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## Clinicopathologic Risk Factors for Gastric Cancer: A Retrospective Cohort Study in China

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Keywords:	Gastric carcinoma, Clinicopathologic risk factors, Clinical stage, Lymph node metastasis rate

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# Clinicopathologic Risk Factors for Gastric Cancer: A Retrospective Cohort Study in China

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## Abstract

**Objective:** To examine the potential clinicopathologic factors affecting the prognosis of patients with stomach cancer after surgical treatment in China.

**Design:** This was a retrospective cohort study.

**Participants:** All participants were recruited from China.

**Methods:** Between January 1<sup>st</sup>, 2001 to December 31<sup>st</sup>, 2012, 716 patients aged 22–84 years with gastric cancer were enrolled in the study. Kaplan-Meier method and Cox proportional hazard regression models were applied to evaluate the prognostic significance of clinicopathological characteristics in terms of survival time.

**Results:** Of the twenty-three demographic and pathological variables collected in the data, 18 unfavorable prognostic factors of gastric cancer were found to have the remarkable influence on survival time from the unadjusted analyses. The adjusted analysis furtherly revealed that age, lymph node metastasis rate, tumor size, surgical type II, and clinical stage were independent and important prognosis and clinicopathologic factors for gastric cancer in Chinese.

**Conclusion:** Gastric cancer remains a disease with low survival rate and identification of these prognostic factors usually depend on a large part of the postoperative histological examinations, which may not be available to a surgeon at the time of treatment. Results from the current analyses can be used to assist clinical decision-making, and serve as a benchmark for the planning of future prognosis and therapy for patients with gastric carcinoma.

**Keywords:** Gastric carcinoma; Clinicopathologic risk factors, Clinical stage, Lymph

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4 node metastasis rate.  
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7 **Strengths and limitations of this study**  
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- 9
- 10 • This was a retrospective cohort study including seven hundred and sixteen  
11 participants.  
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  - 13 • We followed up participants for at least five years.  
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  - 15 • Data from twenty-three independent variables were collected.  
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  - 17 • This study has some limitations, for instance, there were missing values for  
18 some of the variables; for some subjects, the exact death time was not available  
19 and then estimated instead.  
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## 1. Introduction

Gastric cancer is a heterogeneous, multifactorial disease, which is known as the fifth most common cancer and the third leading cause of cancer-related death worldwide in 2018.<sup>1,2</sup> The incidence and mortality of gastric carcinoma were varying geographically and were dramatically different between Western countries and Eastern countries<sup>3</sup>. According to reports, approximately, 0.7 million people died because of gastric cancer each year<sup>3,4</sup>, the second highest incidence and mortality rate after lung cancer, in which alone accounts for 42% of all gastric cancer cases worldwide<sup>5</sup>. About 70% of the case translates into a high fatality, significantly higher than other cancers such as liver and breast cancers.<sup>6</sup> China is most notable among these countries having the highest incidence and mortality of gastric cancer. It was reported from WHO that there were approximately 456,124 new cancer cases and more than 390,128<sup>7</sup> cancer deaths in 2018 and the overall estimated age-standardized (World) incidence rate in 2018 was 23.7 per 100,000 in China.<sup>1,7</sup>

The epidemiological and clinicopathological characteristics of gastric cancer still largely remain unknown, although some risk factors have been identified in the previous literature. It has been reported that the incidence ratio of gastric cancer could vary wildly in different gender and across different geography; For example, the incidence rate was 2~3-folds higher in men compared to women;<sup>8</sup> Among different countries, the relatively highest incidence rates were found in East Asia, East Europe, and part of South America, whereas the lowest rates were reported in North America, United Kingdom and most parts of Africa.<sup>9</sup> Furthermore, the survival rates were poorer

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4 among smokers, alcohol drinkers, obesity, and people who have the symptom of  
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6 esophageal acid reflux and consume pickled, salty and smoked food.<sup>10-12</sup> Studies also  
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8 reported that the incidence rate of gastric cancer was highly correlated with age,  
9  
10 especially among patients aged between 50 and 70 years old.<sup>13-15</sup> Of those cases  
11  
12 confirmed between 2005 and 2009 in the United States, around 1% of patients ages  
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14 from 20 to 34 years occurred and the disease considerably raised to 29% among people  
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16 who were between 75 and 84 years old<sup>16</sup>. In comparison, cases in patients younger than  
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18 30 years are very rare. On the other hand, gastric carcinoma is one of the heaviest  
19  
20 burdens of cancer-related cost.<sup>4</sup> Recently, with the advancement of medical standards,  
21  
22 the trend of declining incidence and mortality rate of gastric cancer have been reported.  
23  
24 However, the absolute numbers of gastric cancer cases and the prognosis remain big  
25  
26 issues in the health programs. Moreover, survival times of gastric cancer patients  
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28 remained dismal, and the overall five-year relative survival rate was only about 35% in  
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30 the most area of the world.<sup>17</sup> For the therapy of stomach cancer, most of the current  
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32 methods are still surgery combined with chemotherapy. Surgery is the most preferred  
33  
34 treatment for gastric carcinoma, but the survival rate of patients undergoing surgery  
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36 remains very low. Many studies have revealed that the average survival time of  
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38 advanced gastric cancer is less than 12 months<sup>18-21</sup>. Therefore, how to timely assess the  
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40 condition, to judge the prognosis, and to develop a reasonable postoperative care  
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42 program become a vital part of gastric cancer treatment.<sup>22-24</sup> However, there are many  
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44 factors influenced on the prognosis in patients with gastric carcinoma, mainly due to  
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46 some clinicopathological features. Based on the literature, the major  
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4 clinicopathological features related to the prognosis of gastric cancer include clinical  
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6 stage, tumor size, infiltration depth, Lauren classification, and lymph node metastasis  
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9 rate<sup>21,25,26</sup>.

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11 Although there are numerous factors have been shown to be related to the prognosis  
12  
13 of stomach cancer, most of the previous cohort studies focused on the effect of a single  
14  
15 pathological factor on the prognosis with small sample size<sup>21</sup>. It is not easy to identify  
16  
17 the most significant factors concerning prognosis because of the high correlations  
18  
19 among those variables. Therefore, in order to get a further systematically understanding  
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21 of gastric carcinoma and to identify the effects of various risk variables on postoperative  
22  
23 survival of gastric cancer patients, we collected and analyzed the data from patients  
24  
25 with stomach carcinoma undergoing surgical treatment during the period from January  
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27 1<sup>st</sup>,2001 to December 31<sup>th</sup>,2012 in the First Affiliated Hospital of Anhui Medical  
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29 University.

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31 In the present study, we grouped the data according to the classification criteria of  
32  
33 each pathological factor. On the basis of sufficient follow-ups, survival analysis was  
34  
35 used to analyze the various pathological factors.

## 36 37 38 39 40 41 42 43 44 45 **2. Method**

### 46 47 48 **Study cohort**

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50 Between January 1<sup>st</sup>, 2001 and December 31<sup>th</sup>, 2012, seven hundred and sixteen  
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52 patients aged between 22–84 years with gastrectomy were registered with gastric  
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54 adenocarcinoma and underwent surgery in the First Affiliated Hospital of Anhui  
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56 Medical University in Anhui, China.



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4 The WHO classification criteria and the 7<sup>th</sup> edition of the American Joint  
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6 Committee on Cancer (AJCC) <sup>27</sup> were used for gastric cancer macroscopic and  
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8 histological classifications  
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11 Categorical and continuous clinicopathologic variables were collected and  
12  
13 examined to determine prognostic factors as listed in Table 1. Data on age (24-88), age  
14  
15 square, gender (male, female), Borrmann's type (types I-IV), Lauren's classification  
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17 (intestinal type, diffuse type, others), clinical stage (0-4), T stage (I-IV, Tis), N stage  
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19 (0-3), M stage (0/1), tumor location (proximal, body, distal, more than two sites), type  
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21 I surgical (all stomach, proximal, distal), surgical type II groups (radical, palliative),  
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23 and lymphovascular invasion (no, yes), were collected for each patient.  
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30 Other clinicopathologic variables, such as positive lymph nodes number, total  
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32 lymph nodes number, lymph node metastasis rate, surgical margin, tumor size, invasion  
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34 degree tumor nodes number were originally recorded as continuous variables and  
35  
36 subsequently categorized for the current analysis. Accordingly, categorical variables:  
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38 positive lymph nodes number (0, 1-6,7-15,≥16), surgical margin (negative, positive),  
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40 tumor size(≤4cm, 4-8cm, ≥8cm), invasion degree (mucosa, submucosa, muscular, all  
41  
42 layer), lymph node metastasis rate (0, ≤0.35, 0.35-0.73, ≥0.74), and total lymph nodes  
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44 number (0,1-6,7-15,≥16) were also used in the analyses.  
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50 The current study complied with the of Strengthening the reporting of  
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52 observational studies in epidemiology (STROBE) reporting guidelines for  
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54 observational studies.  
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### 58 **Ethics statement**

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4 The current study complied with the principles of the Declaration of Helsinki and  
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6 was overseen by the human ethics committees at the First Affiliated Hospital of Anhui  
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9 Medical University in China, as well as by a data and safety monitoring board (IRB  
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11 approval number: PJ-2019-01-14). All patient in the present study were informed and  
12  
13 acknowledged that their medical records were potentially recorded for scientific  
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15 research and that their confidentiality would be maintained.  
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### 18 19 **Patient and Public Involvement**

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22 Patients and public were not involved in the study design, nor the recruitment.  
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### 24 25 **Statistics analyses**

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27 In all of the analyses, the survival time defined as the period between the dates of  
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29 surgery and death (or last follow-up) would be the dependent variable. Firstly, an  
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31 unadjusted analysis was performed for each of the independent variables. Specifically,  
32  
33 for each independent variable, Kaplan-Meier method<sup>28</sup> was applied to see whether it is  
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35 associated with the dependent variable. Then a Cox proportional hazard regression  
36  
37 model with backward variable selection was performed to determine which prognostic  
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39 variables independently affected gastric cancer and to estimate the adjusted hazard  
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41 ratios (HR) at the same time.<sup>29</sup> 95% confidence intervals were examined, and two-  
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43 sided p-values <0.05 were defined as statistically significant in the present study. All  
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45 endpoints were updated in 2018 June to 2019 January, that makes every case have  
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47 enough time for follow-up ( $\geq 5$  years). For this study, all analyses were performed using  
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49 SAS (SAS Institute Inc., Cary, NC, USA) and SAS (r) Proprietary Software 9.4  
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51 (TS1M2).  
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### 3. Results

#### Results from the unadjusted analyses

Univariable analyses were performed to evaluate significant relationships between each clinicopathological feature and the patient's survival time. The results were reported in Table 1. Of the 23 demographic and pathological variables entered in this study, 18 of them were found to have a significant influence on survival time. This cohort was composed of 553 males and 163 females. Based on the clinical TNM classification, the numbers of patients in stage II, and III cancer were 155 and 411, respectively. Most patients (N=612) did not have the lymphovascular invasion. Gastric lesions were located on the proximal of the stomach for 400 patients, on the body of the stomach for 164 patients, on the distal of stomach for 97, and more than two sites among 52 participants. Among the entire patients, 673 patients were proceeded to radical resection, and 41 proceed to palliative resection. About 569 patients had all layer invasion of their stomachs. In addition, a total of 580 patients had received stomach surgery. 253 participants had 0 lymph node metastasis rate, 200 patients had lymph node metastasis rate smaller than 0.35, 149 had lymph node metastasis rate between 0.35-0.7, and the rest of them had lymph node metastasis rate greater than 0.7. Furthermore, in this study, 299 patients had tumor sizes smaller than 4cm, 275 of the total cohort had tumor sizes between 4-8cm, and 129 patients' tumor sizes were larger than 8 cm.

Unfavorable prognostic factors of gastric cancer included the Borrmann's type, the margin, M stage, N stage, T stage, lymph node metastasis rate, surgical type II groups,

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4 clinical stage, tumor size, invasion degree, tumor location, positive lymph nodes  
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6 number, total lymph nodes number and tumor nodes number. Those factors had  
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8 prognostic significance ( $p < 0.05$ ) from the unadjusted analyses. However, there were no  
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10 significant differences in survival rate among age, age square, Lauren's classification,  
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12 surgical type I groups, lymphovascular invasion, lymph node metastasis rate, and  
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14 gender in the current unadjusted analysis according to their larger p-values (p-  
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16 value  $> 0.05$ ).

