Effects of Clavien-Dindo classification on long-term survival of patients with advanced gastric cancer after radical resection: A propensity score-matched study

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Research

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Abstract

Background The impact of postoperative complications (POCs) classified by the Clavien-Dindo (C-D) system on long-term survival after radical resection in patients with advanced gastric cancer (AGC) is not yet clear.

Methods This study analyzed 531 patients with AGC who underwent radical resection in an institution between January 2015 and December 2017. Patients were divided into two groups according to the occurrence of POCs and recorded according to C-D classifications. The long-term survival outcomes of the entire cohort after propensity score matching (PSM) were compared.

Results After PSM, there was no significant difference in baseline data between the complications (C) group (n = 92) and the non-complications (NC) group (n = 92). Survival analysis showed that the 5-year overall survival (OS) and relapse-free survival (RFS) were lower in the C group (48.9% vs. 62.0%, $p = 0.040$; 38.5% vs. 54.9%, $p = 0.005$; respectively). Subgroup analysis showed that severe complications (C-D grade > II) were associated with a decrease in 5-year OS and RFS compared with the matched NC group (40.0% vs. 62.0%, $p = 0.008$; 29.4% vs. 54.9%, $p = 0.001$; respectively). Multivariate analysis confirmed adjuvant chemotherapy, tumor size, and complications were independent risk factors for poor survival outcomes. Further multivariate analysis showed that older age, combined excision, and comorbidities were independent risk factors for POCs.

Conclusions Severe complications reduced the survival outcome of patients. Older age, combined excision, and comorbidities were independent risk factors for POCs. More attention should be paid to perioperative management of patients with high risk factors for complications.

Introduction

Gastric cancer is a global disease, the fourth leading cause of cancer-related deaths worldwide[1], and the second leading cause of cancer-related deaths in China[2]. Radical resection of gastric cancer lesions combined with adequate lymph node dissection is key to treatment of gastric cancer. However, radical resection of gastric cancer is still technically difficult; the incidence of postoperative complications (POCs) of gastric cancer was reported to be 12.9–24.4% [3–5]. The most common POCs are anastomotic problems, obstruction, infectious complications such as pneumonia, abdominal abscess, urinary tract infection, incision infection, etc.

POCs were defined as any deviation from normal postoperative course[6], which were always associated with longer hospital stays, increased economic costs, and increased mortality[7, 8]. In recent years, studies have reported that POCs are a negative predictor of long-term survival outcomes[9–11]. Some researchers have suggested that the immune response of POCs may provide a suitable microenvironment for tumor cells remaining after surgery, thus promoting tumor recurrence and deterioration of survival outcomes[12, 13].

In this study, propensity score matching (PSM) was used to assess the impact of POCs on patient long-term survival outcomes to reduce potential confounders. C-D grade above level I was considered to have complications, otherwise it was considered to have no complications. Complications above grade II were considered serious. Multiple complications occurred in one patient, with only the most severe recorded. This study will provide a strong basis for us to reduce the incidence of POCS and better preoperative communication with patients and their families.

Materials And Methods

Patients

Patients were selected from our prospectively maintained gastric cancer database from January 2015 to December 2017. Inclusion criteria for the study were as follows: (1) adenocarcinoma confirmed by gastroscopy and pathological biopsy; (2) invasion depth greater than pT1; (3) no distant metastasis; (4) radical resection (R0) was performed; (5) other malignant tumors were not present; (6) emergency surgery was not performed; and (7) preoperative chemotherapy or radiotherapy was not performed. Pathological staging was graded according to the 8th Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC) staging system of gastric cancer [14]. PSM with a 0.02 caliper width was used to match the two groups on a 1:1 basis. The study was approved by our institute's ethics review committee.

Postoperative evaluation and follow-up

POCs were classified according to the Clavien-Dindo (C-D) classification system [6, 15]. Patients were followed up every 3 months for the first 2 years, then every 6 months for 2 to 5 years, and then once a year. OS was defined as the time from surgery to death or the last follow-up. RFS was defined as the time of surgical to recurrence, death, or the last follow-up. The final follow-up date was October 2020.

