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Identification of Candidates for Early Discharge After Gastrectomy

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ABSTRACT

Objective. The aim of this study was to analyze clinical and laboratory variables associated with complications after gastrectomy for gastric cancer to predict candidates for successful early discharge.

Methods. Consecutive patients undergoing gastrectomy at Seoul National University Hospital from January through December 2013 were identified from a prospective complications database. Clinicopathologic and postoperative laboratory parameters were analyzed to determine variables associated with complications. An additional validation study was performed from March through May 2014.

Results. Overall, complications occurred in 180/855 patients (21.1 %). Age >68 years (odds ratio [OR] 1.64), use of an open approach (OR 1.9), and use of combined resection (OR 1.67) were significant independent risk factors for complications ($p < 0.05$). The postoperative day (POD) 5 to preoperative white blood cell count (WBC) ratio (risk ratio [RR] 2.01), C-reactive protein (CRP) level on POD 5 (RR 1.1), and maximum body temperature on POD 4 (RR 2.36) independently predicted complications in a multivariate analysis ($p < 0.05$). After establishing an early discharge profile (EDP) based on these six variables, 152/855 patients (17.8 %) were predicted to have an uncomplicated course. Of these, 8/152 (5.3 %) experienced complications. In a validation study of 217 patients, 43/217 (19.8 %) were candidates for early discharge on POD 5, and 3 (7.0 %) had a false-positive EDP.

Conclusions. Patients younger than 68 years of age who underwent laparoscopic gastrectomy without combined resection might be candidates for early discharge on POD 5 if the POD 5 to preoperative WBC ratio is ≤1.2, POD 5 CRP level is ≤5.38 g/mL, and POD 4 body temperature is ≤37.4 °C.

Post-gastrectomy complications in patients with gastric cancer can be associated with increased morbidity, often resulting in long hospital stays, disturbances of oral nutrition, increased socioeconomic costs, and even poor long-term oncologic outcomes.[1,2] Despite significant efforts to control complications, the rate of morbidity following gastrectomy is reported to be 10–28 %. [3–7]

To date, many clinical studies related to the risk of complications after gastrectomy have focused on the detection of risk factors. Age, extent of gastrectomy, combined resection, comorbidities, the surgeon's experience, and extent of lymphadenectomy have been reported as predictive factors.[4,7–9] In terms of laboratory parameters, white blood cell count (WBC) and C-reactive protein (CRP) level are widely used markers for predicting infectious complications in various surgical fields.[10–13] Although many studies have examined risk factors for complications, few reports have specifically focused on the factors predicting an uncomplicated hospital stay.

Ji-Ho Park and Young-Gil Son have contributed equally to this study.

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With increasing medical costs, safely reducing the length of a patient's hospital stay has become a major focus for optimizing the utilization of healthcare resources.[14] Determining which factors influence the length of hospital stay might provide information on how to reduce costs and improve treatment delivery.[15] Enhanced recovery pathways have standardized perioperative care, facilitated 'fast-track' recovery, and been proven to reduce length of hospital stay after gastrectomy.[16,17] For successful fast-track recovery, identifying patients with complications is indispensable before discharge. Thus, in this study, we investigated clinical and laboratory data for patients following gastrectomy to identify those patients who might be candidates for successful, uncomplicated early discharge.

PATIENTS AND METHODS

Patients

We retrospectively collected data from 855 patients who underwent gastric cancer surgery at Seoul National University Hospital between January and December 2013 who satisfied our inclusion criteria of having a primary gastric cancer diagnosis and who underwent gastrectomy. Patients who underwent preoperative chemotherapy and/or had other primary malignancies, recurrent cancer, or remnant gastric cancers were excluded.

Data on patient demographics, operative procedures, pathological results based on the American Joint Committee on Cancer (AJCC) TNM 7th edition,[18] hospital course, laboratory results, and postoperative complications were reviewed. Data on complications were collected prospectively. The hospital course was monitored daily by the attending surgeon. In addition, based on a consensus of faculty at a weekly conference, the type and classification of each complication was defined using the Clavien–Dindo classification.[19] Complications that occurred within 30 days postoperatively were considered relevant to the operation and were collected for this study. The data included that of patients who were discharged and then revisited the emergency room or outpatient clinic because of complications. Data for complications resulting in readmission and/or occurring outside of the hospital course were also collected; complications were defined based on our previous report on complications following gastrectomy.[4] Comorbidity data were collected and scored according to the Charlson Comorbidity Index.[20]

The independent risk factors for overall postoperative complications were used to determine constituent units of an early discharge profile (EDP). Patients who satisfied the criteria of the EDP were defined as positive for EDP; however, patients who did satisfy all of the criteria were considered negative for EDP. A false-positive EDP was defined as a patient who was predicted to have an uncomplicated course but who experienced any postoperative complication.

