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PREVALENCE OF HUMAN EPIDERMAL GROWTH FACTOR II IN GASTROESOPHAGEAL AND GASTRIC ADENOCARCINOMA (A Multi-center study)

Ashraf Mounir [(1)],Salsabel Ibrahim [(1)],Reham Hani[(1)],Amro Sakr [(1)]

[(1)] *Departement of Clinical Oncology Cairo University*

Article Info

Corresponding Author:
Ashraf Mounir
achrafmounir@hotmail.com

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Abstract

Metastatic Gastric cancer (GC) is a prevalent disease with a median overall survival (OS) between 32-37 weeks. Targeting human epidermal growth transmembrane factor receptor 2 (HER-2) has a predictive however controversial prognostic impact. This study was conducted to reveal the incidence of HER2 status in Egyptian and Yemeni GC patients. we aimed evaluating the association between different factors and HER2 overexpression. Moreover, the factors affecting (OS) and Progression-free survival (PFS) were assessed in HER2 positive cases. **Methods:** This is a Multi-center retrospective study. Gastric or gastro-esophageal junction carcinoma cases were collected. Epidemiological, clinicopathological and treatment data were analyzed. The HER2 status was assessed. Survival analysis was calculated and the determinants affecting it were analyzed. **Results:** out of 62 patients diagnosed with GC,10 patients had HER-2 +ve disease.50 % had metastatic disease. brain metastasis (3.3%) was presented in HER2-positive cases only, while bone (10%) and peritoneal

metastasis (46.7%) were presented in HER2-negative cases only. The median survival was 25 months.HER-2 -ve and HER-2 +ve subgroups were 25 and 28 months respectively (P=0.68).the median (PFS) for entire group was 12 months and for HER-2 -ve vs HER-2 +ve cases ,it was 9 months in both groups(P=0.73). **conclusion:** the (HER2) rate in our cohort was 16.1% . The current study has highlighted the possible association between HER2-positivity and brain metastasis in gastric cancer patients and could confirm the higher incidence of liver metastasis and absence of peritoneal metastasis in those HER2 positive patients.

1. Background:

Gastric cancer is a prevalent malignancy that exhibits significant fatality rates on a global scale. In 2020,800000 patients died from cancer stomach worldwide. Asia, Eastern Europe, and certain regions of Latin America exhibit the greatest incidence rate. about 75 % of all new cases of cancer stomach are reported in Asia. Also,it has the lowest incidence in Africa reporting 4/100000 population.(1) In Egypt, the prevalence of Gastric cancer (GC) ranks 10th among all types of cancer, accounting for 1.6% of all malignancies in 2015. it accounts for 2.2% of the overall cancer mortality and the 12th highest cancer-related death (2).

The Human epidermal growth transmembrane factor receptor 2 (ErbB-2, c-erbB2 or Her2/neu) is located on chromosome 17. *HER2* amplification and overexpression promote proliferation and tumorigenesis and are involved in pathogenesis of several human cancers (2).

In advanced and metastatic gastric and gastro-esophageal cancers, targeting HER2 overexpression has a predictive however controversial prognostic impact. ToGA trial showed longer survival after adding trastuzumab to the standard treatment in advanced HER2 positive gastric and gastro-esophageal cancer patients (4).

The DESTINY-Gastric-01 study demonstrated a substantial improvement in response rate and overall survival (median OS 12.5 vs. 8.4 months; (P=0.01)) when trastuzumab deruxtecan was added to chemotherapy compared to chemotherapy alone in subsequent treatment regimens (5).

However, the association between the HER2 status and the prognosis of individuals with gastric cancer is still a subject of debate. Several investigations have demonstrated a strong correlation between HER2 positive and a notably worse outcome (6)(7)(7), Conversely, several studies found no association between HER2 status and the prognosis of gastric cancer(9)(10). Furthermore, several trials demonstrated that the median overall survival (OS) was better in individuals who were HER2-positive compared to those who were HER2-negative(11), and some trials did not.

