ORIGINAL

Impact of neutrophil–lymphocyte ratio, Glasgow Prognostic Score, and postoperative decrease in psoas muscle index on recurrence after curative gastrectomy

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Abstract : Aim : We investigated whether preoperative or postoperative inflammatory markers and psoas muscle index (PMI), and their change after surgery, could predict postoperative recurrence in gastric cancer (GC). Methods : Thirty-five patients who underwent curative gastrectomy for pStage II and III GC were retrospectively reviewed. The relationship between neutrophil–lymphocyte ratio (NLR), prognostic nutritional index (PNI), Glasgow Prognostic Score (GPS), and PMI, as well as postoperative recurrence, was analyzed presurgery and at 6 months after surgery. Results : In the preoperative data, there was a significant association between postoperative recurrence and high NLR, low total protein, low albumin, low PNI, and high GPS. In the data from 6 months after surgery, there was a significant association between postoperative recurrence and high NLR, high C-reactive protein, and high GPS. The reduction in PMI at 6 months after surgery relative to preoperative data was significantly greater in the cases with recurrence than in those without recurrence. No patients whose PMI increased compared with presurgery had recurrence. Conclusions : The postoperative reduction in PMI at 6 months after surgery relative to presurgery could be a predictive marker of recurrence after curative gastrectomy for patients with pStage II and III GC. J. Med. Invest. 68 : 119-124, February, 2021

Keywords **:** *Gastric cancer, Recurrence, Psoas muscle index (PMI), Sarcopenia, Systemic inflammatory markers*

INTRODUCTION

Gastric cancer (GC) is one of the most common malignancies and is the third-leading cause of malignancy-related death in the world (1). Although the clinical outcome of patients with GC has improved their disease-free status following curative resection and postoperative adjuvant chemotherapy (2), there is still much room for further improvement (3). To develop a perioperative treatment strategy for GC, it is important to identify predictors of its recurrence.

Assessment of prognostic efficacy of systemic inflammatory factors is meaningful to managing patients with GC (4). Several previous reports have revealed that comprehensive systemic inflammatory markers, including the prognostic nutritional index (PNI), Glasgow Prognostic Score (GPS), and neutrophil–lymphocyte ratio (NLR), were independent predictors of survival in patients with GC (4-6). Many reports have only focused on the association between preoperative systemic inflammatory factors and prognoses (7-9). However, systemic inflammatory factors can drastically change after radical surgery for GC, and its association with patients' prognoses is an unresolved issue (10). From the perspective of cancer recurrence, we considered the importance of postoperative comprehensive systemic inflammatory markers.

Sarcopenia is defined as a reduction in skeletal muscle mass with aging (10), and it is recognized as an important factor in cancer management. In GC, several reports have been published focusing on the association between cancer and sarcopenia (11-15). Many GC studies have focused only on the association between preoperative sarcopenia and postoperative complications and/or prognoses, and the cutoff points, such as psoas muscle index (PMI) and skeletal muscle mass index, have varied from report to report (16-19). Therefore, further research is needed to clarify the clinical significance of sarcopenia in GC.

Although much evidence has been accumulated concerning the significance of inflammatory markers and sarcopenia in patients with GC, few reports have investigated the importance of their evaluation postsurgery or of their change between presurgery and postsurgery. The purpose of this study was to clarify the predictive impact of inflammatory markers and PMI on postoperative recurrence in patients with pStage II and III GC. In this study, we focused on both preoperative and 6 months postoperative data, as well as the difference between presurgery and 6 months after surgery.

PATIENTS AND METHODS

Patients

A total of 35 patients who underwent curative surgery for pStage II and III GC between 2010 and 2014 at the Numata National Hospital Department of Surgery in Numata, Japan, were retrospectively reviewed. The patients with GC were staged according to the Japanese Classification of Gastric Carcinoma (20). Data were collected on patient characteristics, such as age, sex, height, body weight, and body mass index (BMI). In addition, both surgical information (such as surgical methods, lymph node dissection, operative time, and blood loss) and pathological information (such as depth of tumor invasion and lymph node metastasis) were recorded. This study was approved by the institutional review board of Numata National Hospital.

