BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-017266
Article Type:	Research
Date Submitted by the Author:	11-Apr-2017
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Primary Subject Heading:	Global health
Secondary Subject Heading:	Gastroenterology and hepatology
Keywords:	Gastric cancer, Epidemiology < ONCOLOGY, Mortality, Health care costs, Panama

Epidemiology, mortality and direct costs associated to treatment of gastric cancer patients at the National Oncology Institute of Panama from 2012 to 2015: a hospital-based observational study.

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Abstract word count: 292 words.

Manuscript word count: 3548 words.

Tables and figures count: 4 tables, 1 figure.

Keywords: Gastric cancer; Epidemiology; Mortality; Health care costs; Panama.

Abstract

Objectives: Comprehensive epidemiological and economical studies of gastric cancer (GC) in Panama are limited. This study aims to evaluate the association between socioeconomic and clinical variables with all-cause mortality, describe the survival outcomes according to clinical stage, and estimate the direct costs associated to GC care in a Panamanian population with GC.

Design and setting: A retrospective observational study was conducted at the leading public institution for cancer treatment in Panama.

Participants: Data was obtained from 611 records of patients diagnosed with gastric adenocarcinoma (codes C16.0-C16.9 of the International Classification of Diseases 10th revision, ICD-10), attended between January 1st, 2012 and December 31st, 2015.

Methods: Cox proportional hazards models were used to calculate hazard ratios (HR) with 95% confidence intervals (95%CI) to examine associations between the variables and all-cause mortality. Kaplan-Meier curves were used to assess overall and stage-specific survival. Direct costs (based on 2015 USD) were calculated per patient using standard costs provided by the institution for hospital admission (occupied bed-days), radiotherapy, surgery and chemotherapy, yielding total and overall mean costs (OMC). A comparison of OMC between groups (sex, social security status, clinical stage) was performed applying the bootstrap method with a t-test of unequal variances.

Results: An increased mortality risk was observed for patients without social security coverage (HR: 2.02; 95%CI: 1.16-3.53), overlapping tumors (HR: 1.50; 95%CI: 1.02-2.22), poorly-differentiated tumors (HR: 2.27; 95%CI: 1.22-4.22), and stage IV disease (HR: 5.54; 95%CI: 3.38-9.08) (adjusted models). Overall one-year survival rate was 41%. The estimated OMC of GC care per patient was 4,259 USD. No statistically significant differences were found between OMC.

Conclusions: Socioeconomic disparities influence GC outcomes and healthcare utilization. Policies addressing healthcare disparities related to GC are needed, as well as in-depth studies evaluating barriers of access to GC related services.

Article summary:

Strengths and limitations of this study:

- This is the first study in Panama assessing epidemiology and mortality of gastric cancer (GC), as well as costs related to its care.
- The results reflect the impact of socioeconomic determinants in GC outcomes, having implications for policymakers in Panama.
- Strengths of this study include:
  - Mortality data was ascertained with the National Mortality Registry.
  - The use of actual chemotherapeutic doses administered allowed a more accurate calculation of medication costs.
  - Applying the bootstrap method for mean cost comparison purposes provided us with a more flexible tool to compare costs.
- Limitations of this study include:
  - This study encompassed patients from a single cancer institution and our results cannot be extrapolated to the whole population, however, the National Oncology Institute of Panama is the biggest and main cancer referral public hospital in the country.
  - There was a considerable amount of underreporting and missing variables such as incomplete data regarding chemotherapy protocol sessions, resource utilization and outpatient expenses, which most likely led to underestimation of costs.

1. Introduction

Latin-America presents one of the highest incidences of Gastric Cancer (GC) worldwide.[1] In 2011, GC was responsible for the sixth highest incidence, and the highest mortality rate from cancer in Panama.[2] Although GC treatment is evolving rapidly at the expense of increasing costs of care, there is scarcity of comprehensive epidemiological and economical studies of GC in the region.[3]

Understanding the epidemiology of GC and its costs in low-and middle-income countries is a crucial step to addressing the burden of GC and will guide disease surveillance, screening, prevention activities as well as healthcare resource allocation. Thus, the aims of this study were to evaluate the association between socioeconomic and clinical variables with all-cause mortality, describe the survival outcomes according to clinical stage, and describe the direct costs associated to GC care in a Panamanian population with GC.

2. Methods

2.1. Study population

A descriptive, hospital-based retrospective study was conducted at the National Oncology Institute (NOI). The NOI is the leading public institution for cancer treatment in Panama, receiving cases referred from all over the country.[4 5]

Data derived from patient records (electronic and paper-based) with a histopathological diagnosis of gastric adenocarcinoma having their first appointment at the NOI between January 1st, 2012 and December 31st, 2015 was retrieved. Cases were registered according to codes C16.0 to C16.9 based on the tenth revision of the International Classification of Diseases (ICD-10).

A list containing 697 patients was provided by the Department of Clinical Files at the NOI. A total of 12 clinical records could not be located and were therefore excluded. Of the remaining 685 records, those with a diagnosis different from gastric adenocarcinoma were excluded (mucosa-associated lymphoid tissue (MALT) lymphomas, gastrointestinal stromal tumors (GIST), neuroendocrine tumors (NETs), sarcomas, as well as tumors confirmed to be from a different primary site (e.g., esophageal), for a total study population of 611 patients (Supplementary Figure 1).

All-cause mortality from 2012 to 2015 was verified with the National Mortality Registry (NMR) supplied by the National Institute of Statistics and Census of Panama (Instituto Nacional de Estadística y Censo, INEC). The research protocol was approved by the Gorgas Memorial Institute Ethics Committee and the Ministry of Health.

2.2. Study variables

Socioeconomic (sex, age at diagnosis, social security status, employment status, marital status, province of residence, ethnicity) and clinical variables (location by endoscopy, histological type, tumor grade and clinical stage) were recorded. Costs were ascertained using length of stay in hospital, surgical procedures performed, chemotherapy and radiotherapy received.

Age at diagnosis was categorized considering the cutoff value of 45 years for early onset GC (EOGC), as done in previous studies,[6] and age strata as reported by the Surveillance, Epidemiology, and End Results (SEER).[7] Social security status was categorized as having or not coverage by health institutions of the Panamanian Social Insurance Fund, in which a monthly amount is discounted from contributors' salaries (active public and private workforce) in order to receive health coverage for them and their first degree relatives, allowing children and unemployed adults to have coverage (beneficiaries). The Social Insurance Fund also serves as a retirement fund for workers at a certain age (retired), or in case of permanent disability (pensioners). The NOI is not an institution from the Panamanian Social Insurance Fund, but patients with social security are granted free healthcare services, while those without social security are required to pay out-of-pocket fees.[8]

Provinces of residence were grouped according to geographic proximity to the NOI and common socioeconomic characteristics,[9] and categorized as Panama and Colon, Veraguas and Cocle, Herrera and Los Santos and Other provinces (Bocas del Toro, Chiriqui, Darien, Guna Yala, Ngäbe-Bugle).

Anatomic location of the tumor was based on endoscopic reports and categorized as non-cardia, cardia and overlapping. Cases in which the endoscopic report could not be found in the clinical files were labeled as "unspecified".[10] Histological type was based on the Lauren classification (intestinal, diffuse),[11] and mixed tumors were shown as a different category.[12] Tumor grade was categorized using ICD for Oncology (ICD-O), and clinical stage was based on the 7th edition of the TNM Staging System of the American Joint Committee on Cancer (AJCC), taking into consideration the first staging reported in the clinical file by the physician at the NOI.[13]

Type of care was defined according to hospital admission (recorded as occupied bed days), radiotherapy (number of sessions), surgery and chemotherapy. Surgery was defined as the performance of gastrectomy (total, subtotal) with lymph node resection, gastroenteric anastomosis, stent placement (esophageal, duodenal) or exploratory laparotomy. Chemotherapy regimens for GC were based on the latest National Comprehensive Cancer Network (NCCN) guidelines.

Because the intention of treatment (e.g., curative vs palliative) was under-reported in the patient records, and due to the possibility of non-completion of regimens (loss to follow-up or death) or change in the regimen received (e.g., progression of disease,

differences between clinical TNM and pathological TNM), expenditure on chemotherapy was calculated using actual medication doses and sessions administered on an individual basis instead of assuming completion of a single, invariable regimen.

2.3. Statistical analyses

Qualitative variables were expressed as percentages. As a complementary analysis, cases per 100,000 population were calculated for each province individually, using population data from the INEC.[14] Kaplan Meier curves were used to examine overall survival for all patients and for each clinical stage group. Median survival and median follow-up times in days were calculated and one-year survival rates were reported.

Cox proportional hazards models were used to examine the association between socioeconomic and clinical variables with all-cause mortality. Crude hazard ratios (HR) and 95% confidence intervals (95% CI) were estimated. Adjusted models including all variables were also performed, in order to evaluate their impact on the results obtained. Ethnicity was evaluated, however excluded from the final model due to the high admixture of the Panamanian population. Due to statistical power, provinces of residence were grouped as previously mentioned. In order to avoid collinearity, we performed sensitivity analyses by running two different adjusted models, one including tumor grade but not histological type, and other including histological type but not tumor grade, observing similar point estimates. The assumption of proportional risk was verified using the Schoenfeld residuals method.

Total direct costs of care, expressed in US dollars (USD), were calculated per patient and for the whole study population using standard unit costs provided by the NOI and the Ministry of Health. Since no variation in costs was seen along the 2012-2015 period, calculations were based on 2015 estimates.

Total and mean direct costs were calculated according to social security status, sex, and clinical stage. Overall mean cost (OMC) comparisons among groups were performed using the bootstrap method.[15] This involved repeated resampling (1000 repetitions) of the original cost data by random selection. After resampling, a t-test with unequal variances was conducted to compare means and a p-value was reported.

Statistical analyses were performed using SPSS 20.0 and Stata 14.0.

3. Results

Table 1 shows the socioeconomic and clinical variables of the study population. Overall, 62.2% of the total population were males, 77.4% had social security and 34.9% were unemployed. The group of provinces of Panama and Colon reported the highest number of patients (64.5%). According to age groups, 14.7% were younger than 45 years old, whereas 26.0% were ≥75 years old. Median (interquartile range)

age at diagnosis was 65 (52-75) years. Regarding the complementary analysis, when calculating the number of cases per 100,000 population by province separately, Herrera had 8.29 cases per 100,000, followed by Veraguas with 6.58. Among patients where ethnicity was reported (n=608), 83.2% patients were registered as Mestizo.