This study was conducted to reveal the incidence rate of HER2 status in Egyptian and Yemeni GC patients, who underwent HER2 status testing. 62 patients were included from Kasr el Eini Oncology Center (26 Egyptians) and Orchid Oncology Center (36 yemeni). Also, we aimed at evaluating the association between different demographic, clinical, pathological, and metastatic factors and HER2 overexpression in patients with gastric cancer. Moreover, the factors affecting OS and Progression-free survival (PFS) were assessed in HER2 positive cases.

2. Methods:

This is a Multi-center retrospective study conducted at Kasr El Eini Oncology center and Orchid Oncology Center in Egypt, after ethical committee approval. Gastric or gastro-esophageal junction carcinoma cases of those older than 18 years, in the period between January 2020 till December 2022, were collected from their electronic medical records. Cases must have undergone HER2 testing to be included in the study. Cases without HER2 status testing were excluded. Epidemiological, clinicopathological and treatment data were collected. The HER2 status was assessed using defined standards and classified as 0, 1+, 2+, or 3+. Values of 0 and 1+ were deemed negative, while a score of 3+ was seen as positive. Upon discovering a result of 2+ on the test, further FISH testing was conducted influencing it were examined.to determine the status of HER2 gene amplification. Survival

analysis was studied and the determinants affecting it were analyzed.

Statistical analysis:

The categorical variables were analyzed using descriptive statistics, which were provided in terms of the number and percentage (N, %). Data that was not available was eliminated from the analysis. The data was stratified using the Fisher exact test to compare proportions. Overall survival was calculated by determining the time from the first diagnosis of the first patient to either the date of death or the most recent recorded date of surviving. Progression-free survival was determined by measuring the period from the initial diagnosis to the first instance of progression, recurrence, or death. The Kaplan-Meier method was utilized to evaluate the median overall survival and progression-free survival rate. Both univariate and multivariate analyses were performed using a Cox proportional hazards model. The data were presented as hazard ratios (HR) with a 95% confidence interval (CI). Two-sided hypothesis tests were conducted with a preset alpha level set at 0.05. The analyses were performed utilizing the R statistical program (Version 4.1.3, R Foundation for Statistical Computing, Vienna, Austria).

3. Results:

During the period from January 2020 till December 2022, a total of two hundred patients with pathology confirmed early or metastatic GC were assessed in the current study. One hundred and thirty eight patients were excluded due to unavailable HER2 assessment and only sixty two patients were included due to available HER-2 test. The study flow chart is summarized in ***Figure 1***

Demographic and clinical characteristics

The majority of our eligible patients were males (67.7%), 35 patients (56.5%) were between 50-70 years. Performance status of these patients were 0 (24.2%), 1 (54.8%), 2 (19.4%), or 3 (1.6%). The majority of patients had lesions at GEJ (33.9%), followed by those at the body (27.4%), then pylorus (22.6%), or whole gastric lesions (16.1%). Most of the patients presented with stage IV representing (50%) and patients with stage III represent (40.3%).

Our results showed that the stage at presentation (localized, locoregional or metastatic) was non-significantly correlated with different sites of the primary lesion (GEJ, body, pylorus, and

whole gastric lesions) (P=0.38). Surgery was performed in 27 (43.5%) patients. The surgical modalities included palliative resection (3.2%), partial gastrectomy (22.6%), or total gastrectomy (17.7%). The intent of treatment was adjuvant (12.9%), palliative (46.8%), or best supportive care (4.8%). About (33.5%) received neoadjuvant treatment.

Pathological characteristics

All patients included were presented with adenocarcinoma. The diffuse and intestinal pathological subtypes represent 48.4% and 43.5% of patients respectively. Poor cell differentiation was detected in 28 patients (45.2%) versus 34 patients (54.8%) had moderate cell differentiation. Signet-ring was detected in 24 patients (38.7%). The pathological subtypes (diffuse, intestinal or mixed) were not-significantly correlated with the different cancer stages (P=0.18). Our results showed that 10 out of all patients (16.1%) were tested HER2 positive (score 3). The incidence of HER2-positive was (15.4%) and (16.7%) in Egyptian and Yemeni patients respectively. ***(table 1)***

Metastatic characteristics

Our data showed that 31/62 (50%) patients initially had metastatic disease. Among them, 10 (16.1%), 14 (22.6%), 2 (3.2%), 3 (4.8%), 3 (4.8%) and 1 (1.6) presented with liver, peritoneum, lung, bone, Krukenberg and brain metastasis respectively.

