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The primary task of *WJG* is to rapidly publish high-quality original articles, reviews, and commentaries in the fields of gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, hepatobiliary surgery, gastrointestinal oncology, gastrointestinal radiation oncology, gastrointestinal imaging, gastrointestinal interventional therapy, gastrointestinal infectious diseases, gastrointestinal pharmacology, gastrointestinal pathophysiology, gastrointestinal pathology, evidence-based medicine in gastroenterology, pancreatology, gastrointestinal laboratory medicine, gastrointestinal molecular biology, gastrointestinal immunology, gastrointestinal microbiology, gastrointestinal genetics, gastrointestinal translational medicine, gastrointestinal diagnostics, and gastrointestinal therapeutics. *WJG* is dedicated to become an influential and prestigious journal in gastroenterology and hepatology, to promote the development of above disciplines, and to improve the diagnostic and therapeutic skill and expertise of clinicians.

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ORIGINAL ARTICLE

Case Control Study

Clinical utility of the platelet-lymphocyte ratio as a predictor of postoperative complications after radical gastrectomy for clinical T2-4 gastric cancer

Kenichi Inaoka, Mitsuro Kanda, Hiroaki Uda, Yuri Tanaka, Chie Tanaka, Daisuke Kobayashi, Hideki Takami, Naoki Iwata, Masamichi Hayashi, Yukiko Niwa, Suguru Yamada, Tsutomu Fujii, Hiroyuki Sugimoto, Kenta Murotani, Michitaka Fujiwara, Yasuhiro Kodera

Kenichi Inaoka, Mitsuro Kanda, Hiroaki Uda, Yuri Tanaka, Chie Tanaka, Daisuke Kobayashi, Hideki Takami, Naoki Iwata, Masamichi Hayashi, Yukiko Niwa, Suguru Yamada, Tsutomu Fujii, Hiroyuki Sugimoto, Kenta Murotani, Michitaka Fujiwara, Yasuhiro Kodera, Department of Gastroenterological Surgery (Surgery II), Nagoya University Graduate School of Medicine, Nagoya 4668550, Japan

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Author contributions: Inaoka K wrote the manuscript; Kanda M and Kodera Y revised the text and contributed to the scientific analysis in the manuscript; Uda H, Tanaka Y, Tanaka C, Kobayashi D, Takami H, Iwata N, Hayashi M, Niwa Y, Yamada S, Fujii T, Sugimoto H, Fujiwara M contributed to data collection; Murotani K conducted the statistical analyses.

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Informed consent statement: This study conforms to the ethical guidelines of the World Medical Association Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects, and written informed consent for the use of clinical data were obtained from all patients.

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Abstract

AIM

To identify simple and sensitive markers for post-operative complications after gastrectomy, the predictive values were compared among candidate preoperative factors.

METHODS

Three-hundred and twelve patients with previously untreated clinical T2-4 gastric cancer who underwent a D2 standard gastrectomy (distal gastrectomy or total gastrectomy) were included in the analysis.

Correlations between 21 parameters that can be determined by preoperative routine blood tests and clinically relevant postoperative complications (grade Ⅱ or higher according to the Clavien-Dindo classification) were evaluated. The optimal cutoff values and clinical significance of the selected markers were further evaluated by subgroup analyses according to age, body mass index, operative procedure and clinical disease stage.

RESULTS

Sixty-six patients (21.1%) experienced grade Ⅱ or higher postoperative complications. The platelet-lymphocyte ratio (PLR, total lymphocyte count/platelet count × 100) exhibited the highest area under the curve value (0.639) for predicting postoperative complications among the 21 parameters, and the optimal cutoff value was determined to be 0.71 (sensitivity = 70%, specificity = 56%). In the univariate analysis, the odds ratio of a low PLR for the occurrence of postoperative complications was 2.94 (95%CI: 1.66-5.35, $P < 0.001$), and a multivariate binomial logistic analysis involving other potential risk factors identified a low PLR as an independent risk factor for postoperative complications (OR = 3.32, 95%CI: 1.82-6.25, $P < 0.001$). In subgroups classified according to age, body mass index, operative procedure and clinical disease stage, the low PLR group exhibited an increased incidence of postoperative complications.

