

Online ISSN: 2682-2628  
Print ISSN: 2682-261X

# IJC CBR

## INTERNATIONAL JOURNAL OF CANCER AND BIOMEDICAL RESEARCH

<https://jcbr.journals.ekb.eg>

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Prof. Mohamed Labib Salem, PhD

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## **Welcome letter from Editor-in-Chief**



Welcome to the Int J Cancer and Biomedical Research (IJCBR)!

It is with great pleasure that I write this editorial to welcome you to the IJCBR. This journal provides a platform for publication of original and reviews research articles, short communications, letter to editor, thesis abstract, conference report, and case studies. These types of publication are directed at the interface of the fields of cancer and biomedical research.

The IJCBR relies on a distinguished expert of the Advisory and Editorial Board Members from the top international league covering in depth the related topics. They timely review all manuscripts and maintain highest standards of quality and scientific methodology and ethical concepts. Meanwhile, we take all possible means to keep the time of the publication process as short as possible.

I take this chance to welcome your contributions to the IJCBR and have every expectation that it will soon become one of the most respected journals in both the fields of cancer and biomedical research.

A handwritten signature in blue ink that reads "Mohamed L. Salem". The signature is fluid and cursive.

**Mohamed L. Salem,**

Editor in Chief

## Early onset gastric cancer in Egyptian patients: Is it really a different clinical entity?

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### ABSTRACT

**Background:** Little is known about characteristics of young patients with gastric carcinoma (GC) in Egypt. **Aim:** The purpose of this study was to define the clinicopathological features and survival of young GC patients in our population. **Patients and Methods:** We retrospectively analyzed data of 197 GC patients who were treated at our institution from 2011 to 2016. The clinicopathological characteristics and survival were compared between 61 young ( $\leq 45$  years) and 136 older ( $> 45$  years) GC patients. We also studied variables impacting survival of younger patients. **Results:** The proportion of females, positive family history, and poorly differentiated tumors were significantly higher in young patients. Younger group showed significantly longer interval between symptoms and diagnosis (all  $P < 0.05$ ). The mean overall survival (OS) of young patients was lower compared to older patients (10.7 vs. 18.7 months, respectively;  $P=0.06$ ). Multivariate analyses revealed that distant metastasis and CA19-9 were independent factors for reduced survival in younger patients. **Conclusion:** We conclude that clinicopathological characteristics of GC are different between young and old patients. Aggressive tumor biology and a significant diagnostic delay may have contributed to worse survival in younger patients.

**Keywords:** Gastric carcinoma; young age; clinicopathological features; prognosis

Editor-in-Chief: Prof. M.L. Salem, PhD - Article DOI: 10.21608/jcbr.2020.48678.1089

### ARTICLE INFO



#### Article history

Received: November 3, 2020

Revised: December 20, 2020

Accepted: December 26, 2020

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## INTRODUCTION

Gastric carcinoma (GC) represents the fifth most common and the third most deadly malignancy worldwide based on data from GLOBOCAN 2018 [Bray et al., 2018]. Classically, GC is considered a disease of elderly with the mean age at diagnosis ranging from 50 to 60 years [Piazuelo and Correa, 2013]. Although younger people are less affected by GC, it has been recognized that the incidence rate of GC in young patients shows an increasing trend over the past few decades [Kuller, 1999; Anderson et al., 2010; Al-Refaie et al., 2011]. Studies have reported the percentage of patients with GC under 40 years of age ranging from 2% to 16% [Wang et al., 2014].

The data on whether clinicopathological features and prognosis of GC in young patients differ from that in older population have been

controversial. Some reports have suggested that young patients have adverse features and worse prognosis compared with older subjects, while other studies reported equivalent or even better prognosis among GC patients of young age [Santoro et al., 2007; Saito et al., 2012; Hsieh et al., 2012; Takatsu et al., 2015]. These conflicting results reflect the fact that clinical characteristics of younger group were analyzed on the basis of a heterogeneous population of patients with respect to races and different definitions of young age across studies [Kunisaki et al., 2006; Kong et al., 2012; Isobe et al., 2013]. Another issue is the variation in access to care between different countries that may have a significant impact on survival. Because of the lack of data on the characteristics of young GC patients in our geographical area, we performed a retrospective cohort study to assess the clinicopathological features and

survival of GC patients aged 45 years old or younger compared with the more typical GC population of patients > 45 years old.

