

Impact of postoperative complications on long-term survival of gastric cancer patients: results from a high-volume institution in China

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Research

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Abstract

Background

This study was aimed to evaluate the impact of postoperative complications (POCs) on long-term survival for gastric cancer (GC) patients with curative resection.

Methods

From January 2009 to December 2014, a total of 1667 GC patients with curative gastrectomy were analyzed. Patients with any complications Clavien–Dindo (CD) grade II or higher were divided into complication group. Independent risk factors for the development of POCs and the relationship between POCs and long-term survival (excluding death within 90 days after surgery) were analyzed.

Results

Overall POCs CD ≥ 2 were diagnosed in 285 (17.10%) patients including infectious complications (ICs) in 231 (13.9%) and noninfectious complications (NICs) in 78 (4.68%) patients. Age ≥ 65 (P = 0.003), presence of comorbidity (P = 0.019), extensive lymphadenectomy (P = 0.027) and perioperative blood transfusion (P = 0.040) were independent risk factors of POCs. Multivariate analysis identified that presence of POCs (P < 0.001) was an independent prognostic factor and further analysis by complication type demonstrated that the deteriorated overall survival was mainly caused by ICs (P = 0.007) rather than NICs (P = 0.075), moreover, among all complications, pulmonary infection (P < 0.001) was the only significant prognostic factor.

Conclusion

POCs may be an independent prognostic factor for long-term survival of GC patients and the risk is mainly driven by ICs, particular pulmonary infection.

Introduction

Gastric cancer (GC) is the fifth most frequently diagnosed cancer and the third leading cause of cancer death worldwide [1]. Gastrectomy with curative resection is the most effective treatment strategy which provides the chance to dramatically extend the long-term survival of gastric cancer patients. However, surgery for gastric cancer still remains technically demanding and the following postoperative complications (POCs) have been reported to be with a wide range of incidence of 7–46% [2–5].

Recent studies have shown that POCs increase the length of hospital stay and early mortality [6,7]. Moreover, POCs decrease the overall survival (OS) and disease free survival (DFS) in several types of cancer like lung, breast and colon [8–10], and this effect might be mainly strengthened by infectious complications (ICs) not noninfectious complications (NICs) [11–13]. Therefore, the prevention and treatment of POCs may play a crucial role to improve the surgical outcomes of cancer patients.

Currently, in gastric cancer, although increasing numbers of studies have suggested that presence of POCs is adversely correlated with long-term survival [14–18], several studies reported from both eastern and western countries have negative findings [19–22]. What's more, which kind of specific complication in gastric cancer would have a crucial effect on the long-term survival has only been discussed in few studies [21, 23] and remains far from resolved.

The aim of this study was to explore the relationship between POCs and the long-term survival, and to identify factors associated with the development of POCs.

Methods

Patients and ethical issues

A total of 2210 consecutive patients with gastric adenocarcinoma who underwent gastrectomy were selected from the database of Surgical Gastric Cancer Patient Registry in West China Hospital (WCH-SGCPR) from January 2009 to December 2014, with registration number WCH-SGCPR 2018-03 and the establishment of this database was approved by the Research Ethics Committee of West China Hospital. The inclusion criteria included: 1) histologically proven gastric adenocarcinomas; 2) with radical surgical resection (R0); 3) without preoperative therapy; 4) no distant metastasis. The exclusion criteria of our study included: 1) with other synchronous or metachronous (within 5 years) cancers; 2) remnant gastric cancer; 3) with harvested number of lymph node less than 15; 4) with emergency treatment. Additionally, patients died within 90 days (all the death was directly associated with serious intra- or post-operative complications) after surgery were also excluded to avoid exaggerating the effect of POC on long-term survival. Finally, 1667 patients who underwent gastrectomy with potentially curative resection were enrolled into this study, as shown in **Fig. 1**.

Potentially curative resection is regarded as gastrectomy with R0 resection combined with adequate lymphadenectomy. The surgery was performed by experienced surgeons according to the Japanese gastric cancer treatment guidelines [24]. The resected specimens were pathologically classified according to the JGCA classification [25], and staged with the updated AJCC 8th TNM system [26].

Assessment of postoperative complications

In the present study, the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [27], which is enough exhaustive in terms of postoperative morbidities, was used to define complications, and any morbidity classified as Clavien–Dindo (CD) grade II or higher that developed during hospitalization or within 30 days after surgery was identified as a POC using Clavien–Dindo grade system [28,29]. However, grade I complications were not evaluated considering the potential description bias in the patient records. If a patient suffered more than one POC, the highest-ranked complication was used for grade analysis.