Based on endoscopic findings, tumors were most commonly reported as overlapping, observed in 46% of the patients. According to the histological classification, a predominance of intestinal type adenocarcinomas was observed (53.7%). Poorly differentiated tumors were observed in 62.3% of patients. Out of the 611 patients, 52.9% had the clinical stage recorded. From these cases, 4.6% were categorized as stage I, 13.9% as stage II, 15.8% and 65.6% as stage III and IV, respectively.

Table 1
Socioeconomic and clinical variables of patients with gastric cancer treated at the NOI. 2012-2015.

Socioeconomic and clinical variables	n	%
Sex		
Female	231/611	37.8
Male	380/611	62.2
Age		
Less than 45 years	90/611	14.7
45-64 years	207/611	33.9
65-74 years	155/611	25.4
75 years or more	159/611	26.0
Social security status		
With social security	473/611	77.4
Without social security	138/611	22.6
Employment status[a]		
Formal employment	116/610	19.0
Informal employment	119/610	19.5
Retired/pensioner	162/610	26.6
Unemployed	213/610	34.9
Marital status[b]		
Married/common law marriage	397/610	65.1
Single	161/610	26.4
Widowed	52/610	8.5
Province of residence		
Panama and Colon	394/611	64.5
Veraguas and Cocle	118/611	19.3
Herrera and Los Santos	57/611	9.3
Other provinces[c]	42/611	6.9
Ethnicity[d]		
White	71/608	11.7
Mestizo/Afrocaribbean/Indigenous	537/608	88.3
Anatomic location by endoscopy		
Non-cardia	239/611	39.1
Cardia	69/611	11.3

Overlapping	281/611	46.0
Unspecified	22/611	3.6
Histologic type[e]		
Intestinal type	232/432	53.7
Diffuse type	154/432	35.6
Mixed type	46/432	10.6
Tumor grade[f]		
Well/moderately differentiated	223/592	37.7
Poorly differentiated	369/592	62.3
Clinical stage[g]		
I-III	111/323	34.4
IV	212/323	65.6

[a]Employment status: 1 missing; [b]Marital status: 1 missing; [c]Other provinces: 7 from Bocas del Toro, 20 from Chiriqui, 12 from Darien, 1 from Guna Yala, and 2 from Ngäbe-Bugle; [d]Ethnicity: only 23 afrocaribbean and 8 indigenous patients reported, 3 missing; [e]Histologic type: 179 missing; [f]Tumor grade: only 1 undifferentiated, 18 missing; [g]Clinical stage: 288 missing.

3.1. Mortality

In total, n=407 (67.5%) patients died of any cause during the study period. Figure 1 shows overall and stage-specific survival curves. Overall one-year survival rate was 41%, median survival was 287 days (9.5 months) and median follow-up was 604 days (20.1 months). Patients with stage I disease had a one-year survival rate of 93%, whereas stages II, III and IV presented a 78%, 76% and 38% one-year survival rate, respectively.

Table 2 presents the associations between socioeconomic and clinical variables with all-cause mortality. In the adjusted models, patients without social security presented a higher all-cause mortality risk (HR: 2.02; 95% CI: 1.16-3.53) compared to those with social security. Regarding anatomic location, having an overlapping tumor was related with an increased risk of dying (HR: 1.50; 95% CI: 1.02-2.22) in comparison to non-cardia tumors. Poorly differentiated tumors were associated with a higher all-cause mortality risk (HR: 2.27; 95% CI: 1.22-4.22) compared to well/moderately differentiated tumors, as well as those with stage IV disease (HR: 5.54; 95% CI: 3.38-9.08) in comparison to stage I-III disease.

Table 2

Cox proportional hazards models for the associations between socioeconomic and clinical variables with gastric cancer mortality in patients treated at the NOI. 2012-2015.

Socioeconomic and clinical variables	Crude HR		Adjusted HR	
	HR	95% CI	HR	95% CI
Sex				
Female	Reference		Reference	
Male	0.93	(0.70-2.13)	0.67	(0.41-1.01)
Age				
45-64 years	Reference		Reference	
Less than 45 years	1.43	(0.96-2.13)	0.91	(0.53-1.58)
65-74 years	0.90	(0.61-1.32)	0.66	(0.38-1.16)
75 years or more	1.14	(0.78-1.68)	1.68	(0.91-3.10)
Social security status				
With social security	Reference		Reference	
Without social security	**1.44** [f]	**(1.01-2.05)** [f]	**2.02** [f]	**(1.16-3.53)** [f]
Employment status[a]				
Formal employment	Reference		Reference	
Informal employment	1.04	(0.66-1.63)	1.29	(0.68-2.44)
Retired/pensioner	0.87	(0.57-1.35)	1.48	(0.78-2.79)
Unemployed	1.12	(0.77-1.65)	0.75	(0.40-1.44)
Marital status[b]				
Married/common law marriage	Reference		Reference	
Single	1.06	(0.76-1.47)	0.87	(0.57-1.32)
Widowed	0.72	(0.41-1.25)	0.57	(0.24-1.37)
Province				
Panama and Colon	Reference		Reference	
Veraguas and Cocle	0.87	(0.58-1.32)	0.86	(0.50-1.47)
Herrera and Los Santos	0.62	(0.36-1.07)	0.71	(0.33-1.52)
Other provinces	0.82	(0.48-1.41)	1.06	(0.48-2.33)
Anatomic location by endoscopy[c]				
Non-cardia	Reference		Reference	
Cardia	1.30	(0.78-2.19)	0.94	(0.42-2.13)
Overlapping	1.34	(0.99-1.83)	**1.50** [f]	**(1.02-2.22)** [f]
Histologic type[d]				
Intestinal type	Reference		Reference	
Diffuse type	**1.64** [f]	**(1.13-2.40)** [f]	0.79	(0.43-1.47)
Mixed type	**2.12** [f]	**(1.31-3.44)** [f]	1.57	(0.80-3.07)
Tumor grade[e]				
Well/moderately differentiated	Reference		Reference	
Poorly differentiated	**1.91** [f]	**(1.38-2.65)** [f]	**2.27** [f]	**(1.22-4.22)** [f]
Clinical stage				
I-III	Reference		Reference	
IV	**4.37** [f]	**(3.02-6.33)** [f]	**5.54** [f]	**(3.38-9.08)** [f]

[a]Employment status: 1 missing; [b]Marital status: 1 missing; [c]Anatomic location: 11 missing; [d]Histologic type: 83 missing; [e]Tumor grade: 9 missing; [f]$p < 0.05$.

3.2. Costs

A total of 524 patients (85.8%) received any type of care, for an overall total cost of 2,231,728 USD and an OMC per patient of 4,259 USD (95% CI: 3,915-4,603), as shown in Table 3. When stratifying patients by type of care, 73.5% were admitted to the NOI, 66.4% were given chemotherapy, 30.3% underwent a surgical procedure, and 18% received radiotherapy. The highest expenses were attributed to hospital admissions (1,156,460 USD). Chemotherapy accounted for the second highest total cost (652,370 USD), being three times greater than the total cost of radiotherapy (206,872 USD). However, when comparing mean costs, radiotherapy exceeded chemotherapy by 274 USD per patient. For surgical procedures the total cost was 216,026 USD, representing 9.7% of the overall cost.

Table 3
Direct cost estimates (total and means) according to type of care received in patients with gastric cancer at the NOI. 2012-2015.

Type of care	Patients receiving care (%)[a]	Total cost (USD)	Mean cost per patient (USD)	95% CI
Overall	524/611 (85.8)	2,231,728	4,259	(3,915-4,603)
Hospital admission	449/611 (73.5)	1,156,460[b]	2,576[b]	(2,359-2,792)
Radiotherapy	110/611 (18.0)	206,872	1,881	(1,729-2,033)
Chemotherapy	406/611 (66.4)	652,370	1,607	(1,363-1,851)
Surgery	185/611 (30.3)	216,026	1,168	(1,077-1,259)

USD: US dollars; CI: Confidence intervals; [a]Since a single patient could receive different types of care, calculations were made separately for each category and percentages do not add up to 100%; [b]Calculated for occupied bed-days.

Table 4 presents the costs stratified by sex, social security status and disease stage groups, according to type of care received. Women had an OMC per patient of 4,258 USD, while for men it was 4,260 USD. For those with social security, the OMC per patient was 4,414 USD, whereas for those without social security, it was 3,657 USD. Patients with stage I-III disease presented an OMC of 5,174 USD, compared to 4,930 USD for those with stage IV disease (see Supplementary Figure 2 for detailed cost distributions). No statistically significant differences were observed in the OMC between groups.

Table 4
Direct cost estimates by sex, social security status and clinical stage of patients with gastric cancer according to type of care received at the NOI. 2012-2015.

	Male patients n=380			**Female patients n=231**			
Type of care	**Received care (%)[a]**	**Mean cost (USD)**	**95% CI**	**Received care (%)[a]**	**Mean cost (USD)**	**95% CI**	**Bootstrap p-value**
O	324/380 (85.3)	4,260	(3,789-4,731)	200/231 (86.6)	4,258	(3,774-4,741)	0.994
HA	281/380 (73.9)	2,487[b]	(2,219-2,755)	168/231 (72.7)	2,724[b]	(2,340-3,108)	
CT	247/380 (65.0)	1,694	(1,257-2,131)	159/231 (68.8)	1,472	(1,204-1,740)	

RT	69/380 (18.2)	1,915	(1,695-2,135)	41/231 (17.7)	1,823	(1,582-2,064)	
SR	117/380 (30.8)	1,118	(1,028-1,209)	68/231 (29.4)	1,253	(1,074-1,432)	
	Patients with social security n=473			**Patients without social security n=138**			
Type of care	**Received care (%)[a]**	**Mean cost (USD)**	**95% CI**	**Received care (%)[a]**	**Mean cost (USD)**	**95% CI**	**Bootstrap p-value**
O	417/473 (88.2)	4,414	(4,014-4,813)	107/138 (77.5)	3,657	(3,014-4,299)	0.059
HA	357/473 (75.5)	2,562[b]	(2,318-2,806)	92/138 (66.7)	2,628[b]	(2,111-3,145)	
CT	326/473 (68.9)	1,722	(1,376-2,069)	80/138 (58.0)	1,136	(833-1,439)	
RT	93/473 (19.7)	1,848	(1,665-2,031)	17/138 (12.3)	2,060	(1,702-2,417)	
SR	160/473 (33.8)	1,202	(1,103-1,302)	25/138 (18.1)	945	(871-1,019)	
	Stage I - III n=111			**Stage IV n=212**			
Type of care	**Received care (%)[a]**	**Mean cost (USD)**	**95% CI**	**Received care (%)[a]**	**Mean cost (USD)**	**95% CI**	**Bootstrap p-value**
O	108/111 (97.3)	5,174	(4,516-5,832)	201/212 (94.8)	4,930	(4,330-5,529)	0.598
HA	86/111 (77.5)	2,994[b]	(2,353-3,635)	179/212 (84.4)	2,853[b]	(2,484-3,221)	
CT	85/111 (76.6)	890	(683-1,097)	173/212 (81.6)	2,055	(1,579-2,530)	
RT	60/111 (54.1)	2,341	(2,243-2,440)	27/212 (12.7)	1,297	(897-1,697)	
SR	85/111 (76.6)	1,003	(930-1,075)	69/212 (32.5)	1,302	(1,127-1,477)	

O: Overall; HA: Hospital admission; CT: Chemotherapy; RT: Radiotherapy; SR: Surgery; USD: US dollars; CI: Confidence intervals; [a]Since a single patient could receive different types of care, calculations were made separately for each category and percentages do not add up to 100%. [b]Calculated for occupied bed-days.

