

# Smoking and Histological Factors Influencing Long-term Survival of Gastric Carcinoma in Consecutive Patient Series

Ali Delpisheh\*, Yousef Veisani\*\*†, Kourosh Sayehmiri\*\*\*,  
Ezzatollah Rahimi\*\*\*\*

\*Department of Clinical Epidemiology, Ilam University of Medical Sciences, Ilam, Iran

\*\* Student Research Committee, Ilam University of Medical Sciences, Ilam, Iran

\*\*\*Prevention of Psychosocial Injuries Research Center, Ilam University of Medical Sciences, Ilam, Iran

\*\*\*\*Liver and Digestive Research Center, Kurdistan University of Medical Sciences, Sanandaj, Iran

## Abstract

**Background:** There is little information about the possible influence of lifestyle and etiologic risk factors on survival amongst patients with gastric cancer.

**Methods:** We recruited a consecutive series of 249 patients with definite diagnosis of gastric cancer who had been hospitalized in Towhid Hospital, Sanandaj, Kurdistan Province in Western Iran during a five-year period from 2006 until 2011. Survival rate was calculated according to the Kaplan-Meier and log rank statistical methods. Cox hazard regression was used to investigate the effect of the variables and adjust for the effect of age.

**Results:** According to univariate analysis, related variables that included age, gender, Residence, histology grade, histology type, familial history of gastrointestinal cancer and mental illness during the disease had no significant effects on survival rate variation. Significant independent factors on survival included past medical history of gastrointestinal diseases ( $P$ -value = 0.010), tobacco smoking ( $P$ -value = 0.012), and early diagnosis ( $P$ -value = 0.008). Cox-regression analysis of demographic, lifestyle and histological factors with >45 years of age as the reference revealed that patients 46-65 years of age at diagnosis (HR=0.602; 95% CI=0.250-1.44;  $P$ =0.256) and those >66 years of age (HR=1.07, 95% CI=0.46-2.50,  $P$ ≤0.001) had an increased risk for disease progression and death.

**Conclusions:** Past medical history of gastrointestinal diseases, tobacco smoking and early stage diagnosis might influence the long-term survival of patients with gastric cancer.

**Keywords:** Gastric cancer, Survival rate, Lifestyle factors, Histological factors, Iran

†Corresponding Author:

Yousef Veisani  
Student Research Committee,  
Ilam University of Medical  
Sciences, Ilam, Iran  
Email: yousefveisani@yahoo.com

## Introduction

According to the World Health Organization (WHO), the worldwide incidence of cancer was 10.5 million in 2000 and it will be 30 million by 2020.<sup>1</sup> Currently, more than 25 million people are living with cancer. Over the next decades, cancers will considerably affect the global burden of disease.<sup>2</sup>

Gastric cancer is one of the leading causes of cancer-related deaths throughout the world.<sup>3,4</sup> The effects of cancer are considerably higher than the estimated number of patients and this figure is increasing.<sup>5</sup> Gastrointestinal cancers are the fourth most common cancer after lung, breast and colon, but it is still the second leading cause for cancer deaths.<sup>6</sup> According to the Iranian Cancer Research Center, gastric cancer is the most common cancer among men and the third most common cancer in women following breast and colon cancers.<sup>7</sup> Geographic variations in Iran show that the incidence and mortality of gastric cancer is higher in the West and Northwest regions, particularly in Kurdistan Province.<sup>8,9</sup> Unlike the intestinal type which is decreasing the diffuse type of gastric cancer is increasing which has led to a decline in the incidence rate and an annual increase in mortality rate.<sup>10</sup>

Gastric cancer survivors have been studied in multiple series with patients stratified according to disease stage, tumor type, tumor location and type of therapy. An association between survival and cancer stage was shown frequently. Improvements in the five-year survival rate have been reported over the past several decades.<sup>11</sup> In 2007, the one- and five-year survival rates in patients with upper gastrointestinal cancer in Ardabil Province were reported as 40.5% (one-year) and 0.8% (five-year).<sup>12</sup>

Considering the importance of the survival rate estimation after diagnosis, the present study aimed to evaluate the potential prognostic factors that possibly affected gastric cancer patient survival during the period 2006-2011.

