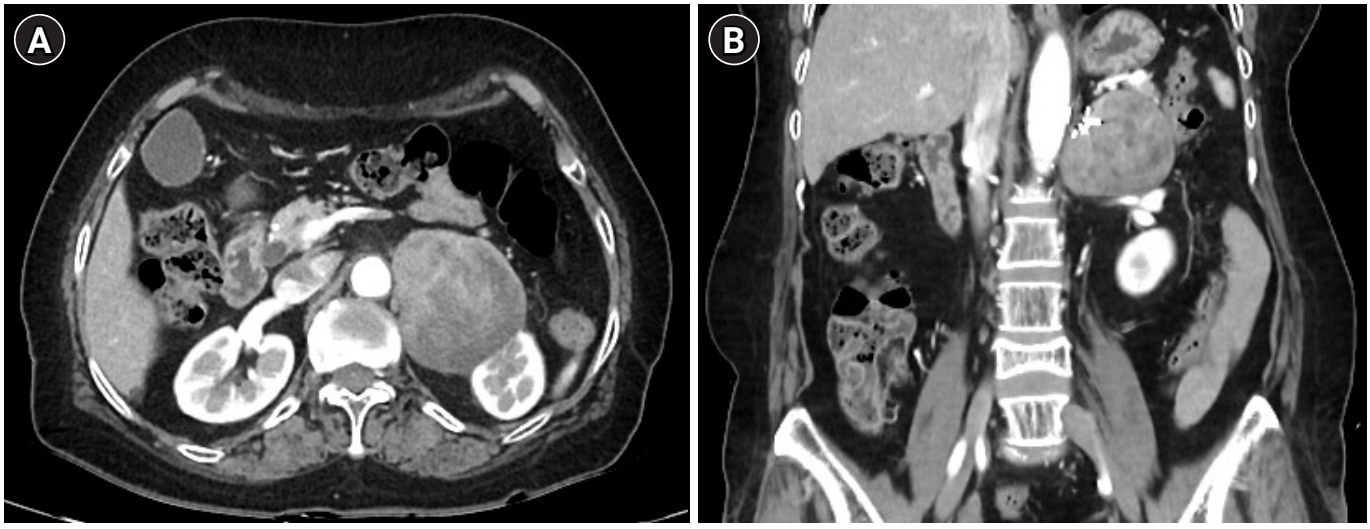


**Fig. 2.** Contrast-enhanced computed tomography of the abdomen and pelvis, showing a 7.1×6.4×6.2 cm heterogeneously enhancing mass in the left adrenal bed. (A) Axial view. (B) Coronal view.

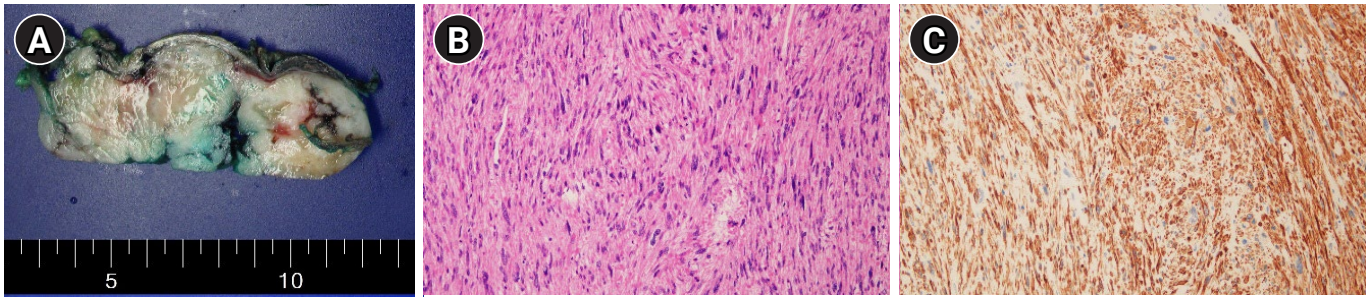


**Fig. 3.** Macroscopic and microscopic findings. (A) Gross appearance of the tumor. The mass is firm and rubbery, and the cut surface is tan to white in color. (B) High-magnification hematoxylin and eosin staining shows marked cellular atypia with pronounced nuclear pleomorphism, including hyperchromatic and enlarged nuclei with coarse chromatin. The mitotic index is approximately 5 mitoses per 10 high-power fields in the most proliferative areas (hematoxylin and eosin, ×200). (C) Immunohistochemical staining shows diffuse strong cytoplasmic positivity for desmin. The surgical margin is positive for sarcoma (×200).

identified. Immunohistochemical staining was positive for desmin, SMA, and h-caldesmin, with focal positivity for NSE and synaptophysin; chromogranin A was negative. The combined histopathological and immunohistochemical features confirmed a diagnosis of moderately differentiated adrenal leiomyosarcoma.

Three months after the second surgery, follow-up contrast-enhanced abdominal CT revealed a 3.6-cm enhancing lesion with an associated fluid collection in the left suprarenal area, suggesting residual or recurrent tumor. Given the imaging findings and the positive surgical margin, the patient was referred to another hospital for palliative radiotherapy. She remained clinically stable at the time of transfer. After referral, the patient was not followed further at our institution, and additional clinical outcomes could not be obtained.

## Discussion

PAL is an aggressive mesenchymal tumor representing 0.1%–0.2% of adult retroperitoneal soft-tissue sarcomas, with fewer than 50 documented cases [2,7]. This rarity has hindered complete characterization of its natural history, optimal treatment, and long-term outcomes. PAL is believed to arise from the smooth muscle cells of the central adrenal vein or its branches, rather than from the adrenal cortex or medulla. Because the tumor is typically nonfunctional and presents with non-specific symptoms, diagnosis is often delayed and frequently made incidentally on imaging or postoperative histopathologic examination.

Management principle for leiomyosarcoma depends on disease extent. In localized leiomyosarcoma, including retroperitoneal and adrenal cases, complete surgical resection with negative margins remains the cornerstone of curative therapy and the strongest determinant of long-term survival [8-10]. Adjuvant radiotherapy has been shown to reduce local recurrence in extremity and retroperitoneal leiomyosarcoma, particularly in high-grade or margin-positive disease, although its benefit in PAL remains unproven due to limited cases [11-13]. Once leiomyosarcoma progresses to advanced or metastatic disease, systemic therapy is the primary option for disease control. Doxorubicin-based regimens remain the first-line option, followed by agents such as trabectedin, gemcitabine/docetaxel, or pazopanib for disease progression [8,14,15]. Radiation therapy serves primarily for palliation or control of oligometastatic lesions [10].

