BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-030639
Article Type:	Research
Date Submitted by the Author:	26-Mar-2019
Complete List of Authors:	Hu, Kongwang ; First Affiliated Hospital of Anhui Medical University, Department of General Surgery Wang, Shuaili ; University of Science and Technology of China, School of Life Sciences Wang, Zikun ; Indiana University Bloomington Li, Longlong ; First Affiliated Hospital of Anhui Medical University, Department of General Surgery Huang, Zhiguo ; First Affiliated Hospital of Anhui Medical University, Department of General Surgery Yu, Weiqiang ; University of Science and Technology of China, School of Life Sciences Chen, Zhongxue; Indiana University Bloomington, Wu, Qing-Fa ; University of Science and Technology of China, School of Life Sciences
Keywords:	Gastric carcinoma, Clinicopathologic risk factors, Clinical stage, Lymph node metastasis rate

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

Kongwang Hu[1], Shuaili Wang[2], Zikun Wang[3], Longlong Li[1], Zhiguo Huang[1], Weiqiang Yu[2], Zhongxue Chen[3,*], Qing-Fa Wu[2,4,*]

1. Division of Gastrointestinal Surgery, Department of General Surgery, The First Affiliated Hospital of Anhui Medical University, Hefei 230022, China

2. Division of Molecular Medicine, Hefei National Laboratory for Physical Sciences at Microscale, the Chinese Academy of Sciences (CAS) Key Laboratory of Innate Immunity and Chronic Disease, School of Life Sciences, University of Science and Technology of China, Hefei 230026, China

3. Department of Epidemiology and Biostatistics, School of Public Health, Indiana University Bloomington.

4. School of Data Science, University of Science and Technology of China, Hefei 230026, China

* Correspondence author:

Zhongxue Chen: zc3@indiana.edu, Tel.: 1-812-855-1163

Qing-Fa Wu: wuqf@ustc.edu.cn, Tel.: 86-551-63607631

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 1st, 2001 to December 31st, 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

node metastasis rate.

Strengths and limitations of this study

- This was a retrospective cohort study including seven hundred and sixteen participants.
- We followed up participants for at least five years.
- Data from twenty-three 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 thrid leading cause of cancer-related death worldwide in 2018.[1,2] The incidence and mortality of gastric carcinoma were varying geographically and were dramatically different between Western countries and Eastern countries[3]. According to reports, approximately, 0.7 million people died because of gastric cancer each year [3,4], the second highest incidence and mortality rate after lung cancer, in which alone accounts for 42% of all gastric cancer cases worldwide [5]. About 70% of the case translates into a high fatality, significantly higher than other cancers such as liver and breast cancers.[6] 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 [7]cancer deaths in 2018 and the overall estimated age-standardized (World) incidence rate in 2018 was 23.7 per 100,000 in China. [1,7]

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; [8] 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.[9] Furthermore, the survival rates were poorer

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

clinicopathological features related to the prognosis of gastric cancer include clinical stage, tumor size, infiltration depth, Lauren classification, and lymph node metastasis rate[21,25,26].

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

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

2. Method

Study cohort

Between January 1st, 2001 and December 31th, 2012, seven hundred and sixteen patients aged between 22–84 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 7th edition of the American Joint Committee on Cancer (AJCC) [27] were used for gastric cancer macroscopic and histological classifications

Categorical and continuous clinicopathologic variables were collected and examined to determine prognostic factors as listed in Table 1. Data on age (24-88), age square, gender (male, female), Borrmann's type (types I-IV), 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), type I surgical (all stomach, proximal, distal), surgical type II groups (radical, palliative), and lymphovascular invasion (no, yes), were collected for each patient.

Other clinicopathologic variables, such as positive lymph nodes number, total lymph nodes number, lymph node metastasis rate, surgical margin, tumor size, invasion degree tumor nodes number were originally recorded as continuous variables and subsequently categorized for the current analysis. Accordingly, categorical variables: positive lymph nodes number (0, 1-6,7-15,≥16), surgical margin (negative, positive), tumor size(≤4cm, 4-8cm, ≥8cm), invasion degree (mucosa, submucosa, muscular, all layer), lymph node metastasis rate (0, ≤0.35, 0.35-0.73, ≥0.74), and total lymph nodes number (0,1-6,7-15,≥16) were also used in the analyses.

The current study complied with the of Strengthening the reporting of observational studies in epidemiology (STROBE) reporting guidelines for observational studies.

Ethics statement

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

Patient and Public Involvement

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

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. Firstly, an unadjusted analysis was performed for each of the independent variables. Specifically, for each independent variable, Kaplan-Meier method [28] was applied to see whether it is associated with the dependent variable. Then a Cox proportional hazard regression model with backward variable selection was performed to determine which prognostic variables independently affected gastric cancer and to estimate the adjusted hazard ratios (HR) at the same time.[29] 95% confidence intervals were examined, and two-sided p-values <0.05 were defined as statistically significant in the present study. All endpoints were updated in 2018 June to 2019 January, that makes every case have enough time for follow-up (≥5years). For this study, 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

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,

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

Results from the adjusted analysis

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

4. Discussion

In this study with total 716 gastric cancer patients, we identified the following clinicopathologic factors which were independently significantly associated with gastric carcinoma in term of the adjusted analysis: age, lymph node metastasis rate, tumor size, type II Surgery, and clinical stage. The adjusted analysis revealed that other variables, such as gender, Borrmann's type, TMN stage, tumor location, surgical type I groups, surgical margin, lymphovascular invasion, and total lymph nodes number, might not independently play a major role in the prognosis. For the factor age, we found it had a non-linear effect on the outcome: both age and its square were statistically significantly assocaited with survival time.

In our current study, among these potential risk factors, the prognosis of patients with gastric carcinoma was seen strongly affected by the rate of metastatic lymph nodes, which also has been emphasized in previous studies performed in different countries[30,31]. The result from the study by Kim, Lee et al. indicated that the survival rate was remarkably decreased in association to increased metastatic lymph nodes rate.[32] Msika et al. also found that lymph node metastasis played an important role and was the only independent prognostic risk factor in their study among 86 participants who underwent curative resection.[33] Furthermore, the German Gastric Carcinoma Study (GGCS)[34] suggested that the lymph node ratio should be considered as the significant independent prognostic variables among patients underwent resected stomach carcinoma, and indicated that extended lymph node dissection was the most critical treatment among patients with radical gastrectomy for long-term survival.

The clinical stages, which were defined by the "depth of tumor invasion (T), the

location of perigastric lymph node metastases (N), and the presence or absence of distant metastases (M)" [35], was seen significantly associated with stomach cancer in the present study. Based on the results, the hazard ratios of gastric cancer were very small on stage 0, I, II III compared to stage IV; this could be caused by late presentation of symptoms combined to the lack of pathognomonic signs together with the absence of a screening programme. The prognostic significance of a more advanced stage in our adjusted analysis was comparable to results from other studies.[36,37,38] Specifically, the AJCC was formally applied the TNM, and now it is the most remarkable instrument for treatment planning in oncology and also efficient for evaluating the patient's prognosis in 1970.

Our results also displayed a significant reversed effect (HR=0.869, p-value=0.002) among young patients with gastric cancer, compared to older participants. A review for the white population from 1974 to 2006 in the U.S. displayed similar trends: the incidence of gastric cancer in patients aged 25–39 had raised from 0.27 to 0.45 per 100,000 individuals whereas the incidence had been declining for older populations. More specifically, among patients aged between 60 and 84, the incidence of gastric carcinoma had dropped from 19.8 to 12.8 per 100,000.[39] Some studies provided possible explanation why younger patients with stomach carcinoma have an unfavorable prognosis than older patients: younger patients could have a larger percentage with advanced tumors stage due to lower suspicion of malignant disease and aggressive tumor biology.[40,41]

According to our adjusted analysis results, we found that tumor size was an

independent risk factor for prognostic. In fact, tumor size is a valuable risk factor since it can be examined quite easily before the surgery, although the prognostic risk of tumor size among patients with stomach carcinoma maintains inconsistent. Some researches suggested that tumor size is not an independent prognostic variable in patients who had stomach carcinoma. [42,43,44] 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 [45-48,49], 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 of enbloc resection so that patients need a higher level of expertise and experience for their treatment. There was also a trend that tumor size can raise with the depth of tumor invasion and the extent of lymph node metastasis: the size of the tumor is profoundly associated to "Borrmann's type IV, adjacent organ invasion (T4) and higher lymph node and distant metastasis rate". [43,50] The possible reason for this is that most patients with stage III or stage IV cancers had a relatively lower radical resection and remained a lower 5-year survival rate in many cases.[51]

Additionally, our results show that poorer prognosis among patients who had palliative gastrectomy with a higher risk of gastric cancer compared with radical gastrectomy. Although, the results from Dutch clinical randomize trial [52] suggested that palliative gastrectomy could be beneficial for younger patients (age<70) whose tumor load was restricted to one metastatic site, another previous study[53] indicated that "palliative gastrectomy has no survival benefit (p-value = 0.705, 0.331, respectively) in the peritoneal dissemination and multi-organ metastases groups". Furthermore,

palliative gastrectomy showed no obvious favorable effect on the long-term survival or improvement of the quality of life among patients with gastric cancer.[54] Currently, bursectomy has become a vital part of radical gastrectomy with extended lymphadenectomy as a therapy for advanced gastric carcinoma in Japan.[55] Moreover, Maruyama K et al. also suggested that radical gastrectomy remains the only curative treatment option for gastric cancer.[56]

There were several strengths, and limitations of our current study should be considered. We used the Cox proportional hazard regression model, which is one of the most reliable and generally used methods for multivariable analyses. Our findings showed that tumor size encompasses powerful prognostic information for gastric cancer. From Jun K.H et al., [57] a statistically significant independent association has been found to prove the association between tumor size and stomach carcinoma-related survival and it was a vital predictor for advanced gastric cancer, but may not be detectable in early gastric carcinoma. In addition, our dataset includes patients with long-term follow-up duration, which was rare for other current studies conducted in China, from January 1st to December 31th 2012. However, all the patients in this study were 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 is subject to limitations inherent to all observational studies. For instance, some potential residual confounders may not be recognized in the analysis and possible selection bias due to loss to follow up.

5. Conclusion

In our study, five prognostic risk characteristics have been identified in patients with gastric carcinoma. However, the survival rate for stomach carcinoma patients remains very low. As a result, identifying and predicting important and useful prognosis indicators before treatment are critical for gastric cancer patients. Since these prognostic factors usually depend largely on the postoperative histological examination, they may not be available to a surgeon at the time of treatment. Therefore, a useful, simple prognostic index could be produced with distinct survival rates in specific risk groups. The findings from the current study can be applied to help clinical decision-making, and to be considered as a benchmark for planning future prognosis and treatment. Finally, it is of substantial vital to improve early detection and to investigate the feasibility and survival benefit of therapy for patients with stomach carcinoma.

Acknowledgments: The authors thank Dr. Qiang Wu, Dr. Hao Li, and Dr. Xianghong Chen at Department of Pathology, the First Affiliated Hospital of Anhui Medical University for providing excellent technical support that greatly improved the manuscript. The authors are also extremely grateful all the persons who contributed to the construction of the cohort.