### 21 22 **Results from the adjusted analysis**

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24 The Cox's proportional hazard model was applied to identify the most important  
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26 independent prognostic factors among the 23 variables. The results of the estimated  
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28 regression coefficients and standard error were displayed in Table 2. Adjusted analysis  
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30 revealed that survival time was independently correlated with five factors. In summary,  
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32 the important prognosis and clinicopathologic factors retained were the following: age  
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34 (HR=0.891, p-value=0.0017, 95% CI: 0.829-0.958), age square (HR =1.001, p-value<  
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36 0.0007, 95% CI: 1.000-1.002), lymph node metastasis rate (HR for  $\leq 0.35$ , 0.35-0.73,  
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38  $\geq 0.74$ : 0.592, 1.016, and 1.276, respectively; p-value<0.0001, 95% CI: 0.377-0.930,  
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40 0.641-1.612, 0.791-2.060, respectively), surgical type II groups (HR for Palliative is  
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42 1.587, p-value = 0.0319, 95% CI: 1.041-2.421), tumor size (HR for 4-8cm and  $\geq 8$ cm:  
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44 1.303 and 1.529, respectively, p-value =0.0134, 95% CI: 1.022-1.679, 1.141-2.049,  
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46 respectively), and clinical stage (HR for 1, 2, and 3: 0.201, 0.376 and 0.791 respectively,  
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48 p-value  $< 0.0001$ , 95% CI: 0.106-0.384, 0.215-0.658, 0.486-1.289, respectively).

## 49 50 **4. Discussion**

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4 In this study with total 716 gastric cancer patients, we identified the following  
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6 clinicopathologic factors which were independently significantly associated with  
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8 gastric carcinoma in term of the adjusted analysis: age, lymph node metastasis rate,  
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10 tumor size, type II Surgery, and clinical stage. The adjusted analysis revealed that other  
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12 variables, such as gender, Borrmann's type, TMN stage, tumor location, surgical type  
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14 I groups, surgical margin, lymphovascular invasion, and total lymph nodes number,  
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16 might not independently play a major role in the prognosis. For the factor age, we found  
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18 it had a non-linear effect on the outcome: both age and its square were statistically  
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20 significantly associated with survival time.  
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27 In our current study, among these potential risk factors, the prognosis of patients  
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29 with gastric carcinoma was seen strongly affected by the rate of metastatic lymph nodes,  
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31 which also has been emphasized in previous studies performed in different countries<sup>30,31</sup>.  
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33 The result from the study by Kim, Lee et al. indicated that the survival rate was  
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35 remarkably decreased in association to increased metastatic lymph nodes rate.<sup>32</sup> Msika  
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37 et al. also found that lymph node metastasis played an important role and was the only  
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39 independent prognostic risk factor in their study among 86 participants who underwent  
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41 curative resection.<sup>33</sup> Furthermore, the German Gastric Carcinoma Study (GGCS)<sup>34</sup>  
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43 suggested that the lymph node ratio should be considered as the significant independent  
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45 prognostic variables among patients underwent resected stomach carcinoma, and  
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47 indicated that extended lymph node dissection was the most critical treatment among  
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49 patients with radical gastrectomy for long-term survival.  
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58 The clinical stages, which were defined by the "depth of tumor invasion (T), the  
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4 location of perigastric lymph node metastases (N), and the presence or absence of  
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6 distant metastases (M)<sup>35</sup>, was seen significantly associated with stomach cancer in the  
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8 present study. Based on the results, the hazard ratios of gastric cancer were very small  
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10 on stage 0, I, II III compared to stage IV; this could be caused by late presentation of  
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12 symptoms combined to the lack of pathognomonic signs together with the absence of a  
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14 screening programme. The prognostic significance of a more advanced stage in our  
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16 adjusted analysis was comparable to results from other studies.<sup>36,37,38</sup> Specifically, the  
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18 AJCC was formally applied the TNM, and now it is the most remarkable instrument for  
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20 treatment planning in oncology and also efficient for evaluating the patient's prognosis  
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22 in 1970.  
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30 Our results also displayed a significant reversed effect (HR=0.869, p-value=0.002)  
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32 among young patients with gastric cancer, compared to older participants. A review for  
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34 the white population from 1974 to 2006 in the U.S. displayed similar trends: the  
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36 incidence of gastric cancer in patients aged 25–39 had raised from 0.27 to 0.45 per  
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38 100,000 individuals whereas the incidence had been declining for older populations.  
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40 More specifically, among patients aged between 60 and 84, the incidence of gastric  
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42 carcinoma had dropped from 19.8 to 12.8 per 100,000.<sup>39</sup> Some studies provided  
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44 possible explanation why younger patients with stomach carcinoma have an  
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46 unfavorable prognosis than older patients: younger patients could have a larger  
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48 percentage with advanced tumors stage due to lower suspicion of malignant disease and  
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50 aggressive tumor biology.<sup>40,41</sup>  
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58 According to our adjusted analysis results, we found that tumor size was an  
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4 independent risk factor for prognostic. In fact, tumor size is a valuable risk factor since  
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6 it can be examined quite easily before the surgery, although the prognostic risk of tumor  
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8 size among patients with stomach carcinoma maintains inconsistent. Some researches  
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10 suggested that tumor size is not an independent prognostic variable in patients who had  
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12 stomach carcinoma.<sup>42,43,44</sup> However, other previous studies have displayed that tumor  
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14 size should be considered as a risk feature for long-term survival after resection of  
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16 gastric carcinoma<sup>45-48,49</sup>, and there was a significant relationship between larger tumor  
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18 size and lesion resectability. Tumor size of gastric cancer was a vital variable that  
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20 affects the success of enbloc resection so that patients need a higher level of expertise  
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22 and experience for their treatment. There was also a trend that tumor size can raise with  
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24 the depth of tumor invasion and the extent of lymph node metastasis: the size of the  
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26 tumor is profoundly associated to “Borrmann’s type IV, adjacent organ invasion (T4)  
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28 and higher lymph node and distant metastasis rate”.<sup>43,50</sup> The possible reason for this is  
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30 that most patients with stage III or stage IV cancers had a relatively lower radical  
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32 resection and remained a lower 5-year survival rate in many cases.<sup>51</sup>

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43 Additionally, our results show that poorer prognosis among patients who had  
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45 palliative gastrectomy with a higher risk of gastric cancer compared with radical  
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47 gastrectomy. Although, the results from Dutch clinical randomize trial<sup>52</sup> suggested that  
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49 palliative gastrectomy could be beneficial for younger patients ( age<70) whose tumor  
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51 load was restricted to one metastatic site, another previous study<sup>53</sup> indicated that  
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53 “palliative gastrectomy has no survival benefit (p-value = 0.705, 0.331, respectively) in  
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55 the peritoneal dissemination and multi-organ metastases groups”. Furthermore,  
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4 palliative gastrectomy showed no obvious favorable effect on the long-term survival or  
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6 improvement of the quality of life among patients with gastric cancer.<sup>54</sup> Currently,  
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9 bursectomy has become a vital part of radical gastrectomy with extended  
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11 lymphadenectomy as a therapy for advanced gastric carcinoma in Japan.<sup>55</sup> Moreover,  
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14 Maruyama K et al. also suggested that radical gastrectomy remains the only curative  
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17 treatment option for gastric cancer.<sup>56</sup>

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20 There were several strengths, and limitations of our current study should be  
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22 considered. We used the Cox proportional hazard regression model, which is one of the  
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24 most reliable and generally used methods for multivariable analyses. Our findings  
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26 showed that tumor size encompasses powerful prognostic information for gastric cancer.  
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29 From Jun K.H et al.,<sup>57</sup> a statistically significant independent association has been found  
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31 to prove the association between tumor size and stomach carcinoma-related survival  
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33 and it was a vital predictor for advanced gastric cancer, but may not be detectable in  
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35 early gastric carcinoma. In addition, our dataset includes patients with long-term  
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38 follow-up duration, which was rare for other current studies conducted in China, from  
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41 January 1<sup>st</sup> to December 31<sup>th</sup> 2012. However, all the patients in this study were from  
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44 Anhui, a province of China. This fact could lead to a lack of generalizability of our  
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47 findings to the general Chinese population. Finally, the present study is subject to  
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50 limitations inherent to all observational studies. For instance, some potential residual  
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53 confounders may not be recognized in the analysis and possible selection bias due to  
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56 loss to follow up.

## 58 **5. Conclusion**



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4 In our study, five prognostic risk characteristics have been identified in patients  
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6 with gastric carcinoma. However, the survival rate for stomach carcinoma patients  
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8 remains very low. As a result, identifying and predicting important and useful prognosis  
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10 indicators before treatment are critical for gastric cancer patients. Since these  
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12 prognostic factors usually depend largely on the postoperative histological examination,  
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14 they may not be available to a surgeon at the time of treatment. Therefore, a useful,  
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16 simple prognostic index could be produced with distinct survival rates in specific risk  
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18 groups. The findings from the current study can be applied to help clinical decision-  
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20 making, and to be considered as a benchmark for planning future prognosis and  
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22 treatment. Finally, it is of substantial vital to improve early detection and to investigate  
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24 the feasibility and survival benefit of therapy for patients with stomach carcinoma.  
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42  
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51  
52 collection, and analysis, decision to publish, or preparation of the manuscript.  
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55 **Conflict of interest:** The authors declare no conflict of interest in this study.  
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58 **Patient consent for publication:** Not required.  
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**Ethics approval:** This study was approved by the Institutional Review Board of the First Affiliated Hospital of Anhui Medical University in China (IRB approval number: PJ-2019-01-14).

**Data sharing statement:** No additional data are available.

**Contributors:** KH, ZC, QW designed and oversaw the study; SW, ZW, LL, ZH, WY contributed to data collection and analysis; KH, SW, ZW, ZC, and QW drafted the manuscript. All authors participated in discussion and approved the final manuscript.

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## Tables

**Table 1. Results from unadjusted analyses of clinical and pathologic variables.**

Variable	Frequency	X <sup>2</sup> ab	DF	P-value
<b>Gender</b>		0.70	1	0.40
Female	163			
male	553			
<b>Borrmann's Type</b>		12.32	5	0.030*
Type I	29			
Type II	510			
Type III	56			
Type IV	76			
Type V	32			
<b>Surgical margin</b>		7.80	2	0.020*
negative	641			
positive	46			
<b>Lauren's classification</b>		1.88	3	0.39
Intestinal type	206			
Diffuse type	460			
Others	27			
<b>M stage</b>		19.21	2	<.0001 *
0	685			
1	28			
<b>N stage</b>		107.14	4	<0.0001*
0	253			
1	170			
2	176			
3	115			
<b>T stage</b>		59.60	4	<0.0001*
1	63			
2	74			
4	566			
Tis	11			
<b>Lymph node metastasis rate</b>		118.64	4	<.0001*
0	253			
≤0.35	200			
0.35-0.7	149			
≥0.7	108			
<b>Surgical type I groups</b>		5.52	3	0.13
All Stomach	580			
Proximal	28			
Distal	101			

<b>Surgical type II groups</b>		45.35	2	<.0001*
Radical	673			
Palliative	41			
<b>Lymphovascular invasion</b>		0.34	2	0.56
No	612			
Yes	98			
<b>Clinical stage</b>		107.73	5	<.0001*
0	11			
1	108			
2	155			
3	411			
4	29			
<b>Tumor nodes number</b>		22.30	3	<.0001*
0	638			
1-2	55			
≥3	15			
<b>Tumor size</b>		60.78	3	<.0001*
≤4cm	299			
4-8cm	275			
≥8cm	129			
<b>Invasion degree</b>		52.68	4	<.0001*
Mucosa	25			
Submucosa	38			
Muscular	82			
All layer	569			
<b>Positive lymph nodes number</b>		99.45	4	<.0001*
0	258			
1-6	338			
7-15	99			
≥16	18			
<b>Tumor location</b>		14.18	4	0.0067*
Proximal	400			
Body	164			
Distal	97			
More than two sites	52			
<b>Total lymph nodes number</b>		8.13	5	0.15
0	2			
1-6	196			
7-15	394			
≥16	117			
<b>Age</b>	716	1.98	1	0.19
<b>Age<sup>2</sup></b>	716	3.42	1	0.064
<b>Positive lymph nodes number</b>	713	79.65	1	<.0001*



<b>Total lymph nodes number</b>	710	5.97	1	0.015*
<b>Lymph node metastasis rate</b>	710	1.59	1	0.21
<b>Tumor nodes number</b>	708	27.24	1	<.0001*

\*: P-value<0.05; a: Test of Equality over Strata; b: Log Rank Test.

