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### Authors

Turgeon, Michael K  
Lee, Rachel M  
Keilson, Jessica M  
[et al.](#)

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## Is there a difference in utilization of a perioperative treatment approach for gastric cancer between safety net hospitals and tertiary referral centers?

Michael K. Turgeon, MD<sup>1</sup>, Rachel M. Lee, MD, MSPH<sup>1</sup>, Jessica M. Keilson, MD<sup>1</sup>, Michelle R. Ju, MD<sup>2</sup>, Matthew R. Porembka, MD<sup>2</sup>, Rodrigo E. Alterio, MD<sup>2</sup>, Joshua Kronenfeld, MD<sup>3</sup>, Jashodeep Datta, MD<sup>3</sup>, Neha Goel, MD<sup>3</sup>, Annie Wang, MD<sup>4</sup>, Ann Y. Lee, MD<sup>4</sup>, Manuel Fernandez, MD<sup>5</sup>, Harry Richter, MD<sup>5</sup>, Ajay V. Maker, MD<sup>6</sup>, Shishir K. Maithel, MD<sup>1</sup>, Maria C. Russell, MD<sup>1</sup>

<sup>1</sup>Division of Surgical Oncology, Department of Surgery, Winship Cancer Institute, Emory University, Atlanta, Georgia, USA

<sup>2</sup>Division of Surgical Oncology, Department of Surgery, University of Texas Southwestern Medical School, Dallas, Texas, USA

<sup>3</sup>Division of Surgical Oncology, Department of Surgery, Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, Miami, Florida, USA

<sup>4</sup>Division of Surgical Oncology, Department of Surgery, NYU Langone Health, New York City, New York, USA

<sup>5</sup>Division of Surgical Oncology, Department of Surgery, University of Illinois College of Medicine, Chicago, Illinois, USA

<sup>6</sup>Division of Surgical Oncology, Department of Surgery, University of California San Francisco, San Francisco, California, USA

### Abstract

**Background and Objectives:** Perioperative therapy is a favored treatment strategy for gastric cancer. We sought to assess utilization of this approach at safety net hospitals (SNH) and tertiary referral centers (TRC).

**Materials and Methods:** Patients in the US Safety Net Collaborative (2012–2014) with resectable gastric cancer across five SNH and their sister TRC were included. Primary outcomes were receipt of neoadjuvant chemotherapy (NAC) and perioperative therapy.

**Results:** Of 284 patients, 36% and 64% received care at SNH and TRC. The distribution of Stage II/III resectable disease was similar across facilities. Receipt of NAC at SNH and TRC was similar (56% vs. 46%,  $p = 0.27$ ). Compared with overall clinical stage, 38% and 36% were pathologically downstaged at SNH and TRC, respectively. Among patients who received NAC, those who also

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**Correspondence:** Maria C. Russell, Division of Surgical Oncology, Department of Surgery, Winship, Cancer Institute, Emory University, 550, Peachtree St, 9th floor MOT, Atlanta, GA, 30308, USA. maria.c.russell@emory.edu.

#### CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

received adjuvant chemotherapy at SNH and TRC were similar (66% vs. 60%,  $p = 0.50$ ). Asian race and higher clinical stage were associated with receipt of perioperative therapy (both  $p < 0.05$ ) while treatment facility type was not.

**Conclusions:** There was no difference in utilization of a perioperative treatment strategy between facility types for patients with gastric cancer. Pathologic down-staging from NAC was similar across treatment facilities, suggesting similar quality and duration of therapy. Treatment at an SNH is not a barrier to receiving standard-of-care perioperative therapy for gastric cancer.

### Keywords

gastric cancer; health disparities; perioperative therapy; safety net hospitals

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## 1 | INTRODUCTION

Gastric cancer is the fifth most common cancer worldwide.<sup>1</sup> Given the survival benefit demonstrated in the landmark MAGIC and FLOT-4 randomized Phase III clinical trials, current National Comprehensive Cancer Network (NCCN) guidelines recommend a perioperative treatment approach for Stage II and III disease.<sup>2,3</sup> As a result, this treatment paradigm has emerged as the standard-of-care for advanced gastric cancer.

