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ORIGINAL ARTICLE

Presentation and Survival of Gastric Cancer Patients at an Urban Academic Safety-Net Hospital

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Abstract

Introduction Gastric cancer is decreasing nationally but remains pervasive globally. We evaluated our experience with gastric cancer at a safety-net hospital with a substantial immigrant population.

Methods Demographics, pathology, and treatment were analyzed for gastric adenocarcinoma at our institution (2004–2017). Chi-square analyses were performed for dependence of staging on demographics. Survival was evaluated with Kaplan-Meier and Cox regression analyses.

Results We identified 249 patients (median age 65 years). Patients were predominantly born outside the USA or Canada (74.3%), non-white (70.7%), and federally insured (71.4%), and presented with late-stage disease (52.2%). Hispanic ethnicity, Central American birthplace, Medicaid insurance, and zip code poverty > 20% were associated with late-stage presentation (all $p < 0.05$). Univariate analyses showed decreased survival for patients with late-stage disease, highest zip code poverty, and age ≥ 65 (all $p < 0.05$). On multivariate analysis, survival was negatively associated with late-stage presentation (HR 4.45, $p < 0.001$), age ≥ 65 (1.80, $p = 0.018$), and *H. pylori* infection (2.02, $p = 0.036$).

Conclusion Hispanic ethnicity, Central American birthplace, Medicaid insurance, and increased neighborhood poverty were associated with late-stage presentation of gastric cancer with poor outcomes. Further study of these populations may lead to screening protocols in order to increase earlier detection and improve survival.

Keywords Gastric cancer · Cancer outcomes · Safety net hospital · Immigrant population · Health disparities

Introduction

Gastric cancer (GC) incidence and mortality have steadily decreased in the USA and similarly developed countries over the past several decades.[1–4] Despite this improvement nationally, GC continues to be a pervasive global health concern and remains the fourth most common cancer among men and the fifth among women worldwide.[5] This epidemiological disparity is most notable in underdeveloped countries, where GC accounts for more deaths than all cancers other than lung and liver malignancies. With a substantial number of immigrants from these countries and other high-incidence regions such as East Asia, the patient population in the USA likely demonstrates heterogeneous patterns and outcomes from GC.

Declining overall rates of gastric cancer in the USA may mask the experience of select at-risk populations. The most well-studied risk factor for the development of GC is *Helicobacter pylori* infection, yet other patient characteristics such as male gender, increased age, and non-white race may be predictive for increased GC incidence and mortality.[6–8] Hispanic race specifically has been identified as a risk factor for distant stage presentation of GC, and GC is one of several malignancies that presents later in patients who reside in impoverished counties.[9,10] Diet, smoking, and comorbid obesity have each been identified as independent risk factors for GC as well.[11–13]

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Several of these previously identified predictors of adverse outcomes in GC may be observed more frequently in immigrant populations.[14,15] When combined with environmental exposures in higher-incidence countries prior to immigration, these factors may lead to fundamentally different patterns of GC presentation and progression in a heavily immigrant population. This type of patient population may be more likely to be seen at safety-net hospitals, which have previously been defined as those medical centers delivering a significant level of care to uninsured patients or patients receiving Medicaid.[16]

To our knowledge, survival and stage at presentation for GC have not been analyzed in a majority-immigrant population representing multiple ethnicities. In this paper, we analyze the experience of patients treated for GC at an urban safety-net hospital that serves a diverse, largely foreign-born population.

Materials and Methods

This retrospective observational study was performed with a cohort of patients diagnosed with or treated for gastric cancer at an urban, tertiary academic medical center between January 1, 2004, and June 30, 2017. Patients were identified by querying our institutional tumor registry database for patients with a tumor site of C16.0–C16.9, corresponding to cancers of the stomach. An institutional billing database and oncology dataset were cross-referenced to ensure that all applicable patients were identified. After reviewing each patient's medical record, 249 patients with gastric adenocarcinoma not involving the gastroesophageal junction were identified.

