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Original Research

# Prognostic Factors for Survival in Patients with Gastric Cancer Treated at Two Public Health Institutions in Mexico

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| *Alejandro Trujillo-Rivera* | Centro de Alta Especialidad “Dr. Rafael Lucio”, Xalapa, Veracruz, México |
| *Clara Luz Sampieri* | Institute of Public Health, Veracruzana University, Av. Luis Castelazo Ayala S / N, Col. Industrial Animas 91190. Xalapa, Veracruz, Mexico |
| *Linda Morales* | Instituto Nacional de Salud Pública, Cuernavaca, Morelos, México |
| *Alejandra Montoya* | Instituto Nacional de Salud Pública, México, Cuernavaca, Morelos, México |
| *Héctor Lamadrid-Figueroa* | Instituto Nacional de Salud Pública, Cuernavaca, Morelos, México |

**Objective:** To analyze the clinical records of patients with gastric adenocarcinoma, treated at two different public health institutions in Mexico to determine survival rates.
**Methods:** Cox proportional-hazards model was fitted to identify the factors involved in survival of patients.
**Result:** The results show that subjects aged 41 to 50 years of age had a 56% lower risk of death from gastric cancer compared to those <40 years of age. Asthenia and/or adynamia, weight loss and leukocytosis increased the risk of dying. The incidence of melena was found to be a protective factor for mortality.
**Conclusion:** At age <40 years, symptoms such as asthenia, adynamia and weight loss and leukocytosis are poor prognosis predictors in patients with gastric cancer. Melena seems to be a protective sign of gastric cancer mortality in Mexico. Given the low 5-year survival rate in patients with gastric cancer, further studies are necessary to explore the factors associated with survival to contribute to effective intervention.

## Introduction

Globally, gastric cancer is the third highest cause of death by cancer and, despite biomedical advances, fewer than 30% of patients survive for more than 5 years [1]. In the year 2016, it was estimated that 834,701 deaths occurred globally, totalling 18.35 million years of life lost through gastric cancer [2]. Although the incidence of gastric cancer has presented a downwards trend, it remains a public health problem and continues to be a common cause of mortality worldwide, probably as a consequence of its typical diagnosis in advanced stages, and the high percentage of patients for which curative surgery is impossible [3]. Moreover, in the initial stages of the disease, few or no symptoms are presented [4].

In Mexico, the low survival, high mortality and impact on the quality of life of the people who suffer this disease represent a public health problem [5, 6]. By law, gastric cancer is subject to epidemiological monitoring [7].

The few studies conducted in Mexico that have addressed prognostic factors in patients with gastric cancer show that the stage at which the cancer is diagnosed is the most important prognostic factor, [8] a finding that concurs with international reports [9, 10]. Other studies in Mexico report that patients of less than 45 years of age who have undergone a gastrectomy for

advanced gastric cancer present greater survival than those of more than 45 years of age [6] and that, in patients with unresectable or metastatic gastric cancer treated with palliative chemotherapy, the new schemes of treatment have no impact on survival [11]. The objective of this study was to determine the clinical pathological factors involved in the survival of subjects with adenocarcinoma type gastric cancer attended in two public health institutions in the city of Xalapa, in Veracruz, Mexico. We hypothesize that certain signs associated with survival will be characteristic of our population.

# Materials and Methods

## Ethical considerations

A retrospective cohort study was conducted, approved by the Committee of Ethics in Research of the Centro de Alta Especialidad “Dr. Rafael Lucio” (CAE), a hospital of second level attention, and of the Centro Estatal de Cancerología “Dr. Miguel Dorantes Mesa” (CECAN), a hospital of third level attention. Both hospitals are dependencies of the State Secretary of Health and are in the city of Xalapa, Veracruz. The study included 294 patients with diagnosis of adenocarcinoma type gastric cancer, attended during the period from the 1$^{st}$ of January 2010 to the 31$^{st}$ of March 2015 in the CAE, and from the 1$^{st}$ of January 2010 to the 28$^{th}$ of May 2016 in the CECAN.

## Study variables

Time of survival was calculated in days from diagnosis of gastric cancer until the date of death or date of the last recorded status of life or of loss of monitoring. Deaths from cancer were considered faults and subjects that remained alive, or those lost from the monitoring were considered censorships, for which reason they were of unknown status.

Age was categorized into 10 and five year periods, taking the subjects of age ≤40 years as a reference. Education level was classified into one of four categories:

1) None, 2) Primary, 3) Secondary, 4) High school and beyond. Main occupation of the patient for most of his/her life was classified as: 1) Housewife; 2) Agriculture and 3) Others. Civil status was considered as: married-cohabiting or single-widow/widower-divorced.