CONCLUSION

The preoperative PLR is a simple and useful predictor of complications after curative gastrectomy in patients with clinical T2-4 gastric cancer.

Key words: Gastric cancer; Gastrectomy; Platelet-lymphocyte ratio; Postoperative complication; Prediction

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Core tip: The prediction of postoperative complications is important for providing appropriate perioperative management. In the present study, the predictive values for postoperative complications after gastrectomy with systemic lymphadenectomy for gastric cancer were compared among candidate preoperative factors to identify a simple and sensitive marker. Our results indicated that the preoperative platelet-lymphocyte ratio is a simple and useful predictor for complications after curative gastrectomy in patients with gastric cancer.

Inaoka K, Kanda M, Uda H, Tanaka Y, Tanaka C, Kobayashi D, Takami H, Iwata N, Hayashi M, Niwa Y, Yamada S, Fujii T, Sugimoto H, Murotani K, Fujiwara M, Kodera Y. Clinical utility of the platelet-lymphocyte ratio as a predictor of postoperative complications after radical gastrectomy for clinical T2-4 gastric cancer. *World J Gastroenterol* 2017; 23(14): 2519-2526 Available from: URL: http://www.wjgnet.com/1007-9327/full/v23/i14/2519.htm DOI: http://dx.doi.org/10.3748/wjg.v23.i14.2519

INTRODUCTION

Gastrectomy with systemic lymphadenectomy is the mainstay of treatment for resectable gastric cancer (GC)[1,2]. Despite advances in surgical techniques and devices, some patients who undergo the procedure experience clinically relevant postoperative complications, such as anastomotic leakage and intraabdominal abscess, leading to a protracted recovery period, delayed administration of adjuvant chemotherapy and impaired quality of life[3,4]. Risk management is an increasingly important healthcare issue. Developing a prediction tool based exclusively on preoperatively determined factors to identify patients most at risk of postoperative complications enables surgeons to provide appropriate informed consent information and perioperative management, ultimately minimizing the medical cost burden[5,6].

Increasing evidence indicates that multiple factors influence local infection control and the process of wound healing[7]. Accordingly, numerous reports on predictive factors for postoperative complications, including inflammatory, immunological, nutritional, coagulation and organ functional indicators, have been published[8-11]. However, limited information from cross-comparisons of these factors is available for patients who undergo a D2 gastrectomy for GC.

The aim of the present study was to compare the predictive values for postoperative complications after gastrectomy among candidate preoperative factors based on routinely obtained laboratory data. After the factor that demonstrated the highest predictive value was determined, the optimal cutoff value and its clinical significance were evaluated.

MATERIALS AND METHODS

Ethics

This study conforms to the ethical guidelines of the World Medical Association Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects, and written informed consent for surgery and the use of clinical data were obtained from all patients as required by the Institutional Review Board of Nagoya University.

Patients, surgical procedure and perioperative treatment

A total of 1194 patients underwent a gastrectomy for GC at the Department of Gastroenterological Surgery, Nagoya University between 1999 and 2016. We retrospectively analyzed the data of 312 patients according to the following inclusion criteria: no preoperative treatment; clinical T2-4 (advanced) GC according to the TNM Classification of Malignant

Table 1 Demographic and preoperative clinical characteristics of 312 patients

Variables	Number of patients
Age, median (range)	66 (20-96)
Sex	
Male	233
Female	79
Diabetes mellitus	
Absent	273
Present	39
Cardiac comorbidities	
Absent	217
Present	95
Pulmonary comorbidities	
Absent	292
Present	20
Preoperative symptoms	
Absent	172
Present	140
Preoperative body mass index, mean ± SD	21.9 ± 3.2
Tumor location	
Entire	8
Upper third	68
Middle third	120
Lower third	116
Tumor size (mm)	
< 50	176
⩾ 50	136
UICC cT factor	
cT1	0
cT2	150
cT3	95
cT4	67
UICC cN factor	
cN0	157
cN1	93
cN2	53
cN3	9
UICC clinical stage	
ⅠB	98
ⅡA	71
ⅡB	69
ⅢA	55
ⅢB	14
ⅢC	5

UICC: Union for International Cancer Control.

