Original Article

High-sensitivity modified Glasgow prognostic score (HS-mGPS) is a prognostic biomarker for small duct-type intrahepatic cholangiocarcinoma—a retrospective cohort study

Xintao He[1,2#], Zixin Liang[3#], Shuo Zhang[4], Youxiang Ding[1], Xiaoping Qian[3], Hongyan Wu[1], Jun Chen[1,2]

[1]Department of Pathology, Nanjing Drum Tower Hospital Clinical College of Nanjing University of Chinese Medicine, Nanjing, China; [2]Department of Biobank, Nanjing Drum Tower Hospital Clinical College of Nanjing University of Chinese Medicine, Nanjing, China; [3]Department of Oncology, Nanjing Drum Tower Hospital Clinical College of Nanjing University of Chinese Medicine, Nanjing, China; [4]Department of Pancreatic and Metabolic Surgery, Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing, China

Contributions: (I) Conception and design: X He, Z Liang, J Chen; (II) Administrative support: J Chen, H Wu, X Qian, Y Ding; (III) Provision of study materials or patients: J Chen, H Wu; (IV) Collection and assembly of data: X He, S Zhang, Z Liang; (V) Data analysis and interpretation: X He, Z Liang, Y Ding; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Jun Chen, MD. Department of Pathology, Nanjing Drum Tower Hospital Clinical College of Nanjing University of Chinese Medicine, 321 Zhong Shang Road, Nanjing 210000, China; Department of Biobank, Nanjing Drum Tower Hospital Clinical College of Nanjing University of Chinese Medicine, Nanjing, China. Email: ichenjun@qq.com; Hongyan Wu, MD. Department of Pathology, Nanjing Drum Tower Hospital Clinical College of Nanjing University of Chinese Medicine, 321 Zhong Shang Road, Nanjing 210000, China. Email: daiyan1828@njglyy.com.

Background: Serum biomarkers are often used as part of preoperative prediction strategies to help assess a patient's surgical risk and prognosis. The high-sensitivity modified Glasgow prognostic score (HS-mGPS) has been shown to offer better predictive accuracy compared to the traditional Glasgow prognostic score (GPS) and the modified Glasgow prognostic score (mGPS) in various cancers, but its ability to predict outcomes in patients with resected intrahepatic cholangiocarcinoma (ICC) has not been well-studied. The aim of the study was to investigate the prognostic value of HS-mGPS in ICC and its subtypes.

Methods: This study was a single-center retrospective study. All patients who were pathologically diagnosed with ICC after surgery in Nanjing Drum Tower Hospital from 2012 and 2022. Relevant laboratory data such as serum C-reactive protein (CRP), albumin (ALB), neutrophils, lymphocytes, and platelets were included. Overall survival (OS) information was collected, serum CRP and ALB level were used for scoring GPS, mGPS and HS-mGPS. Univariate and multivariate analyses were conducted to identify factors influencing prognosis by using Kaplan-Meier (KM) curve and Cox proportional hazards models. Additionally, through histological analysis, ICC was classified into large duct type (LD-type) and small duct type (SD-type), and the performance of the three scoring systems in these subtypes was examined.

Results: A total of 185 patients were included in this study, 57 cases were of the LD-type, and 128 cases were of the SD-type. Tumor subtypes was a significant factor influencing prognosis for all ICC patients [hazard ratio (HR) =1.76, 95% confidence interval (CI): 1.036–2.994, P=0.04]. HS-mGPS demonstrated a better ability to predict outcomes compared to GPS and mGPS, and was an independent prognostic factor of OS (HR =2.1, 95% CI: 1.001–4.374, P=0.049). HS-mGPS was also more effective in predicting prognosis for SD-type ICC compared to GPS and mGPS (HR =3.13, 95% CI: 1.018–9.604, P=0.046), while it was ineffective for LD-type ICC. Further analysis revealed that SD-type ICC with higher HS-mGPS scores typically had larger tumors and poorer differentiation, while LD-type ICC showed no significant differences.

Conclusions: HS-mGPS provides a more accurate prognostic indication for SD-type, but its effectiveness for LD-type requires further investigation with larger sample sizes. Therefore, for preoperatively biopsy-diagnosed SD-type ICC, the HS-mGPS has a certain level of prognostic predictive potential.

Keywords: High-sensitivity modified Glasgow prognostic score (HS-mGPS); intrahepatic cholangiocarcinoma (ICC); small-duct type

Submitted Jun 15, 2024. Accepted for publication Dec 17, 2024. Published online Feb 24, 2025.
doi: 10.21037/tcr-24-917
View this article at: https://dx.doi.org/10.21037/tcr-24-917

Introduction

Primary liver cancer is one of the most leading causes of cancer-related deaths globally (1). Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver malignancy after hepatocellular carcinoma (HCC) (2), representing about 15% of all primary liver cancers. Over the past several years, the incidence of ICC has been on the rise (3). At present, the best pharmacological treatment strategies have not been clearly defined or standardized (4). Surgery is still the primary treatment for ICC (5).

ICC originates from various intrahepatic bile duct structures, including the epithelial lining, peri-biliary glands, and the stem cells/liver progenitor cells in the canals of Hering. Hepatocytes can also transform into ICC (6). The 5th edition of World Health Organization classification for digestive system tumors identifies two main pathological subtypes for ICC: large duct type (LD-type) and small duct type (SD-type) (7).

Research indicates that these subtypes differ not only morphologically but also in terms of their biological behavior (8). LD-type ICC is often associated with elevated carbohydrate antigen 199 (CA-199) levels and typically involves mucin production, with liver fluke infection or sclerosing cholangitis as risk factors. It grows in an infiltrative manner, tends to be more aggressive, and generally has a poorer prognosis (9). In contrast, SD-type ICC generally grows as a mass, is less likely to invade nearby bile ducts, lymphatic vessels, and nerves. Immunohistochemically, SD-type ICC is more likely to express C-reactive protein (CRP). And in our earlier study on LD-type ICC, we also found that the two subtypes of ICC exhibited different nutritional and metabolic profiles (10). However, the prognosis for ICC patients after surgery remains poor due to high rates of tumor recurrence and metastasis, and the exact risk factors impacting survival are not yet fully understood. Another study suggested that the number of lymph node metastases can affect prognosis, but more real-world evidence is needed to confirm this (11).

Inflammatory responses are believed to be closely associated with tumor progression and the composition of the tumor microenvironment (12). Studies from several years ago have demonstrated that the preoperative inflammatory and nutritional state of the body significantly affect postoperative outcomes (13,14). Many analyses have examined common preoperative blood serum factors, including CRP, albumin (ALB), neutrophils, lymphocytes, and platelets, and by analyzing their ratios to evaluate their impact on prognosis (15,16). CRP is a classic inflammatory protein that is produced in response to mediators such as interleukin-6 and interleukin-1, reflecting the body's inflammatory response (17). ALB, synthesized by hepatocytes (18), plays various critical physiological roles and indicates the nutritional status of a patient before surgery.