**Table 1.** Demographic and histological characteristics of gastric cancer patients.

Factors	No. of patients (%)
<b>Age (years)</b>	
Under 45	9 (3.8)
45 to 65	90 (37.7)
Above 65	139 (58.8)
<b>Sex</b>	
Male	178 (74.5)
Female	61 (25.5)
<b>Residence</b>	
City	120 (50.2)
Village	119 (49.8)
<b>Histology type</b>	
Intestinal type	145 (60.6)
Diffuse type	36 (15)
Unknown	58 (24.4)
<b>Histology grade</b>	
Poorly differentiated	28 (33.3)
Moderately differentiated	25 (29.7)
Well differentiated	31 (36.9)
<b>Stage of disease</b>	
Stage 1	25 (7.2)
Stages 2-3	142 (92.8)
<b>Past medical history of gastrointestinal diseases</b>	
Yes	49 (24.6)
No	153 (76.4)
<b>Family history of gastric cancer in first-degree relatives</b>	
Yes	87 (43)
No	115 (76.6)
<b>Smoking status</b>	
Yes	103 (50.9)
No	99 (49.1)
<b>Lack of psychiatric illness during treatment</b>	
Yes	34 (16.8)
No	168 (83.2)

## Materials and Methods

### *Patients and methods*

Data were sourced mainly from the patient reports of pathology laboratories and hospital database records. This was a concurrent (prospective) study that used the census method to locate all eligible patients diagnosed with upper gastrointestinal cancers (249 gastric cancers) who had been hospitalized at Towhid Hospital, Sanandaj, Kurdistan Province in Western Iran. Inclusion criteria included those with definite diagnosis of upper gastrointestinal cancer during

**Table 2.** Median survival of gastric cancer patients.

Factors	Median survival (by month)(95%CI)	P-value
<b>Gender</b>		<b>0.448</b>
Male	11 (9.54-12.06)	
Female	13 (11.46-14.86)	
<b>Age (years)</b>		<b>0.267</b>
Under 45	12 (7.98-16.02)	
46-65	12 (8.54-16.46)	
Above 65	10 (8.71-11.29)	
<b>Residence</b>		<b>0.198</b>
City	11 (9.47-12.53)	
Village	10 (10.08-11.92)	
<b>Histological type</b>		<b>0.611</b>
Intestinal	11 (9.82-12.18)	
Diffuse	13 (11.21-14.79)	
Other	10 (9.19-10.81)	
<b>Histology grade</b>		0.309
Poorly differentiated	10 (7.06-12.94)	
Moderately differentiated	16 (13.94-18.06)	
Well differentiated	13 (9.17-16.83)	
Undifferentiated	11 (10.09-11.91)	
<b>Stage of disease</b>		<b>0.008</b>
Stage 1	15 (13.77-16.94)	
Stages 2-3	11 (9.55-13.35)	
<b>Past medical history of gastrointestinal diseases</b>		<b>0.003</b>
Yes	9 (7.72-11.28)	
No	12 (9.34-15.64)	
<b>Family history of gastric cancer in first-degree relatives</b>		<b>0.210</b>
Yes	10 (7.72-13.28)	
No	10 (7.90-13.10)	
<b>Smoking status</b>		<b>0.012</b>
Yes	10 (8.78-11.22)	
No	11 (8.98-12.02)	
<b>Lack of psychiatric illness during treatment</b>		<b>0.321</b>
Yes	12 (8.90-15.10)	
No	9 (6.48-15.52)	
<b>Type of treatment</b>		<b>&lt;0.001</b>
Surgery	11 (4.42-19.57)	
Chemotherapy	6 (3.92-6.07)	
Radiotherapy	6 (2.91-7.09)	

