





ORIGINAL ARTICLE

Significance of intra/post-operative prognostic scoring system in hepatectomy for colorectal liver metastases

Kenei Furukawa  | Shinji Onda | Mitsuru Yanagaki | Tomohiko Taniai |
Ryoga Hamura | Koichiro Haruki  | Yoshihiro Shirai  | Masashi Tsunematsu |
Taro Sakamoto | Toru Ikegami 

Division of Hepatobiliary and Pancreas Surgery, Department of Surgery, The Jikei University School of Medicine, Tokyo, Japan

Correspondence

Kenei Furukawa, Department of Surgery, The Jikei University School of Medicine, 3-25-8, Nishi-Shinbashi, Minato-ku, Tokyo 105-8461, Japan.
Email: k-furukawa@jikei.ac.jp

Abstract

Aim: The prognostic impact of postoperative systemic inflammatory response using an intra/post-operative prognostic scoring system in patients with colorectal liver metastases (CRLM) after hepatic resection had never been investigated previously.

Methods: In total, 149 patients who underwent hepatic resection for CRLM were analyzed retrospectively. Intra/post-operative prognostic scoring was performed using the postoperative modified Glasgow Prognostic Score (mGPS) at the first visit, after discharge, or a month after surgery during hospitalization. We investigated the association between clinicopathologic variables and disease-free survival or overall survival by univariate and multivariate analyses.

Results: The median evaluation period of postoperative mGPS was 30 (26-36) days after hepatectomy. Seventy-one patients (48%) were classified as postoperative day 30 mGPS 1 or 2. In multivariate analysis, an extrahepatic lesion ($P = .02$), multiple tumors ($P = .05$), and postoperative day 30 mGPS 1 or 2 ($P < .01$) were independent and significant predictors of disease-free survival. Moreover, extrahepatic lesion ($P = .04$), and postoperative day 30 mGPS 1 or 2 ($P = .02$) were independent and significant predictors for overall survival. Patients with postoperative day 30 mGPS 1 or 2 had significantly more advanced tumors, more invasive surgery, and more chances of infectious postoperative complications than those with postoperative day 30 mGPS 0.

Conclusion: Postoperative systemic inflammatory response, as evidenced by intra/post-operative prognostic scoring system using postoperative day 30 mGPS, was a strong predictor for outcomes in patients who underwent liver resection for CRLM.

KEYWORDS

colorectal liver metastases, Glasgow Prognostic Score, hepatic resection, prognostic factor, systemic inflammatory response

1 | INTRODUCTION

Colorectal cancer is the third most common cancer worldwide, and the fourth leading cause of cancer-related death.¹ The liver is the most common site for metastases from colorectal cancer, and approximately 15% of patients with colorectal cancer liver metastases (CRLM) present with a liver lesion at the initial diagnosis (synchronous metastasis), and a further 40%-50% will develop metachronous CRLM after the primary tumor resection.²

Liver resection is the only treatment that can provide the possibility of prolonged survival for patients with CRLM, the 10-year survival rate following such operations is 22%-38.5%.³⁻⁵ Despite advances in systemic therapy, a considerable number of patients with CRLM still develop recurrence even after curative resection, leading to high mortality rates. Thus, it is important to identify reliable predictive factors for patients with CRLM after hepatic resection, for a better prognosis.^{4,5}

A systemic inflammatory response is strongly linked to cancer development, progression, and metastasis resulting in poor prognosis.⁶ Many studies have demonstrated a strong association between preoperative systemic inflammatory response and prognosis in various malignancies,^{7,8} including CRLM.⁹ However, only a few reports have shown the impact of the postoperative systemic inflammatory response on prognosis in cancer patients.

The negative impact of postoperative complications on the long-term outcomes has been reported in patients who underwent resection for malignancies.^{10,11} Postoperative complications are among the major factors that could cause postoperative inflammation and systemic inflammatory response, which may create a favorable environment for faster progression of microscopic cancer and immunosuppression,¹² leading to poor prognosis. Therefore, not only preoperative but also postoperative systemic inflammatory response should be focused on as a prognostic marker.

This study aimed to determine whether postoperative systemic inflammatory response impacts the outcome, using intra/post-operative prognostic scoring system in patients with CRLM after hepatic resection.

2 | METHODS

2.1 | Patients

We retrospectively analyzed 149 patients with CRLM who underwent initial hepatic resection at the Department of Surgery, Jikei University Hospital, Tokyo, Japan, between June 2002 and December 2018. We excluded patients with two-stage hepatectomy, other malignancies, and lack of data. The patients' characteristics, surgical and pathological findings, and postoperative clinical courses were reviewed from medical records and databases at our institution.