Despite achieving complete tumor removal, recurrence rates remain common. In previously published cases of PAL, most recurrences have occurred within months to a few years after adrenalectomy [6], with the longest reported interval to recurrent or progressive disease being 53 months [16] and no clearly documented recurrence beyond 5 years. Therefore, to our knowledge, the 7-year disease-free interval observed in our patient is the longest recurrence interval reported to date. This unusually delayed recurrence suggests that PAL, despite periods of apparent quiescence, may harbor persistent malignant potential for extended periods, a pattern that contrasts with many other malignancies in which recurrence risk diminishes over time [8,9]. These observations underscore the importance of prolonged surveillance well beyond the traditional 5-year follow-up window.

Immunohistochemical analysis of the recurrent tumor matched the primary lesion profile, confirming true recurrence rather than a de novo neoplasm. Notably, the mitotic index of the recurrent tumor (5/10 HPFs) was lower than that of the primary lesion (13/10 HPFs). This difference may reflect underlying intratumoral heterogeneity, with the recurrent mass arising from a less proliferative tumor clone that persisted after the initial surgery. However, a reduced mitotic index alone does not reliably predict clinical behavior in leiomyosarcoma. Prior studies have shown that recurrence can occur even in tumors with relatively low proliferative activity, and that overall prognosis is influenced by multiple factors including tumor size, necrosis, and margin status [17]. Margin involvement is consistently identified as a major predictor of local recurrence and poor disease-specific survival in retroperitoneal and soft-tissue leiomyosarcoma [9], highlighting its prognostic relevance in our case.

Although neuroendocrine markers such as NSE and synaptophysin are not typically expressed in smooth muscle tumors, their focal positivity in this case is likely non-specific. In the context of strong smooth muscle marker expression and negative chromogranin A staining, these findings do not indicate true neuroendocrine differentiation. Instead, they most likely reflect staining variability or tumor heterogeneity.

Due to PAL rarity, no consensus exists regarding adju-

vant therapy or surveillance protocols. While some studies have suggested adjuvant radiotherapy or chemotherapy for high-grade or margin-positive tumors, supporting evidence remains limited [6,18,19]. Because our patient's recurrent tumor showed microscopic margin involvement, the consideration of adjuvant radiotherapy may be appropriate, although robust data to support routine use are lacking [20].

This case also highlights the critical importance of continuous, long-term surveillance following surgical resection of adrenal leiomyosarcoma. Although a 5-year disease-free interval is often considered a marker for cancer remission, our case demonstrates that PAL can recur beyond this period and progress rapidly within a short interval. Such late but aggressive recurrences suggest that the traditional 5-year follow-up may be insufficient. Therefore, extended or lifelong radiologic monitoring should be considered, even in patients who remain recurrence-free for many years after initial treatment

In summary, PAL is a rare, aggressive malignancy with high recurrence rates, typically occurring within months to several years postoperatively. Our case demonstrates the longest reported recurrence interval of 7 years to date and challenges conventional surveillance paradigms. These findings emphasize the need for extended surveillance beyond standard 5-year follow-up protocols and contribute to the limited but growing understanding long-term outcomes in PAL.

## Article information

### Conflicts of interest

No potential conflict of interest relevant to this article was reported.

### Funding

This research was supported by a clinical research grant from Pusan National University Hospital in 2025.

### Author contributions

Conceptualization: MI, BHK. Data curation: MI, DK, SR. Formal analysis: MI. Funding acquisition: BHK. Investigation: MI, DK, SR. Methodology: MI. Project administration: BHK. Resources: BHK. Supervision: BHK. Validation: BHK. Visualization: MI. Writing-original draft: MI. Writing-review & editing: MI, DK, SR, BHK. All authors read and approved the final manuscript.

### ORCID

Myungsoo Im, https://orcid.org/0009-0009-2758-9461
Doohwa Kim, https://orcid.org/0009-0001-9289-355X
Soree Ryang, https://orcid.org/0000-0002-5251-5554
Bo Hyun Kim, https://orcid.org/0000-0001-9632-9457

## References

1. Jabarkhel F, Puttonen H, Hansson L, Muth A, Ragnarsson O. Primary adrenal leiomyosarcoma: clinical, radiological, and histopathological characteristics. J Endocr Soc 2020;4:bvaa055.
2. Zhou Y, Tang Y, Tang J, Deng F, Gong G, Dai Y. Primary adrenal leiomyosarcoma: a case report and review of literature. Int J Clin Exp Pathol 2015;8:4258–63.
3. Lujan MG, Hoang MP. Pleomorphic leiomyosarcoma of the adrenal gland. Arch Pathol Lab Med 2003;127:e32–5.
4. Mohanty SK, Balani JP, Parwani AV. Pleomorphic leiomyosarcoma of the adrenal gland: case report and review of the literature. Urology 2007;70:591.
5. Quildrian S, Califano I, Carrizo F, Daffinoti A, Calonico N. Primary adrenal leiomyosarcoma treated by laparoscopic adrenalectomy. Endocrinol Nutr 2015;62:472–3.
6. Mongardini FM, Paolicelli M, Catauro A, Conzo A, Flagiello L, Nesta G, et al. Outcomes and follow-up trends in adrenal leiomyosarcoma: a comprehensive literature review and case report. J Clin Med 2024;13:3499.
7. Sakellariou M, Dellaportas D, Grapsa E, Tzikanoulas M, Dellis A, Theodosopoulos T, et al. Primary adrenal leiomyosarcoma: a case report. Mol Clin Oncol 2020;12:317–20.
8. Lacuna K, Bose S, Ingham M, Schwartz G. Therapeutic advances in leiomyosarcoma. Front Oncol 2023;13:1149106.
9. Bilgeri A, Klein A, Lindner LH, Nachbichler S, Knosel T, Birkenmaier C, et al. The effect of resection margin on local recurrence and survival in high grade soft tissue sarcoma of the extremities: how far is far enough? Cancers (Basel) 2020;12:2560.
10. Strander H, Turesson I, Cavallin-Stahl E. A systematic overview of radiation therapy effects in soft tissue sarcomas. Acta Oncol 2003;42:516–31.
11. Gulpinar MT, Yildirim A, Gucluer B, Atis RG, Canakci C, Gurbuz C, et al. Primary leiomyosarcoma of the adrenal gland: a case report with immunohistochemical study and literature review. Case Rep Urol 2014;2014:489630.
12. Folkert MR, Singer S, Brennan MF, Kuk D, Qin LX, Kobayashi

