Original Article

Latin American young patients with gastric adenocarcinoma: worst prognosis and outcomes

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Background: Incidence of young patients (aged 40 years or younger) diagnosed with gastric carcinoma has increased worldwide. Young GC diagnosis, have clinicopathological features that differ from elderly, and is correlated with bad prognosis factors. The purpose of this work is to describe the prevalence, clinic-pathological features, and prognosis of overall survival (OS) of young Latin-American patients with GC.

Methods: Retrospective, observational study. Included patients treated at the National Cancer Institute [2004–2020]. Statistical analysis: χ^2 and *t*-test, Kaplan-Meier, Log-Rank and Cox-Regression. Statistical significance differences were assessed when P was bilaterally <0.05.

Results: A total of 2,543 patients fulfilled the inclusion criteria. Young-patients were predominantly female (54%), with diffuse-type adenocarcinoma (68%), signet-ring-cell (72%), poor-differentiation (90%), and metastatic (79%). In OS analysis, patients with metastatic disease, showed differences regarding age, young patients reported a median-OS of 8 versus 13 months for elderly patients (P=0.001). Among young patients, differences were also observed regarding gender, young-female patients had a median-OS of 5 versus 11 months for young-man (P=0.001).

Conclusions: This is one of the pioneer studies correlating age with gender and the prognostic features of bad prognosis in Latin-American population. Besides, supports the idea that a global effort is required to improve awareness, prevention, and early diagnosis of GC.

Keywords: Gastric adenocarcinoma; young population; prognostic factors; overall survival (OS); female patients

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Introduction

Gastric cancer is the 6th most common cancer and the 4th most frequent cancer related to death worldwide (1). In Mexico, gastric cancer is the 6th cause of cancer-related death (1). Incidence rates are twice as high in men, predominantly diagnosed in older age groups with a median age of 68 years old in USA, and 58 in Mexico (1,2).

Studies have indicated an increasing incidence of GC in the young population over the past decade (3,4). Young patients (aged 40 years or younger) diagnosed with GC

incidence have increased from 4.6% to 6.2% out of the total cases in the USA (4), and up to 6% in Mexican population (2). GC in young patients, has been described to have several clinicopathological features that differ from elderly patients, including a higher female to male ratio, more diffuse type, poorly differentiated carcinoma, familial susceptibility of tumors, advanced stage of the disease and an increased familial cancer aggregation, as described in China, Korea, and Mexico (2,3,5,6). These clinicopathological features have been associated to an "aggressive growth pattern" which may lead to a different prognosis between young and elderly patient (5,7,8).

Recent studies, have demonstrated poor survival outcomes for young patients when compared to middle-age patients (35–64 years) and elderly patients (65–74 years) (9). Likewise, Wong *et al. and Li et al.* described that young population with GC showed a three-year OS of 6.9% (10,11). Other studies have also demonstrated that young populations with GC have lower progression free survival rates (P=0.012) (12), and higher cancer related mortality (P=0.048) (13), which can be explained by tumor location, ethnicity, tumor size, surgery, tumor, node, metastasis (TNM) stage, clinical stage of disease, poorly differentiated, signet cell type, and female gender prevalence (9,10,12-14).

On the other hand, studies revealed that younger patients showed better overall survival (OS) rates; 62.1% versus 28.1% for elderly patients ranging different races and TNM stage (14-16), Additionally several meta-analyses have associated young age with a better prognosis, favored by a good performance status, surgery and adjuvant chemotherapy (12,15,16). Moreover, other studies found no differences in survival rates between young and elderly patients (17,18). Therefore, the role of age in prognosis remains controversial (14) and many questions regarding carcinogenesis, treatment, prognosis and prevention remain unexplained (19,20), representing a challenge for physicians and research (19). For this reason, the present study aims to describe the prevalence, clinic-pathological features, and prognosis of young Latin American patients with gastric adenocarcinoma (GC). We present this article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-259/rc).

Highlight box

Key findings

- The incidence of gastric cancer in young patients increased from 2% to 18%.
- Young female patients reported a high percentage of diffuse-type adenocarcinoma, signet ring cells, poorly differentiated tumors, and metastatic disease, with lower overall survival (OS) rates than man.

What is known and what is new?

