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Preoperative Systemic Inflammation and Complications Affect Long-term Gallbladder Carcinoma Outcomes Following Surgery with Curative Intent

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Abstract. *Background/Aim: Gallbladder carcinoma (GBCA) has extremely poor outcomes. We aimed to investigate clinicopathological prognostic variables, including the modified Glasgow prognostic score (mGPS), for patients with resected GBCA. Patients and Methods: This retrospective study included 54 patients with GBCA resected between 1996 and 2014. Univariate and multivariate analyses were performed to identify prognostic factors associated with overall and recurrence-free survival. Results: Curative resection (R0) was achieved in 43 patients (79.6%). The median patient age was 74 years (range=25-99 years), and the majority (n=33, 61.1%) were women. Incidental GBCA was detected in 18 patients (33.3%). The overall and recurrence-free survival rates were 63.3% and 55.8% at 3 years and 58.4% and 51.3% at 5 years, respectively. In multivariate analysis, postoperative intra-abdominal complications (p=0.015), non-curative resection (p=0.008), worse histological type (p=0.003), and elevated mGPS (p=0.002) were independent predictors of worse overall survival. Surgical complications (p=0.015), non-curative resection (p=0.005), worse histological type (p=0.002), and elevated mGPS (p=0.022) were also independent predictors of worse recurrence-free survival. Conclusion: Curative resection was important for long-term survival for GBCA. A high preoperative mGPS and occurrence of surgical complications were independent prognostic indicators of poor survival in GBCA.*

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Key Words: Gallbladder carcinoma, postoperative complication, modified Glasgow prognostic score, survival.

Progress in anesthesiology, perioperative management, and radiological intervention has made it possible to treat patients with gallbladder carcinoma (GBCA). Nonetheless, the prognosis of GBCA remains unsatisfactory, with reported 5-year survival rates below 20% (1, 2). GBCA is a relatively rare disease compared to gastrointestinal carcinoma; however, its incidence has been increasing worldwide as the most common malignant biliary neoplasm and seventh-most common type of gastrointestinal cancer (3).

Lymph node (LN) metastasis, poor tumor differentiation, and non-curative resection have been reported as independent predictors of poor prognosis following surgical resection in patients with GBCA (4-8). Although negative effects of preoperative inflammation associated with GBCA have been encountered in clinical settings, there is strong evidence that systemic inflammation plays an important role in cancer progression (2, 9). Inflammation-associated cytokines promote tumor development; interleukin-6, interleukin-1 and epidermal growth factor receptor are well-known factors produced by tumors and immune cells in the tumor environment (10). Serum C-reactive protein (CRP) and albumin levels are influenced by these pro-inflammatory cytokines, leading to hypoalbuminemia and elevated CRP (11, 12). Preoperative CRP concentration and hypoalbuminemia could be related to the dismal long-term outcomes after resection with curative intent in various cancer types (2, 13). Among several predictive prognostic scores, including the Glasgow prognostic score (GPS), neutrophil-to-lymphocyte ratio, and modified GPS (mGPS), the assessment of patient prognosis by mGPS was shown to be effective in several cancer types (14-17). However, the relationship between mGPS and GBCA patient prognosis has not been reported to our knowledge.

Postoperative intra-abdominal complications negatively impacted long-term outcomes in patients with colorectal,

Table I. *Univariate and multivariate analysis of prognostic factors for overall survival in patients with gallbladder carcinoma following curative resection (n = 54).*

