Incidence and management of hepatic immune-related adverse events in advanced urologic cancers treated with immune checkpoint inhibitors: A multicenter retrospective study

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Abstract. The present study aimed to evaluate the incidence, characteristics and management of hepatic immune-related adverse events (irAEs) in patients with advanced or metastatic urothelial carcinoma (UC) and renal cell carcinoma (RCC) receiving immune checkpoint inhibitors (ICIs). Data regarding the demographics, ICI regimens and hepatic irAEs from 213 patients with metastatic UC or metastatic RCC receiving ICIs between February 2018 and September 2023 at three tertiary medical centers (Inje University Busan Paik Hospital, Busan, South Korea; Dongnam Institute of Radiological and Medical Sciences Cancer Center, Busan, South Korea; Pusan National University Hospital, Busan, South Korea) in South Korea were collected and retrospectively analyzed. Hepatic irAEs were graded using the Common Terminology Criteria for Adverse Events version 5.0 and classified based on R value patterns. Among the 213 patients evaluated, 76 (35.6%) experienced at least one irAE, whereas 48 (22.5%) developed hepatic irAEs. The median onset time for hepatic irAEs was 6.5 weeks, with incidence rates being higher with combination therapies than with monotherapies (31.8 vs. 18.3%; P=0.014). Furthermore, 72.9 and 27.1% of the patients had grade 1-2 and 3-4 hepatic irAEs, respectively. The patterns of liver toxicity included cholestatic (35.4%), mixed (35.4%) and hepatocellular (29.2%). All patients with grade 1-2 hepatic irAE recovered with supportive treatment without ICI discontinuation or corticosteroids use. Among the 13 patients with grade ≥3 hepatic irAEs, 12 recovered with high-dose corticosteroids, while 1 died due to fulminant hepatitis. Hepatic irAEs are common in patients with advanced and metastatic urologic cancers who are treated with ICIs, particularly with combination therapies. Most cases have low-grade irAE that are manageable without ICI discontinuation; however, severe cases require prompt recognition and treatment with corticosteroids. These findings emphasize the importance of regular liver function monitoring and appropriate management strategies for hepatic irAEs in patients with urologic cancer receiving ICI therapy.

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Introduction

In recent years, immune checkpoint inhibitors (ICIs) have revolutionized the treatment landscape for advanced or metastatic urothelial carcinoma (UC) and renal cell carcinoma (RCC). In particular, multiple ICIs targeting programmed cell death 1 (PD-1), PD-1 ligand (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) have promoted significantly improved overall survival and responses rates among patients with these malignancies (1-8).

For advanced or metastatic UC, PD-1 inhibitors such as nivolumab and pembrolizumab are used as fundamental systemic therapies, while the PD-L1 inhibitor avelumab is used for maintenance therapy following first-line chemotherapy In advanced or metastatic RCC, nivolumab and pembrolizumab are used as backbone treatments, often in combination with either the CTLA-4 inhibitor ipilimumab or tyrosine kinase inhibitors like cabozantinib, axitinib, or lenvatinib (9). Although the efficacy of ICIs in advanced or metastatic UC and RCC is well-established, their use has been associated with a unique spectrum of immune-related adverse events (irAEs), which commonly include dermatologic, gastrointestinal, endocrine, and pulmonary toxicities, affecting various organ systems (10,11). Despite the growing body of knowledge surrounding irAEs, hepatic irAEs remain less poorly

characterized, particularly in the context of genitourinary cancers. Most large clinical trials have reported only aggregate rates of hepatotoxicity without detailed characterizations of the clinical presentations, management approaches, or outcomes.

Given the liver's crucial role in maintaining peripheral tolerance, a better understanding of hepatic irAEs in genitourinary malignancies is imperative. Furthermore, managing patients with these types of cancer requires a delicate balance between treatment efficacy and toxicity. As the use of ICIs for urologic malignancies continues to increase, the incidence of hepatic irAEs is expected to rise correspondingly, underscoring the need for improved understanding and management of this complication. The current study, therefore, aimed to comprehensively evaluate the incidence, clinical features, and management of hepatic irAEs among patients with advanced or metastatic UC and RCC receiving ICIs at three tertiary care centers.

Materials and methods

Patients and data collection. This multicenter, observational, retrospective study involving human participants was conducted in accordance with the ethical standards of the institutional and national research committees and the ethical principles stated in the Declaration of Helsinki. The protocol for this study was approved by the Institutional Review Boards of the three participating institutions: Inje University Busan Paik Hospital (BPIRB 2024-10-001), Pusan National University Hospital (2408-017-110), and Dongnam Institute of Radiological & Medical Sciences (D-2312-021-007). The requirement for informed consent was waived due to the retrospective nature of this study. All participating centers obtained approval from their local research ethics boards prior to data collection. A total of 267 patients aged 20 years or older with advanced or metastatic UC or RCC, who received ICIs between February 2018 and September 2023, were retrospectively identified from three tertiary medical centers in South Korea. Patients who lacked follow-up data on oncological outcomes after ICI treatment, had been diagnosed with other malignancies or received systemic therapy within the past 5 years or had liver metastases from metastatic UC or RCC were excluded. The final study cohort comprised 213 patients with a median age of 70 years (IQR, 38-86 years). Demographic, clinical, and laboratory variables prior to ICI treatment initiation were collected.

ICI treatment. ICI treatment was administered in accordance with the Korean National Health Insurance regulations and National Comprehensive Cancer Network guidelines (9,12). The ICIs used for the treatment of advanced or metastatic UC and RCC included ipilimumab (a CTLA-4 inhibitor), nivolumab and pembrolizumab (PD-1 inhibitors), and atezolizumab and avelumab (PD-L1 inhibitors). The specific drugs and regimens administered to the patients included herein are summarized in Table I. All participating centers administered these medications without dose escalation or reduction, strictly following the regimens outlined in Table I. None of our patients received ICIs as first-line therapy for advanced or metastatic UC or as adjuvant treatment for increased risk of RCC recurrence. For advanced UC patients, second-line treatment included avelumab maintenance therapy administered after 4-6 cycles of chemotherapy. Patients continued therapy until disease progression or unacceptable toxicity occurred. Progression was defined as clinical progression or fulfillment of radiographic criteria based on the Response Evaluation Criteria in Solid Tumors version 1.1.

