Original Article

Initial adjustments in the dosage and rest period of gemcitabine plus cisplatin therapy for patients with incurable biliary tract cancer based on baseline estimated glomerular filtration rate (eGFR) values may be crucial for treatment outcomes and the preservation of renal function

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Background: Gemcitabine (GEM) and cisplatin (CDDP) combination therapy (GC therapy) is the standard 1st-line regimen for incurable biliary tract cancers (BTCs). However, the correlation between dynamic changes in renal function and the outcomes of GC therapy remains unclear. This study aimed to clarify the association between renal function alterations and treatment outcomes after GC therapy.

Methods: We retrospectively examined 44 patients with incurable BTC who underwent GC therapy (January 2015 to December 2022). The patients were stratified according to their baseline estimated glomerular filtration rate (eGFR). Changes in eGFR, overall survival (OS), and progression-free survival (PFS).

Results: The median baseline eGFRs were 65.0 mL/min/1.73 m^2 (low group, n=22) and 90.7 mL/min/1.73 m^2 (high group, n=22). No significant background differences were observed between the groups. During the 1st course, 86.4% and 54.5% of patients in the low and high groups underwent dose adjustments and/or administration postponement, which was found to be significantly greater in the low group. In the high group, eGFR decreased with an increase in the CDDP dose (100 mg =–12.0, 200 mg =–12.7, 300 mg =–25.9, and 400 mg =–25.7 mL/min/1.73 m^2). In the low group, eGFR remained stable (100 mg =0.8, 200 mg =7.5, 300 mg =4.5, and 400 mg =–0.3 mL/min/1.73 m^2). The decrease in the eGFR in the high group was significantly greater at each CDDP dose. However, the median OS and PFS were longer in the low group (OS: 16.3 *vs.* 9.2 months, P=0.02; PFS: 5.4 *vs.* 3.6 months, P=0.02). No significant differences in adverse events were observed between the groups.

Conclusions: Adjusting GC therapy based on baseline estimated glomerular eGFR may be pivotal for therapeutic benefits and renal function protection in patients with incurable BTC.

Keywords: Biliary tract cancer (BTC); gemcitabine (GEM); cisplatin (CDDP); renal function

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Introduction

Biliary tract cancers (BTCs), including cholangiocarcinomas (CCA), gallbladder cancers (GBC), and ampullary tumors, present significant challenges. CCA can be divided into intrahepatic cholangiocarcinoma (iCCA) and extrahepatic cholangiocarcinomas (eCCA). BTCs are associated with poor prognosis, with an estimated 5-year overall survival (OS) rate of <20% (1). BTC, excluding iCCA, is the 6th leading cause of cancer-related deaths in Japan and affects approximately 18,000 patients (2,3). Systemic chemotherapy has emerged as the primary treatment for patients with advanced BTC, who are typically diagnosed at an advanced stage. Systemic chemotherapy has been used to treat all BTC subtypes uniformly because of its relative rarity among all cancers (2).

Gemcitabine (GEM) and cisplatin (CDDP) combination therapy (GC therapy) has been the standard chemotherapy regimen for advanced/recurrent BTC since the 2010s (3,4). In a recent international randomized controlled trial (RCT), the median OS of GC group patients was 13.0 months. GC therapy is vital as an adjuvant or neoadjuvant chemotherapy for operable BTC, as well as palliative chemotherapy for unresectable BTC. Several clinical trials have recently been conducted using regimens incorporating GEM and CDDP as adjuvant or neoadjuvant therapies (5,6). S-1, an oral fluorinated pyrimidine drug, has shown promise as a second-line therapy for BTCs in Japan. Single-arm phase II studies reported the efficacy of S-1 monotherapy as a 2nd-line regimen, with response rates between 7.5–22.5%, a median survival time of 7.3–13.5 months, and a median progression-free survival (PFS) time of 2.5–5.5 months (7,8). The JCOG1113 study demonstrated the non-inferiority of using a combination therapy of GEM and S-1 for GC in phase 3 trials, establishing GS as a new and convenient treatment option for advanced BTC that does not require hydration (9). Additionally, GCS, the first regimen to show survival benefits and a greater response rate than GC in a randomized phase III trial, could become the standard first-line chemotherapy for advanced BTC (10). The median OS and 1-year OS rates were 13.5 months and 59.4%, respectively, in the GCS arm and 12.6 months and 53.7% in the GC arm (10).