Tumours, 7th Edition[12]; D2 gastrectomy (distal gastrectomy or total gastrectomy) performed according to the Japanese Gastric Cancer Treatment Guidelines[13]; no combined resection of other organs except for the spleen and gallbladder; R0 gastrectomy performed and sufficient data for analysis. The choice of the reconstruction method was at the surgeon's discretion. A first-generation cephem-based antibiotic was administered immediately before surgery and every 3 h during surgery. Oral intake was routinely started on postoperative day 1 if no obvious problems were found. Percutaneous drainage or the replacement of drainage tubes was performed when signs of inadequate drainage were noted by computed tomography or ultrasound scans. Clinically relevant postoperative complications were defined as those of grade Ⅱ or higher according to the Clavien-Dindo classification[14].

Study parameters

Blood tests were routinely performed two days before surgery. Data were collected retrospectively from the medical records focusing on five categories: blood cell count, coagulation, nutrition, renal function and inflammation. The parameters investigated as candidate predictive factors for postoperative complications, which can be rapidly measured in every hospital, included the following: white blood cell count, neutrophil count, total lymphocyte count (TLC), hemoglobin concentration, platelet count, prothrombin time, activated partial thromboplastin time, fibrinogen, total protein, albumin, cholinesterase, total cholesterol, urea nitrogen, creatinine and C-reactive protein (CRP). In addition, some simple indices were employed as candidate indicators: neutrophil-lymphocyte ratio (NLR = neutrophil count/TLC), platelet-neutrophil ratio (PNR = neutrophil count/platelet count × 100), platelet-lymphocyte ratio (PLR = TLC/platelet count × 100), Onodera's PNI (PNI = 10 × albumin g/dL + 0.005 × TLC/mm^3), Glasgow prognostic score (GPS) and the modified GPS[7,8,15].

Subgroup analyses

Subgroup analyses according to age, body mass index (BMI), operative procedure and clinical disease stage were performed to evaluate the correlations between the selected predictive factors and the incidence of clinically relevant postoperative complications.

Statistical analysis

A receiver operating characteristic (ROC) curve analysis was employed to calculate the area under the curve (AUC) and the sensitivity and specificity of the indicated variables to predict postoperative complications. The optimal cutoff value was determined using the Youden index[16]. The qualitative χ^2 test and quantitative Mann-Whitney test were used to compare the two groups. Multivariable analysis was performed to identify independent risk factors for postoperative complications using binomial logistic analysis, and variables with a value of $P < 0.05$ were included as covariates in the final model. All statistical analyses were performed using JMP 10 software (SAS Institute Inc., NC, United States). A statistically significant difference was indicated by a P-value < 0.05.

RESULTS

Patient characteristics

The demographic and preoperative characteristics of the 312 patients are presented in Table 1. The median age was 66 years, and the male-to female ratio was 233:79. With respect to preoperative staging, 98, 71, 69, 55, 14 and 5 patients were classified as clinical TNM stages ⅠB, ⅡA, ⅡB, ⅢA, ⅢB and ⅢC, respectively.