There was no statistically significant difference between HER-2 +ve and HER-2 -ve patients concerning metastatic sites including peritoneum (P=0.1), lung (P=0.3), bone (P>0.99), brain (P=0.16), and Krukenberg (P>0.99). However, liver metastasis was significantly higher in HER2-positive cases (P = 0.007).

When analyzing the data of all HER2 positive and negative metastatic cases, the site of metastasis was significantly different between the study groups (P=0.002), such that brain metastasis (3.3%) was presented in HER2-positive cases only, while bone (10%) and peritoneal metastasis (46.7%) were presented in HER2-negative cases only.

Comparing baseline clinical and demographic characteristics based on HER2 status

Upon comparing studied groups, age (P=0.480), gender (P>0.99), performance status (P=0.16), site of the primary lesion (P>0.99), and stage of disease at first

presentations (P=0.82) have showed no significant differences between both groups. Also, there were no significant differences when comparing the HER2 positive and negative groups with respect to the pathological subtype of the primary lesion (P=0.06), cell differentiation (P=0.1), and signet ring (P=0.29).

Survival analysis

The median overall survival of our 62 patients was 25 months. ***Figure 2***

The Cox-regression model identified only cancer stage (HR 2.72, 95% CI 1.07, 6.88, P=0.035), and poor cell differentiation (HR 4.8, 95% CI 1.35, 17.00, P=0.015) as significant predictors to overall survival. Other tested covariates demonstrated a non-significant impact on survival, including nationality (P=0.65), age category (P=0.057), gender (P=0.45), performance score (P=0.17), HER2 status (P= 0.17), signet ring (P=0.31), and the incidence of progression and/or recurrence (p=0.52). Median survival for HER2-negative vs. HER2-positive subgroups were 25 vs. 28 months respectively (P=0.68). ***figure 3***

The median progression-free survival for the entire group was 12 months (95% CI 10-20 months). The Cox-regression model identified only performance score (HR 3.06, 95% CI 1.64-5.72, P<0.001) as a significant predictor of 'time to progression/recurrence'. Other tested covariates demonstrated a non-significant impact on progression free survival, including nationality (P=0.13), age category (P=0.58), gender (P=0.94), HER2 status (P= 0.72), cancer stage (P=0.23), cell differentiation (P= 0.43), and signet ring (P=0.24). Median PFS for HER2-negative vs. HER2-positive cases (9 months in both groups; P=0.73). ***Figure 4***

4. Discussion:

Human epidermal growth factor receptor 2 (HER2) is implicated in the pathogenesis of various forms of cancer. Targeting HER2 is important in the treatment of advanced or metastatic gastric and gastroesophageal junction cancers. To date, there is conflicting data about the clinicopathological characteristics and the prognostic features of HER2-positive gastric cancer cases (3).

In our study, the epidemiological and clinical data of our cohort reflected the general features of gastric cancer. The ages of 67.7% of our patients were between (50-70), and 67.7% were males. There were 26 (41.9%) Egyptian patients,

and 36 (58.1%) Yemeni patients. 61 (98.4%) of the patients had performance score of ≤ 2. Gastro-esophageal junction disease is the most frequent site of disease, representing (33.9%) of patients. 31 (50%) patients were stage IV. 30/62 (48.4%) of our patients had diffuse pathological subtype, while (43.5%) had intestinal pathology. This coincides with most of the international and national data. (12)

Furthermore, our results showed that HER2-positive cases were 10 representing (16.1%). This incidence was less than that reported by ToGA study which demonstrated an incidence rate of around 22.1% (13). However, our rate lies in the range of 8.2% to 62.5% as reported by different articles. (14)(14) Moreover, these results were lower than that reported by the Egyptian trial published by Abdel Salam in 2018, where they stated that HER2-positive cases were 54%. This high rate could be attributed to inclusion of all HER2 score 2+ and 3+ cases as positive ones (16).On the contrary, we included only the HER2 +3 and HER2 +2/FISH +ve cases.