WK, et al. Comparison of local recurrence with conventional and intensity-modulated radiation therapy for primary soft-tissue sarcomas of the extremity. J Clin Oncol 2014;32:3236–41.
13. Kim HJ, Koom WS, Cho J, Kim HS, Suh CO. Efficacy of postoperative radiotherapy using modern techniques in patients with retroperitoneal soft tissue sarcoma. Yonsei Med J 2018;59:1049–56.
14. Kawai A, Yonemori K, Takahashi S, Araki N, Ueda T. Systemic therapy for soft tissue sarcoma: proposals for the optimal use of pazopanib, trabectedin, and eribulin. Adv Ther 2017;34:1556–71.
15. Seddon B, Strauss SJ, Whelan J, Leahy M, Woll PJ, Cowie F, et al. Gemcitabine and docetaxel versus doxorubicin as first-line treatment in previously untreated advanced unresectable or metastatic soft-tissue sarcomas (GeDDiS): a randomised controlled phase 3 trial. Lancet Oncol 2017;18:1397–410.
16. Tomasich FD, Luz Mde A, Kato M, Targa GZ, Dias LA, Zucoloto FJ, et al. Primary adrenal leiomyosarcoma. Arq Bras Endocrinol Metabol 2008;52:1510–4.
17. Farshid G, Pradhan M, Goldblum J, Weiss SW. Leiomyosarcoma of somatic soft tissues: a tumor of vascular origin with multivariate analysis of outcome in 42 cases. Am J Surg Pathol 2002;26:14–24.
18. Bhalla A, Sandhu F, Sieber S. Primary adrenal leiomyosarcoma: a case report and review of the literature. Conn Med 2014;78:403–7.
19. Grimer R, Judson I, Peake D, Seddon B. Guidelines for the management of soft tissue sarcomas. Sarcoma 2010;2010:506182.
20. Gronchi A, Miah AB, Dei Tos AP, Abecassis N, Bajpai J, Bauer S, et al. Soft tissue and visceral sarcomas: ESMO-EURACAN-GENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2021;32:1348–65.

# Instructions to authors

KMJ
KOSIN MEDICAL JOURNAL

The *Kosin Medical Journal* (KMJ) is an international, open access, peer-reviewed, quarterly journal of medicine published online, in English, on March 31, June 30, September 30, and December 31 of each year. The Journal's publisher is the Kosin University College of Medicine. Anyone considering submitting a manuscript is advised to carefully read the aims and scope section of this journal. Manuscripts submitted to KMJ should be prepared according to the following instructions. For issues not addressed in these instructions, the author is referred to the International Committee of Medical Journal Editors (ICMJE) "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals."

## I. AIMS AND SCOPE

*The Kosin Medical Journal* (Kosin Med J, KMJ, pISSN 2005-9531, eISSN 2586-7024, https://www.kosinmedj.org), the official publication of Kosin University College of Medicine, is a peer-reviewed and open access journal of research in all medical fields, including medicine, medical science, medical ethics, medical policy, and medical education. Its regional focus is Korea, but it welcomes submissions from researchers all over the world.

The KMJ aims to communicate new medical information to medical personnel, and to facilitate the development of medicine, medical science, medical ethics, medical policy, and medical education, as well as the propagation of medical knowledge by publishing high-quality, evidence-based articles.

The KMJ publishes editorials, review articles, original articles, and case reports. All manuscripts should be creative, informative, and helpful for the diagnosis and treatment of medical diseases and the communication of valuable information about all fields of medicine, medical science, medical ethics, medical policy, and medical education.

## II. MANUSCRIPT SUBMISSION

Authors should submit manuscripts using the KMJ's electronic manuscript management system at https://submit.kosinmedj.org. Please log in first as a member of the system and follow the directions. **Manuscripts should be submitted by the corresponding author, who should supply the address, phone number, and email address for correspondence in the title page of the manuscript. If available, a fax number would be helpful.**

**Document forms**

Before you log into the online submission portal, it is helpful to prepare the following documents as you will be asked to upload them during the electronic submission process.

- **Author statement forms**
- **The IRB/IACUC approval** report must be uploaded (when reporting results on human subjects/animals).
- **A cover letter** that includes the address, telephone number, and email address of the corresponding author
- **English proofreading documentation**—authors whose native language is not English must show that their manuscript has been edited by an English-language proofreading or editing service

The revised manuscript should be submitted through the same web portal using the same identification numbers. Items pertaining to manuscripts submitted for publication, as well as letters or other forms of communication regarding the editorial management of the KMJ, should be sent to:

Editor-in-Chief
Kosin Medical Journal Editorial Board Office
Kosin University College of Medicine
#262, Gamcheon-ro, Seo-gu, Busan 49267, Korea
Tel: +82-51-990-3088
Fax: +82-51-241-5458
E-mail: office@kosinmedj.org

## III. CATEGORIES OF PUBLICATIONS

The KMJ publishes editorials, review articles, original articles, and case reports.

- **Editorials** are invited perspectives on an area of medical science that deal with active fields of research and current

medical interests and provide fresh insights and debate.

- **Review articles** provide a concise review of a subject of importance to medical researchers. They are usually solicited by the Editor, but we will also consider unsolicited material. Please send us a Presubmission Inquiry before writing a review article.
- **Original articles** are papers reporting the results of basic and clinical investigations that are sufficiently well documented to be acceptable to critical readers.
- **Case reports** deal with clinical cases of medical interest or innovation.

## IV. ETHICAL CONSIDERATIONS

**Authorship**

The KMJ accepts authorship criteria recommended by the ICMJE (http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html) and the Good Publication Practice Guidelines by the Korean Association of Medical Journal Editors (KAMJE, 2019, http://kamje.or.kr).

Each author is expected to have made a substantial contribution to the conception or design of the work; the acquisition, analysis, or interpretation of data; the creation of new software used in the work; or have drafted the work or substantively revised it; AND to have approved the submitted version (and any substantially modified version that involves the author's contributions to the study); AND to have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even those in which the author was not personally involved, are appropriately investigated and resolved, and the resolution documented in the literature.

Those who do not meet the above criteria should be acknowledged as contributors rather than authors. The corresponding author is responsible for completing this information at submission, and it is expected that all authors will have reviewed, discussed, and agreed to their individual contributions ahead of this time.

When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. When submitting a manuscript authored by a group, the corresponding author should clearly indicate the preferred citation and identify all individual authors as well as the group name. Journals generally list other members of the group in the Acknowledgments. Acquisition of funding, collection of data, or general supervision of the research group alone does not constitute authorship.

**Contributor Roles Taxonomy (CRediT)**

- Conceptualization
- Data curation
- Formal analysis
- Funding acquisition
- Investigation
- Methodology
- Project administration
- Resources
- Software
- Supervision
- Validation
- Visualization
- Writing – original draft
- Writing – review and editing

The KMJ accepts notice of equal contributions for the first or corresponding authors when the study was clearly performed by co-first or co-corresponding authors. The KMJ does not allow authorship corrections after publication unless the editorial staff made an obvious mistake. Before publication, authorship can be changed if all authors request the authorship correction.