Pathological personal backgrounds such as alcoholism, addiction to tobacco, diabetes mellitus, arterial systemic hypertension or pulmonary tuberculosis were established dichotomously, as was the presence or absence of general and specific symptoms. The tumor site was classified dichotomously according to location at the gastroesophageal junction: in the upper, middle, or lower third, although these categories were not mutually exclusive. The diagnostic of pathology was identified as intestinal or diffuse adenocarcinoma. The variables of metastasis were dichotomized, and these were considered as: metastasis to adjacent ganglions; liver, lung and/or pleura; colon and/or duodenum and metastasis to the pancreas and/or kidney and or ovary.

The treatment performed was not recorded at a basal time and was therefore analyzed in a descriptive manner only: subtotal gastrectomy, chemotherapy, total gastrectomy, radiotherapy, gastroyeyunostomy and other palliative treatments.

The biomarker values were analyzed in a categorical manner. Anemia: <12 mg/dl in women and <13 mg/dl in men. Mean corpuscular volume: normal: 80 to 96.1 fL; low <80 fL and high >96.1 fL. Platelets: normal from 150,000 to 450,000 $10^3$/µL; low <150,000 $10^3$/µL and high >450 000 $10^3$/µL. Leucocytes: normal from 5000 to 10,000; low <5000 and high >10,000. Level of attention: second or third. The p value for significance was <0.05.

## Statistical analysis

Descriptive statistics were conducted for the quantitative variables through mean and standard deviation values, and frequencies and proportions were determined for the categorical variables. The characteristics of the subjects with censorship and the subjects who died were compared through Mann Whitney U tests for numerical variables and the Chi squared test for qualitative variables [12]. The length of survival was calculated using the Kaplan-Meir estimator (supplementary material).

Prior to fitting the explanatory models, an exploratory analysis of the data was performed to identify the patterns of lost data and to understand their distribution. We found percentage values of missing data in 16 variables ranging from 4.7% to 19.7%, which would have excluded 126 (42.8%) people from the analysis. The treatment of these data was conducted with multiple imputation by chained equations (MICE) [13]. With this procedure, the non-specific data are replaced by their most probable value, identified through a process of estimation through random iterative resampling of the study population (bootstrap). For each model, the variables available in the databases, related to the probability of occurrence of a missing value, were used as predictor variables. Ten cycles of iteration were specified [14]. Following imputation of the values of biomarkers, hemoglobin, hematocrit, mean corpuscular volume, leucocytes and platelets, we conducted a reclassification of each variable in order to evaluate them in a categorical manner.

A Cox proportional-hazards model was fitted [15] in order to analyze the survival of patients with diagnosis of gastric cancer. The model included the variables of: sex, age, education level, civil status, alcoholism, addiction to tobacco, diabetes, systemic arterial hypertension, epigastric pain, sensation of fullness, dysphagia, asthenia and/or adynamia, weight loss, melena, hematemesis, nausea, emesis, pyrosis, diarrhea or constipation, palpable tumor in the abdomen, dyspnea, jaundice, gastroesophageal junction (upper third, middle third and lower third), diagnosis of pathology, metastasis (to adjacent ganglions, liver, lung, pleura, colon, duodenum, kidney, pancreas and ovary), hemoglobin, mean corpuscular volume, platelets, leucocytes and level of attention. All the variables utilized were measured at a basal time, i.e., at the time of diagnosis of gastric cancer. We estimated hazard ratios (HR) with a 95% confidence interval.

The specification of the model took the following form: $h(t) = h0(t) \exp(S\lambda + A\delta + C\varphi + B\chi + D\alpha + E\xi + F\phi)$ [14]

Where:[16]

$h0(t)$= Basal risk as a function of time (in days)

$S\lambda$= Vector of covariables of sociodemographic characteristics

$A\delta$= Vector of covariables of personal pathological background

$C\varphi$= Vector of covariables of the clinical symptoms

$B\chi$= Vector of covariables of location and type of tumor

$D\alpha$= Vector of covariables of location of metastasis

$E\xi$= Vector of covariables of biomarkers

$F\phi$= level of attention

The variable of occupation was not included in the Cox regression model since it was collinear with the variable sex. The variable of hematocrit was also excluded for being collinear with hemoglobin.

