Original Article

Sarcomatoid change in combined hepatocellular carcinoma and cholangiocarcinoma as a poor prognostic factor

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Background: Sarcomatoid change is rarely seen in epithelial malignancy that can be observed in diverse organs. Although a sarcomatoid change in combined hepatocellular-cholangiocarcinoma (cHCC-CC) is assumed to be a poor prognostic factor, this issue has not been studied due to its rare incidence. In this study, we aimed to identify the oncological impact of sarcomatoid change in patients with cHCC-CC and verify that sarcomatoid change is a poor prognostic factor for resected cHCC-CC.

Methods: Between January 2006 and December 2020, 102 patients who underwent surgical resection for cHCC-CC were retrospectively reviewed. The hazard ratio (HR) according to sarcomatoid change was calculated using other known prognostic factors for cHCC-CC. In addition, the patients were divided into two groups according to the sarcomatoid change, and their survival was compared.

Results: The multivariate analysis demonstrated that sarcomatoid change in cHCC-CC is a poor prognostic factor {disease-free survival (DFS), HR =3.84 [95% confidence interval (CI): 1.63–9.10], P=0.002; overall survival (OS), HR =3.94 (95% CI: 1.67–9.31), P=0.002}. In the survival analysis, the sarcomatoid change group displayed a worse prognosis compared to the non-sarcomatoid change group {DFS: 4.0 [interquartile range (IQR): 1.2–6.8] *vs.* 23.0 (IQR: 9.3–36.7) months, P=0.001; OS: 19.0 (IQR: 7.2–30.8) *vs.* 85.0 (IQR: 31.8–138.2) months, P=0.004}.

Conclusions: Sarcomatoid change is a poor prognostic factor for resected cHCC-CC.

Keywords: Combined hepatocellular-cholangiocarcinoma (cHCC-CC); hepatectomy; prognosis; sarcomatoid change; survival analysis

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Introduction

Combined hepatocellular-cholangiocarcinoma (cHCC-CC) is one of the primary hepatic malignancies. The cHCC-CC combines two different histological features: elements of both hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (iCCA), and is rare, accounting for 2–5% of primary liver cancers (1). Moreover, cHCC-CC displays more aggressive behavior and worse

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survival outcomes than either hepatocellular carcinoma or cholangiocarcinoma (2).

Although only studies with small sample sizes are available due to its rare incidence, several prognostic factors of cHCC-CC have been reported as follows: large tumor size, presence of satellite nodules, lymph node involvement, multifocality, vascular invasion, high TNM stage, high levels of carbohydrate antigen (CA) 19-9, decreased capsule formation, and free surgical margins (3-7).

Sarcomatoid change is rarely seen in epithelial malignancy. The change can be observed in diverse organs, including the lung, breast, bladder, prostate, skin, and liver. Malignant cells of the sarcomatoid change harbor histological, cytological, or molecular features of both epithelial and mesenchymal tumors (8). The prognosis of this rare form of cancer is unfavorable due to rapid growth, frequent metastasis, a low resectability rate, and a high incidence of recurrence even after curative resection (9). Most reported sarcomatoid changes in the liver were associated with HCC and identified in about 2% of resected HCC (10).

In HCC, the occurrence of sarcomatoid change is recognized as a poor prognostic factor. Such a change demonstrates a worse prognosis and higher aggressiveness than conventional HCC (11). Therefore, sarcomatoid change can be assumed to be a risk factor for cHCC-CC. Several case reports have reported an unfavorable prognosis of sarcomatoid cHCC-CC with frequent nodal or distant metastasis and a clinically high metastatic potential to the portal vein and central venous system (12,13).

However, due to the rare incidence of cHCC-CC, no study was statistically analyzed. In this study, we aimed to identify the oncological impact of sarcomatoid change in patients with cHCC-CC and verify that sarcomatoid change is a poor prognostic factor for resected cHCC-CC. We present this article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-313/rc).

Highlight box

Key findings

- Patients exhibiting sarcomatoid change demonstrated a worse prognosis than those who did not for both disease-free survival and overall survival.

What is known and what is new?

