Lifestyle factors on the long-term survival of gastric cancer patients after radical resection: A cohort study

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Background: This retrospective cohort study aimed to evaluate the effect of lifestyle factors (e.g., smoking, drinking, physical exercise, and sleep duration) on the long-term survival of gastric cancer (GC) patients after radical resection. **Materials and Methods:** GC patients after radical resection were enrolled from January 2016 to December 2017. Their baseline clinical data, lifestyle factors, and prognosis were collected. The primary endpoint was all-cause death. The relationship between the variables and survival was examined using the Cox proportional hazards model. **Results:** A total of 309 patients were enrolled and 296 patients were followed up for a median of 54.0 months, with 130 confirmed deaths. Older age (>60 years) (hazard ratio [HR]: 1.307, 95% confidence interval [CI]: 1.056–2.161, $P = 0.006$), advanced tumor, node, and metastasis stage ($P < 0.05$), poorly pathological differentiation (HR: 1.765, 95% CI: 1.080–2.884, $P = 0.023$), history of smoking ($P < 0.001$), never physical exercise (HR: 2.057, 95% CI: 1.170–3.617, $P = 0.012$), long sleep duration (≥8 h) (HR: 4.160, 95% CI: 1.501–11.533, $P = 0.006$), and short sleep duration (<6 h) (HR: 3.417, 95% CI: 1.312–8.900, $P = 0.012$) were independent indicators of a poor overall survival in GC patients after radical resection. **Conclusion:** Smoking cessation, proper sleep duration, and regular physical exercise habits can improve the long-term survival of GC patients after radical resection.

Key words: Gastric cancer, lifestyle factors, prognosis, survival

INTRODUCTION

According to the data of the epidemiology of gastric cancer (GC) published in 2019, the third leading cause of cancer-related death worldwide and the fifth most frequently diagnosed malignancy is GC.[1] The current clinical treatment of GC is a comprehensive treatment mode based on surgical treatment.[2] With the standardization of radical gastrectomy for GC, the effect of surgical treatment remains at a relatively stable level.[3] How to improve the long-term survival of GC patients after surgery and improve their postoperative quality of life has become a hot topic of concern.

According to estimates from the World Health Organization (WHO), unhealthy lifestyle choices including smoking, drinking, and insufficient physical activity are to blame for around one-third of cancer cases.[4] Lifestyle factors not only influence the occurrence of malignant tumors but also have an impact on cancer development, cancer patient prognosis, and treatment outcomes. Some researchers have included diet, lifestyle, and psychological interventions as part of the overall treatment of GC,[5] indicating that these factors may assist and enhance the effect of traditional treatments, thereby improving the prognosis and quality of life of patients. Moreover, quality of life has become one of the main parameters for evaluating treatment results and even one of the main criteria for selecting different

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interventions with similar efficacy.[6] As for the factors affecting the long-term survival of GC patients after radical resection, the recognized prognostic factors are tumor stage, histological type, depth and scope of invasion, thoroughness of tumor resection, and metastasis,[7,8] while there are few studies about lifestyle factors on the long-term survival of GC patients after radical resection. This study aimed to evaluate lifestyle factors on the long-term survival of GC patients after radical resection.

MATERIALS AND METHODS

Patients
This was a single-center retrospective cohort study from China. The clinical parameters of 309 GC patients who received curative surgical resection at The Second Hospital of Hebei Medical University from January 2016 to December 2017 were included and analyzed retrospectively. This study was approved by the Institutional Review Boards of The Second Hospital of Hebei Medical University (No. 2021-R322).

The inclusion criteria were (1) patients pathologically diagnosed with GCs, (2) patients who underwent curative surgical resection, (3) patients ≥18 years of age, (4) patients with complete clinical data and follow-up records, and (5) patients willing to participate in the study. Exclusion criteria were defined as follows: patients with other tumors, autoimmune diseases, inflammation, cardiovascular diseases, and diabetes, which increase mortality.