**Declaration of ethics including authorship**

The corresponding author must agree to abide by research ethics guidelines, including those involving authorship, by including the following sentences in a cover letter.

"All of the bylined authors meet the ICMJE criteria for authorship. We well understand the privilege and responsibility of authorship of scientific publications. We declare that we are following global and/or local guidelines of research and publication ethics strictly including authorship."

All authors should provide details of their position in the affiliated institution on the online submission system (e.g., professor, college lecturer, graduate student, researcher, college student, post-doctoral fellow, middle or high school teacher, or high school student, etc.).

**Redundant publication and plagiarism**

Redundant publication is defined as "reporting (publishing

or attempting to publish) substantially the same work more than once, without attribution of the original source(s)." Characteristics of reports that are substantially similar include the following: (a) "at least one of the authors must be common to all reports (if there are no common authors, it is more likely plagiarism than redundant publication)," (b) "the subjects or study populations are the same or overlapped," (c) "the methodology is typically identical or nearly so," and (d) "the results and their interpretation generally vary little, if at all."

When submitting a manuscript, authors should include a letter informing the editor of any potential overlap with other already published material or material being evaluated for publication and should also state how the manuscript submitted to the KMJ differs substantially from other materials. If all or part of a patient population was previously reported, this should be mentioned in the Methods, with citation of the appropriate reference(s). The duplication will be checked through crosscheck (https://app.ithenticate.com) or eTBLAST (https://bio.tools/etblast) before submission. If duplicate publication related to the papers in this journal is detected, the manuscripts may be rejected, the authors will be announced in the journal, and their institutes will be informed. There will also be penalties for the authors.

**Secondary publication**

It is possible to republish manuscripts if the manuscripts satisfy the conditions for secondary publication in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals established by the ICMJE (http://www.icmje.org).

- The authors have received approval from the editors of both journals (the editor concerned with the secondary publication must have access to the primary version).
- The priority for the primary publication is respected in the form of a publication interval negotiated by the editors of both journals and the authors.
- The paper for secondary publication is intended for a different group of readers; an abbreviated version could be sufficient.
- The secondary version faithfully reflects the data and interpretations of the primary version.
- The secondary version informs readers, peers, and documenting agencies that the paper has been published in whole or in part elsewhere—for example, with a note reading, "This article is based on a study first reported in (journal title, with full reference)"—and the secondary version cites the primary reference.
- The title of the secondary publication should indicate that it is a secondary publication (complete or abridged republication or translation) of a primary publication. Of note, the US National Library of Medicine (NLM) does not consider translations to be "republications" and does not cite or index them when the original article was published in a journal indexed in MEDLINE.

**Conflict of interest statement**

The corresponding author must inform the editor of any potential conflicts of interest that could influence the authors' interpretation of the data. Examples of potential conflicts of interest are financial support from or connections to pharmaceutical companies, political pressure from interest groups, and academically related issues. In particular, all sources of funding applicable to the study should be explicitly stated.

**Commercial sponsorships or funding**

The corresponding author must inform the editor of any commercial sponsorships or fundings.

**Registration of the clinical trial research**

A clinical trial defined as "any research project that prospectively assigns human subjects to intervention and comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome" should be registered with the primary registry prior to publication. The KMJ accepts registration in any of the primary registries that participate in the WHO International Clinical Trials Portal (https://www.who.int/clinical-trials-registry-platform), NIH ClinicalTrials.gov (http://www.clinicaltrials.gov), ISRCTN Resister (www.ISRCTN.org), or the Clinical Research Information Service (CRIS), Korea CDC (https://cris.nih.go.kr/cris/index.jsp). The clinical trial registration number shall appear at the end of the abstract.

**Data-sharing statement**

The KMJ accepts the "ICMJE Recommendations for Data Sharing Statement Policy." All manuscripts reporting clinical trial results from July 1, 2018 should submit a data-sharing statement following the ICMJE guidelines. Authors can refer to the editorial, "Data Sharing Statements for Clinical Trials: A Requirement of the International Committee

of Medical Journal Editors," in JKMS Vol. 32, No. 7:1051-1053 (http://crossmark.crossref.org/dialog/?doi=10.3346/jkms.2017.32.7.1051&domain=pdf&date_stamp=2017-06-05).

**Statement of informed consent and IRB approval**

Copies of written informed consent and institutional review board (IRB) approval for clinical research (original article and case report) should be kept. Authors should include the IRB approval number in the manuscript. If necessary, the editor or reviewers may request copies of these documents to resolve questions about IRB approval and study conduct. For studies involving human subjects, the method through which informed consent was obtained from the participants must be stated in the Methods section.

**Statement on human and animal rights**

Clinical research should be done in accordance with the Ethical Principles for Medical Research Involving Human Subjects, as outlined in the Helsinki Declaration (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/). Clinical studies that do not meet the Helsinki Declaration will not be considered for publication. For publication, the human subjects' identifiable information, such as the patients' names, initials, hospital numbers, dates of birth, or other protected healthcare information should not be disclosed. For animal subjects, the research should be performed based on the National or Institutional Guide for the Care and Use of Laboratory Animals, and the ethical treatment of all experimental animals should be maintained.

**Process to manage the research and publication misconduct**

When the Journal faces suspected cases of research and publication misconduct, such as a redundant (duplicate) publication, plagiarism, fabricated data, changes in authorship, undisclosed conflicts of interest, an ethical problem with a submitted manuscript, a reviewer who has appropriated an author's idea or data, complaints against editors, and other issues, the resolution process will follow the flowchart provided by the Committee on Publication Ethics (http://publicationethics.org/resources/flowcharts). The Editorial Board of the KMJ will discuss the suspected cases and reach a decision. The KMJ will not hesitate to publish errata, corrigenda, clarifications, retractions, and apologies when needed.

**Errata**

Errata provide a means of correcting errors that occur during the writing, typing, editing, or publication (e.g., a misspelling, dropped word or line, or mislabeling of a figure) of a published article. Errata can be submitted through the KMJ online manuscript management portal as a Microsoft Word file. In the Abstract section of the submission form (a required field), enter "Not Applicable" and upload the text of the proposed erratum. Please see a recent issue for correct formatting.

**Author corrections**

If the addition or deletion of authors or a change to the order of authorship is required, the corresponding author must complete the authorship change form and submit it through the KMJ online manuscript management portal with the signature of all existing authors and new authors. In the Abstract section of the submission form (a required field), enter "Not Applicable." The text of the proposed erratum should be uploaded as a Microsoft Word file. When there is a request for a change by the author, the editorial committee assembles an ethics committee to judge whether the change is appropriate. If a new author should be added or an author should be deleted after submission, it is the responsibility of the corresponding author to ensure that all authors are aware of and agree to the change in authorship. The KMJ assumes no responsibility for such changes. Please see a recent issue for correct formatting.