Statistical analysis

To reduce the impact of clinicopathological characteristics on survival outcomes, 1:1 PSM was performed using a logistic regression model and the following covariates: sex, age, body mass index (BMI), preoperative albumin, surgical method, resection range, history of upper abdominal surgery, combined resection, tumor size, comorbidities, pT stage, pN stage, pTNM stage, and adjuvant chemotherapy. The chi-square or Fisher's exact test was used to compare categorical variables between the two groups. The survival rate was compared by the Kaplan-Meier method and long-rank test. Multivariate analysis was performed using the Cox proportional hazard model to determine independent risk factors for OS and RFS reduction. Multivariate analysis was performed using a binary logistic regression model to identify independent risk factors for POCs. P-values less than 0.05 were considered statistically significant. SPSS version 25.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis and PSM.

Results

Clinicopathological characteristics

Table 1 shows the patient characteristics of the entire cohort (n = 531) and the PSM cohort (n = 184). There were differences in age, preoperative albumin, combined resection, comorbidities, and pT staging between the C and NC groups ($P < 0.05$). After PSM, patient characteristics were balanced in terms of age, sex, BMI, preoperative albumin, comorbidities, surgical method, resection range, combined resection, tumor size, pT stage, pN stage, pTNM stage, and postoperative chemotherapy.

Postoperative complications

Table 2 shows the details of POCs classified by C-D classification. The overall incidence of POCs was 17.7% (94/531) among the 531 patients in the entire cohort. The incidence of serious complications was 6.6% (35/531).

Survival outcomes

The median follow-up time was 47 months. POCs were associated with decreased 5-year OS (48.9% vs. 62.0%, $p = 0.040$) (Fig. 1A) and RFS (38.5% vs. 54.9%, $p = 0.005$) (Fig. 1B), indicating that the survival status of the C group was better than that of the NC group, this difference was statistically significant.

To further assess the impact of different C-D levels, we analyzed the survival outcomes of grade II POCs and matched NC groups. Grade II POCs had a tendency to decrease 5-year OS (54.4% vs. 62.0%, $p = 0.262$) (Fig. 2A) and RFS (43.9% vs. 54.9%, $p = 0.074$) (Fig. 2B), although the difference was not statistically significant. Another subgroup analysis showed that severe complications (C-D grade $> \text{II}$) reduced OS (40.0% vs. 62.0%, $p = 0.008$) (Fig. 3A) and RFS (29.4% vs. 54.9%, $p = 0.001$) (Fig. 3B) compared with the matched NC group; this difference was statistically significant.

We also assessed the differences between grade C-D II and severe complications. The results showed that severe complications reduced OS (37.2% vs. 59.2%, $p = 0.023$) (Fig. 4A) in a statistically significant manner and tended to reduce RFS (28.6% vs. 46.9%, $p = 0.054$) (Fig. 4B), but this difference was not statistically significant.

Risk factors for POCs

Multivariate analysis showed that age over 50, combined resection, and comorbidities were independent predictors of POCs (Table 3).

Risk factors associated with decreased OS and RFS

Multivariate analysis showed that POCs, stage pTNM III, tumor diameter > 5 cm, and absence of adjuvant chemotherapy were independent predictors of OS and RFS reduction (Table 4).

Discussion

This study investigated the relationship between POCs and OS and RFS after radical gastrectomy for advanced gastric cancer. POCs can prolong hospital stay, and increase cost and postoperative mortality. Studies have shown that POCs can reduce the long-term survival outcome of colorectal cancer[16-18]; the same trend has also been observed in gastric cancer[9, 19, 20].

In this study, we use C-D classification to classify POCs; this system has been regarded as a classical classification method and has been used to classify a variety of POCs [6, 15]. It has also been used to classify POCs of gastric cancer [21, 22]. The cohort was divided into two groups according to the presence of complications. Because the baseline characteristics of patients between the two groups were not comparable, we used PSM to reduce potential confounding factors and selection bias.

The present study showed that POCs were related to poor long-term survival outcomes. To evaluate the relationship between complication grade and survival outcome, we further analyzed the impact of C-D grade complications and severe complications on survival outcome. We found that grade complications had a negative effect on 5-year OS and RFS, but the results were not statistically significant, in contrast with a previous study[23]. Another subgroup analysis showed that severe complications reduced OS and RFS in patients with severe complications; this difference was statistically significant. Further subgroup analysis showed that severe complications reduced RFS in patients with severe complications compared with grade II complications. At the same time, there was a trend of negative impact on OS, but the results did not reach statistical significance ($P > 0.05$).