# Results

## Population description

The average age of the subjects included in the study was 59.85±4.84 years. Of the total number of subjects, 57.48% had no formal education and most were male (58.84%). The predominant occupation was in agriculture or construction (41.5%), followed by housewife (38.7%). A total of 53.55% of the subjects who consumed alcohol died, in contrast to 36.14% of the subjects who survived (p<0.01) (Table 1). A total of 86.26% of the patients who died had presented weight loss, compared to 69.88% in those who survived (p<0.01). Moreover, there was a greater percentage of people with melena among the subjects who survived, than among those who died (43.37% and 25.12%, respectively, p= 0.001) (Table 1).

| Characteristic | General | Censorships | Deaths | P value |
|---|---|---|---|---|
| | n=294 | n=83 | n=211 | |
| | | Mean ± SD or n (%) | | |
| Sociodemographic | | | | |
| Age at diagnosis (years) | 59.85 ± 14.84 | 59.23 ± 13.45 | 60.10 ± 15.38 | 0.36 |
| Age at diagnosis median (RIC) | 63 (50-70) | 60 (50-69) | 64 (50-72) | |
| Age (years) | | | | 0.16 |
| <=40 | 36 (12.24) | 6 (7.23) | 30 (14.22) | |
| 41 to 50 | 42 (14.29) | 17 (20.48) | 25 (11.85) | |
| 51 to 60 | 58 (19.73) | 20 (24.10) | 38 (18.01) | |
| 61 to 65 | 35 (11.90) | 11 (13.25) | 24 (11.37) | |
| 66 to 70 | 53 (18.03) | 14 (16.87) | 39 (18.48) | |
| 71 to 75 | 35 (11.90) | 6 (7.23) | 29 (13.74) | |
| 76 and over | 35 (11.90) | 9 (10.84) | 26 (12.32) | |
| Sex | | | | 0.2 |
| Female | 121 (41.16) | 39 (46.99) | 82 (38.86) | |
| Male | 173 (58.84) | 44 (53.01) | 129 (61.14) | |
| Education level | | | | 0.36 |
| None | 169 (57.48) | 42 (50.6) | 127 (60.19) | |
| Primary | 72 (24.49) | 22 (26.51) | 50 (23.70) | |
| Secondary | 30 (10.20) | 12 (14.46) | 18 (8.53) | |
| High school and beyond | 23 (7.82) | 7 (8.43) | 16 (7.58) | |
| Occupation | | | | NA |
| Housewife | 114 (38.78) | 35 (42.17) | 79 (37.44) | |
| Agriculture or construction | 122 (41.50) | 25 (30.12) | 97 (45.97) | |
| Others | 37 (12.59) | 14 (16.87) | 23 (10.90) | |
| Not recorded | 21 (7.14) | 9 (10.87) | 12 (5.69) | |
| Civil status | | | | 0.15 |
| Married or cohabiting | 200 (68.03) | 56 (67.47) | 144 (68.25) | |
| Single, widow/widower or divorced | 80 (27.21) | 20 (24.10) | 60 (28.44) | |
| Not recorded | 14 (4.76) | 7 (8.43) | 7 (3.32) | |
| Personal pathological history | | | | |
| Alcoholism | | | | 0.01 |
| No | 130 (44.22) | 45 (54.22) | 85 (40.28) | |
| Yes | 143 (48.64) | 30 (36.14) | 113 (53.55) | |
| Not recorded | 21 (7.14) | 8 (9.64) | 13 (6.16) | |

| | | | | |
|---|---|---|---|---|
| Tobacco addiction | | | | 0.26 |
| No | 174 (59.18) | 52 (62.65) | 122 (57.82) | |
| Yes | 98 (33.33) | 23 (27.71) | 75 (35.55) | |
| Not recorded | 22 (7.48) | 8 (9.64) | 14 (6.64) | |
| Diabetes mellitus | | | | 0.18 |
| No | 249 (84.69) | 74 (89.16) | 175 (82.94) | |
| Yes | 45 (15.31) | 9 (10.84) | 36 (17.06) | |
| Systemic arterial hypertension | | | | 0.33 |
| No | 245 (83.33) | 72 (86.75) | 173 (81.99) | |
| Yes | 49 (16.67) | 11 (13.25) | 38 (18.01) | |
| Pulmonary tuberculosis | | | | 0.62 |
| No | 289 (98.30) | 81 (97.59) | 208 (98.58) | |
| Yes | 5 (1.70) | 2 (2.41) | 3 (1.42) | |
| Symptoms at time of diagnosis | | | | |
| Epigastric pain | | | | 0.05 |
| No | 57 (19.39) | 22 (26.51) | 35 (16.59) | |
| Yes | 237 (80.61) | 61 (73.49) | 176 (83.41) | |
| Sensation of fullness | | | | 0.42 |
| No | 198 (67.35) | 53 (63.86) | 145 (68.72) | |
| Yes | 96 (32.65) | 30 (36.14) | 66 (31.28) | |
| Dysphagia | | | | 0.38 |
| No | 199 (67.69) | 53 (63.86) | 146 (69.19) | |
| Yes | 95 (32.31) | 30 (36.14) | 65 (30.81) | |
| Asthenia and/or adynamia | | | | 0.97 |
| No | 166 (56.46) | 47 (56.63) | 119 (56.40) | |
| Yes | 128 (43.54) | 36 (43.37) | 92 (43.60) | |
| Weight loss | | | | 0.001 |
| No | 54 (18.37) | 25 (30.12) | 29 (13.74) | |
| Yes | 240 (81.63) | 58 (69.88) | 182 (86.26) | |
| Melena | | | | <0.01 |
| No | 205 (69.73) | 47 (56.63) | 158 (74.88) | |
| Yes | 89 (30.27) | 36 (43.37) | 53 (25.12) | |
| Hematemesis | | | | 0.36 |
| No | 240 (81.63) | 65 (78.31) | 175 (82.94) | |
| Yes | 54 (18.37) | 18 (21.69) | 36 (17.06) | |
| Nausea | | | | 0.22 |
| No | 164 (55.78) | 51 (61.45) | 113 (53.55) | |
| Yes | 130 (44.22) | 32 (38.55) | 98 (46.45) | |
| Emesis | | | | 0.21 |
| No | 193 (65.65) | 59 (71.08) | 134 (63.51) | |
| Yes | 101 (34.35) | 24 (28.92) | 77 (36.49) | |
| Pyrosis | | | | 0.22 |
| No | 220 (74.83) | 58 (69.88) | 162 (76.78) | |
| Yes | 74 (25.17) | 25 (30.12) | 49 (23.22) | |
| Constipation | | | | 0.78 |
| No | 276 (93.88) | 79 (95.18) | 197 (93.36) | |
| Yes | 18 (6.12) | 4 (4.82) | 14 (6.64) | |
| Diarrhea | | | | 0.19 |
| No | 288 (97.96) | 83 (100) | 205 (97.16) | |
| Yes | 6 (2.04) | 0 | 6 (2.84) | |