In the early 21st century, Forrest and colleagues proposed the Glasgow prognostic score (GPS), based on serum CRP and ALB levels (19). The scoring system is as follows: a CRP level below 10 mg/L and ALB at or above 35 mg/L result in a score of 0; a CRP level above 10 mg/L or ALB below 35 mg/L result in a score of 1; a CRP level above 10 mg/L and ALB below 35 mg/L result in a score of 2. The GPS has been validated as a promising marker in various cancers, including colorectal cancer, gastric cancer, HCC, and ICC (20-23). Due to the potential impact of CRP on ALB, McMillan and colleagues modified the

Highlight box

Key findings

- We discovered that for intrahepatic cholangiocarcinoma classified pathologically as small duct type, there may exist a scoring system that integrates preoperative laboratory examinations to prognosticate its outcomes.

What is known and what is new?

- In previous studies, the high-sensitivity Glasgow score has been considered advantageous in predicting the prognosis of other tumors
- Our research revealed that the high-sensitivity Glasgow score demonstrates an advantage in prognosticating the outcomes of one subtype of intrahepatic cholangiocarcinoma

What is the implication, and what should change now?

- For patients diagnosed with intrahepatic cholangiocarcinoma of the small bile duct type after surgery, their preoperative laboratory tests may serve as a predictive tool.

GPS, creating the modified Glasgow prognostic score (mGPS), which assigns score 1 only when CRP is above 10 mg/L. This modification was designed to further refine prognosis assessment (24). As research progressed, Proctor and colleagues in a study of 2,742 cases of colorectal cancer, suggested lowering the CRP cutoff to better reflect cancer-related changes and prognosis. This modification became known as the high-sensitivity modified Glasgow prognostic score (HS-mGPS), with a CRP cutoff of 3 mg/L (25). Wu, Tsai, Ando, and Nakamura validated the prognostic significance of HS-mGPS in gastric cancer, colorectal cancer, oral cancer, and soft tissue sarcomas, respectively. However, no studies have yet investigated its predictive value in ICC (26-29).

Some studies have demonstrated that other inflammation-based factors can predict postoperative survival in ICC. Prognostic indices, including lymphocyte-C-reactive protein ratio, the neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), platelet-to-lymphocyte ratio (PLR), preoperative systemic inflammation score (15,30,31), are based on measurements such as CRP, routine blood tests, and ALB levels. Due to the relationship between SD-type ICC and CRP, CRP-based scoring may play a role in predicting the prognosis of ICC compared to other scoring systems. What's more, these serological scores typically divide cases into only two groups. In contrast, the Glasgow scoring system can categorize cases into a third, intermediate-risk group, which may offer more nuanced risk prediction for ICC. None of these scoring systems have explored or accounted for the different subtypes of ICC, which may limit their effectiveness in accurately predicting prognosis across various forms of the disease.

To investigate the relationship between the HS-mGPS and the prognosis of ICC, while also exploring the differences between two subtypes of ICC, we initiated our study. We present this article in accordance with the REMARK reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-917/rc).

Methods

Study design

This study was a retrospective study included a cohort of all patients diagnosed with ICC who underwent radical resection at Nanjing Drum Tower Hospital between 2012 and 2022 confirmed postoperatively by pathology. The survival status of each patient was obtained from a prospectively maintained database using a predefined format for data collection. General patient information, such as age, gender, and body mass index (BMI), was included. The outcome variable of this study was overall survival (OS), calculated from date of surgery and was collected by phone called every 6 months. Patients who received neoadjuvant chemotherapy before surgery, had distant metastases, lack of CRP and ALB test data or OS status were excluded from the study.

Prior to surgical resection of their primary tumors, blood samples were collected from each patient within one week. These samples were analyzed for various parameters including tumor markers [carcinoembryonic antigen (CEA) and CA-199], total bilirubin, total protein, ALB, CRP, white blood cell (WBC) count, hemoglobin, gamma-glutamyl transpeptidase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AKP), lactate dehydrogenase (LDH), neutrophil count, lymphocyte count, and platelet count. All data were collected from the patients' previous medical records.

The pathological data, encompassing tumor grade and number, histological subtype, and microvascular invasion, were meticulously interpreted by two pathologists in accordance with the literature based on the hematoxylin and eosin (HE) staining slides.

CRP and ALB are used as scoring criteria, and their relationship with prognosis is being explored. Other indicators are also used in conjunction with the GPS to analyze their significance in predicting prognosis.

The study was approved by the Ethics Committee of Nanjing Drum Tower Hospital (No. 2023-188-01) and was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and government policies. All participants provided written informed consent.

Assay methods

The GPS was calculated as follows: patients with both an elevated CRP level (>10 mg/L) and hypoalbuminemia (<35 g/L) were assigned a score of 2, those with only an abnormal CRP level or hypoalbuminemia were given a score of 1, and patients with a normal CRP level (≤10 mg/L) were assigned a score of 0. The mGPS was only assigned score of 1 by the abnormal CRP level. Additionally, the HS-mGPS was calculated using a cutoff value of CRP decreased to 3 mg/L.

The histological subtype was ascertained following the 2019 World Health Organization diagnostic criteria for ICC classification. Additionally, the pathological tumor-

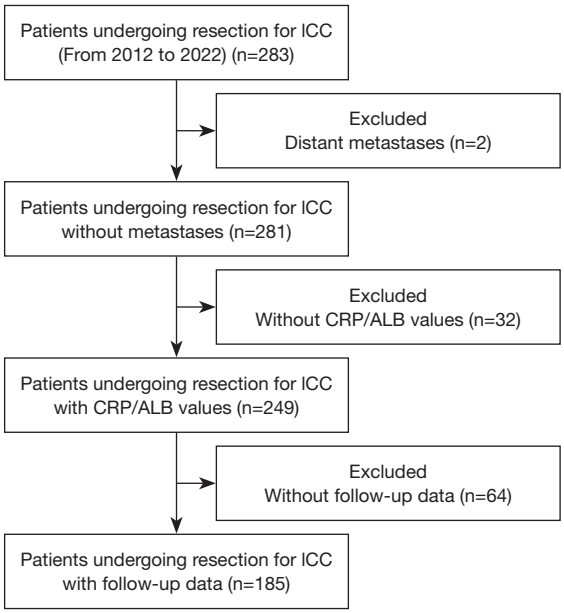

Figure 1 Flow diagram of the recruitment of intrahepatic cholangiocarcinoma patients. ICC, intrahepatic cholangiocarcinoma; CRP, C-reactive protein; ALB, albumin.

node-metastasis (TNM) stage was established based on the eighth edition of the American Joint Committee on Cancer guidelines.

Statistical analysis

Routine blood test samples were categorized as normal or abnormal based on clinical cutoff values for subsequent statistical analysis. Tumor sizes were divided into two groups by 5 cm as cut off value. Statistical analyses were conducted in R software (v4.2.0). The Kaplan-Meier (KM) curve was used to compare OS of different subtype of ICC and different score of GPS (HS-mGPS), The predictive ability of GPS (HS-mGPS) was evaluated by the area under curve (AUC) of receiver operating characteristic curve (ROC) by utilizing the survminer, survival ROC and survival package in R. Prognostic factors were identified through both univariate and multivariate Cox proportional hazards model, Individual variables with a significance of P value <0.05 in the univariate were selected for inclusion in the multivariate analysis. Welch two sample *t*-test was used for continuous variables and Fisher's exact test was utilized for categorical variables. Survival analysis was measured using the log-rank test. Two-sided P<0.05 indicated a significance level.

Results

The LD-type ICC is associated with a poorer overall prognosis

A total of 283 ICC patients were initially considered for the study. However, 64 patients were lost to follow-up, 32 patients had missing CRP/ALB values, and 2 patients had distant metastases. Consequently, 185 ICC patients were ultimately included in the study (*Figure 1*).

