Surgery Today (2020) 50:232–239
https://doi.org/10.1007/s00595-019-01862-1

ORIGINAL ARTICLE

Preoperative change of modified Glasgow prognostic score after stenting predicts the long-term outcomes of obstructive colorectal cancer

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Received: 30 May 2019 / Accepted: 29 July 2019 / Published online: 12 August 2019

Abstract

Purpose Inflammation-based markers predict the long-term outcomes of various malignancies. We investigated the relationship between the modified Glasgow prognostic score (mGPS) and the long-term outcomes of obstructive colorectal cancer in patients who underwent self-expandable metallic colonic stent placement and subsequently received curative surgery.

Methods We retrospectively analyzed 63 consecutive patients with pathological stage II and III obstructive colorectal cancer from 2013 to 2018. The mGPS was calculated before stenting and surgery, and the difference of the scores was defined as the d-mGPS.

Results All d-mGPS = 2 patients were > 70 years of age ($p = 0.01$). Postoperative complications were more common in the preoperative mGPS = 2 group ($p = 0.02$). The postoperative hospital stay was significantly longer in the mGPS = 2 group ($p = 0.007$). Multivariate analyses revealed that d-mGPS was an independent prognostic factor for overall survival (OS) (hazard ratio [HR] = 9.18, $p = 0.004$) and cancer-specific survival (HR = 9.98, $p = 0.01$). Preoperative mGPS = 2 was significantly associated with poor OS (HR = 5.53, $p = 0.04$).

Conclusion The results indicated that mGPS might serve as a valuable indicator of the immunonutritional status of preoperative patients, and a preoperative change of the status might affect the long-term outcomes of patients with obstructive colorectal cancer.

Keywords Modified glasgow prognostic score · Obstructive colorectal cancer · Retrospective study · Self-expandable metallic stent

Introduction

Accumulating evidence suggests that the progression of the cancer is not solely dependent on tumor characteristics, but also on the systemic environment of the host. Inflammation is regarded as one of the hallmarks of cancer [1], and malnutrition manifested as hypoalbuminemia is associated with poor long-term outcomes [2]. Inflammation-based markers are easily calculated from routinely measured laboratory results and are considered to reflect the systemic inflammatory response and nutritional status of the host. These markers have shown to predict long-term outcomes of various malignancies [3–7]. They were calculated by serum albumin, globulin, and CRP values, and the neutrophil, lymphocyte, and platelet counts of the peripheral blood. Most markers, such as the neutrophil-lymphocyte ratio (NLR), globulin-to-albumin ratio (GAR) and prognostic nutritional index (PNI), are presented as continuous data. However, there are no standard cut-off values, which raises the question of reproducibility and reliability [4, 5]. In contrast, the Glasgow prognostic score (GPS) and modified Glasgow prognostic score (mGPS) are cumulative scores composed of serum C-reactive protein (CRP) elevation and reduced

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serum albumin. Some investigators prefer using the GPS and mGPS over other markers since they are validated cumulative scores that are simpler and more consistent [4, 5]. The GPS and mGPS were demonstrated to be independent prognostic factors in colon, esophageal, gastric, liver, and pancreatic cancer [4–7].

Intestinal obstruction is a common presenting symptom among patients with colorectal cancer. Its incidence was reported to be as high as 30% [8], and obstructive colorectal cancer (OCRC) accounted for 85% of colonic emergencies [9]. Self-expandable metallic colonic stent (SEMS) insertion has been shown to be an effective bridge to elective surgery and is associated with reduced morbidity and stoma in comparison to emergency surgery [10, 11]. The decompression allows bowel preparation, medical stabilization with correction of dehydration and electrolyte abnormalities, and the optimization of comorbid illnesses, which theoretically improves a patient's inflammatory and nutritional status.

The mGPS was shown to be an independent prognostic factor in various groups of colorectal cancer patients, independent of TMN stage [7]. However, the prognostic value of mGPS in OCRC patients was unknown. In the present study, we investigated the relationship between mGPS and the long-term outcomes in OCRC patients who underwent SEMS insertion and subsequently received curative surgery. We also focused on the preoperative change of the immunonutritional status after stenting, which was represented by the change of the mGPS, and evaluated its prognostic significance.