Other Egyptian series reported HER2 positivity rate of 14.2% by IHC and this rate was increased up to 27% by adding FISH positive cases. (17) The different ranges of the reported incidence rates could be due to the different examination methods including fixative type, staining method, diagnostic criteria and pathologist's experience level. (18)(19)

Our results showed also that the HER2-positive Egyptian and Yemeni patients were 4 (15.4%) and 6 (16.7%) GC patients respectively, with no statistically significant differences between Egyptian and Yemeni patients (P>0.99). This is consistent with the analysis provided by Cutsem et al., reporting no significant differences between Europe, Asia, and Central/South America. (13)

Our current study concluded that there were no statistically significant differences between HER2-positive and HER2-negative patients regarding the clinical and demographic characteristics including age, gender, performance score, site of the primary lesion, and stage of disease. This was coinciding with Roy et al., Nadaf et al. and Alvarado-Cabrero et al. studies which showed no significant correlation between HER2 status, age, gender, or pathological subtype. (20)(21)(22)

However, Bermúdez et al. study showed male: female is almost 2:1 in HER2-

positive cases, which was significantly different. (23) Dai et al. also showed a significant difference regarding gender toward male predominance. (24) Our results showed a non-statistically significant, however, numerically higher percentage of male are HER2 positive (70%). This could be attributed to the small sample size in addition to the presence of other factors that might be involved.

In this study, despite being non-significantly different, HER2-positive cases demonstrated higher prevalence of intestinal vs. diffuse pathologies (80% vs. 20%), moderate cell differentiation vs. poor cell differentiation (80% vs. 20%), higher prevalence of GEJ tumors (40%) compared to the gastric body (30%), pylorus (20%), or whole gastric tumors (10%) and more advanced stages (III-IV) vs. early stages (I-II) (90% vs 10%).

This agrees with many previous studies that found a significant HER-2/neu overexpression in GEJ tumors versus gastric (25)(13). Also, intestinal subtype was reported to be significantly higher than diffuse type, and well differentiated vs poorly differentiated subtype. (26)(27)(28)(29) These heterogeneous data could be mainly due to heterogeneous group of patients included in the study regarding their epidemiological and clinicopathological data, and inclusion of all stages of the disease. Also, the small number of our patients could lead to these discrepancies.

Metastasis pattern

Our results showed that the occurrence of liver metastasis was much greater in those with HER2-positive status compared to those with HER2-negative status (50% vs. 9.6%, p=0.007). It was evident also that Brain metastasis was presented only in HER2-positive cases, while peritoneum and bone metastasis were only presented in HER2-negative cases.

In concordance with our results, Matsusaka et al study demonstrated the absence of peritoneal metastasis OR=0.58 (CI 0.39-0.86 P=0.007), and the presence of hepatic metastasis OR=1.61 (CI 1.05-2.48, P=0.029) are significant independent factors in HER2 positive cases (30). Similarly, Janjigian et al. found significantly higher rates of HER2 positivity in patients with liver metastasis (HER2 positivity among liver metastasis cases 31%; vs no liver metastasis 11%; P = 0.025) (10).

Our study suggests that there might be a correlation between HER2 status and brain metastasis which was only present in a HER2-positive patient. This coincides with Cavanna et al who found that the incidence of CNS involvement in Gastric cancer is low around 1%, however, there was a higher frequency of HER2 overexpression in these patients. (31) Similarly, Feilchenfeldt et al included a larger population (100 patients) with gastric/GEJ carcinomas with CNS involvement, concluded that there were a higher proportion of HER2-positive patients than expected (32).