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|---|---|---|---|---|
| Palpable tumor in abdomen | | | | 0.63 |
| No | 239 (81.29) | 66 (79.52) | 173 (81.99) | |
| Yes | 55 (18.71) | 17 (20.48) | 38 (18.01) | |
| Dyspnea | | | | 0.06 |
| No | 280 (95.24) | 76 (91.57) | 204 (96.68) | |
| Yes | 14 (4.76) | 7 (8.43) | 7 (3.32) | |
| Jaundice | | | | 0.17 |
| No | 272 (92.52) | 74 (89.16) | 198 (93.84) | |
| Yes | 22 (7.48) | 9 (10.84) | 13 (6.16) | |
| Location and type of tumor | | | | |
| Gastroesophageal junction | | | | 0.6 |
| No | 192 (65.31) | 57 (68.67) | 135 (63.98) | |
| Yes | 72 (24.49) | 19 (22.89) | 53 (25.12) | |
| Not recorded | 30 (10.20) | 7 (8.43) | 23 (10.90) | |
| Upper third | | | | 0.33 |
| No | 195 (66.33) | 53 (63.86) | 142 (67.30) | |
| Yes | 69 (23.47) | 23 (27.71) | 46 (21.80) | |
| Not recorded | 30 (10.2) | 7 (8.43) | 23 (10.90) | |
| Middle third | | | | 0.2 |
| No | 131 (44.56) | 33 (39.76) | 98 (46.45) | |
| Yes | 133 (45.24) | 43 (51.81) | 90 (42.65) | |
| Not recorded | 30 (10.20) | 7 (8.43) | 23 (10.9) | |
| Lower third | | | | 0.69 |
| No | 113 (38.44) | 34 (40.96) | 79 (37.44) | |
| Yes | 151 (51.36) | 42 (50.60) | 109 (51.66) | |
| Not recorded | 30 (10.20) | 7 (8.43) | 23 (10.90) | |
| Diagnostic of pathology | | | | 0.53 |
| Diffuse adenocarcinoma | 168 (57.14) | 45 (54.22) | 123 (58.29) | |
| Intestinal adenocarcinoma | 126 (42.86) | 38 (45.78) | 88 (41.71) | |
| Location of metastasis | | | | |
| Ganglions | | | | 0.35 |
| No | 189 (64.29) | 53 (63.86) | 136 (64.45) | |
| Yes | 47 (15.99) | 10 (12.05) | 37 (17.54) | |
| Not recorded | 58 (19.73) | 20 (24.10) | 38 (18.01) | |
| Pleura | | | | 0.12 |
| No | 227 (77.21) | 63 (75.90) | 164 (77.73) | |
| Yes | 9 (3.06) | 0 | 9 (4.27) | |
| Pleura | | | | |
| Not recorded | 58 (19.73) | 20 (24.10) | 38 (18.01) | |
| Pancreas | | | | 1 |
| No | 221 (75.17) | 59 (71.08) | 162 (76.78) | |
| Yes | 15 (5.10) | 4 (4.820) | 11 (5.21) | |
| Not recorded | 58 (19.73) | 20 (24.10) | 38 (18.01) | |
| Colon | | | | 0.35 |
| No | 230 (78.23) | 63 (75.90) | 167 (79.15) | |
| Yes | 6 (2.04) | 0 | 6 (2.84) | |
| Not recorded | 58 (19.73) | 20 (24.10) | 38 (18.01) | |
| Kidney | | | | 1 |
| No | 231 (78.57) | 62 (74.70) | 169 (80.09) | |