- Young gastric cancer diagnosis has clinicopathological features correlated with a bad prognosis.
- This is one of the pioneer studies correlating age with gender and the prognostic factors in Latin-American population. Female patients reported more rates of metastatic disease, diffuse-type, signet-ring cells, poorly differentiated tumors, and worse rates of OS than male patients.

What is the implication, and what should change now?

- It is fundamental to increase knowledge in first-contact physicians to promote early diagnosis of gastric adenocarcinoma in young population.
- Screening campaigns at early-age are needed, and must include the awareness of the disease and the modifiable risk factors related.

Methods

This study is a retrospective, observational study that included the registry of patients treated at the National Cancer Institute from 2004 to 2020. The study conformed to the provisions of the Declaration of Helsinki (as revised in 2013). This study has been approved by the Ethics and Clinical Research Committee of the National Cancer Institute, Mexico as a retrospective study (No. 2021/046), without risks for patients since data was obtained from clinical records. Therefore, the approval of informed consent is not necessary.

Study size

In the present study a non-probabilistic consecutive sampling was used.

Inclusion/exclusion criteria

Inclusion criteria: patients diagnosed with GC, treated at the National Cancer Institute, Mexico, between January 2004 and December 2020. Exclusion criteria: loss of follow up, and abandonment, or patients with missing information.

Clinical data collection

Clinical data included age, gender, tumor size, TNM stage (defined by the eighth American Joint Committee on Cancer TNM system), surgical procedure, lymphadenectomy,

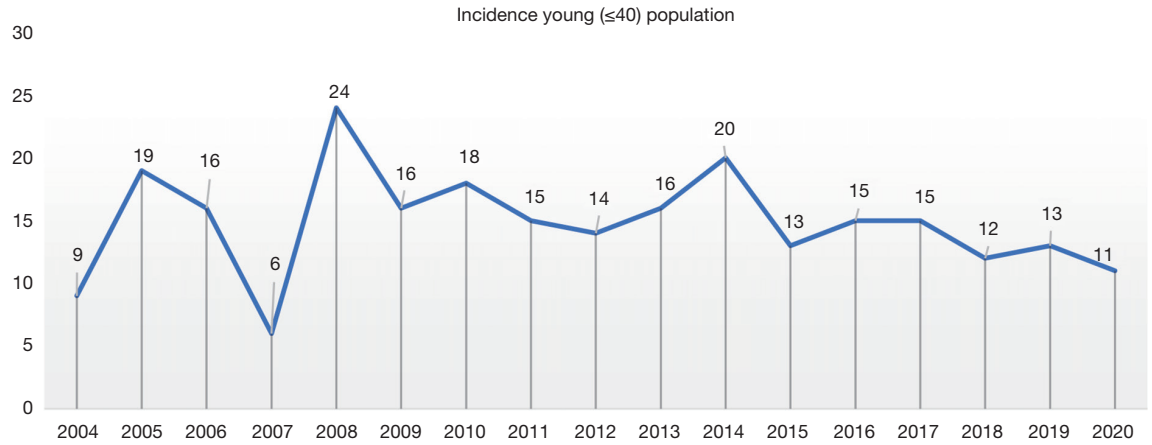

Figure 1 Median age of young patients with gastric cancer. Incidence of young (≤40) patients diagnosed with gastric adenocarcinoma over the years. The incidence of cases among the young population increased over the years, from 6% in 2004 to 15% by 2020.

histological differentiation, chemotherapy, radiotherapy, and at least 3-month follow-up status.

Statistical analysis

For all analyses, patients were classified into two groups: young (≤40 years) and elderly (≥41 years). Statistical analysis was performed using SPSS v. 24 software. Continuous variables were expressed as mean ± standard deviation values or as median and range (minimum and maximum) values according to their distribution (normal *vs.* not normal). Categorical variables were expressed as percentages. Statistical comparisons among groups were performed using the *t*-test when data were normally distributed; otherwise, the Mann-Whitney *U* test was performed. Statistical significance differences were assessed when P was bilaterally <0.05.

OS analysis

OS was defined as the time from GC diagnosis to death by any cause. OS rates were calculated using the Kaplan-Meier method, and different variables were compared using the log-rank test. Statistical significance differences were assessed when P was bilaterally <0.05.