Funding: This work was supported in part by the Hefei National Laboratory for Physical Sciences at Microscale. The funders played no role in the study design, data collection, and analysis, decision to publish, or preparation of the manuscript.

Conflict of interest: The authors declare no conflict of interest in this study.

Patient consent for publication: Not required.

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.

Reference

1. WHO. International Agency for Research on Cancer. Cancer Today. 2018; http://gco.iarc.fr/today/. Accessed 2.10, 2019.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *Ca-Cancer J Clin.* 2018;68(6):394-424.
3. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. *J Clin Oncol.* 2006;24(14):2137-2150.
4. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018.
5. Parkin DM WS, Ferlay WJ, Teppo L, Thomas DB. Cancer Incidence in five continents *IARC Scientific Publication No 155.*VIII.
6. Guggenheim DE, Shah MA. Gastric cancer epidemiology and risk factors. *J Surg Oncol.* 2013;107(3):230-236.
7. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. *CA Cancer J Clin.* 2016;66(2):115-132.
8. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer.* 2010;127(12):2893-2917.
9. Forman D, Burley VJ. Gastric cancer: global pattern of the disease and an overview of environmental risk factors. *Best Pract Res Clin Gastroenterol.* 2006;20(4):633-649.
10. Lindblad M, Rodriguez LA, Lagergren J. Body mass, tobacco and alcohol and risk of esophageal, gastric cardia, and gastric non-cardia adenocarcinoma

among men and women in a nested case-control study. *Cancer Causes Control.* 2005;16(3):285-294.
11. Lagergren J, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N Engl J Med.* 1999;340(11):825-831.
12. Strumylaite L, Zickute J, Dudzevicius J, Dregval L. Salt-preserved foods and risk of gastric cancer. *Medicina (Kaunas).* 2006;42(2):164-170.
13. Liang YX, Deng JY, Guo HH, et al. Characteristics and prognosis of gastric cancer in patients aged >/= 70 years. *World J Gastroenterol.* 2013;19(39):6568-6578.
14. Crew KD, Neugut AI. Epidemiology of gastric cancer. *World J Gastroenterol.* 2006;12(3):354-362.
15. Karimi P, Islami F, Anandasabapathy S, Freedman ND, Kamangar F. Gastric cancer: descriptive epidemiology, risk factors, screening, and prevention. *Cancer Epidemiol Biomarkers Prev.* 2014;23(5):700-713.
16. Howlader NJhscgc. SEER cancer statistics review, 1975-2008. 2011.
17. Allemani C, Matsuda T, Di Carlo V, et al. Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *Lancet.* 2018;391(10125):1023-1075.
18. Strong VE, Song KY, Park CH, et al. Comparison of gastric cancer survival following R0 resection in the United States and Korea using an internationally validated nomogram. *Ann Surg.* 2010;251(4):640-646.
19. Song KY, Park YG, Jeon HM, Park CH. A nomogram for predicting individual survival of patients with gastric cancer who underwent radical surgery with extended lymph node dissection. *Gastric Cancer.* 2014;17(2):287-293.
20. Wagner AD, Grothe W, Haerting J, Kleber G, Grothey A, Fleig WE. Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. *J Clin Oncol.* 2006;24(18):2903-2909.
21. Qiu MZ, Cai MY, Zhang DS, et al. Clinicopathological characteristics and prognostic analysis of Lauren classification in gastric adenocarcinoma in China. *J Transl Med.* 2013;11:58.
22. Penson DF. Re: variation in surgical-readmission rates and quality of hospital care. *J Urol.* 2014;191(5):1363-1364.
23. Lee KG, Lee HJ, Yang JY, et al. Risk factors associated with complication following gastrectomy for gastric cancer: retrospective analysis of prospectively collected data based on the Clavien-Dindo system. *J Gastrointest Surg.* 2014;18(7):1269-1277.
24. Paulino Filho A, Paulino F, de LC. [Preoperative and postoperative care of patients with gastric cancer]. *Hospital (Rio J).* 1961;59:201-209.
25. Vauhkonen M, Vauhkonen H, Sipponen P. Pathology and molecular biology of gastric cancer. *Best Pract Res Clin Gastroenterol.* 2006;20(4):651-674.
26. Smith DD, Schwarz RR, Schwarz RE. Impact of total lymph node count on staging and survival after gastrectomy for gastric cancer: data from a large US-

population database. *J Clin Oncol.* 2005;23(28):7114-7124.
27. Edge SB, Cancer AJCo. *AJCC cancer staging handbook: from the AJCC cancer staging manual.* Vol 2010: Springer New York; 2010.
28. Kaplan EL, Meier PJJotAsa. Nonparametric estimation from incomplete observations. 1958;53(282):457-481.
29. Cox DRJJotRSSSB. Regression models and life-tables. 1972;34(2):187-202.
30. Lee WJ, Lee PH, Yue SC, Chang KC, Wei TC, Chen KM. Lymph node metastases in gastric cancer: significance of positive number. *Oncology.* 1995;52(1):45-50.
31. Yokota T, Ishiyama S, Saito T, et al. Lymph node metastasis as a significant prognostic factor in gastric cancer: a multiple logistic regression analysis. 2004;39(4):380-384.
32. Kim J-P, Lee J-H, Kim S-J, Yu H-J, Yang H-KJGc. Clinicopathologic characteristics and prognostic factors in 10 783 patients with gastric cancer. 1998;1(2):125-133.
33. Msika S, Benhamiche AM, Jouve JL, Rat P, Faivre J. Prognostic factors after curative resection for gastric cancer. A population-based study. *Eur J Cancer.* 2000;36(3):390-396.
34. Roder JD, Böttcher K, Siewert JR, et al. Prognostic factors in gastric carcinoma. Results of the German Gastric Carcinoma Study 1992. 1993;72(7):2089-2097.
35. Kennedy BJ. T N M classification for stomach cancer. *Cancer.* 1970;26(5):971-983.
36. Andrew R, Tiggemann M, Clark L. Positive body image and young women's health: Implications for sun protection, cancer screening, weight loss and alcohol consumption behaviours. *J Health Psychol.* 2016;21(1):28-39.
37. Costa ML, de Cassia Braga Ribeiro K, Machado MA, Costa AC, Montagnini AL. Prognostic score in gastric cancer: the importance of a conjoint analysis of clinical, pathologic, and therapeutic factors. *Ann Surg Oncol.* 2006;13(6):843-850.
38. Cunningham SC, Kamangar F, Kim MP, et al. Survival after gastric adenocarcinoma resection: eighteen-year experience at a single institution. 2005;9(5):718-725.
39. Anderson WF, Camargo MC, Fraumeni JF, Jr., Correa P, Rosenberg PS, Rabkin CS. Age-specific trends in incidence of noncardia gastric cancer in US adults. *JAMA.* 2010;303(17):1723-1728.
40. Tso PL, Bringaze WL, 3rd, Dauterive AH, Correa P, Cohn I, Jr. Gastric carcinoma in the young. *Cancer.* 1987;59(7):1362-1365.
41. Zhang J, Gan L, Xu MD, et al. The prognostic value of age in non-metastatic gastric cancer after gastrectomy: a retrospective study in the U.S. and China. *J Cancer.* 2018;9(7):1188-1199.
42. Michelassi F, Takanishi DM, Jr., Pantalone D, Hart J, Chappell R, Block GE. Analysis of clinicopathologic prognostic features in patients with gastric adenocarcinoma. *Surgery.* 1994;116(4):804-809; discussion 809-810.
43. Yokota T IS, Saito T, Teshima S, Yamada Y, Iwamoto K, et al. Is tumor size a

prognostic indicator for gastric carcinoma? . *Anticancer Res 2002.* 2002;22:3673–3677(Nov-Dec;22(6B):3673-7.).

44. Yu CC, Levison DA, Dunn JA, et al. Pathological prognostic factors in the second British Stomach Cancer Group trial of adjuvant therapy in resectable gastric cancer. *Br J Cancer.* 1995;71(5):1106-1110.
45. Isomoto H, Shikuwa S, Yamaguchi N, et al. Endoscopic submucosal dissection for early gastric cancer: a large-scale feasibility study. *Gut.* 2009;58(3):331-336.
46. Oda I, Gotoda T, Hamanaka H, et al. Endoscopic submucosal dissection for early gastric cancer: technical feasibility, operation time and complications from a large consecutive series. 2005;17(1):54-58.
47. Dassen A, Lemmens V, Van De Poll-franse L, et al. Trends in incidence, treatment and survival of gastric adenocarcinoma between 1990 and 2007: a population-based study in the Netherlands. 2010;46(6):1101-1110.
48. Adachi Y, Oshiro T, Mori M, Maehara Y, Sugimachi KJAoso. Tumor size as a simple prognostic indicator for gastric carcinoma. 1997;4(2):137-140.
49. Giuliani A, Caporale A, Di Bari M, et al. Maximum gastric cancer diameter as a prognostic indicator: univariate and multivariate analysis. 2003;22(4):531-538.
50. Shiraishi N, Sato K, Yasuda K, Inomata M, Kitano S. Multivariate prognostic study on large gastric cancer. *J Surg Oncol.* 2007;96(1):14-18.
51. Yasuda K, Shiraishi N, Adachi Y, Inomata M, Sato K, Kitano S. Risk factors for complications following resection of large gastric cancer. *Br J Surg.* 2001;88(6):873-877.
52. Hartgrink HH, Putter H, Klein Kranenbarg E, Bonenkamp JJ, van de Velde CJ, Dutch Gastric Cancer G. Value of palliative resection in gastric cancer. *Br J Surg.* 2002;89(11):1438-1443.
53. Chen S, Li YF, Feng XY, Zhou ZW, Yuan XH, Chen YB. Significance of palliative gastrectomy for late-stage gastric cancer patients. *J Surg Oncol.* 2012;106(7):862-871.
54. Ouchi K, Sugawara T, Ono H, et al. Therapeutic significance of palliative operations for gastric cancer for survival and quality of life. *J Surg Oncol.* 1998;69(1):41-44.
55. Maruyama K, Okabayashi K, Kinoshita T. Progress in gastric cancer surgery in Japan and its limits of radicality. *World J Surg.* 1987;11(4):418-425.
56. Sano T, Sasako M, Yamamoto S, et al. Gastric cancer surgery: morbidity and mortality results from a prospective randomized controlled trial comparing D2 and extended para-aortic lymphadenectomy-Japan Clinical Oncology Group study 9501. 2004;22(14):2767-2773.
57. Jun KH, Jung H, Baek JM, Chin HM, Park WB. Does tumor size have an impact on gastric cancer? A single institute experience. *Langenbecks Arch Surg.* 2009;394(4):631-635.