a five-year period from 2006 to 2011. Samples were coded under the direct supervision of clinical pathologists according to the International Classification of Diseases for Oncology. Clinical data such as practice treatment were obtained through a structured questionnaire and the patients' clinical records. Vital status and date of death were determined from patients' official death certificates, with a maximum follow-up of 90 months. Survival time (in months) was calculated from the date of diagnosis through the date of

death or last follow-up. Failure was defined as death by any cause during the follow-up period and patients alive at the end of the follow-up period were censored. We excluded 10 patients from the analyses according to the following - 6 patients lost to follow-up; 2 had illegible data; and 2 patients emigrated. Overall, 239 patients with gastric cancer were enrolled. Clinical and pathologic variables, which were sub-layered into age, gender, setting, histological type of tumor and practice treatment were entered into parametric

**Table 3.** Multivariate Cox regression analyses.**Cox-regression analysis for age, gender, setting, histology grade and tumor location**

Characteristics	$\beta$	HR (95% CI)	P value
<b>Age (years)</b>	-	Overall	0.016
Under 45	Reference	1	Reference
46-65	-0.508	0.602 (0.250-1.44)	0.256
Over 65	0.076	1.07 (0.46-2.50)	0.859
<b>Histology grade</b>	-	Overall	0.010
Poorly differentiated	Reference	1	Reference
Moderately differentiated	-1.25	0.285 (0.135-0.604)	0.001
Well differentiated	-0.68	0.502 (0.26-0.95)	0.954
<b>Past medical history of gastrointestinal disease</b>	-	Overall	0.051
Yes	Reference	1	Reference
No	-0.413	0.662 (0.437-1.00)	0.051

regression models (by considering and not considering heterogeneity) for multivariate analysis in order to assess the relationships between characteristics and prognostic factors for survivors. The present study was approved (Code no.: 91002; date: 22/08/2012) by the Ilam University of Medical Sciences Ethics Committee. Results of the study eventually would be published in general.

### Statistical analysis

We used the Kaplan Meier method and log rank statistics to compare survival rates in different subgroups. Using a life table, survival rates and survival density function was assessed at yearly intervals. Breslow (generalized Wilcoxon) statistics was used to compare median survival time in three age groups. To investigate the effect of the variables and adjust for the effect of age, we used Cox hazards regression. Graphical methods (diagram Log (S) t vs. time) and an analytical method (time-varying covariate) were assessed to appropriateness of Cox's proportional hazard.<sup>13</sup>  $P < 0.05$  was considered statistically significant. Statistical analysis was performed using SPSS, version.<sup>16</sup>

### Results

We recruited 239 patients (74.5% males) with gastric cancer. Mean age  $\pm$  standard deviation was  $68.8 \pm 11.97$  years with a range of 37 to 97 years (Table 1). Overall, 49 (24.6%) had histories

of gastrointestinal disease and 87 (43%) had a positive familial history of cancer. In general, 103 (50.9%) patients were smokers and 34 (16.8%) had histories of mental disorders. Based on tumor type, 145 (60.6%) had intestinal type histology and 36 (15.0%) had diffuse type tumors. In univariate analysis, related variables that included age, gender, residence, histology grade, histology type, familial history of gastrointestinal cancer and mental illness during disease showed no significant effects on survival rate variation. Past medical history of gastrointestinal diseases ( $P$  value = 0.010), tobacco smoking ( $P$  value = 0.012), and early diagnosis ( $P$  value = 0.008) were significant independent factors for survival (Table 2).

