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ORIGINAL ARTICLE

Tumor lymphocytic infiltration is a good prognostic factor for survival in locally advanced gastric cancer patients.

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Abstract

Introduction: The relationship between survival and lymphocytic infi ltration in gastric cancer has been determined to be a beneficial prognostic factor. This local study aims to assess the probability of survival in patients with gastric cancer stages IB to IIIC according to the percentage of lymphocytic infiltration.

Methodology: This longitudinal study was conducted at the Solón Espinosa Ayala Solca-Núcleo Cancer Hospital in Quito. The study period was from January 2013 to January 2016; the follow -up time ended in December 2018. The sample calculation was nonprobabilistic and included cases of patients older than 18 diagnosed with gastric cancer with clinical stages IB at IIIC, which had a histopathological sample of gastrectomies. The variable "percentage of infiltration" was used to analyze the sample, and it was divided into three groups: G1: mild lymphocytic infiltration, G2: moderate, and G3: intense. Survival estimates were calculated using the Kaplan–Meier method and compared groups with the log-rank test.

Results: A total of 173 patients with gastric cancer with clinical stages IB to IIIC were followed up for 72 months; 60% were men, and 40% were women. According to the percentage of lymphocytic infiltration, 52% reported a rate of mild infiltration, 21% moderate, and 27% intense. At 72 months of follow -up, sur- vival was 31% in G1, 48% in G2, and 77% in G3 (P= 0.001).

Conclusion: The degree of intense lymphocytic infiltration in gastric cancer patients was associated with better survival at the 72-month follow-up.

Keywords:
MESH: gastric neoplasms, tumor-infiltrating lymphocytes, survival analysis, survival, tumor biomarkers.

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Introduction

Cancer is a public health problem; its incidence is increasing due to the growth and aging of the population, as well as a growing prevalence of established risk factors such as smoking, overweight, physical inactivity, infectious factors, and changes in reproductive patterns associated with urbanization and economic development [1, 2]. Gastric cancer is the fifth most frequently diagnosed cancer and the third leading cause of oncological death worldwide [3, 4]. The incidence of gastric cancer varies across different geographic regions, with rates highest in East Asia, Eastern Europe, and South America and lowest in North America and parts of Africa [2].

Approximately 85% of malignant neoplasms of the stomach correspond to adenocarcinomas, while 15% correspond to lymphomas, stromal tumors, and leiomyosarcomas [5]. Within the molecular study of gastric cancer, it has been determined that the expression of the HER2 molecule is a prognostic and therapeutic biomarker [6-8]. However, the studies are inconclusive since a group of studies reported that the HER2 molecule is not associated with prognosis, while two studies retrospectively reported a significant positive association. Another biomarker is PD-L1 (Program Dead – Ligand 1); its initials are given by Ligand 1 of programmed death, also known as CD 274, whose primary function is to reduce the proliferation of CD8 lymphocytes, which would have a fundamental role in the pathophysiological development of some malignant neoplasms [9].

Tumor lymphocyte infiltration (TIL) assessment is growing in importance as evidence. It has prognostic and potentially predictive value for TILs in many different types of tumors, and immunotherapy shows exciting results in trials and clinical practice.

For some solid tumors, quantification of lymphocyte infiltration would appear to have prognostic significance, suggesting that lymphocyte infiltration is not passive but may actively promote or inhibit tumor growth [10]. For example, the meta-analysis by Yu X. et al. showed a significant correlation between TIL and clinical features in patients with breast cancer. The higher the TIL value, the more it predicts a response to neoadjuvant chemotherapy, and a reply implies a better prognosis [11]. Knowing the forecast of a cancer patient is of the utmost importance. This study aims to determine whether the percentage of tumor lymphocyte infiltration and the presence of tumor human epidermal receptor 2 (HER 2) affect the survival of patients with gastric cancer.

Materials and methods

Study design

The present study is a retrospective observational, longitudinal cohort study.