Tables

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

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

Surgical type II groups		45.35	2	<.0001*
Radical	673			
Palliative	41			
Lymphovascular invasion		0.34	2	0.56
No	612			
Yes	98			
Clinical stage		107.73	5	<.0001*
0	11			
1	108			
2	155			
3	411			
4	29			
Tumor nodes number		22.30	3	<.0001*
0	638			
1-2	55			
≥3	15			
Tumor size		60.78	3	<.0001*
≤4cm	299			
4-8cm	275			
≥8cm	129			
Invasion degree		52.68	4	<.0001*
Mucosa	25			
Submucosa	38			
Muscular	82			
All layer	569			
Positive lymph nodes number		99.45	4	<.0001*
0	258			
1-6	338			
7-15	99			
≥16	18			
Tumor location		14.18	4	0.0067*
Proximal	400			
Body	164			
Distal	97			
More than two sites	52			
Total lymph nodes number		8.13	5	0.15
0	2			
1-6	196			
7-15	394			
⩾16	117			
Age	716	1.98	1	0.19
Age²	716	3.42	1	0.064
Positive lymph nodes number	713	79.65	1	<.0001*

Total lymph nodes number	710	5.97	1	0.015*
Lymph node metastasis rate	710	1.59	1	0.21
Tumor nodes number	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.

Variables	Estimated coefficient	Estimated SE	Estimated HR	95% CI of HR	P-value
Age	-0.115	0.037	0.891	0.829-0.958	0.0017
Age square	0.001	0.00032	1.001	1.000-1.002	0.0007
Lymph node metastasis rate					<.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	
Surgical type II groups					0.032
Radical	-	-	1.000	-	
Palliative	0.462	0.215	1.587	1.041-2.421	
Tumor size					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	
Clinical Stage					<.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
Title and abstract	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
Introduction			
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
Methods			
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
Results			
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

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 (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9-10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
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
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
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-14
Other information			
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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-030639.R1
Article Type:	Original research
Date Submitted by the Author:	19-Jun-2019
Complete List of Authors:	Hu, Kongwang ; First Affiliated Hospital of Anhui Medical University, Department of General Surgery Wang, Shuaili ; University of Science and Technology of China, School of Life Sciences Wang, Zikun ; Indiana University Bloomington Li, Longlong ; First Affiliated Hospital of Anhui Medical University, Department of General Surgery Huang, Zhiguo ; First Affiliated Hospital of Anhui Medical University, Department of General Surgery Yu, Weiqiang ; University of Science and Technology of China, School of Life Sciences Chen, Zhongxue; Indiana University Bloomington, Wu, Qing-Fa ; University of Science and Technology of China, School of Life Sciences
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Gastroenterology and hepatology
Keywords:	Gastric carcinoma, Clinicopathologic risk factors, Clinical stage, Lymph node metastasis rate

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

Kongwang Hu[1], Shuaili Wang[2], Zikun Wang[3], Longlong Li[1], Zhiguo Huang[1], Weiqiang Yu[2], Zhongxue Chen[3,*], Qing-Fa Wu[2,4,*]

1. Division of Gastrointestinal Surgery, Department of General Surgery, The First Affiliated Hospital of Anhui Medical University, Hefei 230022, China

2. Division of Molecular Medicine, Hefei National Laboratory for Physical Sciences at Microscale, the Chinese Academy of Sciences (CAS) Key Laboratory of Innate Immunity and Chronic Disease, School of Life Sciences, University of Science and Technology of China, Hefei 230026, China

3. Department of Epidemiology and Biostatistics, School of Public Health, Indiana University Bloomington.

4. School of Data Science, University of Science and Technology of China, Hefei 230026, China

* Correspondence author:

Zhongxue Chen: zc3@indiana.edu, Tel.: 1-812-855-1163

Qing-Fa Wu: wuqf@ustc.edu.cn, Tel.: 86-551-63607631

Abstract

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

Methods: Between January 1st, 2001 and December 31st, 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.[1,2] According to previous reports, approximately 0.7 million people died because of gastric cancer each year[3], and about 70% of the gastric cancer cases had high fatality, significantly higher than other cancers such as the liver and breast cancers[4]. However, the incidence and mortality of gastric carcinoma vary geographically; they were dramatically different between Western and Eastern countries[3]. 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.[5] 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. [1,6]

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. [7-9] 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.[10-13] 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[14].

The current most popular therapy for stomach cancer is surgery combined with chemotherapy. Surgery is the most preferred treatment for gastric carcinoma, but the survival rate of patients undergoing surgery remains very low. Previous studies have revealed that the average survival time of patients with advanced gastric cancer is less than 12 months[15-18]. Therefore, how to timely assess the condition, judge the prognosis risk after therapy, and develop a reasonable postoperative care program becomes a vital part of gastric cancer treatment.[19-21]

Many clinicopathological factors, including clinical stage, tumor size, infiltration depth, Lauren classification, and lymph node metastasis rate, might jointly influence the prognosis in patients with gastric carcinoma[18,22,23]. However, most of the previous cohort studies in this area had small sample sizes and each focused on the effect of a single pathological factor[18]. It is important but challenging to identify the most significant and independent factors associated with prognosis since many factors are hihgly correlated. To have a systematically comprehension of gastric carcinoma and to identify independent risk factors on gastric cancer patients, we conducted the current study.

2. Method

Design

This was a retrospective cohort study.

Participants

All participants were recruited from Anhui, China.

Ethics statement

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

Patient and Public Involvement

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

Study cohort

Between January 1st, 2001 and December 31th, 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 7th edition of the American Joint Committee on Cancer (AJCC)[24] 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), type I surgical (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, total lymph nodes number (the total number of lymph nodes), lymph node metastasis rate (the metastasis rate of lymph nodes), surgical margin, tumor size, tumor nodes number (number of tumor nodes), invasion degree were also collected. For those variables originally recorded as continuous were also categorized for the current analysis. Accordingly, categorical variables: positive lymph nodes number group (0, 1-6,7-15,≥16), surgical margin (negative, positive), tumor size group (≤4cm, 4-8cm, ≥8cm), invasion degree (mucosa, submucosa, muscular, all layer), lymph node metastasis rate group (0, ≤0.35, 0.35-0.73, ≥0.74), and total lymph nodes number group (0,1-6,7-15,≥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 assocaited with the survival time, and to estimate their adjusted hazard ratios (HR). 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

The results from the univariable analyses were reported in Table 1. Table 1 also listed the frequencies for each variable. This cohort was composed of 553 males and 163 females. Based on the clinical TNM classification, the numbers of gastric cancer patients in stage 0, I, II, III, and IV were 11, 108,155, 411, and 29, respectively. 98 patients had lymphovascular invasion while 612 did not. 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 the stomach for 97, and 52 participants had more than two sites gastric lesions. Moreover, 673 patients proceeded to radical resection, and 41 proceed to palliative resection. 569 patients had all layer invasion of their stomachs. In addition, 580, 28, and 101 patients received all stomach, proximal, and distal gastric surgery, respectively. The numbers of participants whose lymph node metastasis rate were 0,

between 0 and 0.35, between 0.35 and 0.7, and greater than 0.7 were 253, 200, 149, and 108, respectively. Furthermore, in this study, there were 299, 275, and 129 patients whose tumor sizes were smaller than 4cm, between 4 and 8cm, and larger than 8 cm, respectively.

Sixteen significant prognostic factors of gastric cancer including Borrmann's type, surgical margin, M stage, N stage, T stage, lymph node metastasis rate group, surgical type II group, clinical stage, tumor nodes number group, tumor size group, invasion degree, positive lymph nodes number group, tumor location, positive lymph nodes number, total lymph nodes number, and tumor nodes number were identified ($p<0.05$) from the unadjusted analyses. However, there were no significant associations between survival time and gender, Lauren's classification, surgical type I group, lymphovascular invasion, total lymph node number, age, age square, and lymph node metastasis rate from the unadjusted analysis according to their large p-values (>0.05).

Results from the adjusted analysis

The results of the estimated hazar ratios and their 95% confidence interval from the adjusted analysis were reported in Table 2. The adjusted analysis identified six variables, each was independently associated with survival time. These variables and their estiamted adjusted HR after adjusting for the other effects in the model were: age (HR=0.891, p-value=0.0017, 95% CI: 0.829-0.958), age square (HR =1.001, p-value= 0.0007, 95% CI: 1.000-1.002), lymph node metastasis rate group (HR for ≤0.35, 0.35-0.73, ≥0.74: 0.592, 1.016, and 1.276, respectively; p-value<0.0001, 95% CI: 0.377-0.930, 0.641-1.612, 0.791-2.060, respectively), surgical type II group (HR=1.587, p-

value = 0.0319, 95% CI: 1.041-2.421), tumor size group (HR for 4-8cm and ≥8cm: 1.303 and 1.529, respectively, p-value =0.0134, 95% CI: 1.022-1.679, 1.141-2.049, respectively), and clinical stage (HR for 1, 2, and 3: 0.201, 0.376 and 0.791 respectively, p-value < 0.0001, 95% CI: 0.106-0.384, 0.215-0.658, 0.486-1.289, respectively).

4. Discussion

In this study with total 716 gastric cancer patients, we identified the following clinicopathologic factors which were independently associated with gastric carcinoma from the adjusted analysis: age (and age square), lymph node metastasis rate, tumor size, type II surgery, and clinical stage. The adjusted analysis revealed that other variables, such as gender, Borrmann's type, TMN stage, tumor location, surgical type I group, surgical margin, lymphovascular invasion, and total lymph nodes number, might not independently play a major role in the prognosis. For the variable "age", we found that it had a non-linear effect on the outcome: both age and its square were significantly associated with survival time.

In our current study, among these identified risk factors, the prognosis of patients with gastric carcinoma was seen strongly affected by the rate of metastatic lymph nodes, which also has been emphasized in previous studies performed in different countries[25,26]. The result from the study by Kim, Lee et al. indicated that the survival rate was remarkably decreased with metastatic lymph nodes rate increased.[27] Msika et al. also found that lymph node metastasis played an important role and was the only independent prognostic risk factor among 86 participants who underwent curative resection in their study.[28] Furthermore, the German Gastric Carcinoma Study (GGCS)[29]

suggested that the lymph node metastasis rate should be considered as the significant independent prognostic variables among patients underwent resected stomach carcinoma, and indicated that extended lymph node dissection was the most critical treatment among patients with radical gastrectomy for long-term survival.

The clinical stages, which were defined by the "depth of tumor invasion (T), the location of perigastric lymph node metastases (N), and the presence or absence of distant metastases (M)" [30], was found significantly associated with stomach cancer in the present study. Based on the results, the hazard ratios of gastric cancer were minima on stage 0, I, II III compared to stage IV; this could be caused by the late presentation of symptoms combined to the lack of pathognomonic signs together with the absence of a screening program. The prognostic significance of a more advanced stage in our adjusted analysis was comparable to results from other studies.[31,32,33]

Based on our adjusted analysis, age had a significant nonlinear effect on the survival time. We also found that tumor size was an independent risk factor for prognostic. In fact, tumor size is a valuable risk factor since it can be examined quite easily before the surgery, although the prognostic risk of tumor size among patients with stomach carcinoma maintains inconsistent. Some researches suggested that tumor size is not an independent prognostic variable in patients who had stomach carcinoma. [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

of enbloc resection; patients with larger tumor sizes need higher level of expertise and experience for their treatment. Tumor size could raise with the depth of tumor invasion and the extent of lymph node metastasis increase: the size of the tumor is profoundly associated to "Borrmann's type IV, adjacent organ invasion (T4) and higher lymph node and distant metastasis rate". [35,42] A possible explaination is that most patients with stage III or stage IV cancers had a relatively lower radical resection and remaind a lower 5-year survival rate.[43]

Our results also showed that patients who received palliative gastrectomy had poorer prognosis and higher risks compared to patients with radical gastrectomy. The results from Dutch clinical randomize trial [44] suggested that palliative gastrectomy could be beneficial for younger patients (age<70) whose tumor load was restricted to one metastatic site. On the contrary, a previous study[45] indicated that "palliative gastrectomy has no survival benefit (p-value = 0.705, 0.331, respectively) in the peritoneal dissemination and multi-organ metastases group". Another study found that palliative gastrectomy showed no obvious favorable effect on long-term survival or improvement of the quality of life among patients with gastric cancer.[46] Moreover, Maruyama K et al. suggested that radical gastrectomy remained the only curative treatment option for gastric cancer.[47]

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 multivariable analyses with survival time as dependent variable. Our findings showed that tumor size encompasses important prognostic information for

gastric cancer. Based on Jun K.H et al., [48] the tumor size was statistically significantly and independently associated with stomach 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, five independent prognostic risk characteristics 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 early detection and to investigate the feasibility and survival benefit of therapy for patients with stomach carcinoma.