While considerable progress has been made in both the diagnosis and treatment of gastric cancer, a disproportionate burden of disease is evident among racial/ethnic minorities in the United States, who are more likely to receive care at safety net hospitals. This may translate to disparities in the receipt of guideline-concordant care and subsequently worse oncologic outcomes.<sup>4,5</sup> Understanding the differences in care by facility type and mitigating disparities in the utilization of multimodality therapy is critical to achieve equitable care among racial/ethnic minority patients. Thus, we sought to assess the utilization of perioperative treatment approach at safety net hospitals and tertiary referral centers.

## 2 | MATERIALS AND METHODS

### 2.1 | Data source and study cohort

We conducted a retrospective cohort study including patients from the US Safety Net Collaborative (US-SNC) gastric cancer database. The US-SNC is a multi-institutional consortium of five safety net hospitals, Grady Memorial Hospital, Parkland Memorial Hospital, Bellevue Hospital, Jackson Memorial Hospital, John H. Stroger Jr. Hospital of Cook County, and their sister tertiary referral centers, Emory University, University of Texas Southwestern, New York University, University of Miami, and University of Illinois at Chicago. All patients more than or equal to 18 years of age with primary, nonmetastatic gastric adenocarcinoma who received perioperative therapy and underwent curative-intent resection from 2012 to 2014 were included. Patients with recurrent disease, Stage IV disease, who underwent a palliative operative, who had a positive macroscopic margin at the time of surgery (R2), or who did not receive multimodality therapy were excluded. Institutional Review Board approval was obtained at each site before data collection.

## 2.2 | Study variables and outcomes

Demographic, perioperative, intraoperative, histopathologic, and survival data were collected via a retrospective review of patient medical records. Clinical and pathologic staging for gastric cancer was based on the American Joint Committee on Cancer (AJCC) eighth edition. Perioperative therapy was considered having received treatment both before and following surgery. Neoadjuvant therapy included chemotherapy, radiation therapy, and/or chemoradiation before surgery. Adjuvant therapy included chemotherapy, radiation therapy, and/or chemoradiation after surgery. Survival data was verified with the Social Security Death Index. Primary outcomes were receipt of neoadjuvant therapy and receipt of perioperative therapy.

## 2.3 | Statistical analysis

Statistical analysis was performing with SPSS 26.0 software (IBM Inc.). A significance level ( $\alpha$ ) of 0.05 defined for two-tailed tests. Descriptive statistics were performed for the entire cohort.  $\chi^2$  or Fisher's exact tests were used for the comparison of categorical variables. Student's *t*-test or Mann-Whitney tests were used for the comparison of means and medians of continuous variables. Univariate and multivariable binary logistic regression were used to determine the association of demographic and clinicopathologic variables and the receipt of neoadjuvant chemotherapy and perioperative therapy. Covariates deemed clinical and/or statistically significant were select for inclusion in multivariable models.

# 3 | RESULTS

## 3.1 | Patient characteristics

Of the 802 patients in the US-SNC database, 284 met the inclusion criteria. Baseline demographic, clinical, treatment, operative, perioperative, histopathologic, and long-term outcomes are outlined in Table 1. Thirty-six percent ( $n = 64$ ) received care at a safety net hospital and 64% ( $n = 112$ ) received care at a tertiary referral center. Median age of patients was 63 years (interquartile range [IQR] 54–72). Patients who were treated at safety net hospitals were more often Black or Asian race, Hispanic, had no health insurance, had independent functional status, and received their cancer diagnosis in the emergency department, compared with those treated at tertiary referral centers (all  $p < 0.05$ ). Considering clinicopathologic factors, patients treated at safety net hospitals had tumors more likely to be located in the stomach body/antrum, compared with the gastroesophageal junction (GEJ) junction/cardia ( $p = 0.03$ ). A higher proportion of patients at safety net hospitals received adjuvant radiation therapy (27%,  $n = 20$ ) compared with patients at tertiary referral center (8%,  $n = 8$ ). Of note, the proportion of patients who received neoadjuvant therapy and perioperative therapy were similar (all  $p > 0.05$ ). There was no difference in rates of postoperative complications between patients treated at safety net hospitals or tertiary referral centers.