Results

Clinicopathological features

A total of 2,543 patients met the inclusion criteria. Only 15% (n=380) corresponded to young patients (≤40 years), and the remaining 85% corresponded to elderly patients. Nevertheless, the number of cases among the young population has been increasing over the years, from 6% in 2004 to 15% by 2020 (*Figure 1*). Besides, young females have shown an increased incidence by year with only 3% in 2004 up to 17% by 2020, compared to young males whose incidence have decreased from 15% to 9% between over the same period (*Table 1*). Among patients' clinical characteristics, young populations where predominantly female (54%), with histological classification of diffuse type adenocarcinoma (68%), signet ring cell component, which was identified in 72% of the patients, and poor differentiation in 90% of the cases. Compared to elderly patients who were mostly male (n=1,232), in male population, the diffuse type was observed in 43% of the cases, signet ring cell component in 50%, and poor differentiation in 76% (*Table 1*).

By November 2010, the determination of Her2neu (performed by immunohistochemistry) was incorporated into the histological report. Her2 determination was available for 53 young patients, 45 of them were negative, and the remaining 8 positive. Contrarily, Her2 determination in elderly patients was available in 669 cases, 508 of them were negative, 91 Her2 3(+), 54 Her2 1(+), and 16 Her2 2(+).

The extent of the disease at the time of evaluation by Medical Oncology Department was based on operative and histological findings (in patients who underwent initial surgical exploration, either with staging or therapeutic purpose). In patients who did not undergo surgery, data was

Table 1 Clinicopathological characteristics of patients with gastric cancer

Characteristics	CS I–III			CS LA unresectable			CS metastatic		
	Young (≤40 years)	Elderly patient (≥41 years)	P	Young (≤40 years)	Elderly patient (≥41 years)	P	Young (≤40 years)	Elderly patient (≥41 years)	P
Gender									
Men	12 (50%)	125 (52%)	1.000	39 (70%)	309 (60%)	0.153	124 (41%)	798 (57%)	<0.001**
Woman	12 (50%)	117 (48%)		17 (30%)	209 (40%)		176 (59%)	606 (43%)	
Diffuse									
Negative	4 (17%)	118 (49%)	0.002**	27 (48%)	325 (63%)	0.043**	91 (30%)	718 (51%)	<0.001**
Diffuse	20 (83%)	124 (51%)		29 (52%)	193 (37%)		209 (70%)	686 (49%)	
Grade									
Well	0	8 (3%)		2 (4%)	28 (5%)		1 (0%)	30 (2%)	
Moderated	1 (4%)	47 (19%)		6 (11%)	127 (25%)	0.032**	15 (5%)	226 (16%)	<0.001**
Poor	23 (96%)	176 (73%)	0.181	45 (80%)	353 (68%)		275 (92%)	1,107 (79%)	
ND	0	11 (5%)		3 (5%)	10 (2%)		9 (3%)	36 (3%)	
Signet ring cells									
No	3 (12%)	116 (48%)	0.001**	22 (39%)	285 (55%)	0.018**	71 (24%)	635 (45%)	<0.001**
Yes	21 (88%)	126 (52%)		34 (61%)	233 (45%)		229 (76%)	769 (55%)	
HER2									
Negative	22 (92%)	181 (75%)	0.078	52 (93%)	426 (82%)	0.057	261 (87%)	1,005 (72%)	<0.001**
HER2	2 (8%)	61 (25%)		4 (7%)	92 (18%)		39 (13%)	399 (28%)	
Surgery									
Absent	0	2 (1%)	1.00	33 (59%)	397 (77%)	0.005**	223 (74%)	1,054 (75%)	0.826
Surgery	24 (100%)	240 (99%)		23 (41%)	119 (23%)		77 (26%)	350 (25%)	
Chemotherapy									
Absent	1 (4%)	67 (28%)	0.012**	11 (20%)	211 (41%)	0.002**	83 (28%)	551 (39%)	<0.001**
Chemotherapy	23 (96%)	175 (72%)		45 (80%)	307 (59%)		217 (72%)	853 (61%)	

Most young patients were diagnosed with metastatic disease (79%). Besides statistical differences were found between the clinicopathological characteristics and age. **, statistical significance. CS, clinical stage; LA, locally Advanced disease (unresectable); ND, undetermined.

collected from clinical examination, CT scans and upper gastrointestinal endoscopy studies. Young patients' most frequent clinical stage at diagnosis was metastatic (79%), followed by locally advanced disease (LA-unresectable) (15%), and early stages I–III (6%). Accordingly for elderly patients, 65% were diagnosed at metastatic disease, 24% LA-unresectable and the remaining 11% at early stages I–III (*Table 1*).