Acknowledgments: The authors would like to thank Drs. Qiang Wu, Hao Li, and Xianghong Chen from the Department of Pathology at the First Affiliated Hospital of Anhui Medical University for providing excellent technical support of this study. The

authors are grateful to the reviewers for their helpful comments which result in an improved presentation of this report.

Funding: This work was supported in part by the Hefei National Laboratory for Physical Sciences at Microscale. The funders played no role in the study design, data collection, and analysis, decision to publish, or preparation of the manuscript.

Conflict of interest: The authors declare no conflict of interest in this study.

Patient consent for publication: Not required.

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 the discussion and approved the final manuscript.

Reference

1. WHO. International Agency for Research on Cancer. Cancer Today. 2018; http://gco.iarc.fr/today/. Accessed 2.10, 2019.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *Ca-Cancer J Clin.* 2018;68(6):394-424.
3. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. *J Clin Oncol.* 2006;24(14):2137-2150.
4. Guggenheim DE, Shah MA. Gastric cancer epidemiology and risk factors. *J Surg Oncol.* 2013;107(3):230-236.
5. Forman D, Burley VJ. Gastric cancer: global pattern of the disease and an overview of environmental risk factors. *Best Pract Res Clin Gastroenterol.* 2006;20(4):633-649.
6. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. *CA Cancer J Clin.* 2016;66(2):115-132.

7. Lindblad M, Rodriguez LA, Lagergren J. Body mass, tobacco and alcohol and risk of esophageal, gastric cardia, and gastric non-cardia adenocarcinoma among men and women in a nested case-control study. *Cancer Causes Control.* 2005;16(3):285-294.
8. Lagergren J, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N Engl J Med.* 1999;340(11):825-831.
9. Strumylaite L, Zickute J, Dudzevicius J, Dregval L. Salt-preserved foods and risk of gastric cancer. *Medicina (Kaunas).* 2006;42(2):164-170.
10. Liang YX, Deng JY, Guo HH, et al. Characteristics and prognosis of gastric cancer in patients aged >/= 70 years. *World J Gastroenterol.* 2013;19(39):6568-6578.
11. Crew KD, Neugut AI. Epidemiology of gastric cancer. *World J Gastroenterol.* 2006;12(3):354-362.
12. Karimi P, Islami F, Anandasabapathy S, Freedman ND, Kamangar F. Gastric cancer: descriptive epidemiology, risk factors, screening, and prevention. *Cancer Epidemiol Biomarkers Prev.* 2014;23(5):700-713.
13. Howlader NJhscgc. SEER cancer statistics review, 1975-2008. 2011.
14. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018.
15. Strong VE, Song KY, Park CH, et al. Comparison of gastric cancer survival following R0 resection in the United States and Korea using an internationally validated nomogram. *Ann Surg.* 2010;251(4):640-646.
16. Song KY, Park YG, Jeon HM, Park CH. A nomogram for predicting individual survival of patients with gastric cancer who underwent radical surgery with extended lymph node dissection. *Gastric Cancer.* 2014;17(2):287-293.
17. Wagner AD, Grothe W, Haerting J, Kleber G, Grothey A, Fleig WE. Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. *J Clin Oncol.* 2006;24(18):2903-2909.
18. Qiu MZ, Cai MY, Zhang DS, et al. Clinicopathological characteristics and prognostic analysis of Lauren classification in gastric adenocarcinoma in China. *J Transl Med.* 2013;11:58.
19. Penson DF. Re: variation in surgical-readmission rates and quality of hospital care. *J Urol.* 2014;191(5):1363-1364.
20. Lee KG, Lee HJ, Yang JY, et al. Risk factors associated with complication following gastrectomy for gastric cancer: retrospective analysis of prospectively collected data based on the Clavien-Dindo system. *J Gastrointest Surg.* 2014;18(7):1269-1277.
21. Paulino Filho A, Paulino F, de LC. [Preoperative and postoperative care of patients with gastric cancer]. *Hospital (Rio J).* 1961;59:201-209.
22. Vauhkonen M, Vauhkonen H, Sipponen P. Pathology and molecular biology of gastric cancer. *Best Pract Res Clin Gastroenterol.* 2006;20(4):651-674.
23. Smith DD, Schwarz RR, Schwarz RE. Impact of total lymph node count on staging and survival after gastrectomy for gastric cancer: data from a large US-population database. *J Clin Oncol.* 2005;23(28):7114-7124.
24. Edge SB, Cancer AJCo. *AJCC cancer staging handbook: from the AJCC cancer staging manual.* Vol 2010: Springer New York; 2010.
25. Lee WJ, Lee PH, Yue SC, Chang KC, Wei TC, Chen KM. Lymph node metastases in gastric cancer:

significance of positive number. *Oncology.* 1995;52(1):45-50.

26. Yokota T, Ishiyama S, Saito T, et al. Lymph node metastasis as a significant prognostic factor in gastric cancer: a multiple logistic regression analysis. 2004;39(4):380-384.
27. Kim J-P, Lee J-H, Kim S-J, Yu H-J, Yang H-KJGc. Clinicopathologic characteristics and prognostic factors in 10 783 patients with gastric cancer. 1998;1(2):125-133.
28. Msika S, Benhamiche AM, Jouve JL, Rat P, Faivre J. Prognostic factors after curative resection for gastric cancer. A population-based study. *Eur J Cancer.* 2000;36(3):390-396.
29. Roder JD, Böttcher K, Siewert JR, et al. Prognostic factors in gastric carcinoma. Results of the German Gastric Carcinoma Study 1992. 1993;72(7):2089-2097.
30. Kennedy BJ. T N M classification for stomach cancer. *Cancer.* 1970;26(5):971-983.
31. Andrew R, Tiggemann M, Clark L. Positive body image and young women's health: Implications for sun protection, cancer screening, weight loss and alcohol consumption behaviours. *J Health Psychol.* 2016;21(1):28-39.
32. Costa ML, de Cassia Braga Ribeiro K, Machado MA, Costa AC, Montagnini AL. Prognostic score in gastric cancer: the importance of a conjoint analysis of clinical, pathologic, and therapeutic factors. *Ann Surg Oncol.* 2006;13(6):843-850.
33. Cunningham SC, Kamangar F, Kim MP, et al. Survival after gastric adenocarcinoma resection: eighteen-year experience at a single institution. 2005;9(5):718-725.
34. Michelassi F, Takanishi DM, Jr., Pantalone D, Hart J, Chappell R, Block GE. Analysis of clinicopathologic prognostic features in patients with gastric adenocarcinoma. *Surgery.* 1994;116(4):804-809; discussion 809-810.
35. Yokota T IS, Saito T, Teshima S, Yamada Y, Iwamoto K, et al. Is tumor size a prognostic indicator for gastric carcinoma? . *Anticancer Res 2002.* 2002;22:3673–3677(Nov-Dec;22(6B):3673-7.).
36. Yu CC, Levison DA, Dunn JA, et al. Pathological prognostic factors in the second British Stomach Cancer Group trial of adjuvant therapy in resectable gastric cancer. *Br J Cancer.* 1995;71(5):1106-1110.
37. Isomoto H, Shikuwa S, Yamaguchi N, et al. Endoscopic submucosal dissection for early gastric cancer: a large-scale feasibility study. *Gut.* 2009;58(3):331-336.
38. Oda I, Gotoda T, Hamanaka H, et al. Endoscopic submucosal dissection for early gastric cancer: technical feasibility, operation time and complications from a large consecutive series. 2005;17(1):54-58.
39. Dassen A, Lemmens V, Van De Poll-franse L, et al. Trends in incidence, treatment and survival of gastric adenocarcinoma between 1990 and 2007: a population-based study in the Netherlands. 2010;46(6):1101-1110.
40. Adachi Y, Oshiro T, Mori M, Maehara Y, Sugimachi KJAoso. Tumor size as a simple prognostic indicator for gastric carcinoma. 1997;4(2):137-140.
41. Giuliani A, Caporale A, Di Bari M, et al. Maximum gastric cancer diameter as a prognostic indicator: univariate and multivariate analysis. 2003;22(4):531-538.
42. Shiraishi N, Sato K, Yasuda K, Inomata M, Kitano S. Multivariate prognostic study on large gastric cancer. *J Surg Oncol.* 2007;96(1):14-18.
43. Yasuda K, Shiraishi N, Adachi Y, Inomata M, Sato K, Kitano S. Risk factors for complications following resection of large gastric cancer. *Br J Surg.* 2001;88(6):873-877.
44. Hartgrink HH, Putter H, Klein Kranenbarg E, Bonenkamp JJ, van de Velde CJ, Dutch Gastric Cancer G. Value of palliative resection in gastric cancer. *Br J Surg.* 2002;89(11):1438-1443.

45. Chen S, Li YF, Feng XY, Zhou ZW, Yuan XH, Chen YB. Significance of palliative gastrectomy for late-stage gastric cancer patients. *J Surg Oncol.* 2012;106(7):862-871.
46. Ouchi K, Sugawara T, Ono H, et al. Therapeutic significance of palliative operations for gastric cancer for survival and quality of life. *J Surg Oncol.* 1998;69(1):41-44.
47. Sano T, Sasako M, Yamamoto S, et al. Gastric cancer surgery: morbidity and mortality results from a prospective randomized controlled trial comparing D2 and extended para-aortic lymphadenectomy-Japan Clinical Oncology Group study 9501. 2004;22(14):2767-2773.
48. Jun KH, Jung H, Baek JM, Chin HM, Park WB. Does tumor size have an impact on gastric cancer? A single institute experience. *Langenbecks Arch Surg.* 2009;394(4):631-635.

Tables

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

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

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

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

***: P-value<0.05**

Table 2. Results from adjusted analysis of prognostic variables.