Effect on survival

Our data from the current study indicated that the OS of GC patients is 25 months. No significant differences were found in OS between HER2-positive and HER2-negative (28 months vs. 25 months, P=0.68). The median progression-free survival for the entire group was estimated at 12 months (95% CI 10-20 months). Non-significant differences between HER2-positive and HER2-negative patients were found in terms of progression-free survival (9 months for both groups, P=0.73). This was in agreement with Janjigian et al., Terashima et al, Sung Son et al., who found no significant impact of HER2 overexpression on OS and PFS in gastric cancer patients (33)(34)(10)

On the contrary, in a large multicenter study including 1148 patients diagnosed with gastric cancer and underwent gastrectomy, the multivariate analysis Kurokawa et al. demonstrated that HER2 overexpression was an independent poor prognostic factor (Hazard Ratio 1.96, 95 % CI 1.51-2.55) (27). Moreover, Lei et al conducted a meta-analysis including 41 trials, concluded that HER2 overexpression was associated with poor overall survival compared to HER2 negative patients (12). Wang et al. conducted a meta-analysis involving 6344 gastric cancer patients, of which 1148 were HER2 positive. The study revealed that patients with HER2-positive status had a considerably poorer 5-year survival rate compared to HER2-negative patients (OR 0.58, 95% CI 0.37-0.91, P = 0.02). (35)

However**,** Baykara et al proposed another concept of a differential effect of HER2 overexpression, they found that median OS was significantly shorter among HER2-positive patients versus HER2-negative patients in the early stages of disease. While the median OS was similar

in patients in both HER2-positive and HER2-negative disease with advanced stages (stages III and IV) (16.2 months for Her2-positive versus 13.7 months in Her2-negaive, p 0.72) .This could explain the non-significant differences in survivals of our patients, since 88.7% of our patients were staged at stage III or IV.

5. Conclusion and limitations:

The current study has highlighted the possible association between HER2-positivity and brain metastasis in gastric cancer patients and also confirmed the higher incidence of liver metastasis and absence of peritoneal metastasis in those HER2 positive patients. However, the major limitation of our study is the small sample size of patients. This could be attributed to the relatively low incidence of gastric cancer cases and to the financial cost of HER2 testing, which is not a part of the routine care provided to the GC patients in our centers.