OS analysis

For OS analysis patients were subdivided into young and elderly. The First analysis included clinical stage, young patients diagnosed at stage I–III had a median OS of 33 months, versus elderly patients who had a median OS of 233 months (P=0.001) (*Figure 2A*). Likewise, young patients diagnosed at LA-unresectable stage of the disease showed a median OS of 20 versus 25 months for elderly patients

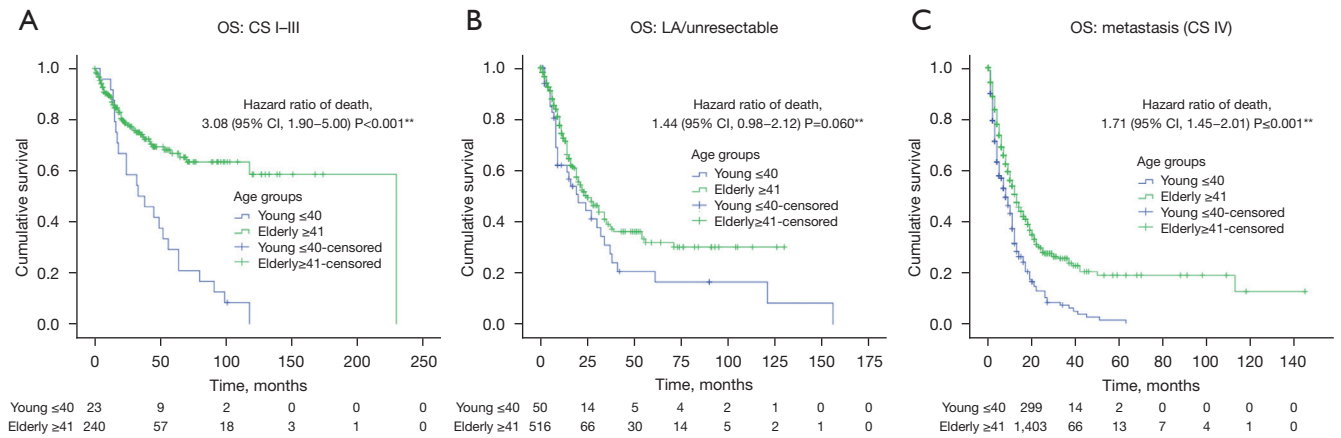

Figure 2 OS for patients diagnosed with gastric adenocarcinoma comparing clinical stage and gender, Kaplan-Meier estimates OS among patients diagnosed with gastric adenocarcinoma according to clinical stage and gender. (A) Young patients diagnosed at stage I–III had a median OS of 33 months, versus elderly patients who had a median OS of 233 months (P=0.001). (B) Young patients diagnosed at CS LA-unresectable, had a median OS of 20 months, versus elderly patients who had a median OS of 25 months (P=0.055). (C) Young patients with metastatic disease had a median OS of 8 months, versus elderly patients who had a median OS of 13 months (P=0.001). **, statistical significance. CS, clinical stage; CI, confidence interval; LA, locally Advanced disease (unresectable); OS, overall survival.

(P=0.055) (*Figure 2B*). Regarding metastatic disease, young patients had a median OS of 8 months versus elderly patients who had a median OS of 13 months (P=0.001) (*Figure 2C*).

A second analysis was performed for mainly for advanced disease, comparing the 2 groups mentioned above (young *vs.* elderly) and sex, regarding advanced stages of the disease (LA-unresectable versus metastatic). Among patients with LA-unresectable disease, young female patients had a median OS of 8 months versus male patients, who had a median OS of 24 months (*Figure 3A*). Moreover, elderly female patients had a median OS of 20 versus 27 months for male patients (P=0.039) (*Figure 3B*). Likewise, amid patients with metastatic disease, young female patients had a median OS of 5 versus 11 months for male patients (P=0.001) (*Figure 4A*), moreover, elderly patients reported a median OS of 13 months for both female and male patients (P=0.994) (*Figure 4B*). *Table 2* illustrates the univariate and multivariate analysis, variables such as female-gender, metastatic stage, diffuse type adenocarcinoma, poor differentiation and signet ring cell component remained predictors of OS in young population.