Variables	Estimated coefficient	Estimated SE	Estimated HR	95% CI of HR	P-value
Age	-0.115	0.037	0.891	0.829-0.958	0.0017
Age square	0.001	0.00032	1.001	1.000-1.002	0.0007
Lymph node metastasis rate					<.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	
Surgical type II group					0.032
Radical	-	-	1.000	-	
Palliative	0.462	0.215	1.587	1.041-2.421	
Tumor size					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	
Clinical Stage					<.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	

BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-030639.R2
Article Type:	Original research
Date Submitted by the Author:	08-Aug-2019
Complete List of Authors:	Hu, Kongwang ; First Affiliated Hospital of Anhui Medical University, Department of General Surgery Wang, Shuaili ; University of Science and Technology of China, School of Life Sciences Wang, Zikun ; Indiana University Bloomington Li, Longlong ; First Affiliated Hospital of Anhui Medical University, Department of General Surgery Huang, Zhiguo ; First Affiliated Hospital of Anhui Medical University, Department of General Surgery Yu, Weiqiang ; University of Science and Technology of China, School of Life Sciences Chen, Zhongxue; Indiana University Bloomington, Wu, Qing-Fa ; University of Science and Technology of China, School of Life Sciences
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Gastroenterology and hepatology
Keywords:	Gastric carcinoma, Clinicopathologic risk factors, Clinical stage, Lymph node metastasis rate

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

Kongwang Hu[1], Shuaili Wang[2], Zikun Wang[3], Longlong Li[1], Zhiguo Huang[1], Weiqiang Yu[2], Zhongxue Chen[3,*], Qing-Fa Wu[2,4,*]

1. Division of Gastrointestinal Surgery, Department of General Surgery, The First Affiliated Hospital of Anhui Medical University, Hefei 230022, China
2. Division of Molecular Medicine, Hefei National Laboratory for Physical Sciences at Microscale, the Chinese Academy of Sciences (CAS) Key Laboratory of Innate Immunity and Chronic Disease, School of Life Sciences, University of Science and Technology of China, Hefei 230026, China
3. Department of Epidemiology and Biostatistics, School of Public Health, Indiana University Bloomington.
4. School of Data Science, University of Science and Technology of China, Hefei 230026, China
* Correspondence author:

Zhongxue Chen: zc3@indiana.edu, Tel.: 1-812-855-1163

Qing-Fa Wu: wuqf@ustc.edu.cn, Tel.: 86-551-63607631

Abstract

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

Methods: Between January 1st, 2001 and December 31st, 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.[1,2] According to previous reports, approximately 0.7 million people died because of gastric cancer each year[3], and about 70% of the gastric cancer cases had high fatality, significantly higher than other cancers such as the liver and breast cancers[4]. However, the incidence and mortality of gastric carcinoma vary geographically; they were dramatically different between Western and Eastern countries[3]. 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.[5] 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. [1,6]

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. [7-9] 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.[10-13] 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[14].

The current most popular therapy for gastric cancer is surgery combined with chemotherapy. Surgery is the most preferred treatment for gastric carcinoma, but the survival rate of patients undergoing surgery remains very low. Previous studies have revealed that the average survival time of patients with advanced gastric cancer is less than 12 months[15,16]. Therefore, how to timely assess the condition, judge the prognosis risk after therapy, and develop a reasonable postoperative care program becomes a vital part of gastric cancer treatment.[17-19]

Many clinicopathological factors, including clinical stage, tumor size, infiltration depth, Lauren classification, and lymph node metastasis rate, might jointly influence the prognosis in patients with gastric carcinoma[20-22]. It is important but challenging to identify the most significant and independent factors associated with prognosis since many factors are highly correlated. To have a systematic comprehension of gastric carcinoma and to identify independent risk factors on gastric cancer patients, we conducted the current study.

2. Method

Design: This was a retrospective cohort study.

Participants: All participants were recruited from Anhui, China.

Ethics statement

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

Patient and Public Involvement

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

Study cohort

Between January 1st, 2001 and December 31th, 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 7th edition of the American Joint Committee on Cancer (AJCC)[23] 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, ≥3), positive lymph nodes number group (0, 1-6,7-15,≥16), surgical margin (negative, positive), tumor size group (≤4cm, 4-8cm, ≥8cm), invasion depth (mucosa, submucosa, muscular, all layer), lymph node metastasis rate group

(0, ≤0.35, 0.35-0.73, ≥0.74), and number of retrieved lymph node group (0,1-6,7-15,≥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 assocaited with the survival time, and to estimate their adjusted hazard ratios (HR). In the adjusted analysis, all possible two-way interactiosn 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

listed the frequencies for each variable. This cohort was composed of 552 males and 163 females. Based on the clinical TNM classification, the numbers of gastric cancer patients in stage 0, I, II, III, and IV were 11, 109, 296, 269, and 28, respectively. 98 patients had lymphovascular invasion while 611 did not. Gastric lesions were located on the proximal of the stomach for 399 patients, on the body of the stomach for 164 patients, on the distal of the stomach for 99, and 52 participants had more than two sites gastric lesions. Moreover, 672 patients proceeded to radical resection, and 42 proceed to palliative resection. 565 patients had all layer invasion of their stomachs. In addition, 579, 28, and 101 patients received all stomach, proximal, and distal gastric surgery, respectively. The numbers of participants whose lymph node metastasis rate were 0, between 0 and 0.35, between 0.35 and 0.7, and greater than 0.7 were 253, 201, 157, and 95, respectively. Furthermore, in this study, there were 299, 275, and 128 patients whose tumor sizes were smaller than 4cm, between 4 and 8cm, and larger than 8 cm, respectively.

Sixteen significant prognostic factors of gastric cancer including Borrmann's type, surgical margin, M stage, N stage, T stage, lymph node metastasis rate group, surgical type II group, clinical stage, number of cancer nodules group, tumor size group, invasion depth group, positive lymph nodes number group, tumor location, positive lymph nodes number, number of retrieved lymph nodes, and number of cancer nodules were identified ($p<0.05$) from the unadjusted analyses. However, there were no significant associations between survival time and gender, Lauren's classification, surgical type I group, lymphovascular invasion, number of retrieved lymph nodes group, age, age square, and lymph node metastasis rate from the unadjusted analysis according to their large p-values (>0.05).

Results from the adjusted analysis

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

4. Discussion

In this study with total 716 gastric cancer patients, we identified the following clinicopathologic factors which were independently associated with gastric carcinoma from the adjusted analysis: age (and age square), number of cancer nodules, lymph node metastasis rate, tumor size, type II surgery, invasion depth group and interaction between surgical type II and tumor size. The adjusted analysis revealed that other variables, such as gender, Borrmann's type, TMN stage, tumor location, surgical type I group, surgical margin, lymphovascular invasion, and number of retrieved lymph node, might not independently play a major role in the prognosis. For the variable "age", we found that it had a non-linear effect on the outcome: both age and its square were significantly associated with survival time.

In our current study, among these identified risk factors, the prognosis of patients with gastric carcinoma was seen strongly affected by the rate of metastatic lymph nodes, which also has been emphasized in previous studies performed in different countries[24,25]. The result from the study by Kim, Lee et al. indicated that the survival rate was remarkably decreased with metastatic lymph nodes rate increased.[26] Msika et al. also found that lymph node metastasis played an important role and was the only independent prognostic risk factor among 86 participants who underwent curative resection in their study.[27] Furthermore, the German Gastric Carcinoma Study (GGCS)[28] suggested that the lymph node metastasis rate should be considered as the significant independent prognostic variables among patients underwent resected gastric carcinoma, and indicated that extended lymph node dissection was the most critical treatment among patients with radical gastrectomy for long-term survival. Of the many factors relevant to survival time, depth of invasion also has been identified as one of the major prognostic factors from our current adjusted analysis. This finding is consistant with those from the literature.[29-32] .

Based on our adjusted analysis, age had a significant nonlinear effect on the survival time. We also found that tumor size and the number of cancer nodules were independent risk factors for prognostic. These two variables are recognized as tumor burden, which are related to poor prognosis susceptibility in another study as well.[33] One Chinese cohort provided that a poorer prognosis in patients with gastric cancer whose number of cancer nodules were more than 3.[34] In addition, a Turkish study stated that cancer nodules are more observed in patients with the intestinal type and vascular invasive gastric cancers.[35] On the other hand, tumor size is a valuable risk factor since it can be examined quite easily before the surgery, although the prognostic risk of tumor size among patients with gastric carcinoma maintains inconsistent. Some researches suggested that tumor size is not an independent prognostic variable in patients who had gastric

carcinoma. [36,37,38] 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 [39-42,43], 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 of enbloc resection; patients with larger tumor sizes need higher level of expertise and experience for their treatment. Tumor size could raise with the depth of tumor invasion and the extent of lymph node metastasis increase: the size of the tumor is profoundly associated to "Borrmann's type IV, adjacent organ invasion (T4) and higher lymph node and distant metastasis rate". [37,44] A possible explaination is that most patients with stage III or stage IV cancers had a relatively lower radical resection and remained a lower 5-year survival rate.[45]

Our results also showed that patients who received palliative gastrectomy had poorer prognosis and higher risks compared to patients with radical gastrectomy. The results from Dutch clinical randomize trial [46] suggested that palliative gastrectomy could be beneficial for younger patients (age<70) whose tumor load was restricted to one metastatic site. On the contrary, a previous study[47] indicated that "palliative gastrectomy has no survival benefit (p-value = 0.705, 0.331, respectively) in the peritoneal dissemination and multi-organ metastases group". Another study found that palliative gastrectomy showed no obvious favorable effect on long-term survival or improvement of the quality of life among patients with gastric cancer.[48] Moreover, Maruyama K et al. suggested that radical gastrectomy remained the only curative treatment option for gastric cancer.[49] The interaction between tumor size and surgical type II was found significant from our adjusted analysis. It showed that patients who had tumor size ≤4 cm and palliative gastrectomy had the lowest risk while the highest risk was found in patients who had tumor size ≤4 cm and

palliative gastrectomy. On the contrary, patients who had larger tumor size (≥8cm) 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., [50] 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

early detection and to investigate the feasibility and survival benefit of therapy for patients with gastric carcinoma.

Acknowledgments: The authors would like to thank Drs. Qiang Wu, Hao Li, and Xianghong Chen from the Department of Pathology at the First Affiliated Hospital of Anhui Medical University for providing excellent technical support of this study. The authors are grateful to the reviewers for their helpful comments which result in an improved presentation of this report.

Funding: This work was supported in part by the Hefei National Laboratory for Physical Sciences at Microscale. The funders played no role in the study design, data collection, and analysis, decision to publish, or preparation of the manuscript.

Conflict of interest: The authors declare no conflict of interest in this study.

Patient consent for publication: Not required.

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 the discussion and approved the final manuscript.