## 3.2 | Receipt of neoadjuvant chemotherapy

Fifty-six percent ( $n = 36$ ) at safety net hospitals and 46% ( $n = 46$ ) at tertiary referral centers received neoadjuvant chemotherapy. More advanced clinical stage at diagnosis was

associated with receipt of neoadjuvant chemotherapy on both univariate (Stage II odds ratio [OR] 7.94, 95% confidence interval [CI] 2.39–26.39,  $p < 0.01$ ; Stage III OR 41.43, 95% CI 11.09–154.81,  $p < 0.01$ ), and multivariable analysis (Stage II OR 7.74, 95% CI 2.30–26.01,  $p < 0.01$ ; Stage III OR 40.14, 95% CI 10.59–152.10,  $p < 0.01$ ) (Table 2). The treatment facility was not associated with receipt of neoadjuvant chemotherapy.

### 3.3 | Receipt of perioperative therapy

Thirty-six percent ( $n = 23$ ) at safety net hospitals and 29% ( $n = 33$ ) at tertiary referral centers received perioperative therapy. Factors associated with receipt of perioperative therapy included Asian race (OR 2.84, 95% CI 1.05–7.69,  $p = 0.04$ ) and more advanced clinical stage at diagnosis (Stage II OR 16.55, 95% CI 2.06–133.24,  $p < 0.01$ ; Stage III OR 47.16, 95% CI 5.92–375.16,  $p < 0.01$ ) (Table 3). On multivariable binary logistic regression, Asian race (OR 5.18, 95% CI 1.24–21.67,  $p = 0.02$ ) and more advanced clinical stage (Stage II OR 22.31, 95% CI 2.58–192.76,  $p < 0.01$ ; Stage III OR 46.69, 95% CI 5.45–400.17,  $p < 0.01$ ) were associated with an increased odds of receiving perioperative therapy. Notably, treatment facility was not an independent predictor for receipt of perioperative therapy on either univariate or multivariable analysis.

### 3.4 | Pathologic response

The distribution of overall clinical Stage II (38%,  $n = 43$ ) and Stage III (30%,  $n = 35$ ) for resectable disease was similar both at safety net hospitals and tertiary referral centers, respectively ( $p = 0.20$ ). Compared with overall clinical stage, 38% and 36% of patients were pathologically downstaged at safety net hospitals and tertiary referral centers, respectively (Figure 1).

## 4 | DISCUSSION

Neoadjuvant and perioperative chemotherapy have emerged as the standard-of-care treatment paradigm for locally advanced gastric cancer by offering an in vivo assessment of tumor biology, improved rates of curative resection, and treatment of micro-metastatic disease. However, its utilization across different facility types has not yet been characterized. In our multi-institutional study of patients with resectable gastric cancer treated at high-volume centers in the United States, we found no difference in the use of neoadjuvant chemotherapy or a perioperative treatment strategy between safety net hospitals and tertiary referral centers.

More advanced disease is an established predictor for the receipt of perioperative therapy, given literature demonstrating its role in mitigating the potential for disease progression.<sup>6</sup> This was consistent with our study as a higher clinical stage was a predictor for receiving neoadjuvant chemotherapy or perioperative therapy. In a prior study from our group, patients with gastric cancer at safety net hospitals were more likely to present with more advanced disease, which may lead to worse clinical outcomes.<sup>7</sup> Nevertheless, when patients at safety net hospitals received appropriate care, their long-term outcomes were equivalent to those of their peers at tertiary referral centers.