| | | | | |
|---|---|---|---|---|
| Yes | 5 (1.70) | 1 (1.20) | 4 (1.90) | |
| Not recorded | 58 (19.73) | 20 (24.10) | 38 (18.01) | |
| Liver | | | | 0.76 |
| No | 183 (62.24) | 48 (57.83) | 135 (63.98) | |
| Yes | 53 (18.03) | 15 (18.07) | 38 (18.01) | |
| Not recorded | 58 (19.73) | 20 (24.10) | 38 (18.01) | |
| Lung | | | | 0.25 |
| No | 220 (74.83) | 61 (73.49) | 159 (75.36) | |
| Yes | 16 (5.44) | 2 (2.41) | 14 (6.64) | |
| Not recorded | 58 (19.73) | 20 (24.10) | 38 (18.01) | |
| Ovary | | | | 1 |
| No | 233 (79.25%) | 62 (74.70) | 171 (81.04) | |
| Yes | 3 (1.02) | 1 (1.20) | 2 (0.95) | |
| Not recorded | 58 (19.73) | 20 (24.10) | 38 (18.01) | |
| Duodenum | | | | 0.16 |
| No | 222 (75.51) | 57 (68.67) | 165 (78.20) | |
| Yes | 14 (4.76) | 6 (7.23) | 8 (3.79) | |
| Not recorded | 58 (19.73) | 20 (24.10) | 38 (18.01) | |
| Treatment | | | | |
| Subtotal gastrectomy | | | | 0.03 |
| No | 137 (46.6) | 33 (39.76) | 104 (49.29) | |
| Yes | 59 (20.07) | 23 (27.71) | 36 (17.06) | |
| Not recorded | 98 (33.33) | 27 (32.53) | 71 (33.65) | |
| Chemotherapy | | | | 0.14 |
| No | 99 (33.67) | 33 (39.76) | 66 (31.28) | |
| Yes | 97 (32.99) | 23 (27.71) | 74 (35.07) | |
| Not recorded | 98 (33.33) | 27 (32.53) | 71 (33.65) | |
| Total gastrectomy | | | | 0.51 |
| No | 185 (62.93) | 52 (62.65) | 133 (63.03) | |
| Yes | 11 (3.74) | 4 (4.82) | 7 (3.32) | |
| Not recorded | 98 (33.33) | 27 (32.53) | 71 (33.65) | |
| Radiotherapy | | | | 0.67 |
| No | 181 (61.56) | 51 (61.45) | 130 (61.61) | |
| Yes | 15 (5.10) | 5 (6.02) | 10 (4.74) | |
| Not recorded | 98 (33.33) | 27 (32.53) | 71 (33.65) | |
| Gastroyeyunostomy | | | | 0.63 |
| No | 164 (55.78) | 48 (57.83) | 116 (54.98) | |
| Yes | 32 (10.88) | 8 (9.64) | 24 (11.37) | |
| Not recorded | 98 (33.33) | 27 (32.53) | 71 (33.65) | |
| Other palliative treatments | | | | 0.29 |
| No | 155 (52.72) | 47 (56.63) | 108 (51.18) | |
| Yes | 41 (13.95) | 9 (10.84) | 32 (15.17) | |
| Not recorded | 98 (33.33) | 27 (32.53) | 71 (33.65) | |
| Laboratory studies | | | | |
| Hemoglobin (mg/dl) | 10.94 ± 2.58 | 10.85 ± 2.55 | 10.97 ± 2.6 | 0.72 |
| Level of hemoglobin | | | | 0.94 |
| Without anemia | 75 (25.51) | 20 (24.10) | 55 (26.07) | |
| With anemia | 194 (65.99) | 56 (67.47) | 138 (65.4) | |
| Not recorded | 25 (8.50) | 7 (8.43) | 18 (8.53) | |
| Mean corpuscular volume MCV (fL) Level of MCV | 83.75 ± 9.09 | 83.72 ± 8.66 | 83.76 ± 9.27 | 0.88 |