## PATIENTS AND METHODS

This is a retrospective observational study of all patients diagnosed with GC and treated at Department of Medical Oncology, Mansoura University, Egypt from 2011 to 2016. In this study, the data of one hundred and ninety-seven GC patients were collected and examined. Of these, 61 patients aged 45 years old or younger were classified as the young group and 136 patients aged over 45 years old were classified as the old group. The reason behind this grouping was to maintain consistency with prior studies, including largest population-based study, that have categorized younger gastric cancer patients as those below cut off age of 40 to 50 years [Al-Refaie et al., 2011; Hsieh et al., 2012; Dai et al., 2017].

Clinical and pathological characteristics including gender, family history, presenting symptoms, tumor shape, tumor size, tumor location, histological type, histological grade, depth of invasion, nodal involvement, extent of cancer spread, and tumor markers were compared between both groups. Data on therapies applied in metastatic cases were also obtained. Metastatic cases were followed for response to therapy by CT scans every 3 months using RECIST 1.1 criteria. Clinicopathological data and follow-up data were retrieved from the patients' electronic records. Survival was measured in months from date of diagnosis of GC to date of death. For alive patients, overall survival was censored on December 31, 2019. This study was approved by the Ethical Committee of Mansoura University, Mansoura, Egypt (IRB code number: MS/17.12.90).

### Statistical Analysis

Statistical analysis was done using **SPSS** program (SPSS, Inc, Chicago, IL) version 21. Chi square or Fisher's exact tests were used to compare groups. The Kaplan-Meier method was used to calculate the OS rates. The log-rank test was used for univariate analysis of the relationship between clinicopathological variables and survival. Variables that showed significance in the univariate analysis were

included in the multivariate analysis using the Cox proportional hazard model. P-values of <0.05 were considered significant.

## RESULTS

In our analysis, the mean ages of the young and old groups were about 37 and 58 years old, respectively. There was a significant difference in the proportion of females between both groups. In the young group, females represented 63.9% of patients compared to only 38.2% in the old group ( $P < 0.001$ ). For the young group, the percentage of patients giving positive family history for cancer was higher than that in old group (5% vs. 0.7%,  $P = 0.03$ ). The proportion of patients testing positive for hepatitis C virus (HCV) antibodies was significantly higher in older patients than in young patients (33.1% vs. 14.8%,  $P < 0.001$ ).

The main presenting symptom in young patients was vomiting (49.2%) while older patients manifested mainly with epigastric pain (43.3%). Regarding tumor morphology, it was more common for GC in young patients to present as stomach wall thickening (44.3%) compared to gastric mass in older patients (55.9%). The latent period between symptoms and diagnosis was significantly higher in young patients compared to old patients (median: 6 vs. 2 months,  $P = 0.05$ ). Regarding histological grade, the percentage of poorly differentiated tumors in young group was higher than that in old group (65.6% vs. 39%,  $P = 0.004$ ). There were no statistically significant differences in tumor location, tumor size or pathological type. Other clinical and demographic data are shown in Table 1. Although it was not statistically significant, the rate of curative resection was numerically higher in younger patients (52.4% vs. 46.3%). Table 2 illustrates the extent of cancer spread in both groups at presentation. For the operated cases, no difference was found in depth of invasion or lymph node metastasis between the two groups. Similarly, there was no difference in the rate of metastatic disease at presentation or site of metastases between both groups. However, for younger patients who were metastatic at presentation, there was a trend toward multiple sites of metastases compared with older group (39.4% vs. 29.5%,  $P = 0.08$ ).