4. Discussion

Our findings suggest that lack of social security, a poorly differentiated tumor, clinical stage IV and overlapping anatomic location were associated with increased all-cause mortality, independently of other socioeconomic and clinical variables. Furthermore, the overall one-year survival rate in our study was 41% and the estimated OMC of GC care per patient was 4,259 USD.

Socioeconomic factors such as insurance coverage and geographic location have been implicated in mortality outcomes and healthcare disparities.[16-20] Likewise, cultural differences have been documented as strong factors influencing medical care in many Latin American countries, especially in cancer.[19 21] According to national estimates, 80% of the Panamanian population has social security, of which 57% are active workers and 43% are beneficiaries.[22] In our results, patients without social

security had a two-fold higher risk of dying in comparison to those with social security. Similarly, in Colombia, patients with a more affluent socioeconomic status and a private health insurance regimen had a significantly higher GC survival.[23] The lack of social security has been related to late stage diagnosis,[24] and health insurance regimes facilitate greater access to physician care and increase medical service utilization, thus granting patients longer survival times.[25] In addition, lacking social security has been documented as a barrier in access for other cancers in Panama.[4 5] Likewise, a previous study conducted in Sweden has shown the importance of socioeconomic factors in GC mortality, where a higher educational level was associated with a lower mortality and patients living in rural areas had a higher risk of dying due to this type of cancer.[26] Of note, one third of our patients were unemployed, most of them being older than 65 years and beneficiaries from the social security system. The higher proportion of unemployed patients observed, compared to another study of GC in the region,[27] highlights the importance of social security as an aid in front of the complex socioeconomic situation of this population, heavily dependent on having a formally-employed relative in order to have better access to GC-related services. Taken together, these findings emphasize the importance of socioeconomic determinants in the disease outcomes of GC.

Geographic disparities in Panama are a well-known problem, as for some indigenous and other remote regions, human resources and equipment available for diagnosis and treatment are limited.[28] Together, Panama and Colon comprise more than half of the national population and have higher access to healthcare services, one of them being host to the NOI.[29] Herrera was the province with most patients treated at the NOI per 100,000 population, which could be explained by the fact of having the country's highest number of health professionals per capita,[29] giving the patients higher chances of being diagnosed and referred to the NOI. Nevertheless, with half of the amount of health professionals per capita, Veraguas province was second in patients treated at the NOI per 100,000 population, and according to national estimates it ranks first in incidence and second in mortality in the country.[30] Interestingly, the provinces of Veraguas and Cocle, despite having the highest proportion of their patients with stage IV disease (74.1% and 69.6% respectively), accounted for two of the smallest proportions of their residents being diagnosed in institutions inside their territory (10.9% and 7.4% respectively). Although geography was not associated with higher all-cause mortality in our study, these findings underscore the need of further research on GC to determine geographical disparities in depth, as well as lifestyle, environmental, genetic factors, and the interaction among them.[31-34]

In agreement with other studies,[10 35] the male to female ratio was 1.64 and GC was most common in the elderly group.[10 36] Nevertheless, we found a high proportion of EOGC (14.7%) compared to those reported in most countries of the region,[36] only surpassed by Guatemala in Central-America with national estimates of 16.5%,[10] a

comparison worth noting even if our results are based on a single institution. Likewise, in a hospital-based study conducted in Mexico, a similar proportion of EOGC was reported.[37] These discrepancies might mirror differences in underreporting, risk factors and information seeking, making it difficult to compare.

Clinical stage was only reported in half of the patients, a five-fold lower rate than that reported by the SEER,[7] and twice as low as the one reported in a rural community in Chile.[38] Moreover, two thirds had stage IV disease, compared to 25% and 60%, as reported in other studies from developed and developing countries.[38 39] It is widely known that being initially diagnosed at an advanced clinical stage of the disease correlates with delayed diagnosis.[40] Given that up to 50% of GC patients have unspecific gastrointestinal symptoms,[41] and alarm symptoms are usually present at advanced stage in most cases,[42 43] early diagnosis is a challenge. Remarkably, 14.2% of the patients in our study were diagnosed and then lost to follow-up, compared to other studies that have shown higher compliance rates to appointments or treatment.[44] Also, socioeconomic disparities negatively influence access to endoscopic services causing delayed diagnoses,[45 46] access to further appointments, and inadequate adherence to treatment,[47] and might have hampered the successful staging and follow-up of patients.

Non-cardia tumors were three times as frequent as cardia tumors, and intestinal type tumors were predominant versus diffuse type tumors, a consistent finding in the region.[10 36] However, poorly differentiated tumors were twice as common in comparison to the well/moderately differentiated group. Despite the histological paradigm stating that intestinal type tumors are well differentiated and that diffuse type tumors are poorly differentiated,[48 49] other studies have reported similar results.[50 51] Yet, a possible explanation for this discordance is the high under-reporting of the histological type variable versus the almost complete reporting of the tumor grade variable.

The one year survival rate was 41%, higher than those from other studies of the region (32%) but lower in comparison to developed countries (57%).[7 23] Other studies have shown that unfavorable clinical and histological features (advanced clinical stage, diffuse type, overlapping and poorly differentiated tumors) are poor prognostic factors for GC survival.[38 52] Nevertheless, our survival estimates should be interpreted with caution, given that our study only included patients attending the NOI. National studies are needed to determine the true GC rates of the whole Panamanian population.

Published data regarding costs of cancer care are limited in Latin-America. A recent study conducted in Chile, evaluating direct and indirect costs of cancer (expressed as 2012 USD), reported that GC accounted for the highest direct costs among all cancers.[16] In a report published by the Panamanian Ministry of Health in 2010, GC was responsible for the fourth highest cost among all cancers in Panama.[28] A

similar finding was seen in a population-based study conducted in the United States, in which costs of care for 18 different tumor sites were calculated using SEER and Medicare claims data from 1999 to 2003 (expressed as 2004 USD).[53]

The OMC of care per patient in our study was 4,259 USD, compared to the Chilean study that reported an OMC per patient of 3,706,145 Chilean pesos (CLP) (approximately 7,642 USD) for public health insurance regimes, and 3,102,978 CLP (approximately 6,398 USD) for private health insurance regimes.[16] The study conducted in the United States reported these costs by phases of care, reaching mean net costs as high as 46,501 USD in the initial phase (first 12 months after diagnosis), and 54,947 USD during the last year of life. On the other hand, in a 2015 cross-sectional study from Iran, the mean cost per patient was 2,596 USD.[54] Differences in OMC between studies might be explained by distinct definitions of types of care, since costs for a different range of services were included in each report.

Hospital admission accounted for the highest proportion of the total costs of care (51.8%), as reported previously.[53] Given the introduction of newer, costly chemotherapeutic agents in the latest years, and that a majority of patients in our study was reported with stage IV disease, one would expect chemotherapy to be accountable for the highest proportion of costs.[55] Nevertheless, underestimation of chemotherapy costs is likely, since we only included costs for medications and not chemotherapy sessions. Supporting this, in a previous local report, chemotherapy represented the highest institutional expenditure at the NOI in 2009.[28]

Women tend to have higher health resource utilization and expenditures than men.[56] This pattern, however, has not been reported for most tumor sites,[53] and was neither seen in our study. When assessing costs by tumor stage, some cancers may reflect higher costs with more advanced stages, but for cancers that are usually diagnosed in an advanced stage and with relatively short survival times as GC, differences in costs by stage are slighter,[53] as observed in our results. Despite not finding statistically significant differences, the greatest gap in OMC was observed when comparing social security status groups. In fact, in our study, patients without social security accounted for only 20.4% of the patients receiving care, versus 79.6% patients who had social security. This highlights the possibility that lack of social security and thus high out-of-pocket expenses is an important barrier in seeking care, resulting in lower healthcare utilization and therefore reflecting lower institutional expenditure in GC patients without social security.

To the best of our knowledge, this is the first study assessing epidemiology of GC and costs related to its care in Panama. A key strength of this study was that mortality data was ascertained with the NMR. The use of actual chemotherapeutic doses administered allowed a more accurate calculation of medication costs, and using the bootstrap method for mean cost comparison purposes provided us with a more

flexible tool to compare arithmetic mean costs, avoiding the assumptions and limitations inherent to other methods.[57-59]

Several limitations deserve mentioning. This study encompassed patients from a single cancer institution and our results cannot be extrapolated to the whole population. However, the NOI is the biggest and main cancer referral public hospital in the country, where the majority of the cancer patients from all over the country are treated.[4 5] There was a considerable amount of underreporting and missing variables (e.g., Helicobacter pylori infection status, genetic factors), which have demonstrated to have a central role in disease outcomes. Lastly, incomplete data regarding chemotherapy protocol sessions, resource utilization and outpatient expenses, most likely led to underestimation of costs.

In conclusion, socioeconomic disparities strongly influence GC outcomes and healthcare utilization. Our results suggest the need for an in-depth characterization of the barriers in access to GC related services, particularly for diagnosis and to address geographical disparities, such as the one observed in the Veraguas province.

Given that efforts directed towards making earlier diagnoses have proven to reduce the gap in cancer survival between different socioeconomic groups,[60] health policies should move towards a more inclusive system for GC patients from lower socioeconomic strata. Further, building capacity training, boosting the investment in medical equipment and improving databases to have more accurate estimates of GC data in our population are strongly encouraged, including social security status in future studies evaluating cancer mortality in Panama.