| | | | | |
|---|---|---|---|---|
| Low | 79 (26.87) | 19 (22.89) | 60 (28.44) | |
| Normal | 167 (56.80) | 49 (59.04) | 118 (55.92) | |
| High | 13 (4.42) | 3 (3.61) | 10 (4.74) | |
| Not recorded | 35 (11.90) | 12 (14.46) | 23 (10.90) | |
| Hematocrit (%) | 33.76 ± 7.19 | 33.77 ± 6.94 | 33.76 ± 7.31 | 0.99 |
| Level of hematocrit | | | | 0.84 |
| Low | 201 (68.37) | 57 (68.67) | 144 (68.25) | |
| Normal | 65 (22.11) | 17 (20.48) | 48 (22.75) | |
| Not recorded | 28 (9.52) | 9 (10.84) | 19 (9.00%) | |
| Platelets ($10^3$/μL) | 324,401 ± 142,411 | 317,493 ± 155,427 | 327,172 ± 137,199 | 0.41 |
| Level of platelets | | | | 0.39 |
| Low | 12 (4.08) | 6 (7.23) | 6 (2.84) | |
| Normal | 198 (67.35) | 55 (66.27) | 143 (67.77) | |
| High | 45 (15.31) | 12 (14.46) | 33 (15.64) | |
| Not recorded | 39 (13.27) | 10 (12.05) | 29 (13.74) | |
| Leucocytes | 8,719 ± 4,875 | 8,821 ± 6,060 | 8,680 ± 4,359 | 0.46 |
| Level of leucocytes | | | | 0.92 |
| Low | 43 (14.63) | 13 (15.66) | 30 (14.22) | |
| Normal | 130 (44.22) | 36 (43.37) | 94 (44.55) | |
| High | 73 (24.83) | 19 (22.89) | 54 (25.59) | |
| Not recorded | 48 (16.33) | 15 (18.07) | 33 (15.64) | |
| Attention level | | | | 0.87 |
| Second level | 27 (9.18) | 8 (9.64) | 19 (9.00%) | |
| Third level | 267 (90.82) | 75 (90.36) | 192 (91.00%) | |
| Length of survival | | | | |
| Days | 752.70 ± 964.93 | 1,873.47 ± 1,024.01 | | <0.001 |
| Median (RIC)* | 311 (96, 1076) | 1871 (909, 2619) | 163 (70, 377) | |

**Table 1. Characteristics of the Subjects Included.**

*Interquartile range; The p value was obtained through the Mann Whitney U test for numerical variables and the chi squared test for qualitative variables. NA - not applicable

The most frequent tumor sites were generally found in the middle third (45.24%) and the lower third (51.36%), with no differences found between these two groups. Of the total number of subjects, 18.03% presented metastasis to the liver and 15.99% presented metastasis to the adjacent ganglions, with these representing the most frequent sites of invasion. In general, the most selected treatment was chemotherapy (32.99%), followed by subtotal gastrectomy (20.07%). Differences were found in the latter: 27.71% of the subjects who had undergone subtotal gastrectomy survived and were considered censorships, compared to 17.06% of those who died (p= 0.03) (Table 1).

In general, the average hemoglobin value was 10.94 mg/dl, with no differences found between groups. About platelets, more than 60% were considered to be within normal parameters. In the values of the rest of the laboratory studies, no differences were found between the groups (Table 1).

Most (90.82%) of the patients received third level attention, and there were no differences in this regard between the subjects who survived and those who died. Finally, in general, the mean time of survival was 752.7 days; the subjects considered censorships presented mean survival of 1,873 days and those who died presented 311 days, a difference that was found to be significant (p<0.001) (Table 1).

## Survival model

In the survival model of the entire population, it can be seen that subjects between the ages of 41 and 50 years presented a 56% lower risk of dying from gastric cancer (HR=0.44, CI95% 0.24, 0.79), compared to those diagnosed before 40 years of age. Moreover, subjects of between 51 and 60 years of age demonstrated a 47% lower risk of death (HR=0.53, CI95% 0.3, 0.95) than those of below 40 years of age. Finally, there was also a 51% lower risk of death (HR=0.49, CI95% 0.26, 0.93) in subjects of between 61 and 65 years of age, compared to the reference category (Table 2).