Variable				Univariate analysis	Multivariate analysis		
	N (%)	3-Year survival	5-Year survival	*p*-Value	HR	95% CI	*p*-Value
Gender							
Male	21 (38.9%)	61.0%	53.3%	0.983			
Female	33 (61.1%)	64.9%	57.2%				
Median age							
<74 Years	26 (48.1%)	63.4%	58.5%	0.520			
≥74 Years	28 (51.9%)	63.2%	53.0%				
Concomitant ADM							
No	48 (88.9%)	65.1%	56.4%	0.791			
Yes	6 (11.1%)	50.0%	50.0%				
Concomitant GB stone							
No	38 (70.4%)	59.0%	52.5%	0.441			
Yes	16 (29.6%)	73.9%	64.6%				
Abdominal pain							
None	33 (61.1%)	72.4%	68.8%	0.045	1.210	0.421-3.477	0.724
Present	21 (38.9%)	47.1%	29.4%				
Anomalous arrangement of the pancreaticobiliary ducts							
No	45 (83.3%)	55.4%	48.9%	0.113			
Yes	9 (16.7%)	100%	87.5%				
Incidental GB cancer							
No	36 (66.7%)	65.6%	55.3%	0.883			
Yes	18 (33.3%)	57.4%	57.4%				
Preoperative CA19-9							
<35 U/ml	33 (63.5%)	74.3%	65.0%	0.048	3.010	0.743-12.187	0.123
≥35 U/ml	19 (36.5%)	45.9%	40.2%				
Preoperative CEA							
<5 ng/ml	44 (84.6%)	71.3%	62.1%	0.012	1.146	0.397-3.308	0.801
≥5 ng/ml	8 (15.4%)	25.0%	25.0%				
Bile duct reconstruction							
Without	33 (61.1%)	68.0%	59.2%	0.438			
With	21 (38.8%)	56.4%	50.8%				
Lymphadenectomy							
No	19 (35.2%)	62.3%	62.3%	0.696			
Yes	35 (64.8%)	63.9%	51.6%				
Median operation time							
<286min	27 (50.0%)	72.0%	54.8%	0.618			
≥286min	27 (50.0%)	55.3%	55.3%				
Median bleeding volume							
<255 ml	27 (50.0%)	76.0%	64.1%	0.152			
≥255ml	27 (50.0%)	51.5%	42.9%				
Complications (Clavien-Dindo ≥3a)							
None	43 (79.6%)	70.9%	61.7%	0.015	4.777	1.352-16.880	0.015
Present	11 (20.4%)	32.7%	32.7%				
Resection							
R0	43 (79.6%)	71.5%	65.6%	0.003	5.462	1.571-18.990	0.008
R1, 2	11 (20.4%)	25.0%	12.5%				
Histological type							
Pap/well	49 (90.7%)	67.8%	62.1%	<0.001	8.491	2.103-34.279	0.003
Mod/poor/other	5 (9.3%)	20.0%	0%				
Lymph duct invasion							
None	33 (61.1%)	71.8%	71.8%	0.022	1.600	0.431-5.938	0.482
Present	21 (38.3%)	50.0%	26.8%				
Lymph node metastasis							
None	14 (25.9%)	68.9%	65.6%	0.026	1.119	0.194-6.448	0.900
Present	40 (74.1%)	46.4%	24.8%				

Table I. *Continued*

Table I. *Continued*

Variable				Univariate analysis		Multivariate analysis	
	N (%)	3-Year survival	5-Year survival	*p*-Value	HR	95% CI	*p*-Value
pTNM classification							
1/2	32 (63.3%)	74.5%	70.6%	0.015	0.834	0.153–4.548	0.834
3/4	22 (36.7%)	46.3%	31.7%				
Postoperative adjuvant chemotherapy							
No	40 (74.1%)	67.0%	59.9%	0.518			
Yes	14 (25.9%)	50.8%	42.3%				
GPS							
0	43 (79.6%)	65.7%	56.0%	0.658			
1, 2	11 (20.4%)	54.5%	54.5%				
mGPS							
0	48 (88.9%)	69.5%	60.9%	0.009	4.670	1.272–17.153	0.020
1, 2	6 (11.1%)	16.7%	16.7%				
NLR							
<2	21 (39.6%)	68.3%	54.6%	0.550			
≥2	32 (60.4%)	58.8%	54.6%				

ADM, Adenomyomatosis; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; Pap/well: papillary/well-differentiated adenocarcinoma; Mod/poor/other: moderately/poorly differentiated adenocarcinoma/other types; CI, confidence interval; GB, gallbladder; GPS, Glasgow prognostic score; HR, hazard ratio; mGPS, modified GPS; NLR, neutrophil to lymphocyte ratio; pTNM, pathological tumor-node-metastasis.

esophageal, and gastric cancer (18-21). In regard to GBCA, there have been no reports indicating whether postoperative abdominal complications have a negative impact on long-term outcomes. Concerns have been raised as to whether immune system suppression caused by preoperative systemic inflammation and surgical complications might promote cancer seeding.