This study was approved by the Ethics Committee of the Jikei University School of Medicine (27-177). All data were subject to strict

privacy policies. The requirement for the acquisition of informed consent from patients was waived because of the retrospective nature of this study and the anonymized data.

2.2 | Treatment and patient management

All patients with no unresectable extrahepatic tumor underwent hepatic resection regardless of the size, number, or location of liver metastases as long as curative resection would leave sufficient remnant liver. Generally, parenchymal-sparing hepatectomy was performed. Anatomical resection included lobectomy, extended lobectomy, segmentectomy, or sub-segmentectomy and non-anatomical resection included limited partial resection. Neoadjuvant chemotherapy was given when liver metastases were unresectable or borderline.

The infectious postoperative complication was defined as a condition wherein purulent discharge was observed with or without microbiological evidence in the incision or in an organ or space, which occurred within 30 days after surgery. Organ or space infection was determined by radiologic evidence of a fluid collection necessitating antibiotic therapy or drainage.

The date of the first visit was set 2 or 3 weeks after discharge. The surveillance after surgery was performed using tumor markers every 3 months, and chest and abdominal contrast-enhanced computed tomography (CT) or gadoxetic acid-enhanced magnetic resonance imaging (MRI) were performed every 6 months. Recurrence of colorectal cancer after hepatic resection for CRLM was defined as newly detected local or distant metastatic tumors on radiographic imaging with or without an increase in serum carcinoembryonic antigen (CEA) or carbohydrate antigen 19-9 (CA19-9). For recurrent tumors, resection, radiotherapy, or systemic chemotherapy with or without molecular-targeted agents, depending on the patient's performance status, genetic test results, and previous treatment regimens, was performed.

2.3 | Systemic inflammatory response

The systemic inflammatory response was represented by the Japanese modified Glasgow Prognostic Score (mGPS).^{13,14} Intra/post-operative prognostic scoring was assessed using postoperative mGPS. The mGPS was defined by albumin (Alb) and C-reactive protein (CRP) as follows: patients with normal Alb (≥ 3.5 mg/dL) and normal CRP (≤ 0.5 mg/dL) levels were scored an mGPS of 0, low Alb (< 3.5 mg/dL) or elevated CRP (> 0.5 mg/dL) levels as an mGPS of 1, and both low Alb (< 3.5 mg/dL) and elevated CRP (> 0.5 mg/dL) levels as an mGPS of 2. Preoperative mGPS was assessed within 30 days before surgery, while postoperative mGPS was assessed at the first visit after discharge or a month after surgery during hospitalization.

2.4 | Analyses of risk factors for recurrence and overall survival

We investigated the association between clinicopathologic variables and disease-free survival, or overall survival after initial liver resection by univariate and multivariate analyses. The clinicopathological data included location, T factor and regional lymph node metastases of primary colorectal cancer, the timing of tumor (synchronous or metachronous CRLM), extrahepatic lesion, tumor number, tumor size, preoperative mGPS, intraoperative transfusion, curability (R1, R2 or R0), infectious complication, and postoperative Alb, CRP, and mGPS. A right-sided colorectal cancer was defined as that located in the cecum, ascending, and transverse colon, while that located within the splenic flexure and beyond was defined as left-sided colorectal cancer. Tumor size was classified into two groups (≥ 50 or < 50 mm) for the Cox proportional hazard regression model based on the H factor, in the Japanese Society for Cancer of the Colon and Rectum guidelines 2019.¹⁵

Next, we investigated the relationship between clinical variables and postoperative mGPS by univariate analysis. The clinical variables included age, gender, location, T factor and regional lymph node metastases of primary colorectal cancer, the timing of tumor, neoadjuvant chemotherapy, extrahepatic lesion, tumor number, tumor size, serum CEA, preoperative mGPS, operation time, intraoperative blood loss, intraoperative transfusion, surgical procedures, curability, postoperative infectious complication, evaluation period of postoperative mGPS, length of postoperative stay, change of mGPS, and postoperative chemotherapy.

2.5 | Statistical analysis

The data were expressed as the median (interquartile range). The Mann-Whitney *U* and Chi-squared tests were used to compare the continuous and dichotomous variables, respectively. Univariate and multivariate analyses of disease-free and overall survival were performed using the Cox proportional regression model. The survival curve was calculated using the Kaplan-Meier method with the Log-rank test. Area Under Curve (AUC) of postoperative Alb, CRP, and mGPS was determined by receiver operating characteristic (ROC) curves, 3 years after surgery for disease-free and overall survival. Statistical significance was set at *P*-value less than .05.