All complications were categorized as ICs or NICs. ICs included pulmonary infection, abdominal abscess, anastomotic leakage, wound infection, pancreatic leakage, pancreatitis, intestinal leakage, cholecystitis,

urinary system infection, appendicitis and bacteremia. NICs included gastroparesis, intestinal obstruction, intra-abdominal hemorrhage, pleural effusion, ascites, atelectasis, respiratory failure, heart failure, arrhythmia, deep venous thrombosis.

Follow-up

The follow-up was mainly performed by out-patient visit, meanwhile, routine telephone interviews were regarded as important supplementary methods. The last update of follow-up information was Jan 1, 2019. In the 1667 patients, 168 of them lost contact during follow-up, the follow-up rate was 89.92% with the median follow-up time 78.05 (3.20-118.50) months. The main reasons for lost follow-up are because of the change of telephone number and address and refusal to attend to out-patient interview of our hospital.

Statistical Analysis

The analyses were all performed with software IBM SPSS Statistics version 23.0 (International Business Machines Corporation, Armonk, NY, USA). Statistical analysis was performed using descriptive statistics for demographic data. For group-wise comparisons, Student t test (normal distribution) or Mann-Whitney U test (nonparametric distributions) were used. To compare nominal data, the Chi-square test or the Fisher exact test was used. The subsequent multivariate logistic regression analysis was performed to detect independent risk factors of POCs. The Kaplan–Meier method and log-rank test were used to calculate survival rates and compare the survival rates respectively. Univariate and multivariate Cox proportional hazards regression models were used to analyze the hazard ratios for overall survival. P value less than 0.05 was considered to be statistically significant.

Results

Description of entire study cohort population

The characteristics of the entire study cohort was presented in **Table 1**. The mean age of this population was 57.96 ± 11.27 years old with 69.23% male patients and 26.63% of them had a different kinds of comorbidities. Among these patients, distal gastrectomy (59.87%) was the main surgical procedure followed by total (27.41%) and proximal (12.72%) gastrectomy combined with D2/D2 + lymphadenectomy (95.98%) which is routinely performed in our center. Additionally, 15.72% of this population received perioperative blood transfusion. Regarding to pathological features, the advanced gastric cancer took up to 79.12% of the entire population and nodal involvement was observed in 68.51% patients. Besides, nearly 50% patients received adjuvant chemotherapy.

The details of POCs of this population were shown in **Table S1**. A total of 285 (17.10%) patients developed complications $CD \geq II$ (II: 241 [14.46%]; III: 24[1.44%]; IV: 20[1.20%]) in this cohort. Further, 246 ICs were found at 231 (13.86%) patients, of which pulmonary infection (184 patients; 11.04%) was the most common adverse event followed by intra-abdominal abscess (26 patients; 1.56%) and wound

infection (11 patients; 0.66%). Meanwhile, 84 NICs were observed in 78 (4.68%) patients including gastroparesis (30 patients; 1.80%), intestinal obstruction (11 patients; 0.72%) and pleural effusion (9 patients; 0.54%).

Predictors related to occurrence of POCs

Relationships between the occurrence of POCs and clinicopathological parameters are shown in **Table 2**. In univariate analysis, age 65 or higher (OR = 1.65; 95%CI: 1.26–2.17; $P < 0.001$), presence of comorbidities (OR = 1.62; 95%CI: 1.20–2.13; $P < 0.001$), extensive lymphadenectomy (OR: 3.29; 95%CI: 1.02–10.66; $P = 0.038$) and perioperative blood transfusion (OR = 1.60; 95%CI: 1.16–2.21; $P = 0.001$) were associated with POCs, other factors like histopathological parameters showed no significant relation with POCs. Further multivariate analysis identified that age 65 or higher (OR = 1.54; 95%CI: 1.16–2.04; $P = 0.003$), presence of comorbidities (OR = 1.42; 95%CI: 1.06–1.91; $P = 0.019$), extensive lymphadenectomy (OR = 3.80; 95%CI: 1.16–12.41; $P = 0.027$) and perioperative blood transfusion (OR = 1.43; 95%CI: 1.02–2.01; $P = 0.040$) were independent risk factors for development of POCs.