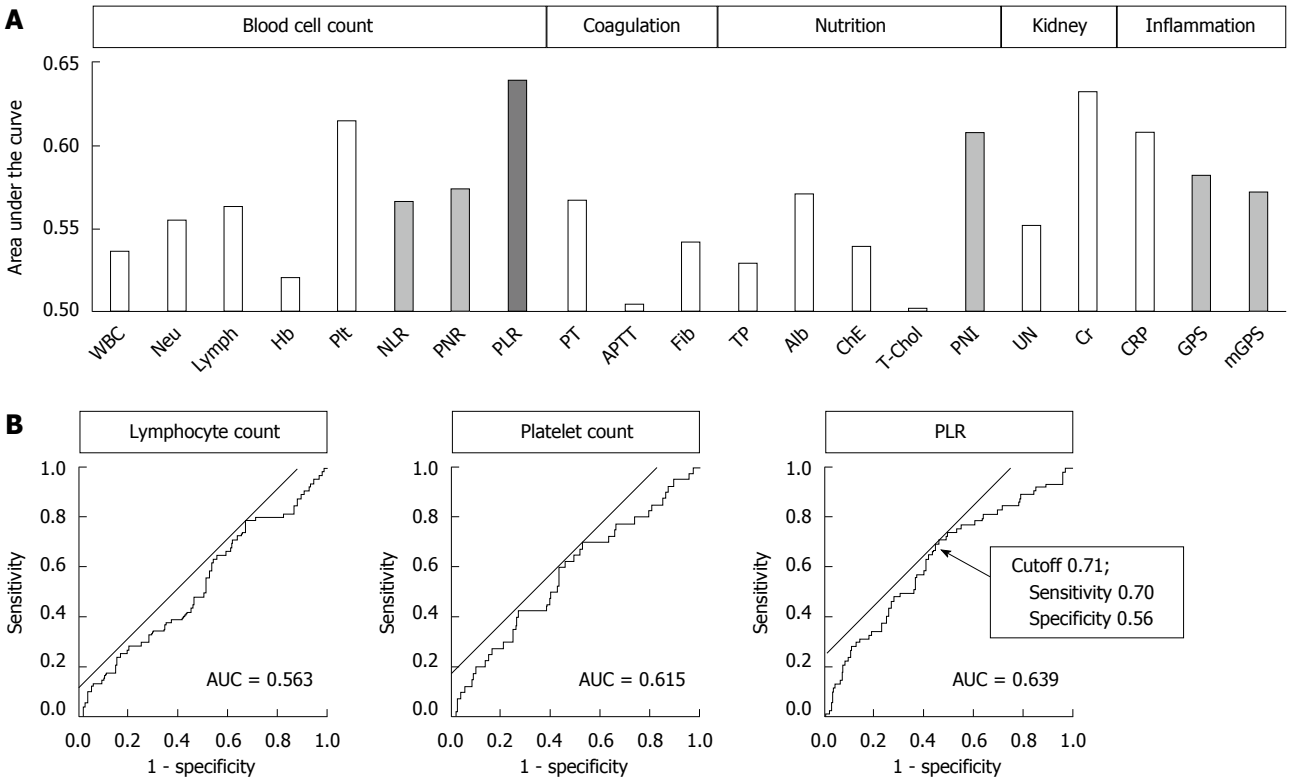

Figure 1 Comparison of the predictive value of potential indicators. A: Area under the curve values of potential predictors; B: Predictive values of lymphocyte count, platelet count and PLR for postoperative complications evaluated by receiver operating characteristic curve analysis. PLR: Platelet-lymphocyte ratio.

Comparison of predictive values among the candidate parameters

In total, 66 patients (21.1%) had grade Ⅱ or higher postoperative complications. In terms of the types of complications, the cumulative numbers of patients who experienced anastomotic leakage, leakage of pancreatic fluids, intraabdominal abscess and bowel obstruction were 20 (6.4%), 12 (3.8%), 19 (6.1%) and 6 (1.9%), respectively. When the AUC value, which indicates the power to predict postoperative complications, of the 21 parameters was analyzed, the PLR demonstrated the highest AUC value (0.639) (Figure 1A). This value was greater than the values of the PLR components TLC (AUC 0.563) and platelet count (AUC 0.615) (Figure 1B). The optimal cutoff value for predicting complications using the PLR was set at 0.71 (sensitivity = 70%, specificity = 56%) (Figure 1B). The AUC values of NLR, PNR, PNI and GPS were 0.566 (cutoff = 3.06), 0.574 (cutoff = 1.36), 0.608 (cutoff = 47.0) and 0.582 (cutoff = 1), respectively (Figure 1A).