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Assessment of systemic inflammatory markers

Results from laboratory tests, such as white blood cell count, NLR, hemoglobin, total protein (TP), albumin, and C-reactive protein (CRP) were collected both before surgery and at 6 months after surgery. The PNI was calculated as 10 × albumin + 0.05 × lymphocyte count (21). The GPS was decided on the basis of CRP and albumin. Patients with elevated CRP (>0.3 mg/dL) and reduced albumin (<3.5 mg/dL) were assigned a score of 2 points. Patients who had either of these two factors were assigned a score of 1 point. Patients who had neither of these factors were assigned a score of 0 points (22).

Assessment of sarcopenia

Computed tomography (CT) was performed in all cases at preoperative staging and at 6 months after surgery as a routine follow-up. The third lumbar vertebra (L3) was chosen as an evaluation point. The PMI was defined as the cross-sectional area of muscle at the L3 level normalized on the basis of patients' height (cm^2/m^2). Sarcopenia was defined as a PMI of < 6.0 cm^2/m^2 for men and of <3.4 cm^2/m^2 for women (23). We also set the value of preoperative PMI at 100% and calculated the percentage at 6 months after surgery relative to preoperative data.

Statistical analysis

Statistically significant differences were analyzed using a Mann–Whitney U test for continuous variables and a chi-squared test for categorical variables. Univariate survival analyses were performed using the Cox proportional hazards model. A probability value of <0.05 was considered to be statistically significant. All analyses were performed using JMP Pro 12.0 software (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patient characteristics

Of the 35 patients, 21 were men. Mean age was 70.6 years (range 52.0–90.0 years). Mean BMI was 21.1 (range 14.3–24.8 kg/m^2). Of the 35 patients, the depth of tumor invasion was deeper than the subserosa in 32 patients, and 30 patients had lymph node metastasis. There were eight patients with pStage II (22.9%) and 27 patients with pStage III (77.1%). No patients had recurrence within 6 months after surgery. The surgical methods were distal gastrectomy in 21 (60.0%) patients and total gastrectomy (TG) in 14 (40.0%) patients. Regarding the postoperative complications, there were no patients with higher than grade 3 Clavien–Dindo classification. During the study period, S-1 was administered to 28 (80%) patients as postoperative adjuvant chemotherapy. The reasons for absence of postoperative adjuvant chemotherapy in the remaining 7 (20%) patients were advanced age, poor performance status, comorbid conditions, and an inability to obtain consent.

Association between patients' clinical data and postoperative recurrence

Recurrence was observed in 15 (42.9%) of 35 patients. The association between recurrence and clinicopathological features in the 35 patients with GC is shown in Table 1. There were significant associations between recurrence and the presence of lymph node metastasis ($p = 0.013$) and advanced pathological stage ($p = 0.036$). In contrast, there was no significant association in terms of age, sex, BMI, depth of tumor invasion, operative method, lymph node dissection, blood loss, or administration of adjuvant chemotherapy with S-1.

Table 1. The relationship between clinicopathological features and postoperative recurrence in 35 GC patients.

Factors	Recurrence		*P* value
	Absent	Present	
	n = 20	n = 15	
Age (years)	68.1 ± 2.0	73.9 ± 2.3	0.07
Gender			
Male	12	9	1.00
Female	8	6	
BMI (kg/m^2)	20.5 ± 0.6	21.8 ± 0.6	0.15
Depth			
M, SM, MP	3	0	0.06
SS, SE, SI	17	15	
Lymph node metastasis			
Absent	5	0	0.013*
Present	15	15	
Stage			
Ⅱ	7	1	0.036*
Ⅲ	13	14	
Operative method			
Distal gastrectomy	13	8	0.49
Total gastrectomy	7	7	
Lymph node dissection			
D1, D1+	6	8	0.18
D2	12	6	
Operative time (min)	329.1 ± 19.7	377.7 ± 25.3	0.14
Blood loss (ml)	393.6 ± 82.2	542.5 ± 105.2	0.27
Adjuvant chemotherapy			
Not-performed	3	4	0.4
Performed	17	11	

Systemic inflammatory factors and PMI at presurgery and 6 months after surgery with regard to recurrence

In the preoperative evaluation, there was a significant relationship between postoperative recurrence and high NLR ($p = 0.011$), low TP ($p = 0.025$), and low albumin ($p = 0.0077$), as shown in Table 2. Regarding PNI and GPS, many recurrences were found in the cases with low PNI ($p = 0.0041$) and high GPS ($p = 0.0011$).