3 | RESULTS

3.1 | Patients' characteristics

The characteristics including preoperative, intraoperative, and postoperative factors are summarized in Table 1. The median age was 66 years, with a range of 28-90 years. The study included 103 men and 46 women. The median evaluation period of postoperative mGPS was 30 (26-36) days after hepatectomy. In total, 109 patients (73%) and 40 patients (27%) were classified as preoperative mGPS 0 and preoperative mGPS 1 or 2, respectively, while 78 patients (52%) and 71 patients (48%) were

TABLE 1 Patients' characteristics

Variables	Patients (n = 149)
Preoperative factors	
Age, years	66 (58-72)
Gender	
Female	46 (31%)
Male	103 (69%)
BMI, kg/m ²	22.3 (20.2-24.2)
Location	
Right side	46 (31%)
Left side	103 (69%)
T factor	
T1	5 (3%)
T2	6 (4%)
T3	92 (62%)
T4	46 (31%)
Lymph node metastases	
Yes	100 (67%)
No	49 (33%)
Timing of tumor	
Synchronous	92 (62%)
Metachronous	57 (38%)
Neoadjuvant chemotherapy	
Yes	51 (34%)
No	98 (66%)
Extrahepatic lesion	
Yes	33 (22%)
No	116 (78%)
Tumor number	
Solitary	71 (48%)
Multiple	78 (52%)
Tumor size, mm	
	27 (17-43)
Serum CEA, ng/ml	
	11.7 (4.4-40.6)
Preoperative mGPS, 1 or 2	
0	109 (73%)
1	34 (23%)
2	6 (4%)
Intraoperative factors	
Operation time, min	369 (275-479)
Intraoperative blood loss, ml	480 (169-1063)
Intraoperative transfusion	
Yes	35 (23%)
No	114 (77%)
Simultaneous resection	
Yes	42 (28%)
No	107 (72%)

(Continues)

TABLE 1 (Continued)

Variables	Patients (n = 149)
Surgical approach	
Open	127 (85%)
Laparoscopic	22 (15%)
Hepatectomy	
Lobectomy	45 (30%)
Segmentectomy	24 (16%)
Subsegmentectomy	8 (5%)
Partial hepatectomy	72 (48%)
Curability	
R0	127 (85%)
R1 or 2	22 (15%)
Postoperative factors	
Infectious complication	
Yes	16 (11%)
No	133 (89%)
Postoperative day 30 mGPS	
0	78 (52%)
1	32 (21%)
2	39 (26%)
Evaluation period of postoperative mGPS, days after hepatectomy	
30 (26-36)	
Change of mGPS	
Improved	16 (11%)
No changed	78 (52%)
Worsened	55 (37%)
Length of postoperative stay, days	
12 (10-17)	
Postoperative chemotherapy	
Yes	92 (62%)
No	57 (38%)

Abbreviations: CEA, carcinoembryonic antigen; mGPS, modified Glasgow Prognostic Score.

classified as postoperative mGPS 0 and postoperative mGPS 1 or 2, respectively. Before and after surgery, mGPS improved in 16 (11%), did not change in 78 (52%), and worsened in 55 (37%).

The median follow-up duration for disease-free and overall survival were 1.00 (0.46-2.53) and 3.00 (2.04-5.84) years, respectively. In this study, the 3-year disease-free and overall survival rates after hepatic resection for CRLM were 29% and 72%, respectively.

3.2 | Univariate and multivariate disease-free survival analyses of patients after hepatic resection for CRLM

Table 2 shows the association between the clinicopathological characteristics and disease-free survival after hepatic resection for CRLM.

In univariate analysis, the disease-free survival was significantly worse in patients with lymph node metastases ($P < .01$), extrahepatic lesion ($P = .02$), multiple tumors ($P = .02$), intraoperative transfusion ($P = .03$), curability R1 or 2 ($P = .03$), and postoperative day 30 mGPS 1 or 2 ($P < .01$). In multivariate analysis, an extrahepatic lesion (hazard ratio 1.82, 95% confidence interval 1.10-3.03, $P = .02$), multiple tumors (hazard ratio 1.50, 95% confidence interval 1.01-2.24, $P = .05$), and postoperative day 30 mGPS 1 or 2 (hazard ratio 1.78, 95% confidence interval 1.19-2.67, $P < .01$) were independent and significant predictors for disease-free survival.