Because of the negative impact of POCs on survival outcome, it is necessary to understand the risk factors and take intervening measures. We carried out single- and multi-factor analyses in the whole cohort of in this study. Multivariate analysis showed that age over 50, combined resection, and comorbid diseases were independent risk factors for POCs. Many studies have shown that there is a relationship between advanced age and the occurrence of POCs[24, 25], which is consistent with our research. Old age will lead to a decrease in the physiological function of various organs, deterioration of nutritional status, and a decrease of anesthetic tolerance, which may be related to the increase of POCs. Therefore, in the perioperative management of patients, more attention should be paid to elderly patients.

A number of studies have shown that combined resection is associated with an increase in POCs[24, 26]; our study came to the same conclusion. Combined organ resection can prolong the operation time and increase the scope of surgical injury, which may increase POCs compared with gastrectomy alone. Previous studies have shown that gastrectomy combined with splenectomy or pancreatectomy increases the incidence of POCs and does not improve survival[27-29]. In addition, studies have shown that combined resection may negatively affect the recurrence-free survival of patients[30]. Therefore, more caution should be taken in deciding whether to perform multiple organ resection.

In terms of comorbidities, many studies have shown that comorbidities increase POCs [31-33], which is consistent with our results. This may be related to the fact that co-disease can reduce the patient's

respiratory and cardiac reserves. In addition, studies have shown that diabetes is associated with infectious complications [34, 35]. Therefore, appropriate perioperative management of patients with comorbid diseases is necessary.

A large number of studies have indicated that adjuvant chemotherapy can significantly improve the survival outcome of patients with advanced gastric cancer [36-38]. In our study, the chemotherapy data of the two groups were similar after PSM. As a result, the potential effect of adjuvant chemotherapy on survival outcome was eliminated to the greatest extent.

Thus far, the mechanism by which complications lead to poor survival outcomes is unclear. The generally accepted explanation is that the inflammatory microenvironment can promote tumor development, while complications can lead to a severe inflammatory response, which suppresses the patient's immune system and promotes tumor recurrence and metastasis[12, 13].

There were some limitations of this study. First, this study was a single-center retrospective study. Second, the operation was performed by multiple groups of physicians, and the influence of surgical experience on the outcome of the operation could not be ruled out[31]. Finally, PSM could not rule out all deviations; there may be other variables that affect surgical outcomes and survival outcomes that were not included in the study.

Conclusions

In conclusion, POCs had a negative impact on the long-term survival of patients with advanced gastric cancer, and severe complications (C-D grade > II) significantly reduced survival. Therefore, more attention should be paid to the perioperative management of patients older than 50 years, with combined resection and comorbid diseases.

Abbreviations

POCs: postoperative complications; C-D: Clavien-Dindo; AGC: advanced gastric cancer; PSM: propensity score matching; C: complications; NC: non-complications; OS: overall survival; RFS: relapse-free survival; UICC: Union for International Cancer Control; AJCC: American Joint Committee on Cancer; BMI: body mass index; HUAS: history of upper abdominal surgery; OG: open gastrectomy; LG: laparoscopic gastrectomy; OR: odds ratio; CI: confidence interval; HR: hazard ratio

Declarations

Authors' contributions

Y-WW designed this research and reviewed and edited the manuscript; D J prepared the original draft and completed the manuscript; L-QY, Y-CS, and Z-MX were in charge of data collection. W-JG contributed to

the conception, design, and data interpretation, as well as revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. The retrospective study was approved by the Ethics Committee of Yijishan Hospital. The informed consent requirement was waived.

Conflict of interest statement

All authors declared that they have no conflicts of interest.

Consent for publication

Not applicable.

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Tables

Table 1 Characteristics of patients

Variables	Enter chort			PSM chort		
	C groupn=94	NC groupn=437	P	C groupn=92	NC groupn=92	P
Age(years)			0.005			1.000
≤50	2	51		2	2	
>50	92	386		90	90	
Sex			0.566			
Male	69	333		69	67	0.737
Female	25	104		23	25	
BMI (kg/m ²)			0.658			0.835
≤25	79	375		78	79	
>25	15	62		14	13	
Preoperative albumin (g/L)			0.008			0.412
≤30	14	29		12	16	
>30	80	408		80	76	
Surgical method			0.332			0.544
LG	33	177		33	37	
OG	61	260		59	55	
Resection extent			0.641			0.376
Total	41	199		41	45	
Subtotal	53	238		51	47	
Combined resection			0.025			0.321
Yes	13	30		11	7	
No	81	407		81	85	
Combidities			0.002			0.880
Yes	38	109		37	36	
No	56	328		55	56	
HUAS			0.152			0.268
Yes	8	21		7	4	
NO	86	416		85	88	
Tumou size (cm)			0.284			0.404
≤5	70	301		70	65	
>5	24	136		22	27	
pTNM			0.135			0.770
I	6	40		6	6	
II	23	130		22	24	
III	65	267		64	62	
pT			0.008			0.876
2	11	91		11	9	