A combination of automated chart extraction and individual chart review was employed to record demographic information. Gender was recorded as a dichotomous variable, and patients were divided into racial and ethnic groups based on hospital registration. Patient birthplaces were categorized by continent, with the USA and Canada combined into a reference category. Insurance status was recorded with Medicare-Medicaid dual-eligible patients categorized under "Medicare." Quartiles were established using percentage of the population living beneath the poverty line in each patient's zip code based on information from the U.S. Census Bureau.[17]

Tumor characteristics were recorded from tumor registry data and pathology reports. Stage at presentation was determined using the best available AJCC staging from tumor registry data. The Lauren classification system was used to categorize histology into intestinal, diffuse, and mixed/indeterminate types. Tumor grade ranging from well-differentiated to undifferentiated was recorded, as well as anatomical location using the tumor registry's C16.0–C16.9 codes. Results from tests for *H. pylori* infection and Her2neu expression were recorded when performed. Patients with confirmed gastric cancer were most often staged with a combination of computed tomography (CT) and endoscopy. Endoscopic ultrasound was used selectively in patients with locally or regionally advanced disease. Positron emission tomography was used in patients with regionally advanced disease or with concerning findings on staging CT that required further diagnostic evaluation. All patients identified as surgical candidates underwent diagnostic laparoscopy prior to resection to evaluate for occult metastases. In our analyses, we have defined stage I and II disease as "early-stage" to denote localized disease, and we have defined stage III and IV disease as "late-stage" to identify patients with regional or distant metastases, as previously described in similar studies.[18,19]

Treatment modalities including surgical and endoscopic resection, palliative procedures, chemotherapy, and radiation were recorded. Patient survival measured in months was included in the Tumor Registry data corresponding to date of confirmed death or last patient contact. Patients with a recorded date of death and/or cause of death in the Tumor Registry data were marked as deceased for survival analyses.

Statistical analyses were conducted on SPSS (IBM Corp. Released 2017. IBM SPSS Statistics for McIntosh, Version 25.0. Armonk, NY: IBM Corp.). SAS software version 9.4 (SAS Institute, Cary, NC) was also used. Chi-square analyses were performed to determine the independence of demographic factors from stage at presentation. Select demographic groups with the highest incidence of late-stage presentation were analyzed separately as dichotomous variables using Fisher's exact test. Univariate survival analyses for demographic factors were performed with Kaplan-Meier curves using the log-rank statistic for significance. Multivariate survival analyses were performed using a Cox regression analysis with demographic factors, tumor characteristics, and multiple patient comorbidities as variables. Individual variables that did not conform to the proportional hazards assumption were excluded from survival analyses. All statistical analyses sought a significance level of $p < 0.05$.

Results

We identified 249 patients diagnosed with or treated for gastric cancer at our institution between January 1, 2004, and June 30, 2017. Patients were predominantly male (61.8%) with a median age of 65.0 years (Table 1). The most common racial group was Black/African-American (41.0%), followed by White (29.3%). A large number of patients were of Hispanic ethnicity as well (24.1%). Most patients identified were born outside of the USA or Canada, with the most common birthplaces being the Caribbean (28.1%), Africa (10.8%), and Central America or Mexico (10.4%). The majority of the cohort was insured through federal programs such as Medicare (37.3%) or Medicaid (34.1%). Approximately half

Table 1 Characteristics of patients presenting with gastric cancer

		N = 249 (%)
Sex	Male	154 (61.8)
	Female	95 (38.2)
Age	< 65 years	119 (47.8)
	> 65 years	125 (50.2)
Race	White	73 (29.3)
	Black	102 (41.0)
	Asian	6 (2.4)
	Other/undetermined	68 (27.3)
Ethnicity	Hispanic	60 (24.1)
	Non-Hispanic	189 (75.9)
Birthplace	USA and Canada	64 (25.7)
	Mexico and Central America	26 (10.4)
	Caribbean	70 (28.1)
	Africa	27 (10.8)
	Europe	18 (7.2)
	South America	13 (5.2)
	Asia	7 (2.8)
	Unknown	24 (9.6)
Insurance	Medicare	93 (37.3)
	Medicaid	85 (34.1)
	Non-Federal	46 (18.5)
	Other	25 (10.0)
Stage	1	49 (19.7)
	2	39 (15.7)
	3	53 (21.3)
	4	77 (30.9)
	Incomplete	31 (12.4)
Poverty level of zip code	0–12.9%	62 (24.9)
	13–20%	63 (25.3)
	20.1–25%	54 (21.7)
	> 25%	64 (25.7)
	Unknown	6 (2.4)
Marital status	Married	99 (39.8)
	Widowed	32 (12.9)
	Single	73 (29.3)
	Divorced	16 (6.4)
	Separated	9 (3.6)
	Unknown	20 (8.0)
Smoking history	Never smoker	154 (61.8)
	Former smoker	61 (24.5)
	Current smoker	34 (13.7)

(47.4%) of all patients resided in zip codes where > 20% of the population lived below the poverty line.