3.3 | Univariate and multivariate overall survival analyses of patients after hepatic resection for CRLM

Table 3 shows the association between the clinicopathological characteristics and overall survival after hepatic resection for CRLM. In univariate analysis, the overall survival was significantly worse in patients with T4 ($P = .02$), lymph node metastases ($P < .01$), extrahepatic lesion ($P = .03$), intraoperative transfusion ($P < .01$), infectious complication ($P < .01$), and postoperative day 30 mGPS 1 or 2 ($P < .01$). In multivariate analysis, an extrahepatic lesion (hazard ratio 1.93, 95% confidence interval 1.02-3.66, $P = .04$), and postoperative day 30 mGPS 1 or 2 (hazard ratio 2.05, 95% confidence interval 1.14-3.70, $P = .02$) were independent and significant predictors for overall survival.

3.4 | Impact of preoperative and postoperative mGPS for disease-free and overall survival after hepatic resection for CRLM

The disease-free and overall survival of patients with preoperative mGPS 1 or 2 were not significantly lower than those of patients with mGPS 0 (log-rank $P = .36$, 0.23, respectively) (Figure 1A,B).

The disease-free survival of patients with postoperative day 30 mGPS 1 or 2 was significantly lower than that of patients with postoperative day 30 mGPS 0 (log-rank $P < .01$; 3-year survival, 17.2% vs 39.6%) (Figure 1C). The overall survival of patients with postoperative day 30 mGPS 1 or 2 was significantly lower than that of patients with postoperative day 30 mGPS 0 (log-rank $P < .01$; 3-year survival, 58.8% vs 82%) (Figure 1D).

3.5 | Impact of perioperative change of mGPS for disease-free and overall survival after hepatic resection for CRLM

The disease-free survival and overall survival of patients with worsened mGPS before and after surgery was significantly lower than that of patients with non-worsened mGPS before and after surgery (log-rank $P = .02$; 3-year survival, 18% vs 35.7% and log-rank $P = .02$; 3-year survival, 58.6% vs 78.3%, respectively) (Figure 2A,B).

TABLE 2 Univariate and multivariate analyses of clinicopathological variables in relation to disease-free survival after hepatic resection for colorectal liver metastases

Variables	N	DFS univariate analysis		DFS multivariate analysis	
		Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Preoperative factors					
Location					
Right side	46	0.85	.45		
Left side	103	(0.56-1.30)			
T factor					
T1 or 2 or 3	103	0.83	.37		
T4	46	(0.55-1.25)			
Lymph node metastases					
Yes	100	1.81	<.01	1.54	.07
No	49	(1.16-2.82)		(0.97-2.43)	
Timing of tumor					
Synchronous	92	1.36	.14		
Metachronous	57	(0.91-2.04)			
Extrahepatic lesion					
Yes	23	1.84	.02	1.82	.02
No	126	(1.12-3.03)		(1.10-3.03)	
Tumor number					
Multiple	78	1.57	.02	1.50	.05
Solitary	71	(1.06-2.31)		(1.01-2.24)	
Tumor size, mm					
≥50	29	0.99	.96		
<50	120	(0.60-1.63)			
Preoperative mGPS					
1 or 2	40	1.22	.36		
0	109	(0.80-1.86)			
Intraoperative factors					
Transfusion					
Yes	35	1.58	.03	1.10	.67
No	114	(1.03-2.42)		(0.70-1.73)	
Curability					
R1 or 2	22	1.71	.03	1.40	.20
R0	127	(1.05-2.79)		(0.84-2.34)	
Postoperative factors					
Infectious complication					
Yes	16	1.59	.17		
No	133	(0.84-2.71)			
Postoperative day 30 mGPS					
1 or 2	71	1.73	<.01	1.78	<.01
0	78	(1.17-2.56)		(1.19-2.67)	

Abbreviations: CI, confidence interval; DFS, disease-free survival; mGPS, modified Glasgow Prognostic Score.