	3	22	125	22	26	
	4	61	221	59	57	
pN			0.398			0.950
	0	24	100	23	26	
	1	16	86	16	15	
	2	28	98	27	22	
	3	26	153	26	29	
Adjuvant chemotherapy			0.886			0.555
Yes	44	201		43	47	
No	50	236		49	45	

HUAS history of upper abdominal surgery, OG open gastrectomy, LG laparoscopic gastrectomy

Table 2 Postoperative complications

Variables	C-D classification					Total
	Grade Ⅰ	Grade Ⅱa	Grade Ⅱb	Grade Ⅲa	Grade Ⅲb	
Wound problem	7	4	2	0	0	13
Pulmonary	8	6	0	1	1	16
Thromboembolus	1	0	0	0	0	1
Gastroparesis	6	1	0	0	0	7
Duodenal stump leakage	5	0	3	0	1	9
Anastomotic fistula	3	2	1	1	0	7
Anastomotic bleeding	2	0	1	0	0	3
Anastomotic stricture	2	2	0	0	0	4
Cardiac	3	0	0	2	0	5
Hepatic	3	0	0	0	0	3
Pancreatic fistula	2	1	0	0	0	3
Intestinal obstruction	5	0	1	0	0	6
Intra-abdominal bleeding	2	0	4	0	0	6
Intraperitoneal abscess	6	3	0	1	0	10
Splenic infarction	2	0	0	0	0	2
Total	57	19	12	5	2	94

Table 3 Multivariate analysis of risk factors for POCs

Variables	No. of patient		Multivariate		P
	C group	NC group	OR	95%CI	
Age(yaers)					0.025
≤50	2	51	1		
≥50	92	386	5.192	1.226-21.993	
Preoperative albumin(g/L)					0.089
≥30	80	408	1		
≤30	14	29	1.850	0.911-3.759	
Combined resection					0.038
Yes	41	199	1		
No	53	238	2.135	1.045-4.364	
Combidities					0.048
Yes	38	109	1		
No	56	328	1.632	1.004-2.652	
pT					0.054
2	11	91	1		
3	22	125	1.476	0.673-3.237	
4	61	221	2.204	1.095-4.438	

OR odds ratio , CI confidence interval

Table 4. Analysis of prognostic factors associated with decreased survival outcomes

Variables	Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P
Relapse-free survival						
Adjuvant chemotherapy						
Yes	1			1		
No	0.622	0.415-0.932	0.021	0.667	0.440-1.012	0.057
Tumor size (cm)						
≤5	1			1		
>5	1.758	1.144-2.701	0.010	1.408	0.958-2.287	0.077
pTNM			0.000			0.000
I	1			1		
II	1.321	0.289-6.030	0.719	1.254	0.274-5.745	0.771
III	6.022	1.481-24.489	0.012	5.379	1.313-22.037	0.019
C-D grade			0.007			0.008
No	1			1		
I	1.517	0.955-2.410	0.078	1.798	1.124-2.877	0.014
IIa-IIb	2.216	1.337-3.674	0.002	2.031	1.220-3.381	0.006
Overall survival						
Adjuvant chemotherapy						
Yes	1			1		
No	0.501	0.320-0.784	0.002	0.507	0.320-0.802	0.004
Tumor size (cm)						
≤5	1			1		
>5	2.036	1.290-3.213	0.002	1.725	1.085-2.741	0.021
pTNM			0.000			0.001
I	1			1		
II	1.166	0.252-5.398	0.844	1.097	0.236-5.107	0.906
III	4.522	1.109-18.444	0.035	3.892	0.944-16.050	0.060
C-D grade			0.041			0.041
0	1			1		
I	1.337	0.085-2.222	0.262	1.641	0.977-2.754	0.061
IIa-IIb	2.009	1.169-3.453	0.012	1.886	1.094-3.254	0.023

HR hazard ratio

Figures

1A

1B

Figure 1

Comparison of survival outcomes between the C group and NC group of all patients in the propensity score-matched cohort(A).

2A

2B

Figure 2

Comparison of matched NC group and grade II complications(B).

3A

3B

Figure 3

Comparisons of matched NC groups and severe complications(C).

4A

4B

Figure 4

Comparison of grade II complications and severe complications(D).