Methods

We retrospectively analyzed 63 consecutive pathological stage II and III OCRC patients who underwent SEMS insertion as "a bridge to surgery" at Sendai City Medical Center between 2013 and 2018. All patients subsequently underwent curative surgical resection. None of the patients received neoadjuvant chemoradiation therapy. Patients with benign disease, distant metastasis, a positive surgical margin, and invasion from a non-colonic malignancy were excluded from the study. There were no patients with chronic inflammation. Postoperative complications were classified according to the Clavien–Dindo classification [12].

Patients who had both elevated serum CRP (> 1.0 mg/dL) and hypoalbuminemia (< 3.5 g/dL) were allocated an mGPS of 2. Patients who had only elevated serum CRP but not hypoalbuminemia were allocated an mGPS of 1, and patients who had neither or only hypoalbuminemia were allocated an mGPS of 0 [7]. The serum CRP and albumin levels were measured, and the mGPS was determined at 2 time points: within three days before SEMS insertion and within four days before surgery. The difference in the mGPS (pre-operative mGPS—pre-stenting mGPS) was defined as the d-mGPS.

A diagnosis of OCRC was made based on a physical examination, contrast-enhanced computed tomography, contrast enema, and colonoscopy, and was confirmed based on a histological examination. Pathological tumor staging was performed according to the AJCC cancer staging manual (7th edition) [13]. Colonic lesions proximal to the splenic flexure were defined as right-sided tumors.

SEMS insertion was performed by endoscopists. A guidewire was introduced across the neoplastic stenosis under endoscopic and fluoroscopic guidance. A Niti-S colonic stent (TaeWoong Medical, Gimpo-si, Korea) was deployed over the wire and through the scope, without balloon dilatation. The colon proximal to the stenotic site was evaluated by water-soluble contrast enema, and colonoscopy was performed after surgery.

The primary endpoint of the study was the long-term outcomes, which were defined as overall survival (OS) and cancer-specific survival (CSS). OS was measured from the date of the surgery to the date of death from any cause, while CSS was measured until death from recurrent cancer.

Continuous variables were presented as the mean ± SD and were analyzed using Student's *t* test. Associations between the d-mGPS and mGPS and clinicopathological parameters were evaluated in a cross-table using Fisher's exact test. The cut-off values for d-mGPS and mGPS were determined by receiver operating characteristic (ROC) curve analyses. The cut-off values were defined using the most prominent point on the ROC curve (Youden index = maximum [sensitivity-(1-specificity)]). We also calculated the area under the ROC (AUROC) curve.

Survival curves were generated according to the Kaplan–Meier method and were analyzed by the log-rank test. Multivariate analyses were performed using a Cox proportional hazards backward elimination model. Factors with a p value of < 0.1 in the univariate analyses were included in the analysis. T stage, N stage, venous invasion, and lymphatic invasion were incorporated into the analysis as potential confounding factors.

EZR (Saitama medical center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria), was used for statistical analyses. p values of < 0.05 were considered to indicate statistical significance [14].

Results

The characteristics of the 63 patients are summarized in Table 1. There were 36 men and 27 women. The mean age of the patients was 71.2 years (range 37–90), and the median follow-up time was 23 months (range 1–61). The

Table 1 Characteristics of the 63 colorectal cancer cases

Value		Value	
Age	71.2 ± 12.0	Interval between stenting and operation (days)	16.7 ± 8.1
[min–max]	[37–90]	[min–max]	[5–46]
Sex		Stenting-related complications	2
Male	36	Resume normal diet after drainage	40
Fmale	27	Type of surgery	
Tumor site		Resection with primary anastomosis	57
Left	45	Resection with diverting stoma	2
Right	18	Hartmann's procedure	4
Depth of invasion (T stage)		Laparoscopic resection (conversion)	18 (2)
T3	46	Harvested lymph node	
T4	17	< 12	4
Lymph node metastasis (N stage)		≥ 12	59
−	33	Postoperative complications[a]	
+	30	Grade I	12
Lymphatic invasion		Grade II	9
−	8	Grade III	3
+	55	Grade IV	0
Venous invasion		Grade V	1
−	22	Postoperative hospital stay (days)	19.2 ± 11.6
+	41	[min–max]	[8–77]
Histological differentiation		Adjuvant chemotherapy	
Tub	61	−	32
Por	2	+	31

[a]Clavien-Dindo classification

mean interval between SEMS insertion and surgery was 16.7 days (range 5–46), and the mean postoperative hospital stay was 19.2 days (range 8–77).