Discussion

This study describes the incidence and mortality of Latin patients diagnosed with GC.This type of cancer is the second most common neoplasm within gastrointestinal pathologies in our hospital and one of the leading cancer diagnoses and mortality in our country and the Latin Hispanic population (21,22). Even though the incidence and mortality of GC is mostly in patients aged 50 years or more, in the past 30 years, the diagnosis of GC has increased in younger adults (5,23,24). In the present study the incidence of GC in younger population increased from 2% up to 18% between 2004 and 2019.

In developed countries, incidence of GC is more predominant in male population with a ratio of 2.5:1 (men: women) (19,25). Nevertheless, in Latin and Asian population, this ratio decreases significantly to 2:1 (men: women) (3,25,26). In the present study, GC diagnosis is slightly more frequent in women with a ratio of 1:1.1 (men: women). Chen *et al.*, reported that ratio distribution is modified according primary tumor location, such as distal location (2:1) and proximal (5:1) male: female (12). In our analysis the ratio was 1:1.2 (male: female) in distal gastric cancer and 2.5:1 (male: female) in esophagogastric junction.

Around 90–95% of gastric tumors are adenocarcinomas; according to Lauren's classification, subtypes are divided into two: intestinal and diffuse type (27). Intestinal type is more common in older African-American men, while the diffuse type is similar between men and women (28,29). These three components such as diffuse type, signet ring cells, and a poorly differentiation have been described as

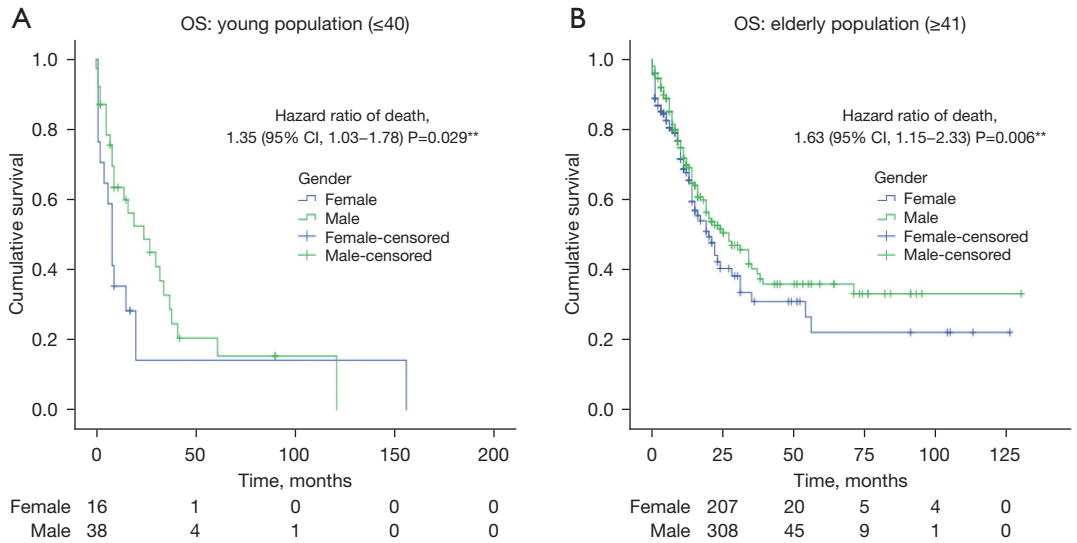

Figure 3 OS of patients with local-advanced GC. OS of patients with local-advanced disease comparing age and gender. Kaplan-Meier estimates OS among patients with local-advanced unresectable disease according to age and gender. (A) Young female diagnosed with LA-unresectable disease had a median OS of 8 months *vs.* male patients who had a median OS of 24 months. (B) Elderly female diagnosed with LA-unresectable had a median OS of 20 months *vs.* male patients who had a median OS of 27 months (P=0.039). **, statistical significance. CI, confidence interval; LA, locally Advanced disease (unresectable); OS, overall survival; GC, gastric cancer.