| Characteristic | Hazard Ratio ¥ | p value | CI95% |
|---|---|---|---|
| Age (years) | | | |
| <40 | 1 | | |
| 41 to 50 | 0.44 | <0.01 | 0.24, 0.79 |
| 51 to 60 | 0.53 | <0.05 | 0.3, 0.95 |
| 61 to 65 | 0.49 | <0.05 | 0.26, 0.93 |
| 66 to 70 | 0.57 | 0.06 | 0.31, 1.03 |
| 71 to 75 | 0.68 | 0.22 | 0.37, 1.26 |
| 76 and above | 0.68 | 0.25 | 0.35, 1.31 |
| Sex | | | |
| Female | 1 | | |
| Male | 1.36 | 0.2 | 0.85, 2.17 |
| Education level | | | |
| None | 1 | | |
| Primary | 0.82 | 0.37 | 0.53, 1.27 |
| Secondary | 0.77 | 0.41 | 0.41, 1.45 |
| High school and beyond | 0.65 | 0.18 | 0.35, 1.21 |
| Civil status | | | |
| Married or cohabiting | 1 | | |
| Single, widow/widower or separated | 1.01 | 0.96 | 0.7, 1.46 |
| Alcoholism | 1.27 | 0.39 | 0.73, 2.22 |
| Tobacco addiction | 0.95 | 0.8 | 0.66, 1.37 |
| Diabetes mellitus | 1.15 | 0.52 | 0.75, 1.77 |
| Systemic arterial Hypertension | 1.12 | 0.61 | 0.72, 1.75 |
| Epigastric pain | 1.51 | 0.06 | 0.99, 2.32 |
| Sensation of fullness | 1.01 | 0.98 | 0.69, 1.47 |
| Dysphagia | 0.81 | 0.31 | 0.53, 1.22 |
| Asthenia and/or adynamia | 1.45 | <0.05 | 1.04, 2.01 |
| Weight loss | 2 | <0.01 | 1.27, 3.16 |
| Melena | 0.54 | <0.01 | 0.37, 0.81 |
| Hematemesis | 1.06 | 0.81 | 0.66, 1.70 |
| Nausea | 1.2 | 0.38 | 0.80, 1.81 |
| Emesis | 0.89 | 0.6 | 0.57, 1.38 |
| Pyrosis | 0.81 | 0.28 | 0.55, 1.19 |
| Diarrhea or constipation | 1.15 | 0.63 | 0.65, 2.02 |
| Palpable tumor in abdomen | 1.23 | 0.35 | 0.80, 1.90 |
| Dyspnea | 0.68 | 0.39 | 0.28, 1.64 |
| Jaundice | 0.79 | 0.48 | 0.41, 1.53 |
| Gastroesophageal junction | 1.34 | 0.31 | 0.75, 2.39 |
| Upper third | 0.63 | 0.05 | 0.4, 1.0 |
| Middle third | 1.06 | 0.74 | 0.75, 1.51 |
| Lower third | 1.16 | 0.49 | 0.76, 1.76 |

| | | | |
|---|---|---|---|
| Diagnostic of pathology | | | |
| Diffuse adenocarcinoma | 1 | | |
| Intestinal adenocarcinoma | 0.83 | 0.26 | 0.59, 1.15 |
| Metastasis to ganglions | 1.13 | 0.62 | 0.70, 1.82 |
| Metastasis to liver | 0.98 | 0.95 | 0.63,1.54 |
| Metastasis to lung and/or pleura | 1.34 | 0.33 | 0.74, 2.42 |
| Metastasis to colon and/or duodenum | 0.74 | 0.4 | 0.35, 1.55 |
| Metastasis to kidney and/or pancreas and/ or ovary | 1.12 | 0.65 | 0.67, 1.89 |
| Hemoglobin | | | |
| Normal | 1 | | |
| Anemia | 0.83 | 0.34 | 0.56, 1.22 |
| Mean corpuscular volume | | | |
| Normal | 1 | | |
| Low | 1.04 | 0.85 | 0.71, 1.51 |
| High | 1.24 | 0.56 | 0.60, 2.56 |
| Platelets | | | |
| Normal | | | |
| Low | 1.11 | 0.81 | 0.48, 2.56 |
| High | 1.05 | 0.84 | 0.67, 1.64 |
| Leucocytes | | | |
| Normal | 1 | | |
| Low | 0.76 | 0.23 | 0.48 ,1.20 |
| High | 1.57 | <0.05 | 1.08, 2.27 |
| Attention level | | | |
| Second level | 1 | | |
| Third level | 1.09 | 0.81 | 0.56, 2.11 |

**Table 2. Cox Regression Model* for Death in Subjects with Gastric Cancer (n=294).**

The variables of occupation and hematocrit were excluded from analysis since these were collinear with other variables. ¥ estimates correspond to the model with imputation.

Presentation of asthenia and/or adynamia as symptoms increased the risk of death by 45% (HR=1.45, CI95% 1.04, 2.01) in patients with gastric cancer, compared to cases with no presentation of these symptoms. In addition, the presentation of involuntary weight loss doubled the risk of death (HR=2, CI95% 1.27, 3.16), compared to subjects with no such weight loss (Table 2). The median values of survival related to the studied variables were also calculated (Table 1).

The presence of melena was found to be a protective factor, reducing the risk of death by 46% (HR=0.54, CI95% 0.37, 0.81), compared to the cases in which it was absent. If the tumor was in the upper third, this resulted in 37% lower mortality (HR=0.63, CI95% 0.4, 1.0) than when found at another site. Finally, the presence of leukocytosis increased the risk of death by 57% (HR=1.57, CI95% 1.08, 2.27) relative to subjects with normal levels of this biomarker. The general survival of the studied population was estimated (Supplementary material), as well as the length of survival associated with the presentation of weight loss, melena and metastasis to the lung and pleura, in which differences were found between the groups (Supplementary material).