In SEMS insertion, technical success was defined as correct placement, while clinical success was defined as resolution of occlusive symptoms. The technical and clinical success rates were 100% and 98%, respectively. Drainage-related complications were observed in 2 cases. One patient complained of mild abdominal pain after SEMS insertion, and another patient with inadequate drainage required insertion of a transanal drainage tube for additional drainage. Parenteral nutrition was administered to meet the patients' nutritional requirements when needed. Forty patients (64%) could resume a normal diet after drainage.

Fifty-seven patients (90%) underwent curative resection with primary anastomosis. A stoma was created in 6 patients, including a diverting stoma in two cases. Laparoscopic surgery was performed in 18 cases, and conversion to an open procedure was noted in 2 cases due to severe adhesion ($n = 1$) and a tumor with direct invasion to the bladder ($n = 1$). There were four major postoperative complications (Clavien–Dindo grade ≥ 3), including one in-hospital death secondary to anastomotic leakage. Adjuvant chemotherapy was administered in 31 cases (49%).

The optimal cut-off value for d-mGPS was 2, which provided 95% sensitivity, 57% specificity, and an AUROC of 0.64. The clinicopathological findings of the 63 patients according to the d-mGPS (2/< 2) are summarized in Table 2. All d-mGPS = 2 patients were over 70 years of age ($p = 0.01$). Other clinicopathological parameters, including sex, tumor site, T stage, and N stage were comparable between the groups. In the two groups, the interval between SEMS insertion and surgery, and the postoperative hospital stay did not differ to a statistically significant extent.

The Kaplan–Meier survival curves demonstrated that OS was significantly shorter in the d-mGPS = 2 group ($p < 0.001$; Fig. 1a). In the univariate analyses, only adjuvant chemotherapy was identified as a prognostic factor, with marginal significance (hazard ratio [HR] = 7.56, 95% confidence interval [CI] 0.9–62.9, $p = 0.06$). In multivariate analysis that included adjuvant chemotherapy and potential confounding factors, including T stage, N stage, venous invasion, and lymphatic invasion, d-mGPS = 2 (HR = 9.18, 95% CI 2.05–41.1, $p = 0.004$) was identified as an independent prognostic factor (Table 3). CSS was significantly worse in the d-GPS = 2 group ($p = 0.002$; Fig. 1b), and it was the only factor associated with CSS in the univariate analyses. In the multivariate analysis adjusted for T stage, N stage, venous invasion, and lymphatic invasion, d-mGPS = 2

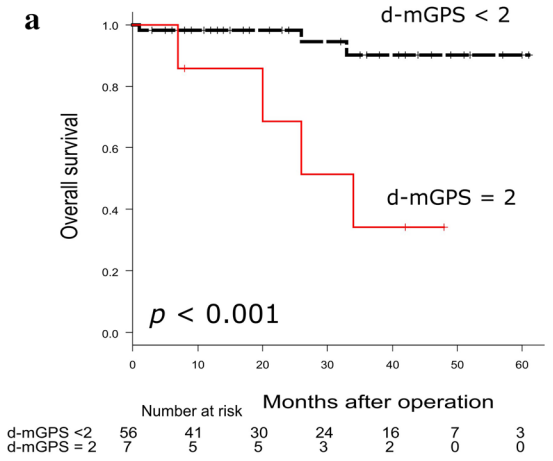
Table 2 Association between inflammation-based markers and clinicopathological parameters in 63 colorectal cancer cases

Value	d-mGPS		*p* value	mGPS		*p* value
	<2	2		0.1	2	
Age						
<70	28	0	0.01	20	8	0.30
≥70	28	7		20	15	
Sex						
Male	32	4	1.00	22	14	0.79
Female	24	3		18	9	
CEA						
<5	27	3	1.00	17	13	0.29
≥5	28	4		23	9	
CA 19–9						
<37	50	7	1.00	37	20	1.00
≥37	5	0		3	2	
Tumor site						
Left	41	4	0.40	30	15	0.56
Right	15	3		10	8	
Depth of invasion (T stage)						
T3	41	5	1.00	29	17	1.00
T4	15	2		11	6	
Lymphnode metastasis (N stage)						
−	30	3	0.70	17	16	0.07
+	26	4		23	7	
Lymphatic invasion						
−	8	0	0.58	5	3	1.00
+	48	7		35	20	
Venous invasion						
−	21	1	0.41	16	6	0.29
+	35	6		24	17	
Histological differentiation						
Tub	54	7	1.00	39	22	1.00
Por	2	0		1	1	
Harvested lymph node						
<12	3	1	0.38	1	3	0.13
≥12	53	6		39	20	
Adjuvant chemotherapy						
−	26	6	0.10	19	13	0.60
+	30	1		21	10	
Complication CD Grade ≥ III						
−	53	6	0.38	40	19	0.02
+	3	1		0	4	
Interval between stenting and operation (days)						
	17.3 ± 8.1	10.6 ± 5.2	0.08	18.3 ± 7.6	14.1 ± 8.4	0.048
Postoperative hospital stay (days)						
	18.3 ± 9.3	26.7 ± 22.8	0.07	16.3 ± 4.8	24.3 ± 17.1	0.007