Data collection and 5-year follow-up
Patient charts were reviewed for gender, age, operation method, tumor location, tumor, node, and metastasis (TNM) stage, and pathological differentiation. TNM stage was evaluated by the American Joint Committee on Cancer TNM classification, and the degree of tumor pathological differentiation was determined by the criteria of the WHO.

To gather information on lifestyle factors, a self-reported questionnaire was created. All patients were followed up by telephone, WeChat, or outpatient visits to collect data of lifestyle factors and prognosis. The 5-year survival rate was the primary outcome. In the 1st year, there were follow-up visits every 6 months, and afterward, they were done once a year. Lifestyle factors measured in this study included history of smoking (never, postoperative smoking cessation, and always), history of drinking (never, postoperative drinking cessation, and always), physical exercise (never, 1–3 times/week, and ≥4 times/week), and sleep duration (6–8 h, ≥8 h, and <6 h). All lifestyle factors were measured by trichotomous questions. Twenty min of swimming, cycling, brisk walking, aerobic activity, or jogging (either separately or in combination) qualified as physical exercise one time. From the date of surgery to the date of death or the final follow-up, the survival time was determined.

Statistical analysis
Statistical analysis was performed using the Statistical analysis was performed using the SPSS version 22.0 statistical software(SPSS Inc., Chicago, IL, USA). Continuous variables were expressed by mean ± standard deviation or median and interquartile range, and the *t*-test or Mann–Whitney *U*-test was used to compare groups. Numbers (percentages) were utilized to indicate categorical variables, and the χ^2 test was applied to compare group differences. To evaluate differences between survival distributions, Kaplan–Meier curves and the log-rank test were applied. The relationship between the variables and survival was examined using the Cox proportional hazards model. Variables with statistical significance in univariate analysis are included in multivariable analysis. $P < 0.05$ was considered statistically significant. GraphPad Prism 7 was used to plot the Kaplan–Meier curves.

RESULTS

General characteristics of participants
A total of 309 GC patients were enrolled, and 13 GC patients without follow-up data were excluded from the study. Finally, 296 GC patients were included in the study overall [Figure 1]. Two hundred sixteen (73.0%) of the 296 GC patients who participated in the study were male, and 80 (27.0%) were female. The median age was 62 years (range: 31–78 years). Table 1 briefly summarizes the clinicopathologic characteristics of 296 GC patients.

Lifestyle factors on the long-term survival of gastric cancer patients after radical resection
The range of follow-up was 3–104 months, with a median of 54.0 months. A total of 130 (43.9%) deaths occurred, of which 90 (69.2%) were males and 40 (30.8%) were females. The 1-, 3- and 5-year survival rates for GC patients after radical resection were 93.9%, 63.9%, and 35.6%, respectively.
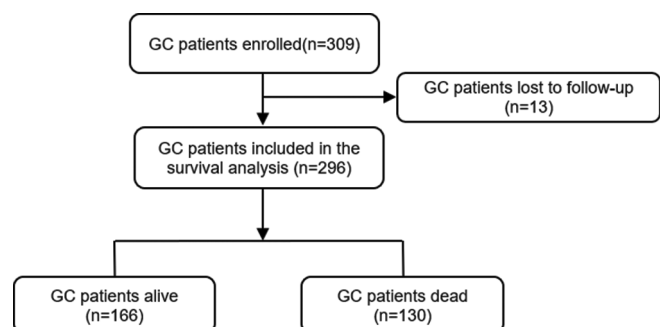
Figure 1: Flowchart of patient selection process. GC: Gastric cancer

Smoking, physical exercise, and sleep duration had an effect on the 5-year survival rate of GC patients after radical resection, but drinking had no effect [Table 2]. The Kaplan–Meier curves for the probability of survival for various lifestyle factors in GC patients following radical resection are shown in Figure 2a-d. The 5-year overall survival (OS) was the highest for the never-smoking group, whereas the lowest 5-year OS was in the always-smoking group ($P < 0.001$). Compared to patients who never exercised, patients who exercised more than 4 times a week had a higher 5-year OS ($P < 0.001$). Patients who slept for 6–8 h had a higher 5-year OS than those who slept for more than 8 h or <6 h ($P < 0.001$).