In terms of 6 months after surgery, there was a significant relationship between recurrence and high NLR ($p = 0.013$) and high CRP ($p = 0.040$). Regarding PNI and GPS, we found that GPS was significantly associated with recurrence ($p = 0.046$), whereas PNI was not.

There was no significant correlation between PMI and recurrence for either presurgery or 6 months after surgery.

Changes in systemic inflammatory factors and PMI between presurgery and at 6 months after surgery with regard to recurrence

The decrease in PMI at 6 months after surgery relative to preoperative data was significantly greater in the cases with recurrence than those without recurrence (96.8 ± 3.7% vs. 82.0 ± 4.3%, $p = 0.014$), whereas no significant correlations were found in NLR, PNI, or GPS, as shown in Table 3.

Association between patients' clinical data and the changes in PMI

Reductions in PMI were observed in 28 (80%) of 35 patients. The association between changes in PMI and clinicopathological features in 35 patients with GC is shown in Table 4. There

Table 2. PMI and systemic inflammatory factors at the point of before operation and 6 months after operation with regard to recurrence.

Factors	Before operation		*P* value	6 months after operation		*P* value
	Recurrence			Recurrence		
	Absent (n = 20)	Present (n = 15)		Absent (n = 20)	Present (n = 15)	
White Blood Cell (WBC)						
mm^3	5873.5 ± 407.5	6596.0 ± 470.6	0.25	4211.5 ± 372.1	5340.7 ± 429.7	0.055
NLR						
	2.2 ± 0.3	3.6 ± 0.4	0.011*	1.2 ± 0.2	2.0 ± 0.2	0.013*
Hemoglobin						
g/dl	12.4 ± 0.6	11.1 ± 0.7	0.16	11.8 ± 0.4	11.4 ± 0.7	0.57
Total Protein						
g/dl	7.0 ± 0.2	6.3 ± 0.2	0.025	7.0 ± 0.1	6.8 ± 0.2	0.22
Albumin						
g/dl	4.3 ± 0.1	3.7 ± 0.2	0.0077*	4.4 ± 0.1	4.1 ± 0.11	0.12
C-reactive protein						
mg/dl	0.06 ± 0.2	0.7 ± 0.2	0.050	0.05 ± 0.08	0.3 ± 0.09	0.040*
PNI						
Score	51.1 ± 1.6	43.7 ± 1.8	0.0041*	52.4 ± 1.5	50.0 ± 1.8	0.31
GPS						
Score	0.0 ± 0.1	0.7 ± 0.1	0.0011*	0.0 ± 0.1	0.3 ± 0.1	0.046*
PMI						
Score	4.2 ± 0.3	3.9 ± 0.4	0.52	4.1 ± 0.4	3.2 ± 0.5	0.14
Sarcopenia						
(Using PMI cut-off point)						
Non-sarcopenia	6	3	0.50	3	0	0.06
Sarcopenia	14	12		17	15	

NLR Neutrophil-to-Lymphocyte Ratio, *PNI* Prognostic Nutritional Index, *GPS* Glasgow Prognostic Score, *PMI cut-off point* 6.0cm^2/m^2 (men) and 3.4cm^2/m^2 (women)

Table 3. Changes of PMI and systemic inflammatory factors from before operation to 6 months after operation with regard to recurrence.

Factors	Recurrence		*P* value
	Absent (n = 20)	Present (n = 15)	
NLR			
%	63.9 ± 9.2	66.6 ± 10.6	0.85
PNI			
%	87.4 ± 9.0	96.3 ± 10.3	0.52
GPS			
Increase	0	2	0.064
Same/Decrease	19	13	
PMI			
%	96.8 ± 3.7	82.0 ± 4.3	0.014*

NLR Neutrophil-to-Lymphocyte Ratio, *PNI* Prognostic Nutritional Index, *GPS* Glasgow Prognostic Score, Each percentage was calculated as following ; the value at 6 months after operation/the value before operation × 100.