Tumor characteristics were recorded as well, with the majority of neoplasms having intestinal (53.4%) or diffuse (32.9%) histology (Supplemental Table 1). Tumors were most often poorly differentiated (42.2%) or moderately to poorly differentiated (18.5%). The most common primary tumor site was the antrum of the stomach (28.5%). *H. pylori* testing was performed on pathologic specimens from 173 patients, with 40 testing positive. Her2neu testing was performed on tissue from 104 patients, with only 13 testing positive. Most patients (51.0%) underwent resection for their cancer (Supplemental Table 2). Patients without resection were most often non-surgical candidates due to disease spread, with a minority of patients declining surgical management (Supplemental Table 3). A majority of patients received chemotherapy (61.0%), whereas radiation therapy was employed less frequently (30.1%) (Supplemental Table 4).

Two hundred eighteen patients had completed staging of their cancer, and 59.6% of those with known staging had late-stage disease at presentation (stage III/IV) (Table 1). Chi-square analyses for patients with known staging identified several demographic factors that associated with stage at presentation. When utilizing contingency tables with all possible groups for each factor, stage at presentation was dependent on only race ($p = 0.006$) and ethnicity ($p = 0.004$), approaching significance for birthplace ($p = 0.051$) as well (Table 2). Further dichotomous analyses using Fisher's exact test were performed for groups within each variable that displayed the highest frequency of late-stage presentation; associations with late-stage presentation were identified for Hispanic ethnicity (77%; $p = 0.002$), Central American/Mexican birthplace (87%; $p = 0.003$), zip code poverty levels > 20% (69%; $p = 0.007$), and Medicaid insurance (68%; $p = 0.042$) (Table 3).

Univariate survival analyses were performed for demographic variables listed in Table 1. A significant survival disadvantage was observed for patients with later stage presentation; patients with stage I or II disease experienced similar estimated median survival, with stage III and IV patients faring significantly worse (I 61.5 months; II 67.3; III 29.9; IV 13.0; $p < 0.001$) (Fig. 1a). Older patients above the age of 65 were shown to have decreased survival as well (median 30.0 vs. 18.0 months; $p = 0.034$) (Fig. 1b). A similar survival disadvantage was seen when comparing survival for patients who resided in zip codes with > 20% of the population living in poverty as compared to more affluent neighborhoods (24.0 vs 16.0 months; $p = 0.006$) (Fig. 1c). Other analyzed factors were not significant predictors for survival on univariate analysis.

A multivariate survival analysis was performed using a Cox regression model that included stage, age, sex, race, birthplace, insurance type, zip code poverty level, tumor histology, *H. pylori* status, history of alcohol use/abuse, and smoking history. Patient characteristics with increased hazard ratios for death by any cause in this model included late-stage presentation (HR = 4.45 [95% CI = 2.65–7.45]; $p < 0.001$), age ≥ 65 (1.80 [1.06–3.03]; $p = 0.029$), and positive *H. pylori* testing

Table 2 Chi-square analyses for dependence of late-stage presentation on demographic factors based on patients with completed staging

		n	% late stage disease	*p* value
Age	< 65 years old	106	63.2%	0.295
	≥ 65 years old	112	56.3%	
Sex	Male	135	59.3%	0.886
	Female	83	60.2%	
Race	White	62	48.4%	0.006
	Black	89	57.3%	
	Asian	4	25.0%	
	Unspecified	63	76.2%	
Ethnicity	Hispanic	52	76.9%	0.004
	Non-Hispanic	166	54.2%	
Birthplace	USA or Canada	58	55.2%	0.051
	Mexico and Central America	23	87.0%	
	Caribbean	61	55.7%	
	Africa	26	69.2%	
	Europe	16	50.0%	
	South America	12	75.0%	
	Asia	5	40.0%	
	Unknown	17	41.2%	
Poverty level of zip code	0–12.9%	56	51.8%	0.126
	13–20%	51	51.0%	
	20.1%–25%	50	72.0%	
	>25%	55	65.5%	
	Unknown	6	50.0%	
Insurance type	Medicare	85	51.8%	0.194
	Medicaid	78	67.9%	
	Non-Federal	43	58.1%	
	Other	12	66.7%	
Marital status	Married	91	61.5%	0.859
	Widowed	27	51.9%	
	Single	64	62.5%	
	Divorced	15	53.3%	
	Separated	9	66.7%	
	Unknown	12	50.0%	

(2.02 [1.10–3.70]; $p = 0.02$) (Fig. 2). Non-Federal health insurance (2.00 [1.00–4.02]; $p = 0.051$) approached significance as well. A decreased hazard ratio was observed for patients with mixed/indeterminate tumor histology (0.42 [0.19–0.95]; $p = 0.038$).