IrAEs. IrAEs were defined as adverse events with a probable immunologic basis that required monitoring and potential intervention. The irAEs were categorized into dermatologic, hepatic, renal, gastrointestinal, endocrine, rheumatologic, pulmonary, hematologic, and other subgroups. Clinical data on irAEs, including ICI types, duration of ICI therapy, and time to irAE onset were extracted from outpatient clinic notes, hospitalization records, and radiological reports. All evaluated patients had comprehensive clinical documentation of irAEs, including descriptions of severity and management approaches. Toxicity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (13).

Characterization of hepatic irAE. Hepatic irAEs were classified into grades 1-4 using the CTCAE version 5.0, considering that the enrolled patients presented with normal baseline liver tests. Hepatic irAEs were defined based on elevations in aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin levels relative to the upper limit of normal (ULN). Grade 1 events were defined as those in which AST or ALT was greater than the ULN to 3 times the ULN and/or total bilirubin was greater than the ULN to 1.5 times the ULN. Grade 2 events were defined as those in which AST or ALT was 3-5 times the ULN and/or total bilirubin was greater than 1.5-3 times the ULN. Grade 3 events were defined as those in which AST or ALT was greater than 5-20 times the ULN and/or total bilirubin was 3-10 times the ULN. Grade 4 events were defined as those in which AST or ALT was greater than 20 times the ULN and/or total bilirubin was greater than 10 times the ULN. These criteria were applied to participants who previously had normal results on their liver function tests. Given that most patients with hepatic irAEs remain asymptomatic, liver function tests were performed at baseline and before each treatment cycle. For patients with liver function test results outside the ULN prior to ICI treatment, an extensive workup was performed to rule out other causes of liver enzyme abnormalities, including viral hepatitis, autoimmune disease, cancer progression, vascular complications, and other potential treatments that could cause drug-induced liver injury. Liver imaging studies were systematically performed in these cases. The pattern of hepatitis was analyzed using the R value calculated as (ALT/ULN)/(ALP/ULN) (14). To help determine the predominant type of liver injury and guide further management and treatment decisions, hepatic irAE patterns were categorized as cholestatic ($R \leq 2$), mixed ($2 < R < 5$), or hepatocellular ($R \geq 5$).

Management of hepatic irAEs. Hepatic irAEs were managed based on the American Society of Clinical Oncology Clinical Practice Guideline, which presents practical recommendations according to the hepatotoxicity grade defined by the CTCAE

Table I. Immune-check point inhibitor regimens used in the present study for the treatment of advanced and metastatic RCC and UC.

A, Advanced or metastatic RCC

Drug combination	Regimen	Indication
Pembrolizumab (monotherapy)	200 mg IV every 3 weeks or 400 mg IV every 6 weeks	Second-line or later treatment
Nivolumab (monotherapy)	240 mg IV every 2 weeks or 480 mg IV every 4 weeks	Second-line or later treatment
Pembrolizumab + axitinib	Pembrolizumab: 200 mg IV every 3 weeks or 400 mg IV every 6 weeks; axitinib: 5 mg orally twice daily	First-line treatment for IMDC all risk groups
Nivolumab + ipilimumab	Nivolumab: 3 mg/kg IV every 3 weeks for 4 doses, then 240 mg IV every 2 weeks or 480 mg IV every 4 weeks; ipilimumab: 1 mg/kg IV every 3 weeks for 4 doses	First-line treatment for IMDC intermediate or poor-risk
Nivolumab + cabozantinib	Nivolumab: 240 mg IV every 2 weeks or 480 mg IV every 4 weeks; cabozantinib: 40 mg orally once daily	First-line treatment for IMDC all risk groups
Pembrolizumab + lenvatinib	Pembrolizumab: 200 mg IV every 3 weeks or 400 mg IV every 6 weeks; lenvatinib: 20 mg orally once daily	First-line treatment for IMDC all risk groups

B, Advanced or metastatic UC

Drug combination	Regimen	Indication
Pembrolizumab	200 mg IV every 3 weeks or 400 mg IV every 6 weeks	Second-line or later treatmentafter progression on platinum-based chemotherapy
Atezolizumab	1,200 mg IV every 3 weeks	Second-line or later treatment after progression on platinum-based chemotherapy
Nivolumab	240 mg IV every 2 weeks or 480 mg IV every 4 weeks	Second-line or later treatment after progression on platinum-based chemotherapy
Avelumab	10 mg/kg IV every 2 weeks	Maintenance therapy post-platinum-based chemotherapy

RCC, renal cell carcinoma; UC, urothelial carcinoma; IV, intravenous; IMDC, International Metastatic RCC Database Consortium.

grading system (4). The management approach utilized in our study was as follows: patients with grade 1 and 2 hepatic irAEs did not receive corticosteroids or discontinue ICI therapy in the early stage of treatment; instead, their hepatic irAEs were managed with heptatonic agents such as ursodeoxycholic acid (UDCA) and biphenyl dimethyl dicarboxylate (DDB). However, for patients with grade 2 hepatic irAEs, the use of corticosteroids and discontinuation of ICI therapy were left to the discretion of the treating physician. All patients with grade 3 or higher hepatic irAEs discontinued ICI therapy and received high-dose intravenous corticosteroids (1 mg/kg). In patients with corticosteroid resistance, second-line immunosuppressive agents were administered.

Statistical analysis. Continuous variables were presented as either mean and standard deviation or median and interquartile range (IQR), whereas categorical variables were presented as frequencies and percentages. Differences between groups were evaluated using Pearson's chi-squared test, Fisher's exact test, and linear-by-linear association for categorical variables. For continuous variables, unpaired Student's t-test, one-way ANOVA with Tukey's post hoc test and Kruskal-Wallis test with Dunn's post hoc test were used. The cumulative probability of hepatic irAE according to ICI regimens was estimated using Kaplan-Meier analysis. Multiple pairwise comparisons between groups were performed using log-rank tests with Bonferroni correction to control for type I error.

Table II. Patient characteristics.