Reference

1. WHO. International Agency for Research on Cancer. Cancer Today. 2018; http://gco.iarc.fr/today/. Accessed 2.10, 2019.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *Ca-Cancer J Clin.* 2018;68(6):394-424.
3. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five

continents: defining priorities to reduce cancer disparities in different geographic regions of the world. *J Clin Oncol.* 2006;24(14):2137-2150.
4. Guggenheim DE, Shah MA. Gastric cancer epidemiology and risk factors. *J Surg Oncol.* 2013;107(3):230-236.
5. Forman D, Burley VJ. Gastric cancer: global pattern of the disease and an overview of environmental risk factors. *Best Pract Res Clin Gastroenterol.* 2006;20(4):633-649.
6. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. *CA Cancer J Clin.* 2016;66(2):115-132.
7. Lindblad M, Rodriguez LA, Lagergren J. Body mass, tobacco and alcohol and risk of esophageal, gastric cardia, and gastric non-cardia adenocarcinoma among men and women in a nested case-control study. *Cancer Causes Control.* 2005;16(3):285-294.
8. Lagergren J, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N Engl J Med.* 1999;340(11):825-831.
9. Strumylaite L, Zickute J, Dudzevicius J, Dregval L. Salt-preserved foods and risk of gastric cancer. *Medicina (Kaunas).* 2006;42(2):164-170.
10. Liang YX, Deng JY, Guo HH, et al. Characteristics and prognosis of gastric cancer in patients aged >/= 70 years. *World J Gastroenterol.* 2013;19(39):6568-6578.
11. Crew KD, Neugut AI. Epidemiology of gastric cancer. *World J Gastroenterol.* 2006;12(3):354-362.
12. Karimi P, Islami F, Anandasabapathy S, Freedman ND, Kamangar F. Gastric cancer: descriptive epidemiology, risk factors, screening, and prevention. *Cancer Epidemiol Biomarkers Prev.* 2014;23(5):700-713.
13. Howlader NJhscgc. SEER cancer statistics review, 1975-2008. 2011.
14. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018.
15. Magalhães H, Fontes-Sousa M, Machado M. Immunotherapy in advanced gastric Cancer: an overview of the emerging strategies. *Canadian Journal of Gastroenterology and Hepatology.* 2018;2018.
16. Ajani JA. Is the addition of cisplatin to S-1 better than S-1 alone for patients with advanced gastroesophageal cancer? *Nature Reviews Clinical Oncology.* 2008;5(9):508.
17. Penson DF. Re: variation in surgical-readmission rates and quality of hospital care. *J Urol.* 2014;191(5):1363-1364.
18. Lee KG, Lee HJ, Yang JY, et al. Risk factors associated with complication following gastrectomy for gastric cancer: retrospective analysis of prospectively collected data based on the Clavien-Dindo system. *J Gastrointest Surg.* 2014;18(7):1269-1277.
19. Paulino Filho A, Paulino F, de LC. [Preoperative and postoperative care of patients with gastric cancer]. *Hospital (Rio J).* 1961;59:201-209.
20. Qiu MZ, Cai MY, Zhang DS, et al. Clinicopathological characteristics and prognostic analysis of Lauren classification in gastric adenocarcinoma in China. *J Transl Med.* 2013;11:58.
21. Vauhkonen M, Vauhkonen H, Sipponen P. Pathology and molecular biology of gastric cancer. *Best Pract Res Clin Gastroenterol.* 2006;20(4):651-674.
22. Smith DD, Schwarz RR, Schwarz RE. Impact of total lymph node count on staging and survival after gastrectomy for gastric cancer: data from a large US-population database. *J Clin Oncol.* 2005;23(28):7114-7124.
23. Edge SB, Cancer AJCo. *AJCC cancer staging handbook: from the AJCC cancer staging manual.* Vol 2010: Springer New York; 2010.
24. Lee WJ, Lee PH, Yue SC, Chang KC, Wei TC, Chen KM. Lymph node metastases in gastric cancer: significance of positive number. *Oncology.* 1995;52(1):45-50.
25. Yokota T, Ishiyama S, Saito T, et al. Lymph node metastasis as a significant prognostic factor in gastric cancer: a multiple logistic regression analysis. 2004;39(4):380-384.
26. Kim J-P, Lee J-H, Kim S-J, Yu H-J, Yang H-KJGc. Clinicopathologic characteristics and prognostic factors in 10 783 patients with gastric cancer. 1998;1(2):125-133.
27. Msika S, Benhamiche AM, Jouve JL, Rat P, Faivre J. Prognostic factors after curative resection for gastric cancer. A population-based study. *Eur J Cancer.* 2000;36(3):390-396.
28. Roder JD, Böttcher K, Siewert JR, et al. Prognostic factors in gastric carcinoma. Results of the German Gastric Carcinoma Study 1992. 1993;72(7):2089-2097.
29. Shimizu H, Ichikawa D, Komatsu S, et al. The decision criterion of histological mixed type in "T1/T2" gastric carcinoma--comparison between TNM classification and Japanese Classification of Gastric Cancer. *J Surg*

Oncol. 2012;105(8):800-804.
30. Ikeda M, Furukawa H, Imamura H, et al. Poor prognosis associated with thrombocytosis in patients with gastric cancer. *Ann Surg Oncol.* 2002;9(3):287-291.
31. Han SL, Tang HJ, Hua YW, Ji SQ, Lin DX. Expression of COX-2 in stomach cancers and its relation to their biological features. *Dig Surg.* 2003;20(2):107-114.
32. Joo YE, Oh WT, Rew JS, Park CS, Choi SK, Kim SJ. Cyclooxygenase-2 expression is associated with well-differentiated and intestinal-type pathways in gastric carcinogenesis. *Digestion.* 2002;66(4):222-229.
33. Chu DZ, Lang NP, Thompson C, Osteen PK, Westbrook KC. Peritoneal carcinomatosis in nongynecologic malignancy. A prospective study of prognostic factors. *Cancer.* 1989;63(2):364-367.
34. Quanwen. L, Zhengfang., Zhou, Jianxin., Cui. Hongqing.,Xi. Bing., Chen. The value of cancer nodules in staging and prognosis evaluation of gastric cancer patients. *Chinese Journal of Gastrointestinal Surgery.* 2017;2017,20(3) 277-282.
35. Ersen A, Unlu MS, Akman T, et al. Tumor deposits in gastric carcinomas. *Pathol Res Pract.* 2014;210(9):565-570.
36. Michelassi F, Takanishi DM, Jr., Pantalone D, Hart J, Chappell R, Block GE. Analysis of clinicopathologic prognostic features in patients with gastric adenocarcinoma. *Surgery.* 1994;116(4):804-809; discussion 809-810.
37. Yokota T IS, Saito T, Teshima S, Yamada Y, Iwamoto K, et al. Is tumor size a prognostic indicator for gastric carcinoma? . *Anticancer Res 2002.* 2002;22:3673–3677(Nov-Dec;22(6B):3673-7.).
38. Yu CC, Levison DA, Dunn JA, et al. Pathological prognostic factors in the second British Stomach Cancer Group trial of adjuvant therapy in resectable gastric cancer. *Br J Cancer.* 1995;71(5):1106-1110.
39. Isomoto H, Shikuwa S, Yamaguchi N, et al. Endoscopic submucosal dissection for early gastric cancer: a large-scale feasibility study. *Gut.* 2009;58(3):331-336.
40. Oda I, Gotoda T, Hamanaka H, et al. Endoscopic submucosal dissection for early gastric cancer: technical feasibility, operation time and complications from a large consecutive series. 2005;17(1):54-58.
41. Dassen A, Lemmens V, Van De Poll-franse L, et al. Trends in incidence, treatment and survival of gastric adenocarcinoma between 1990 and 2007: a population-based study in the Netherlands. 2010;46(6):1101-1110.
42. Adachi Y, Oshiro T, Mori M, Maehara Y, Sugimachi KJAoso. Tumor size as a simple prognostic indicator for gastric carcinoma. 1997;4(2):137-140.
43. Giuliani A, Caporale A, Di Bari M, et al. Maximum gastric cancer diameter as a prognostic indicator: univariate and multivariate analysis. 2003;22(4):531-538.
44. Shiraishi N, Sato K, Yasuda K, Inomata M, Kitano S. Multivariate prognostic study on large gastric cancer. *J Surg Oncol.* 2007;96(1):14-18.
45. Yasuda K, Shiraishi N, Adachi Y, Inomata M, Sato K, Kitano S. Risk factors for complications following resection of large gastric cancer. *Br J Surg.* 2001;88(6):873-877.
46. Hartgrink HH, Putter H, Klein Kranenbarg E, Bonenkamp JJ, van de Velde CJ, Dutch Gastric Cancer G. Value of palliative resection in gastric cancer. *Br J Surg.* 2002;89(11):1438-1443.
47. Chen S, Li YF, Feng XY, Zhou ZW, Yuan XH, Chen YB. Significance of palliative gastrectomy for late-stage gastric cancer patients. *J Surg Oncol.* 2012;106(7):862-871.
48. Ouchi K, Sugawara T, Ono H, et al. Therapeutic significance of palliative operations for gastric cancer for survival and quality of life. *J Surg Oncol.* 1998;69(1):41-44.
49. Sano T, Sasako M, Yamamoto S, et al. Gastric cancer surgery: morbidity and mortality results from a prospective randomized controlled trial comparing D2 and extended para-aortic lymphadenectomy-Japan Clinical Oncology Group study 9501. 2004;22(14):2767-2773.
50. Jun KH, Jung H, Baek JM, Chin HM, Park WB. Does tumor size have an impact on gastric cancer? A single institute experience. *Langenbecks Arch Surg.* 2009;394(4):631-635.

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
Gender					0.40
Female	163	86	4.94	1.00	
Male	552	314	4.59	1.10	
Missing	1	-	-	-	
Borrmann's Type					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	-	-	-	
Surgical margin					0.020*
Negative	648	353	4.94	1.00	
Positive	46	34	1.55	1.71	
Missing	22	-	-	-	
Lauren's classification					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	-	-	-	
M stage					<.0001 *
0	684	373	5.06	1.00	
1	28	25	1.34	2.79	
Missing	4	-	-	-	
N stage					<.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	-	-	-	
T stage					<.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	-	-	-	
Lymph node metastasis rate group					<.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	-	-	-	
Surgical type I group					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	-	-	-	
Surgical type II group					<.0001*
Radical	672	363	5.25	1.00	
Palliative	42	36	1.13	3.19	
Missing	2	-	-	-	
Lymphovascular invasion					0.56
No	611	344	4.74	1.00	
Yes	98	55	4.61	1.09	
Missing	7	-	-	-	
Clinical stage					<.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	-	-	-	
Number of cancer nodules group					<.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	-	-	-	
Tumor size group					<.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	-	-	-	
Invasion depth group					<.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	-	-	-	
Positive lymph nodes number group					<.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	-	-	-	
Tumor location					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	-	-	-	
Number of retrieved Lymph Nodes group					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	-	-	-	
Age(Missing=1)	715			1.01	0.144
Age²(Missing=1)	715			1.00	0.056
Positive lymph nodes number (Missing=4)	712			1.08	<.0001*
Number of retrieved Lymph Nodes group (Missing=7)	709			1.02	0.014*
Lymph node metastasis rate (Missing=7)	709			1.04	0.232
Number of cancer nodules (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
Age	-0.119	0.038	0.888	0.825-0.956	0.0016
Age square	0.001	0.0003	1.001	1.000-1.002	0.0005
Number of cancer nodules	0.103	0.040	1.108	1.024-1.199	0.0106
Lymph node metastasis rate					<.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	
Invasion depth group					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	
Surgical type II group					<.0001
Radical	-	-			
Palliative	1.757	0.364			
Tumor size					0.0010
≤4cm (reference)	-	-			
4-8cm	0.240	0.132			
≥8cm	0.566	0.152			
Surgical type II group* Tumor size					0.0003
Palliative vs radical *≤4cm (reference)	-	-			
Palliative *4-8cm	-1.026	0.453			
Palliative *≥8cm	-2.097	0.517			

BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-030639.R3
Article Type:	Original research
Date Submitted by the Author:	28-Aug-2019
Complete List of Authors:	Hu, Kongwang ; First Affiliated Hospital of Anhui Medical University, Department of General Surgery Wang, Shuaili ; University of Science and Technology of China, School of Life Sciences Wang, Zikun ; Indiana University Bloomington Li, Longlong ; First Affiliated Hospital of Anhui Medical University, Department of General Surgery Huang, Zhiguo ; First Affiliated Hospital of Anhui Medical University, Department of General Surgery Yu, Weiqiang ; University of Science and Technology of China, School of Life Sciences Chen, Zhongxue; Indiana University Bloomington, Wu, Qing-Fa ; University of Science and Technology of China, School of Life Sciences
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Gastroenterology and hepatology
Keywords:	Gastric carcinoma, Clinicopathologic risk factors, Clinical stage, Lymph node metastasis rate

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

Kongwang Hu[1], Shuaili Wang[2], Zikun Wang[3], Longlong Li[1], Zhiguo Huang[1], Weiqiang Yu[2], Zhongxue Chen[3,*], Qing-Fa Wu[2,4,*]

1. Division of Gastrointestinal Surgery, Department of General Surgery, The First Affiliated Hospital of Anhui Medical University, Hefei 230022, China
2. Division of Molecular Medicine, Hefei National Laboratory for Physical Sciences at Microscale, the Chinese Academy of Sciences (CAS) Key Laboratory of Innate Immunity and Chronic Disease, School of Life Sciences, University of Science and Technology of China, Hefei 230026, China
3. Department of Epidemiology and Biostatistics, School of Public Health, Indiana University Bloomington.
4. School of Data Science, University of Science and Technology of China, Hefei 230026, China
* Correspondence author:

Zhongxue Chen: zc3@indiana.edu, Tel.: 1-812-855-1163

Qing-Fa Wu: wuqf@ustc.edu.cn, Tel.: 86-551-63607631

Abstract

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

Methods: Between January 1st, 2001 and December 31st, 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.[1,2] According to previous reports, approximately 0.7 million people died because of gastric cancer each year[3], and about 70% of the gastric cancer cases had high fatality, significantly higher than other cancers such as the liver and breast cancers[4]. However, the incidence and mortality of gastric carcinoma vary geographically; they were dramatically different between Western and Eastern countries[3]. 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.[5] 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. [1,6]

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. [7-9] 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.[10-13] 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[14].

The current most popular therapy for gastric cancer is surgery combined with chemotherapy. Surgery is the most preferred treatment for gastric carcinoma, but the survival rate of patients undergoing surgery remains very low. Previous studies have revealed that the average survival time of patients with advanced gastric cancer is less than 12 months[15,16]. Therefore, how to timely assess the condition, judge the prognosis risk after therapy, and develop a reasonable postoperative care program becomes a vital part of gastric cancer treatment.[17-19]

Many clinicopathological factors, including clinical stage, tumor size, infiltration depth, Lauren classification, and lymph node metastasis rate, might jointly influence the prognosis in patients with gastric carcinoma[20-22]. It is important but challenging to identify the most significant and independent factors associated with prognosis since many factors are highly correlated. To have a systematic comprehension of gastric carcinoma and to identify independent risk factors on gastric cancer patients, we conducted the current study.

2. Method

Design: This was a retrospective cohort study.

Participants: All participants were recruited from Anhui, China.

Ethics statement

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

Patient and Public Involvement

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

Study cohort

Between January 1st, 2001 and December 31th, 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 7th edition of the American Joint Committee on Cancer (AJCC)[23] 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, ≥3), positive lymph nodes number group (0, 1-6,7-15,≥16), surgical margin (negative, positive), tumor size group (≤4cm, 4-8cm, ≥8cm), invasion depth (mucosa, submucosa, muscular, all layer), lymph node metastasis rate group

(0, ≤0.35, 0.35-0.74, ≥0.74), and number of retrieved lymph node group (0,1-6,7-15,≥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 assocaited with the survival time, and to estimate their adjusted hazard ratios (HR). In the adjusted analysis, all possible two-way interactiosn 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

listed the frequencies for each variable. This cohort was composed of 552 males and 163 females. Based on the clinical TNM classification, the numbers of gastric cancer patients in stage 0, I, II, III, and IV were 11, 109, 296, 269, and 28, respectively. 98 patients had lymphovascular invasion while 611 did not. Gastric lesions were located on the proximal of the stomach for 399 patients, on the body of the stomach for 164 patients, on the distal of the stomach for 99, and 52 participants had more than two sites gastric lesions. Moreover, 672 patients proceeded to radical resection, and 42 proceed to palliative resection. 565 patients had all layer invasion of their stomachs. In addition, 579, 28, and 101 patients received all stomach, proximal, and distal gastric surgery, respectively. The numbers of participants whose lymph node metastasis rate were 0, between 0 and 0.35, between 0.35 and 0.74, and greater than 0.74 were 257, 200, 159, and 95, respectively. Furthermore, in this study, there were 299, 275, and 128 patients whose tumor sizes were smaller than 4cm, between 4 and 8cm, and larger than 8 cm, respectively.

Sixteen significant prognostic factors of gastric cancer including Borrmann's type, surgical margin, M stage, N stage, T stage, lymph node metastasis rate group, surgical type II group, clinical stage, number of cancer nodules group, tumor size group, invasion depth group, positive lymph nodes number group, tumor location, positive lymph nodes number, number of retrieved lymph nodes, and number of cancer nodules were identified ($p<0.05$) from the unadjusted analyses. However, there were no significant associations between survival time and gender, Lauren's classification, surgical type I group, lymphovascular invasion, number of retrieved lymph nodes group, age, age square, and lymph node metastasis rate from the unadjusted analysis according to their large p-values (>0.05).

Results from the adjusted analysis

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

4. Discussion

In this study with total 716 gastric cancer patients, we identified the following clinicopathologic factors which were independently associated with gastric carcinoma from the adjusted analysis: age (and age square), number of cancer nodules, lymph node metastasis rate, tumor size, type II surgery, invasion depth group and interaction between surgical type II and tumor size. The adjusted analysis revealed that other variables, such as gender, Borrmann's type, TMN stage, tumor location, surgical type I group, surgical margin, lymphovascular invasion, and number of retrieved lymph node, might not independently play a major role in the prognosis. For the variable "age", we found that it had a non-linear effect on the outcome: both age and its square were significantly associated with survival time.

In our current study, among these identified risk factors, the prognosis of patients with gastric carcinoma was seen strongly affected by the rate of metastatic lymph nodes, which also has been emphasized in previous studies performed in different countries[24,25]. The result from the study by Kim, Lee et al. indicated that the survival rate was remarkably decreased with metastatic lymph nodes rate increased.[26] Msika et al. also found that lymph node metastasis played an important role and was the only independent prognostic risk factor among 86 participants who underwent curative resection in their study.[27] Furthermore, the German Gastric Carcinoma Study (GGCS)[28] suggested that the lymph node metastasis rate should be considered as the significant independent prognostic variables among patients underwent resected gastric carcinoma, and indicated that extended lymph node dissection was the most critical treatment among patients with radical gastrectomy for long-term survival. Of the many factors relevant to survival time, depth of invasion also has been identified as one of the major prognostic factors from our current adjusted analysis. This finding is consistant with those from the literature.[29-32] .

Based on our adjusted analysis, age had a significant nonlinear effect on the survival time. We also found that tumor size and the number of cancer nodules were independent risk factors for prognostic. These two variables are recognized as tumor burden, which are related to poor prognosis susceptibility in another study as well.[33] One Chinese cohort provided that a poorer prognosis in patients with gastric cancer whose number of cancer nodules were more than 3.[34] In addition, a Turkish study stated that cancer nodules are more observed in patients with the intestinal type and vascular invasive gastric cancers.[35] On the other hand, tumor size is a valuable risk factor since it can be examined quite easily before the surgery, although the prognostic risk of tumor size among patients with gastric carcinoma maintains inconsistent. Some researches suggested that tumor size is not an independent prognostic variable in patients who had gastric

carcinoma. [36,37,38] 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 [39-42,43], 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 of enbloc resection; patients with larger tumor sizes need higher level of expertise and experience for their treatment. Tumor size could raise with the depth of tumor invasion and the extent of lymph node metastasis increase: the size of the tumor is profoundly associated to "Borrmann's type IV, adjacent organ invasion (T4) and higher lymph node and distant metastasis rate". [37,44] A possible explaination is that most patients with stage III or stage IV cancers had a relatively lower radical resection and remained a lower 5-year survival rate.[45]

Our results also showed that patients who received palliative gastrectomy had poorer prognosis and higher risks compared to patients with radical gastrectomy. The results from Dutch clinical randomize trial [46] suggested that palliative gastrectomy could be beneficial for younger patients (age<70) whose tumor load was restricted to one metastatic site. On the contrary, a previous study[47] indicated that "palliative gastrectomy has no survival benefit (p-value = 0.705, 0.331, respectively) in the peritoneal dissemination and multi-organ metastases group". Another study found that palliative gastrectomy showed no obvious favorable effect on long-term survival or improvement of the quality of life among patients with gastric cancer.[48] Moreover, Maruyama K et al. suggested that radical gastrectomy remained the only curative treatment option for gastric cancer.[49] The interaction between tumor size and surgical type II was found significant from our adjusted analysis. It showed that patients who had tumor size ≤4 cm and palliative gastrectomy had the lowest risk while the highest risk was found in patients who had tumor size ≤4 cm and

palliative gastrectomy. On the contrary, patients who had larger tumor size (≥8cm) 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., [50] 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

early detection and to investigate the feasibility and survival benefit of therapy for patients with gastric carcinoma.

Acknowledgments: The authors would like to thank Drs. Qiang Wu, Hao Li, and Xianghong Chen from the Department of Pathology at the First Affiliated Hospital of Anhui Medical University for providing excellent technical support of this study. The authors are grateful to the reviewers for their helpful comments which result in an improved presentation of this report.

Funding: This work was supported in part by the Hefei National Laboratory for Physical Sciences at Microscale. The funders played no role in the study design, data collection, and analysis, decision to publish, or preparation of the manuscript.

Conflict of interest: The authors declare no conflict of interest in this study.

Patient consent for publication: Not required.

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 the discussion and approved the final manuscript.