CD clavien-dindo

(HR = 9.98, 95% CI 1.67–59.8, $p = 0.01$) was identified as an independent prognostic factor for CSS (Table 3).

The optimal cut-off value for preoperative mGPS was 2, which provided 68% sensitivity, 71% specificity, and an AUROC of 0.69. When the patients were divided into the mGPS = 0.1 group and mGPS = 2 group, postoperative complications were more common in the mGPS = 2 group ($p = 0.02$; Table 2). The interval between SEMS insertion



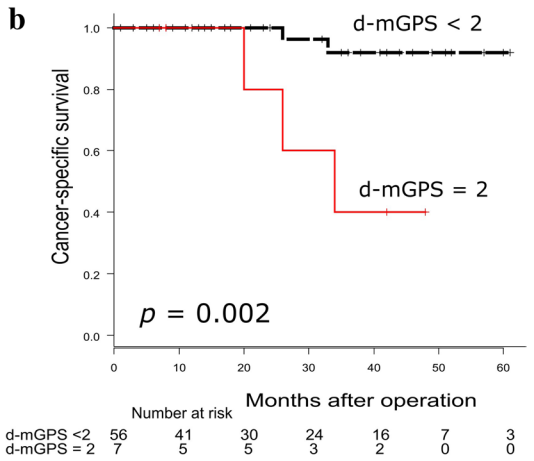


Fig. 1 Survival curves according to the d-mGPS values of 63 pathological stage II and III colorectal cancer patients who underwent endoscopic drainage, according to the d-mGPS, which is the difference of the mGPS (pre-operative mGPS—pre-stenting mGPS). Overall survival curves (**a**) and cancer-specific survival curves (**b**) according to the d-mGPS

Table 3 Multivariate analysis of factors associated with survival

Value	*n*	HR (95% CI)	*p* value
OS[a]			
d-mGPS			
<2	56	1.00 (Reference)	0.004
2	7	9.18 (2.05–41.1)	
mGPS			
0.1	40	1.00 (Reference)	0.04
2	23	5.53 (1.07–28.6)	
CSS[b]			
d-mGPS			
<2	56	1.00 (Reference)	0.01
2	7	9.98 (1.67–59.8)	

OS overall survival, *CSS* cancer-specific survival

[a]Adjusted for adjuvant chemotherapy, T stage, N stage, venous invasion, and lymphatic invasion

[b]Adjusted for T stage, N stage, venous invasion, and lymphatic invasion

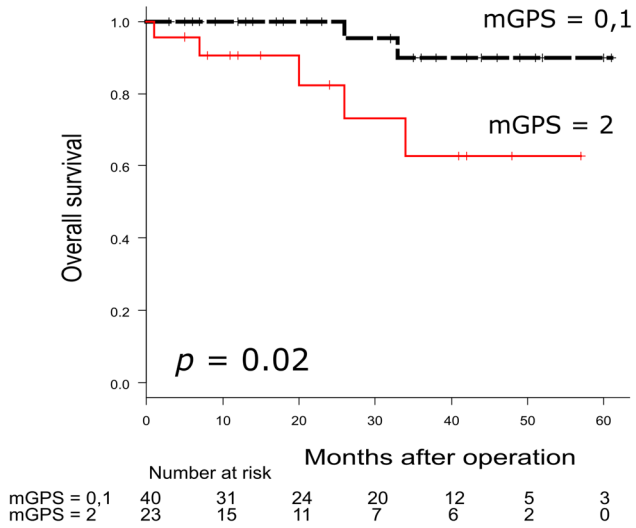


Fig. 2 Survival curves according to pre-operative mGPS values of 63 pathological stage II and III colorectal cancer patients who underwent endoscopic drainage

and surgery was 14.1 days in the mGPS = 2 group and 18.3 days in the mGPS = 0.1 group; however, the difference was only marginally significant ($p = 0.048$). The postoperative hospital stay was significantly longer in the mGPS = 2 group (24.3 days vs. 16.3 days, $p = 0.007$).