Among the 185 patients who underwent curative resection for ICC, the median age was 61 years, and 50.8% were male. The median tumor size was 5.0 cm, with a median CA-199 level of 65 U/L. Approximately 67% of patients were in stages I–II, with 79.5% showing moderate differentiation. Notably, 14.6% presented with multiple nodules, and 24.9% had evidence of microvascular invasion. The median levels of ALB, CRP, and CEA were 40.2 g/L, 5 g/L, and 2 U/L, respectively. The remaining laboratory tests are detailed in *Table 1*. Following resection, the overall 5-year survival rate was 65.7% (*Figure 2A*).

Histological analysis allowed the classification of ICC into LD-type and SD-type, with 31% (57/185) being categorized as the LD-type. Moreover, subtypes classification emerged as an independent predictor of OS [hazard ratio (HR) =1.76, 95% confidence interval (CI): 1.036–2.994, P=0.04; *Table 2*]. KM analysis underscored a markedly superior prognosis for the SD-type ICC relative to the LD-type ICC. The 5-year survival rate was 71.1% for the SD-type and 61.8% for the LD-type, with a P value of 0.03 (*Figure 2B*). Typical HE images were showed in *Figure 3*.

HS-mGPS is superior to the GPS and mGPS in predicting the prognosis of ICC

HS-mGPS emerges as a more effective evaluation tool for ICC patients. Through multivariate Cox regression analysis, we identified HS-mGPS as an independent risk factor for OS (HR =2.1, 95% CI: 1.001–4.374, P=0.049), whereas GPS and mGPS was only positive in univariate analysis. In addition to tumor subtype, T stage (HR =2.20, 95% CI: 1.225–3.08, P<0.001), and abnormal AKP (HR =1, 95% CI: 1–1.003, P=0.04) levels are also independent risk factors for ICC (*Table 2*).

By employing the log-rank test to generate KM curves for both assessment methods, it becomes clear that HS-mGPS offers a notably more precise prognostic assessment for ICC patients (P=0.004) compared to GPS (P=0.02) and mGPS (P=0.03). Higher HS-mGPS scores correspond to

Table 1 Clinicopathological and pathological features of 185 intrahepatic cholangiocarcinoma patients

Characteristic	Values (N=185)
Age (years)	61 [34, 83]
Gender	
Female	91 (49.2)
Male	94 (50.8)
WBC (10^9/L)	5.70 [2.50, 14.80]
HB (g/L)	130 [3, 327]
PLT (10^9/L)	190 [41, 413]
LP (10^9/L)	1.50 [0.40, 3.80]
ALT (U/L)	24 [6, 428]
AST (U/L)	24 [11, 317]
AKP (U/L)	103 [35, 1,681]
GGT (U/L)	64 [12, 1,249]
TB (μmol/L)	12 [4, 272]
LDH (U/L)	198 [13, 632]
CA-199 (U/L)	65 [1, 25,209]
CEA (U/L)	2 [0, 395]
ALB (g/L)	40.2 [3.2, 49.4]
CRP (g/L)	5 [0, 121]
Microvascular invasion	46 (24.9)
Subtype	
Large duct type	57 (30.8)
Small duct type	128 (69.2)
Tumor size (cm)	5.00 [1.20, 14.00]
Multiple nodules	27 (14.6)
Tumor differentiation	
Well	12 (6.5)
Moderately	147 (79.5)
Poor	26 (14.1)
T	
1	103 (55.7)
2	58 (31.4)
3	22 (11.9)
4	2 (1.1)
N	
N0	57 (30.8)
N1	41 (22.2)
Nx	87 (47.0)
TNM stage	
I–II	124 (67.0)
III–IV	61 (33.0)

Data are presented as median [range] or n (%). WBC, white blood cell; HB, hemoglobin; PLT, platelet; LP, lymphocytes; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AKP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; LDH, lactate dehydrogenase; CA-199, carbohydrate antigen 199; ALB, albumin; CEA, carcinoembryonic antigen; CRP, C-reactive protein; TB, total bile acid; TNM, tumor-node-metastasis.

poorer OS outcomes especially in 1 year survival prediction (*Figure 4A-4C*).

HS-mGPS demonstrates better diagnostic efficacy for SD-type ICC, while it is ineffective for LD-type

We conducted single and multivariate analyses using these bile duct types as grouping criteria for this cohort of cases. Surprisingly, we discovered that in the SD-type, HS-mGPS remained an effective evaluation method, retaining its status as an independent risk factor in multivariate Cox regression analysis (HR =3.13, 95% CI: 1.018–9.604, P=0.046). At the same time, T stage (HR =2.12, 95% CI: 1.307–3.427, P=0.002) and tumor size (HR =1.17, 95% CI: 1.037–1.319, P=0.01) are also independent risk factors for the SD-type (*Table 3*). KM curve analysis revealed that HS-mGPS (P<0.001) also had superior predictive efficacy for SD-type ICC compared to GPS (P=0.005) and mGPS (P=0.006; *Figure 4D-4F*). It also shows more clearly in predict for the score 0 patients, whose 1 year's survival was 100% (30/30).

We did the same thing on the LD-type, however, in the LD-type, only T stage can serve as an independent factor (HR =1.95, 95% CI: 1.205–3.147, P=0.006; *Table 4*). And it showed no correlation for GPS (P=0.78), mGPS (P=0.93) and even HS-mGPS (P=0.98; *Figure 4G-4I*) with prognosis.

The ROC curve shows that in predicting OS, HS-mGPS

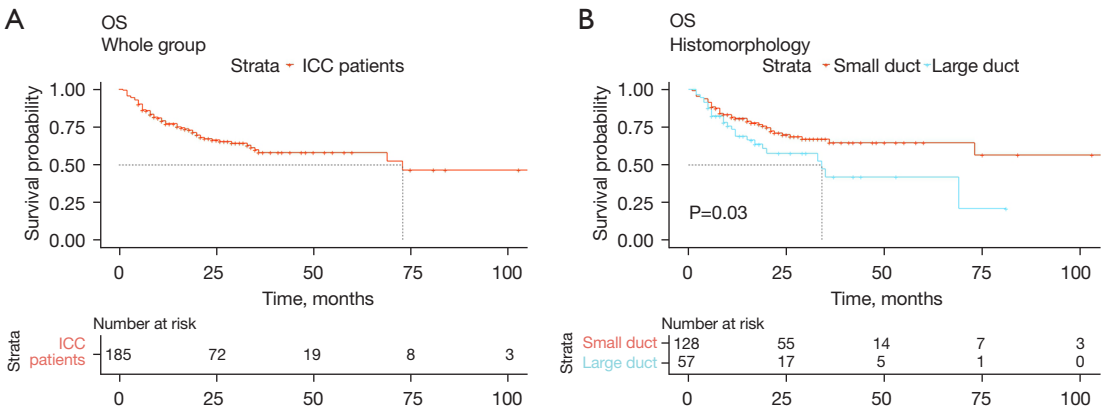

Figure 2 The Kaplan-Meier curves demonstrate that different subtypes of ICC have varying impacts on patient prognosis. (A) Overall survival for ICC patients. (B) Differences in overall survival between large duct-type and small duct-type patients. OS, overall survival; ICC, intrahepatic cholangiocarcinoma.