Beyond clinicopathologic features, clinicians should consider the social, environmental, and demographic drivers for receiving multimodality therapy. In our study cohort, patients treated at safety net hospitals were more likely to lack health insurance, to have been diagnosed in the emergency department, and thus present with more advanced disease, which is consistent with recent literature describing racial/ethnic disparities among patients with cancer.<sup>8</sup> With a perioperative treatment strategy, clinicians balance the risk of disease progression, tolerance of therapy, and potential for treatment resistance. In underserved communities, however, it is critical to also consider disease biology in the context of societal, healthcare system, and patient-level factors to maximize the delivery, utilization, and completion of perioperative therapy. As health disparities among cancer patients are a result of the complex interaction of many extrinsic and intrinsic determinants, we as clinicians must not only keep in mind the structural inequities our patients face, but also actively work towards removing these barriers to improve their long-term outcomes. To this end, we can take into account the “three-delay” framework, to better identify and address patient barriers to seeking care, reaching a healthcare facility, and receiving the appropriate treatment.<sup>9</sup> While recognizing the safety net hospitals often treat for more vulnerable patient populations with significant barriers to healthcare resources, such as lacking health insurance, patients receive high-quality and appropriate oncologic care.

Prior studies have highlighted racial/ethnic disparities present in vulnerable patient populations, included is the association of Black race with worse oncologic outcomes.<sup>10,11</sup> In our study, a higher proportion of patients treated at safety net hospitals were Black, compared with those treated at tertiary referral centers. However, it is critical to note Black race is often a surrogate for low socioeconomic status, level of educational attainment, or inadequate access healthcare resources.<sup>12</sup> These barriers ultimately lead to decreased rates of cancer screening and delays in cancer diagnosis.<sup>13</sup> Low socioeconomic status has been associated with greater to exposure to *Helicobacter pylori* infection and adverse environmental exposures, both well-described risk factors for the development of gastric cancer.<sup>14</sup> This is compounded in patients where health literacy is a concern, particularly among racial/ethnic minorities, which may impact all three aspects of the three-delays model, and subsequently lead to non-adherence with treatment plans.<sup>15</sup>

In our study cohort, Black race was not associated with a decreased odds of receiving perioperative therapy. This suggests Black patients treated in this select group of safety net hospitals with existing social support mechanisms allowed them to better seek, reach, and receive appropriate oncologic care. Conversely, Asian race was associated with an increased likelihood of receiving perioperative therapy. While prior literature reports Asians and Hispanics/Latinos carry a disproportionate burden of gastric cancer in the United States, increased prevalence does not necessarily translate to worse long-term outcomes.<sup>16</sup> This may be due to earlier diagnosis and ultimately, receipt of definitive treatment, including surgery.<sup>17</sup> In addition, in Asian communities, there may be increased awareness and knowledge of gastric cancer screening programs given the high incidence of gastric cancer in many East Asian countries, such as Japan and Korea.<sup>18</sup> More research is needed to determine the underlying epidemiological and biological factors that contribute to the outcomes in Asian patients with gastric cancer.

Clinical response after neoadjuvant therapy at both treatment facility types was comparable with historic data, suggesting similar quality and duration of preoperative therapy.<sup>19,20</sup> Interestingly, in the adjuvant setting, patients treated at safety net hospitals were more likely to receive radiation therapy. There was no variation in lymph node yield, type of dissection, or disease histology between patients treated at safety net hospitals or tertiary referral centers to account for this observation. Differences in the use of adjuvant radiation therapy may be due to the fact a higher proportion of patients at safety net hospitals presented with Stage II and III disease and had improved preoperative functional status, compared to those treated at tertiary referral centers.

In addition, postoperative complications have the potential to impact the completion of adjuvant or multimodality therapy.<sup>21,22</sup> When postoperative complications did occur, preoperative therapy has been shown to negate the impact of complications on long-term survival.<sup>23</sup> Further, with the use of a neoadjuvant treatment strategy, Badgwell et al.<sup>24</sup> demonstrated postoperative morbidity and mortality rates were not increased. In our study population, there was no difference in postoperative complications among patients treated at safety net hospitals or tertiary referral centers and postoperative complications were not associated with a decreased odds of receiving perioperative therapy.

Despite the progress made in our understanding of the factors that contribute to health disparities, overcoming barriers for gastric cancer treatment in “at-risk” populations remain a challenge. While our study highlights that there was no difference in the utilization of a perioperative treatment strategy among patients treated at safety net hospitals and tertiary referral centers, intentional and concerted efforts are needed to reduce and ultimately eliminate health disparities—spanning the domains of access, treatment, and continued engagement with the healthcare system. Initiatives to increase enrollment in cancer clinical trials, studies that accurately represent the heterogeneous patient groups in the United States, and widespread implementation of patient education and outreach programs will help ensure access to vital healthcare resources for all patients.