In recent years, there have been significant advancements in BTC treatment with the emergence of novel therapeutic targets, including targeted therapies and immunotherapies (11). Immune checkpoint inhibitors (ICIs), actively developed in recent years, improve OS, response rates, and PFS when combined with CDDP and GEM (12). CDDP-GEM-durvalumab should be considered as the first-line treatment for advanced BTC. Another open-label, randomized, phase 3 clinical trial (KEYNOTE-966) showed promising improvements in survival concerning advanced BTC using a combination of pembrolizumab and chemotherapy (13). When administering ICI, it is essential to consider the general conditions and systemic organ functions. For instance, a meta-analysis demonstrated that low albumin levels significantly increased the risk of mortality in patients treated with ICI (14). Another meta-analysis reported a higher incidence of hypertransaminaemia in cancer patients undergoing immunotherapy than in those receiving other chemotherapy (15). In the intrahepatic bile duct (IHBD), drugs targeting fibroblast growth factor receptors (FGFRs), such as pemigatinib and futibatinib, show promising activity (16,17). However, recommended treatment options for unresectable or metastatic diseases are limited. Moreover, when receiving adequate chemotherapy with novel therapeutic targets, including targeted therapies and immunotherapies, it is essential to control adverse events and preserve systemic organ function. This study focused on the relationship between renal and organ function. One or more GEM, CDDP, or S-1 should be used for BTC treatment. Renal function must be considered (18)

Highlight box

Key findings

- When conducting a retrospective analysis among patients with incurable biliary tract cancer (BTC) receiving gemcitabine (GEM) plus cisplatin (CDDP) combination therapy (GC therapy), patients that were pretreated had estimated glomerular filtration rate (eGFR) levels at or below the median of 75 mL/min/1.73 m^2 and showed less decline in eGFR during treatment. They demonstrated favorable survival outcomes compared to those with higher eGFR values, despite the high prevalence of early dose reductions and delay.

What is known and what is new?

- Renal function declines with increasing CDDP dosage in GC therapy. However, limited literature in real world data exists on renal function and treatment outcomes with respect to GC therapy in patients with unresectable BTC.
- Patients with decreased eGFR levels may require early dose reduction or delay to prevent renal impairment.

What is the implication and what should change now?

- Adjusting dosage and rest period based on baseline eGFR levels may be important to obtain therapeutic benefit with GC therapy and protect renal function for patients with incurable BTC.

to prevent toxicity when using drugs such as CDDP and (or) S-1. Gimeracil, a component of S-1, inhibits fluorouracil metabolism and is excreted in the urine (19). In patients with renal dysfunction, the serum concentration of gimeracil increases, theoretically resulting in a higher serum concentration of fluorouracil and a greater incidence of severe adverse events (AEs) leading to treatment discontinuation (20). Preserving renal function is vital not only for continuing chemotherapy but also for supportive care (18).

Preserving renal function is crucial, even when patients are receiving GC + S-1, GC + durvulumab, or GC + pembrolizumab therapy, to ensure that treatment options are not limited. GC therapy confer consistent benefits across various treatments. However, only a few studies have evaluated the relationship between renal function and treatment outcomes in patients with advanced BTCs in a real-world setting. An increase in AEs may result in a poor prognosis due to low dose intensity and a worsened general condition.

Therefore, this study aimed to clarify the relationship between renal function and the treatment outcomes of GC regimens in clinical practice. We present this article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-330/rc).

Methods

Study design and patients

This retrospective study included 44 patients who were diagnosed with incurable BTC in clinical practice and were undergoing GC therapy at Osaka General Medical Center between January 2015 and December 2022, with a total CDDP dose of at least 100 mg. The clinical data of each patient were extracted from the medical records. The following parameters were subsequently acquired: age, sex, Eastern Cooperative Oncology Group (ECOG) performance status (PS), primary tumor site, biliary drainage, laboratory metrics [baseline levels of carbohydrate antigen 19-9 (CA19-9) and sequential estimated glomerular filtration rate (eGFR) levels], pre-and intra-treatment imaging results, specific details of GC treatment (including dosages and schedules of therapeutic agents, treatment course, and adverse effects), post-GC treatment, OS, and PFS duration. Hematological and non-hematological events (AEs) were assessed according to the Common Terminology Criteria for Adverse Events version 4.0. Blood counts and biochemical tests were performed on the day of or the day before chemotherapy administration. Tumor marker values were measured monthly. Follow-up data from the patients were censored on July 31, 2023. The clinical data of all patients were obtained without missing data. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and was approved by the Ethical Review Committee of the Osaka General Medical Center (approval No. 2023-017). Informed consent was obtained using an opt-out form on the hospital website.