Study area

The study was carried out in the statistics and pathology services of the Solón Espinosa Ayala Solca Oncology Hospital-Núcleo de Quito. The study period was divided into two times: the first time included patients from Jan 1, 2013, to Jan 31, 2016, and the follow-up time ended on Dec 31, 2018.

Universe and sample

The population was made up of all the patients registered in the institution. The sample size calculation was nonprobabilistic, census type, in which all incident cases in the study period that met the admission criteria were included.

Participants

Cases of patients older than 18 years diagnosed with gastric cancer with clinical stages IB to IIIC had a histopathological sample of gastrectomies. This study included a percentage of tumoral lymphocytic infiltration. Additionally, renal and hepatic function conservation criteria and a good reserve of bone marrow were established. Pregnant women with gastric cancer, two synchronous tumors, autoimmune diseases, corticosteroid use for more than six months, and palliative care were excluded.

Variables

The variables were age, sex, and histological type of cancer. The "percentage of infiltration" variable was used as a dependent variable for the analysis; the sample was divided into three groups: G1 mild tumoral lymphocytic infiltration, G2 moderate lymphocytic tumoral infiltration, and G3 intense tumoral lymphocytic infiltration, using the percentage of tissue infiltration less than 20%, between 21 to 50% and >50%, respectively.

Procedures, techniques, and instruments

The data were compiled from the institutional medical and computer system in a form designed exclusively. Immunohistochemical techniques determined the HER 2 glycoprotein.

Bias avoidance

The researchers were trained in data collection in this study; they used a double control list to include the cases, the internal registry of the pathology service, the oncology statistics area, and their collation in the institutional electronic clinical file. The data were validated and curated by the principal investigator.

Statistical analysis

The results of the categorical variables are presented as percentages, in the continuous variables as the mean and standard deviation if they follow a normal distribution and median (range) according to distribution asymmetry. Categorical variables were analyzed with Fisher's F test, and patient survival was analyzed according to the percentage of lymphocytic infiltration. Survival estimates were calculated using the Kaplan–Meier method and compared groups with the log-rank test. A value of $p < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS version 19.0 (SPSS, Chicago, IL, USA) and STATA 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

Results

During the study period, 375 cases were identified, of which 202 cases were excluded for not meeting the inclusion criteria, with 173 patients diagnosed with gastric cancer with clinical stages IB to IIIC analyzed (Figure 1). Sixty percent of the cases correspond to men, and 40% correspond to women. The average age for the entire population was 61 ± 15 years. According to the percentage of lymphocyte infiltration, 52% of the cases reported mild infiltration, 21% moderate infiltration, and 27% moderate infiltration. In table 1, the characteristics of the pa- tients are described according to the percentage of lymphocytic infiltration.

Regarding the location of the tumor, in 38.7% of the cases, the location of the cancer was not specified; 16.2% were located in the pyloric antrum, 15.6% in contiguous areas of the stomach, 11% in the cardia, 5.2% in the body of the stomach and the lesser curvature of the stomach, 4.6% in the pylorus, 2.9% in the greater curvature of the stomach and 0.6% in the fundus of the stomach. In table 2, the tumor's location according to the percentage of lymphocytic infiltration is described.