Predictive value of the PLR

The median PLR was 0.71 (range 0.23-3.97), which is identical to the proposed cutoff. Using the cutoff indicated by the ROC curve analysis, we further evaluated the clinical significance of the PLR. Patients were categorized into two groups, the high (n = 158) and low (n = 154) PLR groups, using a PLR cutoff of 0.71. Compared to the high PLR group, patients in the low PLR group were associated with increased prevalence of pulmonary comorbidities, larger macroscopic tumor size and more frequent postoperative complications (Table 2). However, no significant differences were observed between the two groups regarding age, sex, preoperative BMI, clinical stage, type of gastrectomy, operative time, intraoperative blood loss and number of dissected lymph nodes (Table 2). In the univariate analysis, the odds ratio of a low PLR for postoperative complications was 2.94 (95%CI: 1.66-5.35, P < 0.001; Table 3). We next conducted a multivariable binomial logistic analysis involving other potential risk factors determined before surgery and found that a low PLR was an independent risk factor for postoperative complications (odds ratio 3.32, 95%CI: 1.82-6.25, P < 0.001) along with male sex and total gastrectomy (Table 3). With respect to the types of complications, the low PLR group exhibited an increased prevalence of anastomotic leakage, leakage of pancreatic fluids, intraabdominal abscess and bowel obstruction compared to the high PLR group. However, the differences were not statistically significant (Figure 2). By contrast, the incidence of cardiopulmonary dysfunction was comparable between the two groups.

Subgroup analyses

To further evaluate the clinical effect of the preoperative PLR on the postoperative course, subgroup analyses were conducted according to age (< 65 years or ⩾ 65 years), preoperative BMI (< 22 or ⩾ 22),

Table 2 Comparison between two subgroups according to the preoperative platelet-lymphocyte ratio

Variables	PLR < 0.71 (*n* = 154)	PLR ⩾ 0.71 (*n* = 158)	*P* value
Age, median (range)	66 (20-86)	66 (34-96)	0.661
Sex			0.434
Male	112	121	
Female	42	37	
Diabetes mellitus			0.070
Absent	140	133	
Present	14	25	
Cardiac comorbidities			0.785
Absent	106	111	
Present	48	47	
Pulmonary comorbidities			0.021
Absent	149	143	
Present	5	15	
Preoperative symptoms			0.838
Absent	84	88	
Present	70	70	
Preoperative body mass index, mean ± SD	21.6 ± 3.3	22.2 ± 3.1	0.102
Tumor location			0.673
Entire	3	5	
Upper third	32	36	
Middle third	57	63	
Lower third	62	54	
Tumor size (mm)			0.043
< 50	78	98	
⩾ 50	76	60	
UICC cT factor			0.502
cT1	0	0	
cT2	69	81	
cT3	49	46	
cT4	36	31	
UICC cN factor			0.633
cN0	75	82	
cN1	51	42	
cN2	24	29	
cN3	4	5	
UICC clinical stage			0.823
Ⅰ B	45	53	
Ⅱ A	37	34	
Ⅱ B	32	37	
Ⅲ A	31	24	
Ⅲ B	7	7	
Ⅲ C	2	3	
Operative procedure			0.669
Total gastrectomy	52	57	
Distal gastrectomy	102	101	
Splenectomy			0.191
Absent	128	122	
Present	26	36	
Dissected lymph nodes, mean ± SD	37.6 ± 15.8	38.7 ± 18.0	0.823
Operative time (min), mean ± SD	233 ± 56	238 ± 74	0.720
Estimated blood loss (mL), median (range)	237 (1-2350)	245 (8-4267)	0.491
Postoperative complications			< 0.001
Absent	108	138	
Present	46	20	

PLR: Platelet-lymphocyte ratio; UICC: Union for International Cancer Control.

operative procedure (distal or total gastrectomy) and clinical disease stage. The low PLR group exhibited an increased incidence of postoperative complications for all subgroup analyses (Figure 3).