The Kaplan–Meier survival curves showed that OS was significantly shorter in the mGPS = 2 group ($p = 0.02$; Fig. 2). The multivariate analysis identified mGPS = 2 (HR = 5.53, 95% CI 1.07–28.6, $p = 0.04$) as an independent prognostic factor (Table 3). CSS did not differ between the groups to a statistically significant extent ($p = 0.14$).

Discussion

Intestinal obstruction is one of the common presenting symptoms among patients with colorectal cancer. Emergency surgery, which is associated with increased morbidity and mortality in comparison to elective surgery, is usually indicated [8, 9]. This is usually accompanied by multiple-stage surgery with the creation of a temporary or permanent stoma. Stomas are resulted in permanent in up to 40% of patients, and significantly diminish the patient's quality of life (QOL) [8, 15]. Furthermore, emergency surgery might result in oncologically suboptimal

resection [16]. Endoscopic decompression can convert emergency surgery into elective 1-stage surgery. SEMS insertion was originally performed with palliative intent for OCRC patients [17]; however, recently, it has been used as a bridge to curative surgery. Although concerns have been raised about the effect of the colonic stent on the long-term outcomes [18], recent meta-analyses have shown that SEMS insertion did not adversely affect long-term results in comparison to emergency surgery as a bridge to surgery [9, 19], or as palliative therapy [20]. It was also reported that the incidence of local and distant recurrence did not differ to a statistically significant extent [9, 19]. In comparison to patients who underwent drainage by transanal drainage tube, there were no statistically significant differences in recurrence patterns or long-term survival [21].

GPS was first reported in 2003 by Forrest et al. and was shown to predict the prognosis of inoperable lung cancer. Patients with either elevated CRP or hypoalbuminemia were allocated a score of 1, and those with both abnormalities were allocated a score of 2 [22]. In 2007, McMillan et al. revealed that colorectal cancer patients with a GPS of 1 due to hypoalbuminemia had better OS in comparison to those with a GPS of 1 due to an elevated CRP level. Thus, they proposed the mGPS, in which patients with hypoalbuminemia but without elevated CRP are allocated an mGPS of 0 [23].

In the present study, we investigated the relationship between the mGPS and long-term outcomes in OCRC patients who had undergone endoscopic drainage and received curative surgery. Our results demonstrated a preoperative change in the mGPS after stenting, defined as d-mGPS, was significantly associated with OS and CSS. The results indicated that the preoperative change in the inflammatory and nutritional status might affect the long-term outcomes of the patients. Although preoperative optimization of the patient's condition to improve long-term outcomes seems an intriguing concept, such studies are scarce due to difficulty in evaluating patients and developing appropriate intervention strategies. In the present study, the mGPS served as a useful evaluation tool, and the unique therapeutic time course in the "bridge to surgery" setting allowed for the preoperative evaluation of patients at two different time points (i.e., just before SEMS insertion and just before surgery). The SEMS itself does not improve the immunonutritional status, but it can buy time for interventions to improve the status. Various inflammation-based markers have been investigated in a variety of malignancies, but few studies have evaluated the change in these values. Youg et al. [24] measured the difference in the PNI before and after the preoperative chemoradiation therapy for advanced rectal cancer, and demonstrated that difference in the PNI was an independent prognostic factor for disease-free survival (DFS) and CSS. The results of the present study indicated that mGPS could be a valuable indicator of the preoperative immunonutritional condition, and that the preoperative deterioration of the condition might result in shortened long-term survival. The score might be utilized to decide the timing of the operation, and postponing the operation until the score has improved might be justified to yield optimal long-term results. Further studies are warranted to test these hypotheses.