GC regimen

GC therapy consisted of administering 1,000 mg/m^2 GEM and 25 mg/m^2 CDDP intravenously on days 1 and 8, which was repeated every 3 weeks. Dose reduction and postponement of the first course were permitted at the attending physician's discretion. Chemotherapy started and was repeated on the day if the neutrophil count was ≥1,500/mm^3, the platelet count was ≥75,000/mm^3, the total bilirubin concentration was ≤3.0 mg/dL, the AST/ALT ratio was ≤200 IU/L and the creatinine concentration was ≤1.5 mg/dL. Moreover, only patients with no stomatitis/diarrhea of grade 2 or higher and no fever (>38 ℃) caused due to infection or non-hematological toxicity of grade 3 or higher (except for abnormal blood test results that were not relevant to the study drugs) were included. If a patient did not meet these criteria, chemotherapy was postponed until recovery. If neutropenia (grade 3 or higher), thrombocytopenia (grade 4), febrile neutropenia, or non-hematologic toxicity (grade 3) developed during GC treatment and each attending physician determined that dose reduction was preferable, the dose of GEM and CDDP was reduced by 20% after that.

Assessment of renal function

Pretreatment (i.e., baseline) levels and eGFR values over time up to the end date of GC treatment were extracted from all patients. Patients were divided into two groups based on baseline eGFR: one with an eGFR lower than the median baseline eGFR (low group) and the other with an eGFR higher than the median baseline eGFR (high group). Changes in eGFR for each 100 mg dose of CDDP were compared between the two groups by calculating the change from the baseline eGFR for each patient.

Evaluation of OS and PFS

Disease progression was evaluated comprehensively based on the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and clinical physical findings. CT images were obtained every 4–8 weeks or when clinical disease progression was suspected. Disease progression included the assessment of CT images and clinical disease progression without CT images. The OS was calculated from the initiation of GC treatment to the date of death. PFS was calculated from the initiation of GC treatment to the date of assessment of progressive disease or death from any cause.

Statistical analysis

Categorical variables were described as percentages and continuous variables were presented as medians and ranges. Patient characteristics, treatment outcomes, and chemotherapy toxicity were compared between the low and high groups using Fisher's exact test for categorical variables or the Mann-Whitney *U* test for continuous variables. The log-rank test was used to compare OS and PFS. The significance level for the P value was set at 0.05. Statistical analyses were performed using JMP ver. 17.0 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

The patient characteristics are shown in *Table 1*. The median age was similar in both groups [low group: 73.5 (range: 58–81 years) *vs.* high group: 67.5 (range: 38–82 years); P=0.15]. The proportion of males and ECOG PS (0/1) were the same in both groups (P>0.99).

The proportion of patients with a primary tumor site, biliary drainage, or metastasis was not significantly different between the two groups. Postoperative recurrence was frequent in the low group, although the difference was insignificant. In this cohort, 14 patients (63.6%) in the low group and 12 (54.5%) in the high groups received chemotherapy after treatment. The baseline CA19-9 levels were not significantly different between the two groups. The median baseline eGFR was 65.0 mL/min/1.73 m^2 in the low group, substantially lower than the 90.7 mL/min/1.73 m^2 in the high group (P<0.001). The median cumulative dose of CDDP was 326 mg (range, 107.5–1,392.9 mg) in the low group and 183.7 mg (range, 102.2–1,000.7 mg) in the high group. The number of courses and days of GEM and CDDP administration were also more significant in the low group, although the differences were insignificant. The number of patients for whom the initial dose of both drugs was full or reduced to less than 20% and for whom the first and second courses were administered without delay was significantly lower in the low group [3 patients (13.6%)] than in the high group [10 patients (45.5%)].