TABLE 3 Univariate and multivariate analyses of clinicopathological variables in relation to overall survival after hepatic resection for colorectal liver metastases

Variables	N	OS univariate analysis		OS multivariate analysis	
		Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Preoperative factors					
Location					
Right side	46	0.88	.68		
Left side	103	(0.49-1.59)			
T factor					
T1 or 2 or 3	103	0.54	.02	0.60	.07
T4	46	(0.32-0.91)		(0.34-1.05)	
Lymph node metastases					
Yes	100	2.48	<.01	1.92	.07
No	49	(1.15-4.91)		(0.94-3.91)	
Timing of tumor					
Synchronous	92	1.45	.81		
Metachronous	57	(0.86-2.46)			
Extrahepatic lesion					
Yes	23	1.99	.03	1.93	.04
No	126	(1.07-3.70)		(1.02-3.66)	
Tumor number					
Multiple	78	1.45	.17		
Solitary	71	(0.86-2.46)			
Tumor size, mm					
≥50	29	1.57	.15		
<50	120	(0.84-2.92)			
Preoperative mGPS					
1 or 2	40	1.38	.26		
0	109	(0.79-2.42)			
Intraoperative factors					
Transfusion					
Yes	35	2.17	<.01	1.32	.34
No	114	(1.27-3.72)		(0.74-2.37)	
Curability					
R1 or 2	22	1.38	.40		
R0	127	(0.65-2.93)			
Postoperative factors					
Infectious complication					
Yes	16	2.71	<.01	2.05	.06
No	133	(1.37-5.39)		(0.97-4.32)	
Postoperative day 30 mGPS					
1 or 2	71	2.37	<.01	2.05	.02
0	78	(1.38-4.06)		(1.14-3.70)	

Abbreviations: CI, confidence interval; mGPS, modified Glasgow Prognostic Score; OS, overall survival.