Limitations of this study include those inherent to a retrospective design and its inherent biases, such as missing or misclassified data. Specifically, as all the patients were re-coded under the AJCC eighth edition, patients with missing staging data were excluded. Second, the study population represents a well-selected surgical patient population, which lends itself to potential selection bias. Regardless, this multi-institutional collaborative of high-volume safety net hospitals and their sister tertiary referral centers in the United States mitigates single-institution bias and improves generalizability.

## 5 | CONCLUSIONS

In summary, for patients with resectable gastric cancer, there was no difference in the utilization of a perioperative treatment strategy between treatment facility types. In addition, after receipt of neoadjuvant chemotherapy, pathologic response was similar for patients at both treatment facility types. Therefore, treatment at a safety net hospital, in and of itself, is not a barrier to receiving standard-of-care treatment for resectable gastric cancer.



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## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

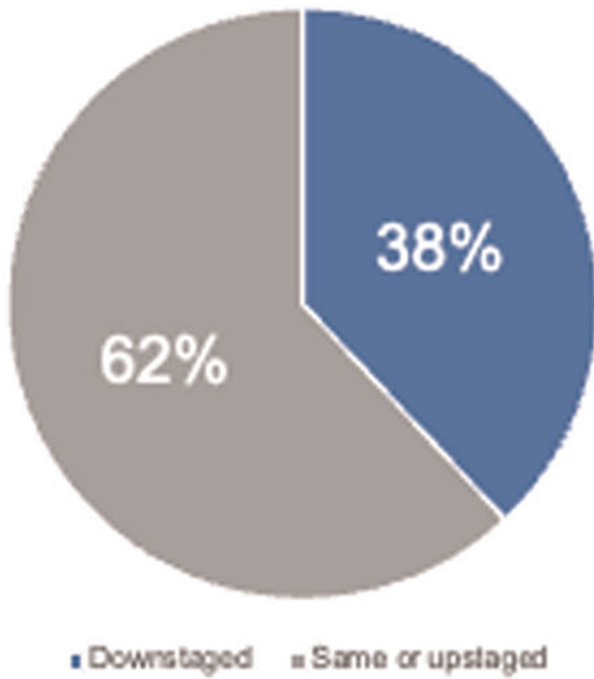
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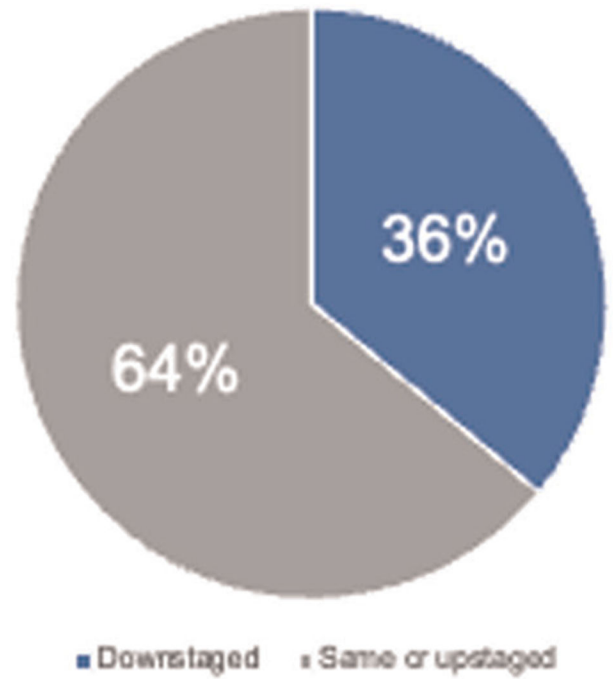


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(A) Safety Net Hospitals



(B) Tertiary Referral Centers



**FIGURE 1.** Pathologic response after neoadjuvant therapy for patients with resectable gastric cancer at safety net hospitals (A) and tertiary referral centers (B)