**Retractions**

Retractions are reserved for major errors or breaches of ethics that, for example, may call into question the source of the data or the validity of the results and conclusions of an article. Retractions should be submitted through the KMJ online manuscript management portal as a Microsoft Word file. In the Abstract section of the submission form (a required field), put "Not Applicable." Letters of agreement signed by all of the authors must be supplied as Miscellaneous Files Not for Publication (scanned PDF files). The retraction will be assigned to the journal's editor-in-chief, and the editor who handled the paper and the chair of the KMJ editorial board will be consulted. If all parties agree to the publication and content of the retraction, it will be sent

to the journals department for publication.

For the policies on research and publication ethics not stated in the Instructions, Guidelines on Good Publication (http://publicationethics.org) or Good Publication Practice Guidelines for Medical Journals (http://kamje.or.kr) can be applied.

## V. MANUSCRIPT PREPARATION AND FORMAT

### 1. General requirements

- Every manuscript should be written in English.
- The main document, including manuscript text and tables, should be prepared in MS Word.
- The manuscript should be double-spaced on 21.6 × 27.9 cm (US letter) or 21.0 × 29.7 cm (A4) paper with top, bottom, right, and left margins of 3.0 cm.
- All manuscript pages are to be numbered consecutively, beginning with the abstract as page 1. Neither the authors' names nor their affiliations should appear on the manuscript pages.
- Use only standard abbreviations; use of nonstandard abbreviations can be confusing to readers. Avoid abbreviations in the title of the manuscript. A spelled-out term followed by the abbreviation in parentheses should be used on first mention unless the abbreviation is widely recognized (e.g., UN for United Nations).
- The names of manufacturers of equipment and non-generic drugs should be given.
- When quoting from other sources, supply a reference number after the author's name or at the end of the quotation (see References section).
- Authors should express all measurements in conventional units, using the International System (SI) of units.
- To make papers more readable and informative, mark the followings in italics.
  - Biological names of organisms: *Saccharomyces cerevisiae*, *E. coli*
  - Restriction enzymes and some enzymes: *EcoRI, Taq polymerase*
  - Names of genes: *src, c-H-ras, myc*
  - Latin words: *in vivo, in vitro, in situ*
  - Centrifugal acceleration: *g* (e.g., 100,000 *g*)

### 2. Reporting guidelines for specific study designs

Research reports frequently omit important information. As such, reporting guidelines have been developed for a number of study designs, and some journals may ask authors to follow them. Authors are also encouraged to consult the reporting guidelines relevant to their specific research design. A good source for reporting guidelines is the EQUATOR Network (http://www.equator-network.org/home) and the United States National Library of Medicine (http://www.nlm.nih.gov/services/research_report_guide.html).

### 3. Original articles

**Manuscript style**

The manuscript should be prepared according to the "ICMJE Recommendations for the Conducts, Reporting, and Publication of Scholarly Work in Medical Journals" (2021) (http://www.icmje.org). In addition to the ICMJE recommendation, a number of reporting guidelines have been developed by experts to facilitate reporting of research studies or clinical trials (http://www.equator-network.org/library). For reporting of randomized controlled trials, the KMJ requires compliance with the CONSORT statement (http://www.consort-statement.org) and the ICMJE Statement on Data Sharing (http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html).

**Manuscript components**

The manuscript, including tables and their footnotes and figure legends, should use the 12-point Times New Roman font and line spacing should be set to "double." The manuscript should be in the following sequence: title page, Conflicts of interest, Sources of funding, Author contributions, ORCID iDs, Abstract and Keywords, Introduction, Methods, Results, Discussion, Acknowledgments, References, Tables (each table complete with a title and footnotes), and Figure Legends (figures should be uploaded separately, not embedded in text). All pages should be numbered consecutively starting from the title page. All numbers should be written in Arabic numerals throughout the manuscript except for the first word of a sentence. Tables and figures should not be inserted in the main text. A combined table file can be uploaded separately from the main manuscript file. A combined figure file or individual figure files can be uploaded separately from the main manuscript.

**File formats**

Drawings, photographs, graphs, or combined figures can be submitted as PDF files. We accept graphic files in the PDF, JPEG, or TIFF formats only. It is permissible to send low-resolution images for peer review, but we will ask for high-resolution files before publication. Acceptable file formats for supplemental video files are mov, wmv, mpg, mpeg, and mp4. The file size and running time of each video should be no more than 25 MB and 5 minutes, respectively.

### *Title page*

Include the following items on the title page: (1) the title of the manuscript (the title should be short, informative, contain the major keywords, and be no more than 200 characters in length, including spaces between words; acronyms and abbreviations should be avoided, and the species of any experimental animal must be indicated in the title; (2) an author list (include ORCID*); (3) the names of each author's institutional affiliation; (4) the name, address, telephone number, and email address of the corresponding author; (5) the source of any research funding, if any, and a list of where and when the study has been presented in part elsewhere; and (6) a running title of no more than 50 characters.

*ORCID: We recommend that the open researcher and contributor ID (ORCID) of all authors be provided. Authors can obtain an ORCID at http://orcid.org. Registration is free to every researcher in the world.

### *Conflict of interest*

State any potential conflict of interest that could influence the authors' interpretation of the data, such as financial support from or connections to pharmaceutical companies, political pressure from interest groups, or academically related issues.

### *Author contributions*

What authors have contributed to the study should be described in this section. To qualify for authorship, all contributors must meet at least one of the 12 core contributions defined by CRediT (conceptualization, methodology, software, validation, formal analysis, investigation, data curation, funding acquisition, project administration, resources, supervision, and visualization), as well as at least one writing contribution (original draft preparation, review, and editing). Authors may also satisfy the other remaining contributions; however, these alone will not qualify them for authorship.

Contributions will be published with the article, and they should accurately reflect contributions to the work. The submitting author is responsible for completing this information at submission, and it is expected that all authors will have reviewed, discussed, and agreed to their individual contributions ahead of this time.

An example:

Conceptualization: GDH. Data curation: YSJ, YC. Formal analysis: CSK. Methodology: YK, GDK.; Software: YK, YSJ. Validation:..... Investigation:..... Funding acquisition:..... Project administration:..... Resources:..... Supervision:..... Visualization:..... Writing - original draft: GDH, YSJ. Writing - review and editing: YC, YK, CSK. All authors read and approved the final manuscript.