- Sarcomatoid change in combined hepatocellular-cholangiocarcinoma (cHCC-CC) has not been extensively studied due to its rare incidence. Although retrospective and small sample-sized analysis, this study is meaningful to statistically display the oncologic impact of sarcomatoid change for patients with cHCC-CC.

What is the implication, and what should change now?

- Currently, no established standard chemotherapy is available for sarcomatoid-changed cHCC-CC. The results of this study could provide clues about post-operative management strategies.

Methods

Study population

Between January 2006 and December 2020, medical records were retrospectively reviewed, including pathology reports of patients who underwent surgical resection for cHCC-CC in Severance Hospital. Finally, a total of 102 patients with cHCC-CC were included in the study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of Yonsei University Health System (IRB No. 4-2023-1069) and individual consent for this retrospective analysis was waived.

Definition of sarcomatoid change of cHCC-CC in the pathologic finding

Primary liver carcinomas with unequivocal presence of both hepatocytic and cholangiocytic differentiation within the same tumor were diagnosed as cHCC-CC. The pathologic diagnosis of sarcomatoid cHCC-CC was made when tumor cells demonstrated mesenchymal transformation resembling sarcoma, characterized by the presence of atypical spindle cells or pleomorphic cells with bizarre nuclei. This diagnosis was further supported by positive immunohistochemical expression of vimentin within the sarcomatoid area. The example of conventional cHCC-CC and cHCC-CC with sarcomatoid change is displayed in *Figure 1*.

Assessment of the oncologic impact of sarcomatoid change in patients with cHCC-CC

Using data from the 102 patients, the hazard ratio (HR) according to sarcomatoid change was calculated using other known prognostic factors for cHCC-CC, such as tumor size, satellite nodules, metastatic lymph nodes, vascular invasion, and margin status (3-6). In addition, the patients were divided into two groups according to whether they had sarcomatoid change, and their disease-free survival (DFS) and overall survival (OS) were compared. In addition, the

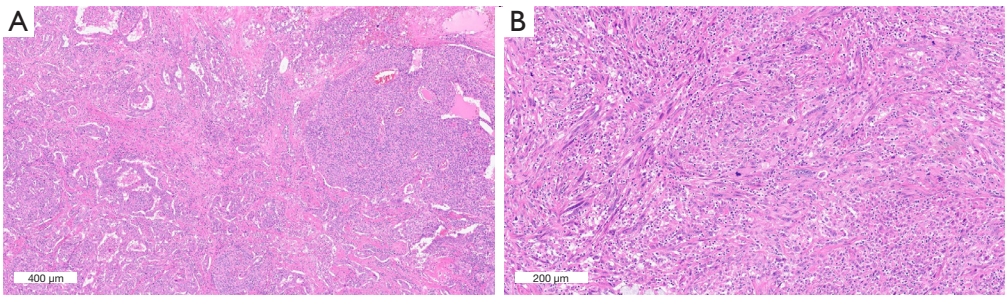

Figure 1 Representative images of conventional cHCC-CC and cHCC-CC with sarcomatoid change. (A) Histologic findings of cHCC-CC displayed both hepatocytic and cholangiocyte differentiation within the same tumor (H&E stain). (B) Sarcomatoid change of cHCC-CC displaying spindle cells with frequent mitotic figures (H&E stain). cHCC-CC, combined hepatocellular-cholangiocarcinoma; H&E, hematoxylin and eosin.

recurrent patterns of the patient cohort were analyzed in terms of sarcomatoid change.

Statistical analysis

Numerical data are presented as mean ± standard deviation. Differences between groups were compared using chi-square and independent *t*-tests. Furthermore, DFS and OS were analyzed using the Kaplan-Meier method and presented as median with interquartile range (IQR). Cox regression analysis was used to assess HRs, and statistical significance was set at P<0.05. Statistical analyses were performed using IBM SPSS 23.0 software.