List of abbreviations

Gastric cancer :GC

Human epidermal growth factor receptor 2 : HER-2

Gastroesophageal junction: GE junction

Overall survival: OAS

Progression free survival: PFS

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Figure 1: flow study chart

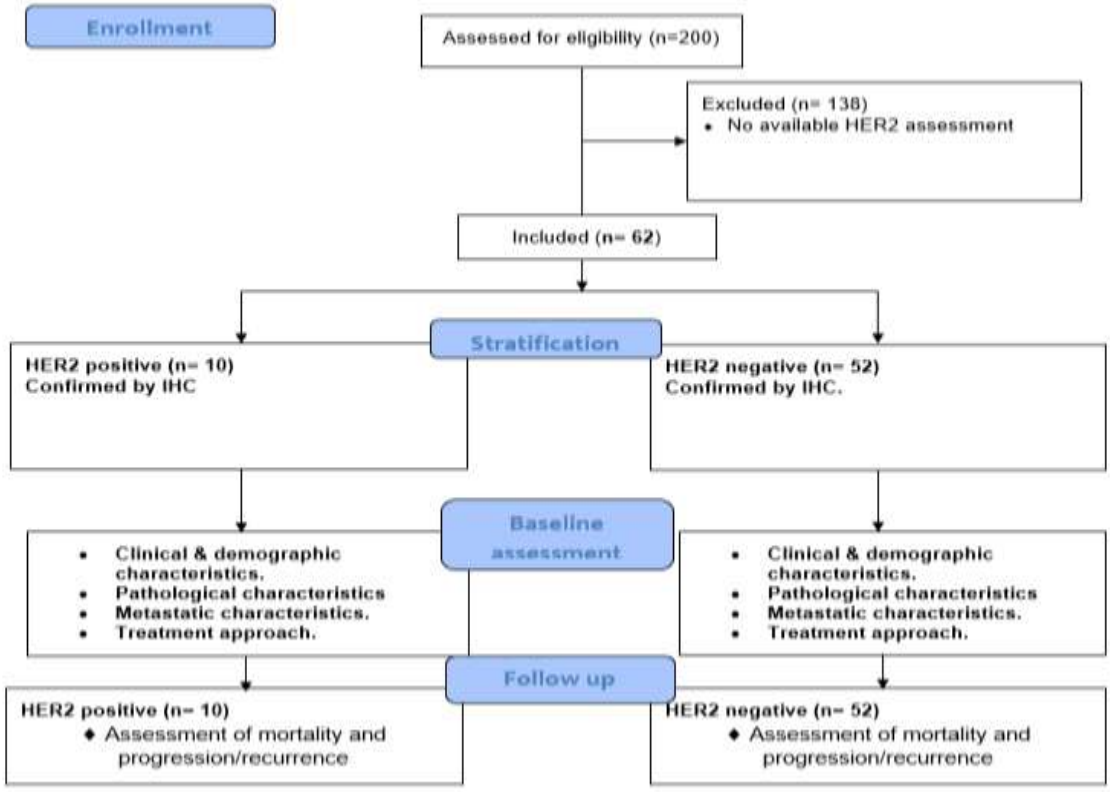

Figure 2: Kaplan Meier curve representing OAS of the study population

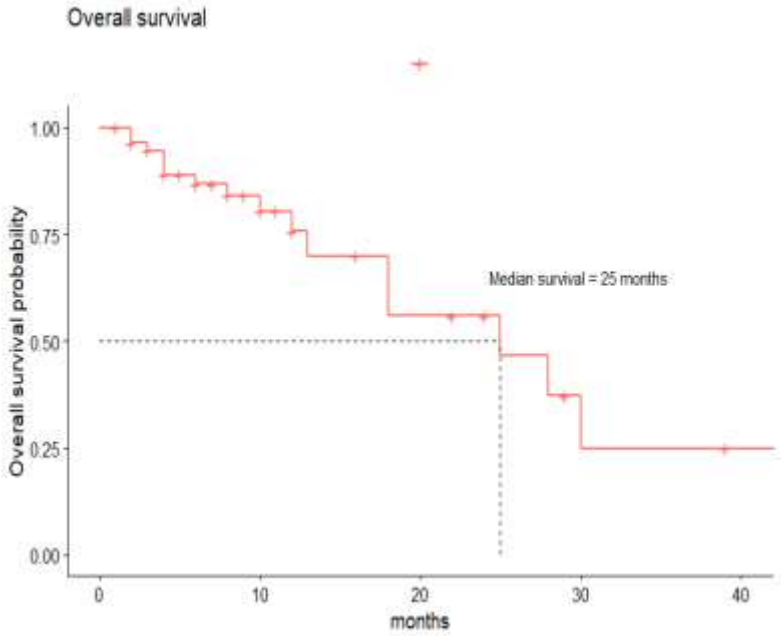

figure 3: Chart representing survival in HER-2 -ve and +ve disease

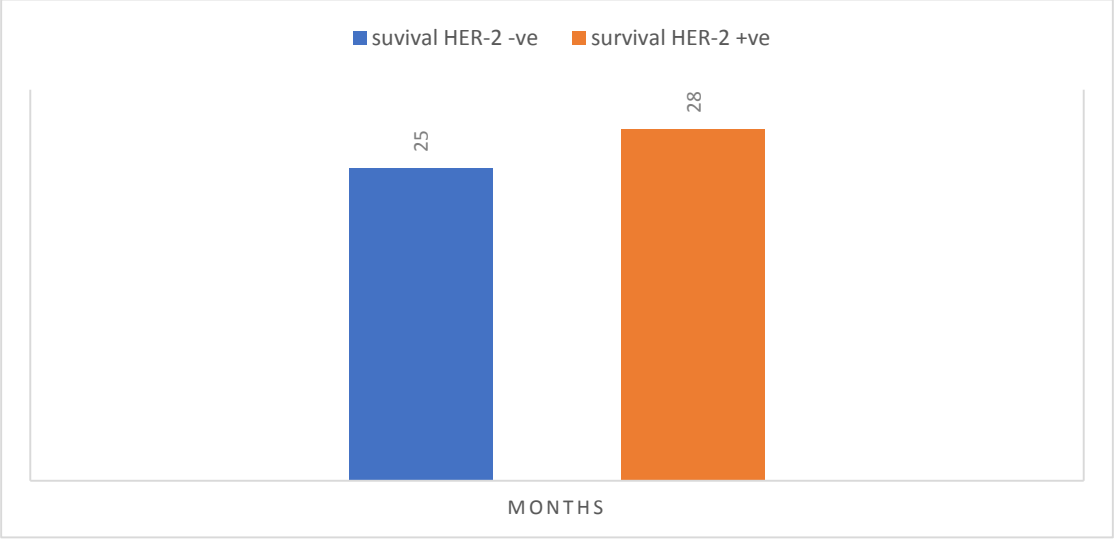

Figure 4 : Kaplan Meier curve representing PFS of the study population

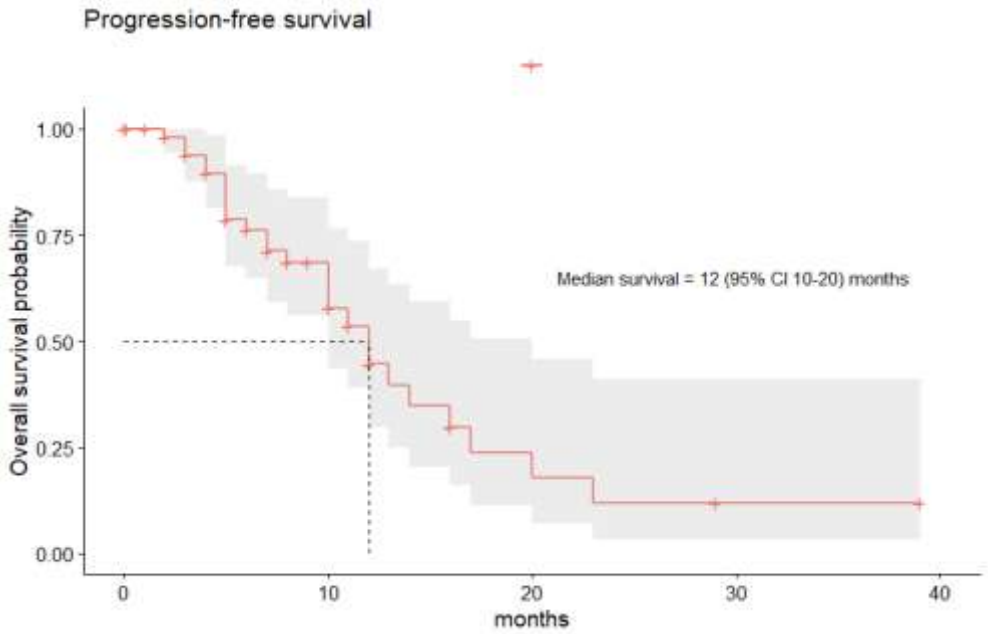

Table 1: Clinical and demographic attributes of the study cohort (N=62)

Characteristic	N = 62[1]
Age (years)	
<35	7 (11.3)
35-49	10 (16.1)
50-70	35 (56.5)
>70	10 (16.1)
Gender	
Female	20 (32.3)
Male	42 (67.7)
Nationality	
Egyptian	26 (41.9)
Yemeni	36 (58.1)
Performance Score	
0	15 (24.2)
1	34 (54.8)
2	12 (19.4)
3	1 (1.6)
HER2 Status	
Negative	52 (83.9)
Positive	10 (16.1)
Adenocarcinoma Pathology	62 (100.0)
Pathological Subtype	
Diffuse	30 (48.4)
Intestinal	27 (43.5)
Non-specified	5 (8.1)
Cell differentiation	
Moderate	34 (54.8)
Poor	28 (45.2)
Signet ring	24 (38.7)
Staging	
1	1 (1.6)
2	6 (9.7)
3	24 (38.7)
4	31 (50)