Table 4. The relationship between clinicopathological features and PMI decrease or increase compared to before operation.

Factors	PMI		*P* value
	Decrease	Increase	
	n = 28	n = 7	
Age (years)	70.6 ± 1.8	70.3 ± 3.6	0.93
Gender			
Male	17	4	0.86
Female	11	3	
BMI (kg/m^2)	21.1 ± 0.5	21.1 ± 1.0	0.94
Depth			
M, SM, MP	3	0	0.55
SS, SE, SI	25	7	
Lymph node metastasis			
Absent	2	3	0.030*
Present	26	4	
Stage			
Ⅱ	7	1	0.53
Ⅲ	21	6	
Operative method			
Distal gastrectomy	16	5	0.48
Total gastrectomy	12	2	
Adjuvant chemotherapy			
Not-performed	5	2	0.54
Performed	23	5	
Recurrence			
Absent	13	7	0.0025*
Present	15	0	

were significant associations between reduced PMI and the presence of lymph node metastasis ($p = 0.030$) and postoperative recurrence ($p = 0.0025$). All the patients with increased PMI compared with presurgery had no recurrence.

Association between systemic inflammatory factors and changes in PMI

Patients with increased PMI had significantly lower preoperative NLR ($p = 0.040$), as shown in Table 5. However, no significant correlation was observed at 6 months after surgery in patients with increased PMI.

DISCUSSION

In this study, we analyzed systemic inflammatory markers and PMI at presurgery and at 6 months after surgery in patients with GC with pStage II and III in terms of postoperative recurrence. There was significant association between postoperative recurrence and high NLR, low TP, low albumin, low PNI, and high GPS in the preoperative evaluation, whereas high NLR, high CRP, and high GPS were shown in the data for postoperative recurrence at 6 months after surgery. There were significant associations between postoperative reductions in PMI and the presence of lymph node metastasis and postoperative recurrence. Furthermore, no cases with postoperative increase of PMI had recurrence. Our results suggest that sarcopenia and inflammatory markers should be evaluated at multiple points peri-operation because they are changeable depending on patients' background factors.

NLR is reported to be strongly associated with sarcopenia (24). In our research, it was useful to predict recurrence both preoperatively and at 6 months after surgery. PNI and GPS are also known as significant predictors of the prognosis in GC (4) ; however, the effectiveness of evaluation at 6 months after surgery is poorly understood. Regarding PNI and GPS, we found that GPS was significantly associated with recurrence ($p = 0.046$) at 6 months after surgery, whereas PNI was not. The following two reasons were considered : First, TP and albumin tended to improve after surgery, which could have influenced PNI. Second, CRP had an association with recurrence at 6 months after surgery, affecting the positive correlation between GPS and recurrence. We should note the change in NLR and CRP in order to predict recurrence at 6 months after surgery.

Previous studies have focused on the effect of sarcopenia on GC outcomes (13, 25, 26). However, there were variations in the sarcopenia evaluation point, cutoff point, patient's background, and study design in each paper. To clarify whether PMI and systemic inflammatory markers had a relationship with recurrence, we focused on patients with pStage II or III GC in this study. In this study, 24 (68.6%) patients were older than 65 years. As mentioned earlier, sarcopenia was defined as a PMI of <6.0 cm^2/m^2 for men and <3.4 cm^2/m^2 for women (23). When we adopted these cutoff points, 26 (74.3%) patients and 32 (91.4%) patients were defined as having sarcopenia presurgery and at 6 months after surgery, respectively. We did not find a significant association between recurrence and sarcopenia while employing the cutoff point of PMI. Kiyama T *et al*. had shown a significant loss of body protein of 8% at 6 months after TG (27). Yamaoka Y *et al*. had also found that approximately 25% of patients showed a significant loss of skeletal muscle of >10% at 1 year after TG (28). Therefore, we set the value of preoperative PMI as 100%

Table 5. Systemic inflammatory factors at the point of before operation and 6 months after operation with regard to PMI decrease or increase compared to before operation in 35 GC patients.