### *Abstract and keywords*

The abstract should briefly describe the content of the manuscript in a structured format within 250 words. The abstract should be structured as follows; Background, Methods, Results, and Conclusions. Initialisms, acronyms and informal abbreviations should be avoided where possible; if needed, they should be kept to an absolute minimum and accompanied by proper definitions. Three to five keywords should be listed below the Abstract on the Abstract page. For the selection of keywords, refer to Medical Subject Headings (MeSH) in PubMed, or http://www.nlm.nih.gov/mesh/MBrowser.html.

### *Main text*

- Introduction

A brief background, references to the most pertinent papers general enough to inform readers, and the relevant findings of others should be included. It is recommended that the introduction include a "General and specific background," "Debating issue," and "Specific purpose of this study."

- Methods

The explanation of the experimental methods used should be concise and sufficient for repetition by other qualified investigators. Procedures that have been published previously should not be described in detail. However, new or significant modifications of previously published

procedures require full descriptions. Clinical studies or experiments using laboratory animals or pathogens should mention approval of the studies by relevant committees in this section. The sources of special chemicals or preparations should be supplied, along with their location (name of company, city and state, and country). The method of statistical analyses and the criteria for determining significance levels should be described. An ethics statement should be placed in this section when the studies are performed using clinical samples or data, and animals. Examples are provided below.

(For clinical study)

The present study protocol was reviewed and approved by the Institutional Review Board of xxx XXXXXX of the University College of Medicine (approval No. 2018001). Informed consent was submitted by all subjects when they were enrolled.

(For animal study)

The procedures used and the care of animals were approved by the Institutional Animal Care and Use Committee at xxxXXXXX University (approval No. 2018002).

(For clinical trials)

This was a randomized clinical trial at the second phase, registered at the Clinical Research Information Service (CRIS, http://cris.nih.go.kr), number KCT0002018.

Other international registration is acceptable. Manuscripts reporting interventional clinical trial should include a data-sharing plan following the ICMJE statement by referring to the ICMJE Statement on Data Sharing.

When describing participants, ensure correct use of the terms sex (for biological factors) and gender (identity, psychosocial, or cultural factors), and, unless inappropriate, report the sex or gender of study participants, the sex of animals or cells, and describe the methods used to determine sex or gender. If the study involved an exclusive population, (e.g., only one sex), authors should justify why, except in obvious cases (e.g., prostate cancer). Authors should describe how they determined race or ethnicity and justify their relevance.

• Results

This section should be presented logically and in a manner consistent with the Methods section. Tables and figures are recommended when they can present data more succinctly and clearly. Do not duplicate the content of tables or figures in the Results section. Briefly describe the core results related to the conclusion in the text when data are provided in tables or in figures. In the Results section, audio or video files are also welcomed. Supplementary results can be placed in an Appendix.

• Discussion

The data should be interpreted concisely without repeating materials already presented in the Results section. A summary or conclusion should be included at the end of this section. We recommend authors describe the clinical or biomedical significance of the study. Speculation is permitted but must be clearly supported by the results or literature published.

### *Acknowledgments*

The authors can list the names of persons who helped plan or conduct the study but are not eligible authors in this section. Funding sources, which are supplied on the title page, should not be duplicated in this section.

### *References*

References should be numbered in the order they appear in the text and should not exceed 40 in number. Citation of references in the text should be identified with Arabic numerals in square brackets (for example, ..... the leading cause of death in Korea [1,2] and preceding any punctuation). References should be listed in the order they are cited in the text, with consecutive numbers in this section. The style for citing papers in periodicals is: last name and initials of all authors, full title of article, journal name abbreviated in accordance with the PubMed style, year, volume, issue number and first and last page numbers. The style for a chapter of a book is: author and title of the chapter, editor of the book, title of the book, edition, volume, publisher, year, and first and last page numbers. Up to six authors can be listed in a reference; the names of all authors after the first 6 should be abbreviated to "et al." The use of software to manage references (e.g., EndNote) is recommended.

Authors are responsible for the accuracy and completeness of their references and correct text citations. Papers in press may be listed among the references with the journal

name and tentative year of publication. Gray literature sources are not allowed for references. Internet materials are acceptable with the correct URL and the date accessed.
Examples of reference style:

1. Journal
   Kim TS, Kang SH, Kang PM, Ha H, Kim SD, Yoon J, et al. Clinical significance of serum neutrophil gelatinase-associated lipocalin in the early diagnosis of renal function deterioration after radical nephrectomy. Kosin Med J 2018;33:20-8.
   Verbalis JG. Renal physiology of nocturia. Neurourol Urodyn 2014;33(Suppl 1):S6-9.
2. Book
   Hong GD, Kim C, Park J. KMJ reference style: a guide for authors. 5th ed. Daehakro Press; 2017.
3. Chapter in a book
   Floch MH. Probiotics, probiotics and dietary fiber. In: Buchman A, editor. Clinical nutrition: a guide for gastroenterologists. SLAK Incorporated; 2005. p. 18-24.
4. Conference
   Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsale, Ireland. Springer; 2002. p. 182-91.
5. Internet or electronic resource
   Testa J. The Thomson Reuters journal selection process [Internet]. Thomson Reuters; c2012 [cited 2013 Sep 30]. http://wokinfo.com/essays/journal-selection-process

### *Tables and figures*

**Tables:** Tables are to be numbered in the order in which they are cited in the text. A table title should concisely describe the content of the table so that a reader can understand the table without referring to the text. Each table must be simple and provided on a separate page with its title. Explanatory matter is placed in the footnotes below the table and not in the title. All non-standard abbreviations should be explained in the footnotes. The symbols a), b), c), d), should be used (in that order) for footnotes. Statistical measures such as standard deviation (SD) or standard error (SE) should be identified. No vertical or horizontal rules should appear between table cells.

**Figures and legends for illustrations:** Figures must be submitted as separate files in JPEG, TIFF or PDF format (do not embed the figures in a Microsoft Word file). To supply figures in other file formats, contact the editorial office. All images should the following image resolutions or greater: line art (an image composed of lines and text): 1,000 dpi; halftone (a continuous tone photograph, which contains no text): 300 dpi; or combination (line art and halftone): 600 dpi.

Photographs of recognizable persons should be accompanied by a signed release from the person in the photograph or an appropriate legal guardian authorizing reproduction. Written permission should be obtained for the use of all previously published illustrations (and copies of permission letters should be included).

Figures should be numbered, using Arabic numerals, in the order in which they are cited. In the case of multiple prints bearing the same number, use English letters immediately after the numerals to indicate the correct order. (e.g., Fig. 1A, Fig. 1B and C; Fig. 2A–D).

If any tables or figures are moved or modified from other papers, authors should obtain permission through the Copyright Clearance Center (https://www.copyright.com) or from the individual publisher if the materials are not from open access journals published under a Creative Commons license. If tables or figures are from open access journals, accurately describe the source of the journal in the footnote. Note that a free access journal is different from that of an open access journal, and it is necessary to obtain permission from the publisher of a free access journal when using tables or figures from these sources.