Table 2 Factors associated with overall survival of 185 intrahepatic cholangiocarcinoma patients: univariate and multivariate analysis

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
ALB	0.95	0.917–0.979	0.001	–	–	–
CRP	1.01	1–1.02	0.004	–	–	–
AKP	1.002	1.001–1.003	<0.001	1	1–1.003	0.04
GGT	1.001	1.001–1.002	0.001	–	–	–
Tumor subtype	1.74	1.04–2.905	0.04	1.76	1.036–2.994	0.04
Tumor size	1.11	1.01–1.22	0.02	–	–	–
Multiple nodules	2.05	1.11–3.79	0.02	–	–	–
T stage	2.03	1.5–2.77	<0.001	2.20	1.225–3.08	<0.001
GPS	1.65	1.15–2.36	0.006	–	–	–
mGPS	1.59	1.103–2.279	0.01	–	–	–
HS-mGPS	2.24	0.389–3.616	<0.001	2.1	1.001–4.374	0.049

HR, hazard ratio; CI, confidence interval; ALB, albumin; CRP, C-reactive protein; AKP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; GPS, Glasgow prognostic score; mGPS, modified Glasgow prognostic score; HS-mGPS, high-sensitivity modified Glasgow prognostic score.

demonstrates better predictive performance for both overall ICC and SD-type ICC compared to GPS (*Figure 5A,5B*). However, its predictive effectiveness is relatively poorer for LD-type ICC (*Figure 5C*).

The SD-type exhibits differences in response to HS-mGPS compared to the LD-type

To explore the reasons for the differences in HS-mGPS between the LD-type and SD-type, we conducted statistical analysis on various baseline laboratory parameters and pathological data. There were no observed differences in pathological data between the two groups. The LD type shows higher in CA-199, AST, ALT, and GGT (P=0.002, P=0.01, P<0.001, *Table 5*).

And we divided them into three groups by HS-mGPS score. We found that the score 2 patients in SD-type had significantly higher in ALT, AKP, AST and GGT (P=0.02,

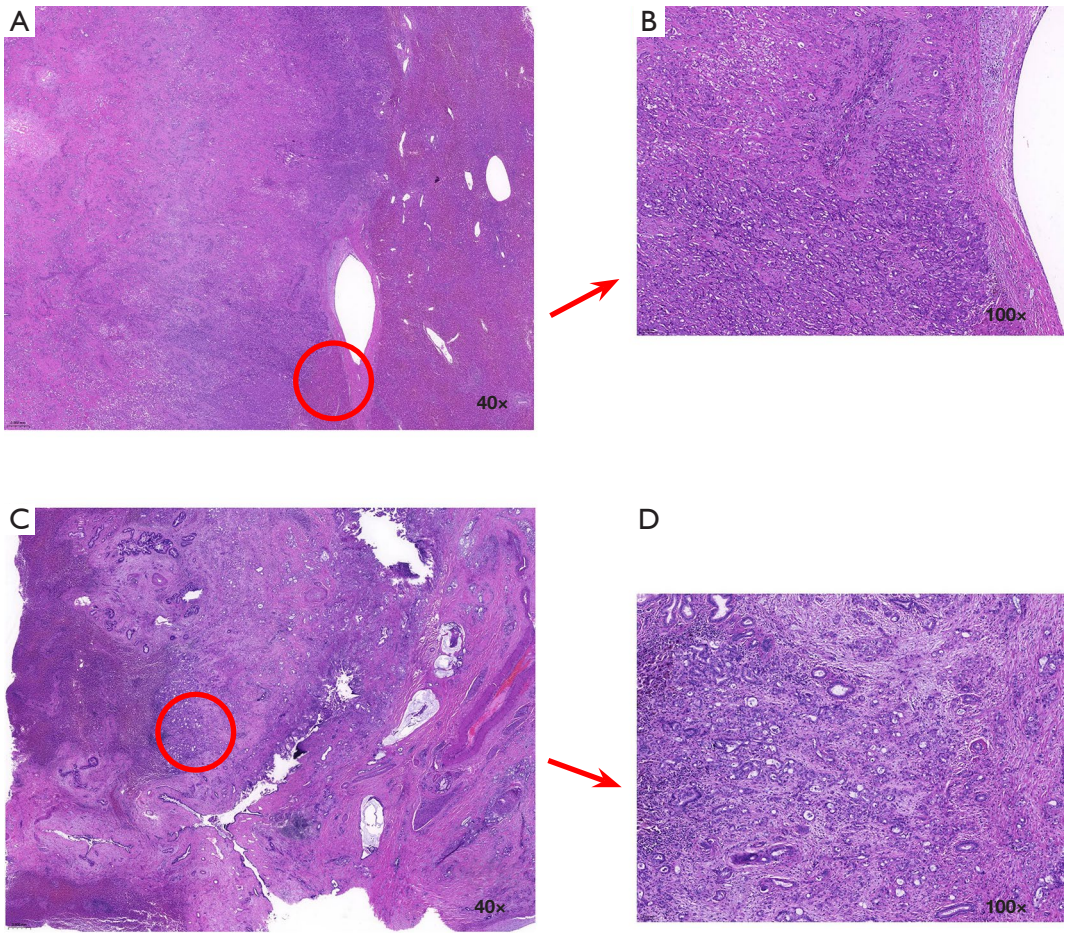

Figure 3 Histological subtypes of intrahepatic cholangiocarcinoma. (A,B) The appearance of small duct-type ICC under HE staining in different magnifications: at 40× (A) and 100× (B). (C,D) The appearance of large duct-type ICC under HE staining at different magnifications: at 40× (C) and 100× (D). The circle pointed by the arrow is a representative tumor area. ICC, intrahepatic cholangiocarcinoma; HE, hematoxylin and eosin.

0.002, <0.001 and 0.008). Also, they had bigger tumor size and poorer tumor differentiation (P=0.02 and 0.03, *Table 6*). But there was still no any positive sign (ALB and CRP were used to defined the Hs-mGPS score) for LD-type except for gender (P=0.04).

Discussion

Inflammation is certainly a poor indication for OS. Our findings suggest that compared to the GPS and mGPS, the HS-mGPS is a more reliable prognostic indicator for ICC, with higher scores associated with worse OS. And compared to Sui *et al.*'s research on GPS (23) for ICC patients, our investigation on HS-mGPS shows a median rick group (score =1) for ICC patients, which can predict OS rate more precisely.

Further investigation revealed that this prognostic accuracy is significant only among patients with the SD-type of ICC. In contrast to the LD-type, the SD-type was associated with better prognosis. Apart from differing survival rates, these subtypes also show distinct responses to inflammatory scoring.