Treatment of metastatic cases according to age group is summarized in Table 3. The percentage of patients who did not undergo any active treatment due to poor performance was significantly lower in the young group (9.1% vs. 21.1%,  $P = 0.04$ ). Similarly, more patients in the young group were fit enough to proceed to third line therapy in progressive cases (18.2% vs. 5.6%,  $P = 0.08$ ). No difference was found in the rate of duplet vs. triplet therapy applied in both groups. Also, no differences were observed in the response rate to first line therapy or the rate of palliative surgery between both groups.

Regarding survival, the mean overall survival (OS) in young patients was 10.7 months (CI 7.8 – 13.6) which was much lower than that of older patients (18.7 months, CI 14.5 - 22.8). The difference showed marginal significance ( $P = 0.06$ ). One-year survival rates were 28.6% for the young group vs. 32.4% for the old group. Three- year survival rates were 8.2% and 20.1%, respectively. The survival curves of the two groups are shown in Figure 1. To explore the variables impacting prognosis in young GC patients, univariate and multivariate analyses were performed. Univariate analysis showed that depth of invasion (T stage), lymph node involvement (N stage), distant metastases and CA19-9 level were prognostic factors (Table 4). Multivariate analysis demonstrated that only distant metastases and elevated CA19-9 level were independent negative prognostic factors of young GC patients.

conducted mainly in Asian countries [Saito et al., 2012; Hsieh et al., 2012; Wang et al., 2014; Takatsu et al., 2015], while only few, if any, data come from Africa and the Middle East. In addition, data on differing prognosis between younger and older patient groups have not been consistent [Santoro et al., 2007; Al-Refaie et al., 2011; Bautista et al., 2014]. That is why we decided to look into the characteristics and prognosis of this group of patients in our population. In the current study, we noted a significantly higher female prevalence among young group compared with older subjects. This was consistent with several other studies [Wang et al., 201; Prochorov et al., 2015; Liu et al., 2016].

Reasons behind such discrepancy are still unknown however hormonal differences may be implicated. Another explanation may be the higher estrogen receptors expression and intracytoplasmic estradiol in young patients with GC [Wakui et al., 2008]. Moreover, a study suggested that the higher female prevalence among young patients may be associated with recent pregnancies [Kath et al., 2000]. However, we did not find female gender to be a prognostic variable in this group of patients. Nevertheless, the evidence connecting gender to GC prognosis remains controversial, and more research is required to confirm whether gender impacts the prognosis of younger patients or not.

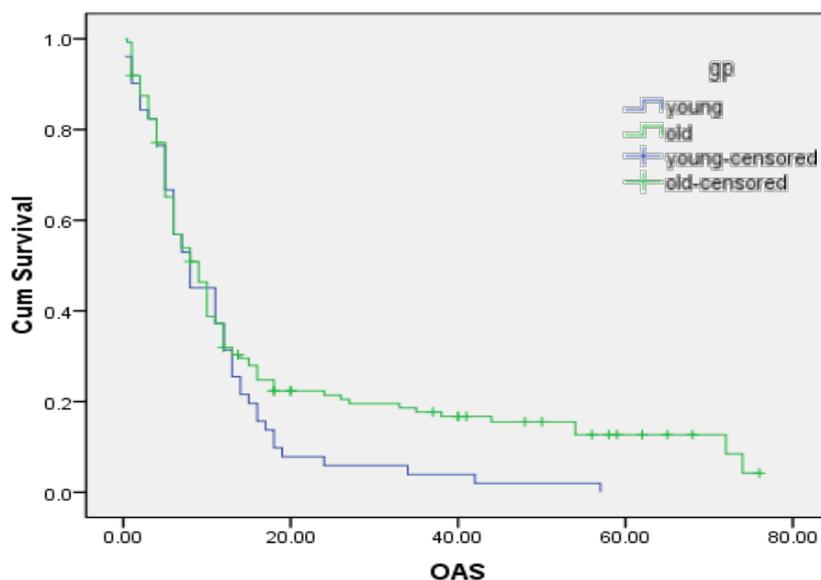


Figure 1. Kaplan Meier curve for OS in young and old group of patients.