Acknowledgements

The authors would like to thank Fulvia Ibarra from the National Institute of Census and Statistics, Cecilio Niño from the Gorgas Memorial Institute for Health Studies, José Jiménez, head of the Department of Clinical Files at the NOI and Erick Trejos, head of the Department of Finance at the NOI.

Footnotes

Contributors: FC and DS curated, analyzed and interpreted the data, did the research, critically revised the draft for important intellectual content and wrote the draft of the work. MT interpreted the data, did the research and critically revised the draft for important intellectual content. IMV analyzed and interpreted the data, did the research and critically revised the draft for important intellectual content and wrote the draft of the work. MTC, VH and MC interpreted the data, critically revised the draft for important intellectual content. BG and JM designed and supervised the work and critically revised the draft for important intellectual content. Final approval of the version to be published was given by FC, DS, MT, IMV, MTC, VH, BG, MC and JM. All the authors agree to be accountable for all aspects of the work in ensuring that questions

related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests: FC, DS, MT, IMV, VH, BG, MC, JM have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare no conflicts of interest. MTC reports medical managing at Sanofi Pasteur, outside the submitted work.

Data sharing statement: No additional data are available.

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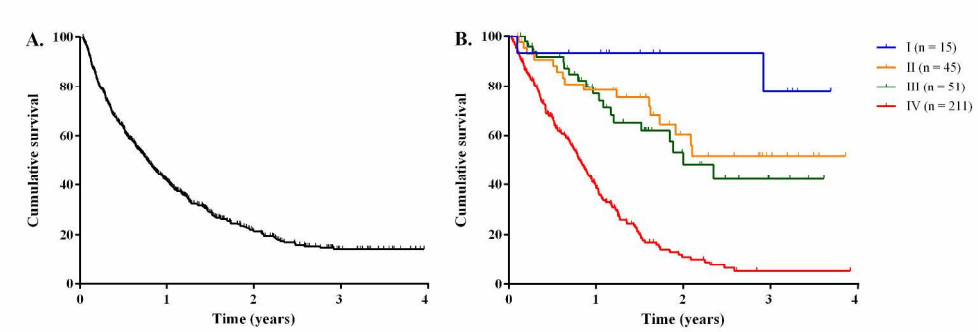
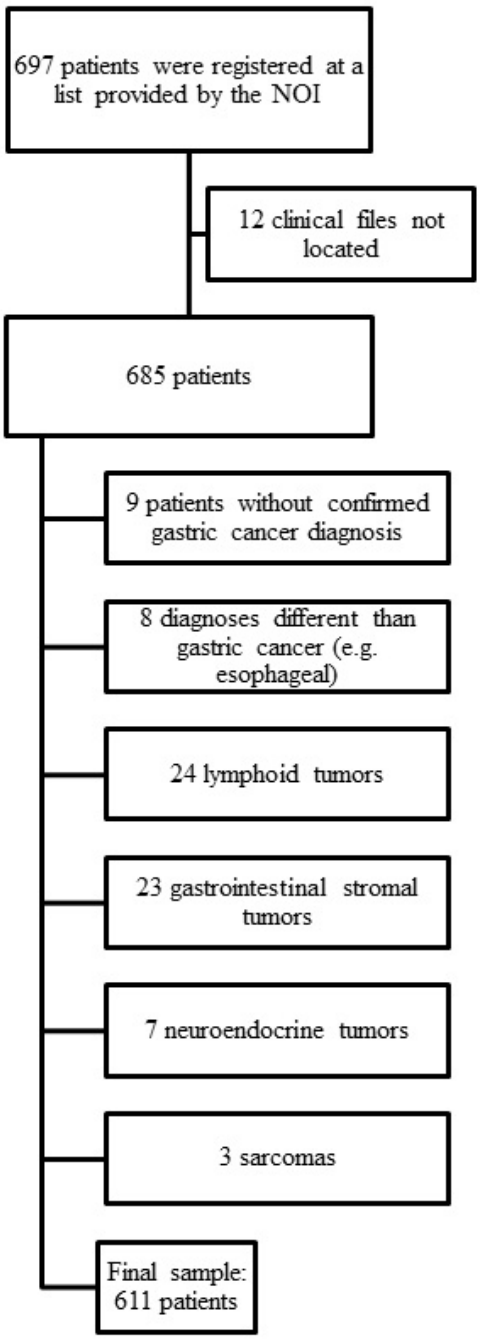


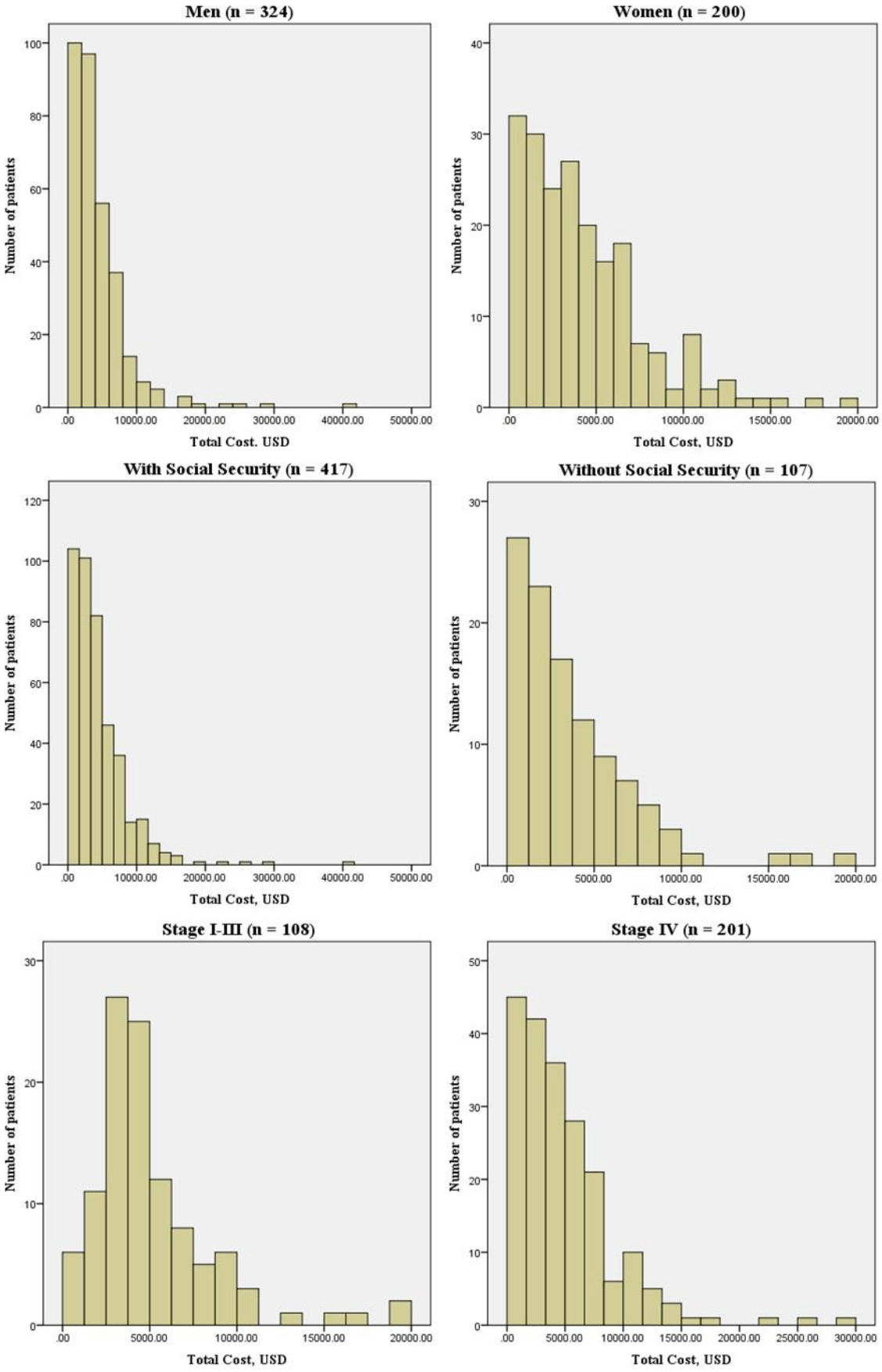
Figure 1. Kaplan-Meier plots for overall survival (A) and stage specific survival (B) for patients with gastric cancer treated at the NOI. 2012-2015.

270x95mm (300 x 300 DPI)

Supplementary Figure 1. Schematic diagram showing sample selection.



Supplementary Figure 2. Frequency distribution of costs of care according to socioeconomic and clinical variables.



STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	*5-6*
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	4-6
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	6
		(*e*) Describe any sensitivity analyses	6
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6-8
		(b) Give reasons for non-participation at each stage	6-8
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6-8
		(b) Indicate number of participants with missing data for each variable of interest	6-8
Outcome data	15*	Report numbers of outcome events or summary measures	6-8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9
		(*b*) Report category boundaries when continuous variables were categorized	6, 10-11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8-9, 10-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11-15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Baseline characteristics, survival and direct costs associated to treatment of gastric cancer patients at the National Oncology Institute of Panama from 2012 to 2015: a hospital-based observational study.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-017266.R1
Article Type:	Research
Date Submitted by the Author:	04-Jul-2017
Complete List of Authors:	Castro, Franz; Instituto Conmemorativo Gorgas de Estudios de la Salud, Department of Research and Health Technology Assessment Shahal, David; Instituto Conmemorativo Gorgas de Estudios de la Salud, Department of Research and Health Technology Assessment Tarajia, Musharaf; Instituto Conmemorativo Gorgas de Estudios de la Salud, Department of Research and Health Technology Assessment Moreno Velásquez, Ilais; Instituto Conmemorativo Gorgas de Estudios de la Salud, Department of Research and Health Technology Assessment Tribaldos Causadias, Maribel; Instituto Conmemorativo Gorgas de Estudios de la Salud, Department of Research and Health Technology Assessment Herrera, Víctor; Instituto Conmemorativo Gorgas de Estudios de la Salud, Department of Research and Health Technology Assessment Gómez, Beatriz; Instituto Conmemorativo Gorgas de Estudios de la Salud, Department of Research and Health Technology Assessment Cukier, Moisés; National Oncology Institute Motta, Jorge; Instituto Conmemorativo Gorgas de Estudios de la Salud, Department of Research and Health Technology Assessment; Secretaria Nacional de Ciencia Tecnologia e Innovacion
Primary Subject Heading:	Global health
Secondary Subject Heading:	Gastroenterology and hepatology
Keywords:	Gastric cancer, Survival, Health care costs, Panama

Baseline characteristics, survival and direct costs associated to treatment of gastric cancer patients at the National Oncology Institute of Panama from 2012 to 2015: a hospital-based observational study.