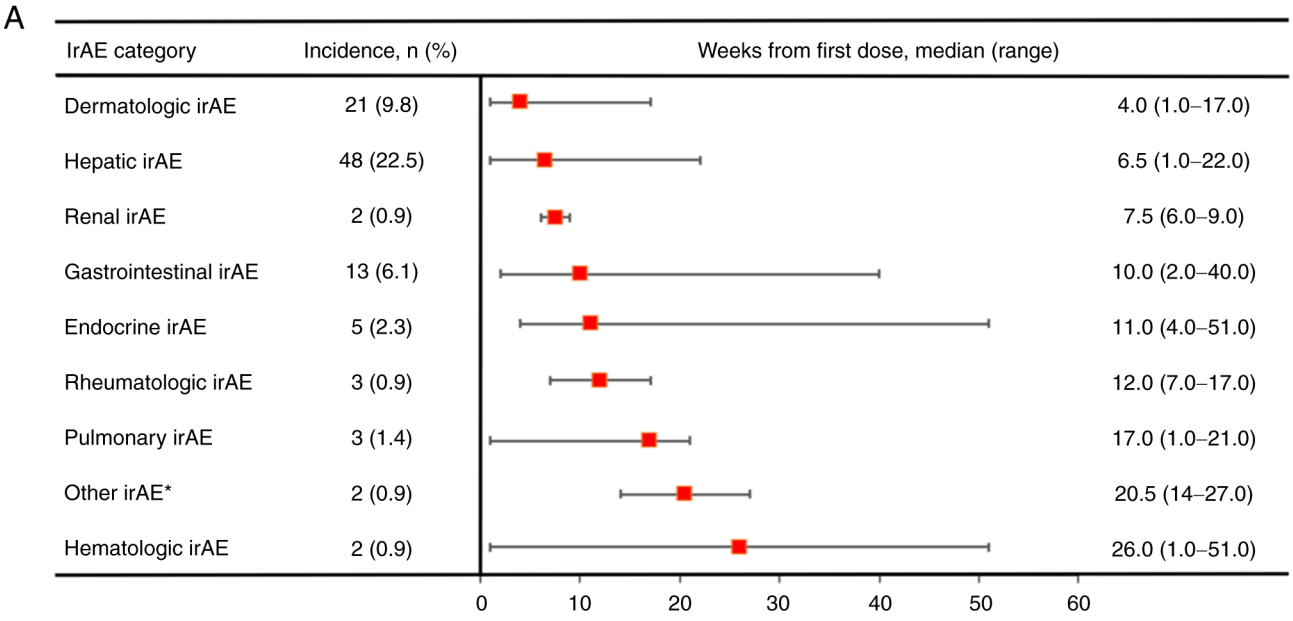
Characteristics	Total (n=213)	No hepatic irAE (n=165)	Hepatic irAE (n=48)	P-value
Median age, years (IQR)	70 (38-86)	71 (43-84)	68 (35-86)	0.057
Sex, n (%)				
Male	155 (72.8)	117 (70.9)	38 (79.2)	0.258
Female	58 (27.2)	48 (29.1)	10 (20.8)	
Type of cancer, n (%)				
Renal cell carcinoma	88 (41.3)	61 (37.0)	27 (56.3)	0.046
Upper tract urothelial carcinoma	63 (29.6)	53 (32.1)	10 (20.8)	
Bladder urothelial carcinoma	62 (29.1)	51 (30.9)	11 (22.9)	
Type of ICI, n (%)				
Anti-PD-L1 monotherapy	88 (41.3)	76 (46.0)	12 (25.0)	0.014
Anti-PD-1 monotherapy	59 (27.7)	44 (26.7)	15 (31.3)	
Anti-PD-1 + TKI	15 (7.0)	11 (6.7)	4 (8.3)	
Anti-PD-1 + CTLA-4	51 (23.9)	34 (20.6)	17 (35.4)	
Line of ICI regimen, n (%)				
First line ICI	72 (33.8)	51 (30.9)	21 (43.8)	0.172
Second line	111 (52.1)	90 (54.5)	21 (43.8)	
≥Third line	30 (14.1)	24 (14.6)	6 (12.4)	
Duration of ICI, months (mean ± SD)	7.9±8.0	7.7±7.0	8.8±10.7	0.491
ECOG performance status at ICI initiation, n (%)				
0	203 (95.3)	160 (97.0)	43 (89.6)	0.337
1	6 (2.8)	1 (0.6)	5 (10.4)	
≥2	4 (1.9)	4 (2.4)	0 (0.0)	
Diabetes mellitus, n (%)				
No	179 (84.0)	144 (87.3)	35 (72.9)	0.017
Yes	34 (16.0)	21 (12.7)	13 (27.1)	
Hypertension, n (%)				
No	138 (64.8)	113 (68.5)	25 (52.1)	0.036
Yes	75 (35.2)	52 (31.5)	23 (47.9)	
Hypothyroidism, n (%)				
No	204 (95.8)	162 (98.2)	42 (87.5)	0.005
Yes	9 (4.2)	3 (1.8)	6 (12.5)	
Pre-existing chronic liver disease[a], n (%)				
No	211 (99.1)	164 (99.4)	47 (97.9)	0.401
Yes	2 (0.9)	1 (0.6)	1 (2.1)	