LD-type ICC exhibits histological traits that closely resemble those of perihilar cholangiocarcinoma (32), with an infiltrative growth pattern and higher aggressiveness. Research on perihilar/extrahepatic cholangiocarcinoma had shown varying outcomes when using the GPS/mGPS, in Okuno *et al.*'s study, mGPS could not distinguish between scores of 1 and 2 (33), whereas Jansson *et al.*'s study struggle with score 1 and 0 when using the mGPS (34). Our study did not show any evidence that HS-mGPS is useful in LD-

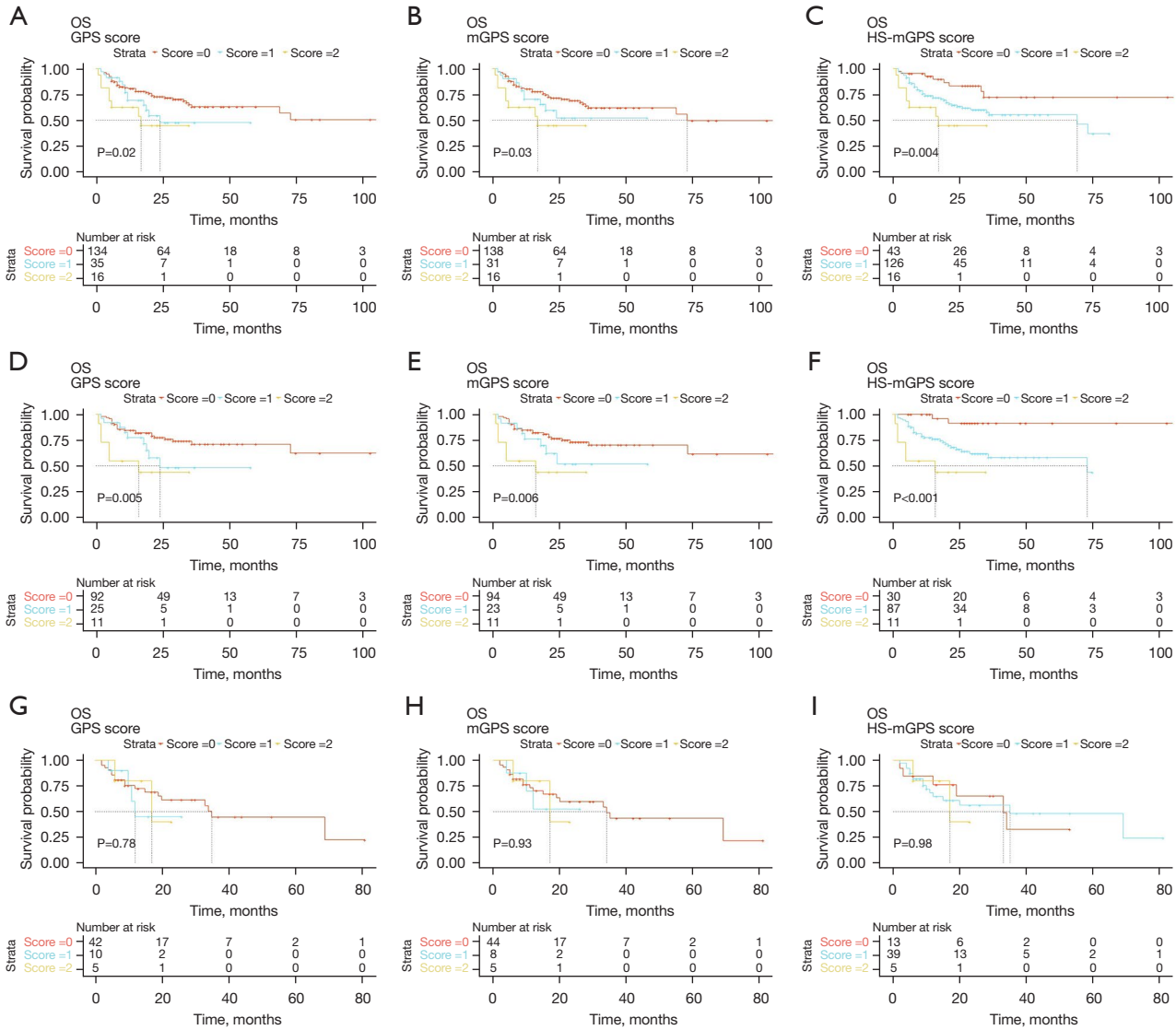

Figure 4 The Kaplan-Meier curves illustrate the predictive performance of three Glasgow scores for ICC and its different subtypes. GPS (A), mGPS (B), and HS-mGPS (C) represent their effectiveness for all ICC patients. GPS (D), mGPS (E), and HS-mGPS (F) indicate their predictive capabilities for small duct-type ICC. GPS (G), mGPS (H), and HS-mGPS (I) demonstrate their performance for large duct-type ICC. OS, overall survival; GPS, Glasgow prognostic score; mGPS, modified Glasgow prognostic score; HS-mGPS, high-sensitivity modified Glasgow prognostic score; ICC, intrahepatic cholangiocarcinoma.

type prognosis. But we also did not find any other indicated prognosis factor for LD-type. The reasons behind these variations remain unclear, limited sample size of LD-type cases in our study might hinder drawing broader conclusions.

In contrast, SD-type ICC showed a strong response to HS-mGPS. We propose several possible reasons for this observation. First, SD-type inherently expresses CRP (35) compared to LD-type, suggesting that an increase in serum CRP levels may indicate tumor proliferation. This aligns with our findings, where patients in the HS-mGPS group with a score of 0 had smaller tumor sizes on average. Second, SD-type shows connection between HS-mGPS and the tumor differentiation. Higher score showed better differentiation in SD-type. Third, the score 2 group showed typically higher level of biomarkers which are associated with worse

Table 3 Factors associated with overall survival of small duct type intrahepatic cholangiocarcinoma patients: univariate and multivariate analysis

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
ALB	0.95	0.913–0.985	0.005	–	–	–
CRP	1.02	1.007–1.028	<0.001	–	–	–
AKP	1.002	1.001–1.003	<0.001	–	–	–
GGT	1.01	1.108–1.383	<0.001	–	–	–
LDH	1.01	1–1.01	0.046	–	–	–
Tumor size	1.3	1.12–1.5	<0.001	1.17	1.037–1.319	0.01
Multiple nodules	2.6	1.307–5.599	0.007	–	–	–
T stage	2.03	1.362–3.017	<0.001	2.12	1.307–3.427	0.002
GPS	2.6	1.56–4.34	<0.001	–	–	–
mGPS	1.93	1.242–2.99	0.003	–	–	–
HS-mGPS	5.36	2.49–11.54	<0.001	3.13	1.018–9.604	0.046

HR, hazard ratio; CI, confidence interval; ALB, albumin; CRP, C-reactive protein; AKP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; LDH, lactate dehydrogenase; GPS, Glasgow prognostic score; mGPS, modified Glasgow prognostic score; HS-mGPS, high-sensitivity modified Glasgow prognostic score.

Table 4 Factors associated with overall survival of large duct type intrahepatic cholangiocarcinoma patients: univariate and multivariate analysis

Variables	Univariate analysis			Multivariate analysis*		
	HR	95% CI	P value	HR	95% CI	P value
T stage	1.95	1.205–3.147	0.006	1.95	1.205–3.147	0.006

*, T stage was the only significant variate so that multivariate analysis data is the same as univariate analysis. HR, hazard ratio; CI, confidence interval.