Reference

1. WHO. International Agency for Research on Cancer. Cancer Today. 2018; http://gco.iarc.fr/today/. Accessed 2.10, 2019.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *Ca-Cancer J Clin.* 2018;68(6):394-424.
3. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five

continents: defining priorities to reduce cancer disparities in different geographic regions of the world. *J Clin Oncol.* 2006;24(14):2137-2150.
4. Guggenheim DE, Shah MA. Gastric cancer epidemiology and risk factors. *J Surg Oncol.* 2013;107(3):230-236.
5. Forman D, Burley VJ. Gastric cancer: global pattern of the disease and an overview of environmental risk factors. *Best Pract Res Clin Gastroenterol.* 2006;20(4):633-649.
6. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. *CA Cancer J Clin.* 2016;66(2):115-132.
7. Lindblad M, Rodriguez LA, Lagergren J. Body mass, tobacco and alcohol and risk of esophageal, gastric cardia, and gastric non-cardia adenocarcinoma among men and women in a nested case-control study. *Cancer Causes Control.* 2005;16(3):285-294.
8. Lagergren J, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N Engl J Med.* 1999;340(11):825-831.
9. Strumylaite L, Zickute J, Dudzevicius J, Dregval L. Salt-preserved foods and risk of gastric cancer. *Medicina (Kaunas).* 2006;42(2):164-170.
10. Liang YX, Deng JY, Guo HH, et al. Characteristics and prognosis of gastric cancer in patients aged >/= 70 years. *World J Gastroenterol.* 2013;19(39):6568-6578.
11. Crew KD, Neugut AI. Epidemiology of gastric cancer. *World J Gastroenterol.* 2006;12(3):354-362.
12. Karimi P, Islami F, Anandasabapathy S, Freedman ND, Kamangar F. Gastric cancer: descriptive epidemiology, risk factors, screening, and prevention. *Cancer Epidemiol Biomarkers Prev.* 2014;23(5):700-713.
13. Howlader NJhscgc. SEER cancer statistics review, 1975-2008. 2011.
14. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018.
15. Magalhães H, Fontes-Sousa M, Machado M. Immunotherapy in advanced gastric Cancer: an overview of the emerging strategies. *Canadian Journal of Gastroenterology and Hepatology.* 2018;2018.
16. Ajani JA. Is the addition of cisplatin to S-1 better than S-1 alone for patients with advanced gastroesophageal cancer? *Nature Reviews Clinical Oncology.* 2008;5(9):508.
17. Penson DF. Re: variation in surgical-readmission rates and quality of hospital care. *J Urol.* 2014;191(5):1363-1364.
18. Lee KG, Lee HJ, Yang JY, et al. Risk factors associated with complication following gastrectomy for gastric cancer: retrospective analysis of prospectively collected data based on the Clavien-Dindo system. *J Gastrointest Surg.* 2014;18(7):1269-1277.
19. Paulino Filho A, Paulino F, de LC. [Preoperative and postoperative care of patients with gastric cancer]. *Hospital (Rio J).* 1961;59:201-209.
20. Qiu MZ, Cai MY, Zhang DS, et al. Clinicopathological characteristics and prognostic analysis of Lauren classification in gastric adenocarcinoma in China. *J Transl Med.* 2013;11:58.
21. Vauhkonen M, Vauhkonen H, Sipponen P. Pathology and molecular biology of gastric cancer. *Best Pract Res Clin Gastroenterol.* 2006;20(4):651-674.
22. Smith DD, Schwarz RR, Schwarz RE. Impact of total lymph node count on staging and survival after gastrectomy for gastric cancer: data from a large US-population database. *J Clin Oncol.* 2005;23(28):7114-7124.
23. Edge SB, Cancer AJCo. *AJCC cancer staging handbook: from the AJCC cancer staging manual.* Vol 2010: Springer New York; 2010.
24. Lee WJ, Lee PH, Yue SC, Chang KC, Wei TC, Chen KM. Lymph node metastases in gastric cancer: significance of positive number. *Oncology.* 1995;52(1):45-50.
25. Yokota T, Ishiyama S, Saito T, et al. Lymph node metastasis as a significant prognostic factor in gastric cancer: a multiple logistic regression analysis. 2004;39(4):380-384.
26. Kim J-P, Lee J-H, Kim S-J, Yu H-J, Yang H-KJGc. Clinicopathologic characteristics and prognostic factors in 10 783 patients with gastric cancer. 1998;1(2):125-133.
27. Msika S, Benhamiche AM, Jouve JL, Rat P, Faivre J. Prognostic factors after curative resection for gastric cancer. A population-based study. *Eur J Cancer.* 2000;36(3):390-396.
28. Roder JD, Böttcher K, Siewert JR, et al. Prognostic factors in gastric carcinoma. Results of the German Gastric Carcinoma Study 1992. 1993;72(7):2089-2097.
29. Shimizu H, Ichikawa D, Komatsu S, et al. The decision criterion of histological mixed type in "T1/T2" gastric carcinoma--comparison between TNM classification and Japanese Classification of Gastric Cancer. *J Surg*

Oncol. 2012;105(8):800-804.
30. Ikeda M, Furukawa H, Imamura H, et al. Poor prognosis associated with thrombocytosis in patients with gastric cancer. *Ann Surg Oncol.* 2002;9(3):287-291.
31. Han SL, Tang HJ, Hua YW, Ji SQ, Lin DX. Expression of COX-2 in stomach cancers and its relation to their biological features. *Dig Surg.* 2003;20(2):107-114.
32. Joo YE, Oh WT, Rew JS, Park CS, Choi SK, Kim SJ. Cyclooxygenase-2 expression is associated with well-differentiated and intestinal-type pathways in gastric carcinogenesis. *Digestion.* 2002;66(4):222-229.
33. Chu DZ, Lang NP, Thompson C, Osteen PK, Westbrook KC. Peritoneal carcinomatosis in nongynecologic malignancy. A prospective study of prognostic factors. *Cancer.* 1989;63(2):364-367.
34. Quanwen. L, Zhengfang., Zhou, Jianxin., Cui. Hongqing.,Xi. Bing., Chen. The value of cancer nodules in staging and prognosis evaluation of gastric cancer patients. *Chinese Journal of Gastrointestinal Surgery.* 2017;2017,20(3) 277-282.
35. Ersen A, Unlu MS, Akman T, et al. Tumor deposits in gastric carcinomas. *Pathol Res Pract.* 2014;210(9):565-570.
36. Michelassi F, Takanishi DM, Jr., Pantalone D, Hart J, Chappell R, Block GE. Analysis of clinicopathologic prognostic features in patients with gastric adenocarcinoma. *Surgery.* 1994;116(4):804-809; discussion 809-810.
37. Yokota T IS, Saito T, Teshima S, Yamada Y, Iwamoto K, et al. Is tumor size a prognostic indicator for gastric carcinoma? . *Anticancer Res 2002.* 2002;22:3673–3677(Nov-Dec;22(6B):3673-7.).
38. Yu CC, Levison DA, Dunn JA, et al. Pathological prognostic factors in the second British Stomach Cancer Group trial of adjuvant therapy in resectable gastric cancer. *Br J Cancer.* 1995;71(5):1106-1110.
39. Isomoto H, Shikuwa S, Yamaguchi N, et al. Endoscopic submucosal dissection for early gastric cancer: a large-scale feasibility study. *Gut.* 2009;58(3):331-336.
40. Oda I, Gotoda T, Hamanaka H, et al. Endoscopic submucosal dissection for early gastric cancer: technical feasibility, operation time and complications from a large consecutive series. 2005;17(1):54-58.
41. Dassen A, Lemmens V, Van De Poll-franse L, et al. Trends in incidence, treatment and survival of gastric adenocarcinoma between 1990 and 2007: a population-based study in the Netherlands. 2010;46(6):1101-1110.
42. Adachi Y, Oshiro T, Mori M, Maehara Y, Sugimachi KJAoso. Tumor size as a simple prognostic indicator for gastric carcinoma. 1997;4(2):137-140.
43. Giuliani A, Caporale A, Di Bari M, et al. Maximum gastric cancer diameter as a prognostic indicator: univariate and multivariate analysis. 2003;22(4):531-538.
44. Shiraishi N, Sato K, Yasuda K, Inomata M, Kitano S. Multivariate prognostic study on large gastric cancer. *J Surg Oncol.* 2007;96(1):14-18.
45. Yasuda K, Shiraishi N, Adachi Y, Inomata M, Sato K, Kitano S. Risk factors for complications following resection of large gastric cancer. *Br J Surg.* 2001;88(6):873-877.
46. Hartgrink HH, Putter H, Klein Kranenbarg E, Bonenkamp JJ, van de Velde CJ, Dutch Gastric Cancer G. Value of palliative resection in gastric cancer. *Br J Surg.* 2002;89(11):1438-1443.
47. Chen S, Li YF, Feng XY, Zhou ZW, Yuan XH, Chen YB. Significance of palliative gastrectomy for late-stage gastric cancer patients. *J Surg Oncol.* 2012;106(7):862-871.
48. Ouchi K, Sugawara T, Ono H, et al. Therapeutic significance of palliative operations for gastric cancer for survival and quality of life. *J Surg Oncol.* 1998;69(1):41-44.
49. Sano T, Sasako M, Yamamoto S, et al. Gastric cancer surgery: morbidity and mortality results from a prospective randomized controlled trial comparing D2 and extended para-aortic lymphadenectomy-Japan Clinical Oncology Group study 9501. 2004;22(14):2767-2773.
50. Jun KH, Jung H, Baek JM, Chin HM, Park WB. Does tumor size have an impact on gastric cancer? A single institute experience. *Langenbecks Arch Surg.* 2009;394(4):631-635.

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
Gender					0.40
Female	163	86	4.94	1.00	
Male	552	314	4.59	1.10	
Missing	1	-	-	-	
Borrmann's Type					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	-	-	-	
Surgical margin					0.020*
Negative	648	353	4.94	1.00	
Positive	46	34	1.55	1.71	
Missing	22	-	-	-	
Lauren's classification					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	-	-	-	
M stage					<.0001 *
0	684	373	5.06	1.00	
1	28	25	1.34	2.79	
Missing	4	-	-	-	
N stage					<.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	-	-	-	
T stage					<.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	-	-	-	
Lymph node metastasis rate group					<.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	-	-	-	
Surgical type I group					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	-	-	-	
Surgical type II group					<.0001*
Radical	672	363	5.25	1.00	
Palliative	42	36	1.13	3.19	
Missing	2	-	-	-	
Lymphovascular invasion					0.56
No	611	344	4.74	1.00	
Yes	98	55	4.61	1.09	
Missing	7	-	-	-	
Clinical stage					<.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	-	-	-	
Number of cancer nodules group					<.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	-	-	-	
Tumor size group					<.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	-	-	-	
Invasion depth group					<.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	-	-	-	
Positive lymph nodes number group					<.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	-	-	-	
Tumor location					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	-	-	-	
Number of retrieved Lymph Nodes group					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	-	-	-	
Age(Missing=1)	715			1.01	0.144
Age²(Missing=1)	715			1.00	0.056
Positive lymph nodes number (Missing=4)	712			1.08	<.0001*
Number of retrieved Lymph Nodes (Missing=7)	709			1.02	0.014*
Lymph node metastasis rate (Missing=5)	711			1.04	0.232
Number of cancer nodules (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
Age	-0.119	0.038	0.888	0.825-0.956	0.0016
Age square	0.001	0.0003	1.001	1.000-1.002	0.0005
Number of cancer nodules	0.103	0.040	1.108	1.024-1.199	0.0106
Lymph node metastasis rate group					<.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	
Invasion depth group					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	
Surgical type II group					<.0001
Radical	-	-			
Palliative	1.757	0.364			
Tumor size					0.0010
≤4cm (reference)	-	-			
4-8cm	0.240	0.132			
≥8cm	0.566	0.152			
Surgical type II group* Tumor size					0.0003
Palliative vs radical *≤4cm (reference)	-	-			
Palliative *4-8cm	-1.026	0.453			
Palliative *≥8cm	-2.097	0.517			