Discussion

As gastric cancer (GC) becomes less prevalent in the USA, the experience of patients domestically may continue to be markedly different than that of patients internationally. For urban,

Table 3 Fisher's exact test for dependence of stage at presentation on selected dichotomous demographic factors with high-frequency late-stage presentation

	n	% late stage	Fisher's exact one-sided *p* value
Hispanic	52	77%	0.002
Non-Hispanic	166	54%	
Central American/Mexican	23	87%	0.003
All other birthplaces	195	56%	
Poverty > 20%	105	69%	0.007
Poverty < 20%	113	51%	
Medicaid	78	68%	0.042
All other insurance	140	55%	

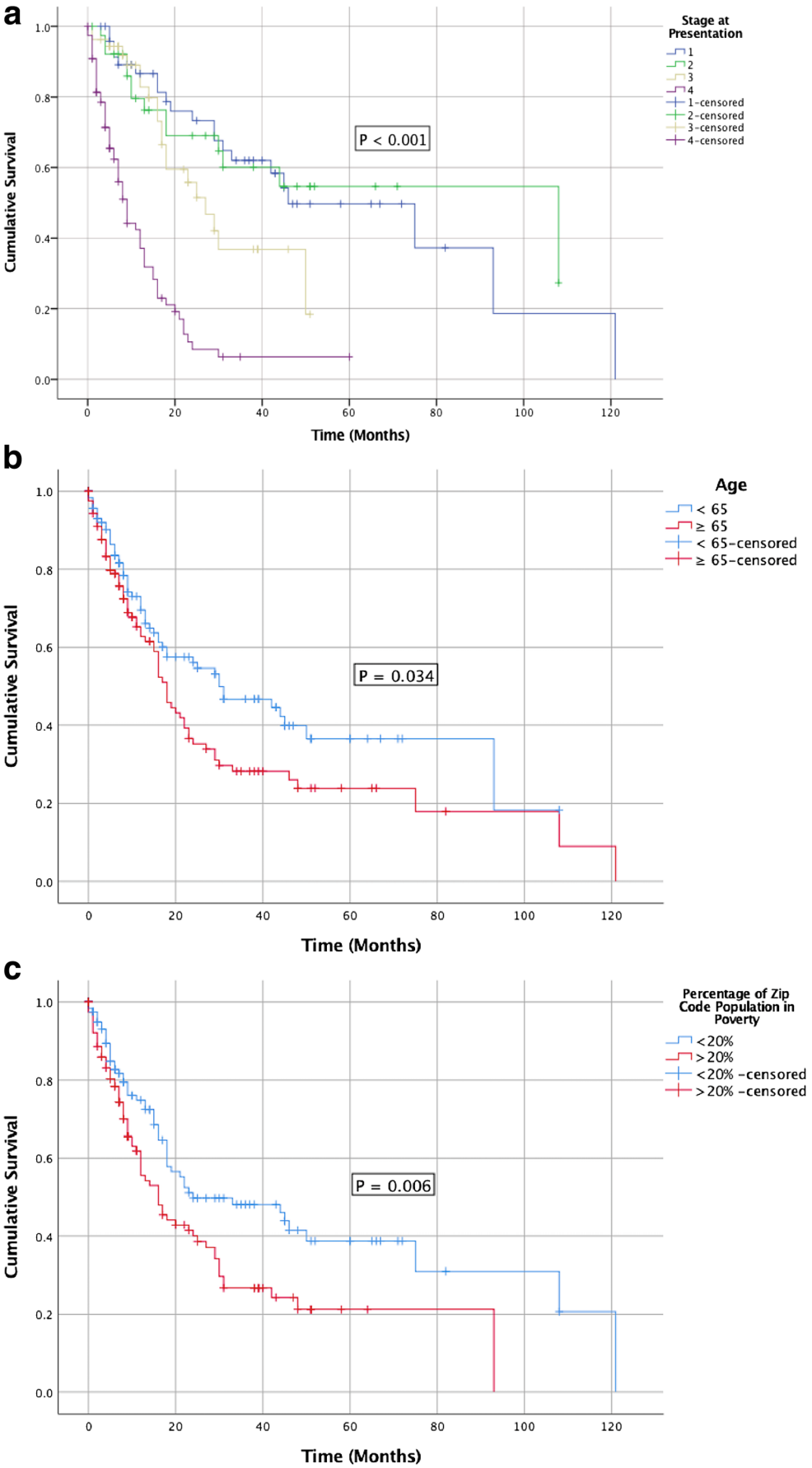

Fig. 1 **a** Kaplan-Meier survival curves by stage at presentation. **b** Kaplan-Meier survival curves for patients 65 years or older compared to younger patients. **c** Kaplan-Meier survival curves based upon zip code poverty level

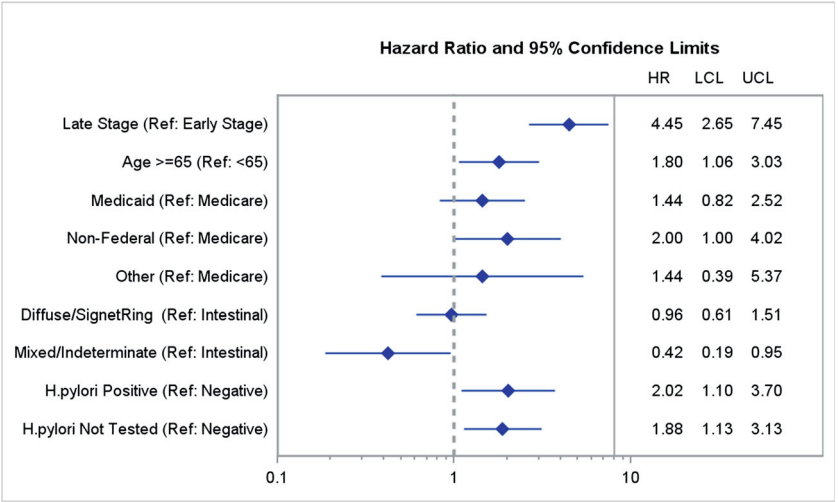

Fig. 2 Hazard ratios predicting mortality for patients presenting with gastric cancer

safety-net hospitals that treat a large immigrant population, it is imperative to understand how to approach patients of various backgrounds. In this study, we found that stage at presentation for GC is dependent on several demographic factors including ethnicity, birthplace, and neighborhood poverty levels. Stage at presentation was then shown to be the strongest predictor of all-cause mortality within this cohort, among other factors such as age and *H. pylori* infection.

Western developed countries have experienced a steady decrease in the incidence of GC over the past century. Studies from the USA have shown this trend across almost all age and racial groups, while similar findings have been published in Great Britain.[2,3] GC remains endemic globally, however, particularly in Eastern Asia and developing nations.