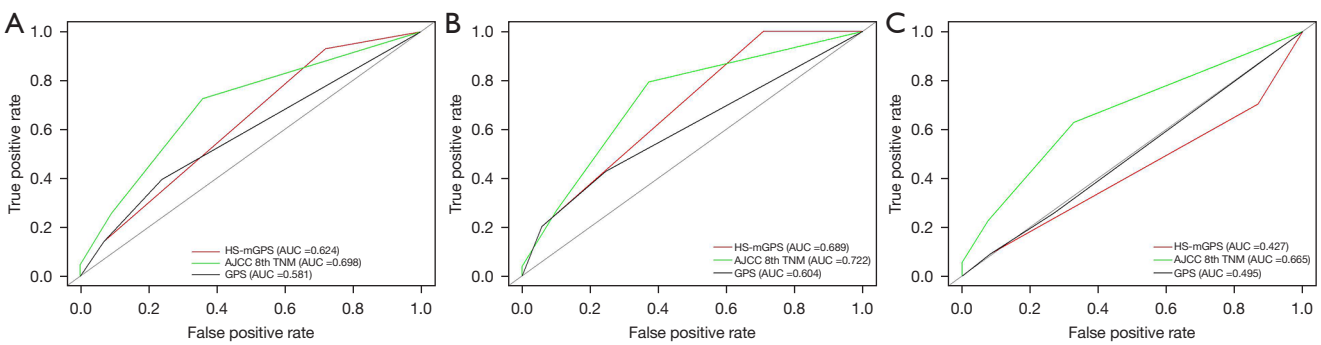

Figure 5 Comparison of the predictive accuracy of GPS and HS-mGPS in ICC and its different subtypes. (A) Total ICC. (B) Small duct-type ICC. (C) Large duct-type ICC. HS-mGPS, high-sensitivity modified Glasgow prognostic score; AUC, area under curve; AJCC, American Joint Committee on Cancer; TNM, tumor-node-metastasis; GPS, Glasgow prognostic score; ICC, intrahepatic cholangiocarcinoma.

Table 5 Comparative analysis of surgically treated patients with respect to subtype of ICC

Characteristic	Large duct type (N=57)	Small duct type (N=128)	P*
Age [years], [range]	62 [41, 83]	61 [34, 81]	0.32
Sex (male)	26 [46]	68 [53]	0.43
HBV infection	34 [60]	84 [66]	0.30
WBC abnormal	4 [7]	24 [19]	0.046
HB abnormal	8 [14]	14 [11]	0.62
PLT abnormal	8 [14]	19 [15]	>0.99
ALT abnormal	19 [33]	20 [16]	0.01
LP abnormal	2 [4]	3 [2]	>0.99
AKP abnormal	41 [72]	74 [58]	0.07
GGT abnormal	47 [82]	64 [50]	<0.001
AST abnormal	15 [26]	11 [9]	0.002
TB abnormal	14 [25]	34 [27]	0.86
LDH abnormal	11 [19]	29 [23]	0.70
ALB abnormal	7 [12]	15 [12]	>0.99
CRP abnormal	15 [26]	42 [33]	0.40
CA-199 abnormal	38 [67]	40 [31]	<0.001
Tumor size >5 cm	25 [44]	77 [60]	0.054
Margin positive	3 [5]	7 [5]	>0.99
Multiple nodules	7 [12]	20 [16]	0.66
Microvascular invasion	13 [23]	33 [26]	0.72
Membrane invasion			0.90
0	39 [69]	88 [69]	
1	11 [19]	22 [17]	
2	7 [12]	18 [14]	
T stage			0.88
1	33 [58]	70 [55]	
2	17 [30]	41 [32]	
3	6 [11]	16 [13]	
4	1 [2]	1 [1]	
N stage			0.46
N0	19 [33]	38 [30]	
N1	15 [26]	26 [20]	
Nx	23 [40]	64 [50]	
TNM stage			0.31
I–II	35 [61]	89 [70]	
III–IV	22 [39]	39 [30]	
Grading			0.31
0	6 [11]	5 [4]	
1	23 [40]	66 [52]	
2	15 [26]	39 [30]	
3	4 [7]	11 [9]	
4	1 [2]	1 [1]	
Staging			0.30
0	18 [32]	39 [30]	
1	21 [37]	41 [32]	
2	4 [7]	15 [12]	
3	3 [5]	6 [5]	
4	3 [5]	21 [16]	

Data are presented as n [%] unless otherwise specified. Grading/Staging items has some N/A value (the pathological material didn't have normal liver tissue, which is used to difine Grading/Staging). *, Welch two sample *t*-test; Fisher's exact test. ICC, intrahepatic cholangiocarcinoma; HBV, hepatitis B virus; WBC, white blood cell; HB, hemoglobin; PLT, platelet; ALT, alanine aminotransferase; LP, lymphocytes; AKP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; AST, aspartate aminotransferase; TB, total bile acid; LDH, lactate dehydrogenase; ALB, albumin; CRP, C-reactive protein; CA-199, carbohydrate antigen 199; TNM, tumor-node-metastasis; N/A, not avaliable.

survival in routine blood test. However, further investigation is required to clarify the exact relationship between these genomic about SD-type's response to HS-mGPS.

Our study is not the first to utilize the HS-mGPS score for prognosis perdition (36), but it is the first to apply HS-mGPS specifically to ICC and found that it offers better diagnostic significance compared to the GPS and mGPS. Additionally, we observed that the responses to HS-mGPS differed between SD-type and LD-type ICC. However, ICC is a highly heterogeneous tumor with possibly different mixing of components in the tumor, and classifying it into just two groups may not capture the entire complexity and

Table 6 Comparative analysis of surgically treated patients with respect to HS-mGPS score

Characteristic	SD-type (score)				LD-type (score)			
	0 (N=30)	1 (N=87)	2 (N=11)	P*	0 (N=13)	1 (N=39)	2 (N=5)	P*
Age (years), [range]	62 [39, 79]	62 [34, 81]	60 [34, 72]	0.43	61 [41, 83]	60 [41, 77]	69 [55, 79]	0.24
Gender				0.17				0.04
Female	10 [33]	43 [49]	7 [64]		3 [23]	25 [64]	3 [60]	
Male	20 [67]	44 [51]	4 [36]		10 [77]	14 [36]	2 [40]	
WBC abnormal	4 [13]	16 [18]	4 [36]	0.29	1 [8]	3 [8]	0 [0]	>0.99
HB abnormal	3 [10]	8 [9]	3 [27]	0.21	3 [23]	4 [10]	1 [20]	0.36
PLT abnormal	3 [10]	14 [16]	2 [18]	0.60	4 [31]	4 [10]	0 [0]	0.16
ALT abnormal	5 [17]	10 [11]	5 [45]	0.02	5 [38]	11 [28]	3 [60]	0.36
AKP abnormal	13 [43]	50 [57]	11 [100]	0.002	8 [62]	28 [72]	5 [100]	0.33
GGT abnormal	9 [30]	46 [53]	9 [82]	0.008	8 [62]	35 [90]	4 [80]	0.054
AST abnormal	2 [7]	4 [5]	5 [45]	<0.001	4 [31]	8 [21]	3 [60]	0.12
TB abnormal	9 [30]	21 [24]	4 [36]	0.56	4 [31]	9 [23]	1 [20]	0.88
LDH abnormal	1 [3]	25 [29]	3 [27]	0.006	1 [8]	9 [23]	1 [20]	0.57
HBV infection	21 [70]	56 [64]	7 [63]	0.95	7 [54]	24 [62]	3 [60]	0.83
Cholelithiasis	8 [27]	22 [26]	4 [36]	0.73	3 [23]	11 [28]	3 [60]	0.31
CEA abnormal	1 [3]	11 [13]	1 [9]	0.40	0 [0]	7 [18]	1 [20]	0.25
CA-199 abnormal	11 [37]	36 [41]	3 [27]	0.65	8 [67]	17 [44]	3 [60]	0.48
ALB abnormal	0 [0]	4 [5]	11 [100]	<0.001	0 [0]	2 [5]	5 [100]	<0.001
CRP abnormal	0 [0]	31 [36]	11 [100]	<0.001	0 [0]	10 [26]	5 [100]	<0.001
Margin positive	1 [3]	6 [7]	0 [0]	0.83	1 [8]	2 [5]	0 [0]	>0.99
Membrane invasion				0.08				0.96
0	23 [77]	50 [57]	8 [72]		7 [53]	23 [59]	3 [60]	
1	2 [7]	17 [20]	1 [9]		2 [15]	5 [13]	1 [20]	
2	5 [17]	11 [13]	0 [0]		2 [15]	4 [10]	0 [0]	
3	0 [0]	0 [0]	1 [9]		0 [0]	1 [3]	0 [0]	
Tumor size >5 cm	12 [40]	56 [64]	9 [82]	0.02	5 [38]	18 [46]	2 [40]	0.91
Multiple nodules	2 [7]	15 [17]	3 [27]	0.18	1 [8]	6 [15]	0 [0]	0.83
Microvascular invasion	5 [17]	25 [29]	3 [27]	0.47	3 [23]	10 [26]	0 [0]	0.61
Differentiation				0.03				0.23
Moderately	29 [97]	65 [75]	7 [64]		8 [62]	33 [85]	5 [100]	
Poor	1 [3]	15 [17]	4 [36]		2 [15]	4 [10]	0 [0]	
Well	0 [0]	7 [8]	0 [0]		3 [23]	2 [5]	0 [0]	
T stage				0.14				0.52
1	19 [63]	45 [52]	6 [55]		8 [62]	20 [51]	5 [100]	
2	6 [20]	31 [36]	4 [36]		3 [23]	14 [36]	0 [0]	
3	5 [17]	11 [13]	0 [0]		2 [15]	4 [10]	0 [0]	
4	0 [0]	0 [0]	1 [9]		0 [0]	1 [3]	0 [0]	