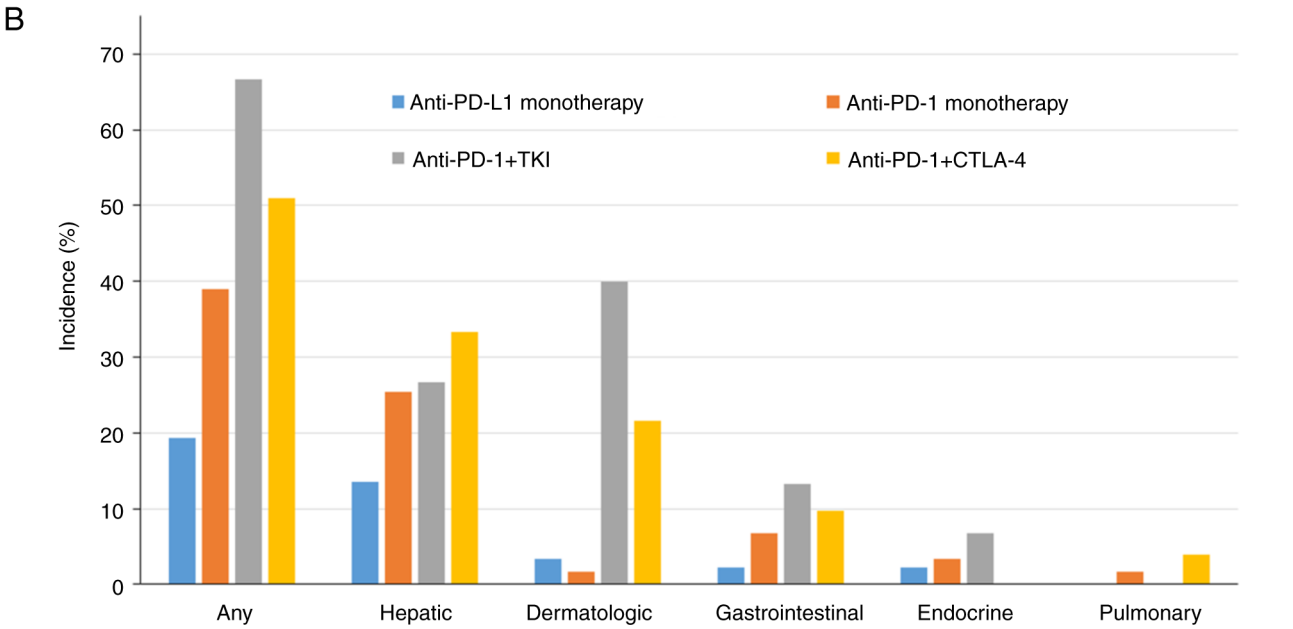
[a]Chronic liver disease: Hepatitis B virus, hepatitis C virus or non-viral liver disease. Categorical variables were compared using Pearson's χ^2 test or Fisher's exact test as appropriate. Continuous variables were analyzed using Student's t-test (unpaired). CTLA-4, cytotoxic T-lymphocyte-associated protein 4; ECOG, Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibitor; IQR, interquartile range; irAE, immune-related adverse event; PD-1, programmed cell death 1; PD-L1, PD-1 ligand; TKI, tyrosine kinase inhibitor.

Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using Cox proportional hazards regression models for between-group comparisons. Progression-free survival (PFS) was estimated using the Kaplan-Meier method with log-rank test. Statistical analysis was performed using SPSS version 27.0 (IBM Corp.) and MedCalc version 22.0 (MedCalc Software Ltd.). For all tests, a two-sided P-value of <0.05 indicated statistical significance.

Results

Patient demographics and irAEs. Throughout the 62-month study period, 213 patients from three tertiary care centers were included in the analysis. The cohort comprised 62 (29.1%), 63 (29.6%), and 88 (41.3%) patients with bladder UC, upper tract UC (UTUC), and RCC, respectively. Table II summarizes the characteristics of the study cohort. The median age at ICI





IrAE category	Anti-PD-L1 monotherapy n=88, (%)	Anti-PD-1 monotherapy n=59, (%)	Anti-PD-1+ TKI n=15, (%)	Anti-PD-1+ Anti-CTLA-4 n=51, (%)	P-value
Any irAE	17 (19.3)	23 (39.0)	10 (66.7)	26 (51.0)	<0.001
Hepatic irAE	12 (13.6)	15 (25.4)	4 (26.7)	17 (33.3)	0.013
Dermatologic irAE	3 (3.4)	1 (1.7)	6 (40.0)	11 (21.6)	<0.001
Gastrointestinal irAE	2 (2.3)	4 (6.8)	4 (13.3)	5 (9.8)	0.028
Endocrine irAE	2 (2.3)	2 (3.4)	1 (6.7)	0 (0.0)	0.939
Pulmonary irAE	0 (0.0)	1 (1.7)	0 (0.0)	2 (3.9)	0.207

Figure 1. irAEs according to organ categories. (A) Time to onset of irAE. The median time and range for each irAE category are shown. *Other, cardiovascular irAE (pericarditis) and ocular irAE (uveitis). (B) Distribution of irAEs for organ categories according to four immune checkpoint inhibitor treatment groups. Statistical comparisons of categorical variables were conducted using Pearson's χ^2 test or Fisher's exact test where appropriate. CTLA-4, cytotoxic T-lymphocyte-associated protein 4; irAE, immune-related adverse event; PD-1, programmed cell death 1; PD-L1, PD-1 ligand; TKI, tyrosine kinase inhibitor.

treatment initiation was 70 years (IQR, 38-86 years), with 155 (72.6%) male patients. The median follow-up duration was 16.0 months (IQR, 1-27 months). A total of 141 (66.2%) patients received at least one prior treatment before an initiating ICI therapy. Regarding ICI agents, 41.3% (n=88) received PD-L1 inhibitors, whereas 27.7% (n=59) received PD-1 inhibitors. Additionally, 7% (n=15) of the patients received PD-1 inhibitors in combination with tyrosine kinase inhibitors (TKIs),