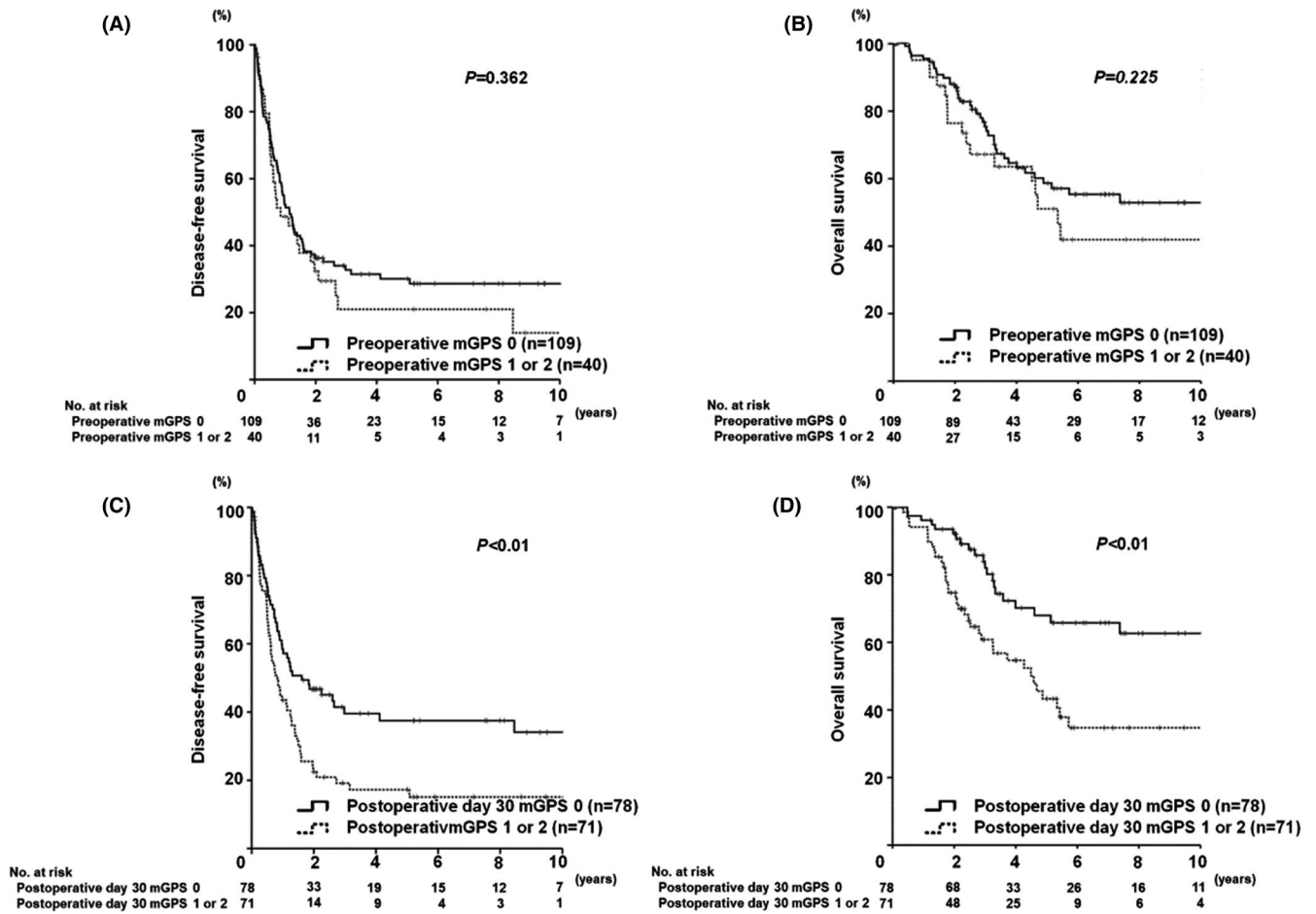


FIGURE 1 A, C, Kaplan-Meier curve for disease-free survival after hepatic resection for colorectal liver metastases. B, D, Kaplan-Meier curve for overall survival after hepatic resection for colorectal liver metastases

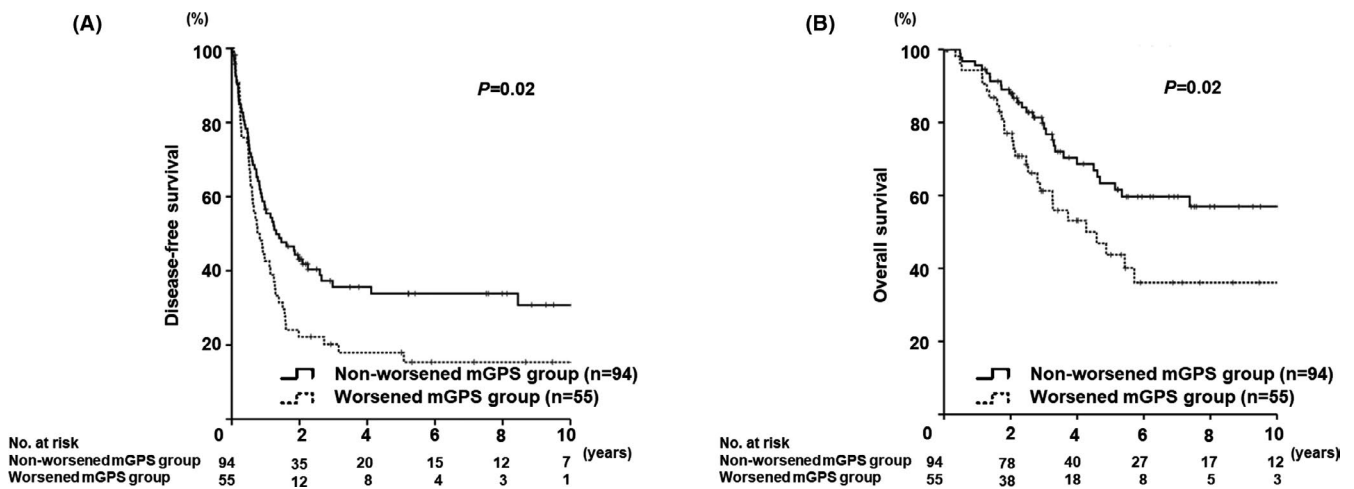


FIGURE 2 The association between prognosis and perioperative change of modified Glasgow Prognostic Score (mGPS) (A) Kaplan-Meier curve for disease-free survival after hepatic resection for colorectal liver metastases. B, Kaplan-Meier curve for overall survival after hepatic resection for colorectal liver metastases

3.6 | Association between clinical variables and postoperative mGPS

Table 4 lists the association between clinicopathological characteristics and postoperative mGPS. In the univariate analysis, patients with mGPS 1 or 2 on postoperative day 30 had a significantly larger tumor size (37 vs 21 mm, $P < .01$), higher serum CEA level (21.4 vs 7.3 ng/mL, $P < .01$), longer operative time (430 vs 324 min, $P < .01$), more intraoperative blood loss (800 vs 305 mL, $P < .01$), more intraoperative transfusions (37% vs 12%, $P < .01$), more simultaneous resections (38% vs 19%, $P = .01$), more open hepatectomies (94% vs 77%, $P < .01$), more anatomical hepatectomies (68% vs 37%, $P < .01$), more infectious complications (18% vs 4%, $P < .01$), more worsened mGPS (77% vs 0%, $P < .01$), and longer postoperative stay (15 vs 10 days, $P < .01$) than those with postoperative day 30 mGPS 0. The evaluation period of postoperative mGPS and postoperative chemotherapy were comparable between the two groups.