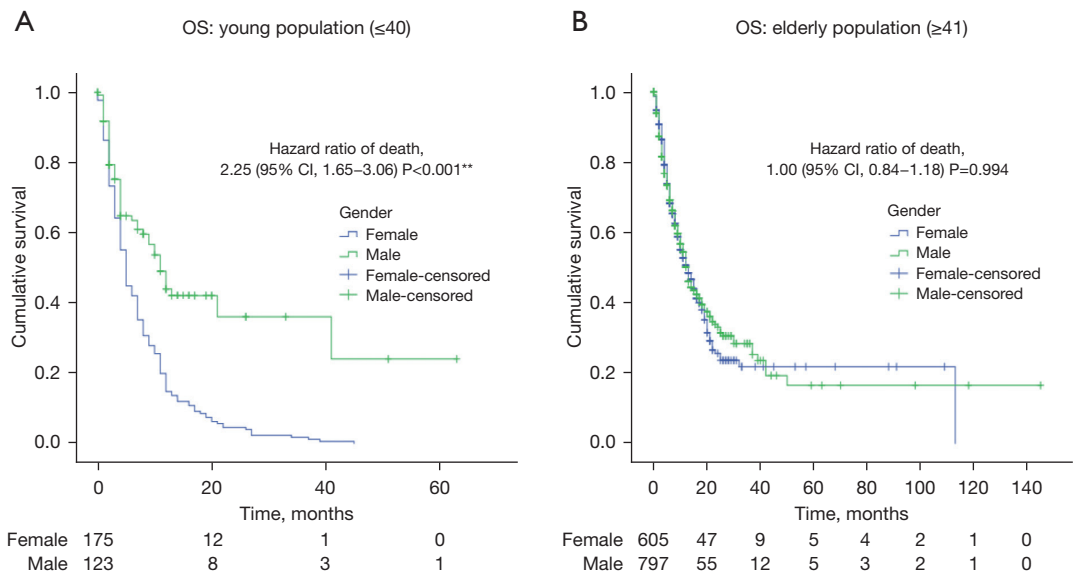

Figure 4 OS of metastatic patients with GC. OS of patients with metastatic disease comparing age and gender. Kaplan-Meier estimates OS among patients with metastatic disease according to age and gender. (A) Young female patients diagnosed with metastatic disease had a median OS of 5 months *vs.* male patients who had a median OS of 11 months (P=0.001). (B) Elderly patients had a median OS of 13 months for both female and male. **, statistical significance. OS, overall survival; GC, gastric cancer.

Table 2 Univariate and multivariate analysis

Characteristics	Univariate		Multivariate	
	P	HR (95% CI)	P	HR (95% CI)
Age	<0.001**	1.98 (1.72–2.28)	<0.001**	1.88 (1.62–2.19)
Gender	0.420	1.05 (0.929–1.19)	–	–
Clinical stage	<0.001**	4.69 (3.70–5.96)	<0.001**	2.03 (1.71–2.41)
Grade	0.620	1.05 (0.829–1.20)	–	–
Signet ring cells	<0.001**	1.45 (1.27–1.64)	<0.001**	1.44 (1.22–1.69)
Her2	0.024**	1.58 (1.06–2.36)	<0.017**	1.63 (1.09–2.44)
Surgery	<0.001**	0.34 (0.29–0.39)	<0.001**	0.46 (0.40–0.54)
Chemotherapy	<0.001**	0.43 (0.37–0.49)	<0.001**	0.33 (0.29–0.39)

Illustrates the univariate and multivariate analysis, variables such as female-gender, metastatic stage, diffuse type adenocarcinoma, poor differentiation and signet ring cell component remained predictors of overall survival in young population. **, statistical significance. HR, hazard ratio; CI, confidence interval.

poor prognosis features amid GC population (21).