Additional internal validation for the application of this profile was performed from March to May 2014 using data from 217 patients based on the same inclusion and exclusion criteria used in this study.

Patients underwent subtotal (including distal, pylorus-preserving, or proximal) or total gastrectomy with regional lymphadenectomy as defined by the Japanese Gastric Cancer Association treatment guidelines.[21] Briefly, laparoscopic gastrectomy with D1+ lymph node dissection was performed for patients preoperatively diagnosed with clinically early gastric cancer (EGC), while open gastrectomy with D2 lymphadenectomy was performed for patients with advanced gastric cancer (AGC). Patients enrolled in the KLASS-02 trial (NCT01456598), a prospective, multicenter, randomized controlled trial comparing laparoscopic and open distal gastrectomy with D2 lymphadenectomy for AGC, underwent laparoscopic distal gastrectomy, even if they were diagnosed with AGC preoperatively.[22] According to the surgeon's preference, either total or proximal gastrectomy was performed for EGC in the upper third of the stomach, and pylorus-preserving or distal gastrectomy was performed for EGC in the middle third of the stomach. All surgical procedures were performed by four experienced faculty surgeons.

Patients were managed perioperatively using the same standardized clinical pathway protocol.[23] Prophylactic antibiotics were administered immediately before skin incision and continued until the first postoperative day (POD 1). Following surgery, sips of water were allowed for patients on POD 3, irrespective of whether flatus could be passed. Serum laboratory tests, including complete blood count, electrolytes, admission panel (i.e. calcium, phosphorus, glucose, blood urea nitrogen [BUN], uric acid, cholesterol, protein, albumin, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, and creatinine) and CRP level, were measured on PODs 2, 5, and 7. If water was ingested successfully, patients were allowed a semi-fluid diet on POD 4. In the absence of complications or complaints, patients were discharged on the seventh or eighth POD after removal of stitches.

Statistical Analysis

Categorical variables were presented as numbers and percentages, and postoperative complications were compared among groups using the Chi square test. Continuous variables were expressed as the means and standard

deviations, and the means were compared using the Student's t test. A univariate analysis was conducted to evaluate the independent association of each factor with the development of postoperative complications. Independent risk factors for postoperative complications were then adjusted in a multivariate logistic regression. During that analysis, variables found to be significant in the univariate analysis were entered into a multivariate analysis. In the multivariate analysis, adjusted odds ratios (ORs) [exponential β] were calculated with 95 % confidence intervals (CIs). Multicollinearity between independent variables (i.e. laboratory data) was assessed by variance inflation factors (VIF) [reference value of 5] before calculating the final output. We configured the EDP using independent risk factors for complications confirmed by multivariate analysis. A receiver operating characteristic (ROC) curve analysis was conducted to evaluate predictors of complications by age, CRP level, WBC count, and maximal body temperature on POD 4. Optimal cut-off values were determined by the maximum value of Youden's index (sensitivity + specificity−1). All tests were two-sided and were performed at a significance level of 5 % using IBM® SPSS® Statistics version 20 software (IBM Corporation, Armonk, NY, USA). This study was approved by the Institutional Review Board of our institution (H-1305-043-488).

RESULTS

Patient Characteristics

A total of 855 patients were included in the study, and their clinicopathological characteristics are shown in Table 1. Overall, 180 patients (21.1 %) developed complications, accounting for 245 clinical events; 71 patients (8.3 %) experienced severe complications (grade IIIa or higher). Detailed descriptions of local and systemic complications are presented in electronic supplementary Table S1.

TABLE 1 Clinicopathologic characteristics

Variable	Total [$n = 855$]
Age, years [mean ± SD]	60.9 ± 11.9
Sex ratio [male:female]	561:294
BMI [mean ± SD]	22.4 ± 3.1
Charlson comorbidity index	
0	570 (66.7)
≥1	345 (33.3)
ASA score	
1	414(48.4)
2	405 (47.4)
≥3	36 (4.2)
Type of gastrectomy	
Distal	438 (51.2)
Pylorus-preserving	209 (24.4)
Total	185 (21.6)
Proximal	23 (2.7)
Surgical method	
Open	310 (36.3)
Laparoscopic or robotic	545 (63.7)
Lymph node dissection	
D1 or D1+	441 (51.6)
D2	414 (48.4)
Combined resection	
No	693 (81.1)
Yes	162 (18.9)
Tumor location	
Upper third	157 (18.4)
Middle third	215 (25.1)
Lower third	464 (54.3)
Entire stomach	19 (2.2)
Tumor invasion	
EGC	541 (63.3)
AGC	314 (36.7)
Operation time, min [mean ± SD]	178.4 ± 68.5
Postoperative length of stay, days [mean ± SD]	9.6 ± 7.5
Postoperative complications	
No	675 (78.9)
Yes	180 (21.1)
Severe complications (grade IIIa or higher)	
No	71 (8.3)
Yes	784 (91.7)