4 | DISCUSSION

In the present study, we demonstrated that postoperative systemic inflammatory response represented by postoperative day 30 mGPS was independently associated with poor disease-free and overall survival rates after hepatic resection for CRLM. Furthermore, postoperative day 30 mGPS was associated with advanced CRLM, invasive surgery, and infectious postoperative complications. To the best of our knowledge, this is the first report to demonstrate the positive impact of the postoperative systemic inflammatory response on the prognosis of CRLM.

Previously, some studies have investigated postoperative systemic inflammatory response and cancer survival. A CRP level >150 mg/L on postoperative day 4 was reported to be significantly associated with poor long-term outcomes following surgery for colorectal cancer.¹⁶ Furthermore, the peak of postoperative CRP was reported to be an independent prognostic factor in patients with

TABLE 4 Univariate analysis of clinical variables in relation to postoperative day 30 mGPS

Variables	Postoperative day 30 mGPS		P-value
	0 (n = 78)	1 or 2 (n = 71)	
Preoperative factors			
Age, years	65 (57-72)	67 (60-76)	.11
Gender, female	28 (36%)	18 (25%)	.16
Location, right side	27 (35%)	19 (27%)	.30
T factor, T4	54 (69%)	49 (69%)	.98
Lymph node metastases, yes	51 (65%)	49 (69%)	.64
Timing of tumor, synchronous	45 (58%)	47 (66%)	.29
Neoadjuvant chemotherapy, yes	27 (35%)	24 (34%)	.92
Extrahepatic lesion, yes	12 (15%)	11 (15%)	.99
Multiple tumor	42 (54%)	36 (51%)	.70
Tumor size, mm	21 (15-32)	37 (23-60)	<.01
Serum CEA, ng/ml	7.3 (3.7-26.6)	21.4 (6.8-87.2)	<.01
Preoperative mGPS, 1 or 2	14 (18%)	27 (38%)	.01
Intraoperative factors			
Operation time, min	324 (230-422)	430 (301-514)	<.01
Intraoperative blood loss, ml	305 (100-620)	800 (346-1306)	<.01
Intraoperative transfusion, yes	9 (12%)	26 (37%)	<.01
Simultaneous resection, yes	15 (19%)	27 (38%)	.01
Open hepatectomy, yes	60 (77%)	67 (94%)	<.01
Anatomical hepatectomy, yes	29 (37%)	48 (68%)	<.01
Curability, R1 or 2	9 (12%)	13 (18%)	.24
Postoperative factors			
Infectious complication, yes	3 (4%)	13 (18%)	<.01
Evaluation period of postoperative mGPS, days after hepatectomy	31 (26-37)	30 (25-34)	.37
Change of mGPS (improved : no changed : worsened)	14:64 : 0	2:14 : 55	<.01
Length of postoperative stay, days	10 (8-12)	15 (11-26)	<.01
Postoperative chemotherapy	49 (63%)	43 (61%)	.78

Abbreviations: CEA, carcinoembryonic antigen; mGPS, modified Glasgow Prognostic Score.

colorectal cancer¹⁷ and esophageal cancer patients.¹⁸ Shibutani et al showed that neutrophil-lymphocyte ratio a month after surgery was an independent prognostic factor in patients with colorectal cancer.¹⁹ We used mGPS a month after surgery as a postoperative systemic inflammatory response marker in this study.

The mGPS, which is based on both serum elevation of CRP and hypoalbuminemia, can represent systemic inflammatory response.^{13,14} CRP is produced by inflammation-related cytokines such as vascular endothelial growth factor and interleukin (IL)-6.²⁰ Furthermore, the low albumin concentration is in accordance with proinflammatory cytokines such as IL-1, IL-6, and tumor necrosis factor, which modulate albumin production.²¹ Cytokines have been reported to play an important role in cancer progression²² because the cytokine-mediated inflammatory response can affect cancer cell growth and host cell-mediated immunity.⁶ Thus, mGPS can serve as a cytokine-mediated inflammatory response as well as its role in prognosis.^{23,24} In the current study, postoperative mGPS, not preoperative mGPS, was a better prognostic marker in patients who underwent liver resection for CRLM than postoperative Alb and CRP (Hazard ratio and AUC of postoperative mGPS for disease-free and overall survival were higher and greater than those of postoperative Alb and CRP; 1.73, 1.59 and 1.58 for disease-free survival and 2.37, 2.05 and 1.82 for overall survival, respectively; 0.635, 0.602 and 0.610 for disease-free survival and 0.639, 0.610 and 0.594 for overall survival, respectively) (Table S1 and Figure S1). Furthermore, the patients with worsened mGPS before and after surgery had a poorer prognosis than those with non-worsened mGPS before and after surgery. In sub-group analysis, the patients with mGPS 1 or 2 on postoperative day 30 had a significantly more worsened mGPS than those with mGPS 0 on postoperative day 0 (77% vs 0%), which suggests that postoperative day 30 mGPS can correspond to the perioperative change of mGPS.