Prognostic Significance of POCs on long-term survival

As shown in **Fig. 2a**, patients with POCs had a significant worse OS compared with those without (3-year OS rate 60.4% vs. 71.3%; $P < 0.001$). The overall survival curves stratified by pathological stage were shown in **Fig. 2b-d**. The curves were significantly separated in stage III cancers with $P < 0.001$, however, no obvious difference was observed in stage I, II. Univariate and subsequent multivariable Cox regression analysis revealed that POCs (HR = 1.47; 95%CI: 1.22–1.78; $P < 0.001$) along with tumor size, tumor invasion depth, nodal involvement and adjuvant chemo-therapy were independent prognostic factors (**Table 3**).

Relation between specific complications and long-term survival

To clarify which kind of complications had a contribution on poor OS, we performed univariate and multivariate analysis using each complication with other parameters. In the univariate analysis, both ICs (3-year OS rate 60.5% vs. 71.2%; $P = 0.002$) and NICs (3-year OS rate 62.0% vs. 69.8%; $P = 0.045$) had an adverse influence on OS (**Fig. 3; Table 3**). However, multivariate analysis demonstrated that only ICs (HR, 1.34; 95%CI: 1.08–1.66; $P = 0.007$) rather than NICs (HR, 1.34; 95%CI: 0.97–1.86; $P = 0.075$) was independent prognostic factor for unfavorable OS.

Among all complications with events five or more, only pulmonary infection had a significant negative effect on OS (3-year OS rate 58.8% vs. 70.7%; $P = 0.004$) in the univariate analysis (**Fig. 3; Table 4**), and subsequent multivariate analysis identified that pulmonary infection was an independent prognostic factors (HR, 1.52; 95%CI: 1.20–1.91; $P < 0.001$) (**Table 4**).

Discussion

Several previous studies have reported the relationship between POCs and long-term survival in gastric cancer, however, the results still remain controversial [11, 15–17, 20–23, 30–36]. Additionally, these studies failed to exclude patients who died in a short postoperative period. Of note, POCs increase the early mortality, which would overshadow the real influence of complications on long-term survival of cancer patients [37, 38]. In the present study, 1667 GC patients with curative resection were analyzed and 17.10% of them occurred POCs C-D \geq II (excluding deaths within 90 days after surgery). Older age, comorbidities, extensive lymph node dissection and perioperative blood transfusion were associated with a high incidence of POCs. With respect to the relationship of complication and survival, we revealed (1) that occurrence of POCs was indeed significantly associated with shortened long-term OS, (2) ICs were the mainly driver for poor survival instead of NICs, (3) among all complications, pulmonary infection in this study was the greatest risk factor for the decreased OS.

The influence of POCs, particularly ICs, on long-term survival has been described in several types of cancer [11–13]. Recently, in a systematic review and meta-analysis about the effect of POCs on long-term survival in patients with curative gastrectomy, Wang et al. identified a 40% higher risk of death in patients with POCs and a much higher (86%) mortality risk in patients with ICs compared with those without, respectively [39], which was in line with our results. Similarly, in lung cancer, a similar outcome reported by Andalib et al. have also demonstrated that major ICs were the main reason for worse long-term survival and NICs had a minor effect on this bad outcome, excluding early deaths [11].

With respect to the mechanism of presence of complications on poor survival, Accumulated evidences [17, 40, 41] had indicated that the surgical stress, especially in major surgery, would induce body inflammatory response which could be enhanced and prolonged by POCs. It's also well established that postoperative inflammatory response has a contribution on host immunosuppression by mainly suppressing cell-mediated immunity [42,43], especially natural killer cells and cytotoxic T lymphocytes are compromised [43], which promotes the proliferation and metastasis of residual tumor cells. Furthermore, numerous researches have confirmed that ICs have a direct effect on cancer cell metastatic ability by activating bacterial antigen-mediated processes [44, 45]. Indeed, in our study, a remarkable difference in overall survival between patients stratified by presence of complication in p-Stage III is likely to reflect the quantity of residual tumor cells which would cause early recurrence.

Nevertheless, we have to admit that whether POCs have a direct cause-effect relationship on shortened survival is still not very clear. Alternatively, the pernicious effect of postoperative complications on long-term survival could be just a confounder, such as surgical technique, may be the reason for both occurrence of POCs and decreased long-term survival. What we can conclude in our study is that POCs have an influence on poor prognosis. Considering the curability of the POCs and its potential benefit on the long-term survival, it's worthy and crucial to prudently deal with POCs with active intervention and remediation. Meanwhile, for patients at risk of occurrence of POCs, such as those with older age, presence of comorbidities, extensive lymphadenectomy and perioperative blood transfusion, more attention should be paid to.