Results

Basic characteristics of the study population

The clinicopathologic characteristics of the 102 patients included in this study are displayed in *Table 1*. The mean age of the patients was 60.0±9.6 years. Eighty-five (83.3%) patients had viral hepatitis and 37 (36.3%) underwent preoperative therapy including 19 (18.6%) transarterial chemoembolization, 6 (5.9%) concurrent chemoradiation therapy, 2 (2.0%) radiotherapy, 4 (3.9%) chemotherapy, 5 (4.9%) radiofrequency ablation, and 1 (1.0%) transarterial radioembolization. Nine (8.8%) patients had sarcomatoid change to cHCC-CC. The median follow-up duration was 40.5 (IQR, 20.0–72.0) months.

Cox regression model for oncologic survival of sarcomatoid change

Univariate analysis revealed that tumor size (>5 cm), satellite nodules, vascular invasion, and sarcomatoid change were significantly poor prognostic factors of DFS {tumor size: HR =2.87 [95% confidence interval (CI): 1.60–5.13], P<0.001; satellite nodules: HR =2.66 (95% CI: 1.23–5.73), P=0.01; vascular invasion: HR =3.04 (95% CI: 1.52–6.10), P=0.002; sarcomatoid change: HR =3.53 (95% CI: 1.56–7.99), P=0.002}. The multivariate analysis demonstrated that tumor size (>5 cm), vascular invasion, and sarcomatoid change were poor prognostic factors of DFS [tumor size: HR =2.98 (95% CI: 1.61–5.52), P=0.001; vascular invasion: HR =2.39 (95% CI: 1.17–4.88), P=0.02; sarcomatoid change: HR =3.84 (95% CI: 1.63–9.10), P=0.002].

The OS analysis displayed similar results and sarcomatoid change was still considered a poor prognostic factor [univariate analysis: tumor size, HR =2.33 (95% CI: 1.30–4.15), P=0.004; satellite nodules, HR =2.56 (95% CI: 1.20–5.49), P=0.02; vascular invasion, HR =3.21 (95% CI: 1.60–6.44), P=0.001; sarcomatoid change, HR =3.88 (95% CI: 1.71–8.77), P=0.001; and multivariate analysis: tumor size, HR =2.45 (95% CI: 1.33–4.50), P=0.004; vascular invasion, HR =2.63 (95% CI: 1.29–5.40), P=0.008; sarcomatoid change, HR =3.94 (95% CI: 1.67–9.31), P=0.002] (*Table 2*).

Clinicopathologic characteristics in terms of sarcomatoid change

When the patient cohort was divided into two groups according to sarcomatoid change, no significant difference was observed between the groups except for adjuvant chemotherapy [sarcomatoid *vs.* non-sarcomatoid: 5 (55.6%) *vs.* 12 (12.9%), P=0.005] (*Table 3*).

Table 1 Basal characteristics of the patient cohort

Characteristics	Values (N=102)
Age (years)	60.0±9.6
Gender	
Male	83 (81.4)
Female	19 (18.6)
Hepatitis (B or C viral)	85 (83.3)
Preoperative therapy	37 (36.3)
TACE	19 (18.6)
CCRTx	6 (5.9)
RTx	2 (2.0)
CTx	4 (3.9)
RFA	5 (4.9)
TARE	1 (1.0)
Operation	
Right lobectomy	26 (25.5)
Right anterior sectionectomy	5 (4.9)
Right posterior sectionectomy	8 (7.8)
Right inferior sectionectomy	3 (2.9)
Right trisectionectomy	1 (1.0)
Central lobectomy	3 (2.9)
Left lobectomy	14 (13.7)
Left lateral sectionectomy	9 (8.8)
Segmentectomy	14 (13.7)
Wedge resection	19 (18.6)
Tumor size (cm)	3.705±2.075
Differentiated	
Well	4 (3.9)
Moderately	49 (48.0)
Poorly	30 (29.4)
Intermediated	1 (0.9)
Undifferentiated	1 (0.9)
Others	17 (16.7)
Adjuvant therapy	17 (16.7)
Sarcomatoid change	9 (8.8)
Tumor size (>5 cm)	24 (23.5)
Satellite nodule	11 (10.7)
Lymph node involvement	5 (4.9)
Vascular invasion	65 (63.7)
Surgical margin (<1 cm)	42 (41.2)
CA19-9 (U/mL) (n=29)	23.9 (6.5–97.6)

Data are presented as n (%), mean ± standard deviation or median (range). TACE, transarterial chemoembolization; CCRTx, concurrent chemoradiation therapy; RTx, radiotherapy; CTx, chemotherapy; RFA, radiofrequency ablation; TARE, transarterial radioembolization; CA, carbohydrate antigen.