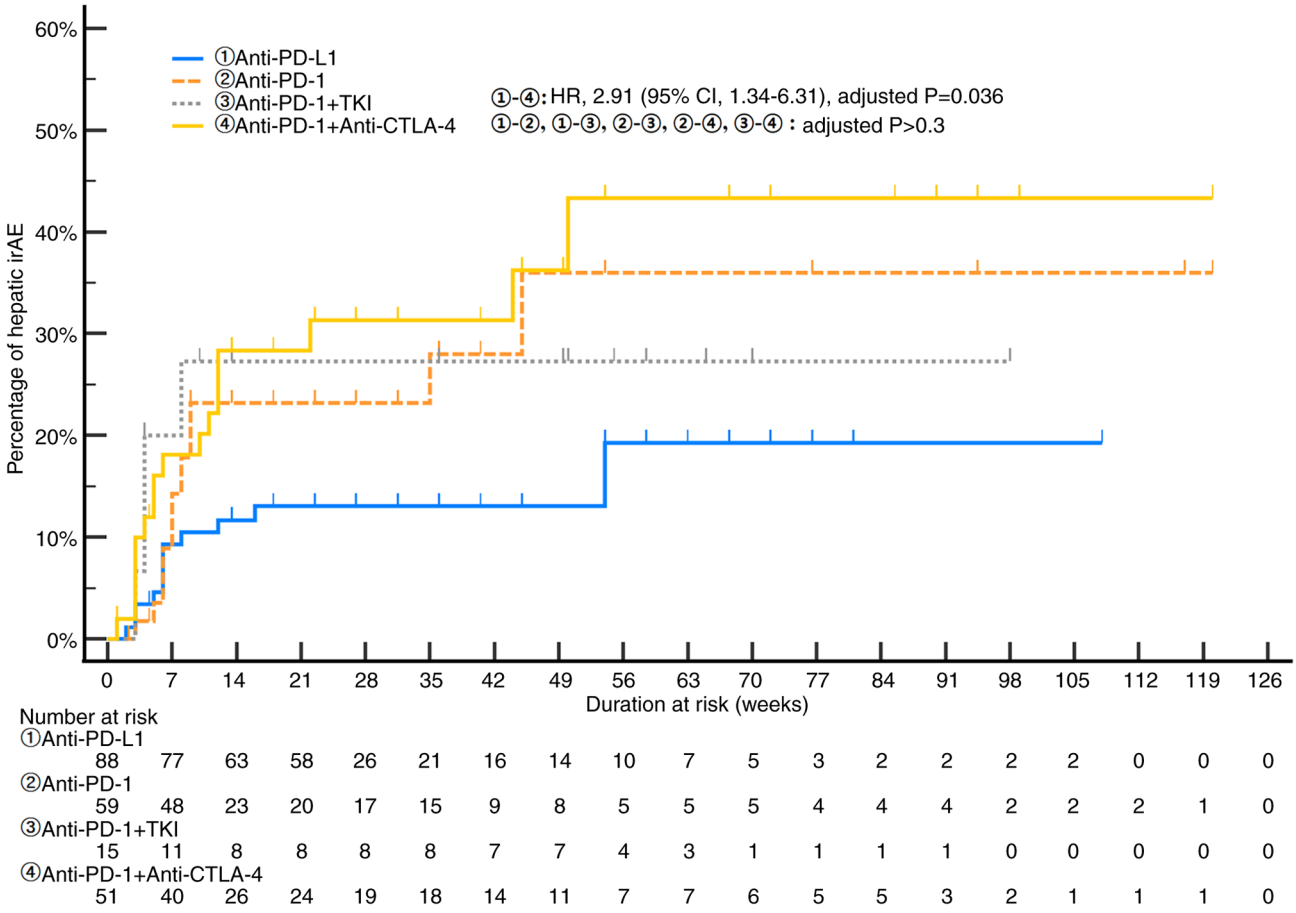


Figure 2. Kaplan-Meier curves showing the probability of hepatic irAEs according to immune checkpoint inhibitor regimens. Log-rank tests with Bonferroni correction were used for multiple pairwise comparisons between groups. HRs and CIs were calculated using Cox proportional hazards regression. CTLA-4, cytotoxic T-lymphocyte-associated protein 4; HR, hazard ratio; irAE, immune-related adverse event; PD-1, programmed cell death 1; PD-L1, PD-1 ligand; TKI, tyrosine kinase inhibitor.

while 23.9% (n=51) received PD-1 inhibitors combined with CTLA-4 inhibitors.

Among the included patients, 76 (35.6%) experienced at least one type of irAE, and 40 (22.5%) developed hepatic irAEs. The median time from ICI initiation to the occurrence of any irAE was 6.5 weeks (IQR, 1-23 weeks). Among those who experienced hepatic irAEs, 33.3% (n=16) also developed other irAEs. The temporal sequence of irAE manifestation was as follows: dermatologic, hepatic, renal, and gastrointestinal (Fig. 1A). Two patients succumbed to irAEs, with the causes of death being pulmonary irAE in one patient and hepatic failure in the other. Patients receiving combination therapy involving PD-1 inhibitors and either TKIs or CTLA-4 inhibitors had a significantly higher incidence of any irAE compared to those who receiving monotherapy (P<0.001), as illustrated in Fig. 1B.

Hepatic irAE and associated factors. Hepatic irAEs were observed in 48 (22.5%) patients, with a median onset time of 6.5 weeks (IQR, 1-22 weeks) following the initiation of ICI therapy. The prevalence of pre-existing comorbidities, including diabetes mellitus, hypertension, and hyperthyroidism, was significantly higher among patients with hepatic irAEs compared to those without hepatic irAEs (P<0.05 for all). However, the prevalence of pre-existing chronic liver disease did not differ significantly between the groups (P=0.401). During ICI treatment, two patients developed liver metastases and subsequently discontinued ICI therapy due to disease progression. After discontinuation of ICI treatment, five additional patients developed liver metastases. None of the seven patients who developed liver metastases experienced hepatic irAEs. The incidence of hepatic irAEs was significantly higher in patients receiving combination therapies than in those on anti-PD-L1 or anti-PD-1 monotherapy (31.8%, n=21 vs. 18.3%, n=27; P=0.014; Table II). Fig. 2 illustrates the temporal dynamics and comparative risks of hepatic irAE development across different ICI regimens. Combination therapy with anti-PD-1 and anti-CTLA-4 inhibitors showed the highest cumulative incidence, reaching approximately 43% by week 56, with an elevated risk compared to anti-PD-L1 monotherapy (HR 2.91; 95% CI, 1.34-6.31; adjusted P=0.036). The cumulative incidences of hepatic irAEs for other treatment regimens, including anti-PD-1 monotherapy (25.4%), anti-PD-1 plus TKI (26.7%), and anti-PD-L1 monotherapy (13.6%), showed no statistically significant differences between groups after adjustment for multiple comparisons (all adjusted P>0.3). Table III presents the biology and incidence rates of hepatic irAEs according to ICI regimen. The median time from ICI initiation to the occurrence of hepatic irAE was 6.5 weeks (IQR, 1-22 weeks) across all treatment regimens. For specific treatments, the median times to the occurrence of hepatic irAE were as follows: anti-PD-L1 (atezolizumab, n=12)

Table III. Characteristics of hepatic irAEs according to ICI regimen in urologic cancer.