We used Cox-regression analysis to predict potential prognostic factors in patients with gastric cancer. The model-building process takes place in three blocks. In the first three blocks demographic factors (age, gender, and setting) were added to the analysis. Histological factors (histology grade, histology type) comprised the second block, whereas lifestyle factor (smoking status) and disease history (family history of gastric cancer among first-degree relatives, past medical history of gastrointestinal disease) were in a three block added in analysis. In cox regression if the step was to add a variable, the inclusion makes sense if the significance of the change is less than 0.05 and remove a variable, if the significance of the change is greater than 0.10. The final model included

**Table 4.** 1-5 year survival rates of gastric cancer according to demographic and histological factors.

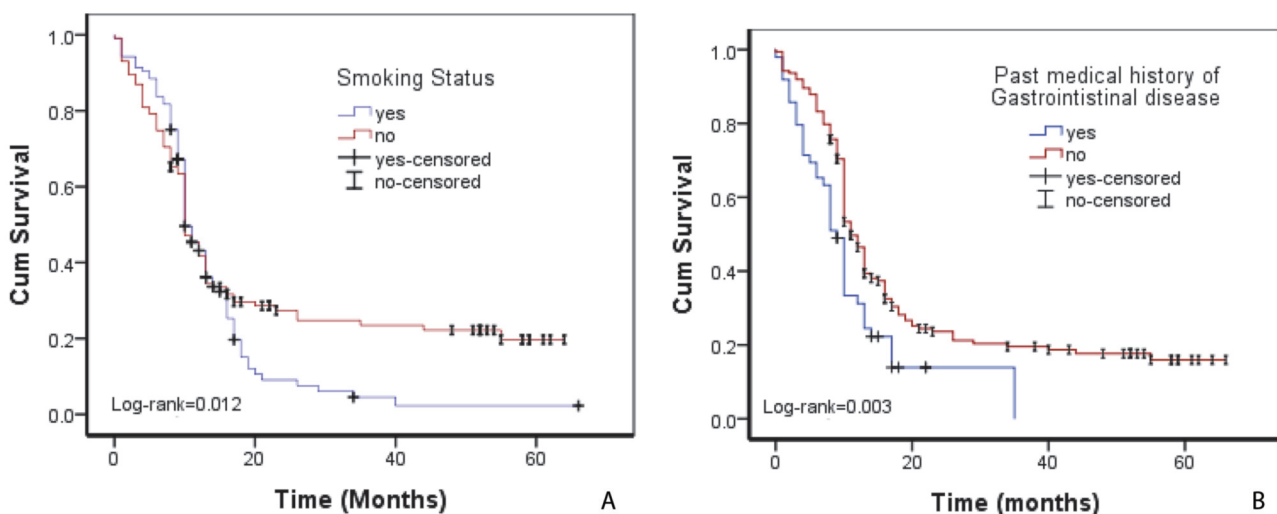
Survival variables	Survival rates (%)					Median survival time (months)
	1-year	2-year	3-year	4-year	5-year	
<b>Gender</b>						
Male	45.1	18.2	13.5	12.6	7.3	11.56
Female	48.2	21.3	19.7	15.6	15.6	11.90
<b>Age (years)</b>						
Under 45	62.3	46.7	24.2	18.1	13.3	15.00
46-65	49.3	24.3	17.2	15.3	12.1	12.62
Over 65	43.4	17.1	14.2	11.3	8.5	11.08
<b>Histological type</b>						
Intestinal	47.3	23.3	18.1	16.3	12.5	11.59
Diffuse	50.5	7.1	4.0	4.0	4.0	13.78

age, histology grade and past medical history of gastrointestinal disease. Cox-regression analysis that used histological factors of >45 years of age as the reference revealed that patients who were 46-65 years of age at diagnosis (HR=0.602, 95% CI = 0.250-1.44,  $P=0.256$ ) and >66 years of age (HR=1.07, 95% CI = 0.46-2.50,  $P\leq 0.001$ ) had increased risk for disease progression and death. Cox-regression analysis for poor grade as the reference showed that patients whose tumors were moderately differentiated (HR=0.285, 95% CI = 0.135-0.604,  $P=0.001$ ) and well differentiated (HR=0.502, 95% CI = 0.26-0.95,  $P=0.954$ ) had decreased risk for death from Gastrointestinal cancer (Table 3).