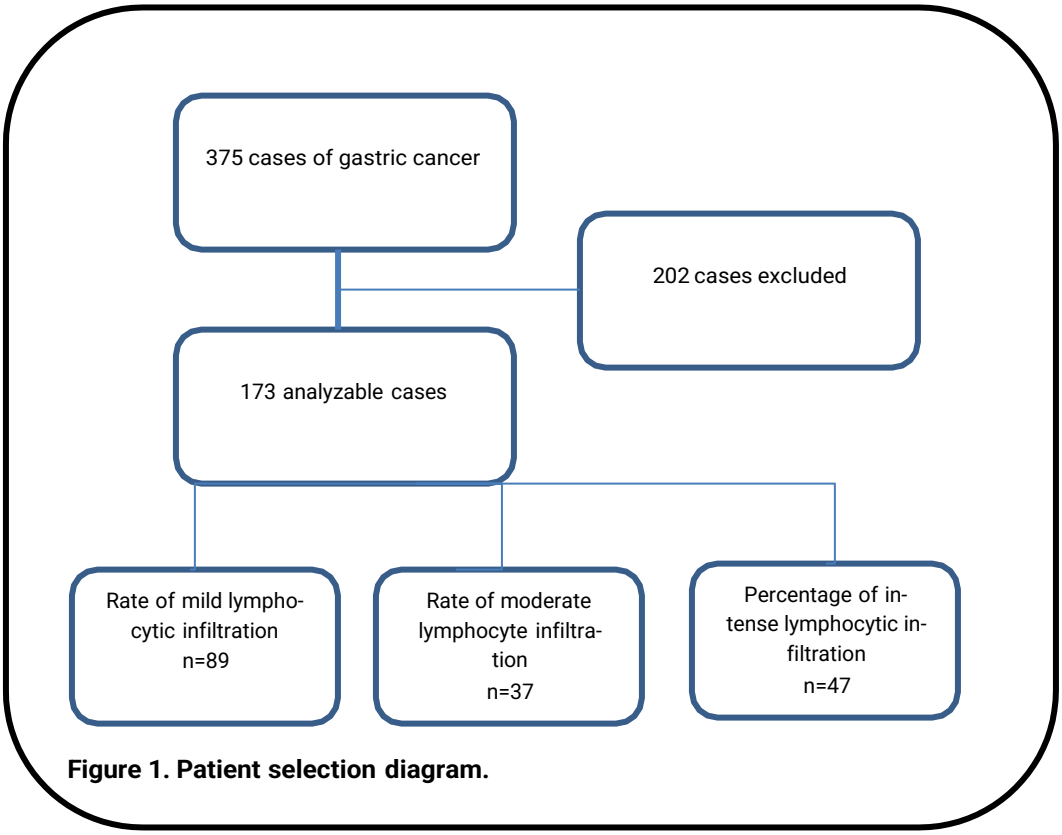

Figure 1. Patient selection diagram.

Table 1. Characteristics of the patients according to the percentage of lymphocytic infiltration

Variable	No. Cases	Mild infiltration group n (%) n= 89	Moderate infiltration group n (%) n= 37	Group with intense infiltration n (%) n= 47
Sex	Man	52 (58.4%)	23 (62.2%)	29 (61.7%)
	Woman	37 (41.6%)	14 (37.8%)	18 (38.3%)
Age (years ±SD)		61±14	57 ±17	62**±15**
Carcinoma, NOS	3	3 (3.4%)	0 (0%)	0 (0)
ADCA, UPS	62	31 (34.8%)	13 (35.1%)	18 (38.3%)
intestinal-type ADCA	5	0 (0%)	3 (8.1%)	2 (4.3%)
Diffuse type carcinoma	two	1 (1.1%)	0 (0%)	1 (2.1%)
tubular ADCA	52	25 (28.1%)	13 (35.1%)	14 (29.8%)
ADCA Papillotubular	4	1 (1.1%)	1 (2.7%)	2 (4.3%)
mucinous ADCA	1	1 (1.1%)	0 (0%)	0 (0)
CCAS	44	27 (30.3%)	7 (18.9%)	10 (21.3%)

SD: Standard deviation. ADCA: Adenocarcinoma. CCAS: signet ring cell carcinoma.

According to the clinical stage, of the 173 patients, 26.3% reported stage EIIIC, 2.2% stage EIIIB, 15.6% stage EIIB, 13.9% stage EIIIA, 11.2% stage EIB, and 9.8% stage EIIA. When review- ing the patients with mild lymphocytic infiltration, the distribution of locations IIIC and IIIB ac- counted for 55% of the cases (Figure 2). In patients with moderate lymphocytic infiltration, 51% of cases were concentrated in stages EIIIC and EIIIA (Figure 3). In patients with intense lymphocytic infiltration, 21% of cases were reported to be in stage EIIIC (Figure 4).