Predictors of long-term survival of gastric cancer patients after radical resection

The long-term survival of GC patients after radical resection was assessed using univariate and multivariable analyses. In Table 3, the univariate analysis demonstrated that age, operation method, TNM stage, degree of pathological differentiation, history of smoking, physical exercise, and sleep duration were important prognostic factors affecting the long-term survival of GC patients after radical resection.

A multivariable analysis enrolled age, operation method, TNM stage, degree of pathological differentiation, history of smoking, physical exercise, and sleep duration into the

Table 1: Characteristics of the study cohorts

Variables	Survivors (*n*=166)	Nonsurvivors (*n*=130)	χ^2	P^a
Gender				
Male	126 (75.9)	90 (69.2)	1.646	0.200
Female	40 (24.1)	40 (30.8)		
Age (years)				
≤60	98 (59.0)	42 (32.3)	20.895	<0.001*
>60	68 (41.0)	88 (67.7)		
Operation method				
Totally laparoscopic gastrectomy	30 (18.1)	8 (6.2)	17.008	0.001*
Hand-assisted laparoscopic gastrectomy	34 (20.5)	32 (24.6)		
Laparoscopic-assisted gastrectomy	98 (59.0)	76 (58.5)		
Open gastrectomy	4 (2.4)	14 (10.8)		
Tumor location				
Proximal GC	95 (57.2)	76 (58.5)	0.295	0.863
Distal GC	67 (40.4)	52 (40.0)		
Total GC	4 (2.4)	2 (1.5)		
TNM stage				
I	32 (19.3)	4 (3.1)	42.194	<0.001*
II	52 (31.3)	20 (15.4)		
III	56 (33.7)	52 (40.0)		
IV	26 (15.7)	54 (41.5)		
Degree of pathological differentiation				
Well-differentiated	16 (9.6)	4 (3.1)	20.581	<0.001*
Moderately differentiated	70 (42.2)	30 (23.1)		
Poorly differentiated	80 (48.2)	96 (73.8)		
History of smoking				
Never	110 (66.3)	4 (3.1)	172.514	<0.001*
Postoperative smoking cessation	50 (30.1)	36 (27.7)		
Always	6 (3.6)	90 (69.2)		
History of drinking				
Never	42 (25.3)	34 (26.2)	4.368	0.113
Postoperative drinking cessation	64 (38.6)	36 (27.7)		
Always	60 (36.1)	60 (46.2)		
Physical exercise				
≥4 times/week	64 (38.6)	24 (18.5)	18.022	<0.001*
1–3 times/week	62 (37.3)	50 (38.5)		
Never	40 (24.1)	56 (43.1)		
Sleep duration				
6–8 h	36 (21.7)	6 (4.6)	22.536	<0.001*
≥8 h	62 (37.3)	42 (32.3)		
<6 h	68 (41.0)	82 (63.1)		