The limitations of our study were its retrospective nature and presence of several confounding factors. And there was a lack of enough information about adjuvant chemotherapy, for example, the starting time of adjuvant chemotherapy among patients was not clear, which may have an effect on survival considering delayed chemotherapy is detrimental to prognosis. Another limitation was the inability to calculate DFS because its potential difficulty to get the precise recurrence time of these cancer patients in such a large population cohort. Despite these limitations, we believe that postoperative complications are an important prognostic factor.

In conclusion, postoperative complications after curative resection of gastric cancer are common and are associated with poor overall survival in gastric cancer patients. The risk is mainly driven by infectious complications (especially pulmonary infection) rather than noninfectious complications. Based on our findings, meticulous surgery is needed and prudent medical intervention in patients with complications is also compulsory to increase the long-term survival of gastric cancer patients.

Abbreviations

GC: gastric cancer

POC: postoperative complication

IC: infectious complication

NIC: noninfectious complication

CD: Clavien–Dindo

OS: overall survival

HR: hazard ratio

OR: odds ratio

CI: confidence index

Declarations

Ethics approval and consent to participate:

This study was based on the information gathered from the database of the Surgical Gastric Cancer Patient Registry of West China Hospital (WCH-SG CPR) under registration number WCH-SG CPR 2018-03. The establishment of this database was approved by the Research Ethics Committee of West China Hospital. Informed consent individual patients were waived because of the retrospective nature of the analysis.

Consent for publication:

Not applicable.

Availability of data and materials:

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

Competing interests:

The authors declare that they have no competing interests.

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Authors' contribution:

Jian-kun Hu, Hua-Yang Pang, Hui Wang make substantial contributions to conception and design for this study. Hua-Yang Pang, Hui Wang collect all the data. Hua-Yang Pang, Hui Wang, Lin-Yong Zhao, Xiao-Long Chen, Kai Liu, Wei-Han Zhang analyze data, Hua-Yang Pang, Hui Wang, Xiao-long Chen draft the article. Kai Liu, Kun Yang, Xin-Zu Chen and Jian-kun Hu give critical revision for important intellectual content. Hua-Yang Pang and Hui Wang revising it critically for important intellectual content. Kun Yang, Xin-Zu Chen and Jian-kun Hu give final approval of the version to be published.

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Tables

TABLE 1. Clinicopathological characteristics of entire cohort.

	No. of patients(1667)
Age (years): mean \pm standard deviation	58.0 \pm 11.3
Sex ratio (Male/Female)	1154/513
Preoperative albumin (g/L) : mean \pm standard deviation	40.46 \pm 4.32
Comorbidities (Yes/No)	444/1223
Surgical approach (Open/ Laparoscopic)	1478/189
Surgical procedure (Distal /Proximal /Total)	998/212/457
Extent of lymphadenectomy (< D2 / \geq D2)	49/1618
Resection of other organs (Yes/No)	67/1600
Perioperative blood transfusion (Yes/No)	262/1405
Tumor location (Upper/Middle/Lower/Multiple)	416/148/955/148
Tumor size (cm) : mean \pm standard deviation	5.18 \pm 2.84
Macroscopic type (Bormann 0/1/2/3/4/5)	316/44/696/518/93
Histological differentiation (G1 + G2/G3 + G4)	518/1149
Depth of invasion (1/2/3/4)	348/242/276/801
Nodal involvement (0/1/2/3)	525/303/293/546
Pathological stage (I/II/III)	402/383/882
Adjuvant chemotherapy (Yes/No)	838/829

TABLE 2. Univariate and multivariable logistic regression analysis of risk factors for POCs