The systemic inflammatory response can be affected by tumor, intraoperative and postoperative factors. Our study revealed that patients with postoperative day 30 mGPS 1 or 2 had larger tumor size and higher serum CEA than those with postoperative day 30 mGPS 0. It is unclear whether preoperative tumor factors affected postoperative day 30 mGPS. However, the half-life of Alb of 21 days and intraoperative factors for advanced tumors may have affected postoperative day 30 mGPS.

Regarding intraoperative factors, McSorley ST. et al reported that perioperative blood transfusion was associated with postoperative systemic inflammation and poorer survival,²⁵ while laparoscopic surgery was significantly associated with a lower postoperative systemic inflammatory response²⁶ in patients undergoing colorectal cancer surgery. The present study showed invasive surgery, such as that having long operative time, significant intraoperative blood loss, intraoperative transfusion, simultaneous resection, open surgery, and anatomical hepatectomy, was significantly correlated with elevated postoperative day 30 mGPS. This study also showed that the patients with postoperative day 30 mGPS 1 or 2 had significantly more infectious, postoperative complications and a longer postoperative stay than those with postoperative day 30 mGPS 0. Watt DG. et al reported that postoperative GPS was associated with an

increase in infectious complications and poor overall survival in patients with colorectal cancer.²⁷ Therefore, a postoperative day 30 mGPS of 1 or 2 might mean the presence of postoperative systemic inflammation caused by intraoperative and postoperative factors.

Although it remains unclear why elevated postoperative inflammatory responses promote recurrence leading to poor prognosis in patients with CRLM, our current study suggested that elevated postoperative inflammatory responses were caused by an advanced tumor, invasive surgery and postoperative complications. Cytokine-mediated inflammatory response might contribute to proliferation of residual micrometastases and survival.

The timing of the evaluation of the postoperative systemic inflammatory response differed between this study and the previous reports. In this study, the postoperative systemic inflammatory response was evaluated 1 month after surgery, while in the previous reports, it was evaluated at 3 days¹⁷ or 4 days¹⁶ after surgery. Post-hepatectomy infectious complications include incisional infection and intra-abdominal infection caused by bile leakage and subphrenic fluid collection. Incisional infection usually occurs within 1 week after hepatectomy²⁸ and bile leakage was defined as bilirubin concentration in the drain fluid at least three times the serum bilirubin concentration on or after postoperative day 3.²⁹ Conversely, late-onset bile leakage occurs approximately 2 weeks after hepatectomy and can lead to intra-abdominal infection including serious complications such as sepsis.³⁰ Therefore, evaluating the systemic inflammatory response 3 days after hepatectomy may be too early to capture the increased inflammatory response caused by postoperative infectious complications of hepatectomy.

There were certain limitations to this study, which included its retrospective nature and single-institution experience with relatively small sample size. Our results should be confirmed in larger prospective studies. Additionally, analysis with other inflammatory markers such as prognostic nutritional index, neutrophil-lymphocyte ratio, and platelet-lymphocyte ratio, along with other evaluation dates is required.

In conclusion, the postoperative systemic inflammatory response as evidenced by the postoperative mGPS was demonstrated to correlate with poor survival and closely contributed to preoperative, intraoperative and postoperative factors in patients who underwent hepatic resection for CRLM. Therefore, surgeons should manage perioperative care from various aspects to avoid postoperative systemic inflammatory response such as preoperative nutrition therapy, preoperative corticosteroid administration, performing less invasive surgery including laparoscopic surgery, and careful postoperative care to prevent postoperative complications, leading to a better prognosis.

CONFLICT OF INTEREST

The authors have no conflicts of interest and funding to declare.

ORCID

Kenei Furukawa  <https://orcid.org/0000-0002-5081-6417>

Koichiro Haruki  <https://orcid.org/0000-0002-1686-3228>

Yoshihiro Shirai  <https://orcid.org/0000-0002-4907-0101>

Toru Ikegami  <https://orcid.org/0000-0001-5792-5045>

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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