Characteristics	Total (n=48)	Anti-PD-L1 (n=12)	Anti-PD-1 (n=15)	Anti-PD-1 + TKI (n=4)	Anti-PD-1 + anti-CTLA-4 (n=17)	P-value
Duration of ICI treatment, months (mean ± SD)	7.9±8.0	7.0±5.0	9.0±11.0	7.6±3.4	8.4±8.9	0.464
Median time to hepatic irAE, weeks (IQR)	6.5 (1.0-22.0)	6.0 (2-16.0); atezolizumab (n=12): 6.0 (2.0-16.0)	7.0 (3.0-9.0); nivolumab (n=7): 8.0 (5.0-35.0); pembrolizumab (n=8): 7.0 (3.0-9.0)	4.0 (3.0-8.0); nivolumab + TKI (n=1): 4.0; pembrolizumab + TKI (n=3): 4.0 (3.0-8.0)	6.0 (1.0-22.0) ipilimumab + nivolumab (n=17) 6.0 (1.0-22.0)	0.764
Severity, n (%)						
Grade 1	27 (56.2)	7 (58.3)	10 (66.7)	3 (75.0)	7 (41.2)	0.649
Grade 2	8 (16.7)	2 (16.7)	3 (20.0)	0 (0.0)	3 (17.6)	
Grade 3	9 (18.8)	2 (16.7)	2 (13.3)	0 (0.0)	5 (29.4)	
Grade 4	4 (8.3)	1 (8.3)	0 (0.0)	1 (25.0)	2 (11.8)	
Biology (any grade hepatic irAE), n (%)						
AST elevation	43 (89.6)	9 (75.0)	15 (100.0)	2 (50.0)	17 (100.0)	0.857
ALT elevation	42 (87.5)	12 (100.0)	12 (80.0)	3 (75.0)	15 (88.2)	0.264
Bilirubin elevation	10 (20.8)	3 (25.0)	2 (13.3)	1 (25.0)	4 (23.5)	0.911
Biology (hepatic irAE grade ≥3), n (%)						
AST elevation	11 (22.9)	2 (16.7)	2 (13.3)	1 (25.0)	6 (35.3)	0.264
ALT elevation	8 (12.5)	0 (0.0)	0 (0.0)	1 (25.0)	5 (29.4)	0.011
Bilirubin elevation	5 (10.4)	2 (16.7)	2 (13.3)	0 (0.0)	1 (5.9)	0.231
Pattern of liver toxicity, n (%)						
Cholestatic	17 (35.4)	3 (25.0)	9 (60.0)	1 (25.0)	4 (23.5)	0.006
Mixed	17 (35.4)	7 (58.3)	6 (40.0)	1 (25.0)	3 (17.6)	
Hepatocellular	14 (29.2)	2 (16.7)	0 (0.0)	2 (50.0)	10 (58.8)	

Categorical variables were analyzed using Pearson's χ^2 test or Fisher's exact test where applicable. Continuous variables were compared using Kruskal-Wallis tests with Dunn's post hoc test. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; ICI, immune checkpoint inhibitor; IQR, interquartile range; irAE, immune-related adverse event; PD-1, programmed cell death 1; PD-L1, PD-1 ligand; TKI, tyrosine kinase inhibitor.

6 weeks (IQR, 2-16 weeks), anti-PD-1 (n=15) 7 weeks (IQR, 3-9 weeks), anti-PD-1 + TKI (n=4) 4 weeks (IQR: 3-8 weeks), and anti-PD-1 + anti-CTLA-4 (ipilimumab + nivolumab, n=17) 6 weeks (IQR, 1-22 weeks). Among anti-PD-1 treatments, nivolumab (n=7) showed a median of 8.0 weeks (IQR: 5-35 weeks) and pembrolizumab (n=8) 7 weeks (IQR: 3-9 weeks). The difference in median time to hepatic irAE onset among treatment groups was not statistically significant (P=0.764). Among the 48 patients with hepatic irAEs, 35 (72.9%) experienced grade 1 or 2 events, whereas 13 (27.1%) developed grade 3 or 4 events. Overall, any-grade and grade ≥3 hepatic irAEs were observed in 87.5 and 12.5% of the patients, respectively. Notably, patients receiving combination therapy with TKIs or CTLA-4 inhibitors had a significantly higher frequency of grade ≥3 hepatic irAEs than did those receiving monotherapy (P=0.011). The distribution of liver toxicity patterns was as follows: cholestatic in 35.4% (n=17), mixed in 35.4% (n=17), and hepatocellular in 29.2% (n=14). The hepatocellular pattern of liver toxicity was significantly more prevalent in the group receiving combination therapy with PD-1 inhibitors and either TKIs or CTLA-4 inhibitors than in those receiving monotherapy (P=0.006).

Outcomes of hepatic irAE treatment. Patients with grade 1 and 2 hepatic irAEs were managed exclusively with UDCA or DDB, without requiring ICI discontinuation or steroid use. All patients achieved resolution of their hepatic irAEs. For the 13 patients who experienced grade 3 or higher hepatic irAEs,

ICI therapy was immediately discontinued, and high-dose intravenous corticosteroids were administered. This treatment approach resulted in the recovery of 12 patients, with only one patient unfortunately succumbing to progressive fulminant hepatitis. Among the 13 patients with grade 3 or higher hepatic irAEs, 7 were subsequently rechallenged with ICI therapy after recovery, with no adverse effects observed following rechallenge. Among the 213 study participants, 5 (2.3%) permanently discontinued ICIs due to hepatic irAEs, whereas 11 (5.2%) discontinued ICIs due to other causes. Notably, neither the occurrence of any irAE nor hepatic irAEs specifically was associated with improved PFS (Fig. S1).