Table 6 (*continued*)

Table 6 (*continued*)

Characteristic	SD-type (score)				LD-type (score)			
	0 (N=30)	1 (N=87)	2 (N=11)	P*	0 (N=13)	1 (N=39)	2 (N=5)	P*
N stage				0.31				0.26
N0	12 [40]	25 [29]	1 [9]		4 [31]	15 [38]	0 [0]	
N1	4 [13]	20 [23]	2 [18]		2 [15]	10 [26]	3 [60]	
Nx	14 [47]	42 [48]	8 [73]		7 [54]	14 [36]	2 [40]	
Grading				0.62				0.98
0	0 [0]	5 [6]	0 [0]		2 [15]	4 [10]	0 [0]	
1	21 [70]	40 [46]	5 [45]		4 [30]	17 [44]	2 [40]	
2	7 [23]	27 [31]	5 [45]		3 [23]	10 [26]	2 [40]	
3	2 [7]	8 [9]	1 [9]		1 [8]	3 [8]	0 [0]	
4	0 [0]	1 [1]	0 [0]		0 [0]	1 [3]	0 [0]	
Staging				0.44				0.85
0	12 [40]	24 [28]	3 [27]		4 [30]	12 [30]	2 [40]	
1	10 [33]	28 [32]	3 [27]		5 [38]	15 [38]	1 [20]	
2	3 [10]	12 [14]	0 [0]		1 [8]	2 [5]	1 [20]	
3	2 [7]	4 [5]	0 [0]		0 [0]	3 [8]	0 [0]	
4	3 [10]	13 [15]	5 [45]		0 [0]	3 [8]	0 [0]	
TNM stage				>0.99				0.52
I–II	21 [70]	60 [69]	8 [73]		9 [69]	24 [62]	2 [40]	
III–IV	9 [30]	27 [31]	3 [27]		4 [31]	15 [38]	3 [60]	

Data are presented as n [%] unless otherwise specified. Grading/Staging items has some N/A value (the pathological material didn't have normal liver tissue, which is used to difine Grading/Staging). *, Kruskal-Wallis rank sum test; Fisher's exact test. HS-mGPS, high-sensitivity modified Glasgow prognostic score; WBC, white blood cell; HB, hemoglobin; PLT, platelet; ALT, alanine aminotransferase; AKP, Alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; AST, aspartate aminotransferase; TB, total bile acid; LDH, lactate dehydrogenase; HBV, hepatitis B virus; CEA, carcinoembryonic antigen; CA-199, carbohydrate antigen 199; ALB, albumin; CRP, C-reactive protein; TNM, tumor-node-metastasis; N/A, not avaliable.

their histological traits (37,38). Our investigation is also limited by our single-center samples and experimental resources, restricting our ability to delve deeper into the relationship between LD-type and HS-mGPS. We can only discuss the tumor subtypes at a macroscopic level, and further studies on the molecular mechanisms that connect these subtypes to HS-mGPS and other inflammatory scores could provide more insights.

Conclusions

In summary, LD-type ICC is indeed with a poorer prognosis. Moreover, we believe that HS-mGPS, compared to GPS and mGPS, is a more reliable prognostic prediction model for surgically treated SD-type ICC, but its effectiveness in LD-type still requires deeper investigation with larger sample sizes. The correlation between ICC subtypes and inflammatory scores could pave the way for further research to understand the underlying molecular mechanisms that drive these differences.

Acknowledgments

None.

Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-917/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-917/dss

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-917/prf

Funding: The study was supported by Clinical Trials from the Affiliated Drum Tower Hospital, Medical School of Nanjing University (grant/award No. 2022-LCYJ-MS27); and Major Project of Nanjing Health Science and Technology Development (grant/award No. ZDX22001).

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-917/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 approved by the Ethics Committee of Nanjing Drum Tower Hospital (No. 2023-188-01) and was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and government policies. All participants provided written informed consent.