**Table 2. Results from adjusted analysis of prognostic variables.**

<b>Variables</b>	<b>Estimated coefficient</b>	<b>Estimated SE</b>	<b>Estimated HR</b>	<b>95% CI of HR</b>	<b>P-value</b>
<b>Age</b>	-0.115	0.037	0.891	0.829-0.958	0.0017
<b>Age square</b>	0.001	0.00032	1.001	1.000-1.002	0.0007
<b>Lymph node metastasis rate</b>					<.0001
0 (reference)	-	-	1.000	-	
≤0.35	-0.524	0.230	0.592	0.377-0.930	
0.35-0.7	0.0159	0.235	1.016	0.641-1.612	
≥0.7	0.244	0.244	1.276	0.791-2.060	
<b>Surgical type II groups</b>					0.032
Radical	-	-	1.000	-	
Palliative	0.462	0.215	1.587	1.041-2.421	
<b>Tumor size</b>					0.013
≤4cm (reference)	-	-	1.000	-	
4-8cm	0.270	0.126	1.310	1.022-1.679	
≥8cm	0.424	0.149	1.529	1.141-2.049	
<b>Clinical Stage</b>					<.0001
4 (reference)	-	-	1.000	-	
0	-12.796	309.130	0.000	(-, -)	
1	-1.602	0.329	0.201	0.106-0.384	
2	-0.979	0.285	0.376	0.215-0.658	
3	-0.234	0.248	0.791	0.486-1.289	



STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-6
Objectives	3	State specific objectives, including any prespecified hypotheses	1, 6
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	2
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	7-8
Study size	10	Explain how the study size was arrived at	6-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	8
<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	9-10

1	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10
2		(b) Report category boundaries when continuous variables were categorized		
3		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		
4	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
5	<b>Discussion</b>			
6	Key results	18	Summarise key results with reference to study objectives	11
7	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
8	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-14
9	Generalisability	21	Discuss the generalisability (external validity) of the study results	11-14
10	<b>Other information</b>			
11	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

\*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

# BMJ Open

## Clinicopathologic Risk Factors for Gastric Cancer: A Retrospective Cohort Study in China

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Secondary Subject Heading:	Gastroenterology and hepatology
Keywords:	Gastric carcinoma, Clinicopathologic risk factors, Clinical stage, Lymph node metastasis rate

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# Clinicopathologic Risk Factors for Gastric Cancer: A Retrospective Cohort Study in China

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## Abstract

**Objective:** To examine the potential clinicopathologic factors affecting the prognosis of patients with stomach cancer after surgical treatment in China.

**Methods:** Between January 1<sup>st</sup>, 2001 and December 31<sup>st</sup>, 2012, a total of 716 patients aged 22–84 years with gastric cancer were enrolled in the study. Survival analysis techniques including log rank test and Cox proportional hazard regression model were applied to evaluate the prognostic significance of clinicopathological characteristics in terms of survival time.

**Results:** Of the twenty-four demographic and pathological variables collected in the data, 16 prognostic factors of gastric cancer were found to have statistically significant influences on survival time from the unadjusted analyses. The adjusted analysis furtherly revealed that age, age square, lymph node metastasis rate group, tumor size group, surgical type II and clinical stage were important prognosis and clinicopathologic factors for gastric cancer in Chinese.

**Conclusion:** Our study with relatively large sample size and many potential risk factors enable us to identify independent risk factors associated with the prognosis of gastric cancer. Findings from the current study can be used to assist clinical decision-making, and serve as a benchmark for the planning of future prognosis and therapy for patients with gastric carcinoma.

**Keywords:** Gastric carcinoma, Clinicopathologic risk factors, Clinical stage, Lymph node metastasis rate.

### Strengths and limitations of this study

- This was a retrospective cohort study, including seven hundred and sixteen participants.
- We followed up all participants for at least five years.
- Data of twenty-four independent variables were collected.
- This study has some limitations, for instance, there were missing values for some of the variables; for some subjects, the exact death time was not available and then estimated instead.

## 1. Introduction

Gastric cancer is a heterogeneous, multifactorial disease, which is known as the fifth most common cancer and the third leading cause of cancer-related death worldwide in 2018.<sup>1,2</sup> According to previous reports, approximately 0.7 million people died because of gastric cancer each year<sup>3</sup>, and about 70% of the gastric cancer cases had high fatality, significantly higher than other cancers such as the liver and breast cancers<sup>4</sup>. However, the incidence and mortality of gastric carcinoma vary geographically; they were dramatically different between Western and Eastern countries<sup>3</sup>. The highest incidence rates were found in East Asia, East Europe, and part of South America, whereas the lowest rates were reported in North America, United Kingdom and most parts of Africa.<sup>5</sup> China is most notable among these countries having the highest incidence and mortality risk of gastric cancer. WHO reported that China had approximately 456,124 new gastric cancer cases and more than 390,128 gastric cancer deaths, with an estimated overall age-standardized incidence rate of 23.7 per 100,000 in 2018.<sup>1,6</sup>

The epidemiological and clinicopathological characteristics of gastric cancer still largely remain uncertain, although some risk factors have been identified in the literature. It has been reported that the survival rates were lower among smokers, alcohol drinkers, obesity, and people who have the symptom of esophageal acid reflux and consume pickled, salty, and smoked food.<sup>7-9</sup> Studies also suggested that the incidence rate of gastric cancer was highly correlated with age, especially among patients aged between 50 and 70 years old.<sup>10-13</sup> It has been reported that gastric

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4 carcinoma is one of the heaviest burdens of cancer-related cost, the absolute numbers  
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6 of gastric cancer cases and the prognosis remain big issues in the health programs<sup>14</sup>.  
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9 The current most popular therapy for stomach cancer is surgery combined with  
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11 chemotherapy. Surgery is the most preferred treatment for gastric carcinoma, but the  
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13 survival rate of patients undergoing surgery remains very low. Previous studies have  
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15 revealed that the average survival time of patients with advanced gastric cancer is less  
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17 than 12 months<sup>15-18</sup>. Therefore, how to timely assess the condition, judge the prognosis  
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19 risk after therapy, and develop a reasonable postoperative care program becomes a vital  
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21 part of gastric cancer treatment.<sup>19-21</sup>  
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27 Many clinicopathological factors, including clinical stage, tumor size, infiltration  
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29 depth, Lauren classification, and lymph node metastasis rate, might jointly influence  
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31 the prognosis in patients with gastric carcinoma<sup>18,22,23</sup>. However, most of the previous  
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33 cohort studies in this area had small sample sizes and each focused on the effect of a  
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35 single pathological factor<sup>18</sup>. It is important but challenging to identify the most  
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37 significant and independent factors associated with prognosis since many factors are  
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39 highly correlated. To have a systematically comprehension of gastric carcinoma and to  
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41 identify independent risk factors on gastric cancer patients, we conducted the current  
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## 50 **2. Method**

### 51 **Design**

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53 This was a retrospective cohort study.  
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### 56 **Participants**



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4 All participants were recruited from Anhui, China.  
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#### 6 **Ethics statement**

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8  
9 The current study complied with the principles of the Declaration of Helsinki and  
10 was overseen by the human ethics committees at the First Affiliated Hospital of Anhui  
11 Medical University in China, as well as by a data and safety monitoring board (IRB  
12 approval number: PJ-2019-01-14). All patients in the present study were informed and  
13 acknowledged that their medical records were potentially recorded for scientific  
14 research and that their confidentiality would be maintained.  
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#### 24 **Patient and Public Involvement**

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26  
27 Patients and the public were not involved in the study design, nor the recruitment.  
28

#### 29 **Study cohort**

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32 Between January 1<sup>st</sup>, 2001 and December 31<sup>th</sup>, 2012, seven hundred and sixteen  
33 patients aged between 22 and 84 years with gastrectomy were registered with gastric  
34 adenocarcinoma and underwent surgery in the First Affiliated Hospital of Anhui  
35 Medical University in Anhui, China.  
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43 The WHO classification criteria and the 7<sup>th</sup> edition of the American Joint  
44 Committee on Cancer (AJCC)<sup>24</sup> were used for gastric cancer macroscopic and  
45 histological classifications. Categorical and continuous clinicopathologic variables  
46 were collected and analyzed. Data on age (24-88), gender (male, female), Borrmann's  
47 type (I-V), Lauren's classification (intestinal type, diffuse type, others), clinical stage  
48 (0-4), T stage (I-IV, Tis), N stage (0-3), M stage (0,1), tumor location (proximal, body,  
49 distal, more than two sites), type I surgical (all stomach, proximal, distal), surgical type  
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4 II group (radical, palliative), and lymphovascular invasion (yes, no), were collected for  
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6 each patient. Moreover, age square was added to investigate the potential nonlinear  
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8 effect of age.  
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11 Other clinicopathologic variables, such as positive lymph nodes number, total  
12  
13 lymph nodes number (the total number of lymph nodes), lymph node metastasis rate  
14  
15 (the metastasis rate of lymph nodes), surgical margin, tumor size, tumor nodes number  
16  
17 (number of tumor nodes), invasion degree were also collected. For those variables  
18  
19 originally recorded as continuous were also categorized for the current analysis.  
20  
21 Accordingly, categorical variables: positive lymph nodes number group (0, 1-6,7-  
22  
23 15,≥16), surgical margin (negative, positive), tumor size group ( $\leq 4$ cm, 4-8cm,  $\geq 8$ cm),  
24  
25 invasion degree (mucosa, submucosa, muscular, all layer), lymph node metastasis rate  
26  
27 group (0,  $\leq 0.35$ , 0.35-0.73,  $\geq 0.74$ ), and total lymph nodes number group (0,1-6,7-  
28  
29 15,≥16) were also used in the analyses. However, some variables may have missing  
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31 values.  
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40 The current study complied with the Strengthening the Reporting of Observational  
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42 Studies in Epidemiology (STROBE) reporting guidelines.  
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#### 45 **Statistics analyses**

46  
47 In all of the analyses, the survival time defined as the period between the dates of  
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49 surgery and death (or last follow-up) would be the dependent variable. All endpoints  
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51 were updated between June 2018 and January 2019, which resulted in an at least 5 years  
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53 follow-up for each participant. First, an unadjusted analysis was performed for each  
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55 independent variable. Specifically, for each categorical (continuous) independent  
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4 variable, the log rank test (the Cox proportional hazard model) was applied to see  
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6 whether it is associated with the dependent variable without adjusting for any other  
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8 independent variables. Then the Cox proportional hazard regression model with  
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10 backward variable selection was performed to identify factors independently associated  
11  
12 with the survival time, and to estimate their adjusted hazard ratios (HR). The 95%  
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14 confidence intervals (CIs) of the HR for significant effects were also reported. In this  
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16 study, the two-sided p-values <0.05 were used to define statistical significance and all  
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18 analyses were performed using SAS (SAS Institute Inc., Cary, NC, USA) and SAS (r  
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20 Proprietary Software 9.4 (TS1M2).  
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### 27 **3. Results**

#### 28 **Results from the unadjusted analyses**

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30 The results from the univariable analyses were reported in Table 1. Table 1 also  
31  
32 listed the frequencies for each variable. This cohort was composed of 553 males and  
33  
34 163 females. Based on the clinical TNM classification, the numbers of gastric cancer  
35  
36 patients in stage 0, I, II, III, and IV were 11, 108, 155, 411, and 29, respectively. 98  
37  
38 patients had lymphovascular invasion while 612 did not. Gastric lesions were located  
39  
40 on the proximal of the stomach for 400 patients, on the body of the stomach for 164  
41  
42 patients, on the distal of the stomach for 97, and 52 participants had more than two sites  
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44 gastric lesions. Moreover, 673 patients proceeded to radical resection, and 41 proceed  
45  
46 to palliative resection. 569 patients had all layer invasion of their stomachs. In addition,  
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48 580, 28, and 101 patients received all stomach, proximal, and distal gastric surgery,  
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50 respectively. The numbers of participants whose lymph node metastasis rate were 0,  
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4 between 0 and 0.35, between 0.35 and 0.7, and greater than 0.7 were 253, 200, 149, and  
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6 108, respectively. Furthermore, in this study, there were 299, 275, and 129 patients  
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8 whose tumor sizes were smaller than 4cm, between 4 and 8cm, and larger than 8 cm,  
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10 respectively.  
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14 Sixteen significant prognostic factors of gastric cancer including Borrmann's type,  
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16 surgical margin, M stage, N stage, T stage, lymph node metastasis rate group, surgical  
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18 type II group, clinical stage, tumor nodes number group, tumor size group, invasion  
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20 degree, positive lymph nodes number group, tumor location, positive lymph nodes  
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22 number, total lymph nodes number, and tumor nodes number were identified ( $p < 0.05$ )  
23  
24 from the unadjusted analyses. However, there were no significant associations between  
25  
26 survival time and gender, Lauren's classification, surgical type I group, lymphovascular  
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28 invasion, total lymph node number, age, age square, and lymph node metastasis rate  
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30 from the unadjusted analysis according to their large p-values ( $> 0.05$ ).  
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### 37 **Results from the adjusted analysis**