Discussion

The present study aimed to evaluate the incidence of hepatic irAEs in patients with advanced or metastatic RCC and UC receiving various combinations of ICIs. Our study findings offer a comprehensive and detailed overview of the entire spectrum of irAEs associated with ICI therapies among patients with urologic cancer. The current study presents three key observations: (1) a high proportion of patients experienced at least one irAE of any grade; (2) the prevalence of grade ≥3 toxicity was substantial with marked variations across ICI regimens; and (3) our study provides more objective clinical data on the impact of ICI therapy on liver function and toxicity given our inclusion of patients with urologic cancers and exclusion of those with hepatic metastasis.

Among various solid tumors, we determined that RCC and UC were the most appropriate solid tumor types for studying hepatic irAEs, which aligns with our research objectives, based on two key considerations. First, RCC and UC are prime examples of solid tumors for which cutting-edge ICI treatments and combinations are extensively implemented. These malignancies have been at the forefront of ICI application since its introduction in solid tumor therapy. Consequently, a substantial body of data has been accumulated regarding the efficacy, adverse event profiles, and management strategies of ICI treatments for RCC and UC, surpassing many other cancer types in this regard. Second, in the absence of direct hepatic metastases, RCC and UC typically have no restrictions regarding antineoplastic agent administration due to liver function concerns during treatment. This characteristic provides an optimal model for investigating ICI-induced hepatic irAEs in malignancies with minimal inherent hepatic involvement.

A previous meta-analysis of clinical trials involving urologic cancer patients reported that the frequency of any irAE was approximately 34%, which closely aligns with the 35.6% observed in our study (11). Only a few of the original phase 3 trials on ICI regimens for urologic cancers had reported incidence of hepatic irAEs, with the proportion of grade 3 or 4 hepatic irAEs varying widely from approximately 3 to 22% (5-7). For context, other studies on ICI have reported that the incidence of hepatotoxicity ranged from 2 to 10% for monotherapies and 25 to 30% for combination therapies (15). This aligns with our findings based on real-world data, which show a significantly higher incidence with combination therapy than with ICI monotherapy. However, the frequency of hepatic irAEs was notably higher in the current study than in previous ones. This discrepancy likely reflects the reality of clinical practice settings. Several factors may contribute to this observed difference. First, 66.2% of the patients included herein had a history of systemic therapy with other regimes for advanced or metastatic urologic cancers, unlike those in landmark clinical trials. The periods in which other antineoplastic agents were used did not overlap or coincide with ICI treatment. Therefore, the possibility of liver function abnormalities due to concurrent use of other antineoplastic agents appears to be low. Additionally, in patients who received chemotherapy prior to ICI, we performed a new baseline liver function test and then investigated the occurrence of hepatic irAEs; hence, related concerns are not expected to be significant. However, drug-induced liver injury may promote a multiplicative effect, where previous damage can feed forward, consequently impairing drug metabolism and causing further toxicity. Second, hepatic irAEs have clear and objective diagnostic criteria based on liver function test abnormalities, allowing for precise grading and early detection, even among asymptomatic patients. This contrasts with other irAEs, which may be underreported without proactive testing or specific patient complaints (16). In this context, we observed a higher frequency of low-grade hepatic irAEs compared to high-grade reactions. This finding is consistent with clinical management protocols that emphasize preventive monitoring and prompt intervention for low-grade irAEs, which contribute to limiting the progression to high-grade hepatic irAEs.

To address the potential underestimation of hepatic irAEs in clinical practice, liver function tests should be performed at baseline and before each treatment cycle. This systematic approach enables the detection of low-grade events and facilitates proactive management to prevent progression to high-grade irAEs. Close monitoring is therefore essential for urologic patients given that minimal changes may indicate early adverse events. It is important to note that drug-induced liver injury, including hepatic irAE, does not often present with unique pathological or imaging manifestations in its early stages, making clinical suspicion and regular monitoring crucial for early detection and prevention of severe complications. Moreover, when evaluating the outcomes of hepatic irAE treatment, assessing for other non-hepatic irAEs is crucial considering their potential for concurrent or independent occurrence, as noted in our findings.

The mechanisms for the development of hepatotoxicity have yet to be fully elucidated. However, studies have suggested the involvement of CD8+ cytotoxic T lymphocytes, CD4+ T cells, cytokines, and secondary activation of the innate immune system (17). Considering the frequent use of ICIs in conjunction with other hepatotoxic drugs, attributing liver injury solely to ICIs can be challenging. As such, we herein investigated the R value, a criterion for classifying hepatotoxicity into hepatocellular, cholestatic, and mixed subtypes (14). Consistent with previous research (18), our study found no significant differences in the distribution of these types. This finding suggests the limited utility of R value-based classification for ICI-induced hepatotoxicity, particularly because it fails to reflect the severity of, prognosis of, or recovery from hepatic irAEs or guide the alteration of treatment approach. Clinically, the R value appears useful only for grade III or higher irAEs, wherein distinguishing hepatotoxicity types may inform treatment. For grade I or II hepatic irAEs, such

classification offers limited value as their treatment remains consistent. More critical are the absolute values of AST and ALT, which serve as reliable indicators of clinical presentation and prognosis.

Our study demonstrated that hepatic irAEs are dependent on the ICI type and regimen, with the frequency of irAEs varying significantly across treatment regimens. In fact, a recent meta-analysis on irAEs in urologic cancers reported that the pooled incidences for any-grade and grade ≥3 irAEs were 29.1 and 9.1% for single anti-PD-1 agent monotherapy, 21.1 and 6.9% for single anti-PD-L1 agent monotherapy, 78.0 and 35.8% for dual ICI therapy, and 48.8 and 12.4% for ICI combined with TKIs, respectively (12). Clinical trial evidence indicates a higher incidence of hepatic irAE among patients receiving combination therapy than among those receiving monotherapy, likely due to the synergistic effect of combining PD-1- or PD-L1-based ICIs with the inherent toxicity of TKIs and CTLA-4 inhibitors. TKIs alone have been associated with all-grade hepatotoxicity rates between 25 and 35% (17), with ipilimumab combination therapies conferring the highest risk of high-grade hepatotoxicity (18). CTLA-4, an inhibitory receptor on regulatory T cells, plays a crucial role in maintaining immune tolerance, and its deficiency can induce immune dysregulation syndromes (10). Our study found a higher frequency of hepatic irAEs among RCC patients, who actively received ipilimumab-nivolumab and TKI + PD-1 inhibitor combination therapies, than among UC patients. This finding aligns with the results of a recent meta-analysis, which reported any-grade and grade ≥3 irAE rates of 42.7 and 11.1% for RCC and 24.9 and 7.6% for UC, respectively (19).