*Statistical significance ($P<0.05$), ᵃThe P values are based on Chi-squared test. All data are presented as percentages. GC=Gastric cancer; TNM=Tumor node metastasis
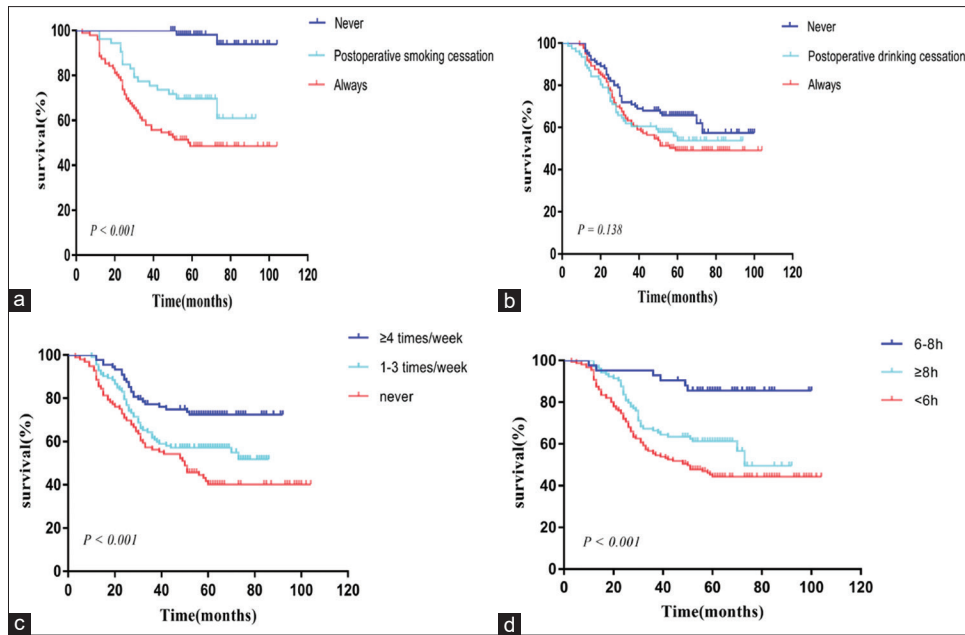
Figure 2: Overall survival rate stratified by different lifestyle factors. (a) Survival rate by smoking group (never vs. postoperative smoking cessation vs. always), (b) survival rate by drinking group (never vs. postoperative drinking cessation vs. always), (c) survival rate by physical exercise group (≥4 times/week vs. 1–3 times/week vs. never), (d) survival rate by sleep duration group (6–8 h vs. ≥8 h vs. <6 h)

Table 2: Survival probability of different lifestyle factors estimated by Kaplan–Meier method

Variables	*n* (%)	5-year survival rate (%)	*P*[a]
History of smoking			
Never	114 (38.5)	63.2	<0.001*
Postoperative smoking cessation	86 (29.1)	33.7	
Always	96 (32.4)	5.2	
History of drinking			
Never	76 (25.7)	32.9	0.138
Postoperative drinking cessation	100 (33.8)	42.0	
Always	120 (40.5)	32.5	
Physical exercise			
≥4 times/week	88 (29.7)	45.5	<0.001*
1–3 times/week	112 (37.8)	34.8	
Never	96 (32.4)	28.1	
Sleep duration			
6-8 h	42 (14.2)	54.8	<0.001*
≥8 h	104 (35.1)	35.6	
<6 h	150 (50.7)	30.7	

*Statistical significance (*P*<0.05); [a]The *P* values are based on log-rank tests

Cox regression model to find independent predictors for the long-term survival of GC patients after radical resection. Multivariable Cox regression analysis indicated that older age (>60 years) (hazard ratio [HR]: 1.307, 95% confidence interval [CI]: 1.056–2.161), advanced TNM stage (*P* < 0.05), poorly pathological differentiation (HR: 1.765, 95% CI: 1.080–2.884), history of smoking (*P* < 0.001), never physical exercise (HR: 2.057, 95% CI: 1.170–3.617), long sleep duration (≥8 h) (HR: 4.160, 95% CI: 1.501–11.533), and short sleep duration (<6 h) (HR: 3.417, 95% CI: 1.312–8.900) were independent indicators of a poor OS in GC patients after radical resection [Table 3].

DISCUSSION

In this study, we investigated lifestyle factors on the long-term survival of GC patients after radical resection based on a single-center retrospective cohort study from China. Our data showed that a history of smoking, never physical exercise, and long/short sleep duration were independent indicators of poor OS in GC patients after radical resection.

Low 5-year survival rate and high morbidity and mortality characterize GC.[1] The 5-year survival rate varies from 30% to 50% for GC patients after radical resection.[9,10] In line with previous studies, our research revealed that the 5-year survival rate of GC patients following radical resection was 35.6%.