	Univariate analysis		Multivariable analysis	
	OR(95%CI)	P value	OR(95%CI)	P value
Age (≥ 65 vs.<65)	1.70(1.29–2.23)	< 0.001	1.54(1.16–2.04)	0.003
Gender (Male vs. female)	0.84(0.63–1.11)	0.220		
Preoperative albumin (≥ 35 vs.<35 g / L)	0.77(0.53–1.14)	0.192		
Comorbidities (Yes vs. No)	1.70(1.29–2.22)	< 0.001	1.42(1.06–1.91)	0.019
Surgery approach (Laparoscopic vs. Open)	1.25(0.86–1.84)	0.243		
Gastrectomy (Total vs. Partial)	1.20(0.91–1.59)	0.196		
Lymphadenectomy ($\geq D2$ vs.<D2)	3.24(1.01–10.48)	0.038	3.80(1.16–12.41)	0.027
Resection of other organs (Yes vs. No)	1.42(0.79–2.56)	0.240		
Perioperative blood transfusion (Yes vs. No)	1.69(1.23–2.32)	0.001	1.43(1.02–2.01)	0.040
Tumor size (≥ 5 vs. <5 cm)	1.12(0.87–1.45)	0.378		
Tumor location (Multiple vs. U/M/L)	1.38(0.91–2.09)	0.126		
Macroscopic type (Bormann 3–4 vs. 0–2)	1.07(0.82–1.39)	0.633		
Histological differentiation (G3/G4 vs.G1/G2)	0.88(0.67–1.16)	0.365		
Depth of invasion (T4 vs.T1/2/3)	1.04(0.80–1.34)	0.789		
Nodal involvement (N + vs. N0)	1.02(0.77–1.34)	0.916		

TABLE 3. Univariate and multivariate COX regression analysis of prognostic factors for OS

	Univariate analysis		Multivariate analysis*		Multivariate analysis#	
	HR(95%CI)	P value	HR(95%CI)	P value	HR(95%CI)	P value
Age (≥ 65 vs.<65)	1.26(1.07–1.49)	0.006	1.13(0.95–1.35)	0.164	1.14(0.96–1.36)	0.131
Gender (Male vs. female)	1.02(0.86–1.20)	0.835				
Preoperative albumin (≥ 35 vs. <35 g/ L)	1.04(0.81–1.33)	0.782				
Comorbidities (Yes vs. No)	1.20(1.01–1.42)	0.034	1.07(0.89–1.28)	0.486	1.07(0.90–1.29)	0.447
Surgery approach (Laparoscopic vs. Open)	0.68(0.52–0.90)	0.006	0.83(0.63–1.09)	0.179	0.84(0.64–1.10)	0.204
Gastrectomy (Total vs. Partial)	1.67(1.43–1.96)	< 0.001	1.13(0.95–1.34)	0.164	1.12(0.95–1.33)	0.176
Lymphadenectomy ($\geq D2$ vs.<D2)	0.80(0.53–1.20)	0.277				
Resection of other organs (Yes vs. No)	1.23(0.85–1.78)	0.282				
Perioperative blood transfusion (Yes vs. No)	1.46(1.21–1.77)	< 0.001	1.12(0.91–1.37)	0.293	1.12(0.91–1.37)	0.276
Tumor size (≥ 5 vs. <5 cm)	2.18(1.85–2.57)	< 0.001	1.30(1.07–1.57)	0.007	1.28(1.06–1.54)	0.011
Macroscopic type (Bormann 3–4 vs. 0–2)	1.81(1.55–2.10)	< 0.001	1.06(0.89–1.26)	0.504	1.06(0.90–1.26)	0.492
Histological grade (G3/G4 vs.G1/G2)	1.43(1.20–1.70)	< 0.001	1.15(0.96–1.38)	0.126	1.15(0.96–1.38)	0.132
Depth of invasion (T4 vs.T1/2/3)	3.03(2.57–3.58)	< 0.001	2.05(1.70–2.47)	< 0.001	2.06(1.71–2.49)	< 0.001
Nodal involvement (N+ vs. N0)	3.31(2.67–4.10)	< 0.001	2.42(1.93–3.04)	< 0.001	2.41(1.92–3.02)	< 0.001
Adjuvant chemotherapy (Yes vs. No)	0.92(0.79–1.08)	0.300	0.77(0.66–0.90)	0.001	0.78(0.66–0.91)	0.002

	Univariate analysis		Multivariate analysis*		Multivariate analysis#
POCs (Yes vs. No)	1.50(1.24–1.81)	< 0.001	1.47(1.22–1.78)	< 0.001	
ICs (Yes vs. No)	1.39(1.13–1.72)	0.002			1.34(1.08–1.66) 0.007
NICs (Yes vs. No)	1.39(1.01–1.91)	0.045			1.34(0.97–1.86) 0.075

* Multivariate analysis describing the prognosis of POCs for gastric cancer patients. # Multivariate analysis describing the prognosis of ICs and NICs for gastric cancer patients.