DISCUSSION

The PLR, a combination of circulating platelet and lymphocyte counts, is a representative index of systemic inflammation and immune status[9,17]. Accordingly, a decreased PLR value indicate both systemic inflammation and compromised immune reaction. Although preoperative systemic inflammation has been reported as an underlying characteristic that predisposes the host to postoperative infection, only limited evidence is available[18]. In this study, a significant relationship between the preoperative PLR and postoperative complications was demonstrated. The PLR exhibited the highest AUC value for the incidence of postoperative complications among the candidate parameters obtained from routine preoperative blood tests. A low preoperative PLR was identified as an independent risk factor for postoperative complications in the multivariable analysis. Moreover, a low preoperative PLR was associated with an increased incidence of postoperative complications independent of age, BMI, operative procedure and disease stage, indicating that the preoperative PLR is applicable to various clinical settings.

The PLR can be determined in every hospital and is the subject of interest as a marker of systemic inflammation in various clinical circumstances. Several reports indicate that the PLR can serve as a prognostic factor for digestive malignancies[9,18]. Accumulating evidence indicates that a systemic inflammatory response could play an important role in the development and progression of cancer. Inflammation is closely related to different stages of tumor development, including initiation, invasion, metastasis, immune surveillance and responses to therapy[7,8,10,19,20]. However, the clinical impact of the preoperative PLR on postoperative short-term outcomes, particularly in patients undergoing a gastrectomy, remains unclear. Our results suggested that surgeons can provide precise informed consent information and identify high-risk patients to tailor perioperative care as an attempt to ultimately improve postoperative short-term outcomes for GC patients undergoing a gastrectomy using this prediction tool. Recently, preoperative risk calculation systems based on large-scale integrated databases, such as the Surgical Risk Preoperative Assessment System (SURPAS) and the Physiologic and Operative Severity Score for the enUmeration of Mortality and morbidity (POSSUM) model, have been widely used in clinical practice[5,21]. Our data suggest that the PLR could at least become a potential constituent of integrated scoring systems for surgical risk assessment.

The association between a decreased PLR and the development of postoperative infectious complication

Table 3 Predictive factors for grade 2 or higher complications according to the Clavien-Dindo system: Univariate and multivariable analyses

Variables	Univariate			Multivariable		
	Odds ratio	95%CI	*P* value	Odds ratio	95%CI	*P* value
Age (≥ 65 yr)	1.26	0.73-2.23	0.410			
Gender (male)	4.22	1.88-11.3	< 0.001	4.17	1.78-11.5	< 0.001
Preoperative symptoms	0.95	0.55-1.64	0.864			
Diabetes mellitus	1.14	0.49-2.45	0.755			
Cardiac comorbidities	1.81	1.02-3.18	0.041	1.55	0.83-2.87	0.166
Pulmonary comorbidities	1.26	0.40-3.40	0.669			
Body mass index (≥ 22)	1.62	0.94-2.81	0.084			
Preoperative PLR (< 0.71)	2.94	1.66-5.35	< 0.001	3.32	1.82-6.25	< 0.001
Tumor location (lower third)	0.62	0.34-1.11	0.107			
Macroscopic tumor size (> 50 mm)	1.19	0.69-2.05	0.534			
UICC cT (cT4)	1.30	0.67-2.69	0.457			
UICC cN (cN1-3)	1.75	1.01-3.08	0.045	1.69	0.93-3.08	0.083
Operative procedure (total gastrectomy)	2.42	1.39-4.23	0.002	2.43	1.35-4.43	< 0.001

Analyses were performed using binomial logistic analysis. PLR: Platelet-lymphocyte ratio; UICC: Union for International Cancer Control.

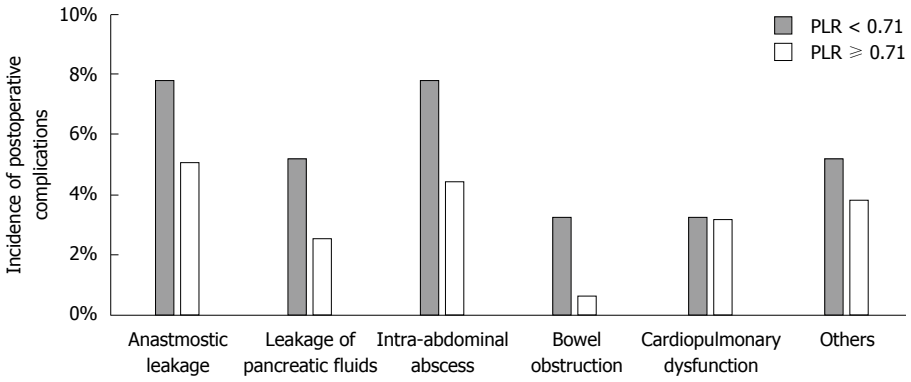

Figure 2 Comparison of the prevalence of each complication type between the high and low platelet-lymphocyte ratio groups.