Table 2 Univariate and multivariate risk analyses of survival for cHCC-CC

Factor	Disease-free survival						Overall survival					
	Univariate			Multivariate			Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Tumor size (>5 cm)	2.87	1.60–5.15	<0.001	2.98	1.61–5.52	0.001	2.33	1.30–4.15	0.004	2.45	1.33–4.50	0.004
Satellite nodule	2.66	1.23–5.73	0.01	1.13	0.49–2.61	0.78	2.56	1.20–5.49	0.02	1.22	0.52–2.86	0.65
Lymph node involvement	1.90	0.59–6.13	0.28	2.10	0.63–6.99	0.23	1.68	0.52–5.43	0.39	1.67	0.50–5.60	0.41
Vascular invasion	3.04	1.52–6.10	0.002	2.39	1.17–4.88	0.02	3.21	1.60–6.44	0.001	2.63	1.29–5.40	0.008
Surgical margin (<1 cm)	1.03	0.59–1.82	0.91	0.82	0.45–1.51	0.53	1.16	0.66–2.06	0.61	1.05	0.58–1.92	0.87
Sarcomatoid change	3.53	1.56–7.99	0.002	3.84	1.63–9.10	0.002	3.88	1.71–8.77	0.001	3.94	1.67–9.31	0.002

CI, confidence interval; HR, hazard ratio; cHCC-CC, combined hepatocellular-cholangiocarcinoma.

Table 3 Basal characteristics according to sarcomatoid change

Parameter	Sarcomatoid group (N=9)	Non-sarcomatoid group (N=93)	P value
Age (years)	61.3 (51.0–65.3)	59.8 (53.4–66.9)	0.73
Sex			0.29
Male	9 (100.0)	74 (79.6)	
Female	0	19 (20.4)	
Hepatitis (B or C viral)	8 (88.9)	76 (81.7)	0.94
Preoperative therapy	2 (22.2)	25 (26.9)	>0.99
Tumor size (cm)	3.5 (2.4–4.2)	3.4 (2.0–5.1)	0.15
Adjuvant therapy	5 (55.6)	12 (12.9)	0.005
Tumor size (>5 cm)	1 (11.1)	23 (24.7)	0.61
Satellite nodules	2 (22.2)	9 (9.7)	0.55
Lymph node involvement	1 (11.1)	4 (4.3)	0.92
Vascular invasion	7 (77.8)	58 (62.4)	0.58
Free surgical margin (≥1 cm)	7 (77.8)	53 (57.0)	0.39
CA19-9 (>34 U/mL) (n=29)	1 (33.3)	9 (34.6)	>0.99

Data are presented as n (%) or median (range). CA, carbohydrate antigen.

Survival analysis according to sarcomatoid change in the patients with cHCC-CC

In the DFS analysis, the sarcomatoid change group demonstrated a worse prognosis than the non-sarcomatoid change group [sarcomatoid *vs.* non-sarcomatoid: 4.0 (IQR: 1.2–6.8) *vs.* 23.0 (IQR: 9.3–36.7), P=0.001]. The OS analysis exhibited a similar result [sarcomatoid *vs.* non-sarcomatoid: 19.0 (IQR: 7.2–30.8) *vs.* 85.0 (IQR: 31.8–138.2), P=0.004] (*Figure 2*).

Recurrent pattern of cHCC-CC after the surgery according to sarcomatoid change

During the study period, 64 (62.7%) patients experienced recurrence. However, no statistically significant difference was noted in recurrent pattern (intrahepatic or extrahepatic recurrence) between the two groups [sarcomatoid *vs.* non-sarcomatoid: 5 (62.5%) *vs.* 25 (44.6%), P=0.57] (*Table 4*).