Therefore, it is important to evaluate the prognostic power of mGPS and surgical complications in patients with GBCA who undergo curative resection, in order to select the patients who will gain the maximal benefit from surgical interventions. The objective of this study was to elicit potential predictors of long-term survival of patients with GBCA.

Patients and Methods

Patients. A retrospective study spanning an 18-year period from January 1996 to December 2014 was performed, and a total of 65 consecutive inpatients were identified. Eleven patients were excluded from this study: three who underwent palliative surgery and eight due to the loss of clinical data. Clinical data, tumor characteristics, and survival outcome were reviewed retrospectively. The study was approved by the local Institutional Review Board (no. 27-10) after informed consent was obtained from all patients.

Surgical procedure. Our strategy for curative resection included simple cholecystectomy for T1 GBCA and extended cholecystectomy with regional LN dissection, with or without wedge resection of the gallbladder bed for T2 GBCA. In the case of invasion of the cystic duct or the hepatoduodenal ligament, or on suspicion of metastatic hepatoduodenal LN, extrahepatic bile duct resection was performed. Liver segments IVa and V were indicated when cancer directly invaded the liver bed, and right hepatectomy when it had invaded the right Glisson's capsule. Regional LN dissection included the common hepatic artery (LN#8), proper hepatic artery (#LN12a), bile duct (#LN12b), portal vein (#LN12p), and retropancreatic LNs (LN#13). If the tumor invasion was T2 or more after simple cholecystectomy, hepatic wedge resection with LN dissection was additionally performed. Tumor staging was performed according to the pathological tumor node metastasis (pTNM) classification, based on the International Union Against Cancer TNM classification (22).

Definitions of the modified GPS and other scores. The following possible prognostic factors were examined with respect to overall and recurrence-free survival: mGPS, age, sex, presence of adenomyomatosis and gallbladder stone, clinical symptoms, anomalous arrangement of the pancreaticobiliary ducts, tumor size, number of tumors, tumor differentiation, microvascular invasion, serum carbohydrate antigen 19-9 (CA19-9), serum carcino-embryonic antigen (CEA) level, bile duct reconstruction, lymphadenectomy, duration of surgery, estimated blood loss, complication, and success of resection. Prior to the operation, blood samples were collected, and routine laboratory analyses of CRP and albumin levels were performed. Values for mGPS were calculated as follows: patients with elevated CRP (defined as >1.0 mg/dl) received a score of 1 or 2 depending on the presence or absence of hypoalbuminemia (<3.5 g/dl); patients without elevated CRP levels were assigned a score of 0.

Morbidity and complications. Complications were defined according to the method described by Clavien *et al*. (23). In this study,

Table II. *Univariate and multivariate analysis of prognostic factors for recurrence-free survival in patients with gallbladder carcinoma following curative resection (n=54).*