Data are expressed as n (%) unless otherwise specified

ASA American Society of Anesthesiologists, *BMI* body mass index, *EGC* early gastric cancer, *AGC* advanced gastric cancer, *SD* standard deviation

Clinical and Laboratory Outcomes Associated with Postoperative Complications

In the univariate analysis, higher complication rates were associated with older age, male sex, type of gastrectomy (e.g. total and proximal gastrectomy), the open surgical method, extent of lymphadenectomy (e.g. D2), combined resection, and higher maximal body temperature on POD 4 (POD 4 BT_{max}; all $p < 0.05$) [Table 2]. In the analysis of laboratory data, POD 2 WBC count, POD 2 CRP level, POD 2 albumin level, POD 5 WBC count, POD 5 CRP level, POD 5 BUN level, and POD 5 albumin level were significantly different between patients with and without complications (all $p < 0.05$) [Table 2]. In addition, the ratios of the WBC count (including the POD 2:preoperative, POD 5:preoperative, and POD 5:POD 2 ratios) and

TABLE 2 Clinical and laboratory data related to postoperative complications

Variables	Without complication [$n = 675$]	With complication [$n = 180$]	p-Value
Age, years [n (%)]			<0.001
≤68	484 (82.2)	105 (17.8)	
>68	191 (71.8)	75 (28.2)	
Sex [n (%)]			0.009
Male	428 (76.3)	133 (23.7)	
Female	247 (84.0)	47 (16.0)	
Charlson comorbidity index [n (%)]			0.059
0	469 (82.3)	101 (17.7)	
≥1	266 (77.1)	79 (22.9)	
ASA score [n (%)]			0.078
1	335 (80.9)	79 (19.1)	
2	314 (77.5)	91 (22.5)	
≥3	26 (72.2)	10 (27.8)	
Type of gastrectomy [n (%)]			0.002
Distal	349 (79.7)	89 (20.3)	
Pylorus-preserving	180 (86.1)	29 (13.9)	
Total	129 (69.7)	56 (30.3)	
Proximal	17 (73.9)	6 (26.1)	
Surgical method [n (%)]			<0.001
Open	215 (69.4)	95 (30.6)	
Laparoscopy or robot	469 (84.4)	85 (15.6)	
Lymph node dissection [n (%)]			0.004
D1 or D1+	366 (83.0)	75 (17.0)	
D2	309 (74.3)	105 (25.7)	
Combined resection [n (%)]			<0.001
No	569 (82.0)	125 (18.0)	
Yes	107 (66.0)	55 (34.0)	
Tumor location [n (%)]			0.257
Upper third	115 (73.2)	42 (26.8)	
Middle third	172 (80.0)	43 (20.0)	
Lower third	374 (80.6)	90 (19.4)	
Entire stomach	14 (73.7)	5 (26.3)	
POD 4 BT_{max} (°C)	37.17	37.44	<0.001
POD 5 BT_{max} (°C)	37.05	37.25	0.08
Preoperative WBC	6016.7	6300.7	0.06
POD 2 WBC	10,907.2	12,670.7	<0.001
CRP	10.39	13.2	<0.001
BUN	10.47	12.14	0.23
Albumin	3.41	3.18	0.004
POD 2/preoperative WBC ratio	1.89	2.12	<0.001
POD 5 WBC	6324.1	7926.3	<0.001
CRP	5.4	9.1	<0.001
BUN	9.12	10.5	0.003
Albumin	3.36	3.17	<0.001
POD 5/preoperative WBC ratio	1.09	1.31	<0.001
POD 5/POD 2 WBC ratio	0.60	0.64	0.002

TABLE 2 continued

Variables	Without complication [$n = 675$]	With complication [$n = 180$]	p-Value
POD 5/POD 2 CRP ratio	0.54	0.70	<0.001

ASA American Society of Anesthesiologists, *POD* postoperative day, BT_{max} maximum body temperature, *WBC* white blood cell count, *CRP* C-reactive protein, *BUN* blood urea nitrogen