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39 The results of the estimated hazard ratios and their 95% confidence interval from  
40  
41 the adjusted analysis were reported in Table 2. The adjusted analysis identified six  
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43 variables, each was independently associated with survival time. These variables and  
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45 their estimated adjusted HR after adjusting for the other effects in the model were: age  
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47 (HR=0.891, p-value=0.0017, 95% CI: 0.829-0.958), age square (HR =1.001, p-value=  
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49 0.0007, 95% CI: 1.000-1.002), lymph node metastasis rate group (HR for  $\leq 0.35$ , 0.35-  
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51 0.73,  $\geq 0.74$ : 0.592, 1.016, and 1.276, respectively; p-value $< 0.0001$ , 95% CI: 0.377-  
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53 0.930, 0.641-1.612, 0.791-2.060, respectively), surgical type II group (HR=1.587, p-  
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4 value = 0.0319, 95% CI: 1.041-2.421), tumor size group (HR for 4-8cm and  $\geq$ 8cm:  
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6 1.303 and 1.529, respectively, p-value =0.0134, 95% CI: 1.022-1.679, 1.141-2.049,  
7  
8 respectively), and clinical stage (HR for 1, 2, and 3: 0.201, 0.376 and 0.791 respectively,  
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10 p-value < 0.0001, 95% CI: 0.106-0.384, 0.215-0.658, 0.486-1.289, respectively).  
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#### 14 **4. Discussion**

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17 In this study with total 716 gastric cancer patients, we identified the following  
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19 clinicopathologic factors which were independently associated with gastric carcinoma  
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21 from the adjusted analysis: age (and age square), lymph node metastasis rate, tumor  
22  
23 size, type II surgery, and clinical stage. The adjusted analysis revealed that other  
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25 variables, such as gender, Borrmann's type, TMN stage, tumor location, surgical type  
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27 I group, surgical margin, lymphovascular invasion, and total lymph nodes number,  
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29 might not independently play a major role in the prognosis. For the variable "age", we  
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31 found that it had a non-linear effect on the outcome: both age and its square were  
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33 significantly associated with survival time.  
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41 In our current study, among these identified risk factors, the prognosis of patients  
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43 with gastric carcinoma was seen strongly affected by the rate of metastatic lymph nodes,  
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45 which also has been emphasized in previous studies performed in different countries<sup>25,26</sup>.  
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47 The result from the study by Kim, Lee et al. indicated that the survival rate was  
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49 remarkably decreased with metastatic lymph nodes rate increased.<sup>27</sup> Msika et al. also  
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51 found that lymph node metastasis played an important role and was the only  
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53 independent prognostic risk factor among 86 participants who underwent curative  
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55 resection in their study.<sup>28</sup> Furthermore, the German Gastric Carcinoma Study (GGCS)<sup>29</sup>  
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4 suggested that the lymph node metastasis rate should be considered as the significant  
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6 independent prognostic variables among patients underwent resected stomach  
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8 carcinoma, and indicated that extended lymph node dissection was the most critical  
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10 treatment among patients with radical gastrectomy for long-term survival.  
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14 The clinical stages, which were defined by the “depth of tumor invasion (T), the  
15  
16 location of perigastric lymph node metastases (N), and the presence or absence of  
17  
18 distant metastases (M)”<sup>30</sup>, was found significantly associated with stomach cancer in  
19  
20 the present study. Based on the results, the hazard ratios of gastric cancer were minima  
21  
22 on stage 0, I, II III compared to stage IV; this could be caused by the late presentation  
23  
24 of symptoms combined to the lack of pathognomonic signs together with the absence  
25  
26 of a screening program. The prognostic significance of a more advanced stage in our  
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28 adjusted analysis was comparable to results from other studies.<sup>31,32,33</sup>  
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35 Based on our adjusted analysis, age had a significant nonlinear effect on the  
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37 survival time. We also found that tumor size was an independent risk factor for  
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39 prognostic. In fact, tumor size is a valuable risk factor since it can be examined quite  
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41 easily before the surgery, although the prognostic risk of tumor size among patients  
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43 with stomach carcinoma maintains inconsistent. Some researches suggested that tumor  
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45 size is not an independent prognostic variable in patients who had stomach carcinoma.  
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34,35,36 However, other previous studies have displayed that tumor size should be  
considered as a risk feature for long-term survival after resection of gastric carcinoma  
37-40,41, and there was a significant relationship between larger tumor size and lesion  
resectability. Tumor size of gastric cancer was a vital variable that affects the success

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4 of enbloc resection; patients with larger tumor sizes need higher level of expertise and  
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6 experience for their treatment. Tumor size could raise with the depth of tumor invasion  
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8 and the extent of lymph node metastasis increase: the size of the tumor is profoundly  
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10 associated to “Borrmann’s type IV, adjacent organ invasion (T4) and higher lymph  
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12 node and distant metastasis rate”.<sup>35,42</sup> A possible explanation is that most patients with  
13  
14 stage III or stage IV cancers had a relatively lower radical resection and remained a lower  
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16 5-year survival rate.<sup>43</sup>

21  
22 Our results also showed that patients who received palliative gastrectomy had  
23  
24 poorer prognosis and higher risks compared to patients with radical gastrectomy.  
25  
26 The results from Dutch clinical randomize trial<sup>44</sup> suggested that palliative gastrectomy  
27  
28 could be beneficial for younger patients ( age<70) whose tumor load was restricted to  
29  
30 one metastatic site. On the contrary, a previous study<sup>45</sup> indicated that “palliative  
31  
32 gastrectomy has no survival benefit (p-value = 0.705, 0.331, respectively) in the  
33  
34 peritoneal dissemination and multi-organ metastases group”. Another study found that  
35  
36 palliative gastrectomy showed no obvious favorable effect on long-term survival or  
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38 improvement of the quality of life among patients with gastric cancer.<sup>46</sup> Moreover,  
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40 Maruyama K et al. suggested that radical gastrectomy remained the only curative  
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42 treatment option for gastric cancer.<sup>47</sup>

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51 There were several strengths and limitations in our current study. We used the Cox  
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53 proportional hazard regression model, which is one of the most commonly used  
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55 methods for multivariable analyses with survival time as dependent variable. Our  
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57 findings showed that tumor size encompasses important prognostic information for  
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4 gastric cancer. Based on Jun K.H et al.,<sup>48</sup> the tumor size was statistically significantly  
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6 and independently associated with stomach carcinoma-related survival, and this risk  
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8 factor was a vital predictor for advanced gastric cancer, although it may not be  
9  
10 detectable in early gastric carcinoma. In addition, our study includes patients with a  
11  
12 long-term follow-up duration, which was rarely seen from other studies conducted in  
13  
14 China. However, all the patients in this study were recruited from Anhui, a province of  
15  
16 China. This fact could lead to a lack of generalizability of our findings to the general  
17  
18 Chinese population. Finally, the present study has limitations inherent to all  
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20 observational studies. For instance, some potential confounders may not be recognized  
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22 and included in the study and selection bias could exist due to loss to follow up.  
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## 30 **5. Conclusion**

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32 Currently, identifying and predicting important prognosis indicators before  
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34 treatment are critical for gastric cancer patients. In our study, five independent  
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36 prognostic risk characteristics have been identified in patients with gastric carcinoma.  
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38 The findings from our study are useful and applicable for clinical decision-making.  
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40 They also provide a benchmark for planning future prognosis and treatment for gastric  
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42 cancer patients. Our findings can also be used to improve early detection and to  
43  
44 investigate the feasibility and survival benefit of therapy for patients with stomach  
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46 carcinoma.  
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17 **Conflict of interest:** The authors declare no conflict of interest in this study.  
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20 **Patient consent for publication:** Not required.  
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23 **Ethics approval:** This study was approved by the Institutional Review Board of the  
24  
25 First Affiliated Hospital of Anhui Medical University in China (IRB approval number:  
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27 PJ-2019-01-14).  
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30 **Data sharing statement:** No additional data are available.  
31

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33 **Contributors:** KH, ZC, QW designed and oversaw the study; SW, ZW, LL, ZH, WY  
34  
35 contributed to data collection and analysis; KH, SW, ZW, ZC, and QW drafted the  
36  
37 manuscript. All authors participated in the discussion and approved the final manuscript.  
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## Tables

Table 1. Results from unadjusted analyses of clinical and pathologic variables.

Variable	Frequency	P-value
<b>Gender</b>		0.40
Female	163	
Male	553	
<b>Borrmann's Type</b>		0.030*
I	29	
II	510	
III	56	
IV	76	
V	32	
Missing	13	
<b>Surgical margin</b>		0.020*
Negative	641	
Positive	46	
Missing	29	
<b>Lauren's classification</b>		0.39
Intestinal type	206	
Diffuse type	460	
Others	27	
Missing	23	
<b>M stage</b>		<.0001 *
0	685	
1	28	
Missing	3	
<b>N stage</b>		<.0001*
0	253	
1	170	
2	176	
3	115	
Missing	2	

<b>T stage</b>		<.0001*
1	63	
2	74	
4	566	
Tis	11	
Missing	2	
<b>Lymph node metastasis rate group</b>		<.0001*
0	253	
≤0.35	200	
0.35-0.7	149	
≥0.7	108	
Missing	6	
<b>Surgical type I group</b>		0.13
All Stomach	580	
Proximal	28	
Distal	101	
Missing	7	
<b>Surgical type II group</b>		<.0001*
Radical	673	
Palliative	41	
Missing	2	
<b>Lymphovascular invasion</b>		0.56
No	612	
Yes	98	
Missing	6	
<b>Clinical stage</b>		<.0001*
0	11	
1	108	
2	155	
3	411	
4	29	
Missing	2	
<b>Tumor nodes number group</b>		<.0001*
0	638	
1-2	55	
≥3	15	
Missing	8	
<b>Tumor size group</b>		<.0001*
≤4cm	299	
4-8cm	275	
≥8cm	129	
Missing	13	

<b>Invasion degree group</b>		<.0001*
Mucosa	25	
Submucosa	38	
Muscular	82	
All layer	569	
Missing	2	
<b>Positive lymph nodes number group</b>		<.0001*
0	258	
1-6	338	
7-15	99	
≥16	18	
Missing	3	
<b>Tumor location</b>		0.0067*
Proximal	400	
Body	164	
Distal	97	
More than two sites	52	
Missing	3	
<b>Total lymph nodes number group</b>		0.15
1-6	198	
7-15	394	
≥16	118	
Missing	6	
<b>Age</b>	716	0.19
<b>Age square</b>	716	0.064
<b>Positive lymph nodes number</b> ( Missing=3)	713	<.0001*
<b>Total lymph nodes number</b> ( Missing=6)	710	0.015*
<b>Lymph node metastasis rate</b> ( Missing=6)	710	0.21
<b>Tumor nodes number</b> ( Missing=8)	708	<.0001*

\*: P-value&lt;0.05

**Table 2. Results from adjusted analysis of prognostic variables.**

Variables	Estimated coefficient	Estimated SE	Estimated HR	95% CI of HR	P-value
<b>Age</b>	-0.115	0.037	0.891	0.829-0.958	0.0017
<b>Age square</b>	0.001	0.00032	1.001	1.000-1.002	0.0007
<b>Lymph node metastasis rate</b>					<.0001
0 (reference)	-	-	1.000	-	
≤0.35	-0.524	0.230	0.592	0.377-0.930	

0.35-0.7	0.0159	0.235	1.016	0.641-1.612	
≥0.7	0.244	0.244	1.276	0.791-2.060	
<b>Surgical type</b>					0.032
<b>II group</b>					
Radical	-	-	1.000	-	
Palliative	0.462	0.215	1.587	1.041-2.421	
<b>Tumor size</b>					0.013
≤4cm (reference)	-	-	1.000	-	
4-8cm	0.270	0.126	1.310	1.022-1.679	
≥8cm	0.424	0.149	1.529	1.141-2.049	
<b>Clinical Stage</b>					<.0001
4 (reference)	-	-	1.000	-	
0	-12.796	309.130	0.000	(-, -)	
1	-1.602	0.329	0.201	0.106-0.384	
2	-0.979	0.285	0.376	0.215-0.658	
3	-0.234	0.248	0.791	0.486-1.289	

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# Clinicopathologic Risk Factors for Gastric Cancer: A Retrospective Cohort Study in China

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## Abstract

**Objective:** To examine the potential clinicopathologic factors affecting the prognosis of patients with gastric cancer after surgical treatment in China.