**Description of *p* value:** $p$ is always italicized and in lower case. When $p$ values are statistically significant, the corresponding data should be marked with superscripted asterisks ($p<0.05$, $p<0.01$, $p<0.001$).

**Abbreviations:** Except for units of measurement, abbreviations are strongly discouraged. Do not use abbreviations in the title or abstract and limit their use in the text. Define all abbreviations at first mention.

**Units of measurement:** Laboratory values are expressed using conventional units of measure, with relevant System International (SI) conversion factors, if necessary expressed secondarily (in parentheses) only at first mention. Figures and tables should use conventional units, with conversion

factors given in legends or footnotes. The metric system is preferred for the expression of length, area, mass, and volume.

**Names of drugs, devices, and other products:** Generic names of pharmaceuticals should be used. When proprietary brands are used, include the brand name and the name of the manufacturer in parentheses after the first mention of the generic name in the Methods section.

**Gene names, symbols and accession number:** Authors describing genes or related structures in a manuscript should include the names and official symbols provided by the US National Center for Biotechnology Information (NCBI) or the HUGO Gene Nomenclature Committee.

### *Supplementary materials*

Authors can submit supplementary materials for online-only publication when there is insufficient space to include the materials in the main article. Supplementary materials should be original and important to the understanding and interpretation of the report. As supplementary materials will not be edited or formatted after publication, authors are responsible for the accuracy and presentation of this material.

Supplementary materials should be submitted in a single MS Word document or a single PDF file, which should include all materials (information, tables, figures, and references). Each element included in supplementary material should be cited in the text of the main manuscript (e.g., Supplementary Table 1, Supplementary Fig. 1, Supplementary Methods). The first page of the online-only document should list the number and title of each element included in the document.

### 4. Review articles

Reviews are comprehensive analyses of specific topics. They are typically solicited by the Editor, but we also consider unsolicited material. Please send us a Presubmission Inquiry before writing a review article. All review articles undergo the same review process as other types of articles prior to acceptance. Reviews are organized as follows: title page, abstract (a single unstructured paragraph of no more than 250 words) and three to five keywords (as in MeSH), introduction, main text, conclusions, acknowledgments, references, tables, and figure legends. Reviews have no restrictions on word count or the number of figures and tables. However, authors should eliminate redundancies, emphasize the central message, and provide only the data necessary to convey that message. A review article is limited to less than 6,000 words, with a maximum of 100 references, excluding tables or figure legends.

### 5. Case reports

Case reports will be published only in exceptional circumstances, if they illustrate a rare occurrence of clinical importance. The manuscript should be in the following sequence: title page, abstract (no more than 250 words) and three to five keywords (as in MeSH), introduction, case(s), discussion, acknowledgments, references (no more than 20), tables, and figure legends. The manuscript should have no more than six tables or figures in total. For case reports involving humans, whether informed consent for publication of clinical data was obtained from the study participants must be stated in the case description section.

### 6. Editorials

Editorials are invited by the Editor and should provide commentary on articles in the current issue. Editorial topics could include active areas of research, fresh insights, and debates in all fields of interest to KMJ readers. Editorials should not exceed 1,000 words, excluding references, tables, and figure legends. No more than 20 references should be cited. The manuscript should have no more than three tables or figures. Any article longer than these limits should be discussed with the editor.

**Table 1.** Specifications for publication types

| Type of article | Original article | Review article | Case report | Editorial |
|---|---|---|---|---|
| Abstract (words) | 250 | 250 | 250 | NR |
| Text (words)[a] | NL | 6,000 | 1,500 | 1,000 |
| References | 40[b] | 100 | 20 | 20 |
| Tables and Figures | NL | NL | 6 | 3 |

NL, not limited; NR, not required.
[a]Maximum number of words is exclusive of the abstract, references, and figure legends.
[b]Except meta-analyses or systematic reviews.

## VI. INSTRUCTIONS FOR SUBMISSION OF REVISED MANUSCRIPTS

To prepare a revised version of your manuscript, authors

should carefully follow the instructions given in the Editor's letter. Failure to do so will delay a decision on a revision. If references, tables, or figures are moved, added, or deleted during the revision process, all subsequent tables, references, and figures should be renumbered to ensure they are cited in order.

Revised manuscript submissions should include a point-by-point response to the reviewers' comments. Authors should describe how each comment was addressed or why it was not be addressed, and clearly indicate which paragraph was revised to address each comment. The response to reviewers will be shared with all reviewers. Authors may include data in support of their argument even if the data are not included in the manuscript.

Changes referring to an Editor or reviewer query regarding moving or adding references, tables, or figures should be highlighted. Deletions should be marked with strikethrough (a line drawn through the selected text, using the ab button) and highlighted. Authors should submit a highlighted clean version without using the track changes function in MS Word.

## VII. PREPRINT POLICY

A preprint can be defined as a version of a scholarly paper that precedes formal peer review and publication in a peer-reviewed scholarly journal.

KMJ allows authors to submit the preprint to the journal. It is not treated as duplicate submission or duplicate publication. KMJ recommend authors to disclose it with DOI in the letter to the editor during the submission process. Otherwise, it may be screened from the plagiarism check program–Similarity Check (Crosscheck) or Copy Killer. Preprint submission will be processed through the same peer-review process with a usual submission. If the preprint is accepted for publication, authors are recommended to update the info at the preprint with a link to the published article in KMJ, including DOI at KMJ. It is strongly recommended that authors cite the article in KMJ instead of the preprint at their next submission to journals.

## VIII. COPYRIGHT AND OPEN ACCESS POLICY

**Copyright**

All authors of accepted manuscripts must sign a copy of the Journal's "Authorship Responsibility and License Agreement" form and submit it by email to office@kosinmedj.org. All published papers become the permanent property of the Kosin University College of Medicine and must not be published elsewhere without written permission. The copyright of all published materials is owned by the Kosin University College of Medicine.

**Open access policy**

The KMJ is an open access journal. Articles are distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by-nc/4.0), which permits unrestricted, non-commercial use, distribution, and reproduction in any medium, provided that the original work is properly cited. To use any tables or figures published in the KMJ in other periodicals, books, or media for scholarly and educational purposes, permission by the publisher of the KMJ is not necessary.