Discussion

Sarcomatoid change in cHCC-CC is extremely rare, and no studies on this issue have been statistically analyzed. In this study, we analyzed clinicopathological characteristics of cHCC-CC to identify the oncologic impact of sarcomatoid change in resected cHCC-CC and discovered that sarcomatoid change in patients with cHCC-CC was associated with a poor prognosis in survival analysis.

Clinically, sarcomatoid HCC is generally caused by necrosis and degeneration due to repeated non-surgical therapy such as transarterial chemoembolization, radiofrequency ablation, and percutaneous ethanol injection (14,15). However, some sarcomatoid cHCC-CC cases have been reported in patients without previous anticancer therapy (12). In our study, sarcomatoid change was observed without preoperative therapy. Further investigations are needed to clarify the pathogenesis of sarcomatoid transformation in cHCC-CC.

Tumor size and vascular invasion were significant risk factors in cHCC-CC. However, unlike the findings of the previous studies, this study discovered no significant correlation between satellite nodules, lymph node involvement, and resection margin. This could be attributed to the limited number of cases. For example, the cut-off distance of the resection margin varied from study to study. Some studies demonstrated R1 resection as a poor prognostic factor, whereas other studies displayed that a resection margin of >10 mm has been associated with prolonged DFS in patients with multifocal disease (6,7). Likewise, studies on certain factors did not reach a unified agreement.

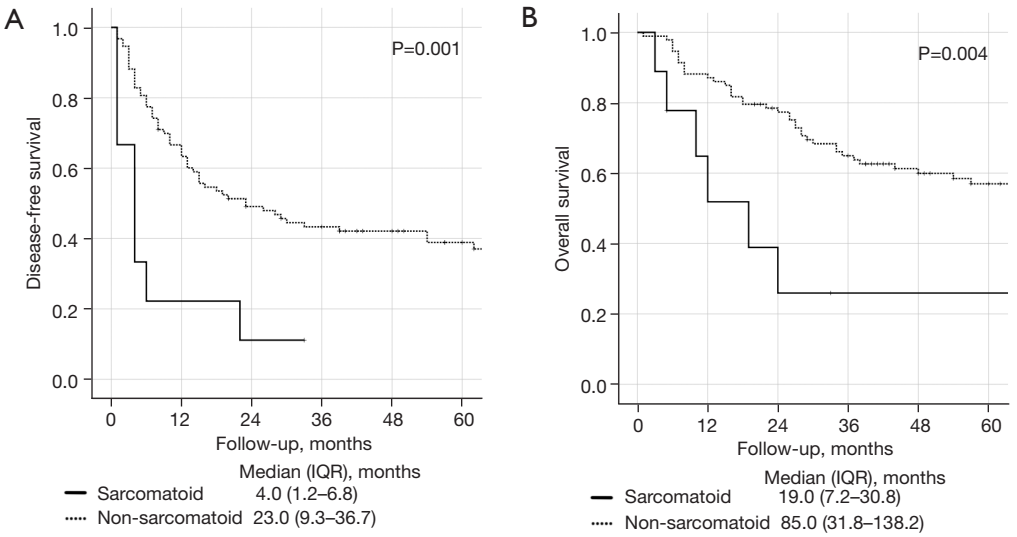

Figure 2 Oncologic outcomes according to sarcomatoid change. IQR, interquartile range.

Table 4 Recurrent pattern of cHCC-CC after the surgery according to sarcomatoid change

Type	Sarcomatoid (N=9)	Non-sarcomatoid (N=93)	P value
Non-recurrence	1 (11.1%)	37 (39.8%)	
Recurrence	8 (88.9%)	56 (60.2%)	0.57
Intrahepatic	3 (37.5%)	31 (55.4%)	
Extrahepatic	5 (62.5%)	25 (44.6%)	

cHCC-CC, combined hepatocellular-cholangiocarcinoma.