TABLE 4. Univariate and multivariate COX regression analysis in terms of specific complication.

	Univariate analysis		Multivariate analysis	
	HR(95%CI)	P value	HR(95CI)	P value
Pulmonary infection	1.40(1.12–1.77)	0.004	1.52(1.20–1.91)	< 0.001
Abdominal abscess	1.50(0.87–2.60)	0.145		
Anastomotic leakage	1.18(0.30–4.74)	0.813		
Wound infection	1.27(0.53–3.07)	0.588		
Cholecystitis	1.75(0.56–5.43)	0.330		
Gastroparesis	1.26(0.76–2.11)	0.373		
Intestinal obstruction	0.89(0.44–2.56)	0.894		
Pleural effusion	1.35(0.50–3.60)	0.571		
Intra-abdominal hemorrhage	0.91(0.29–2.83)	0.911		
Arrhythmia	2.50(0.94–6.68)	0.059		

Figures

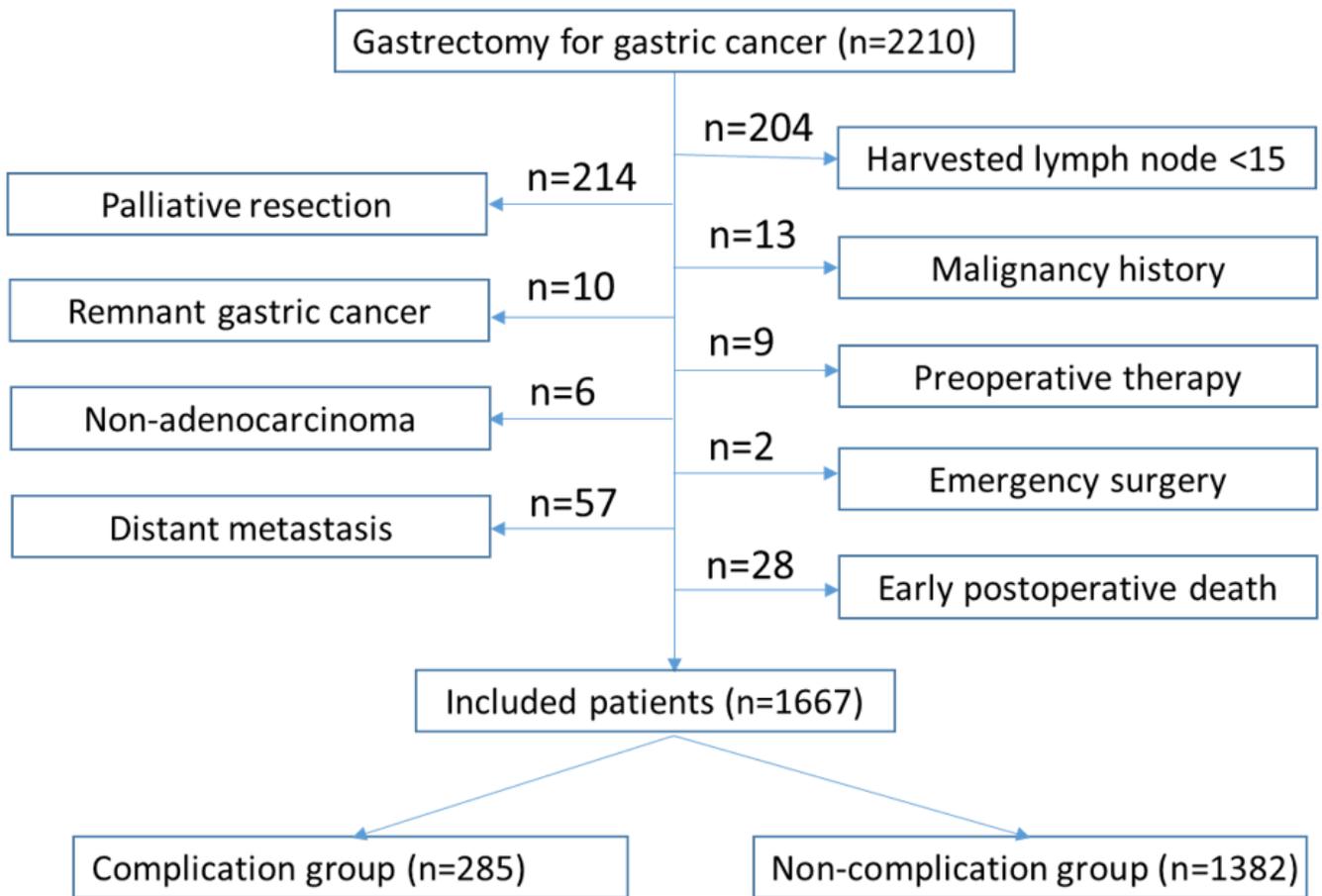


Figure 1

The flow diagram of gastric cancer patients enrolled in this study

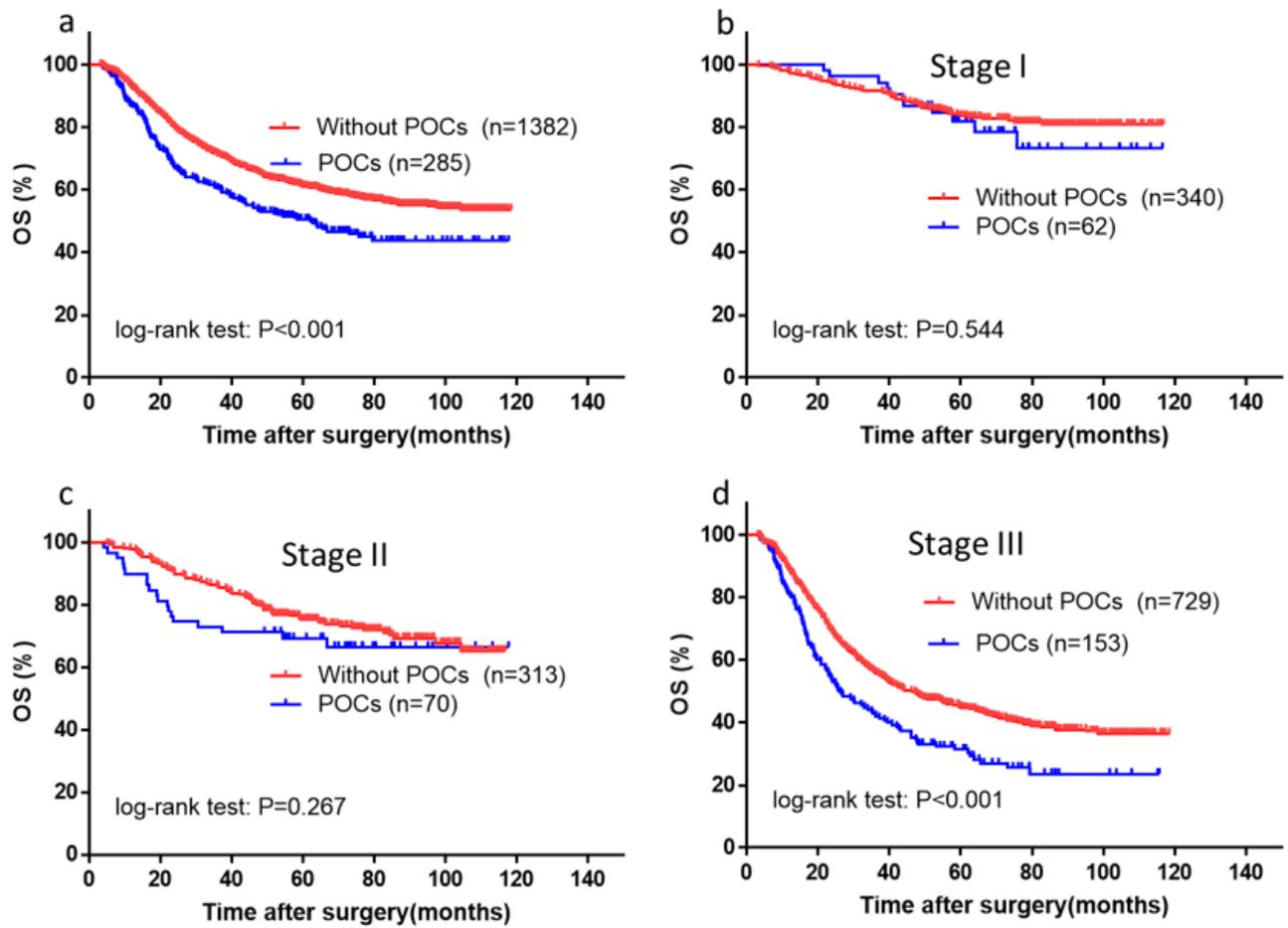


Figure 2

Kaplan-Meier survival analysis of POC in all patients (a) and in Stage I (b), in Stage II (c), and in Stage III (d) patients. The significance of the difference between survival curves was calculated by the log-rank test.

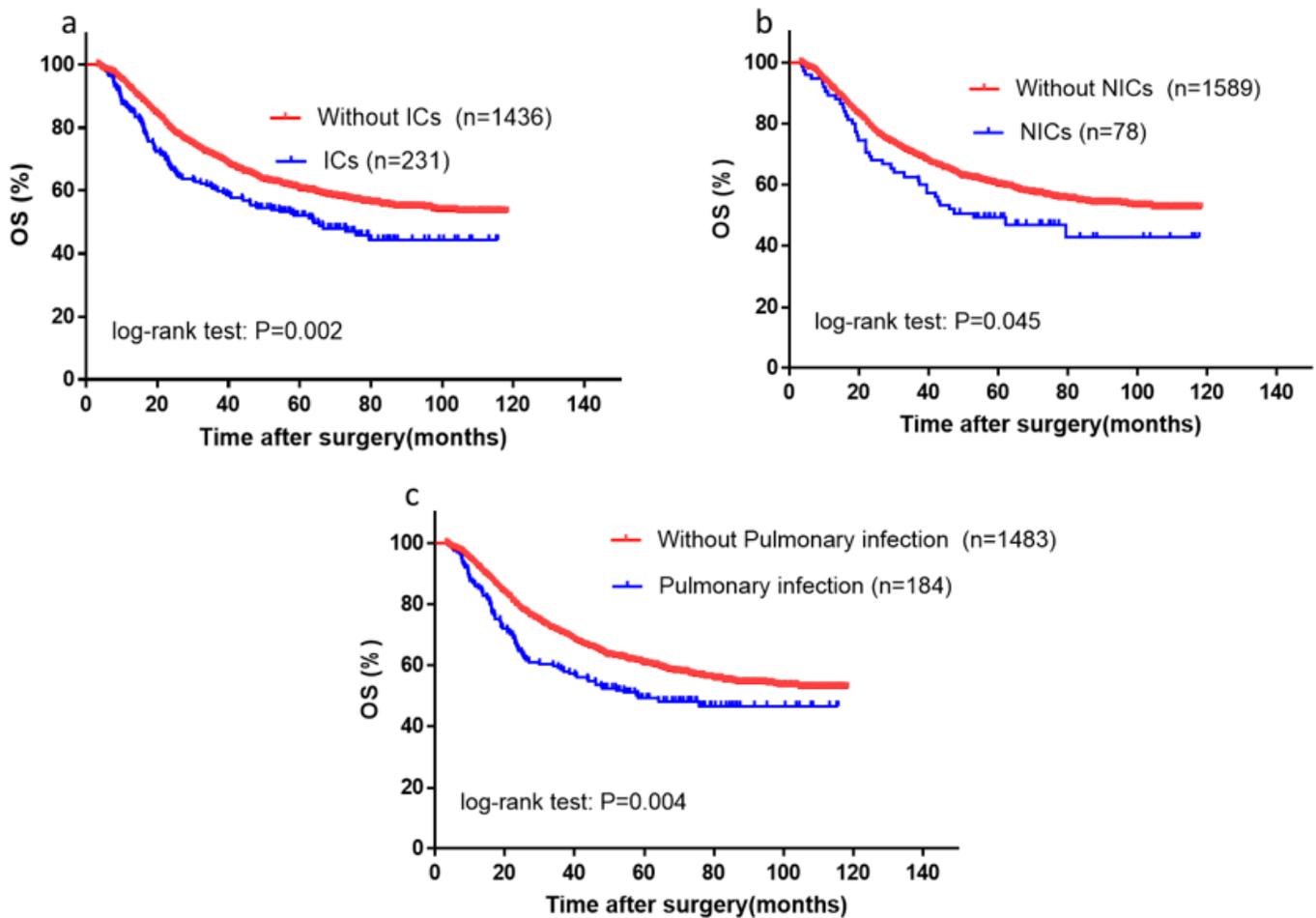


Figure 3

Kaplan-Meier survival analysis according to specific POC in all patients: (a) ICs; (b) NICs, and (c) pulmonary infection. The significance of the difference between survival curves was calculated by the log-rank test.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [TableS1.docx](#)