Variable				Univariate analysis	Multivariate analysis		
	N (%)	3-Year survival	5-Year survival	*p*-Value	HR	95% CI	*p*-Value
Gender							
Male	21 (38.9%)	61.2%	54.4%	0.651			
Female	33 (61.1%)	56.7%	49.6%				
Median age							
<74 Years	26 (48.1%)	60.9%	56.2%	0.403			
≥74 Years	28 (51.9%)	56.0%	46.2%				
Concomitant ADM							
No	48 (88.9%)	59.5%	51.2%	0.995			
Yes	6 (11.1%)	50.0%	50.0%				
Concomitant GB stone							
No	38 (70.4%)	54.6%	48.2%	0.441			
Yes	16 (29.6%)	68.2%	59.7%				
Abdominal pain							
None	33 (61.1%)	69.7%	62.5%	0.051			
Present	21 (38.9%)	44.4%	29.6%				
Anomalous arrangement of the pancreaticobiliary ducts							
No	45 (83.3%)	52.5%	46.7%	0.173			
Yes	9 (16.7%)	87.5%	75.0%				
Incidental GB cancer							
No	36 (66.7%)	60.7%	50.6%	0.980			
Yes	18 (33.3%)	53.8%	53.8%				
Preoperative CA19-9							
<35 U/ml	33 (63.5%)	69.4%	56.9%	0.158			
≥35 U/ml	19 (36.5%)	40.2%	40.2%				
Preoperative CEA							
<5 ng/ml	44 (84.6%)	65.1%	56.5%	0.041	3.394	0.991-11.616	0.052
≥5 ng/ml	8 (15.4%)	25.0%	25.0%				
Bile duct reconstruction							
Without	33 (61.1%)	59.7%	55.7%	0.541			
With	21 (38.8%)	56.4%	44.4%				
Lymphadenectomy							
No	19 (35.2%)	62.3%	62.3%	0.402			
Yes	35 (64.8%)	56.3%	44.7%				
Median operation time							
<286 min	27 (50.0%)	66.4%	49.8%	0.482			
≥286 min	27 (50.0%)	49.2%	49.2%				
Median bleeding volume							
<255 ml	27 (50.0%)	61.9%	61.9%	0.098			
≥255 ml	27 (50.0%)	49.0%	32.6%				
Complications (Clavien-Dindo ≥3a)							
None	43 (79.6%)	64.5%	56.0%	0.041	4.437	1.341-14.66	0.015
Present	11 (20.4%)	32.7%	32.7%				
Resection							
R0	43 (79.6%)	66.9%	60.9%	0.001	4.976	1.616-15.328	0.005
R1, 2	11 (20.4%)	11.4%	11.4%				
Histological type							
Pap/well	49 (90.7%)	64.7%	56.8%	0.000	8.338	2.129-32.661	0.002
Mod/poor/other	5 (9.3%)	0%	0%				
Lymph duct invasion							
None	33 (61.1%)	69.4%	65.8%	0.029	1.471	0.425-5.098	0.543
Present	21 (38.3%)	40.6%	27.1%				
Lymph node metastasis							
None	14 (25.9%)	67.0%	63.8%	0.004	1.034	0.196-5.456	0.969
Present	40 (74.1%)	35.7%	13.4%				

Table II. *Continued*

Table II. *Continued*

Variable				Univariate analysis		Multivariate analysis	
	N (%)	3-Year survival	5-Year survival	*p*-Value	HR	95% CI	*p*-Value
pTNM classification							
1/2	32 (63.3%)	71.7%	68.0%	0.006	1.004	0.254–3.969	0.996
3/4	22 (36.7%)	38.5%	24.1%				
Postoperative adjuvant chemotherapy							
No	40 (74.1%)	67.0%	60.3%	0.087			
Yes	14 (25.9%)	35.7%	28.6%				
GPS							
0	43 (79.6%)	59.6%	50.5%	0.869			
1, 2	11 (20.4%)	54.5%	54.5%				
mGPS							
0	48 (88.9%)	63.8%	55.7%	0.024	4.404	1.244–15.597	0.022
1, 2	6 (11.1%)	16.7%	16.7%				
NLR							
<2	21 (39.6%)	55.9%	49.7%	0.761			
≥2	32 (60.4%)	58.8%	51.0%				

ADM, Adenomyomatosis; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; Pap/well: papillary/well-differentiated adenocarcinoma; Mod/poor/other: moderately/poorly differentiated adenocarcinoma/other types; CI, confidence interval; GB, gallbladder; GPS, Glasgow prognostic score; HR, hazard ratio; mGPS, modified GPS; NLR, neutrophil to lymphocyte ratio; pTNM, pathological tumor node metastasis.

postoperative complications were defined as those that were grade IIIA or greater, while postoperative mortality was defined as any death occurring within 30 days of surgery.