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Abstract word count: 293 words.

Manuscript word count: 3761 words.

Tables and figures count: 4 tables, 1 figure.

Keywords: Gastric cancer; Survival; Health care costs; Panama.

Abstract

Objectives: Comprehensive epidemiological and economic studies of gastric cancer (GC) in Panama are limited. This study aims to evaluate the association between socioeconomic and clinical variables with survival, describe the survival outcomes according to clinical stage, and estimate the direct costs associated to GC care in a Panamanian population with GC.

Design and setting: A retrospective observational study was conducted at the leading public institution for cancer treatment in Panama.

Participants: Data was obtained from 611 records of patients diagnosed with gastric adenocarcinoma (codes C16.0-C16.9 of the International Classification of Diseases 10th revision, ICD-10), identified between January 1st, 2012 and December 31st, 2015.
Methods: Cox proportional hazards models were used to calculate hazard ratios (HR) with 95% confidence intervals (95%CI) to examine associations between the variables and survival. Kaplan-Meier curves were used to assess overall and stage-specific survival. Direct costs (based on 2015 USD) were calculated per patient using standard costs provided by the institution for hospital admission (occupied bed-days), radiotherapy, surgery and chemotherapy, yielding total and overall mean costs (OMC). A comparison of OMC between groups (sex, social security status, clinical stage) was performed applying the bootstrap method with a t-test of unequal variances.

Results: An increased risk of dying was observed for patients without social security coverage (HR: 2.02; 95%CI: 1.16-3.53), overlapping tumors (HR: 1.50; 95%CI: 1.02-2.22), poorly-differentiated tumors (HR: 2.27; 95%CI: 1.22-4.22), and stage IV disease (HR: 5.54; 95%CI: 3.38-9.08) (adjusted models). Overall one-year survival rate was 41%. The estimated OMC of GC care per patient was 4,259 USD. No statistically significant differences were found in OMC between groups.

Conclusions: Socioeconomic disparities influence GC outcomes and healthcare utilization. Policies addressing healthcare disparities related to GC are needed, as well as in-depth studies evaluating barriers of access to GC related services.

Strengths and limitations of this study:

- Strengths of this study include:
  - Data regarding patient deaths was ascertained with the National Mortality Registry.
  - The use of actual chemotherapeutic doses administered allowed a more accurate calculation of medication costs.
  - Applying the bootstrap method for mean cost comparison purposes provided us with a more flexible tool to compare costs.
- Limitations of this study include:
  - This study encompassed patients from a single cancer institution and our results cannot be extrapolated to the whole population, however, the National Oncology Institute of Panama is the biggest and main cancer referral public hospital in the country.
  - There was a considerable amount of underreporting and missing variables such as incomplete data regarding chemotherapy protocol sessions, resource utilization and outpatient expenses, which most likely led to underestimation of costs.

1. Introduction

Latin-America presents one of the highest incidences of Gastric Cancer (GC) worldwide.[1] In 2011, GC was responsible for the sixth highest incidence, and the highest mortality rate from cancer in Panama.[2] Although GC treatment is evolving rapidly at the expense of increasing costs of care, there is scarcity of comprehensive epidemiological and economical studies of GC in the region.[3]

Understanding the epidemiology of GC and its costs in low-and middle-income countries is a crucial step to addressing the burden of GC and will guide disease surveillance, screening, prevention activities as well as healthcare resource allocation. Thus, the aims of this study were to evaluate the association between socioeconomic and clinical variables with survival, describe the survival outcomes according to clinical stage, and describe the direct costs associated to GC care in a Panamanian population with GC.

2. Methods

2.1. Study population

A descriptive, hospital-based retrospective study was conducted at the National Oncology Institute (NOI). The NOI is the leading public institution for cancer treatment in Panama, receiving cases referred from all over the country.[4 5]

Data derived from patient records (electronic and paper-based) with a histopathological diagnosis of gastric adenocarcinoma having their first appointment at the NOI between January 1st, 2012 and December 31st, 2015 was retrieved. Cases were registered according to codes C16.0 to C16.9 based on the tenth revision of the International Classification of Diseases (ICD-10).

A list containing 697 patients was provided by the Department of Clinical Files at the NOI. A total of 12 clinical records could not be located and were therefore excluded. Of the remaining 685 records, those with a diagnosis different from gastric adenocarcinoma were excluded (mucosa-associated lymphoid tissue (MALT) lymphomas, gastrointestinal stromal tumors (GIST), neuroendocrine tumors (NETs), sarcomas, as well as tumors confirmed to be from a different primary site (e.g., esophageal), for a total study population of 611 patients (Supplementary Figure 1).

Patient deaths from 2012 to 2015 were verified with the National Mortality Registry (NMR) supplied by the National Institute of Statistics and Census of Panama (Instituto Nacional de Estadística y Censo, INEC), using all-cause mortality data. This database comprises all deaths reported either from the Civil Registry or the Institute of Legal Medicine (deaths due to external causes). A recent study that assessed civil registration and vital statistics systems reported the quality of Panamanian data as

high[6] The research protocol was approved by the Gorgas Memorial Institute Ethics Committee and the Ministry of Health.

2.2. Study variables

Socioeconomic (sex, age at diagnosis, social security status, employment status, marital status, province of residence, ethnicity) and clinical variables (location by endoscopy, histological type, tumor grade and clinical stage) were recorded. Costs were ascertained using length of stay in hospital, surgical procedures performed, chemotherapy and radiotherapy received.

Age at diagnosis was categorized considering the cutoff value of 45 years for early onset GC (EOGC), as done in previous studies,[7] and age strata as reported by the Surveillance, Epidemiology, and End Results (SEER).[8] Social security status was categorized as having or not coverage by health institutions of the Panamanian Social Insurance Fund, in which a monthly amount is discounted from contributors' salaries (active public and private workforce) in order to receive health coverage for them and their first degree relatives, allowing children and unemployed adults to have coverage (beneficiaries). The Social Insurance Fund also serves as a retirement fund for workers at a certain age (retired), or in case of permanent disability (pensioners). The NOI is not an institution from the Panamanian Social Insurance Fund, but patients with social security are granted free healthcare services, while those without social security are required to pay out-of-pocket fees. Nevertheless, all patients receive the same standards of care despite their insurance status.[9] Formal and informal employment groups were categorized as defined by the International Labour Office.[10]

Provinces of residence were grouped according to geographic proximity to the NOI and common socioeconomic characteristics,[11] and categorized as Panama and Colon, Veraguas and Cocle, Herrera and Los Santos and Other provinces (Bocas del Toro, Chiriqui, Darien, Guna Yala, Ngäbe-Bugle).

Anatomic location of the tumor was based on endoscopic reports and categorized as non-cardia, cardia and overlapping. Cases in which the endoscopic report could not be found in the clinical files were labeled as "unspecified".[12] Histological type was based on the Lauren classification (intestinal, diffuse),[13] and mixed tumors were shown as a different category.[14] Tumor grade was categorized using ICD for Oncology (ICD-O), and clinical stage was based on the 7th edition of the TNM Staging System of the American Joint Committee on Cancer (AJCC), taking into consideration the first staging reported in the clinical file by the physician at the NOI.[15]

Type of care was defined according to hospital admission (recorded as occupied bed days), radiotherapy (number of sessions), surgery and chemotherapy. Surgery was defined as the performance of gastrectomy (total, subtotal) with lymph node resection, gastroenteric anastomosis, stent placement (esophageal, duodenal) or

exploratory laparotomy. Chemotherapy regimens for GC were based on the latest National Comprehensive Cancer Network (NCCN) guidelines.

Because the intention of treatment (e.g., curative vs palliative) was under-reported in the patient records, and due to the possibility of non-completion of regimens (loss to follow-up or death) or change in the regimen received (e.g., progression of disease, differences between clinical TNM and pathological TNM), expenditure on chemotherapy was calculated using actual medication doses and sessions administered on an individual basis instead of assuming completion of a single, invariable regimen.

2.3. Statistical analyses

Qualitative variables were expressed as percentages. As a complementary analysis, cases per 100,000 population were calculated for each province individually, using population data from the INEC.[16] Kaplan Meier curves were used to examine overall survival for all patients and for each clinical stage group. Median survival and median follow-up times in days were calculated and one-year survival rates were reported. Due to the length of the study period, we were not able to calculate 5 year survival rates.

Cox proportional hazards models were used to examine the association between socioeconomic and clinical variables with survival. Crude hazard ratios (HR) and 95% confidence intervals (95% CI) were estimated. Adjusted models including all variables were also performed, in order to evaluate their impact on the results obtained. Ethnicity was evaluated, however excluded from the final model due to the high admixture of the Panamanian population. Due to statistical power, provinces of residence were grouped as previously mentioned. In order to avoid collinearity, we performed sensitivity analyses by running two different adjusted models, one including tumor grade but not histological type, and another one including histological type but not tumor grade, observing similar point estimates. The assumption of proportional risk was verified using the Schoenfeld residuals method.

Total direct costs of care, expressed in US dollars (USD), were calculated per patient and for the whole study population using standard unit costs provided by the NOI and the Ministry of Health. Since no variation in costs was seen along the 2012-2015 period, calculations were based on 2015 estimates.

Total and mean direct costs were calculated according to social security status, sex, and clinical stage. Overall mean cost (OMC) comparisons among groups were performed using the bootstrap method.[17] This involved repeated resampling (1000 repetitions) of the original cost data by random selection. After resampling, a t-test with unequal variances was conducted to compare means and a p-value was reported.

Statistical analyses were performed using SPSS 20.0 and Stata 14.0.

3. Results

Table 1 shows the socioeconomic and clinical variables of the study population. Overall, 62.2% of the total population were males, 77.4% had social security and 34.9% were unemployed. The group of provinces of Panama and Colon reported the highest number of patients (64.5%). According to age groups, 14.7% were younger than 45 years old, whereas 26.0% were ≥75 years old. Median (interquartile range) age at diagnosis was 65 (52-75) years. Regarding the complementary analysis, when calculating the number of cases per 100,000 population by province separately, Herrera had 8.29 cases per 100,000, followed by Veraguas with 6.58. Among patients where ethnicity was reported (n=608), 83.2% patients were registered as Mestizo.

Based on endoscopic findings, tumors were most commonly reported as overlapping, observed in 46% of the patients. According to the histological classification, a predominance of intestinal type adenocarcinomas was observed (53.7%). Poorly differentiated tumors were observed in 62.3% of patients. Out of the 611 patients, 52.9% had the clinical stage recorded. From these cases, 4.6% were categorized as stage I, 13.9% as stage II, 15.8% and 65.6% as stage III and IV, respectively.