[5,20] For surgeons in the USA who treat patients born in these regions, this disparity is informative. A study by Maskarinec et al. last decade showed that while Japanese immigrants living in Hawaii have decreased incidence of GC compared to those remaining in Japan, they have a persistently increased risk of GC compared to local Hawaiians.[21] Within heterogeneous urban populations, patients who have emigrated from endemic areas will likely retain a relatively heightened predisposition to the development of GC.

In this study, with a predominance of foreign-born patients, we sought to characterize how GC presents in the immigrant population and which factors predict improved outcomes. Survival in GC patients has been previously studied using large databases of patients based in the USA; a 2008 paper from Al-Refaie et al. using the National Cancer Database (NCDB) identified several predictors for improved survival, including Asian race, female sex, younger age, treatment at a teaching hospital, and earlier stage.[22] A similar study emerging from the National Cancer Institute's Surveillance, Epidemiology, and End Results Program (SEER) showed African-American race as a predictor for decreased survival.[23] Perhaps surprisingly, foreign-born patients, as a single entity, have been shown to experience relatively higher survival using SEER data.[24] In our study, we find that several factors may independently predict survival, though none as strongly as stage at presentation. The magnitude of staging as a predictor for survival is reflected in previous studies and focuses attention on the importance of early diagnosis.[25] The identification of patients with early-stage disease who will benefit from surgical intervention is paramount.