Statistical analyses. The Kaplan–Meier method was used to analyze overall and disease-free survival; the log-rank test was used to compare different groups. Multivariate analyses were used to assess factors influencing overall and disease-free survival using Cox's regression model. *p*-Values less than 0.05 were considered significant. Calculations were performed using SPSS software (version 22; IBM Corp., Armonk, NY, USA).

Results

Patient characteristics and surgical complications. Clinicopathological characteristics are summarized in Table I. Overall, 54 patients underwent resection with curative intent for GBCA at the Department of Surgery of Onomichi General Hospital during the study period. The median follow-up period after surgery was 3.0 years (range=0.04-13.8 years). The patient population included 21 men and 33 women, with a median age of 74 years (range=25-99 years). Operative procedures consisted of cholecystectomy in 23 cases (42.6%), including lymphadenectomy in six and bile duct resection in three, and liver bed resection in 24 (46.3%), including a secondary operation after diagnosis of GBCA by cholecystectomy with hepatic resection of segment 4a and segment 5 in four (7.4%), extended right lobectomy in two (3.7%), and central bisegmentectomy in one (1.9%). Lymphadenectomy was performed in 35 patients (64.8%), and bile duct reconstruction in 21 (38.9%). mGPS was 0 in 48 patients (88.9%).

In regard to surgical complications, postoperative complications (Clavien-Dindo ≥IIIA) occurred in 11 patients (20.4%), including anastomosis leakage in five (9.3%), abdominal abscess in two (3.7%), septic shock in three (5.6%), and massive postoperative bleeding in one (1.9%). The 1-, 3-, and 5-year survival rates of the 54 patients who underwent resection with curative intent were 83.1%, 63.3%, and 55.8%, respectively. Recurrence was observed in 15 patients (27.8%): four had hepatic recurrence, nine had LN recurrence, and two had peritoneal dissemination. The 1-, 3-, and 5-year recurrence-free survival rates of the whole group were 77.8%, 58.4%, and 51.3%, respectively.

Prognostic variables for overall and recurrence-free survival in univariate and multivariate analyses. In univariate analysis, abdominal pain, preoperative CA19-9 ≥35 U/ml, preoperative CEA ≥5 ng/ml, complication, non-curative resection, poor histological type, pathological lymph duct invasion, LN metastasis, pTNM classification (22), and mGPS of 1 or 2 were significant risk factors for poor overall survival. In multivariate analysis, independent factors indicating poor prognosis included mGPS of 1 or 2 (p=0.020), non-curative resection (p=0.008), moderately/poorly differentiated/other histological type (p=0.003), and occurrence of postoperative complication (p=0.015; Table I). There was no significant difference between patients with mGPS of 0 and mGPS of 1. Compared with patients with mGPS of 0, patients with mGPS of 1 or 2 had a worse prognosis (Figure 1A). Classification