Table 1
Socioeconomic and clinical variables of patients with gastric cancer treated at the NOI. 2012-2015.

Socioeconomic and clinical variables	n	%
Sex		
Female	231/611	37.8
Male	380/611	62.2
Age		
Less than 45 years	90/611	14.7
45-64 years	207/611	33.9
65-74 years	155/611	25.4
75 years or more	159/611	26.0
Social security status		
With social security	473/611	77.4
Without social security	138/611	22.6
Employment status[a]		
Formal employment	116/610	19.0
Informal employment	119/610	19.5
Retired/pensioner	162/610	26.6
Unemployed	213/610	34.9
Marital status[b]		
Married/common law marriage	397/610	65.1
Single	161/610	26.4
Widowed	52/610	8.5
Province of residence		
Panama and Colon	394/611	64.5

Veraguas and Cocle	118/611	19.3
Herrera and Los Santos	57/611	9.3
Other provinces[c]	42/611	6.9
Ethnicity[d]		
White	71/608	11.7
Mestizo	506/608	83.2
Afrocaribbean	23/608	3.8
Indigenous	8/608	1.3
Anatomic location by endoscopy		
Non-cardia	239/611	39.1
Cardia	69/611	11.3
Overlapping	281/611	46.0
Unspecified	22/611	3.6
Histologic type[e]		
Intestinal type	232/432	53.7
Diffuse type	154/432	35.6
Mixed type	46/432	10.6
Tumor grade[f]		
Well/moderately differentiated	223/592	37.7
Poorly differentiated	369/592	62.3
Clinical stage[g]		
I	15/323	4.6
II	45/323	13.9
III	51/323	15.8
IV	212/323	65.6

[a]Employment status: 1 missing; [b]Marital status: 1 missing; [c]Other provinces: 7 from Bocas del Toro, 20 from Chiriqui, 12 from Darien, 1 from GunaYala, and 2 from Ngäbe-Bugle; [d]Ethnicity: 3 missing; [e]Histologic type: 179 missing; [f]Tumor grade: only 1 undifferentiated, 18 missing; [g]Clinical stage: 288 missing.

3.1. Mortality

In total, n=407 (67.5%) patients died of any cause during the study period. Figure 1 shows overall and stage-specific survival curves. Overall one-year survival rate was 41%, median survival was 287 days (9.5 months) and median follow-up was 604 days (20.1 months). Patients with stage I disease had a one-year survival rate of 93%, whereas stages II, III and IV presented a 78%, 76% and 38% one-year survival rate, respectively.

Table 2 presents the associations between socioeconomic and clinical variables with deaths from all causes. In the adjusted models, patients without social security presented a higher risk of dying (HR: 2.02; 95% CI: 1.16-3.53) compared to those with social security. Regarding anatomic location, having an overlapping tumor was related with an increased risk of dying (HR: 1.50; 95% CI: 1.02-2.22) in comparison to non-cardia tumors. Poorly differentiated tumors were associated with a higher risk of dying (HR: 2.27; 95% CI: 1.22-4.22) compared to well/moderately differentiated tumors, as well as those with stage IV disease (HR: 5.54; 95% CI: 3.38-9.08) in comparison to stage I-III disease.

Table 2

Cox proportional hazards models for the associations between socioeconomic and clinical variables with deaths from all causes in patients treated at the NOI. 2012-2015.

Socioeconomic and clinical variables	Crude HR		Adjusted HR[g]	
	HR	95% CI	HR	95% CI
Sex				
Female	Reference		Reference	
Male	0.93	(0.70-2.13)	0.67	(0.41-1.01)
Age				
45-64 years	Reference		Reference	
Less than 45 years	1.43	(0.96-2.13)	0.91	(0.53-1.58)
65-74 years	0.90	(0.61-1.32)	0.66	(0.38-1.16)
75 years or more	1.14	(0.78-1.68)	1.68	(0.91-3.10)
Social security status				
With social security	Reference		Reference	
Without social security	**1.44** [f]	**(1.01-2.05)** [f]	**2.02** [f]	**(1.16-3.53)** [f]
Employment status[a]				
Formal employment	Reference		Reference	
Informal employment	1.04	(0.66-1.63)	1.29	(0.68-2.44)
Retired/pensioner	0.87	(0.57-1.35)	1.48	(0.78-2.79)
Unemployed	1.12	(0.77-1.65)	0.75	(0.40-1.44)
Marital status[b]				
Married/common law marriage	Reference		Reference	
Single	1.06	(0.76-1.47)	0.87	(0.57-1.32)
Widowed	0.72	(0.41-1.25)	0.57	(0.24-1.37)
Province				
Panama and Colon	Reference		Reference	
Veraguas and Cocle	0.87	(0.58-1.32)	0.86	(0.50-1.47)
Herrera and Los Santos	0.62	(0.36-1.07)	0.71	(0.33-1.52)
Other provinces	0.82	(0.48-1.41)	1.06	(0.48-2.33)
Anatomic location by endoscopy[c]				
Non-cardia	Reference		Reference	
Cardia	1.30	(0.78-2.19)	0.94	(0.42-2.13)
Overlapping	1.34	(0.99-1.83)	**1.50** [f]	**(1.02-2.22)** [f]
Histologic type[d]				
Intestinal type	Reference		Reference	
Diffuse type	**1.64** [f]	**(1.13-2.40)** [f]	0.79	(0.43-1.47)
Mixed type	**2.12** [f]	**(1.31-3.44)** [f]	1.57	(0.80-3.07)
Tumor grade[e]				
Well/moderately differentiated	Reference		Reference	
Poorly differentiated	**1.91** [f]	**(1.38-2.65)** [f]	**2.27** [f]	**(1.22-4.22)** [f]
Clinical stage				
I-III	Reference		Reference	
IV	**4.37** [f]	**(3.02-6.33)** [f]	**5.54** [f]	**(3.38-9.08)** [f]

[a]Employment status: 1 missing; [b]Marital status: 1 missing; [c]Anatomic location: 11 missing; [d]Histologic type: 83 missing; [e]Tumor grade: 9 missing; [f]$p < 0.05$; [g]Adjustments were performed including all the covariates.

3.2. Costs

A total of 524 patients (85.8%) received any type of care, for an overall total cost of 2,231,728 USD and an OMC per patient of 4,259 USD (95% CI: 3,915-4,603), as shown in Table 3. Baseline characteristics of the 87 patients (14.2%) that did not receive any type of care are shown in Supplementary Table 1. When stratifying patients by type of care, 73.5% were admitted to the NOI, 66.4% were given chemotherapy, 30.3% underwent a surgical procedure, and 18% received radiotherapy. The highest expenses were attributed to hospital admissions (1,156,460 USD). Chemotherapy accounted for the second highest total cost (652,370 USD), being three times greater than the total cost of radiotherapy (206,872 USD). However, when comparing mean costs, radiotherapy exceeded chemotherapy by 274 USD per patient. For surgical procedures the total cost was 216,026 USD, representing 9.7% of the overall cost.

Table 3
Direct cost estimates (total and means) according to type of care received in patients with gastric cancer at the NOI. 2012-2015.

Type of care	Patients receiving care (%)[a]	Total cost (USD)	Mean cost per patient (USD)	95% CI
Overall	524/611 (85.8)	2,231,728	4,259	(3,915-4,603)
Hospital admission	449/611 (73.5)	1,156,460[b]	2,576[b]	(2,359-2,792)
Radiotherapy	110/611 (18.0)	206,872	1,881	(1,729-2,033)
Chemotherapy	406/611 (66.4)	652,370	1,607	(1,363-1,851)
Surgery	185/611 (30.3)	216,026	1,168	(1,077-1,259)

USD: US dollars; CI: Confidence intervals; [a]Since a single patient could receive different types of care, calculations were made separately for each category and percentages do not add up to 100%; [b]Calculated for occupied bed-days.

Table 4 presents the costs stratified by sex, social security status and disease stage groups, according to type of care received. Women had an OMC per patient of 4,258 USD, while for men it was 4,260 USD. For those with social security, the OMC per patient was 4,414 USD, whereas for those without social security, it was 3,657 USD. Patients with stage I-III disease presented an OMC of 5,174 USD, compared to 4,930 USD for those with stage IV disease (see Supplementary Figure 2 for detailed cost distributions). No statistically significant differences were observed in the OMC between groups.

Table 4
Direct cost estimates by sex, social security status and clinical stage of patients with gastric cancer according to type of care received at the NOI. 2012-2015.

	Male patients n=380			**Female patients n=231**			
Type of care	**Received care (%)[a]**	**Mean cost (USD)**	**95% CI**	**Received care (%)[a]**	**Mean cost (USD)**	**95% CI**	**Bootstrap p-value**
O	324/380 (85.3)	4,260	(3,789-4,731)	200/231 (86.6)	4,258	(3,774-4,741)	0.994
HA	281/380 (73.9)	2,487[b]	(2,219-2,755)	168/231 (72.7)	2,724[b]	(2,340-3,108)	

CT	247/380 (65.0)	1,694	(1,257-2,131)	159/231 (68.8)	1,472	(1,204-1,740)	
RT	69/380 (18.2)	1,915	(1,695-2,135)	41/231 (17.7)	1,823	(1,582-2,064)	
SR	117/380 (30.8)	1,118	(1,028-1,209)	68/231 (29.4)	1,253	(1,074-1,432)	
	Patients with social security n=473			**Patients without social security n=138**			
Type of care	**Received care (%)[a]**	**Mean cost (USD)**	**95% CI**	**Received care (%)[a]**	**Mean cost (USD)**	**95% CI**	**Bootstrap p-value**
O	417/473 (88.2)	4,414	(4,014-4,813)	107/138 (77.5)	3,657	(3,014-4,299)	0.059
HA	357/473 (75.5)	2,562[b]	(2,318-2,806)	92/138 (66.7)	2,628[b]	(2,111-3,145)	
CT	326/473 (68.9)	1,722	(1,376-2,069)	80/138 (58.0)	1,136	(833-1,439)	
RT	93/473 (19.7)	1,848	(1,665-2,031)	17/138 (12.3)	2,060	(1,702-2,417)	
SR	160/473 (33.8)	1,202	(1,103-1,302)	25/138 (18.1)	945	(871-1,019)	
	Stage I - III n=111			**Stage IV n=212**			
Type of care	**Received care (%)[a]**	**Mean cost (USD)**	**95% CI**	**Received care (%)[a]**	**Mean cost (USD)**	**95% CI**	**Bootstrap p-value**
O	108/111 (97.3)	5,174	(4,516-5,832)	201/212 (94.8)	4,930	(4,330-5,529)	0.598
HA	86/111 (77.5)	2,994[b]	(2,353-3,635)	179/212 (84.4)	2,853[b]	(2,484-3,221)	
CT	85/111 (76.6)	890	(683-1,097)	173/212 (81.6)	2,055	(1,579-2,530)	
RT	60/111 (54.1)	2,341	(2,243-2,440)	27/212 (12.7)	1,297	(897-1,697)	
SR	85/111 (76.6)	1,003	(930-1,075)	69/212 (32.5)	1,302	(1,127-1,477)	

O: Overall; HA: Hospital admission; CT: Chemotherapy; RT: Radiotherapy; SR: Surgery; USD: US dollars; CI: Confidence intervals; [a]Since a single patient could receive different types of care, calculations were made separately for each category and percentages do not add up to 100%. [b]Calculated for occupied bed-days.