Moreover, diagnosing cHCC-CC in preoperative studies from other diseases, such as HCC or cholangiocarcinoma, was quite difficult in real-world practice. In this study, only 25 (24.5%) patients underwent lymph node dissection, and preoperative CA19-9 levels were available only for 30 (29.4%) patients. Since surgeries were planned under the assumption that patients had HCC rather than cHCC-CC, alpha-fetoprotein or protein induced by vitamin K absence-II levels were preoperatively tested instead of CA19-9, and the patients did not undergo lymph node dissection, given their anticipated state.

Of course, several studies have attempted to increase the diagnostic accuracy of cHCC-CC in the preoperative phase. cHCC-CC-specific patterns and diagnostic criteria have been suggested using computed tomography, magnetic resolution image, and contrast-enhanced ultrasound (16-18). Unfortunately, however, their criteria have shown suboptimal sensitivity and specificity. Moreover, even when cHCC-CC is strongly suspected, it is often subjected to biopsy for diagnosis. However, some sampling error may exist, as only a part of the tumor tissue is sampled during biopsy (17). This heterogeneous feature of cHCC-CC is also a significant hurdle of this study with low incidence of cHCC-CC. Further study is needed to identify postoperative prognostic factors in cHCC-CC using more accurate diagnostic methods.

According to a review of the treatment of cHCC-CC, surgical resection is considered the only curative method (4,7,19-21). Although recent studies have reported the benefit of liver transplantation (LT) for cHCC-CC patients, other studies demonstrated poor prognosis after the procedure (22-28). One reason for the poorer prognosis of the patients with cHCC-CC who underwent LT than for those with HCC is a higher rate of extrahepatic metastasis, including lymph node metastasis (27). As lymph node dissection is conventionally not performed during LT, the oncologic outcomes might be affected in patients with cHCC-CC who underwent LT. This is still controversial, and the patients who underwent LT for cHCC-CC were excluded from this study for the above-mentioned reasons.

In addition, some studies also reported that sarcomatoid change is likely to cause widespread metastases (9,29). In our study, although the sarcomatoid group displayed a higher rate of extrahepatic metastasis than the non-sarcomatoid group, the results did not exhibit statistical significance due to the small sample size. A large sample size is needed to identify this issue.

Currently, no established standard chemotherapy is available for sarcomatoid-changed cHCC-CC. Even in cHCC-CC, current evidence on chemotherapy relies on small retrospective studies in which patients were treated according to the guidelines of either HCC or CC (30,31). The combination of gemcitabine and platinum drugs (cisplatin or oxaliplatin) is the standard frontline chemotherapy for CC (32). Multivariate analysis displayed that the OS of patients treated with sorafenib was inferior to those treated with platinum-containing regimens (31). A recent study demonstrated that platinum-containing regimens are the most promising first-line chemotherapy for patients with unresectable cHCC-CC, while sorafenib monotherapy appears far less effective (33).

However, the amount of research on effective treatment approaches for sarcomatoid changes in cHCC-CC is still insufficient. For this reason, although the sarcomatoid cHCC-CC group demonstrated a higher adjuvant chemotherapy rate compared to the non-sarcomatoid group in this study, it may have little effect. Moreover, despite more than half (55.6%) of patients being treated with sorafenib as adjuvant chemotherapy, the small sample size of this study made it difficult to assess the oncologic impact of sorafenib (Table S1). However, despite the implementation of adjuvant chemotherapy, a significant difference in survival rates between the two groups was observed.

This study had several limitations. First, this was a single-center retrospective study, so selection bias could not be excluded. Additionally, sarcomatoid changes are rare, and cases of sarcomatoid changes combined with cHCC-CC are even more rare. Reflecting these cases within the overall population numbers could pose challenges. Due to these characteristics, the design of further studies needs to be accurate in representing the entire population. Nonetheless, this study is meaningful to statistically reveal the oncologic impact of sarcomatoid change for patients with cHCC-CC.

Conclusions

Sarcomatoid change is one of the poor prognostic factors for resected cHCC-CC. Further efforts to discover precision therapy for sarcomatoid cHCC-CC are needed.

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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-24-313/rc

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-313/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-24-313/coif). The 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of Yonsei University Health System (IRB No. 4-2023-1069) and individual consent for this retrospective analysis was waived.

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