**Methods:** Between January 1<sup>st</sup>, 2001 and December 31<sup>st</sup>, 2012, a total of 716 patients aged 22–84 years with gastric cancer were enrolled in the study. Survival analysis techniques including log rank test and Cox proportional hazard regression model were applied to evaluate the prognostic significance of clinicopathological characteristics in terms of survival time.

**Results:** Of the twenty-four demographic and pathological variables collected in the data, 16 prognostic factors of gastric cancer were found to have statistically significant influences on survival time from the unadjusted analyses. The adjusted analysis furtherly revealed that age, age square, lymph node metastasis rate group, tumor size group, surgical type II, number of cancer nodules, invasion depth group, and the interaction between surgical type II and tumor size group were important prognosis and clinicopathologic factors for gastric cancer in Chinese.

**Conclusion:** Our study with relatively large sample size and many potential risk factors enable us to identify independent risk factors associated with the prognosis of gastric cancer. Findings from the current study can be used to assist clinical decision-making, and serve as a benchmark for the planning of future prognosis and therapy for patients with gastric carcinoma.

**Keywords:** Gastric carcinoma, Clinicopathologic risk factors, Clinical stage, Lymph node metastasis rate.

### Strengths and limitations of this study

- This was a retrospective cohort study, including seven hundred and sixteen participants.
- We followed up all participants for at least five years.
- Data of twenty-four independent variables were collected.
- This study has some limitations, for instance, there were missing values for some of the variables; for some subjects, the exact death time was not available and then estimated instead.

## 1. Introduction

Gastric cancer is a heterogeneous, multifactorial disease, which is known as the fifth most common cancer and the third leading cause of cancer-related death worldwide in 2018.<sup>1,2</sup> According to previous reports, approximately 0.7 million people died because of gastric cancer each year<sup>3</sup>, and about 70% of the gastric cancer cases had high fatality, significantly higher than other cancers such as the liver and breast cancers<sup>4</sup>. However, the incidence and mortality of gastric carcinoma vary geographically; they were dramatically different between Western and Eastern countries<sup>3</sup>. The highest incidence rates were found in East Asia, East Europe, and part of South America, whereas the lowest rates were reported in North America, the United Kingdom and most parts of Africa.<sup>5</sup> China is most notable among these countries having the highest incidence and mortality risk of gastric cancer. WHO reported that China had approximately 456,124 new gastric cancer cases and more than 390,128 gastric cancer deaths, with an estimated overall age-standardized incidence rate of 23.7 per 100,000 in 2018.<sup>1,6</sup>

The epidemiological and clinicopathological characteristics of gastric cancer still largely remain uncertain, although some risk factors have been identified in the literature. It has been reported that the survival rates were lower among smokers, alcohol drinkers, obesity, and people who have the symptom of esophageal acid reflux and consume pickled, salty, and smoked food.<sup>7-9</sup> Studies also suggested that the incidence rate of gastric cancer was highly correlated with age, especially among patients aged between 50 and 70 years old.<sup>10-13</sup> It has been reported that gastric carcinoma is one of the heaviest burdens of cancer-related cost, the absolute numbers of gastric cancer cases and the prognosis remain big issues in the health programs<sup>14</sup>.

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3 The current most popular therapy for gastric cancer is surgery combined with chemotherapy.  
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5 Surgery is the most preferred treatment for gastric carcinoma, but the survival rate of patients  
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7 undergoing surgery remains very low. Previous studies have revealed that the average survival  
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9 time of patients with advanced gastric cancer is less than 12 months<sup>15,16</sup>. Therefore, how to timely  
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11 assess the condition, judge the prognosis risk after therapy, and develop a reasonable postoperative  
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13 care program becomes a vital part of gastric cancer treatment.<sup>17-19</sup>  
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17 Many clinicopathological factors, including clinical stage, tumor size, infiltration depth,  
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19 Lauren classification, and lymph node metastasis rate, might jointly influence the prognosis in  
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21 patients with gastric carcinoma<sup>20-22</sup>. It is important but challenging to identify the most significant  
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23 and independent factors associated with prognosis since many factors are highly correlated. To  
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25 have a systematic comprehension of gastric carcinoma and to identify independent risk factors on  
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27 gastric cancer patients, we conducted the current study.  
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## 31 32 33 2. Method

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35 **Design:** This was a retrospective cohort study.  
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38 **Participants:** All participants were recruited from Anhui, China.  
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### 40 41 42 **Ethics statement**

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44 The current study complied with the principles of the Declaration of Helsinki and was  
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46 overseen by the human ethics committees at the First Affiliated Hospital of Anhui Medical  
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48 University in China, as well as by a data and safety monitoring board (IRB approval number: PJ-  
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50 2019-01-14). All patients in the present study were informed and acknowledged that their medical  
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52 records were potentially recorded for scientific research and that their confidentiality would be  
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54 maintained.  
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## Patient and Public Involvement

Patients and the public were not involved in the study design, nor the recruitment.

## Study cohort

Between January 1<sup>st</sup>, 2001 and December 31<sup>th</sup>, 2012, seven hundred and sixteen patients aged between 22 and 84 years with gastrectomy were registered with gastric adenocarcinoma and underwent surgery in the First Affiliated Hospital of Anhui Medical University in Anhui, China.

The WHO classification criteria and the 7<sup>th</sup> edition of the American Joint Committee on Cancer (AJCC)<sup>23</sup> were used for gastric cancer macroscopic and histological classifications. Categorical and continuous clinicopathologic variables were collected and analyzed. Data on age (24-88), gender (male, female), Borrmann's type (I-V), Lauren's classification (intestinal type, diffuse type, others), clinical stage (0-4), T stage (I-IV, Tis), N stage (0-3), M stage (0,1), tumor location (proximal, body, distal, more than two sites), surgical type I (all stomach, proximal, distal), surgical type II group (radical, palliative), and lymphovascular invasion (yes, no), were collected for each patient. Moreover, age square was added to investigate the potential nonlinear effect of age.

Other clinicopathologic variables, such as positive lymph nodes number, number of retrieved lymph nodes, lymph node metastasis rate (the metastasis rate of lymph nodes), surgical margin, tumor size, number of cancer nodules, invasion depth were also collected. For those variables originally recorded as continuous were also categorized for the current analysis. Accordingly, categorical variables: number of cancer nodules group(0,1-2,  $\geq 3$ ), positive lymph nodes number group (0, 1-6,7-15, $\geq 16$ ), surgical margin (negative, positive), tumor size group ( $\leq 4$ cm, 4-8cm,  $\geq 8$ cm), invasion depth (mucosa, submucosa, muscular, all layer), lymph node metastasis rate group

(0,  $\leq 0.35$ , 0.35-0.73,  $\geq 0.74$ ), and number of retrieved lymph node group (0,1-6,7-15, $\geq 16$ ) were also used in the analyses. However, some variables may have missing values.

The current study complied with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

### Statistics analyses

In all of the analyses, the survival time defined as the period between the dates of surgery and death (or last follow-up) would be the dependent variable. All endpoints were updated between June 2018 and January 2019, which resulted in an at least 5 years follow-up for each participant. First, an unadjusted analysis was performed for each independent variable. Specifically, for each categorical (continuous) independent variable, the log rank test (the Cox proportional hazard model) was applied to see whether it is associated with the dependent variable without adjusting for any other independent variables. Then the Cox proportional hazard regression model with backward variable selection was performed to identify factors independently associated with the survival time, and to estimate their adjusted hazard ratios (HR). In the adjusted analysis, all possible two-way interactions were considered in the Cox model. The 95% confidence intervals (CIs) of the HR for significant effects were also reported. In this study, the two-sided p-values  $< 0.05$  were used to define statistical significance and all analyses were performed using SAS (SAS Institute Inc., Cary, NC, USA) and SAS (r) Proprietary Software 9.4 (TS1M2).

## 3. Results

### Results from the unadjusted analyses

In this cohort, the total number of events of death is 400, and the overall median survival time is 4.74 years. The results from the univariable analyses were reported in Table 1. Table 1 also

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2  
3 listed the frequencies for each variable. This cohort was composed of 552 males and 163 females.  
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5 Based on the clinical TNM classification, the numbers of gastric cancer patients in stage 0, I, II,  
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7 III, and IV were 11, 109, 296, 269, and 28, respectively. 98 patients had lymphovascular invasion  
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9 while 611 did not. Gastric lesions were located on the proximal of the stomach for 399 patients,  
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11 on the body of the stomach for 164 patients, on the distal of the stomach for 99, and 52 participants  
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13 had more than two sites gastric lesions. Moreover, 672 patients proceeded to radical resection, and  
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15 42 proceed to palliative resection. 565 patients had all layer invasion of their stomachs. In addition,  
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17 579, 28, and 101 patients received all stomach, proximal, and distal gastric surgery, respectively.  
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19 The numbers of participants whose lymph node metastasis rate were 0, between 0 and 0.35,  
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21 between 0.35 and 0.7, and greater than 0.7 were 253, 201, 157, and 95, respectively. Furthermore,  
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23 in this study, there were 299, 275, and 128 patients whose tumor sizes were smaller than 4cm,  
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25 between 4 and 8cm, and larger than 8 cm, respectively.  
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31 Sixteen significant prognostic factors of gastric cancer including Borrmann's type, surgical  
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33 margin, M stage, N stage, T stage, lymph node metastasis rate group, surgical type II group, clinical  
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35 stage, number of cancer nodules group, tumor size group, invasion depth group, positive lymph  
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37 nodes number group, tumor location, positive lymph nodes number, number of retrieved lymph  
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39 nodes, and number of cancer nodules were identified ( $p < 0.05$ ) from the unadjusted analyses.  
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41 However, there were no significant associations between survival time and gender, Lauren's  
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43 classification, surgical type I group, lymphovascular invasion, number of retrieved lymph nodes  
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45 group, age, age square, and lymph node metastasis rate from the unadjusted analysis according to  
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47 their large p-values ( $> 0.05$ ).  
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### 52 **Results from the adjusted analysis**

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3 The results of the estimated hazard ratios and their 95% confidence interval from the adjusted  
4 analysis were reported in Table 2. The adjusted analysis identified seven variables and an interaction  
5 that were associated with survival time. These variables and their estimated adjusted HR after  
6 adjusting for the other effects in the model were: age (HR=0.888, p-value=0.0016, 95% CI: 0.825-  
7 0.956), age square (HR =1.001, p-value= 0.0005, 95% CI: 1.000-1.002), number of cancer nodules  
8 (HR=1.108, p-value=0.0106, 95%CI:1.024-1.199), lymph node metastasis rate group (HR for  
9  $\leq 0.35$ , 0.35-0.73,  $\geq 0.74$ : 1.033, 1.780, and 2.491, respectively; p-value<0.0001, 95% CI: 0.768-  
10 1.390, 1.320-2.401, 1.774-3.497, respectively), invasion depth group (HR for Muscosa, Muscular,  
11 and All layer: 0.415, 1.291, and 2.095 respectively, p-value < 0.0001, 95% CI: 0.091-1.898, 0.625-  
12 2.669, and 1.089-4.032, respectively) , surgical type II group (p-value<0.0001), tumor size group  
13 (p-value=0.0010), and the interaction between surgical type II and tumor size.  
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#### 29 **4. Discussion**