4. Discussion

Our findings suggest that lack of social security, a poorly differentiated tumor, clinical stage IV and overlapping anatomic location were associated with an increased risk of dying, independently of other socioeconomic and clinical variables. Furthermore, the overall one-year survival rate in our study was 41% and the estimated OMC of GC care per patient was 4,259 USD.

Socioeconomic factors such as insurance coverage and geographic location have been implicated in survival outcomes and healthcare disparities.[18-22] Likewise, cultural differences have been documented as strong factors influencing medical care in many Latin American countries, especially in cancer.[21 23] According to national

estimates, 80% of the Panamanian population has social security, of which 57% are active workers and 43% are beneficiaries.[24] In our results, patients without social security had a two-fold higher risk of dying in comparison to those with social security. Similarly, in Colombia, patients with a more affluent socioeconomic status and a private health insurance regimen had a significantly higher GC survival.[25] The lack of social security has been related to late stage diagnosis,[26] and health insurance regimes facilitate greater access to physician care and increase medical service utilization, thus granting patients longer survival times.[27] In addition, reports on other types of cancer in Panama have identified lack of social security as a barrier in access to healthcare.[4 5] Likewise, a previous study conducted in Sweden has shown the importance of socioeconomic factors in GC survival, where a higher educational level was associated with a higher survival and patients living in rural areas had a higher risk of dying due to this type of cancer.[28] Of note, one third of our patients were unemployed, most of them being older than 65 years and beneficiaries from the social security system. The higher proportion of unemployed patients observed, compared to another study of GC in the region,[29] highlights the importance of social security as an aid in front of the complex socioeconomic situation of this population, heavily dependent on having a formally-employed relative in order to have better access to GC-related services. Taken together, these findings emphasize the importance of socioeconomic determinants in the disease outcomes of GC.

Geographic disparities in Panama are a well-known problem, as for some indigenous and other remote regions, human resources and equipment available for diagnosis and treatment are limited.[30] Together, Panama and Colon comprise more than half of the national population and have higher access to healthcare services, one of them being host to the NOI.[31] Herrera was the province with most patients treated at the NOI per 100,000 population, which could be explained by the fact of having the country's highest number of health professionals per capita,[31] giving the patients higher chances of being diagnosed and referred to the NOI. Nevertheless, with half of the amount of health professionals per capita, Veraguas province was second in patients treated at the NOI per 100,000 population, and according to national estimates it ranks first in incidence and second in mortality in the country.[32] Interestingly, the provinces of Veraguas and Cocle, despite having the highest proportion of their patients with stage IV disease (74.1% and 69.6% respectively), accounted for two of the smallest proportions of their residents being diagnosed in institutions inside their territory (10.9% and 7.4% respectively). Although geography was not associated with a higher risk of dying in our study, these findings underscore the need of further research on GC to determine geographical disparities in depth, as well as lifestyle, environmental, genetic factors, and the interaction among them.[33-36]

In agreement with other studies,[12 37] the male to female ratio was 1.64 and GC was most common in the elderly.[12 38] Nevertheless, we found a high proportion of EOGC (14.7%) compared to those reported in most countries of the region,[38] only surpassed by Guatemala in Central-America with national estimates of 16.5%,[12] a comparison

worth noting even if our results are based on a single institution. Likewise, in a hospital-based study conducted in Mexico, a similar proportion of EOGC was reported.[39] These discrepancies might mirror differences in underreporting, environmental risk factors (other infections, exposure to chemicals, alcohol consumption), genetic susceptibility and information seeking patterns, making it difficult to compare.

Clinical stage was only reported in half of the patients, a five-fold lower rate than that reported by the SEER,[8] and twice as low as the one reported in a community in Chile.[40] Moreover, two thirds had stage IV disease, compared to 25% and 60%, as reported in other studies from developed and developing countries.[40 41] It is widely known that being initially diagnosed at an advanced clinical stage of the disease correlates with delayed diagnosis.[42] Given that up to 50% of GC patients have unspecific gastrointestinal symptoms,[43] and alarm symptoms are usually present at advanced stage in most cases,[44 45] early diagnosis is a challenge. Remarkably, 14.2% of the patients in our study were diagnosed and then lost to follow-up for receiving any type of care, compared to other studies that have shown higher compliance rates to appointments or treatment.[46] These patients were mostly male, 75 years or older, had social security coverage (this includes beneficiaries), were unemployed, were married or in a common law marriage, belonged to the group of provinces of Panama and Colon, and were described as being Mestizo. It is well known that socioeconomic disparities negatively influence access to endoscopic services causing delayed diagnoses,[47 48] access to further appointments, and inadequate adherence to treatment,[49] and might have hampered the successful staging and follow-up of patients.

Non-cardia tumors were three times as frequent as cardia tumors, and intestinal type tumors were predominant versus diffuse type tumors, a consistent finding in the region.[12 38] However, poorly differentiated tumors were twice as common in comparison to the well/moderately differentiated group. Despite the histological paradigm stating that intestinal type tumors are well differentiated and that diffuse type tumors are poorly differentiated,[50 51] other studies have reported similar results.[52 53] Yet, a possible explanation for this discordance is the high under-reporting of the histological type variable versus the almost complete reporting of the tumor grade variable.

The one year survival rate was 41%, higher than those from other studies of the region (32%) but lower in comparison to developed countries (57%).[8 25] Other studies have shown that unfavorable clinical and histological features (advanced clinical stage, diffuse type, overlapping and poorly differentiated tumors) are poor prognostic factors for GC survival.[40 54] Nevertheless, our survival estimates should be interpreted with caution, given that our study only included patients attending the NOI. National studies are needed to determine the true GC rates of the whole Panamanian population.

Published data regarding costs of cancer care are limited in Latin-America. A recent study conducted in Chile, evaluating direct and indirect costs of cancer (expressed as 2012 USD), reported that GC accounted for the highest direct costs among all cancers.[18] In a report published by the Panamanian Ministry of Health in 2010, GC was responsible for the fourth highest cost among all cancers in Panama.[30] A similar finding was seen in a population-based study conducted in the United States, in which costs of care for 18 different tumor sites were calculated using SEER and Medicare claims data from 1999 to 2003 (expressed as 2004 USD).[55]

The OMC of care per patient in our study was 4,259 USD, compared to the Chilean study that reported an OMC per patient of 3,706,145 Chilean pesos (CLP) (approximately 7,642 USD) for public health insurance regimes, and 3,102,978 CLP (approximately 6,398 USD) for private health insurance regimes.[18] The study conducted in the United States reported these costs by phases of care, reaching mean net costs as high as 46,501 USD in the initial phase (first 12 months after diagnosis), and 54,947 USD during the last year of life. On the other hand, in a 2015 cross-sectional study from Iran, the mean cost per patient was 2,596 USD.[56] Differences in OMC between studies might be explained by distinct definitions of types of care, since costs for a different range of services were included in each report.

Hospital admission accounted for the highest proportion of the total costs of care (51.8%), as reported previously.[55] Given the introduction of newer, costly chemotherapeutic agents in the latest years, and that a majority of patients in our study was reported with stage IV disease, one would expect chemotherapy to be accountable for the highest proportion of costs.[57] Nevertheless, underestimation of chemotherapy costs is likely, since we only included costs for medications and were not able to include other additional expenses related to chemotherapy sessions. Supporting this, according to previous local estimates, chemotherapy represented the highest institutional expenditure at the NOI in 2009.[30]

Women tend to have higher health resource utilization and expenditures than men.[58] This pattern, however, has not been reported for most tumor sites,[55] and was neither seen in our study. When assessing costs by tumor stage, some cancers may reflect higher costs with more advanced stages, but for cancers that are usually diagnosed in an advanced stage and with relatively short survival times as GC, differences in costs by stage are slighter,[55] as observed in our results. The greatest gap in OMC was observed when comparing social security status groups, with no statistically significant differences found. Even if offered the same standard of care, patients without social security accounted for a lower expenditure (3,657 USD) compared to those with social security (4,414 USD). In fact, in our study, patients without social security comprised only 20.4% of the patients receiving care, versus 79.6% patients who had social security. These disparities highlight the possibility that lack of social security and thus high out-of-pocket expenses are important barriers in

seeking care, resulting in lower healthcare utilization and therefore reflecting lower institutional expenditure in GC patients without social security.

To the best of our knowledge, this is the first study assessing baseline characteristics of patients with GC and costs related to its care in Panama. A key strength of this study was that mortality data was ascertained with the NMR. The use of actual chemotherapeutic doses administered allowed a more accurate calculation of medication costs, and using the bootstrap method for mean cost comparison purposes provided us with a more flexible tool to compare arithmetic mean costs, avoiding the assumptions and limitations inherent to other methods.[59-61]

Several limitations deserve mention. This study encompassed patients from a single cancer institution and our results cannot be extrapolated to the whole population. However, the NOI is the biggest and main cancer referral public hospital in the country, where the majority of the cancer patients from all over the country are treated.[4 5] There was a considerable amount of underreporting and missing variables (e.g., Helicobacter pylori infection status, genetic factors), which have demonstrated to have a central role in disease outcomes. Lastly, incomplete data regarding chemotherapy protocol sessions, resource utilization and outpatient expenses, most likely led to underestimation of costs.

In conclusion, socioeconomic disparities strongly influence GC outcomes and healthcare utilization. Our results suggest the need for an in-depth characterization of the barriers in access to GC related services, particularly for diagnosis and to address geographical disparities, such as the one observed in the Veraguas province.