**Table 1.** Demographic and clinicopathological characteristics of both groups

Parameter	Age group		P value
	Young (N=61)	Old (N=136)	
<b>Age in years:</b> (Mean $\pm$ SD)	37.2 $\pm$ 6.5	58.6 $\pm$ 7.9	<0.001*
<b>Gender:</b> No (%)			
Male	22 (36.1)	84 (61.8)	0.001*
Female	39 (63.9)	52 (38.2)	
<b>Positive Family History:</b> No (%)	3 (5)	1 (0.7)	0.03*
<b>Positive for viral markers:</b> No (%)			
HCV	9 (14.8)	45 (33.1)	0.03*
HBV	1 (1.6)	0 (0)	
<b>Presenting Symptoms:</b> No (%)			
Epigastric pain	15 (24.6)	59 (43.3)	0.003*
Hematemesis and melena	9 (14.8)	28 (20.6)	
Vomiting	30 (49.2)	39 (28.7)	
Abdominal enlargement	5 (8.2)	2 (1.5)	
Anemia & Cachexia	2 (3.2)	8 (5.9)	
<b>Interval between symptoms and diagnosis (months):</b> median (range)	6 (1-12)	2 (1-6)	0.05*
<b>Site:</b> No (%)			
Pylorus & Antrum	30 (49.1)	70 (51.4)	0.4
Body	20 (32.8)	39 (28.6)	
Fundus	4 (6.6)	18 (13.4)	
Undetermined	7 (11.5)	9 (6.6)	
<b>Shape:</b> No (%)			
Mass	23 (37.7)	76 (55.9)	0.04*
Ulcer	11 (18.0)	21 (15.4)	
Thickening	27 (44.3)	39 (28.7)	
<b>Size (cm):</b> median (range)	5 (2-12)	4 (1-9)	0.3
<b>Pathology:</b> No (%)			
Adenocarcinoma	34 (55.7)	87 (64)	0.2
Signet cell carcinoma	27 (44.3)	49 (36)	
<b>Grade:</b> No (%)			
Well differentiated	1 (1.6)	10 (7.4)	0.004*
Moderately differentiated	10 (16.4)	43 (31.6)	
Poorly/undifferentiated	40 (65.6)	53 (39)	
Unknown grade	10 (16.4)	30 (22)	
<b>Tumor markers:</b> median (IQ range)			
CA 19-9	12 (2188)	14 (709)	0.4
CEA	2 (82)	2 (58)	0.5
CA 125	277 (356)	74 (279)	0.9

\*P value is statistically significant

## DISCUSSION

Most research investigating the impact of young age at diagnosis on GC outcome have been Not surprisingly, a higher prevalence of positive family history has been observed in our study among younger patients with GC, a finding that we see in other reports [Bautista et al., 2014]. A possible explanation is that in young patients, the development of GC is more likely a result of genetic predisposition. That is why clinicians

should pay more attention when a positive family history of cancer exists in a young patient who presents with suspicious symptoms and signs.

In our study, we found that the proportion of young patients who were seropositive for HCV was significantly lower than older patients (14.8% vs. 33.1%, P = 0.03). Limited data exist about the association of HCV with GC. A recent Taiwanese study concluded that HCV infection,

**Table 2.** Extent of cancer spread for operated and non-operated cases among both groups

Parameter No (%)	Age group		P value
	Young	Old	
<b>Rate of curative resection:</b>	32 (52.4)	63 (46.3)	0.1
<b>Depth of invasion:</b>			0.3
T1	1 (3.1)	2 (3.2)	
T2	13 (40.6)	27 (42.9)	
T3	12 (37.5)	26 (41.2)	
T4	6 (18.8)	8 (12.7)	
<b>Nodal involvement:</b>			0.1
N0	8 (25)	17 (27)	
N1	9 (28.1)	20 (31.7)	
N2	4 (12.5)	16 (25.4)	
N3	11 (34.4)	10 (15.9)	
<b>Metastatic at presentation:</b>	33 (54.1)	71 (52.2)	0.7
<b>Site of Metastasis:</b>			0.08
Abdomen (ovary or peritoneal deposits or abdominal lymph nodes)	17 (51.5)	43 (60.6)	
Liver	3 (9.1)	7 (9.9)	
Multiple sites	13 (39.4)	21 (29.5)	