References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
2. Khan SA, Emadossadaty S, Ladep NG, et al. Rising trends in cholangiocarcinoma: is the ICD classification system misleading us? J Hepatol 2012;56:848-54.
3. Blechacz B, Komuta M, Roskams T, et al. Clinical diagnosis and staging of cholangiocarcinoma. Nat Rev Gastroenterol Hepatol 2011;8:512-22.
4. Bath NM, Pawlik TM. Narrative review: current management and novel targeted therapies in intrahepatic cholangiocarcinoma. Chin Clin Oncol 2023;12:5.
5. Schnitzbauer AA, Eberhard J, Bartsch F, et al. The MEGNA Score and Preoperative Anemia are Major Prognostic Factors After Resection in the German Intrahepatic Cholangiocarcinoma Cohort. Ann Surg Oncol 2020;27:1147-55.
6. Wang H, Chen J, Zhang X, et al. Expert Consensus on Pathological Diagnosis of Intrahepatic Cholangiocarcinoma (2022 version). J Clin Transl Hepatol 2023;11:1553-64.
7. Nagtegaal ID, Odze RD, Klimstra D, et al. The 2019 WHO classification of tumours of the digestive system. Histopathology 2020;76:182-8.
8. Yamada M, Yamamoto Y, Sugiura T, et al. Comparison of the Clinicopathological Features in Small Bile Duct and Bile Ductular Type Intrahepatic Cholangiocarcinoma. Anticancer Res 2019;39:2121-7.
9. Hayashi A, Misumi K, Shibahara J, et al. Distinct Clinicopathologic and Genetic Features of 2 Histologic Subtypes of Intrahepatic Cholangiocarcinoma. Am J Surg Pathol 2016;40:1021-30.
10. Guo Y, Li Q, Ren W, et al. Quantitative Proteomics Reveals Down-Regulated Glycolysis/Gluconeogenesis in the Large-Duct Type Intrahepatic Cholangiocarcinoma. J Proteome Res 2022;21:2504-14.
11. Kim J, Han DH, Choi GH, et al. The prognostic value of the number of metastatic lymph nodes on the long-term survival of intrahepatic cholangiocarcinoma using the SEER database. J Gastrointest Oncol 2023;14:2511-20.
12. Mantovani A, Allavena P, Sica A, et al. Cancer-related inflammation. Nature 2008;454:436-44.
13. Diakos CI, Charles KA, McMillan DC, et al. Cancer-related inflammation and treatment effectiveness. Lancet Oncol 2014;15:e493-503.
14. Jin J, Wang H, Peng F, et al. Prognostic significance of preoperative Naples prognostic score on short- and long-term outcomes after pancreatoduodenectomy for ampullary carcinoma. Hepatobiliary Surg Nutr 2021;10:825-38.
15. Yugawa K, Itoh S, Yoshizumi T, et al. Lymphocyte-C-reactive protein ratio as a prognostic marker associated with the tumor immune microenvironment in intrahepatic cholangiocarcinoma. Int J Clin Oncol 2021;26:1901-10.
16. Noguchi D, Kuriyama N, Nakagawa Y, et al. The prognostic impact of lymphocyte-to-C-reactive protein score in patients undergoing surgical resection for

intrahepatic cholangiocarcinoma: A comparative study of major representative inflammatory / immunonutritional markers. PLoS One 2021;16:e0245946.
17. Black S, Kushner I, Samols D. C-reactive Protein. J Biol Chem 2004;279:48487-90.
18. Rothschild MA, Oratz M, Schreiber SS. Serum albumin. Am J Dig Dis 1969;14:711-44.
19. Forrest LM, McMillan DC, McArdle CS, et al. Evaluation of cumulative prognostic scores based on the systemic inflammatory response in patients with inoperable non-small-cell lung cancer. Br J Cancer 2003;89:1028-30.
20. Lu X, Guo W, Xu W, et al. Prognostic value of the Glasgow prognostic score in colorectal cancer: a meta-analysis of 9,839 patients. Cancer Manag Res 2018;11:229-49.
21. Yuan SQ, Nie RC, Chen YM, et al. Glasgow Prognostic Score is superior to ECOG PS as a prognostic factor in patients with gastric cancer with peritoneal seeding. Oncol Lett 2018;15:4193-200.
22. Kinoshita A, Onoda H, Imai N, et al. Comparison of the prognostic value of inflammation-based prognostic scores in patients with hepatocellular carcinoma. Br J Cancer 2012;107:988-93.
23. Sui K, Okabayashi T, Umeda Y, et al. Prognostic Utility of the Glasgow Prognostic Score for the Long-Term Outcomes After Liver Resection for Intrahepatic Cholangiocarcinoma: A Multi-institutional Study. World J Surg 2021;45:279-90.
24. McMillan DC, Crozier JE, Canna K, et al. Evaluation of an inflammation-based prognostic score (GPS) in patients undergoing resection for colon and rectal cancer. Int J Colorectal Dis 2007;22:881-6.
25. Proctor MJ, Horgan PG, Talwar D, et al. Optimization of the systemic inflammation-based Glasgow prognostic score: a Glasgow Inflammation Outcome Study. Cancer 2013;119:2325-32.
26. Wu J, Chan YT, Lu Y, et al. The tumor microenvironment in the postsurgical liver: Mechanisms and potential targets of postoperative recurrence in human hepatocellular carcinoma. Med Res Rev 2023;43:1946-73.
27. Ando K, Sakamoto S, Saito S, et al. Prognostic Value of High-Sensitivity Modified Glasgow Prognostic Score in Castration-Resistant Prostate Cancer Patients Who Received Docetaxel. Cancers (Basel) 2021;13:773.
28. Tsai YT, Fang KH, Hsu CM, et al. Prognostic Role of High-Sensitivity Modified Glasgow Prognostic Score for Patients With Operated Oral Cavity Cancer: A Retrospective Study. Front Oncol 2022;12:825967.
29. Nakamura T, Asanuma K, Hagi T, et al. Modified Glasgow Prognostic Score is Better for Predicting Oncological Outcome in Patients with Soft Tissue Sarcoma, Compared to High-Sensitivity Modified Glasgow Prognostic Score. J Inflamm Res 2022;15:3891-9.
30. Sellers CM, Uhlig J, Ludwig JM, et al. Inflammatory markers in intrahepatic cholangiocarcinoma: Effects of advanced liver disease. Cancer Med 2019;8:5916-29.
31. Yang Z, Zhang D, Zeng H, et al. Inflammation-Based Scores Predict Responses to PD-1 Inhibitor Treatment in Intrahepatic Cholangiocarcinoma. J Inflamm Res 2022;15:5721-31.
32. Akita M, Fujikura K, Ajiki T, et al. Dichotomy in intrahepatic cholangiocarcinomas based on histologic similarities to hilar cholangiocarcinomas. Mod Pathol 2017;30:986-97.
33. Okuno M, Ebata T, Yokoyama Y, et al. Evaluation of inflammation-based prognostic scores in patients undergoing hepatobiliary resection for perihilar cholangiocarcinoma. J Gastroenterol 2016;51:153-61.
34. Jansson H, Cornillet M, Björkström NK, et al. Prognostic value of preoperative inflammatory markers in resectable biliary tract cancer - Validation and comparison of the Glasgow Prognostic Score and Modified Glasgow Prognostic Score in a Western cohort. Eur J Surg Oncol 2020;46:804-10.
35. Akita M, Sawada R, Komatsu M, et al. An immunostaining panel of C-reactive protein, N-cadherin, and S100 calcium binding protein P is useful for intrahepatic cholangiocarcinoma subtyping. Hum Pathol 2021;109:45-52.
36. Chen P, Fang M, Wan Q, et al. High-sensitivity modified Glasgow prognostic score (HS-mGPS) Is superior to the mGPS in esophageal cancer patients treated with chemoradiotherapy. Oncotarget 2017;8:99861-70.
37. Terada T. Combined hepatocellular-cholangiocarcinoma with stem cell features, ductal plate malformation subtype: a case report and proposal of a new subtype. Int J Clin Exp Pathol 2013;6:737-48.
38. Liau JY, Tsai JH, Yuan RH, et al. Morphological subclassification of intrahepatic cholangiocarcinoma: etiological, clinicopathological, and molecular features. Mod Pathol 2014;27:1163-73.

Cite this article as: He X, Liang Z, Zhang S, Ding Y, Qian X, Wu H, Chen J. High-sensitivity modified Glasgow prognostic score (HS-mGPS) is a prognostic biomarker for small duct-type intrahepatic cholangiocarcinoma—a retrospective cohort study. Transl Cancer Res 2025;14(2):1297-1310. doi: 10.21037/tcr-24-917