TABLE 3 Risk factors for postoperative complications by multivariate analysis

Laboratory variable	p-Value	Exponential (β)	95 % CI
Age (>68 years)	0.011	1.64	1.12–2.40
Sex	0.265		
Surgical method (open)	0.001	1.9	1.29–2.8
Type of gastrectomy	0.504		
Extent of lymphadenectomy	0.818		
Combined resection (yes)	0.011	1.67	1.06–2.62
POD 4 BT_{max} (°C)	0.001	2.36	1.43–3.9
POD 2 WBC	0.022	1.06	1.01–1.12
POD 5 CRP	<0.001	1.1	1.05–1.15
POD 5/preoperative WBC ratio	0.011	2.01	1.18–3.43

POD postoperative day, BT_{max} maximum body temperature, *WBC* white blood cell count, *CRP* C-reactive protein

TABLE 4 Overall complications according to early discharge profile

	Postoperative complications	
	Absence [$n = 675$]	Presence [$n = 180$]
Negative for early discharge profile [$n = 703$]	531	172
Positive for early discharge profile [$n = 152$]	144	8

Prediction of candidates for early discharge, 17.8 % (152/855); false-positive for early discharge profile, 5.3 % (8/152); sensitivity, 94.7 % (144/152); specificity, 24.5 % (172/703)

the POD 5:POD 2 CRP ratio were significantly different between patients with and without postoperative complications.

In the multivariate analysis, age >68 years (OR 1.64, 95 % CI 1.12–2.40), the open approach (OR 1.9, 95 % CI 1.29–2.8), and combined resection (OR 1.67, 95 % CI 1.06–2.62) were found to be significant independent predictors for overall complications ($p < 0.05$). The POD 5:preoperative WBC ratio (risk ratio [RR] 2.01, 95 % CI 1.18–3.43), POD 5 CRP level (RR 1.1, 95 % CI 1.05–1.15), and POD 4 BT_{max} (RR 2.396, 95 % CI 1.43–3.9) were found to be independent predictors in the multivariate analysis (all $p < 0.05$) [Table 3].

Establishment of an Early Discharge Profile

Using the results of the ROC curve analysis, the cut-off values for each significant continuous variable were (i) age 68.5 years; (ii) POD 5 CRP level 5.38 g/mL; (iii) POD 5:preoperative WBC ratio 1.2; and (iv) POD 4 BT_{max} 37.45 (Electronic Supplementary Fig. S1). With the addition of two categorical variables (laparoscopic approach and the absence of combined organ resection), a total of six values comprised the EDP (Electronic Supplementary Table S2).

Based on the EDP we developed, of the 855 total patients, the number of patients predicted to have an uncomplicated course was 152 (17.8 %). Among these 152 patients, 144 (94.7 %) did not experience any complication and 8 patients (8/152, 5.3 %) did. These 8 patients were considered to have a false-positive EDP (Table 4). In the internal validation study for the EDP, 43/217 patients (approximately one-fifth, 19.8 %) were predicted to have an uncomplicated recovery. Among these 43 patients who met the requirements for the EDP, 3 had a false-positive EDP (false-positive rate 7 %, 3/43) [Table 5].

TABLE 5 Validation of the early discharge profile using additional data

	Postoperative complications	
	Absence [$n = 160$]	Presence [$n = 57$]
Negative for early discharge profile [$n = 174$]	120	54
Positive for early discharge profile [$n = 43$]	40	3

Prediction of candidates for early discharge, 19.8 % (43/217); false-positive for early discharge profile, 7.0 % (3/43); sensitivity, 93.0 % (40/43); specificity, 31.0 % (54/174)

Complications Associated with a False-Positive Early Discharge Profile

Among 152 patients predicted to have uncomplicated recoveries, 8 (5.3 %) developed a total of nine complications, including three grade I complications (two wound complications and one urinary complication), three grade II complications (one motility disorder, one aggravation of previous ulcerative colitis, and one pancreatic leakage), two grade IIIa complications (two anastomotic stenoses), and one grade IIIb complication (one adhesive ileus). For the patient with the grade IIIb complication, laparoscopy-assisted total gastrectomy with Roux-en-Y esophagojejunostomy was performed with adhesiolysis and duodenojejunostomy on POD 29 for adhesive ileus. Two patients with grade IIIa complications successfully recovered after balloon dilation for anastomotic stenosis. The remaining patients with false-positive EDP complications were managed with conservative treatment. Of the three patients with false-positive EDPs in the validation analysis, all three had grade IIIa complications (two with wound dehiscence and one anastomotic stenosis). All of these patients recovered after wound repair under local anesthesia and temporary stent insertion throughout the stenotic anastomosis.