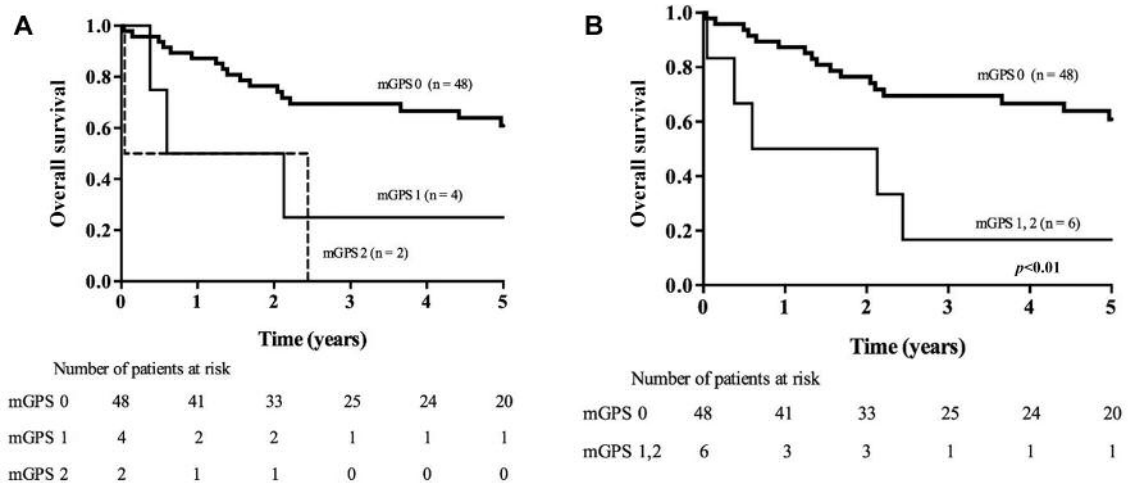

Figure 1. *Overall survival according to modified Glasgow prognostic score (mGPS) status. A: Overall survival curves after surgery with curative intent according to mGPS. There was no significant difference between patients with mGPS 0 and 1. B: The mGPS-negative group (mGPS 0) significantly differed from the mGPS-positive group (mGPS 1 or 2) (p<0.01).*

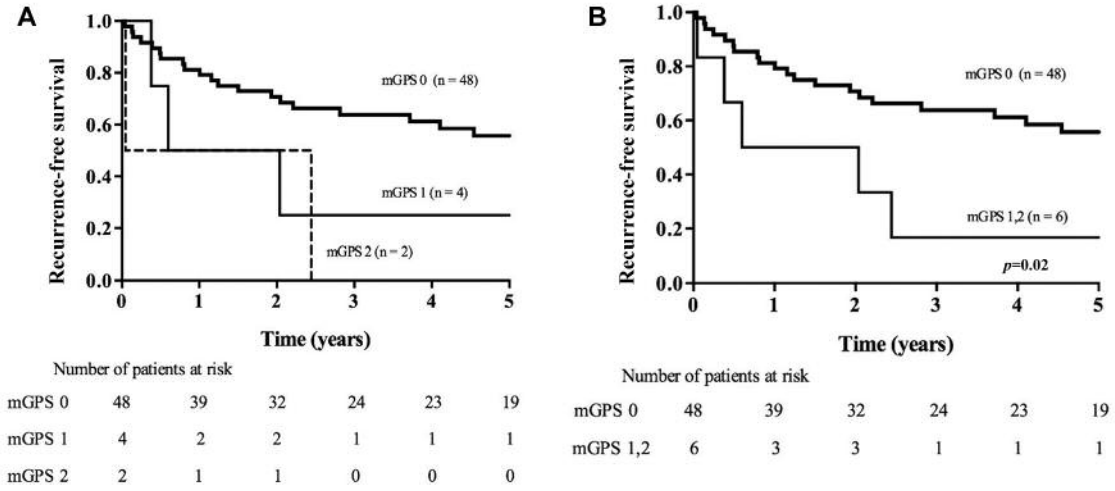

Figure 2. *Recurrence-free survival according to modified Glasgow prognostic score (mGPS) status. A: Recurrence-free survival curves showing the relationship between recurrence-free survival and mGPS in patients after surgery. Patients with mGPS of 1 and 2 had a similar prognosis after surgery. B: The mGPS-negative (mGPS0) group significantly differed from the mGPS-positive group (mGPS 1 or 2) (p=0.02).*

with an mGPS of 0 *versus* an mGPS of 1 or 2 had a strong impact on overall patient survival (p<0.01; Figure 1B).

In univariate analysis, preoperative CEA ≥5 ng/ml, complication, curative resection, poor histological type, pathological lymph duct invasion, LN metastasis, pTNM classification, and mGPS of 1 or 2 were significant risk factors for poor recurrence-free survival. In multivariate analysis, prognostic factors included mGPS of 1 or 2 (p=0.022), curative resection (p=0.005), histological type (moderate/poor/other types) (p=0.002), and occurrence of postoperative complication (p=0.015; Table II). On three-group stratification, there were no significant differences between patients with mGPS of 0 and mGPS of 1 (Figure 2A). Classification with mGPS of 0 *versus* mGPS of 1 or 2 had a strong impact on recurrence-free survival (p=0.020; Figure 2B).