## IX. AUTHOR'S MANUSCRIPT CHECKLIST

- ☐ **Formatting:** Double-spaced typing in A4 or letter-size paper using 12-point Times New Roman font in an electronic file made by Microsoft (MS) Word.
- ☐ **Sequence:** Title page, Conflict of interest, All sources of funding, Author contributions, Abstract and keywords, Main text, (Acknowledgments), References, Tables, and Figure legends. Numbered pages and lines (from Abstract page).
- ☐ **Title page:** (1) The title of the manuscript; (2) author list (include ORCID); (3) names of each author's institutions and an indication of each author's affiliation; (4) the name, address, telephone numbers, and e-mail address of the corresponding author; (5) if necessary, the source of any research funding; and (6) a running title of fewer than 50 characters.
- ☐ **Abstract and Keywords**
  - Original article (structured—background, methods, results, and conclusions—within 250 words)
  - Review article (unstructured, ≤250 words)
  - Case report (unstructured, ≤250 words)

  Three to five keywords as in MeSH
- ☐ **Main text**
  - Original article (introduction, methods, results, discus-

sion)

- Review article (≤6,000 words), Case report (≤1,500 words), Editorial (≤1,000 words)

Turn on serial line numbering from the beginning of the main text.

☐ **References**

Check that all references in the References section are cited in the text and vice versa.

- Original article (≤40 references)
- Review article (≤100 references), Case report (≤20 references), Editorial (≤20 references)

☐ **Tables and Figures**

All table and figure numbers found in the text. No incorrectly numbered sections and mislabeled tables or figures must be found.

Each figure as separate files, in JPEG, TIFF, PDF format, minimum 300 dpi.

Written permission from the copyright holder is required to reproduce any copyrighted material.

Case report (no more than 6 tables or figures), Editorial (no more than 3 tables or figures)

☐ The **IRB/IACUC approval** report must be uploaded (when reporting results on human subjects/animals).

☐ **IRB/IACUC** approval must be stated in the Methods section.

☐ Authors should submit the **Author Statement Forms**, signed by all authors, simultaneously with the submission of their manuscript.

☐ A **covering letter** describing the scientific significance of the research, stating that the material has not been published previously and will not be submitted for publication elsewhere, and listing any conflicts of interest of all listed authors.

# Author checklist

KMJ
KOSIN MEDICAL JOURNAL

Please be sure to read the Instructions for authors on the *Kosin Medical Journal* (KMJ) website (https://submit.kosinmedj.org). This checklist must be completed before the manuscript submission.

☐ **Formatting:** Double-spaced typing in A4 or letter-size paper using 12-point Times New Roman font in an electronic file made by Microsoft (MS) Word.

☐ **Sequence:** Title page, Conflict of interest, All sources of funding, Author contributions, Abstract and keywords, Main text, (Acknowledgments), References, Tables, and Figure legends. Numbered pages and lines (from Abstract page).

☐ **Title page:** (1) The title of the manuscript; (2) author list (include ORCID); (3) names of each author's institutions and an indication of each author's affiliation; (4) the name, address, telephone numbers, and email address of the corresponding author; (5) if necessary, the source of any research funding; and (6) a running title of fewer than 50 characters.

☐ **Abstract and Keywords**

· Original article (structured—background, methods, results, and conclusions—within 250 words)
· Review article (unstructured, ≤250 words)
· Case report (unstructured, ≤250 words)
Three to five keywords as in MeSH

☐ **Main text**

· Original article (introduction, methods, results, discussion)
· Review article (≤6,000 words), Case report (≤1,500 words), Editorial (≤1,000 words)
Turn on serial line numbering from the beginning of the main text.

☐ **References**

Check that all references in the References section are cited in the text and vice versa.
· Original article (≤40 references)
· Review article (≤100 references), Case report (≤20 references), Editorial (≤20 references)

☐ **Tables and Figures**

All table and figure numbers found in the text. No incorrectly numbered sections and mislabeled tables or figures must be found.
Each figure as separate files, in JPEG, TIFF, PDF format, minimum 300 dpi.
Written permission from the copyright holder is required to reproduce any copyrighted material.
Case report (no more than 6 tables or figures), Editorial (no more than 3 tables or figures)

☐ The **IRB/IACUC approval** report must be uploaded (when reporting results on human subjects/animals).

☐ **IRB/IACUC** approval must be stated in the Methods section.

☐ Authors should submit the **Author Statement Forms**, signed by all authors, simultaneously with the submission of their manuscript.

☐ A **covering letter** describing the scientific significance of the research, stating that the material has not been published previously and will not be submitted for publication elsewhere, and listing any conflicts of interest of all listed authors.

# Copyright transfer agreement

KMJ
KOSIN MEDICAL JOURNAL

KMJ AUTHOR STATEMENT FORMS _____

_____

Title of Manuscript _____

Corresponding Author Name/E-mail _____

To publish a paper in the *Kosin Medical Journal* (KMJ), all authors must read and sign the statements on

1. Authorship Responsibility;
2. Authorship Contributions;
3. Role of the Funding Source;
4. Disclosure of Conflicts of Interest;
5. Copyright Transfer Agreement.

**1. Authorship Responsibility**

- All authors have seen and approved the content of the submitted manuscript. The paper presents original work not previously published in similar form and is not currently under consideration by another journal.
- If the paper contains material (data or information in any other form) that is the intellectual property and copyright of any person(s) other than the author(s), permission from the copyright owner(s) to publish that material must be clearly identified and acknowledged in the text of the paper.
- The authors followed ethics guidelines.
- See the Authorship Policy in Instructions for Authors.

**2. Authorship Contributions**

Please indicate the specific contributions made by each author (list the authors' initials, e.g., KDH).

- Conceptualization: _____
- Data curation: _____
- Formal analysis: _____
- Methodology: _____
- Software: _____
- Validation: _____
- Investigation: _____
- Funding acquisition: _____
- Project administration: _____
- Resources: _____
- Supervision: _____
- Visualization: _____

- Writing - original draft: _____
- Writing - review and editing: _____

**3. Role of the Funding Source**

Please disclose any funding sources and their role, if any, in the writing of the manuscript or the decision to submit it for publication. The information provided here must match the role of the funding source statement in the manuscript.

**4. Disclosure of Conflicts of Interest**

Please check A or B.

A. We/I do not have and have not had a financial interest or other relationships in which any individual benefits by receiving a salary, royalty, intellectual property rights, consulting fee, honoraria, ownership interest, or other financial benefit from the research described in the submission.

B. We/I now have or have had a financial interest or other relationships in which any individual benefits by receiving a salary, royalty, intellectual property rights, consulting fee, honoraria, ownership interest, or other financial benefit. Pease list the manufacturers and/or service providers with whom you have a financial relationship, and describe the condition of your relationship(s). Please be specific.

**5. Copyright Transfer Agreement**

In the occasion of the final acceptance of this manuscript, the authors of the article hereby agree that Kosin University College of Medicine holds the copyright to all materials and the right to publish, transmit, sell, and distribute them in the journal or other media.

| Names of Author(s) | Signature(s) | Date |
|---|---|---|
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |