Risk Factors for Complications of Total/Subtotal Gastrectomy for Gastric Cancer: Prospectively Collected, Based on the Clavien-Dindo Classification System

Yehonatan Nevo MD[1,2]*, Yuri Goldes MD[1,2]*, Liran Barda MD[1,2], Roy Nadler MD[1,2], Mordechai Gutman MD[1,2] and Avinoam Nevler MD[1,2,3]

[1]Department of General Surgery and Transplantation, Sheba Medical Center, Tel Hashomer, Israel
[2]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[3]Borenstein Talpiot Medical Leadership Program, 2012, Sheba Medical Center, Tel Hashomer, Israel

ABSTRACT:

Background: Recent studies have analyzed risk factors associated with complications after gastric cancer surgery using the Clavien-Dindo classification (CD). However, they have been based on Asian population cohorts (Chinese, Japanese, Korean).

Objectives: To prospectively analyze all post-gastrectomy complications according to severity using CD classification and identify postoperative risk factors and complications.

Methods: We analyzed all gastrectomies for gastric cancer performed 2009–2014. Recorded parameters included demographic data, existing co-morbidities, neo-adjuvant treatment, intra-operative findings, postoperative course, and histologic findings. Postoperative complications were graded using CD classification.

Results: The study comprised 112 patients who underwent gastrectomy. Mean age was 64.8 ± 12.8 years; 53 patients (47%) underwent gastrectomy, 37 (34%) total gastrectomy, and 22 (19%) total extended gastrectomy. All patients had D2 lymphadenectomy. The average number of retrieved lymph nodes was 35 ± 17. Severe complication rate ($\geq$ IIIa) was 14% and mortality rate was 1.8%. In a univariate analysis, age > 65 years; ASA 3 or higher; chronic renal failure; multi-organ resection; and tumor, node, and metastases (TNM) stage $\geq$ IIIc were found to be significantly associated with CD complication grade > III ($P = 0.01$, $P = 0.05$, $P = 0.04$, $P = 0.04$, and $P = 0.01$, respectively). Multivariate regression analysis revealed advanced stage ($\geq$ IIIc) and age > 65 years to be significant independent risk factors ($P < 0.05$).

Conclusions: Age > 65 and advanced stage ($\geq$ IIIc) were the primary risk factors for complications of grade > III according to the CD classification following gastrectomy for gastric cancer.

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KEY WORDS: gastrectomy, surgical complications, gastric cancer, risk factors

Gastric cancer is the fourth most common cancer diagnosis worldwide in men following lung, prostate, and colorectal cancers; and fifth most common in women following breast, colorectal, cervical, and lung cancers. Approximately 8% of total cases and 10% of annual cancer deaths worldwide are attributed to gastric cancer. This statistic translates into a high fatality-to-case ratio of 70%, which is significantly higher than other prevalent diseases such as prostate and breast cancers that have a fatality-to-case ratio of 30% and 33%, respectively [1]. Surgical resection combined with D2 lymphadenectomy has become the standard treatment for curable gastric cancer; however, it brings a simultaneous increase in surgical complications [2]. The presence or absence of complications was found to be an important factor that can influence the prognosis of patients following curative gastrectomy [3,4]. Precise grading of complications is essential for analysis of surgical outcomes.

Previously, methods for classification of complications were not uniform and the traditional classification was too complicated. Although Western countries have published complication and mortality rates following D2 lymphadenectomy [3,4], to the best of our knowledge none of them has been assessed using the Clavien-Dindo (CD) classification. Several recent studies analyzed risk factors associated with complication following gastric cancer surgery using the CD classification [5-7]; however; these studies have been predominately based on Asian population cohorts (Chinese, Japanese, and Korean). The aim of this study was to prospectively analyze all post-gastrectomy complications in gastric cancer patients, according to severity, using CD classification and to identify risk factors related to postoperative complications.

PATIENTS AND METHODS

This study is a retrospective analysis of a prospectively collected database of gastrectomies performed for gastric adenocarcinoma.

PATIENT POPULATION AND DATA COLLECTION

All patients who underwent total or subtotal gastrectomy for gastric cancer at a university hospital in a single surgical depart-

ment between 2009 and 2014 were included. All patients underwent D2/D2+ lymph node dissection. Those with upper and middle third gastric cancer underwent a total gastrectomy with Roux-en-Y esophagojejunal anastomosis. Patients with lower third gastric cancer underwent subtotal gastrectomy with Roux-en-Y gastrojejunal anastomosis. Patients who underwent proximal gastrectomy or cytoreductive hyperthermic intraperitoneal chemotherapy (HIPEC) surgery, which included gastrectomy, were excluded. Hand sewn anastomosis was applied in all open surgeries. Stapled anastomosis was applied in laparoscopic and robotic surgeries.

All surgeries were performed by a single senior surgeon aided by another surgeon or a senior resident. Recorded parameters included demographic data, existing co-morbidities, pre-operative histology, neo-adjuvant chemotherapy (NACT), intra-operative findings, postoperative course, length of hospital stay, and complete histologic findings. Patients with incomplete or missing histologic or operative data were excluded from the analysis. NACT protocol and degree of completion (complete, partial, or none) were noted. Patients were not routinely admitted to the intensive care unit (ICU) following the surgery, and postoperative ICU admission was considered for individual high-risk patients. ICU transfer as part of postoperative complication management was recorded. The severity of complications was evaluated using the CD classification [9]. Tumor grade and type were recorded, as was lymph node harvest. Tumor, node, and metastases (TNM) staging for all years was revised to comply with the 7th ed. AJCC Cancer Staging Manual [10].

STATISTICAL ANALYSIS

Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 20 (SPSS, IBM Corp, Armonk, NY, USA). Categorical data are expressed as number and percentages where appropriate. Continuous data are expressed as mean ± standard deviation. For the univariate and multivariate regression models, patients encountering complications corresponding to CD grade 3 and above were classified as positive for severe complications. Univariate analysis was performed using Fisher's exact and chi-square tests. Variables that demonstrated association with complication frequency ($P < 0.2$) were included in an initial multivariate logistic regression model and reassessed in a final model containing variables with $P < 0.2$.

ETHICS APPROVAL

This study was approved by the institutional review board at Sheba Medical Center.

RESULTS

A total of 112 patients were identified. Patient characteristics are presented in Table 1.
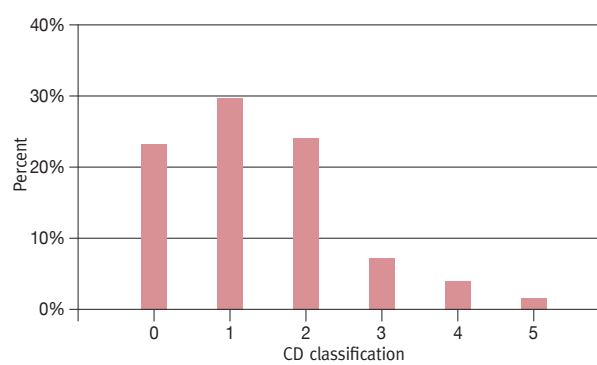
Table 1. Patient characteristics (N=112)

Age, years		64.8 ± 12.8
Gender (male/female)		73/39
Height, cm		168.5 ± 9.8
Weight, kg		74.2 ± 16.5
BMI, kg/m^2		26.0 ± 5.1
ASA	1	5 (5%)
	2	34 (32%)
	3	64 (60%)
	4	3 (3%)
NACT	None	58 (53%)
	Partial	14 (13%)
	Complete	38 (34%)
Surgery type	Distal/subtotal	53 (47%)
	Total	37 (34%)
	Total transhiatal extended	22 (19%)

BMI = body mass index, ASA = American Society of Anesthesiologists, NACT = neoadjuvant chemotherapy

Ninety-two patients (82%) did not undergo any additional operational interventions, whereas 20 (18%) underwent additional surgical procedures, including colectomy, splenectomy, cholecystectomy, and pancreatectomy. All patients had D2 lymphadenectomy. The average number of retrieved lymph nodes was 35 ± 17. Ninety-six patients (86%) underwent open surgery, 11 patients (10%) underwent laparoscopic surgery, and 5 patients (4%) underwent robotic surgery.

The postoperative complications, classified using the CD classification, are presented in Figure 1. The median complication grade was CD-1, mostly due to electrolyte imbalance and postoperative fever on postoperative day (POD 1–3). Severe complication rate (≥ IIIa) was 14% primarily due to anastomotic leak, pancreatic leak, and bleeding. Mortality rate was 1.8% (2 cases) due to multi-organ failure secondary to anastomotic leak in one case and cerebrovascular accident with pontine bleeding

Figure 1. Prevalence of postoperative complications according to Clavien-Dindo (CD) classification

in the second case. Median length of hospital stay was 8 days (4–80 days). Univariate and multivariate linear regression analysis are presented in Table 2 and Figure 2. In a univariate analysis, age more than 65 years, American Society of Anesthesiologists Classification (ASA Class) 3 or higher, chronic renal failure, multi-organ resection, and TNM stage ≥ IIIc were found to be
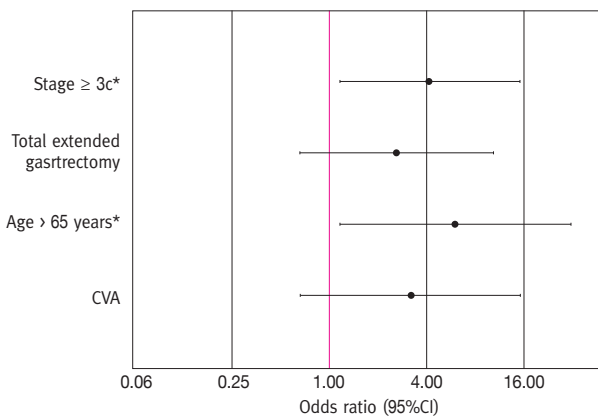
significantly associated with CD complication grade > III (*P* = 0.01, *P* = 0.05, *P* = 0.04, *P* = 0.04, and *P* = 0.01, respectively). Multivariate regression analysis revealed advanced stage (≥ IIIc) and age over 65 years to be significant independent risk factors (*P* < 0.05), as shown in Figure 2.

Table 2. Univariate analysis

		Total number	Severe complications, n (%)	OR (95%CI)	*P* Value
Gender	Male	73	13 (18%)	1	0.17
	Female	39	3 (8%)	0.4 (0.1–1.4)	
Age, years	Age ≤ 65	54	3 (6%)	1	0.01
	Age > 65	58	13 (22%)	4.9 (1.3–18.3)	
ASA	ASA 1	5	0 (0%)		0.05
	ASA 2	34	4 (12%)		
	ASA 3	63	9 (14%)		
	ASA 4	3	2 (67%)		
CRF	No	91	11 (12%)	1	0.04
	Yes	10	4 (40%)	4.8 (1.2–19.9)	
CVA	No	93	12 (13%)	1	0.09
	Yes	8	3 (38%)	4.0 (0.9–19.2)	
Surgical procedure	Total and subtotal	90	10 (11%)	1	0.08
	Total extended	22	6 (27%)	3.0 (1.0–9.4)	
Multi-organ resection	No	92	10 (11%)	1	0.04
	Yes	20	6 (30%)	3.5 (1.1–11.2)	
Stage	‹ 3C	86	8 (9%)	1	0.009
	3C	25	8 (32%)	4.6 (1.5-–13.9)	

OR = odds ratio, 95%CI = 95% confidence interval, ASA = American Society of Anesthesiologists, CVA = cerebrovascular accident, CRF = chronic renal failure

Figure 2. Forest plot of the multivariant analysis. The column on the left lists the names of the factors included in the final multivariate model for complications ≥ Clavien-Dindo III. The column on the right measures the odds ratio in a $\log_2$ scale

*Factor is independently significant at the 0.05 level (2-tailed)
95%CI = 95% confidence interval

DISCUSSION

Gastric cancer is the fourth most common cancer diagnosis worldwide in men, and the fifth most common in women [1]. Gastric adenocarcinoma comprises 90–95% of all gastric malignancies. Its overall 5 year survival rate ranges from virtually no survival for patients with advanced metastatic disease to almost 50% for patients with favorable localized distal gastric cancer with a resectable regional disease [https://www.cancer.gov/types/stomach/hp].

Our aim in this study was to prospectively analyze all post-gastrectomy complications according to severity using CD classification and to identify risk factors related to postoperative complications.

The present study suggests several primary risk factors for complications of grade III or over according to the CD classification following gastrectomy for gastric cancer in a large tertiary referral center. Several large studies have looked at possible factors associated with postoperative complications. Recently, preliminary results from the KLASS-01 study were published [9]. The study, a Korean large scale, multicenter, prospective randomized controlled trial encompassing 1416 patients, compared laparoscopic distal gastrectomy with open distal gastrectomy for stage I gastric cancer patients. Results showed an intra-abdominal complication rate of 7.6–10.3% and a mortality rate of 0.3–0.6% [9]. However, the majority of published data includes data from Asian populations, whereas few studies evaluated post-gastrectomy complications in Western populations. An Israeli study by Lavy and colleagues [11] looked at a patient population similar to ours and compared the complication rate associated with gastrectomies with D1 and D2 lymphadenectomies. They found similar rates of complications, albeit a slightly elevated mortality rate compared to our data. The complications reported in that study did not include the use of the CD grading system. Thus, we were unable to compare that parameter in the studies.

As expected, our analysis showed an advanced cancer stage to be a strong independent risk factor (odds ratio [OR] 4.2, 95% confidence interval [95%CI] 1.2–15.1, *P* < 0.05) for postoperative complications. Similar to previously reported studies [11,12], the current study also demonstrates a statistical trend between the extent of gastrectomy (total/extended gastrectomy) and a higher rate of complications (OR 3.0, 95%CI 1.0–9.4, *P* = 0.08). Extensive multi-organ resections also posed an increased risk for severe complications (OR 3.5, 95%CI 1.1–11.2, *P* < 0.05). Previous studies [12,13] have reported that age older than 60

years was a significant risk factor for postoperative complications. This finding was also evident in our study. It is possible that age itself is not a risk factor, but rather accompanying co-morbidities are responsible for the higher rate of complications. Indeed Lee and colleagues [13] showed that the proportion of ASA score 3 or 4 was considerably higher in septuagenarians and octogenarians and the systemic complication rates were higher with increased age. Specific analysis of pre-morbid conditions showed a significant association between chronic renal failure and severe postoperative complications (OR 4.8, 95%CI 1.2–19.9, $P < 0.05$). This finding corresponds to data from a study by Tanaka et al. [15], which showed preoperative estimated glomerular filtration rate to be a prognostic factor for postoperative complications after curative intent gastrectomy.

Bickenbach and colleagues [16] showed that increased body mass index of ≥ 25 is a predictor of increased postoperative complications, including wound infections and anastomotic leak. Jiang et al. [17] showed that malnutrition, presented as low prognostic nutritional index, is a risk for postoperative complications. Unfortunately, our data were not powered enough to detect such differences. Interestingly, in a multivariate analysis on postoperative morbidity and mortality rates for patients undergoing neoadjuvant therapy, Badgwell and co-authors [18] found male gender to be associated with increased major morbidity rates (OR 1.86, 95%CI 1.18–2.92). Although male gender was included as a risk factor in our initial multivariate analysis, it was not found to be significant and was removed from the final model.

Our study has several limitations. First, this is a single center study, including an almost exclusively Israeli population. As the clinical and pathological features of gastric cancer depend on demographic attributes, this population condition might limit the applicability of our results to other patient samples. Second, the relatively small sample size limits the power of several analyses. Third, the relatively short follow-up period limits the assessment of long-term patient outcome.

Early and reliable assessment of the risk for developing postoperative complications serves as an important contributor to pre-operative, intra-operative, and postoperative decision making. While data available for Eastern and Asian population can serve to guide treatment in these regions of the world, care must be taken when attempting to extrapolate these data to the Western world. The current analysis reveals several factors to be associated with a higher risk of complications. While some of these risks are already described in the literature, others are less frequently reported. Similarly, several factors, which have been described as associated with a higher complication rate, did not demonstrate a comparable association in our series. These discrepancies highlight the caution required in the extrapolation of data. Further studies are required to better assess both local and international contributes to post-gastrectomy complications.

CONCLUSIONS

The CD classification of postoperative complications is an important method to compare and evaluate the safety of different types of gastrectomies. Applying this classification to Western population cohorts is an important step in standardizing data and knowledge.

Correspondence
Dr. A. Nevler
Dept. of Surgery and Transplantation, Sheba Medical Center, Tel Hashomer 5265601, Israel
Phone: 972-3-5302247, **email:** avinoam.nevler@sheba.health.gov.il

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