Smoking is a known risk factor for GC,[11] but it is not clear how it affects long-term survival. A nationwide cohort study in China reported that smoking history conferred a worse prognosis in GC patients after radical resection.[12] Several mechanisms may explain this finding. The latest data in the field of epigenetics show that smoking is associated with abnormal DNA methylation patterns, which are related to carcinogenesis and poor tumor prognosis.[13] In addition to epigenetic regulation, smoking can lead to the destruction of the immune microenvironment. Reformed smokers and current smokers had differing

Table 3: Univariate and multivariable analysis of variables related to prognostic characteristics of gastric cancer patients after radical resection

Variables	Univariate analysis		Multivariable analysis[a]	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Gender				
Male	1	0.134		
Female	1.330 (0.916–1.930)			
Age (years)				
≤60	1	<0.001*	1	0.006*
>60	2.109 (1.459–3.048)		1.307 (1.056–2.161)	
Operation method				
Totally laparoscopic gastrectomy	1		1	
Hand-assisted laparoscopic gastrectomy	2.936 (1.352–6.374)	0.006*	1.186 (0.511–2.756)	0.691
Laparoscopic-assisted gastrectomy	2.563 (1.236–5.312)	0.011*	2.234 (0.983–5.077)	0.055
Open gastrectomy	6.184 (2.588–14.775)	<0.001*	1.493 (0.578–3.855)	0.408
Tumor location				
Proximal GC	1			
Distal GC	0.983 (0.691–1.400)	0.926		
Total GC	0.826 (0.203–3.364)	0.790		
TNM stage				
I	1		1	
II	2.995 (1.023–8.766)	0.045*	1.435 (1.004–2.312)	0.035*
III	5.894 (2.130–16.305)	0.001*	1.815 (1.250–4.641)	0.009*
IV	10.258 (3.708–28.380)	<0.001*	2.329 (1.610–5.015)	<0.001*
Degree of pathological differentiation				
Well-differentiated	1		1	
Moderately differentiated	1.767 (0.622–5.019)	0.285	0.789 (0.380–1.640)	0.525
Poorly differentiated	3.904 (1.434–10.624)	0.008*	1.765 (1.080–2.884)	0.023*
History of smoking				
Never	1		1	
Postoperative smoking cessation	16.207 (5.754–45.648)	<0.001*	4.047 (2.054–8.800)	<0.001*
Always	18.533 (12.030–50.714)	<0.001*	5.840 (3.937–12.201)	<0.001*
History of drinking				
Never	1			
Postoperative drinking cessation	0.726 (0.454–1.160)	0.180		
Always	1.091 (0.717–1.662)	0.684		
Physical exercise				
≥4 times/week	1		1	
1–3 times/week	1.839 (1.130–2.993)	0.014*	0.843 (0.461–1.541)	0.578
Never	2.630 (1.630–4.244)	<0.001*	2.057 (1.170–3.617)	0.012*
Sleep duration				
6–8 h	1		1	
≥8 h	3.390 (1.440–7.979)	0.005*	4.160 (1.501–11.533)	0.006*
<6 h	5.218 (2.276–11.961)	<0.001*	3.417 (1.312–8.900)	0.012*

*Statistical significant (*P*<0.05); [a]Variables with statistical significance in univariate analysis are included in multivariable analysis. HR=Hazard ratio; CI=Confidence interval; GC=Gastric cancer; TNM=Tumor node metastasis

percentages of follicular helper T-cells, M0 macrophages, and central memory CD8+ T-cells, which suggests that smoking status could alter the immunological milieu and impact prognosis.[14] Our study showed that smoking was an independent prognostic factor for GC patients after radical resection and postoperative smoking cessation also contributed to improved prognosis, which indicated the importance of quitting smoking at present. Although a recent study reported that cancer survivors who continued to smoke still had the motivation to quit smoking even after

their initial diagnosis,[15] 50%–83% of patients continue to smoke after diagnosis of cancer.[16] In the general population, smokers report many different smoking cessation barriers, including dependence; stress; lack of smoking cessation resources and support; and home, work, and social environmental factors.[17] Cancer patients experience additional difficulties in life, which can increase the severity of these barriers.[18] Promotion of smoking cessation is an important part of the comprehensive treatment plan for GC patients after radical resection. There is an urgent

need for resources to offer smoking cessation advice to cancer patients due to the complexity of smoking cessation interventions for them.