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32 In this study with total 716 gastric cancer patients, we identified the following  
33 clinicopathologic factors which were independently associated with gastric carcinoma from the  
34 adjusted analysis: age (and age square), number of cancer nodules, lymph node metastasis rate,  
35 tumor size, type II surgery, invasion depth group and interaction between surgical type II and  
36 tumor size. The adjusted analysis revealed that other variables, such as gender, Borrmann's type,  
37 TMN stage, tumor location, surgical type I group, surgical margin, lymphovascular invasion, and  
38 number of retrieved lymph node, might not independently play a major role in the prognosis. For  
39 the variable "age", we found that it had a non-linear effect on the outcome: both age and its square  
40 were significantly associated with survival time.  
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3 In our current study, among these identified risk factors, the prognosis of patients with gastric  
4 carcinoma was seen strongly affected by the rate of metastatic lymph nodes, which also has been  
5 emphasized in previous studies performed in different countries<sup>24,25</sup>. The result from the study by  
6 Kim, Lee et al. indicated that the survival rate was remarkably decreased with metastatic lymph  
7 nodes rate increased.<sup>26</sup> Msika et al. also found that lymph node metastasis played an important role  
8 and was the only independent prognostic risk factor among 86 participants who underwent curative  
9 resection in their study.<sup>27</sup> Furthermore, the German Gastric Carcinoma Study (GGCS)<sup>28</sup> suggested  
10 that the lymph node metastasis rate should be considered as the significant independent prognostic  
11 variables among patients underwent resected gastric carcinoma, and indicated that extended lymph  
12 node dissection was the most critical treatment among patients with radical gastrectomy for long-  
13 term survival. Of the many factors relevant to survival time, depth of invasion also has been  
14 identified as one of the major prognostic factors from our current adjusted analysis. This finding  
15 is consistent with those from the literature.<sup>29-32</sup>

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34 Based on our adjusted analysis, age had a significant nonlinear effect on the survival time. We  
35 also found that tumor size and the number of cancer nodules were independent risk factors for  
36 prognostic. These two variables are recognized as tumor burden, which are related to poor  
37 prognosis susceptibility in another study as well.<sup>33</sup> One Chinese cohort provided that a poorer  
38 prognosis in patients with gastric cancer whose number of cancer nodules were more than 3.<sup>34</sup> In  
39 addition, a Turkish study stated that cancer nodules are more observed in patients with the  
40 intestinal type and vascular invasive gastric cancers.<sup>35</sup> On the other hand, tumor size is a valuable  
41 risk factor since it can be examined quite easily before the surgery, although the prognostic risk of  
42 tumor size among patients with gastric carcinoma maintains inconsistent. Some researches  
43 suggested that tumor size is not an independent prognostic variable in patients who had gastric  
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3 carcinoma. <sup>36,37,38</sup> However, other previous studies have displayed that tumor size should be  
4 considered as a risk feature for long-term survival after resection of gastric carcinoma <sup>39-42,43</sup>, and  
5 there was a significant relationship between larger tumor size and lesion resectability. Tumor size  
6 of gastric cancer was a vital variable that affects the success of enbloc resection; patients with  
7 larger tumor sizes need higher level of expertise and experience for their treatment. Tumor size  
8 could raise with the depth of tumor invasion and the extent of lymph node metastasis increase: the  
9 size of the tumor is profoundly associated to “Borrmann’s type IV, adjacent organ invasion (T4)  
10 and higher lymph node and distant metastasis rate”. <sup>37,44</sup> A possible explanation is that most  
11 patients with stage III or stage IV cancers had a relatively lower radical resection and remained a  
12 lower 5-year survival rate.<sup>45</sup>

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27 Our results also showed that patients who received palliative gastrectomy had poorer  
28 prognosis and higher risks compared to patients with radical gastrectomy. The results from Dutch  
29 clinical randomize trial <sup>46</sup> suggested that palliative gastrectomy could be beneficial for younger  
30 patients ( age<70) whose tumor load was restricted to one metastatic site. On the contrary, a  
31 previous study<sup>47</sup> indicated that “palliative gastrectomy has no survival benefit (p-value = 0.705,  
32 0.331, respectively) in the peritoneal dissemination and multi-organ metastases group”. Another  
33 study found that palliative gastrectomy showed no obvious favorable effect on long-term survival  
34 or improvement of the quality of life among patients with gastric cancer.<sup>48</sup> Moreover, Maruyama  
35 K et al. suggested that radical gastrectomy remained the only curative treatment option for gastric  
36 cancer.<sup>49</sup> The interaction between tumor size and surgical type II was found significant from our  
37 adjusted analysis. It showed that patients who had tumor size  $\leq 4$  cm and palliative gastrectomy  
38 had the lowest risk while the highest risk was found in patients who had tumor size  $\leq 4$  cm and  
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3 palliative gastrectomy. On the contrary, patients who had larger tumor size ( $\geq 8$ cm) with palliative  
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6 gastrectomy have the second lowest prognosis risk.  
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There were several strengths and limitations in our current study. We used the Cox proportional hazard regression model, which is one of the most commonly used methods for adjusted analyses with survival time as the dependent variable. Our findings showed that tumor size, interacted with surgical type II, encompasses important prognostic information for gastric cancer. Based on Jun K.H et al.,<sup>50</sup> the tumor size was statistically significantly and independently associated with gastric carcinoma-related survival, and this risk factor was a vital predictor for advanced gastric cancer, although it may not be detectable in early gastric carcinoma. In addition, our study includes patients with a long-term follow-up duration, which was rarely seen from other studies conducted in China. However, all the patients in this study were recruited from Anhui, a province of China. This fact could lead to a lack of generalizability of our findings to the general Chinese population. Finally, the present study has limitations inherent to all observational studies. For instance, some potential confounders may not be recognized and included in the study and selection bias could exist due to loss to follow up.

## 5. Conclusion

Currently, identifying and predicting important prognosis indicators before treatment are critical for gastric cancer patients. In our study, seven prognostic risk characteristics and one interaction have been identified in patients with gastric carcinoma. The findings from our study are useful and applicable for clinical decision-making. They also provide a benchmark for planning future prognosis and treatment for gastric cancer patients. Our findings can also be used to improve

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3 early detection and to investigate the feasibility and survival benefit of therapy for patients with  
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5 gastric carcinoma.  
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22 decision to publish, or preparation of the manuscript.  
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26 **Conflict of interest:** The authors declare no conflict of interest in this study.  
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29 **Patient consent for publication:** Not required.  
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32 **Ethics approval:** This study was approved by the Institutional Review Board of the First Affiliated  
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34 Hospital of Anhui Medical University in China (IRB approval number: PJ-2019-01-14).  
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37 **Data sharing statement:** No additional data are available.  
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40 **Contributors:** KH, ZC, QW designed and oversaw the study; SW, ZW, LL, ZH, WY contributed  
41  
42 to data collection and analysis; KH, SW, ZW, ZC, and QW drafted the manuscript. All authors  
43  
44 participated in the discussion and approved the final manuscript.  
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## Tables

**Table 1. Results from unadjusted analyses of clinical and pathologic variables. (N=716)**

Variable	Frequency	Event number	Median survival-time (year)	Hazard ratio	P-value
<b>Gender</b>					0.40
Female	163	86	4.94	1.00	
Male	552	314	4.59	1.10	
Missing	1	-	-	-	
<b>Borrmann's Type</b>					0.030*
Type I	29	16	4.40	1.00	
Type II	514	288	4.63	1.06	
Type III	57	31	5.06	1.02	
Type IV	76	49	2.04	1.49	
Type V	32	11	-	0.51	
Missing	8	-	-	-	
<b>Surgical margin</b>					0.020*
Negative	648	353	4.94	1.00	
Positive	46	34	1.55	1.71	
Missing	22	-	-	-	
<b>Lauren's classification</b>					0.39
Intestinal type	214	116	5.67	1.00	
Diffuse type	468	267	4.30	1.19	
Others	32	16	8.95	1.03	
Missing	2	-	-	-	
<b>M stage</b>					<.0001*
0	684	373	5.06	1.00	
1	28	25	1.34	2.79	
Missing	4	-	-	-	
<b>N stage</b>					<.0001*
0	257	101	8.98	1.00	
1	169	90	5.17	1.74	
2	169	114	2.36	2.00	
3	117	94	1.56	3.95	
Missing	4	-	-	-	
<b>T stage</b>					<.0001*
1	63	16	12.29	1.00	
2	73	25	10.02	1.52	
3	533	336	3.19	4.04	
4	33	20	3.93	3.77	
Tis	11	2	8.95	0.79	
Missing	3	-	-	-	
<b>Lymph node metastasis rate group</b>					<.0001*
0	253	101	8.98	1.00	
≤0.35	201	101	5.64	1.53	
0.35-0.7	157	109	2.11	2.86	
≥0.7	95	81	1.50	4.25	



Missing	10	-	-	-	
<b>Surgical type I group</b>					0.13
All Stomach	579	337	4.27	1.00	
Proximal	28	12	6.74	0.78	
Distal	101	48	8.69	0.59	
Missing	7	-	-	-	
<b>Surgical type II group</b>					<.0001*
Radical	672	363	5.25	1.00	
Palliative	42	36	1.13	3.19	
Missing	2	-	-	-	
<b>Lymphovascular invasion</b>					0.56
No	611	344	4.74	1.00	
Yes	98	55	4.61	1.09	
Missing	7	-	-	-	
<b>Clinical stage</b>					<.0001*
0	11	2	8.95	1.00	
1	109	30	12.29	1.41	
2	296	148	5.84	3.36	
3	269	194	2.05	7.12	
4	28	25	1.34	11.53	
Missing	3	-	-	-	
<b>Number of cancer nodules group</b>					<.0001*
0	637	347	5.17	1.00	
1-2	55	36	1.92	1.63	
≥3	15	13	1.38	2.86	
Missing	9	-	-	-	
<b>Tumor size group</b>					<.0001*
≤4cm	299	131	8.69	1.00	
4-8cm	275	170	3.16	1.84	
≥8cm	128	95	1.90	2.54	
Missing	14	-	-	-	
<b>Invasion depth group</b>					<.0001*
Mucosa	25	4	-	1.00	
Submucosa	40	12	12.29	1.79	
Muscular	83	29	10.02	2.48	
All layer	565	354	3.21	6.24	
Missing	3	-	-	-	
<b>Positive lymph nodes number group</b>					<.0001*
0	257	101	8.98	1.00	
1-6	338	204	3.58	2.06	
7-15	99	81	1.50	4.12	
≥16	18	13	1.90	3.04	
Missing	4	-	-	-	
<b>Tumor location</b>					0.0067*
Proximal	399	217	4.88	1.00	
Body	164	96	4.61	1.07	
Distal	99	48	6.14	0.91	
More than two sites	52	38	1.60	1.83	
Missing	3	-	-	-	
<b>Number of retrieved Lymph Nodes group</b>					0.10
0	6	2	-	1.00	

1-6	196	103	6.10	1.77	
7-15	391	221	4.27	2.13	
≥16	116	72	3.17	2.48	
Missing	7	-	-	-	
<b>Age</b> ( Missing=1)	715			1.01	0.144
<b>Age<sup>2</sup></b> ( Missing=1)	715			1.00	0.056
<b>Positive lymph nodes number</b> ( Missing=4)	712			1.08	<.0001*
<b>Number of retrieved Lymph Nodes group</b> ( Missing=7)	709			1.02	0.014*
<b>Lymph node metastasis rate</b> ( Missing=7)	709			1.04	0.232
<b>Number of cancer nodules</b> ( Missing=9)	707			1.18	<.0001*

**Table 2. Results from adjusted analysis of prognostic variables.**

Variables	Estimated coefficient	Estimated SE	Estimated HR	95% CI of HR	P-value
<b>Age</b>	-0.119	0.038	0.888	0.825-0.956	0.0016
<b>Age square</b>	0.001	0.0003	1.001	1.000-1.002	0.0005
<b>Number of cancer nodules</b>	0.103	0.040	1.108	1.024-1.199	0.0106
<b>Lymph node metastasis rate</b>					<.0001
0 (reference)	-	-	1.000	-	
≤0.35	-0.033	0.152	1.033	0.768-1.390	
0.35-0.7	0.577	0.153	1.780	1.320-2.401	
≥0.7	0.825	0.169	2.491	1.774-3.497	
<b>Invasion depth group</b>					0.0041
Submucosa	-	-	1.000	(-, -)	
Mucosa	-0.880	0.776	0.415	0.091-1.898	
Muscular	0.256	0.370	1.291	0.625-2.669	
All layer	0.740	0.334	2.095	1.089-4.032	
<b>Surgical type II group</b>					<.0001
Radical	-	-			
Palliative	1.757	0.364			
<b>Tumor size</b>					0.0010
≤4cm (reference)	-	-			
4-8cm	0.240	0.132			
≥8cm	0.566	0.152			
<b>Surgical type II group* Tumor size</b>					0.0003
Palliative vs radical *≤4cm (reference)	-	-			
Palliative *4-8cm	-1.026	0.453			
Palliative *≥8cm	-2.097	0.517			

# BMJ Open

## Clinicopathologic Risk Factors for Gastric Cancer: A Retrospective Cohort Study in China

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# Clinicopathologic Risk Factors for Gastric Cancer: A Retrospective Cohort Study in China

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## Abstract

**Objective:** To examine the potential clinicopathologic factors affecting the prognosis of patients with gastric cancer after surgical treatment in China.