Table 2. Characteristics of the patients according to the percentage of lymphocytic infiltration.

tumor location	Total	Mild infiltration group n (%) n= 89	Moderate infiltration group n (%) n= 37	The group with intense infiltration n (%) n= 47
SL of cardia	19	6 (6.7%)	11 (29.7%)	2 (4.3%)
SL of fundus of stomach	1	1 (1.1%)	0 (0%)	0 (0%)
SL of the body of the stomach	9	5 (5.6%)	3 (8.1%)	1 (2.1%)
NM of the pyloric antrum	28	11 (12.4%)	10 (27.0%)	7 (14.9%)
NM of pylorus	8	4 (4.5%)	2 (5.4%)	2 (4.3%)
NM of the lesser curvature of the stomach, unspecified	9	5 (5.6%)	2 (5.4)	2 (4.3%)
NM of the greater curvature of the stomach, unspecified	5	1 (1.1%)	0 (0%)	4 (8.5%)
NM of contiguous locations of the stomach	27	16 (18%)	1 (2.7%)	10 (21.3%)
NM of the stomach, unspecified	67	40 (44.9%)	8 (21.6%)	19 (40.4%)

NM: malignant neoplasm

Of the 173 patients included in the study, 54 patients were determined to be positive for the HER2 molecule using immunohistochemical techniques, of which 45 were negative, seven were positive, and two reported an indeterminate result. Regarding the percentage of lymphocytic infiltration and HER2 positivity, five cases were positive in patients with mild lymphocytic infiltration, and one case was positive in patients with moderate and intense lymphocytic infiltration. No statistically significant differences were found between the groups, with $P = 0.58$ (Table 3).

Figure 2. Distribution of clinical-stage in patients with percentage of mild lymphocytic infiltration.

Table 3. Percentage of infiltration according to the HER 2 result

Total samples analyzed from patients with HER 2 gastric cancer n=54	HER2 (+) n=7	HER2 (Undetermined) n=2	HER2 (–) n=45
Mild lymphocytic infiltration	5	0	twenty
Moderate lymphocytic infiltration	1	0	13
Intense lymphocytic infiltration	1	two	12

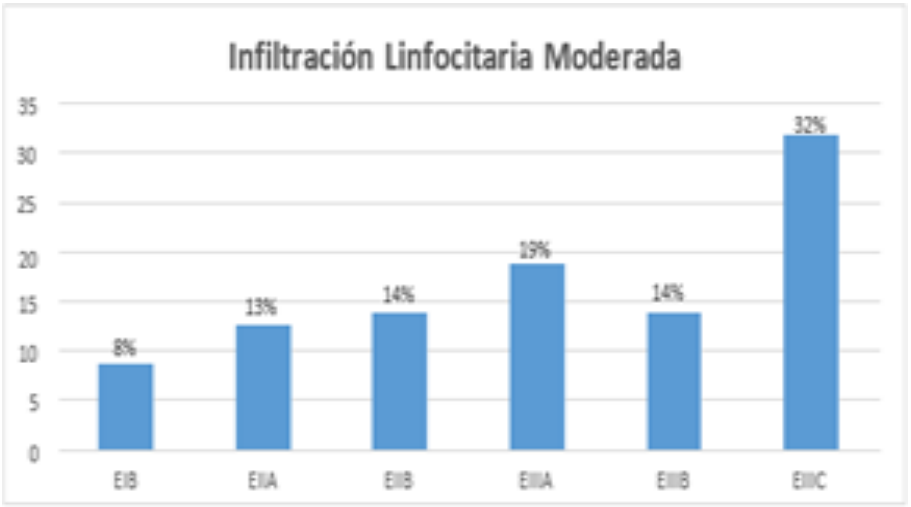

Figure 3. Distribution of the clinical stage in patients with a percentage of moderate lymphocytic infil-tration.