Factors	Before operation		*P* value	6 months after operation		*P* value
	PMI			PMI		
	Decrease (n = 28)	Increase (n = 7)		Decrease (n = 28)	Increase (n = 7)	
White Blood Cell (WBC)						
mm^3	6360.7 ± 344.5	5472.9 ± 689.1	0.26	4763.6 ± 331.7	4422.9 ± 663.4	0.65
NLR						
	3.0 ± 0.3	1.6 ± 0.6	0.040*	1.6 ± 0.2	1.2 ± 0.4	0.4
Hemoglobin						
g/dl	11.9 ± 0.5	11.7 ± 1.0	0.90	11.7 ± 0.4	11.6 ± 0.7	0.94
Total Protein						
g/dl	6.7 ± 0.2	6.7 ± 0.3	0.91	6.9 ± 0.1	7.2 ± 0.2	0.22
Albumin						
g/dl	4.0 ± 0.1	4.1 ± 0.2	0.85	4.2 ± 0.1	4.4 ± 0.2	0.25
C-reactive protein						
mg/dl	0.39 ± 0.2	0.05 ± 0.3	0.38	0.19 ± 0.07	0.04 ± 0.1	0.34
PNI						
Score	47.4 ± 1.5	49.9 ± 3.0	0.45	51.2 ± 1.3	52.1 ± 2.6	0.77
GPS						
Score	0.4 ± 0.1	0.0 ± 0.2	0.17	0.2 ± 0.1	0.0 ± 0.2	0.40
PMI						
Score	4.1 ± 0.3	4.1 ± 0.5	0.94	3.4 ± 0.3	5.2 ± 0.7	0.023*
Sarcopenia						
(Using PMI cut-off point)						
Non-sarcopenia	6	3	0.26	0	3	0.0010*
Sarcopenia	22	4		28	4	

and calculated the percentage at 6 months after surgery relative to preoperative data. We found that PMI was significantly lower at 6 months after surgery in cases with recurrence (96.8 ± 3.7% vs. 82.0 ± 4.3%). The receiver operating characteristic curve constructed to investigate the association between the transition of PMI and recurrence demonstrated that the cutoff point was 93.0%. This cutoff meant that cases with a PMI reduction of >7% had a relative risk of recurrence. In this way, preventing the loss of PMI after surgery could lead to improved patient outcomes. Furthermore, focusing on the transition of PMI is valuable because it is independent of the patient's age. Given sarcopenia and GC prognoses are related, early nutritional status assessments are useful (26, 29). Proinflammatory cytokines, including interleukin (IL)-1, IL-6, and tumor necrosis factor-α, were found to be mediators of skeletal muscle proteolysis loss and are the components of sarcopenia (30). Okumura S *et al*. suggested that decreasing muscle mass should give rise fewer cytokines which causes decreased immunity (31). Lutz CT *et al*. also reported that decreased cytokine levels suppress the function of natural killer cells in sarcopenia (32). Evaluation of these proinflammatory cytokines after surgery might be meaningful.

Our study has some limitations. It had a small sample size, which could bias the results. Further large-scale clinical trials are needed to clarify the potential of the transition of PMI as a new predictive biomarker for GC recurrence. Also, the diagnosis of sarcopenia requires measurement of walking speed and grip strength (33, 34), but it is difficult to evaluate in those with poor physical condition and in the elderly. We focused on CT, which is frequently used in GC management. The significance of walking speed and grip strength to evaluate postoperative change of sarcopenia could be further investigated.

In conclusion, the transition of PMI was significantly correlated with recurrence in pStage II and III patients with GC. Furthermore, evaluating systemic inflammatory factors, such as NLR, PNI, and GPS, was also considered important. NLR and GPS were useful predictive markers both preoperatively and at 6 months after surgery. In particular, the change in PMI at 6 months after surgery compared with presurgery was a useful prognostic predictor. Given CT is performed for preoperative staging and postoperative follow-up in almost all cases of GC, the findings can be used to identify changes in skeletal muscle and provide nutritional assessment, which could improve clinical outcomes.

CONFLICT OF INTERESTS

We have no conflicts of interest to declare.

ETHICAL APPROVAL

All research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The data request and study protocol were approved by the institutional review board of Numata National Hospital.

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