The incidence of young age at the time of diagnosis has increased over the past decade, defined as "early onset of GC", these populations have demonstrated to highlight the prevalence of these 3 features of bad prognosis, besides higher metastatic risk (19,21,30). Besides, the early onset of gastric cancer has also been associated with hereditary diffuse gastric cancer, which is an autosomal dominant cancer syndrome caused by the inactivation of germline mutations in E-cadherin, tumor suppressor gene (CDH1), and less frequently variants in CTNNA1. In this study, young patients reported to have a high percentage of diffuse type adenocarcinoma (70%), signet ring cells (72%) and poorly differentiated (87%). Nevertheless, the association with germline mutations have not been described in our population. On the other hand, when comparing among sex, these three poor prognostic features were higher in the female population with statistical significance, which may be one of the causes young female patients reported worse outcomes when compared with male patients. Along with these three poor prognostic factors, the Her2neu receptor has been described as an additional factor with implications for worse outcome of GC patients (31,32). The "ToGA study" reported a 22% prevalence of this receptor in the Mexican population, nevertheless, in our study this receptor was positive (Her2neu +++) in only 10% of the cases. This is mainly due the inclusion criteria differences in both studies (32,33).

The extent of the disease at the time of diagnosis is the main prognostic factor (19). Most GC patients are diagnosed at advanced stages of the disease (metastatic), as demonstrated in studies from different populations, such as Japanese (25%), Hispanic (45%), American (40%), and Chinese (30%). These findings are similar to the Mexican population included in the present study, where 75% of the patients were diagnosed at stage IV (metastatic disease). In addition, young population presented more metastatic disease (80%) than the elderly (66%). In Latin American population, there are several factors that may be leading to this delay in the diagnosis of GC: absence of awareness campaigns in the prevention and early detection among young population, lack of knowledge or update about GC disease, symptoms and screening in first contact-non oncologist physicians and easy access to drugs against gastritis, which only delays diagnosis at GC onset (4,12,19,34).

This information shows that young female patients are predominantly diagnosed at metastatic disease stage (59%), with tumor location at stomach (70%), histological classification of diffuse type (68%), signet ring cell component (72%); and poor differentiation (90%). All clinical features related to a bad prognosis of OS and outcome in other studies worldwide (14,24,35). Thus, we performed a sub-analysis regarding clinical stage of the disease. Patients with metastatic disease, showed statistical differences of median OS when comparing age and gender. Young females had a lower OS and a higher risk of death compared to young man. On the other hand, elderly males and females had similar median OS. Among the group of LA-disease, differences between gender and age where also

observed, young females had lower OS and higher risk of death compared to young males with statistical differences between the groups. Also, when analyzing elderly patients, women had higher risk of death compared to elderly man. Our findings are in agreement with several publications, where female patients have worse OS than males, regardless of age, due to the greater presence of poor prognostic factors such as histology and clinical stage as mentioned before (4,21,30,36).

In addition, at the multivariate analysis, age (≤40 years), gender (female), clinical stage (IV), and primary tumor location (gastric) remained predictors of worst prognosis and OS. These variables have also been correlated among other studies including different population such as Chinese (9,35), Korean (3), American (29,34), and European (37,38), concluding that young female patients are commonly diagnosed at a metastatic stage of the disease and have worst outcome and higher risk of death.

This study has strengths and limitations; despite our findings, this study has some limitations, such its retrospective nature, the lack of associations with hereditary disease, probable E-cadherin and CDH1 gene mutations (12,39), and/or hormonal components, which have already been implicated in hereditary diffuse gastric cancer (32). It is also possible that many young patients are part of a hereditary-familial component of gastric adenocarcinoma in Mexico. On the other hand, this study has several strengths, including a new population described, the age described, and the fundamental differences demonstrated regarding the identification worse prognosis clinical factors among young female patients.

Conclusions

This is one of the pioneer studies correlating age, gender, and clinical stage in the Latin American population, supporting the idea that a global effort is required to improve awareness of the disease, prevention, as long as, early diagnosis, through screening campaigns in young populations. Besides educational programs in first contact physicians are fundamental to increase the knowledge of the disease and improve an early detection in young populations.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-259/rc

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-259/dss

Peer Review File: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-259/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-259/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are 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. The study conformed to the provisions of the Declaration of Helsinki (as revised in 2013). This study has been approved by the Ethics and Clinical Research Committee of the National Cancer Institute, Mexico as a retrospective study (No. 2021/046), without risks for patients since data was obtained from clinical records. Therefore, the approval of informed consent is not necessary.

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