At 72 months of follow-up, survival in the mild lymphocytic infiltration group was 31% (95% CI: 21-41), in the moderate lymphocytic infiltration group was 48% (95% CI: 30-64), and in the Intense lymphocytic infiltration group was 77% (95% CI: 60 – 87) (Figure 5). The difference between the survival of the three groups at 72 months was statistically significant (P=0.001). An interim analysis was carried out at 36 months, where survival was analyzed for patients with mild, moderate, and intense lymphocytic infiltration, 56%, 63%, and 88%, respectively; in addition, we evaluated the average survival for the group. Reaching a mean survival of 42 months for G1 was 45 months for G2 and G3; survival was not born in this cutoff.

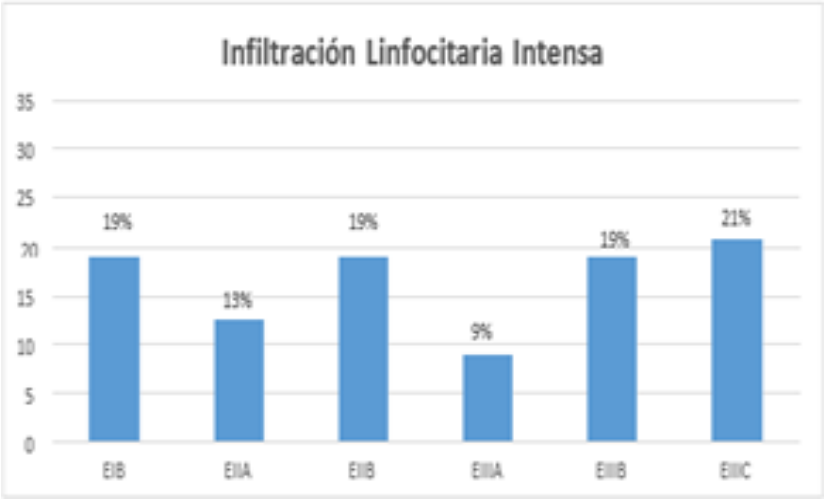

Figure 4. Distribution of the clinical stage in patients with a percentage of Intense lymphocytic infiltration.

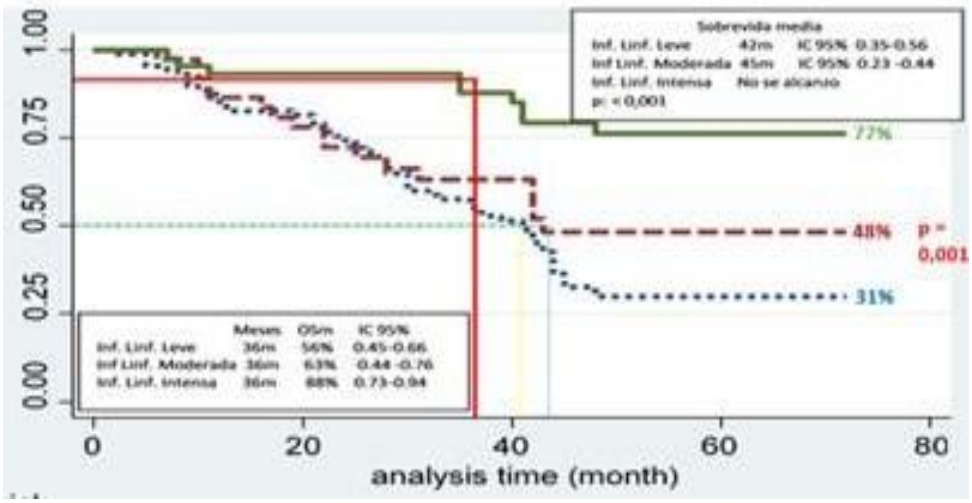

Figure 5. Overall survival according to the percentage of lymphocyte infiltration