**Table 3.** Type of therapy in metastatic cases among both groups

Type of therapy No (%)	Age group		P value
	Young (N=33)	Old (N=71)	
<b>Best supportive care</b>	3 (9.1)	15 (21.1)	0.04*
<b>First line chemotherapy</b>			0.5
Duplet	13 (42.4)	35 (49.3)	
Triplet	16 (48.5)	21 (29.6)	
<b>Response to first line chemotherapy</b>			0.9
Regressive/Stationary	18 (54.5)	43 (60.6)	
Progressive	15 (45.5)	28 (39.4)	
<b>Multiple lines of chemotherapy:</b>			0.08
2 lines	21 (63.6)	43 (60.5)	
≥ 3 lines	6 (18.2)	4 (5.6)	
<b>Palliative surgery</b>	9 (27.3)	9 (12.7)	0.07

\*P value is statistically significant

**Table 4.** Univariate and multivariate survival analysis in young patients

Variable	Univariate analysis (P-value)	Multivariate analysis (P-value)	HR	95% CI
Gender (female)	0.7	-	-	-
HCV (positive)	0.4	-	-	-
Tumor site (pylorus)	0.08	-	-	-
Tumor size (≥5 cm)	0.5	-	-	-
Differentiation (poorly)	0.6	-	-	-
T classification (T3/4)	0.02*	0.7	2.446	0.872-9.992
N classification (N2/3)	<0.001*	0.6	0.865	0.109-4.059
Distant metastasis	<0.001*	0.018*	4.231	1.254-15.872
Serum CEA (elevated)	0.1	-	-	-
Serum CA19-9 (elevated)	0.004*	0.03*	1.983	1.239-3.175

\*P value is statistically significant

male sex and old age were risk factors for GC development and that risk might not be reversed by interferon-based therapy [Chen et al., 2019]. However, it is not clear whether such infection would affect patients' prognosis or not. Further research is needed in this area.

The most frequent symptoms in our study population were vomiting in young patients (49.2%), and epigastric pain in old patients (43.3%). We also observed that distal tumor location was the most frequent location among young group, similar to old group, and in agreement with findings in other studies [Liu et al., 2016]. However, with regard to tumor shape, gastric wall thickening was more frequent in young patients in contrast to old group who presented more commonly with gastric mass ( $P = 0.04$ ). This could be correlated with the differing symptomatology between both groups. However, despite that these differences were statistically significant, we believe that clinical manifestations of gastric cancer are not specific for either young or old age, and that medical community should raise the awareness of GC manifestations and prevalence.

Consistent with previous research, we found that younger patients had more poorly/undifferentiated histological grade tumors compared with older subjects who presented more with well/moderately differentiated tumors [Kong et al., 2012; Bautista et al., 2014; Dai et al., 2017]. Some authors attributed these results to predominance of *H. pylori* infection among young patients compared to older patients and suggested that infection with *H. pylori* may play a role in development of poorly differentiated tumors in young subjects [Hirahashi et al., 2007]. Unfortunately, the data on the rate of *H. pylori* infection among our patients was not available. On the other hand, there was no significant difference in the rate of signet ring carcinoma between both groups in our study.

Regarding survival of our patients, we found that mean OS was lower in young patients compared to older patients (10.7 vs.18.7 months,  $P = 0.06$ ). Studies have reported conflicting results regarding survival rates of younger patients with GC. The poorer survival in

young patient groups that was reported in some studies was thought to be secondary to aggressive tumor behavior reflected by higher grade and advanced stage at diagnosis [Isobe et al., 2013; Wang et al., 2014]. However, one study found that among those who underwent curative resection, patients  $\leq 40$  years had similar 5-year survival rates compared with those  $> 40$  years [Isobe et al., 2013]. Similarly, other studies found equivalent survival between young and older groups of GC patients [Liu et al., 2016]. In contrast, a large population-based study found that despite a higher proportion of young patients had higher histological grades and more advanced stage, the 5-year survival rates were better in young patients than in older patients [Al-Refaie et al., 2011]. This was supported by another recent study that found that 5-year disease-specific survival rate in young patients was significantly higher than that in older group [Dai et al., 2017].