Kaplan-Meier analysis revealed significant differences in five-year survival rate and smoking status (log-rank=0.121; Figure 1A) and past medical history of gastrointestinal disease (log-rank=0.004; Figure 1B). The five-year survival rates (by year) were 46%, 19.5%, 17%, 14% and 11.5% respectively. Overall five-year survival among gastric cancer cases in the present study was 11.5%. There were higher survival rates in women (15.6%) compared to men (7.8%;  $P=0.48$ ; Table 4).

## Discussion

Gastric cancer remains a major cause of cancer mortality.<sup>6</sup> During the last decades, the gastric



**Figure 1.** Survival functions in patients with gastric cancer according to Kaplan-Meier. (A) Smoking status. (B) Past medical history of gastrointestinal disease.

cancer mortality rate has decreased globally.<sup>14</sup> However, this cancer remains a major public health concern with a poor prognosis and high mortality.<sup>1</sup> In a recent review of survival analyses, numerous studies have reported demographic, clinical and pathologic characteristics of patients by investigating variables related to survival.<sup>15-17</sup> In this study, the effects of age, gender, residence, tobacco smoking, histology grade, histology type, familial history of gastrointestinal cancer, mental illness during this disease, and past medical history of gastrointestinal diseases on survival time have been investigated. We found that cancer management in Iran resulted in late diagnosis which significantly reduced the five-year survival rate of patients with gastric cancer. Various studies have reported a number of prognostic factors for gastric cancer.<sup>16,18</sup> In our study there was a significantly greater survival rate among patients whose cancer was detected in the early stages - a finding reported in several corresponding studies.<sup>16,17</sup> Other variables were identified as independent prognostic factors for patients with gastric cancer. In our results, gender showed no impact on survival rate. However some studies found a consistently lower survival for women with gastric cancer.<sup>18</sup> Smoking has been determined to be a risk factor for numerous cancers. As many as 14 types of cancers, including gastric cancer, were found to be associated with smoking in a cohort study of 34439 British doctors over a number of years.<sup>19</sup> Similar findings were also found for patients with gastric cancer in European countries. Smoking status was another important prognostic factor for gastric cancer in our study. This was similar to other studies where patient survival was dependent on a positive history of smoking.

Geographic variability in prognosis of gastric cancer patients has been well documented. Minimum and maximum survival rates have been reported in European countries and East Asia, respectively.<sup>14</sup> Similarly, the five-year relative survival rates for gastric cancer vary from 10% to 95% worldwide.<sup>18</sup> In Iran the prognosis for patients diagnosed with gastric cancers remains

poor. The five-year survival rate for 2006-2011 (the time of the present study) was 5.4%, which was low. Mean age at diagnosis was  $66.8 \pm 11.97$  years in the present study; the corresponding rate in the Chinese population was  $57.5 \pm 10.9$  years,<sup>17</sup> which indicated a late diagnosis in the present study. Gastric cancer has a male-to-female ratio of approximately 2:119; in the present study we reported a male-to-female ratio of 2.9:1. The corresponding rate in the American population in 2009 was 1.54:1.<sup>14</sup>

Although hospital series often provide more optimistic data they are of limited value because of unavoidable selection bias, in particular for case selection and patient characteristics.

## Conclusion

According to the results of this study, early stage diagnosis significantly increases the five-year survival rate in patients with gastric cancer. Thus we recommend intervention for early detection and therapy in the primary stage, which is necessary to increase survival. Late diagnosis of gastric cancer decreases the five-year survival rate which seems to be the main difficulty in cancer management in Iran. Surgery may be an effective treatment for patients in this study. Smoking is associated with decreased survival of patients with gastric cancer.

## Acknowledgement

This study was supported financially by the Student Research Committee of Ilam University of Medical Sciences, Ilam, Iran.

## Conflict of Interest

No conflict of interest is declared.

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