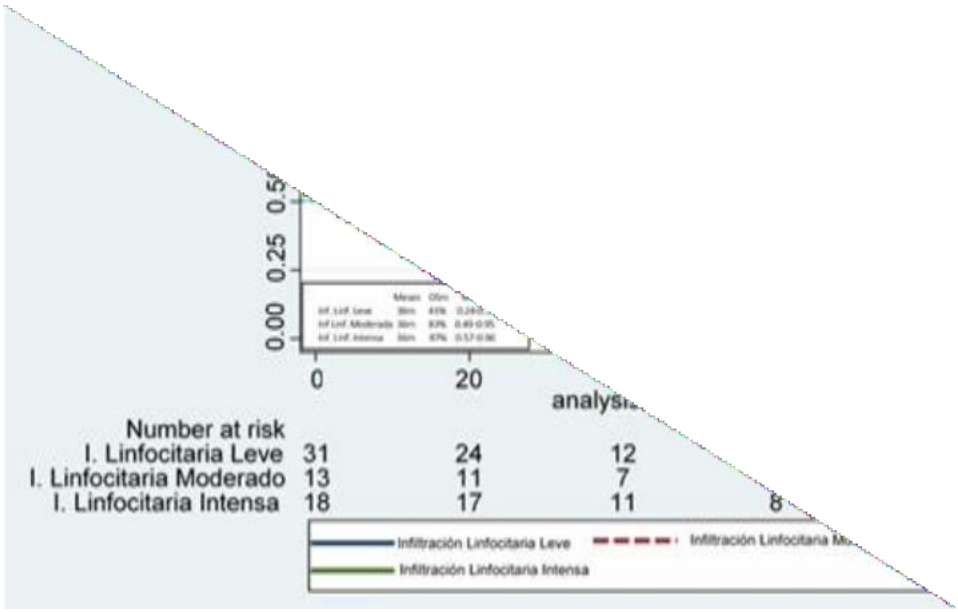

Figure 6. Overall survival in patients with adenocarcinoma, SAI according to the percentage of lym-

Survival analysis according to histological subtype

Adenocarcinoma

Survival in the mild lymphocytic infiltration group was 24% CI 95% in the tubular group with no other indication (SAI). At 72 months of follow-up, moderate lymphocytic infiltration was 72% (95% CI: 34% - 90%), and in the intense lymphocytic infiltration group, it was 71% (95% CI: 40%
- 88%). The difference between the survival of the three groups at 72 months was statistically significant (*P*= 0.001) (Figure 6).

Signet ring cell carcinoma

At 72 months of follow-up, survival in the mild lymphocytic infiltration group was 35% (95% CI: 17% - 53%), in the moderate lymphocytic infiltration group it was 21% (95% CI: 1% - 58%), and in the intense lymphocytic infiltration group it was 69% (95% CI: 30% - 88%). The difference between the survival of the three groups at 72 months was not statistically significant (*P* = 0.11) (Figure 7).