The relationship between renal function and CDDP dose

The cumulative change in eGFR from baseline to the median difference in eGFR per 100 mg of CDDP between the two groups is shown in *Figure 1*. For each CDDP dose, the change was calculated after, excluding cases in which the cumulative dose was not reached. Eight patients in the low group and six in the high group receive >400 mg of CDDP. In the high group, the median change in eGFR decreased by the CDDP dose (100 mg =–12.0 mL/min/1.73 m^2, n=22; 200 mg =–12.7 mL/min/1.73 m^2, n=9 of 22; 300 mg =–25.9 mL/min/1.73 m^2, n=8 of 22; 400 mg =–25.7 mL/min/1.73 m^2, n=6 of 22). However, in the low group, the median change in the eGFR did not decrease (100 mg =0.8 mL/min/1.73 m^2, n=22; 200 mg =7.5 mL/min/1.73 m^2, n=14 of 22; 300 mg =4.5 mL/min/1.73 m^2, n=13 of 22; 400 mg =–0.3 mL/min/1.73 m^2, n=8 of 22). At each CDDP dose, the decrease in the eGFR was significantly greater in the high group than in the low group. No significant difference was observed between the low group baseline and end-of-treatment eGFR levels.

Treatment outcomes and adverse events

The median OS was significantly longer in the low group than in the high group [OS: 16.3 months (95% CI: 7.7–26.5) *vs.* 9.2 months (95% CI: 4.4–14.8), P=0.02] (*Figure 2*). Moreover, the median PFS was also significantly longer in the low group than in the high group [PFS: 5.4 months (95% CI: 2.6–8.9) *vs.* 3.6 months (95% CI: 2.1–5.8), P=0.02]. Sensitivity analyses using the generalized Wilcoxon test resulted in similar findings. In the present study, the low group, which had lower renal function and, as mentioned above, more frequent dose reduction and postponed treatment, had longer OS and PFS than the high group. The grades 3–4 AEs are summarized in *Table 2*. No patient died of AEs due to GC treatment. The two groups had no significant differences in hematological or non-hematological toxicities. Grade 3–4 hematologic toxicities occurred in 16 (72.7%) and 11 patients (50.0%)

Table 1 Patient characteristics in subgroups according to baseline eGFR

Characteristics	Low group (n=22)	High group (n=22)	P value
Age, years	73.5 [58–81]	67.5 [38–82]	0.15
Sex			>0.99
Male	14	14	
Female	8	8	
Performance status			>0.99
0	13	13	
1	9	9	
Primary sites			0.30
Intrahepatic	3	5	
Intrahepatic	5	2	
Hilar	5	7	
Gallbladder	6	8	
Papilla	3	0	
Treatment line			>0.99
1st line	20	21	
2nd line	2	1	
Distant metastasis	14 (63.6)	18 (81.8)	0.31
Postoperative recurrence	13 (59.1)	7 (31.8)	0.13
Biliary drainage	5 (22.7)	11 (50.0)	0.12
Post-GC chemotherapy	14 (63.6)	12 (54.5)	0.76
CA19-9, mg/dL	94.05 [2–202,997]	364.00 [4–335,938]	0.29
eGFR, mL/min/1.73 m^2	65.0 [47.4–74.3]	90.7 [75–148.1]	<0.001

Data are presented as median [range], n or n (%). Low group included patients with an eGFR lower than the median eGFR at baseline, and high group included patients with an eGFR higher than the median eGFR at baseline. GC, gemcitabine plus cisplatin combination therapy; CA19-9, carbohydrate antigen 19-9; eGFR, estimated glomerular filtration rate.

in the low and high groups. Grade 3–4 non-hematologic toxicities were observed in 11 (50.0%) and 15 (68.2%) patients in the low and high groups, respectively. The major (≥5% of patients) grade 3–4 non-hematological toxicities were cholangitis (22.7%/45.5%), appetite loss (9.1%/9.1%), febrile neutropenia (0.0%/13.6%), and fatigue (9.1%/0.0%).

Discussion

This study revealed that adjusting GC therapy doses and rest periods based on baseline eGFR in patients with incurable BTC maintained renal function and provided a favorable therapeutic effect. In clinical practice, the baseline eGFR may factor in adjusting GC therapy's dosage and rest period.