Generally, high-grade hepatic irAEs require drug discontinuation and high-dose intravenous steroid treatment (4). However, recent studies have shown promising results in the management of hepatic irAEs, with some cases resolving spontaneously with ICI discontinuation alone (20,21). The key difference between our study and previous ones in terms of hepatic irAE management is our use of UDCA or DDB for both low- and high-grade cases. All patients with low-grade hepatic irAEs in our cohort recovered with UDCA and DDB alone, while 92.3% of those with grade ≥3 hepatic irAEs resolved with 1 mg/kg/day of methylprednisolone. Although clear evidence regarding the use of these agents for liver toxicity is lacking, their use may be rational given the observed patterns of liver toxicity in our study (i.e., 35.4% cholestatic, 29.4% hepatocellular, and 35.4% mixed). The potential benefit of UDCA in cholestatic patients and the role of DDB in preventing inflammatory liver damage support their use (22,23). Nonetheless, further studies are needed to validate these results and develop tailored management strategies based on both severity and hepatitis patterns.

A recent meta-analysis indicated that irAEs were associated with improved treatment responses and survival outcomes in RCC and UC (11). However, our study found no difference in survival according to the presence of any irAE or hepatic irAE, possibly due to the small sample size. Additionally, the underlying mechanisms linking irAEs and outcomes remain unclear. The hypothesis that irAEs may reflect enhanced ICI effectiveness in patients with solid tumors remains controversial, with unclear mechanisms connecting these events to improved outcomes. One possible explanation is that ICIs enhance T cell activation and proliferation, which can also cause the rapid expansion of cytotoxic T cells, increased inflammation, and autoimmunity, causing T cells to attack both tumor and normal tissues. Hence, the presence of irAEs may reflects T cell function, indicating a robust immune reaction against both tumor and normal tissues, thereby inducing favorable treatment outcomes (19,24).

Although the precise mechanisms underlying hepatic irAEs remain elusive, studies have identified several factors that increase the risk of these events, including younger age (<60 years) (25), high BMI (26), gender-specific responses to different ICIs (25,27,28), and chronic smoking (27,29). Notably, one study showed that the use of acetaminophen increased hepatotoxicity occurrence by 2.1 times, while patients receiving HMG-CoA reductase inhibitors had a 4.7-fold higher risk of grade 3-4 hepatotoxicity (30). We also investigated several other factors, such as diabetes mellitus, hypertension, hypothyroidism, and preexisting liver disease, and observed that patients with underlying conditions showed a slightly increased likelihood of developing hepatic irAEs. However, it is important to note that these increased risks are not exclusive to ICI treatments and may also occur with other types of cancer therapies. As such, although these factors warrant attention, they are not specific risk factors for hepatic irAEs. Therefore, the level of caution required appears to be similar to that typically exercised during general cancer treatments, with an emphasis on the need for routine monitoring and vigilance in all patients receiving immunotherapy.

Despite involving multiple centers, our study was limited by its retrospective and observational design. First, the relatively small sample size of 213 patients from three tertiary medical centers may have restricted the generalizability of our findings to broader populations. Second, unmeasured or immeasurable confounding factors affecting liver function, including previous antineoplastic treatment history and treatment interruptions due to other comorbidities during ICI therapy, may have influenced our results. In addition, the retrospective design limited our ability to collect drinking and smoking histories, potentially influencing our results. However, all patients were strictly prohibited from smoking and drinking alcohol during the cancer treatment period, which we believe minimized significant impacts on our findings. Moreover, the baseline survey of chronic liver disease status revealed no cases of alcohol-induced cirrhosis or other chronic liver diseases. Notably, while two patients had pre-existing HCV infection, neither of these individuals developed hepatic irAEs, further supporting the limited impact of baseline liver conditions on our study outcomes. Third, the study's median follow-up duration of 16.0 months may not have been sufficient to capture long-term outcomes and late-onset irAEs. However, considering that hepatic irAEs, which were the primary focus of this study, tend to occur within 12 months, this follow-up duration was likely adequate for analyzing these events. Lastly, the management strategies for hepatic irAEs were based on institutional practices and may not reflect standardized protocols across all healthcare settings. Despite these limitations, this study provides valuable insights into the incidence and management of hepatic irAEs in patients treated with ICIs.

In conclusion, this multicenter study offers important information regarding the incidence and management of hepatic irAEs in patients with advanced urologic cancers receiving ICIs. Our findings highlight the importance of regular liver function monitoring, especially in patients receiving combination therapies. Our study revealed that the majority of hepatic irAEs were low-grade, with higher grades occurring less frequently. Although most hepatic irAEs were generally manageable with appropriate interventions, underscoring the overall tolerability of the treatments, a significant proportion of patients experienced high-grade events that required more intensive intervention. These results highlight the need for tailored management strategies and close collaboration between oncologists and hepatologists to optimize patient care and treatment outcomes in the era of immunotherapy for urologic cancers.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YJP and CHL contributed to the conception and design of the study. Data collection and analysis were performed by WIS, JIC, JYK, KHK, BJK, HKH and YJP. JIC and HKH confirm the authenticity of all raw data. The first draft of the manuscript was written by YJP and CHL, and all authors commented on previous versions of the manuscript. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was conducted in accordance with the Declaration of Helsinki. The protocol for the present study was approved by the Institutional Review Boards of the three participating institutions: Inje University Busan Paik Hospital Institutional Review Board (approval no. BPIRB 2024-10-001; Busan, South Korea), Pusan National University Hospital Institutional Review Board (approval no. 2408-017-110; Busan, South Korea), and Dongnam Institute of Radiological and Medical Sciences Institutional Review Boards (approval no. D-2312-021-007; Busan, South Korea). For this type of retrospective and/or observational study formal consent was not required. Pursuant to the provisions of the ethics committee and the ethical guidelines of South Korea, written consent was not required for public disclosure of study information in the case of a retrospective and/or observational study using material such as the existing documentation.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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