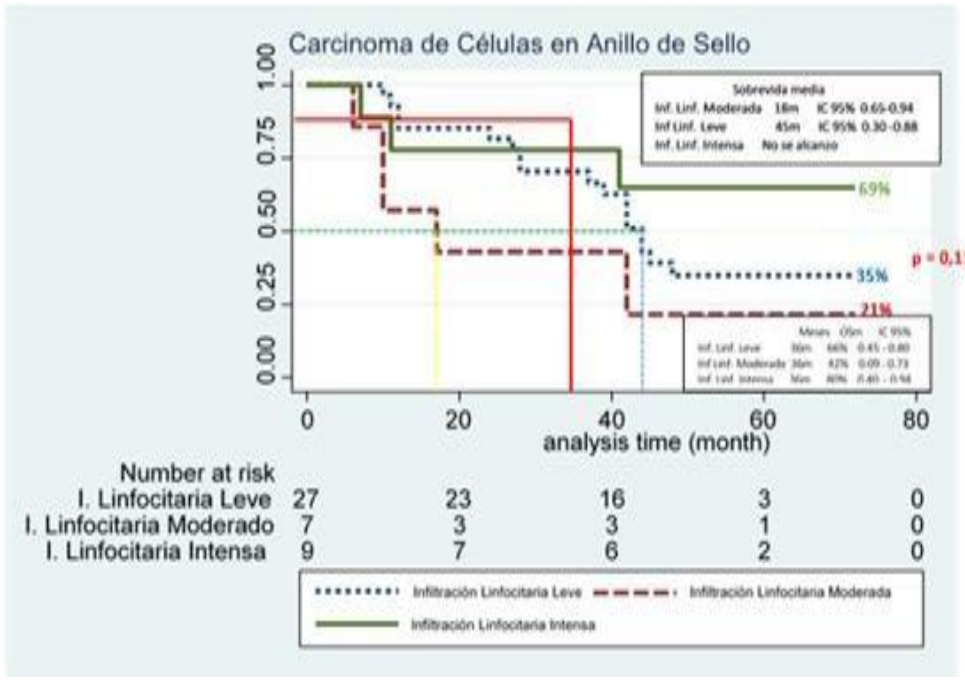

Figure 7. Survival in patients diagnosed with ring cell carcinoma seal according to the percentage of lymphocytic infiltration.

Discussion

Tumor-infiltrating lymphocytes are one of the factors that determine prognosis and therapeutic behavior in cervical and breast cancer, and gastric cancer is currently considered [10-12]. There is consistent evidence linking tumor lymphocyte infiltration with tumor HER 2 overexpression, Epstein Barr virus infection, microsatellite instability, and high PD-L1 expression [13-16] in gastric cancer. Due to technical difficulties, this study is limited by not presenting data on Epstein Barr virus infection, microsatellite instability, and PD-L1 presentation.

Based on the initial studies in 1996 by Setälä, who demonstrated in a retrospective analysis of 321 cases of gastric cancer patients who intense lymphocytic infiltration was a significant prognostic factor with a higher 5-year survival rate (P=0.05), the present study reports mild tumor lymphocytic infiltration in 161 patients, moderate tumor infiltration in 78 cases, and intense lymphocytic infiltration in 19 cases [17].

There is controversy in the intense lymphocyte infiltration group, with a significant difference between the two remaining groups (P = 0.001), which would favor the reports made in 1996 by Setälä.

Another highly studied biomarker in gastric cancer is the HER2 tumor marker since a specific biological drug, trastuzumab, is currently available. In a previous study on the topic of tumor-infiltrating lymphocytes and gastric cancer, as in a meta-analysis [14] in which 15 studies were included, 11 of them indicated an association of risk with worse survival prognosis;

however, the heterogeneity of these studies with different reports of survival from 12 to 79% does not allow objective conclusions. In this study, survival was 77% at 72 months of follow-up. It identified patients with gastric cancer with HER2 expression and treated them with trastuzumab, reporting better overall and progression-free survival [18, 19]. The present study determined the HER2 glycoprotein in 54 patients, corresponding to 31% of the cases. The vast majority of cases were negative 45/54 (83.3%), seven cases were positive, and two cases were reported as indeterminate. The positive cases were not statistically associated with any group of lymphocytic infiltration. They showed five positive cases in patients with mild lymphocytic infiltration and one case in patients with moderate and intense lymphocytic infiltration without a significant difference between groups (*P*= 0.58). The inconclusive results are due to the low number of patients who underwent HER 2, and new prospective studies should evaluate this association.

A descriptive analysis was carried out on the distribution of clinical stages and their relationship with the degree of lymphocytic infiltration, observing that gastric cancer, as in most other cancers, 49.5% of these were diagnosed in clinical stage III. Regarding lymphocytic infiltration, we found that in patients with mild lymphocytic infiltration, the distribution of stages IIIC and IIIB corresponded to 55% of the cases; in patients with moderate lymphocytic infiltration, 51% compared to stages EIIIC and EIIIA. In patients with intense lymphocytic infiltration, 21% were reported to have stage EIIIC disease.