DISCUSSION

In the current study, we developed and internally validated an EDP for predicting which patients would experience uncomplicated recoveries after gastrectomy in order to identify candidates for early discharge. The EDP integrated four clinical variables (age, surgical approach, combined organ resection, and POD 4 BT_{max}) and two laboratory values (POD 5 CRP and POD 5:preoperative WBC ratio) associated with postoperative complications.

In our study, age >68 years, the open surgical method, and combined organ resection independently predicted the occurrence of complications. In addition to these factors, we discovered that POD 4 BT_{max} was significantly associated with complications. In terms of the relationship between laboratory values and complications, Dutta et al. showed that CRP values on PODs 3 and 4 were clinically useful for predicting surgical infectious complications after resection for esophagogastric cancer.[11] A previous report from our institution determined that pre-albumin, a visceral protein that is sensitive to protein malnutrition, is a useful marker for predicting infectious complications after gastric surgery.[24] In another study, we revealed a relationship between hemoglobin level and complications, suggesting that both anemia and transfusion are important factors in the development of complications.[25] In the present study, we analyzed the influence of several laboratory values on the occurrence of post-gastrectomy complications. POD 2 WBC, POD 5 CRP level, and the POD 5:preoperative WBC ratio were significantly related to the development of complications. The concept of the WBC ratio as a laboratory value was introduced in this analysis in order to compensate for baseline differences among patients. In fact, two WBC values (POD 2 WBC and the POD 5:preoperative WBC ratio) were found to be significant predictors. However, POD 2 WBC count was excluded from our EDP because it had a lower relative risk than the POD 5:preoperative WBC ratio (1.06 vs. 2.01, respectively).

Overall, 78.9 % (675/855) of patients had an uncomplicated course, while only 17.8 % of patients were predicted to have an uncomplicated course, which might seem to indicate that the discriminatory power of the EDP is low. However, we created this EDP with a focus on the detection of candidates for safe early discharge on POD 5 without any complications. Based on this profile, approximately one-fifth of patients could be discharged earlier than they would be based on the routine clinical pathway's discharge on POD 7 used in our institution.

Given the complications associated with patients with false-positive EDPs in this study, the developed EDP may not appropriately account for anastomotic stenoses, wound problems, or gastrointestinal motility disorders. Among a total of 12 patients with false-negative risk profiles, three-quarters (9/12) had complications that were classified as one of these types of complications. Among all occurring complications, the EDP was least able to predict anastomotic stenosis (3/19 [15.8 %] compared with wound problems, 3/19 [15.8 %], and gastrointestinal motility disorder, 2/30 [6.7 %]). Monitoring clinical signs and

laboratory values is the cornerstone of routine postoperative care, whereas WBC count and CRP level are the most widely used markers of infectious complications, such as anastomotic leakage, fluid collection, and pneumonia. However, anastomotic stenosis, wound problems, and ileus are not accompanied by inflammatory processes in the initial stage.

Recently, the application of minimally invasive surgery has increased, and gastrectomy could be considered a field in which fast-track surgery could be adopted.[16,17] To accomplish successful fast-track surgery, the selection of patients who will have an uncomplicated postoperative course is essential. In this study, we were able to predict patients who did not experience complications and who could have been successfully discharged early after gastrectomy using clinical data through POD 4 and laboratory values on POD 5. In other words, application of this profile for predicting uncomplicated patients could also be useful for expanding fast-track surgery in gastric cancer surgery. The profile proposed in this study might be a useful means of establishing a reasonable discharge recommendation.

This study had several limitations. First, we did not consider the timing of complication development; however, postoperative complications were detected before POD 5 in 103/855 patients (12.1 %). Our EDP did not consider the development of early complications. Second, the predictive value for early discharge (<20 %) appears low. Finally, in our gastric cancer cohorts, two-thirds of patients were diagnosed in the early stage, which is different from the profile described in Western studies.

CONCLUSIONS

We established and validated an EDP for predicting an uncomplicated hospital course after gastrectomy for gastric cancer. Patients younger than 68 years of age who underwent laparoscopic gastrectomy without combined resection might be candidates for early discharge at POD 5 if the POD 5:preoperative WBC ratio is $\leq$1.2, POD 5 CRP level is $\leq$5.38, and POD 4 BT_{max} is $\leq$37.4 °C.

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Compliance with Ethical Standards

DISCLOSURE Ji-Ho Park, Young-Gil Son, Tae-Han Kim, Yeon-Ju Huh, Jun-Young Yang, Yong-Joon Suh, Yun-Suhk Suh, Seong-Ho Kong, Hyuk-Joon Lee, and Han-Kwang Yang declare no potential conflicts of interest.

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