is likely complex and remains unclear. One plausible explanation is that a decreased PLR may reflect four disadvantages for the postoperative course including an inflammatory status, immune disorders, malnutrition and a tendency for micro-vessel thrombosis[10,18]. A decreased PLR collectively reflects a reduced TLC (compromised cell-mediated immunity and malnutrition) and an increased platelet count (inflammation and high thromphophilic diathesis). Lymphocytopenia is associated with malnutrition and cellular immunosuppression[22-24]. A pro-inflammatory status leads to compromised cell-mediated immunity and an impaired T-lymphocytic response *via* cytokines[25]. The ability of myeloid cells to synthesize pro-inflammatory and anti-inflammatory mediators is affected by their previous state[10,18]. Malnutrition is a major cause of delayed wound healing[11,15]. A decreased lymphocyte-mediated antibacterial immune reaction may weaken the lymphocyte-mediated antibacterial cellular immune response and contribute to increasing bacterial invasion and growth[10,18]. The platelet count is recognized as a marker of a systemic inflammatory response and potential micro-vessel thrombosis[7,9,17]. Formation of micro-vessel thrombosis inhibits wound healing via the deterioration of blood circulation in tissues. Eventually, the crosstalk of these complex factors increases the incidence of postoperative complications. In addition, our findings raised two questions. First, why is the PLR was more sensitive than the other indices, such as the PNI and GPS? We hypothesize that the PLR is indicative of four elements, including inflammatory status, immune disorders, malnutrition and a tendency for micro-vessel thrombosis, and therefore it was more closely associated with postoperative complications than other indices. Another question is whether preoperative modification of the PLR by anti-inflammatory treatment and nutritional support reduces the adverse effects on the postoperative clinical course. Further investigations are needed to answer these questions.

The current study also had several limitations that should not be ignored. This was a retrospective study of a limited number of patients from a single institute. Thus, our findings require validation by further large-scale prospective studies. To further evaluate the association of the PLR with the host inflammatory and nutritional status, information on levels of cytokines and rapid turnover proteins is required.