The results presented seem to indicate that the higher the lymphocytic infiltration, the earlier the clinical stages at the time of diagnosis. However, this variable is subject to many biases, such as cultural level and accessibility to the health system; additionally, we cannot contrast it with other studies due to the lack of scientific evidence to support this relationship pattern.

We correlated the histological subtype and the lymphocytic infiltration and survival variables. Some studies demonstrate this, as described by Chang MS et al. [20].

The data obtained at 72 months of follow-up found that the survival of SAI adenocarcinomas with intense lymphocytic tumor infiltration was 71%, and for the moderate tumor infiltration group, it was 72%. For the mild lymphocytic infiltration group, it was 24%. %, with a statistically significant difference.

In tubular histology related to lymphocytic infiltration, a 72-month survival rate of 90% was observed, compared to 29% and 50% for the mild and moderate lymphocytic infiltration groups, respectively (*P*= 0.02).

In the analysis of the histological subtype of signet ring cells at 72 months of follow-up, the survival of the mild lymphocytic tumor infiltration group was 35%; in the moderate lymphocytic tumor infiltration group, it was 21%; and in the intense lymphocytic tumor infiltration group, it was 69%.

There is limited information on this association; a review by Jin S. et al. with 89 cases with this histological type and TILs was analyzed, which showed that the median overall survival was 23.7 months for those with intense lymphocytic infiltration compared to 15.8 months for those with low TILs. (*P*= 0.033) [21]. Emphasizing that the histological subtype of signet ring cells is not an independent factor of poor prognosis. Our finding was that intense lymphocytic infiltration favors prognosis, and the analysis of other variables, such as age, is pending. Diagnosis, ethnicity, tumor stage, and degree of tumor differentiation intervene in the survival of these patients, as found in the study by Taghavi S et al. [22].

Although this relationship association in the study investigated does not present statistical significance, the trend is that patients with signet ring cell histology added to intense lymphocytic infiltration have better survival than patients with low lymphocytic infiltration. Lympho- cyte infiltration has become a clinical-pathological parameter determining therapeutic behav- ior and projecting the trend in cancer patient survival. Choosing HER 2 in patients with locally advanced gastric cancer is not yet a norm; future studies should consider it a prognostic factor for survival and a prospective study.

Conclusions

The study showed that histopathological samples from patients with gastric cancer and the expression of intense lymphocytic infiltration were associated with more remarkable survival. The correlation between tumor histology and lymphocytic infiltration is fundamental since it allowed us to determine that in patients with SAI adenocarcinoma and tubular adenocarcinoma who presented intense lymphocytic infiltration, survival at 72 months reached 70%; in contrast, mild lymphocytic infiltration at the same time of follow-up, survival exceeded 30%. Regarding the signet ring cell subtype, the results obtained concerning survival were not statistically significant.

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Abbreviations

HER 2: Human epidermal growth factor receptor 2.

Administrative information

Additional Files

The authors declare none.

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Author contributions

José Castillo: conceptualization, validation, visualization, methodology, project management, writing: review and ed-iting.

Henry Caballero: conceptualization, data curation, formal analysis, fundraising, research, resources, software, writing - original draft.

Verónica Tapia: conceptualization, data curation, formal analysis, fundraising, research, resources, software.

All authors read and approved the final version of the manuscript.

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Availability of data and materials

Data availability is available upon request to the corresponding author. In this study, the authors reported no other materials.

Statements

Ethics committee approval

It does not apply to observational studies with databases or medical records reviews.

Consent to publication

The publication consent does not apply to studies that do not publish explicit images suchas CT scans, MRIs, and physical exam images.

Conflicts of interest

The authors declare that they have no conflict of interest or competence.

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