Studies on physical activity as a nonpharmacologic intervention to improve outcomes in populations with cancer are progressing.[19] Higher levels of physical activity decreased cancer-related mortality, especially in populations with breast and colorectal cancer, according to a review of prospective cohort studies involving patients with cancer in all stages.[20] The American College of Sports Medicine's recommendations for cancer patients and survivors state that cancer survivors should engage in 150 min of weekly aerobic activity and two sessions of moderate-to-vigorous strength training to improve their overall health and quality of life.[21] To our knowledge, few studies have assessed the relationship between physical activity and GC patients' survival rates. Our study shows that appropriate physical exercise can prolong the survival time of GC patients after radical resection. It may be explained by the regulation of metabolic hormones, sex hormones, systemic inflammation, oxidative stress, and immune function.[22] The most widely studied way is the effect of physical exercise on metabolic hormones, especially the insulin–glucose axis.[23] Therefore, some healthy physical exercises are beneficial to improve the long-term survival of GC patients after radical resection. However, the best amount, type, and timing of physical activity for GC patients after radical resection to maximize its positive benefits on survival outcomes are yet unknown. Those will be an important part of our next phase of exploration.

Cancer patients frequently experience sleep disturbances, with 45%–80% of them having poor sleep quality,[24,25] as opposed to 29%–32% of the general population.[26] The physical, physiological, and mental condition of patients will alter as a result of surgical therapy, and this frequently results in sleep disturbances as well as other pathological and physiological changes. Based on the multivariable Cox model, this study showed that compared with 6–8 h sleep duration, both long sleep duration (≥8 h) (HR: 4.160, 95% CI: 1.501–11.533, $P = 0.006$) and short sleep duration (<6 h) (HR: 3.417, 95% CI: 1.312–8.900, $P = 0.012$) were independent indicators of a poor OS in GC patients after radical resection. After controlling for variables known to promote survival, a recent prospective cohort study found a curvilinear association between sleep length and mortality: short sleep duration and long sleep duration were linked to higher mortality, which was consistent with our findings.[27] Short sleep duration can significantly reduce the activity of natural killer cells in healthy individuals, resulting in immune system disorders,[28] which may explain the relationship between short sleep duration and prognosis. Uncertainty existed regarding the mechanism behind the association between prolonged sleep and prognosis. One speculation is that long sleep duration may be related to sleep fragmentation, which has been confirmed in animal experiments to be related to larger and more aggressive tumors.[29] However, long sleep duration is related to depression, sleep apnea, fatigue, poor sleep quality, etc.[30] If these potential influences of confounding factors cannot be excluded, long sleep duration cannot be considered an independent factor for prognosis assessment. Hence, we must be cautious about the current conclusion, as further reliable studies are needed to confirm it.

There were several limitations in our study. Being a single-center retrospective, relative small-scale study, a large-scale multi-center prospective is required to verify our findings. The lifestyle factors may not be comprehensive enough, and high salt diet and high BMI should be included as risk factors in follow-up. The lifestyle factors of this study rely entirely on self-reported data, and the validity is elusive. The side effects of chemotherapy may bias the results.

CONCLUSION

Smoking cessation, proper sleep duration, and regular physical exercise habits can improve the long-term survival of GC patients after radical resection. Therefore, lifestyle changes after standard GC therapy are highly recommended, including smoking cessation, proper sleep duration, and regular physical exercise.

Conflicts of interest
There are no conflicts of interest.

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