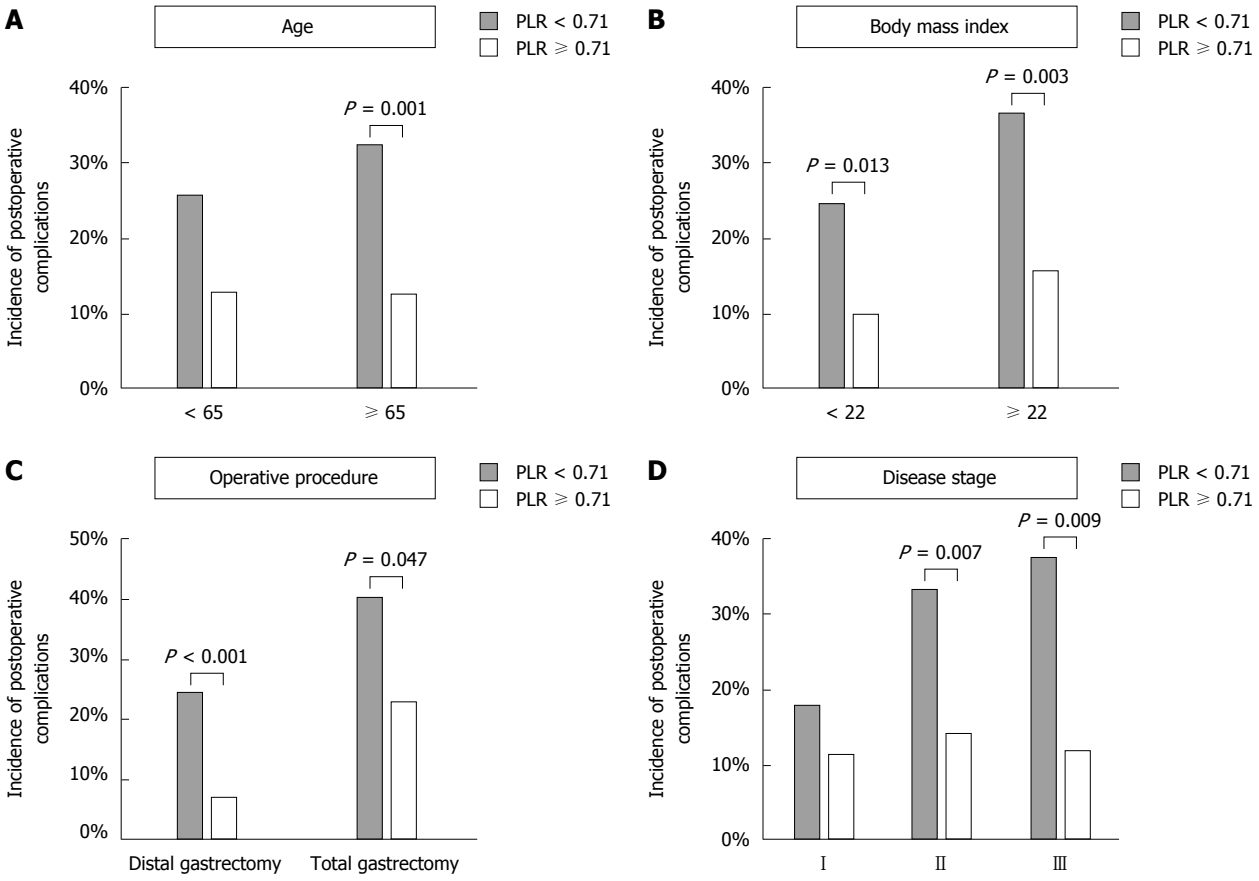

Figure 3 Subgroup analyses. The morbidity rates were compared between the high and low PLR groups according to age (A), body mass index (B), operative procedure (C) and clinical disease stage (D). Comparison of predictive value of potential indicators. PLR: Platelet-lymphocyte ratio.

Taken together, the results indicate that the preoperative PLR is a simple and useful predictor of postoperative complications in patients who undergo a gastrectomy with systemic lymphadenectomy for GC. In the future, the development of an integrated risk stratification system using the PLR may facilitate physicians' decision-making and contribute to the informed consent process before a gastrectomy.

COMMENTS

Background

Patients undergoing a gastrectomy with systemic lymphadenectomy for gastric cancer occasionally experience clinically relevant postoperative complications. Development of a prediction tool based on preoperatively determined factors would be helpful to identify individuals at risk of postoperative complications for whom precise informed consent and tailored perioperative management could be provided.

Research frontiers

Platelet-lymphocyte ratio (PLR) showed the highest predictive value for postoperative complications among the 21 parameters. It was found to be an independent risk factor in a multivariate binomial logistic analysis.

Innovations and breakthroughs

The authors found that PLR served as a predictor of postoperative complications in all subgroups classified according to age, body mass index, operative procedure and clinical disease stage.

Applications

PLR is a simple and useful predictor of postoperative complications in patients who undergo a gastrectomy with systemic lymphadenectomy for gastric cancer. It may facilitate physicians' decision-making and contribute to the informed consent process before a gastrectomy.

Terminology

PLR is a platelet-lymphocyte ratio (total lymphocyte count/platelet count × 100) and is a representative index of systemic inflammation and immune status.

Peer-review

This is an interesting, single center retrospective study on clinical utility of preoperative predictors of postoperative complications for clinical T2-4 gastric cancer. The authors made a high quality statistical analysis and found a new statistical, easy, reproducible and overall available index, the PLR, to predict the postoperative complications after radical gastrectomy for clinical T2-4 gastric cancer.

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