**Methods:** Between January 1<sup>st</sup>, 2001 and December 31<sup>st</sup>, 2012, a total of 716 patients aged 22–84 years with gastric cancer were enrolled in the study. Survival analysis techniques including log rank test and Cox proportional hazard regression model were applied to evaluate the prognostic significance of clinicopathological characteristics in terms of survival time.

**Results:** Of the twenty-four demographic and pathological variables collected in the data, 16 prognostic factors of gastric cancer were found to have statistically significant influences on survival time from the unadjusted analyses. The adjusted analysis furtherly revealed that age, age square, lymph node metastasis rate group, tumor size group, surgical type II, number of cancer nodules, invasion depth group, and the interaction between surgical type II and tumor size group were important prognosis and clinicopathologic factors for gastric cancer in Chinese.

**Conclusion:** Our study with relatively large sample size and many potential risk factors enable us to identify independent risk factors associated with the prognosis of gastric cancer. Findings from the current study can be used to assist clinical decision-making, and serve as a benchmark for the planning of future prognosis and therapy for patients with gastric carcinoma.

**Keywords:** Gastric carcinoma, Clinicopathologic risk factors, Clinical stage, Lymph node metastasis rate.

### Strengths and limitations of this study

- This was a retrospective cohort study, including seven hundred and sixteen participants.
- We followed up all participants for at least five years.
- Data of twenty-four independent variables were collected.
- This study has some limitations, for instance, there were missing values for some of the variables; for some subjects, the exact death time was not available and then estimated instead.

## 1. Introduction

Gastric cancer is a heterogeneous, multifactorial disease, which is known as the fifth most common cancer and the third leading cause of cancer-related death worldwide in 2018.<sup>1,2</sup> According to previous reports, approximately 0.7 million people died because of gastric cancer each year<sup>3</sup>, and about 70% of the gastric cancer cases had high fatality, significantly higher than other cancers such as the liver and breast cancers<sup>4</sup>. However, the incidence and mortality of gastric carcinoma vary geographically; they were dramatically different between Western and Eastern countries<sup>3</sup>. The highest incidence rates were found in East Asia, East Europe, and part of South America, whereas the lowest rates were reported in North America, the United Kingdom and most parts of Africa.<sup>5</sup> China is most notable among these countries having the highest incidence and mortality risk of gastric cancer. WHO reported that China had approximately 456,124 new gastric cancer cases and more than 390,128 gastric cancer deaths, with an estimated overall age-standardized incidence rate of 23.7 per 100,000 in 2018.<sup>1,6</sup>

The epidemiological and clinicopathological characteristics of gastric cancer still largely remain uncertain, although some risk factors have been identified in the literature. It has been reported that the survival rates were lower among smokers, alcohol drinkers, obesity, and people who have the symptom of esophageal acid reflux and consume pickled, salty, and smoked food.<sup>7-9</sup> Studies also suggested that the incidence rate of gastric cancer was highly correlated with age, especially among patients aged between 50 and 70 years old.<sup>10-13</sup> It has been reported that gastric carcinoma is one of the heaviest burdens of cancer-related cost, the absolute numbers of gastric cancer cases and the prognosis remain big issues in the health programs<sup>14</sup>.

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3 The current most popular therapy for gastric cancer is surgery combined with chemotherapy.  
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5 Surgery is the most preferred treatment for gastric carcinoma, but the survival rate of patients  
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7 undergoing surgery remains very low. Previous studies have revealed that the average survival  
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9 time of patients with advanced gastric cancer is less than 12 months<sup>15,16</sup>. Therefore, how to timely  
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11 assess the condition, judge the prognosis risk after therapy, and develop a reasonable postoperative  
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13 care program becomes a vital part of gastric cancer treatment.<sup>17-19</sup>  
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17 Many clinicopathological factors, including clinical stage, tumor size, infiltration depth,  
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19 Lauren classification, and lymph node metastasis rate, might jointly influence the prognosis in  
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21 patients with gastric carcinoma<sup>20-22</sup>. It is important but challenging to identify the most significant  
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23 and independent factors associated with prognosis since many factors are highly correlated. To  
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25 have a systematic comprehension of gastric carcinoma and to identify independent risk factors on  
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27 gastric cancer patients, we conducted the current study.  
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## 31 32 33 2. Method

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35 **Design:** This was a retrospective cohort study.  
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38 **Participants:** All participants were recruited from Anhui, China.  
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### 40 41 42 **Ethics statement**

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44 The current study complied with the principles of the Declaration of Helsinki and was  
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46 overseen by the human ethics committees at the First Affiliated Hospital of Anhui Medical  
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48 University in China, as well as by a data and safety monitoring board (IRB approval number: PJ-  
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50 2019-01-14). All patients in the present study were informed and acknowledged that their medical  
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52 records were potentially recorded for scientific research and that their confidentiality would be  
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54 maintained.  
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## Patient and Public Involvement

Patients and the public were not involved in the study design, nor the recruitment.

## Study cohort

Between January 1<sup>st</sup>, 2001 and December 31<sup>th</sup>, 2012, seven hundred and sixteen patients aged between 22 and 84 years with gastrectomy were registered with gastric adenocarcinoma and underwent surgery in the First Affiliated Hospital of Anhui Medical University in Anhui, China.

The WHO classification criteria and the 7<sup>th</sup> edition of the American Joint Committee on Cancer (AJCC)<sup>23</sup> were used for gastric cancer macroscopic and histological classifications. Categorical and continuous clinicopathologic variables were collected and analyzed. Data on age (24-88), gender (male, female), Borrmann's type (I-V), Lauren's classification (intestinal type, diffuse type, others), clinical stage (0-4), T stage (I-IV, Tis), N stage (0-3), M stage (0,1), tumor location (proximal, body, distal, more than two sites), surgical type I (all stomach, proximal, distal), surgical type II group (radical, palliative), and lymphovascular invasion (yes, no), were collected for each patient. Moreover, age square was added to investigate the potential nonlinear effect of age.

Other clinicopathologic variables, such as positive lymph nodes number, number of retrieved lymph nodes, lymph node metastasis rate (the metastasis rate of lymph nodes), surgical margin, tumor size, number of cancer nodules, invasion depth were also collected. For those variables originally recorded as continuous were also categorized for the current analysis. Accordingly, categorical variables: number of cancer nodules group(0,1-2,  $\geq 3$ ), positive lymph nodes number group (0, 1-6,7-15, $\geq 16$ ), surgical margin (negative, positive), tumor size group ( $\leq 4$ cm, 4-8cm,  $\geq 8$ cm), invasion depth (mucosa, submucosa, muscular, all layer), lymph node metastasis rate group

(0,  $\leq 0.35$ , 0.35-0.74,  $\geq 0.74$ ), and number of retrieved lymph node group (0,1-6,7-15, $\geq 16$ ) were also used in the analyses. However, some variables may have missing values.

The current study complied with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

### Statistics analyses

In all of the analyses, the survival time defined as the period between the dates of surgery and death (or last follow-up) would be the dependent variable. All endpoints were updated between June 2018 and January 2019, which resulted in an at least 5 years follow-up for each participant. First, an unadjusted analysis was performed for each independent variable. Specifically, for each categorical (continuous) independent variable, the log rank test (the Cox proportional hazard model) was applied to see whether it is associated with the dependent variable without adjusting for any other independent variables. Then the Cox proportional hazard regression model with backward variable selection was performed to identify factors independently associated with the survival time, and to estimate their adjusted hazard ratios (HR). In the adjusted analysis, all possible two-way interactions were considered in the Cox model. The 95% confidence intervals (CIs) of the HR for significant effects were also reported. In this study, the two-sided p-values  $< 0.05$  were used to define statistical significance and all analyses were performed using SAS (SAS Institute Inc., Cary, NC, USA) and SAS (r) Proprietary Software 9.4 (TS1M2).

## 3. Results

### Results from the unadjusted analyses

In this cohort, the total number of events of death is 400, and the overall median survival time is 4.74 years. The results from the univariable analyses were reported in Table 1. Table 1 also

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3 listed the frequencies for each variable. This cohort was composed of 552 males and 163 females.  
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5 Based on the clinical TNM classification, the numbers of gastric cancer patients in stage 0, I, II,  
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7 III, and IV were 11, 109, 296, 269, and 28, respectively. 98 patients had lymphovascular invasion  
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9 while 611 did not. Gastric lesions were located on the proximal of the stomach for 399 patients,  
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11 on the body of the stomach for 164 patients, on the distal of the stomach for 99, and 52 participants  
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13 had more than two sites gastric lesions. Moreover, 672 patients proceeded to radical resection, and  
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15 42 proceed to palliative resection. 565 patients had all layer invasion of their stomachs. In addition,  
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17 579, 28, and 101 patients received all stomach, proximal, and distal gastric surgery, respectively.  
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19 The numbers of participants whose lymph node metastasis rate were 0, between 0 and 0.35,  
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21 between 0.35 and 0.74, and greater than 0.74 were 257, 200, 159, and 95, respectively. Furthermore,  
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23 in this study, there were 299, 275, and 128 patients whose tumor sizes were smaller than 4cm,  
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25 between 4 and 8cm, and larger than 8 cm, respectively.  
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31 Sixteen significant prognostic factors of gastric cancer including Borrmann's type, surgical  
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33 margin, M stage, N stage, T stage, lymph node metastasis rate group, surgical type II group, clinical  
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35 stage, number of cancer nodules group, tumor size group, invasion depth group, positive lymph  
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37 nodes number group, tumor location, positive lymph nodes number, number of retrieved lymph  
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39 nodes, and number of cancer nodules were identified ( $p < 0.05$ ) from the unadjusted analyses.  
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41 However, there were no significant associations between survival time and gender, Lauren's  
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43 classification, surgical type I group, lymphovascular invasion, number of retrieved lymph nodes  
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45 group, age, age square, and lymph node metastasis rate from the unadjusted analysis according to  
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47 their large p-values ( $> 0.05$ ).  
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### 52 **Results from the adjusted analysis**

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3 The results of the estimated hazard ratios and their 95% confidence interval from the adjusted  
4 analysis were reported in Table 2. The adjusted analysis identified seven variables and an interaction  
5 that were associated with survival time. These variables and their estimated adjusted HR after  
6 adjusting for the other effects in the model were: age (HR=0.888, p-value=0.0016, 95% CI: 0.825-  
7 0.956), age square (HR =1.001, p-value= 0.0005, 95% CI: 1.000-1.002), number of cancer nodules  
8 (HR=1.108, p-value=0.0106, 95%CI:1.024-1.199), lymph node metastasis rate group (HR for  
9  $\leq 0.35$ , 0.35-0.74,  $\geq 0.74$ : 1.033, 1.780, and 2.491, respectively; p-value<0.0001, 95% CI: 0.768-  
10 1.390, 1.320-2.401, 1.774-3.497, respectively), invasion depth group (HR for Muscosa, Muscular,  
11 and All layer: 0.415, 1.291, and 2.095 respectively, p-value < 0.0001, 95% CI: 0.091-1.898, 0.625-  
12 2.669, and 1.089-4.032, respectively) , surgical type II group (p-value<0.0001), tumor size group  
13 (p-value=0.0010), and the interaction between surgical type II and tumor size.  
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#### 29 **4. Discussion**