**TABLE 1**

Baseline characteristics patients with resectable gastric cancer by facility type

Variable	All patients n = 284 (%)	SNH n = 64 (36)	TRC n = 112 (64)	p value
<b>Demographic features</b>				
Age at diagnosis (median, IQR)	63 (54–72)	58 (51–66)	65 (57–75)	<0.01
<b>Gender</b>				
Female	113 (40)	48 (37)	65 (42)	0.43
Male	171 (60)	82 (63)	89 (58)	
<b>Race</b>				
White	152 (57)	52 (44)	100 (67)	<0.01
Black	72 (27)	39 (33)	33 (22)	
Asian	43 (16)	27 (23)	16 (11)	
<b>Ethnicity</b>				
Non-Hispanic	207 (73)	84 (65)	123 (80)	0.02
Hispanic	75 (27)	45 (35)	30 (20)	
<b>Insurance status</b>				
No insurance	55 (20)	54 (41)	1 (1)	<0.01
Insurance	227 (80)	76 (59)	151 (99)	
<b>Functional status</b>				
Independent	248 (89)	125 (97)	123 (83)	<0.01
Partially/totally dependent	30 (11)	4 (3)	26 (17)	
<b>Location of diagnosis</b>				
ED	95 (34)	71 (55)	24 (16)	<0.01
Primary care clinic	169 (61)	52 (40)	117 (80)	
Incidental	13 (5)	7 (5)	6 (4)	
Median follow-up (median, IQR)	15 (6–30)	17 (6–33)	14 (5–27)	0.10
<b>Clinicopathologic features</b>				
<b>Bleeding symptoms</b>				
No	205 (96)	63 (93)	142 (97)	0.23
Yes	9 (4)	5 (7)	4 (3)	
<b>Obstructive symptoms</b>				
				0.27

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Variable	All patients n = 284 (%)	SNH n = 64 (36)	TRC n = 112 (64)	p value
No	143 (51)	61 (47)	82 (54)	
Yes	138 (49)	69 (53)	69 (46)	
Clinical stage				0.20
I	77 (38)	37 (32)	40 (44)	
II	71 (35)	43 (38)	28 (31)	
III	57 (27)	35 (30)	22 (24)	
Location of tumor				<b>0.03</b>
GE junction/cardia	77 (28)	27 (21)	50 (34)	
Body/antrum	197 (72)	99 (79)	98 (66)	
Pathologic stage				0.45
0	11 (4)	2 (2)	9 (6)	
I	78 (29)	38 (31)	40 (28)	
II	83 (31)	39 (31)	44 (31)	
III	60 (22)	28 (23)	32 (22)	
IV	36 (14)	17 (13)	19 (13)	
Any postoperative complication				0.95
No	95 (66)	41 (66)	54 (67)	
Yes	48 (34)	21 (34)	27 (33)	
Treatment features				
Neoadjuvant therapy				0.33
No	196 (69)	94 (72)	102 (66)	
Yes	88 (31)	36 (28)	52 (34)	
Neoadjuvant chemotherapy				0.27
No	88 (50)	28 (44)	60 (54)	
Yes	88 (50)	36 (56)	52 (46)	
Perioperative therapy				0.47
No	120 (68)	41 (64)	79 (71)	
Yes	56 (32)	23 (36)	33 (29)	
Adjuvant therapy				0.20
No	133 (47)	55 (43)	8 (51)	
Yes	149 (53)	74 (57)	75 (49)	

Variable	All patients n = 284 (%)	SNH n = 64 (36)	TRC n = 112 (64)	p value
Adjuvant chemotherapy				
No	74 (37)	34 (34)	40 (40)	0.50
Yes	127 (63)	66 (66)	61 (60)	
Adjuvant radiation				
No	143 (84)	55 (73)	88 (92)	<b>&lt;0.01</b>
Yes	28 (16)	20 (27)	8 (8)	
Adjuvant chemoradiation				
No	115 (80)	35 (80)	80 (81)	0.86
Yes	28 (20)	9 (20)	19 (19)	

Abbreviations: ED, emergency department; GE, gastroesophageal; IQR, interquartile range.