Given that efforts directed towards making earlier diagnoses have proven to reduce the gap in cancer survival between different socioeconomic groups,[62] health policies should move towards a more inclusive system for GC patients from lower socioeconomic strata. Further, building capacity training, boosting the investment in medical equipment and improving databases to have more accurate estimates of GC data in our population are strongly encouraged, including social security status in future studies evaluating cancer mortality in Panama.

Acknowledgements

The authors would like to thank Fulvia Ibarra from the National Institute of Census and Statistics, Cecilio Niño from the Gorgas Memorial Institute for Health Studies, José Jiménez, head of the Department of Clinical Files at the NOI, Erick Trejos, head of the Department of Finance at the NOI and Dr. Reina Roa, Director of National Planning at the Ministry of Health of Panama.

Footnotes

Contributors: FC and DS curated, analyzed and interpreted the data, did the research, critically revised the draft for important intellectual content and wrote the draft of the

work. MT interpreted the data, did the research and critically revised the draft for important intellectual content. IMV analyzed and interpreted the data, did the research and critically revised the draft for important intellectual content and wrote the draft of the work. MTC, VH and MC interpreted the data, critically revised the draft for important intellectual content. BG and JM designed and supervised the work and critically revised the draft for important intellectual content. Final approval of the version to be published was given by FC, DS, MT, IMV, MTC, VH, BG, MC and JM. All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests: FC, DS, MT, IMV, VH, BG, MC, JM have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare no conflicts of interest. MTC reports medical managing at Sanofi Pasteur, outside the submitted work.

Data sharing statement: No additional data are available.

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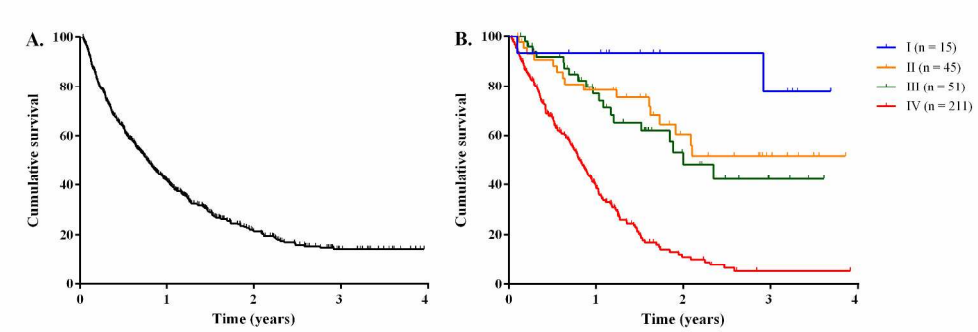


Figure 1. Kaplan-Meier plots for overall survival (A) and stage specific survival (B) for patients with gastric cancer treated at the NOI. 2012-2015.

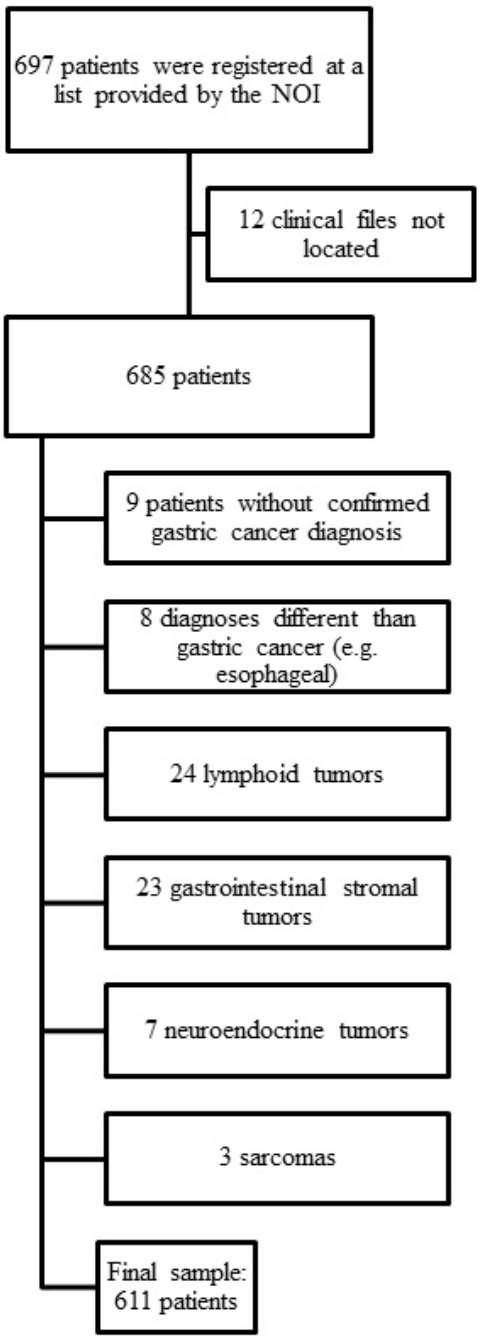
270x95mm (300 x 300 DPI)

Supplementary Table 1. Socioeconomic variables of patients with gastric cancer lost to follow up for receiving any type of care. 2012-2015.

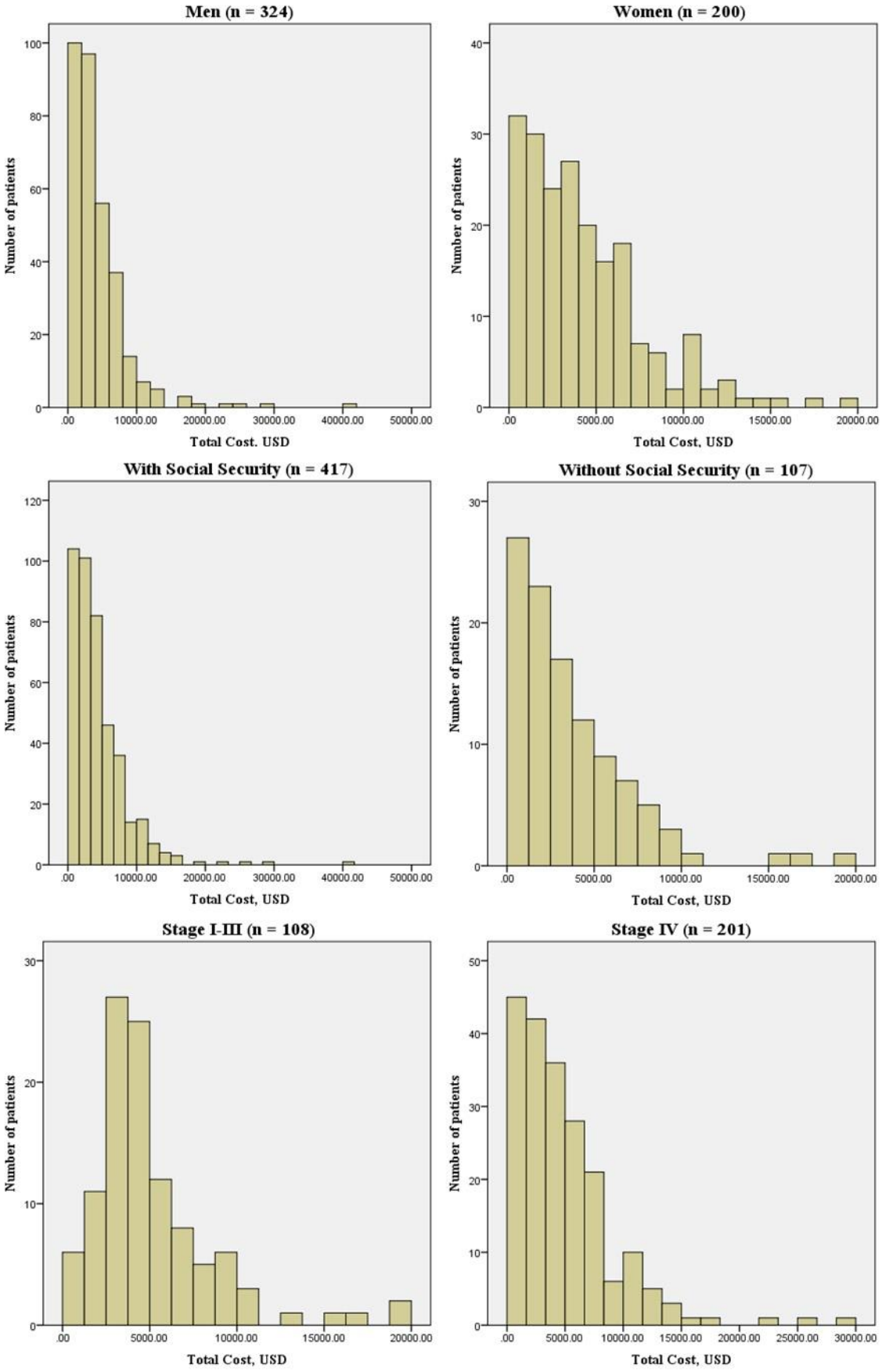
Socioeconomic and clinical variables	n	%
Sex		
Female	31/87	35.6
Male	56/87	64.4
Age		
Less than 45 years	4/87	4.6
45-64 years	19/87	21.8
65-74 years	25/87	28.7
75 years or more	39/87	44.8
Social security status		
With social security	56/87	64.4
Without social security	31/87	35.6
Employment status		
Formal employment	7/87	8.0
Informal employment	15/87	17.2
Retired/pensioner	28/87	32.2
Unemployed	37/87	42.5
Marital status		
Married/common law marriage	53/87	60.9
Single	25/87	28.7
Widowed	9/87	10.3
Province of residence		
Panama and Colon	49/87	56.3
Veraguas and Cocle	23/87	26.4
Herrera and Los Santos	12/87	13.8
Other provinces[a]	3/87	3.4
Ethnicity		
White	9/87	10.3
Mestizo	74/87	85.1
Afrocaribbean	2/87	2.3
Indigenous	2/87	2.3

[a]Other provinces: 1 from Chiriqui and 2 from Darien.

Supplementary Figure 1. Schematic diagram showing sample selection.



Supplementary Figure 2. Frequency distribution of costs of care according to socioeconomic and clinical variables.



STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	*5-6*
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	4-6
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	6
		(*e*) Describe any sensitivity analyses	6
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6-8
		(b) Give reasons for non-participation at each stage	6-8
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6-8
		(b) Indicate number of participants with missing data for each variable of interest	6-8
Outcome data	15*	Report numbers of outcome events or summary measures	6-8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9
		(*b*) Report category boundaries when continuous variables were categorized	6, 10-11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8-9, 10-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11-15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.