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32 In this study with total 716 gastric cancer patients, we identified the following  
33 clinicopathologic factors which were independently associated with gastric carcinoma from the  
34 adjusted analysis: age (and age square), number of cancer nodules, lymph node metastasis rate,  
35 tumor size, type II surgery, invasion depth group and interaction between surgical type II and  
36 tumor size. The adjusted analysis revealed that other variables, such as gender, Borrmann's type,  
37 TMN stage, tumor location, surgical type I group, surgical margin, lymphovascular invasion, and  
38 number of retrieved lymph node, might not independently play a major role in the prognosis. For  
39 the variable "age", we found that it had a non-linear effect on the outcome: both age and its square  
40 were significantly associated with survival time.  
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3 In our current study, among these identified risk factors, the prognosis of patients with gastric  
4 carcinoma was seen strongly affected by the rate of metastatic lymph nodes, which also has been  
5 emphasized in previous studies performed in different countries<sup>24,25</sup>. The result from the study by  
6 Kim, Lee et al. indicated that the survival rate was remarkably decreased with metastatic lymph  
7 nodes rate increased.<sup>26</sup> Msika et al. also found that lymph node metastasis played an important role  
8 and was the only independent prognostic risk factor among 86 participants who underwent curative  
9 resection in their study.<sup>27</sup> Furthermore, the German Gastric Carcinoma Study (GGCS)<sup>28</sup> suggested  
10 that the lymph node metastasis rate should be considered as the significant independent prognostic  
11 variables among patients underwent resected gastric carcinoma, and indicated that extended lymph  
12 node dissection was the most critical treatment among patients with radical gastrectomy for long-  
13 term survival. Of the many factors relevant to survival time, depth of invasion also has been  
14 identified as one of the major prognostic factors from our current adjusted analysis. This finding  
15 is consistent with those from the literature.<sup>29-32</sup>

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34 Based on our adjusted analysis, age had a significant nonlinear effect on the survival time. We  
35 also found that tumor size and the number of cancer nodules were independent risk factors for  
36 prognostic. These two variables are recognized as tumor burden, which are related to poor  
37 prognosis susceptibility in another study as well.<sup>33</sup> One Chinese cohort provided that a poorer  
38 prognosis in patients with gastric cancer whose number of cancer nodules were more than 3.<sup>34</sup> In  
39 addition, a Turkish study stated that cancer nodules are more observed in patients with the  
40 intestinal type and vascular invasive gastric cancers.<sup>35</sup> On the other hand, tumor size is a valuable  
41 risk factor since it can be examined quite easily before the surgery, although the prognostic risk of  
42 tumor size among patients with gastric carcinoma maintains inconsistent. Some researches  
43 suggested that tumor size is not an independent prognostic variable in patients who had gastric  
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3 carcinoma. <sup>36,37,38</sup> However, other previous studies have displayed that tumor size should be  
4 considered as a risk feature for long-term survival after resection of gastric carcinoma <sup>39-42,43</sup>, and  
5 there was a significant relationship between larger tumor size and lesion resectability. Tumor size  
6 of gastric cancer was a vital variable that affects the success of enbloc resection; patients with  
7 larger tumor sizes need higher level of expertise and experience for their treatment. Tumor size  
8 could raise with the depth of tumor invasion and the extent of lymph node metastasis increase: the  
9 size of the tumor is profoundly associated to “Borrmann’s type IV, adjacent organ invasion (T4)  
10 and higher lymph node and distant metastasis rate”. <sup>37,44</sup> A possible explanation is that most  
11 patients with stage III or stage IV cancers had a relatively lower radical resection and remained a  
12 lower 5-year survival rate.<sup>45</sup>

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27 Our results also showed that patients who received palliative gastrectomy had poorer  
28 prognosis and higher risks compared to patients with radical gastrectomy. The results from Dutch  
29 clinical randomize trial <sup>46</sup> suggested that palliative gastrectomy could be beneficial for younger  
30 patients ( age<70) whose tumor load was restricted to one metastatic site. On the contrary, a  
31 previous study<sup>47</sup> indicated that “palliative gastrectomy has no survival benefit (p-value = 0.705,  
32 0.331, respectively) in the peritoneal dissemination and multi-organ metastases group”. Another  
33 study found that palliative gastrectomy showed no obvious favorable effect on long-term survival  
34 or improvement of the quality of life among patients with gastric cancer.<sup>48</sup> Moreover, Maruyama  
35 K et al. suggested that radical gastrectomy remained the only curative treatment option for gastric  
36 cancer.<sup>49</sup> The interaction between tumor size and surgical type II was found significant from our  
37 adjusted analysis. It showed that patients who had tumor size  $\leq 4$  cm and palliative gastrectomy  
38 had the lowest risk while the highest risk was found in patients who had tumor size  $\leq 4$  cm and  
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3 palliative gastrectomy. On the contrary, patients who had larger tumor size ( $\geq 8$ cm) with palliative  
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palliative gastrectomy. On the contrary, patients who had larger tumor size ( $\geq 8$ cm) with palliative gastrectomy have the second lowest prognosis risk.

There were several strengths and limitations in our current study. We used the Cox proportional hazard regression model, which is one of the most commonly used methods for adjusted analyses with survival time as the dependent variable. Our findings showed that tumor size, interacted with surgical type II, encompasses important prognostic information for gastric cancer. Based on Jun K.H et al.,<sup>50</sup> the tumor size was statistically significantly and independently associated with gastric carcinoma-related survival, and this risk factor was a vital predictor for advanced gastric cancer, although it may not be detectable in early gastric carcinoma. In addition, our study includes patients with a long-term follow-up duration, which was rarely seen from other studies conducted in China. However, all the patients in this study were recruited from Anhui, a province of China. This fact could lead to a lack of generalizability of our findings to the general Chinese population. Finally, the present study has limitations inherent to all observational studies. For instance, some potential confounders may not be recognized and included in the study and selection bias could exist due to loss to follow up.

## 5. Conclusion

Currently, identifying and predicting important prognosis indicators before treatment are critical for gastric cancer patients. In our study, seven prognostic risk characteristics and one interaction have been identified in patients with gastric carcinoma. The findings from our study are useful and applicable for clinical decision-making. They also provide a benchmark for planning future prognosis and treatment for gastric cancer patients. Our findings can also be used to improve



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3 early detection and to investigate the feasibility and survival benefit of therapy for patients with  
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5 gastric carcinoma.  
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22 decision to publish, or preparation of the manuscript.  
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26 **Conflict of interest:** The authors declare no conflict of interest in this study.  
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29 **Patient consent for publication:** Not required.  
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32 **Ethics approval:** This study was approved by the Institutional Review Board of the First Affiliated  
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34 Hospital of Anhui Medical University in China (IRB approval number: PJ-2019-01-14).  
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37 **Data sharing statement:** No additional data are available.  
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40 **Contributors:** KH, ZC, QW designed and oversaw the study; SW, ZW, LL, ZH, WY contributed  
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42 to data collection and analysis; KH, SW, ZW, ZC, and QW drafted the manuscript. All authors  
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44 participated in the discussion and approved the final manuscript.  
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## Tables

**Table 1. Results from unadjusted analyses of clinical and pathologic variables. (N=716)**

Variable	Frequency	Event number	Median survival-time (year)	Hazard ratio	P-value
<b>Gender</b>					0.40
Female	163	86	4.94	1.00	
Male	552	314	4.59	1.10	
Missing	1	-	-	-	
<b>Borrmann's Type</b>					0.030*
Type I	29	16	4.40	1.00	
Type II	514	288	4.63	1.06	
Type III	57	31	5.06	1.02	
Type IV	76	49	2.04	1.49	
Type V	32	11	-	0.51	
Missing	8	-	-	-	
<b>Surgical margin</b>					0.020*
Negative	648	353	4.94	1.00	
Positive	46	34	1.55	1.71	
Missing	22	-	-	-	
<b>Lauren's classification</b>					0.39
Intestinal type	214	116	5.67	1.00	
Diffuse type	468	267	4.30	1.19	
Others	32	16	8.95	1.03	
Missing	2	-	-	-	
<b>M stage</b>					<.0001*
0	684	373	5.06	1.00	
1	28	25	1.34	2.79	
Missing	4	-	-	-	
<b>N stage</b>					<.0001*
0	257	101	8.98	1.00	
1	169	90	5.17	1.74	
2	169	114	2.36	2.00	
3	117	94	1.56	3.95	
Missing	4	-	-	-	
<b>T stage</b>					<.0001*
1	63	16	12.29	1.00	
2	73	25	10.02	1.52	
3	533	336	3.19	4.04	
4	33	20	3.93	3.77	
Tis	11	2	8.95	0.79	
Missing	3	-	-	-	
<b>Lymph node metastasis rate group</b>					<.0001*
0	257	101	8.98	1.00	
≤0.35	200	101	5.64	1.53	
0.35-0.74	159	109	2.11	2.86	
≥0.74	95	81	1.50	4.25	

Missing	5	-	-	-	
<b>Surgical type I group</b>					0.13
All Stomach	579	337	4.27	1.00	
Proximal	28	12	6.74	0.78	
Distal	101	48	8.69	0.59	
Missing	7	-	-	-	
<b>Surgical type II group</b>					<.0001*
Radical	672	363	5.25	1.00	
Palliative	42	36	1.13	3.19	
Missing	2	-	-	-	
<b>Lymphovascular invasion</b>					0.56
No	611	344	4.74	1.00	
Yes	98	55	4.61	1.09	
Missing	7	-	-	-	
<b>Clinical stage</b>					<.0001*
0	11	2	8.95	1.00	
1	109	30	12.29	1.41	
2	296	148	5.84	3.36	
3	269	194	2.05	7.12	
4	28	25	1.34	11.53	
Missing	3	-	-	-	
<b>Number of cancer nodules group</b>					<.0001*
0	637	347	5.17	1.00	
1-2	55	36	1.92	1.63	
≥3	15	13	1.38	2.86	
Missing	9	-	-	-	
<b>Tumor size group</b>					<.0001*
≤4cm	299	131	8.69	1.00	
4-8cm	275	170	3.16	1.84	
≥8cm	128	95	1.90	2.54	
Missing	14	-	-	-	
<b>Invasion depth group</b>					<.0001*
Mucosa	25	4	-	1.00	
Submucosa	40	12	12.29	1.79	
Muscular	83	29	10.02	2.48	
All layer	565	354	3.21	6.24	
Missing	3	-	-	-	
<b>Positive lymph nodes number group</b>					<.0001*
0	257	101	8.98	1.00	
1-6	338	204	3.58	2.06	
7-15	99	81	1.50	4.12	
≥16	18	13	1.90	3.04	
Missing	4	-	-	-	
<b>Tumor location</b>					0.0067*
Proximal	399	217	4.88	1.00	
Body	164	96	4.61	1.07	
Distal	99	48	6.14	0.91	
More than two sites	52	38	1.60	1.83	
Missing	3	-	-	-	
<b>Number of retrieved Lymph Nodes group</b>					0.10
0	6	2	-	1.00	

1-6	196	103	6.10	1.77	
7-15	391	221	4.27	2.13	
≥16	116	72	3.17	2.48	
Missing	7	-	-	-	
<b>Age</b> ( Missing=1)	715			1.01	0.144
<b>Age<sup>2</sup></b> ( Missing=1)	715			1.00	0.056
<b>Positive lymph nodes number</b> ( Missing=4)	712			1.08	<.0001*
<b>Number of retrieved Lymph Nodes</b> ( Missing=7)	709			1.02	0.014*
<b>Lymph node metastasis rate</b> ( Missing=5)	711			1.04	0.232
<b>Number of cancer nodules</b> ( Missing=9)	707			1.18	<.0001*

**Table 2. Results from adjusted analysis of prognostic variables.**

Variables	Estimated coefficient	Estimated SE	Estimated HR	95% CI of HR	P-value
<b>Age</b>	-0.119	0.038	0.888	0.825-0.956	0.0016
<b>Age square</b>	0.001	0.0003	1.001	1.000-1.002	0.0005
<b>Number of cancer nodules</b>	0.103	0.040	1.108	1.024-1.199	0.0106
<b>Lymph node metastasis rate group</b>					<.0001
0 (reference)	-	-	1.000	-	
≤0.35	-0.033	0.152	1.033	0.768-1.390	
0.35-0.74	0.577	0.153	1.780	1.320-2.401	
≥0.74	0.825	0.169	2.491	1.774-3.497	
<b>Invasion depth group</b>					0.0041
Submucosa	-	-	1.000	(-, -)	
Mucosa	-0.880	0.776	0.415	0.091-1.898	
Muscular	0.256	0.370	1.291	0.625-2.669	
All layer	0.740	0.334	2.095	1.089-4.032	
<b>Surgical type II group</b>					<.0001
Radical	-	-			
Palliative	1.757	0.364			
<b>Tumor size</b>					0.0010
≤4cm (reference)	-	-			
4-8cm	0.240	0.132			
≥8cm	0.566	0.152			
<b>Surgical type II group* Tumor size</b>					0.0003
Palliative vs radical *≤4cm (reference)	-	-			
Palliative *4-8cm	-1.026	0.453			
Palliative *≥8cm	-2.097	0.517			