There are several options for potentially improving the inflammatory and nutritional status. Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs), statins, and histamine type 2 receptor antagonists (H2RA) are agents with anti-inflammatory properties [25]; however, few studies have investigated the effects of their perioperative use on long-term survival. NSAIDs were demonstrated to reduce systemic inflammation and the CRP level, and daily aspirin was shown to reduce the incidence of colorectal cancer, as well mortality and recurrence rates [26–28]. Currently, randomized trials are underway to study the effect of the adjuvant use of aspirin on cancer mortality [29, 30]. As for statins, a meta-analysis revealed that statin use, both before and after a cancer diagnosis, was associated with reduced all-cause mortality and cancer-specific mortality [31]. The adjuvant use of H2RA, especially cimetidine, resulted in a statistically significant improvement in the OS of colorectal cancer patients; however, most studies on this topic are relatively old [32]. Despite hypoalbuminemia being associated with poor long-term survival in patients with malignancy [2], the effect of nutritional intervention on long-term survival is largely unknown. Perioperative arginine supplementation was demonstrated to significantly improve the long-term survival of malnourished head and neck cancer patients [33]. Immunonutritional formulas supplemented with biologically active nutrients, such as arginine, glutamine, and ω-3 fatty acids, were investigated as perioperative nutritional interventions and were shown to reduce postoperative infectious complications and the length of hospital stay [34]. The effect of immunonutrition on long-term outcomes has not been studied in detail. In a randomized study of perioperative enteral immunonutrition in esophageal cancer patients, patients who received immunonutrition formula showed somewhat better long-term survival; however, the difference was not statistically significant ($p = 0.13$) [35]. These results imply that preoperative medical and nutritional intervention might improve the inflammatory and nutritional status of the patients, resulting in improved long-term survival. In the present study, we could not perform meaningful analyses of medical and nutritional interventions as information about the medications used during the perioperative period was not available, and we did not use immunonutrition. However,

our results indicated that the mGPS could be a valuable indicator to identify the patients with a poor immunonutritional status and to evaluate the efficacy of interventions.

In the present study, the preoperative mGPS was significantly associated with postoperative complications, postoperative hospital stay, and proved to be an independent prognostic factor for OS. A meta-analysis demonstrated that the mGPS was an independent prognostic factor in various groups of colorectal cancer patients who were treated with surgery or chemotherapy [7]. To the best of our knowledge, this is the first study to assess the mGPS in OCRC patients who had undergone SEMS insertion as a bridge to curative surgery. Currently, adjuvant chemotherapy is indicated for stage III and high-risk stage II colorectal cancer patients, and obstruction itself is a poor prognostic feature [36]. Our results demonstrated that the mGPS could further stratify OCRC patients independently of the TNM stage and could identify high-risk patients who might be good candidates for adjuvant chemotherapy. However, previous studies showed conflicting results regarding the assessment of risk according to inflammation-based markers and the effect of adjuvant chemotherapy. Peng et al. [37] demonstrated that low-PNI was independently associated with a poor prognosis in stage III colon cancer patients, and that only patients with a low-PNI showed improved OS and DFS when treated with 6–8 cycles of XELOX adjuvant chemotherapy in comparison to those who received less than 6 cycles. In the high-PNI group, the duration of chemotherapy was not associated with OS. On the other hand, in an analysis of stage III colorectal cancer patients, adjuvant chemotherapy for mGPS = 1.2 patients, who had poorer survival, did not result in improved survival, whereas adjuvant chemotherapy improved survival in mGPS = 0 patients [38]. If the risk identified by the TMN stage is attributed to the tumor characteristics, the risk identified by inflammation-based markers might be attributed to the systemic environment of the host, and such risk might be more aptly mitigated by improving the host immunonutritional status rather than administrating intensive adjuvant chemotherapy. Thus, inflammation-based markers might be more effectively used in accessing and optimizing the patient's condition before surgery, rather than for identifying patients with a high risk of recurrence, and actively improving the patient's condition might exert stronger effects on long-term survival than administering adjuvant chemotherapy; however, further studies are required to test this hypothesis.

This study was associated with some limitations, including the small study population, its retrospective, non-randomized design, and the fact that it was performed in a single institution. The study population consisted of OCRC patients who had undergone endoscopic drainage, who represent a unique subset of the colorectal cancer patients, and it is unknown whether the current findings can be applied to the more general patient population. Moreover, the median follow-up time was relatively short. Thus, the results should be interpreted with caution. However, this study is of paramount importance since this is the first study to assess the mGPS and d-mGPS in OCRC patients who had undergone SEMS insertion as a bridge to curative surgery.

In summary, the results of the present study demonstrated that preoperative change in an inflammation-based marker, the d-mGPS, as well as the preoperative mGPS, were independent prognostic factors for overall survival in OCRC patients who had undergone endoscopic drainage. The results showed that the mGPS could be a valuable indicator of the preoperative immunonutritional condition and raised the possibility that preoperative medical and nutritional interventions to improve immunonutritional status of the patient might result in improved long-term survival. Future studies with large study populations and a longer observation period are warranted to further test these hypotheses.

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest in association with the present study.

Ethical statements The protocol for this research project was approved by the Ethics Committee of the institution (#2019–0008) and conforms to the provisions of the Declaration of Helsinki.

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