Strategies to identify at-risk populations may take several forms. *H. pylori* infection is the most well-studied precipitant of GC and has been estimated as the cause of almost 75% of non-cardia gastric cancers.[26] Moreover, our data showed *H. pylori* infection to be an independent predictor of mortality in GC, regardless of stage. Behavioral and nutritional risk factors have also been identified in the pathogenesis of GC, both related and unrelated to *H. pylori* infection. Diets that are high in sodium, as may be seen in endemic regions such as East Asia, have been associated with GC risk, whereas fruit intake and the use of refrigerators have been inversely correlated to the disease.[11] In non-Asian populations, increased body mass index (BMI) has been shown to increase risk of GC.[13] This relationship with obesity may be in part due to the fact that sustained hyperglycemia can potentiate the risk of GC from *H. pylori* infection.[27] Smoking has also been shown to increase risk in multiple studies, though our data suggests that smoking does not increase mortality when controlled for stage.[12,28] These risk factors that pervade the GC population represent modifiable behaviors and potential targets for primary or secondary prevention.

In order to effectively target at-risk populations where these behaviors may cluster, we focused the current study on the presentation of GC by demographics. When isolated from the rest of the cohort, several demographic groups with a high incidence of advanced disease were shown to be significantly associated with late-stage disease. These groups included Hispanic patients, those born in Central America or

Mexico, those living in zip codes with particularly high poverty levels, and those on Medicaid insurance. Interestingly, stage at presentation was shown to be a predictor for mortality on multivariate analysis, while these smaller groups were not shown to be significant. It is possible that the overlap between these groups creates a masking effect on multivariate analysis; the colinearity between Hispanic patients, those from Central America, and those with lower socioeconomic status (SES) may confound the analysis of their roles as risk factors in GC. Hispanic patients have previously been shown to present more frequently with late-stage disease and occult metastases on staging laparoscopy when compared to white patients.[9] Likewise, patients with lower SES are at risk of late-stage presentation for GC in high-incidence areas.[19] There is a wealth of evidence that patients with low SES present with more advanced disease for a variety of other neoplasms as well, including breast, colon, and cervical cancers.[10,18,29–34] For each of these cancers, however, successful screening strategies have been implemented with mammography, colonoscopy, and HPV testing or Papanicolaou smears, respectively.

Gastric cancer likely does not have a high enough incidence in the USA to justify similarly widespread screening, but focused interventions may benefit select populations. Several options for screening are available if necessary. National screening programs currently exist in Japan and Korea, utilizing photofluorography or upper endoscopy.[35] There is evidence that systematic screening for and eradication of *H. pylori* infection may have utility in Asian individuals as well, though it is not clear whether the same is true for other high-incidence populations.[36] Other non-invasive methods, such as measuring serum pepsinogen, may be increasingly employed in future programs, though no such program has been attempted in the USA to our knowledge.[35]

While we have been able to identify select groups of patients that present with later-stage gastric cancer, it remains unclear as to what specifically delays these patients. The patients in this study live in a state with near-universal healthcare coverage, yet this broad access to healthcare does not guarantee early presentation. There are many potential reasons that, based on our findings, members of certain cultural and ethnic communities, as well as those living in poorer neighborhoods, may delay seeking care. Limited education or literacy, cultural or language barriers, and the perceived inability to pay for medical services may prevent patients from presenting sufficiently early to be treated. While these social impediments to care are not examined in this paper, the benefits of community outreach and patient education to address these factors may contribute to the goal of earlier diagnosis.

This study has several limitations. The database of GC patients from our institution was constructed retroactively and as such is limited by the data available in medical records. This is also a single institution study, and the analyses presented here may also have shown further significant findings if our sample size was enlarged in a multi-center study. A sizable number of patients were also lost to follow-up prior to their cancers being definitively staged, limiting our ability to include them in analyses.

Surgical resection of gastric masses has been shown to improve survival yet remains underutilized even in patients with early-stage disease.[37–39] Locating patients with early-stage disease and then successfully bringing them to the operating room is the key challenge we face in treating this disease. In this paper, we find that several sections of the population may benefit from earlier identification of GC. Hispanic patients, those born in certain regions such as Central America, and those living in our most impoverished communities often present too late for surgical intervention. These patients would likely benefit from earlier identification, as would be possible with a regimented screening program. At urban, safety-net hospitals where care is provided for indigent populations that include these patients, improving diagnostic processes is particularly important. Further studies are warranted and, in conjunction with the current literature, will identify at-risk populations and define the utility of screening programs in the USA.

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