Discussion

Survival after surgical resection for patients with GBCA depends heavily on disease stage and whether curative

resection is achieved. In this single-institution, retrospective analysis of patients with GBCA who underwent surgery with curative intent, we identified postoperative intra-abdominal complications, non-curative resection, poor histological type, and elevated mGPS score as independent predictors of worse overall survival. Postoperative complications, non-curative resection, poor histological type, and elevated mGPS score were independent predictors of worse recurrence-free survival.

Previous reports demonstrated that cancer-related inflammation has a negative impact on the prognosis of patients after surgery for GBCA (2, 9). Consistent with those findings, our study showed that elevated mGPS was associated with worse long-term survival. Among several independent prognostic variables, mGPS can be obtained preoperatively and it is easy to identify patients with elevated mGPS scores. To the best of our knowledge, this study is the first to report the relationship between surgical outcomes of GBCA and mGPS.

We previously found that GPS positivity (GPS>0) has a negative impact on the prognosis of patients with hepatocellular carcinoma who underwent living-donor liver transplantation (24). In general, patients with hepatocellular carcinoma have severe liver dysfunction, with reduced liver production of albumin and CRP. In contrast, GBCA occurrence is not related to liver cirrhosis, and patients with GBCA have a comparatively normal liver.

An advantage of mGPS is that it can be used to predict outcomes preoperatively. The criteria for mGPS are strictly determined by serum CRP, not albumin. Several advocates of the mGPS point out that it has a superior predictive power compared to GPS in patients with hepatocellular carcinoma and colorectal carcinoma since serum albumin is influenced by several factors (14, 15).

The mechanism underlying the relationship between elevated mGPS and poor patient prognosis remains unclear. Several reports have suggested that postoperative infectious complications are highly associated with mGPS elevation due to deterioration of immune cell activity (25, 26). In our study, it is of interest that the postoperative infectious complication rate was similar across mGPS scores. However, the long-term prognosis was dismal in patients who had a postoperative complication, suggesting that the perioperative innate immune system could play an important role in predicting tumor recurrence. Tumor-derived, inflammation-related cytokines have a negative impact on tumor recurrence and survival. Combined with pathological findings, mGPS could be helpful to select appropriate patients who are at high risk of tumor recurrence, even though there is no established adjuvant chemotherapy for GBCA after surgery (27).

Surgical complication was also an indicator for poor prognosis. Anastomotic leakage was the main surgical complication, which can allow seeding of viable cancer cells (28, 29). Another possibility is that complications influence the suppression of immune cell activity, leading to enhanced metastatic growth. Surgical stress and tissue damage by themselves can compromise natural killer cells, which possess high antitumor activity (30). Thus, an elevated mGPS score and postoperative intra-abdominal complications are both strongly related to host immune activity. To prevent surgical complications, a multimodal approach is necessary to increase the likelihood of early recovery from surgery.

This study has several limitations. This was a retrospective, single-center study. Secondly, only six patients had an mGPS greater than 0; the distribution of patient preoperative parameters could make it difficult to elucidate the relationship between preoperative inflammatory state and mGPS. Future prospective cohort studies including multiple institutions are necessary to clarify these potential cross-interaction mechanisms.

Conclusion

The presence of preoperative systemic inflammation has a strong impact on long-term prognosis in patients with GBCA. The preoperative mGPS evaluation is a simple and effective means to predict long-term outcomes in patients with GBCA following surgery with curative intent. Postoperative intra-abdominal complications affect long-term prognosis, even after curative surgery. Surgeons should take meticulous care to prevent and reduce complications.

Conflicts of Interest

There is no conflict of interest to disclose.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

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