Univariate and multivariable binary logistic regression for receipt of neoadjuvant chemotherapy for patients with resectable gastric cancer

**TABLE 2**

	Univariate regression		Multivariable regression	
	OR (95% CI)	p value	OR (95% CI)	p value
Age	0.99 (0.97–1.01)	0.49		
Gender				
Female	Reference			
Male	1.46 (0.80–2.67)	0.22		
Race				
White	Reference			
Black	0.87 (0.43–1.77)	0.70		
Asian	1.58 (0.59–4.24)	0.37		
Ethnicity				
Non-Hispanic	Reference			
Hispanic	-			
Insurance status				
No insurance	Reference			
Insurance	0.94 (0.41–2.14)	0.89		
Functional status				
Independent	Reference			
Non-independent	0.49 (0.21–1.14)	0.10		
Bleeding symptoms				
No	Reference			
Yes	1.80 (0.96–3.37)	0.07		
Obstructive symptoms				
No	Reference			
Yes	0.92 (0.50–1.66)	0.77		
Location of diagnosis				
ED	Reference			
Primary care clinic	1.05 (0.55–2.02)	0.87		
Incidental	2.15 (0.49–9.45)	0.31		

	Univariate regression		Multivariable regression	
	OR (95% CI)	p value	OR (95% CI)	p value
Clinical stage at diagnosis				
I	Reference		Reference	
II	7.94 (2.39–26.39)	<0.01	7.74 (2.30–26.01)	<0.01
III	41.43 (11.09–154.81)	<0.01	40.14 (10.59–152.10)	<0.01
Treatment facility				
SNH	Reference		Reference	
TRC	0.67 (0.36–1.25)	0.21	0.88 (0.36–2.11)	0.88

Abbreviations: CI, confidence interval; ED, emergency department; OR, odds ratio; SNH, safety net hospitals; TRC, tertiary referral centers.



Univariate and multivariable binary logistic regression for receipt of perioperative therapy for patients with resectable gastric cancer

**TABLE 3**

	Univariate Regression		Multivariable Regression	
	OR (95% CI)	p value	OR (95% CI)	p value
Age	0.98 (0.86–1.00)	0.10		
Gender				
Female	Reference			
Male	0.99 (0.52–1.89)	0.98		
Race				
White	Reference		Reference	
Black	0.96 (0.43–2.11)	0.91	0.97 (0.33–2.88)	0.96
Asian	2.84 (1.05–7.69)	<b>0.04</b>	5.18 (1.24–21.67)	<b>0.02</b>
Ethnicity				
Non-Hispanic	Reference			
Hispanic	-			
Insurance status				
No insurance	Reference			
Insurance	0.94 (0.39–2.25)	0.89		
Functional status				
Independent	Reference			
Partially/totally dependent	0.40 (0.14–1.11)	0.08		
Bleeding symptoms				
No	Reference			
Yes	1.27 (0.66–2.45)	0.48		
Obstructive symptoms				
No	Reference			
Yes	1.32 (0.69–2.52)	0.40		
Location of diagnosis				
ED	Reference			
Primary care clinic	0.75 (0.38–1.50)	0.42		
Incidental	2.25 (0.54–9.35)	0.26		

	Univariate Regression		Multivariable Regression	
	OR (95% CI)	p value	OR (95% CI)	p value
Clinical stage at diagnosis				
I	Reference		Reference	
II	16.55 (2.06–133.24)	<0.01	22.31 (2.58–192.76)	<0.01
III	47.16 (5.92–375.16)	<0.01	46.69 (5.45–400.17)	<0.01
Treatment facility				0.18
SNH	Reference		Reference	
TRC	0.75 (0.39–1.43)	0.38	1.94 (0.73–5.16)	
Any postoperative complication				
No	Reference			
Yes	1.05 (0.56–2.00)	0.89		

Abbreviations: CI, confidence interval; ED, emergency department; OR, odds ratio; SNH, safety net hospitals; TRC, tertiary referral centers.