# Discussion

To our knowledge, in Mexico, this study is one of the few to provide evidence for prognostic clinical-

pathological factors, especially symptoms, metastasis and biomarkers, in patients with gastric cancer and without social security. Oñate-Ocaña [8] reported that, in patients with a diagnostic of gastric adenocarcinoma attended during the period 1987 to 1998, the stage of TNM was the most important prognostic factor, where the median values of survival were 29.8, 24.3 and 8.6 months for stages IIIa, IIIb and IV, respectively [8]. We determined that, on average, individuals who died survived for 311 days, compared to those considered censorships, who survived for an average of 1,873 days.

We found that 12.24% of the subjects had a diagnosis of gastric cancer at below 40 years of age, a similar value to the 14.8% (83/558) reported by the Instituto Nacional de Ciencias Médicas y Nutrición “Salvador Zubirán” [17]. International reports state that the incidence of gastric cancer in subjects of below 40 years of age is low, at between 2 and 15 % [18, 19].

The survival analyses indicate that, in the study population, individuals of less than 40 years of age had a greater risk of death compared to those of between 41 and 65 years, with no significant differences between these and those of 66 years of age and above. These data coincide to some extent with reports stating that gastric cancer in young patients develops more aggressively and with a poorer prognosis, compared to that in older subjects. [20-22]. It has been suggested that gastric cancer in young patients has a different clinical-pathological profile to the conventional profile, and in fact represents a separate entity within gastric carcinogenesis. There is evidence at molecular level to support this proposal [19].

On the other hand, conflicting results have been reported regarding prognosis in young patients with gastric cancer [23-25]. A study in japan showed that the prognosis in patients of between 40 and 69 years of age is better than that in those of less than 40 years, or in those of 69 years and above, with no differences found between subjects of ≤40 years compared to those of >40 years of age [26]. In this study, the symptoms detected at the time of diagnosis of gastric cancer that were associated with a greater risk of death were asthenia and/or adynamia and weight loss, although asthenia is the symptom with greatest prevalence in patients who live with cancer and has an important impact on the quality of life that has often been underestimated [27, 28]. Involuntary weight loss at the time of diagnosis of gastric cancer was associated in our study with a two-fold greater risk of death, compared to those subjects who did not present this sign. It has been reported that weight loss occurs in less than 40% of patients with incipient gastric cancer, while it is a common symptom in advanced gastric cancer [29]. Involuntary weight loss has been considered among the possible prognostic factors of gastric cancer by several authors, and is associated with death [30-33].

In contrast to the findings of other authors [30-32, 34, 35] we found no association with death among the other alarm signals for gastric cancer, such as dysphagia and the presentation of a palpable tumor in the abdomen.

To our knowledge, this is the first report in Mexico concerning patients with gastric cancer to identify melena as a protective factor against mortality; we did not find any other published evidence with which to compare this finding. Melena has mainly been studied in relation to colorectal cancer [36, 37] and in other studies that group patients with diagnosis of esophageal and gastric cancer [38, 39]. A study in England demonstrated that the existence of the symptoms of alarm, hematuria, hemoptysis, dysphagia and rectal bleeding, can be predictive factors for diagnosis of urinary tract, lung and gastroesophageal cancer, [38] but differences in the survival of patients with and without symptoms of alarm remains to be adequately explored. Another study, also conducted in England and at first level attention, states that dysphagia, involuntary weight loss and anemia are symptoms of alarm associated with a low sensitivity to gastroesophageal cancer [39]. This is much more complex, since other authors indicate the inconsistency of the evidence regarding the use of these symptoms of alarm as selection criteria for endoscopy, given that they are insufficiently sensitive to detect malign tumors and their prevalence is variable: it is high in dyspeptic patients, but low in cancer gastro-intestinal patients [40].

In this study, we found that, in patients with gastric cancer, leukocytosis can function as a predictor of mortality. Leukocytosis is often a sign of a systemic inflammatory response secondary to an infection, but can also occur during the development of certain malignant tumors [41]. Leukocytosis has been reported as a predictor of early mortality in patients with cancer prior to beginning chemotherapy [42].

In conclusion, this study proposes that age <40 years, asthenia, adynamia, weight loss and leukocytosis are predictors of poor prognosis in patients with gastric cancer, while melena could function as a protective variable, probably because the patient considers it a signal of alarm and thus seeks medical consultation. In this context, doctors must pay attention to patients, both young and old, who refer to gastrointestinal symptoms and must recommend endoscopic examinations in those cases with high clinical suspicion of gastric cancer.

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