Renal function worsened significantly in the high group but not in the low group. The main reason for this may be the CDDP metabolism. GC therapy has been reported to worsen renal function in proportion to the cumulative dose of CDDP (18). The incidence of acute kidney injury (AKI) caused by CDDP varies and is influenced by the background renal function and the dose of CDDP administered. A recent clinical study has reported a rate of 7.5% to 25.8% in cancer patients (21). Another study showed that the nephrotoxicity of CDDP was related to both the maximum blood concentration and

the area under the blood concentration-time curve (22). The maintenance of renal function in the low-dose group may have been due to more appropriate areas under both the maximum blood concentration and blood concentration-time curves due to adjustments in the dosage and rest period. These results are valuable when considering current combination regimens with ICIs. First, severe AKI-associated with ICI treatment alone is rare. The incidence of AKI has been reported to be 1.4% with pembrolizumab monotherapy and less than 1% with durvalumab monotherapy (23,24). However, they can be life-threatening if not anticipated or managed appropriately (25). Therefore, the results of the present study may be helpful for adjusting the dosage and withdrawal period of GC, even when combined with GC + ICI therapy. Further detailed studies are required to determine the optimal dosage and withdrawal period for renal function when ICIs are used in combination therapies.

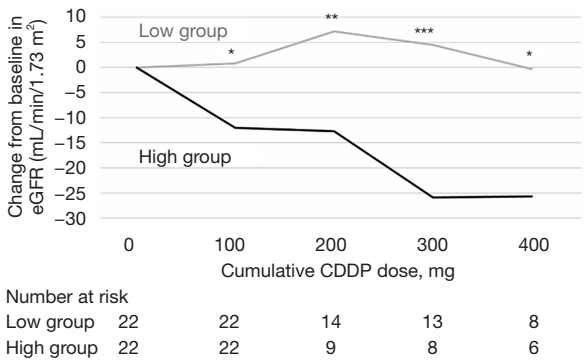

Figure 1 The cumulative change from baseline eGFR to the median difference in eGFR per 100 mg of CDDP. Low group included patients with an eGFR lower than the median eGFR at baseline, and high group included patients with an eGFR higher than the median eGFR at baseline. The median cumulative change from baseline eGFR was tested by the Wilcoxon test between the two groups: *, P=0.03; **, P=0.007; ***, P=0.004. eGFR, estimated glomerular filtration rate; CDDP, cisplatin.

The overall OS and PFS in the low group in this study were similar to those in previous Japanese reports, with a median OS of 11.2–13.4 months and a median PFS of 5.5–5.8 months (4,9,10). Previous reports have shown no differences in OS or PFS according to renal function at treatment initiation (26). However, in the present study, OS and PFS in the high group were significantly lower than those in the low group. Patients in the high group may have developed renal failure because of the recommended dosage, and other adverse events may have led to disease progression because of an inadequate response. This indicates that some patients with good renal function may require a dose reduction during the 1st course. In contrast, the prognosis was better in the low group, where many patients adjusted their dose reduction or rest period after the 1st course. The number of grade 3 or higher adverse events was approximately the same as reported in Japan (4,9,10). Although there was no significant difference in the number of severe adverse events in this study, the occurrence of more grade 1–2 adverse events in the high eGFR group cannot be ruled out. Inappropriate