We looked into the interval between symptom recognition by patients and establishing GC diagnosis in both groups. Younger patients showed significantly longer median duration to diagnosis versus older group (6 vs. 2 months,  $P = 0.05$ ). This longer latency before reaching diagnosis may be in part due to younger patients not seeking medical advice early enough as old patients, and in part due to lower clinical suspicion for malignancy by physicians in younger patients compared to older patients. This goes in line with suggestions that a diagnostic delay in young patients may attribute to poorer outcome observed in some studies [Isobe et al., 2013; Wang et al., 2014; Dai et al., 2017]. This finding together with high rate of metastatic disease at presentation (54.1%), and poor response to first line chemotherapy (45.5% non-responders), are most likely the reasons why the 3-year survival rate in our patient population is less than 10% for the young group. Regarding prognostic variable, other studies have suggested various factors that contribute to poorer survival outcomes [Isobe et al., 2013; Liu et al., 2016; Dai et al., 2017]. In this study, distant metastasis and CA19-9 were independent factors in younger patients for reduced survival by multivariate analysis. Our study had few limitations. First, this was a retrospective analysis with relatively

small patient numbers; a larger well-designed randomized trial should be carried to avoid statistical bias in the future. Second, therapy for metastatic cases was not standardized in our patient population due to variability in access to cancer care in our country (e.g. targeted therapies).

## CONCLUSION

We conclude from our study that the clinical and pathological characteristics of GC are different between young and old patients. We found that survival of young patients was worse than that of older patients. Multiple age-related factors may have contributed to this worse survival, most notably aggressive tumor biology, and a significant diagnostic delay. Thus, despite that young patients are generally healthier and can receive more aggressive treatments compared to older patients, the prognosis for this subset of patients remains poor. Our findings highlight the importance of high clinical suspicion for GC regardless of age. Also, further investigations of the genetic, and environmental factors behind these age-related differences are warranted. This will better define age-specific patterns of gastric cancer which in turn will help in delivering personalized care for patients in each age group to improve survival rates.

## CONFLICTS OF INTEREST

All authors declared no conflicts of interest.

## FUND

No fund was received for this work.

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### **Egyptian Association for Cancer Research (EACR)**

<http://eacr.tanta.edu.eg/>

EACR is an NGO society that was declared by the Ministry of Social Solidarity (Egypt) No. 1938 in 19/11/2014 based on the initiative of Prof. Mohamed Labib Salem, the current Chairman of EACR. EACR aims primarily to assist researchers, in particular young researchers in the field of cancer research through workshops, seminars and conferences. Its first international annual conference entitled "Anti-Cancer Drug Discovery" was successfully organized in April 2019 (<http://acdd.tanta.edu.eg>). Additionally, EACR aims to raise the awareness of the society about the importance of scientific research in the field of cancer research in prediction, early diagnosis and treatment of cancer. EACR is also keen to outreach the scientific community with periodicals and news on cancer research including peer-reviewed scientific journals for the publication of cutting-edge research. The official scientific journal of EACR is "International Journal of Cancer and biomedical Research (IJCBR: <https://jcbjournals.ekb.eg>) was successfully issued in 2017 and has been sponsored by the Egyptian Knowledge Bank (EKB: [www.ekb.eg](http://www.ekb.eg)).

**EACR Chairman,**

**Prof. Mohamed Labib Salem, PhD**

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## GUIDE FOR AUTHORS

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**Scope** :The main aim of IJCBR is to attract the best research in animal and human biology in health and diseases from across the spectrum of the biomedical sciences at the molecular, cellular, organ, and whole animal levels especially those that are related to cancer research, including causes, prediction, diagnosis, prognosis, and therapy.

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**International Journal of Cancer & Biomedical Research**  
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