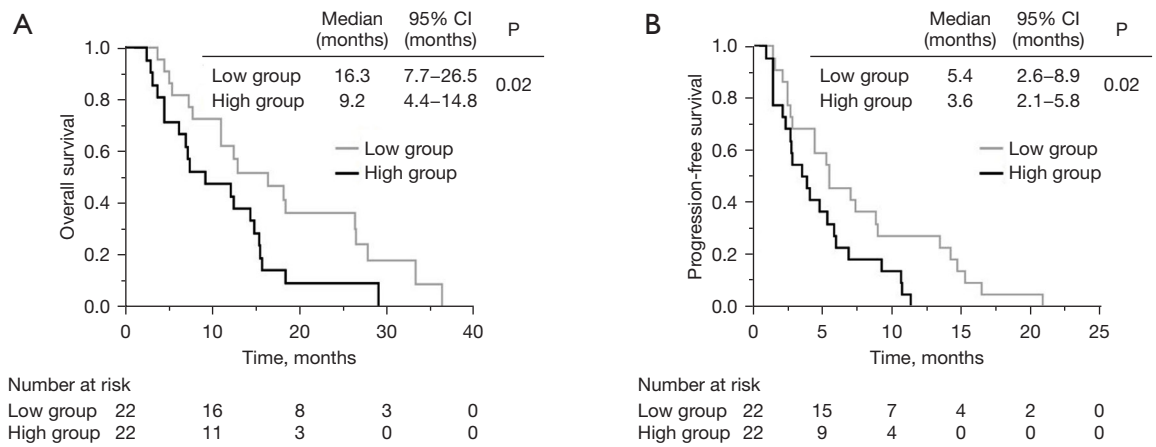

Figure 2 Kaplan-Meier survival curves for (A) overall survival and (B) progression-free survival with P values (log-rank test). Low group included patients with an eGFR lower than the median eGFR at baseline, and high group included patients with an eGFR higher than the median eGFR at baseline. CI, confidence interval; eGFR, estimated glomerular filtration rate.

Table 2 Adverse events (grade 3–4) in both groups

Adverse events	Low group (n=22)	High group (n=22)	P value
Death due to an adverse event	0	0	
Hematologic adverse event (≥ grade 3)	16 (72.7)	11 (50.0)	0.11
Neutropenia	8 (36.4)	6 (27.3)	0.54
Leukopenia	13 (59.1)	9 (40.9)	0.37
Thrombocytopenia	4 (18.2)	3 (13.6)	>0.99
Anemia	7 (31.8)	3 (13.6)	0.28
Nonhematologic adverse event (grade 3–4)	11 (50.0)	15 (68.2)	0.18
Occurring in >3% of patients			
Cholangitis	5 (22.7)	10 (45.5)	0.20
Febrile neutropenia	0	3 (13.6)	0.23
Appetite loss	2 (9.1)	2 (9.1)	>0.99
Fatigue	2 (9.1)	0	0.49
Diarrhea	1 (4.5)	0	>0.99
Liver abscess	1 (4.5)	0	>0.99
Nausea/vomiting	0	1 (4.5)	>0.99

Data are presented as or n (%). Low group included patients with an eGFR lower than the median eGFR at baseline, and high group included patients with an eGFR higher than the median eGFR at baseline. eGFR, estimated glomerular filtration rate.

administration will likely lead to increased adverse events, resulting in shortened OS and PFS.

This study has some limitations. First, this was a single-center, retrospective observational study, and the limited number of patients may have resulted in a selection bias. Although this study revealed that the OS and PFS in the low group were significantly higher than those in the high group with adjusted GC therapy, prospective studies with larger patient populations might yield different results. Second, the adjustment of the GC regimen was based not only on specific criteria but also on the judgment of each attending physician. Third, renal function was evaluated using only the eGFR. Because patients with decreased muscle mass or poor nutritional status have an overestimated eGFR (27), the results of this study may not be applicable to these populations. Therefore, further prospective studies involving more patients and various renal function parameters are required.

This study clarified that the first to highlight the importance of adjusting the doses and rest periods of GC therapy based on the baseline eGFR. Although some studies have reported an association between GC therapy and renal dysfunction, none have investigated administration methods that balance renal protection with therapeutic efficacy (14). Despite the potential of new treatments for incurable BTC, GC therapy remains a crucial component. New treatments are expected to enhance GC therapy by including new drugs. Indeed, several recent clinical trials have been conducted on regimens combining GC with new medicines, and relatively favorable results have been reported (28,29). This study serves as a guide for the effective administration of GC-related regimens.

Conclusions

According to our single-center retrospective study, adjusting the dosage and rest period based on the baseline eGFR may be important for obtaining therapeutic benefits from GC therapy and protecting renal function in patients with incurable BTC.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-330/rc

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-330/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-330/coif). Dr. Takuo Yamai reports honoraria for lectures from Boston Scientific and MSD, and for manuscript writing from Kaneka. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and was approved by the Ethical Review Committee of the Osaka General Medical Center (approval No. 2023-017). Informed consent was obtained using an opt-out form on the hospital website.

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