Indian Journal of Experimental Biology
Vol. 61, August 2023, pp. 654-658
DOI: 10.56042/ijeb.v61i08.4376

NOTES

Utility of risk prediction nomogram for lymph node metastasis in the elderly with undifferentiated early gastric cancer

Yajun Zhang, Tiansheng Yin*, Yang Liu & Jiajun Xiao

Department of General Surgery, First People's Hospital of Shuangliu District, Chengdu, China

Received 19 April 2023; *revised 22 July 2023*

Gastric cancer (also called stomach cancer) is the 5th most common cancer the human population suffer from, particularly in East Asia. For effective prevention, it is important to find biomarkers for early-stage diagnosis and prognosis. Further, finding the risk factors that are associated with undifferentiated early gastric cancer is the utmost required. Here, we explored the clinicopathological characteristics of undifferentiated early gastric cancer (EGC) in the elderly, and the risk factors for lymph node metastasis. A total of 187 elderly patients with undifferentiated EGC were selected as subjects, whose clinical data were analyzed retrospectively. They were divided into lymph node metastasis and non-lymph node metastasis groups, and the risk factors for lymph node metastasis were analyzed by univariate and multivariate logistic regression analyses. A nomogram model was established to predict the risk of lymph node metastasis, and then validated. Lymph node metastasis was detected in 32 (17.11%) of the 187 cases. Univariate analysis showed that tumor diameter, depth of invasion, vascular tumor thrombus and local ulcer affected lymph node metastasis (P <0.05). Multivariate logistic regression analysis revealed that tumor diameter >2 cm, invasion to submucosa, vascular tumor thrombus and local ulcer were independent risk factors (P <0.05). The nomogram model was constructed based on the independent risk factors, and its concordance index and area under the receiver operating characteristic curve were 0.756 (95%CI: 0.684-0.830) and 0.758 (95%CI: 0.701-0.815), respectively. Calibration curve and model calibration curve suggested that the predicted probability of the model was consistent with the actual one, indicating high accuracy. Lymph node metastasis of the elderly with undifferentiated EGC is affected by many factors, among which tumor diameter >2 cm, invasion to submucosa, vascular tumor thrombus and local ulcer are independent risk factors.

Keywords: Elderly, Harrell concordance index (C-index), Lymph node metastasis, Stomach cancer

Gastric cancer (GC), also known as the Stomach cancer, refers to a type of malignancy originating from the gastric mucosal epithelium[1], is reported to be the fifth most common cancer affecting humans across the globe. East Asia has the highest burden because of the large population size and high prevalence of *Helicobacter pylori*, one of the factors causing GC[2]. Early GC (EGC) mainly refers to GC with tumor confined to the submucosa or inner layer of the gastric mucosa[3]. EGC patients have a 5-year survival rate of >90%, and their prognosis is significantly superior to that of patients with advanced GC. As per the Japanese Gastric Cancer Association, EGC is defined as a lesion confined to the mucous membrane and/or submucosa, regardless of the size or lymph node metastasis[4].

In recent years, treatment for EGC has gained considerable attention. At present, there are options such as endoscopic diagnosis and treatment, laparoscopic surgery and open surgery[5]. As human medical technology develops, the early detection and endoscopic minimally invasive treatment of GC have been realized. Differentiated EGC meeting the indications can be treated by endoscopic submucosal dissection (ESD), which is featured by small trauma, quick postoperative recovery and preservation of gastric function. Nevertheless, due to the high risk of lymph node metastasis in undifferentiated EGC, currently, its standard treatment is total/partial gastrectomy + lymph node dissection. Endoscopic treatments such as endoscopic mucosal resection (EMR) and ESD are effective in treating EGC, but lymph node dissection cannot be performed in EGC patients with lymph node metastasis, so standard gastrectomy and lymph node dissection are necessary. When lymph node metastasis is found in EGC patients undergoing conservative localized treatment (endoscopic diagnosis and treatment), further comprehensive treatment based on lymph node dissection should be conducted. Hence, the presence or absence of lymph node metastasis is a crucial influencing factor for predicting the prognosis of EGC patients and choosing treatment methods.

The course of EGC is relatively long, and non-curative resection has little influence on the survival rate. Notably, undifferentiated gastric cancer has a high incidence of lymph node metastasis[6]. A nomogram has previously been reported to predict risk of lymph node metastasis in EGC[7]. Nevertheless, there are few studies on undifferentiated EGC in the

*Correspondence:
E-Mail: Zyj228065@163.com

elderly. Thus, in this study, we investigated the clinical characteristics of undifferentiated EGC and the risk factors for lymph node metastasis in the elderly which may help the surgeons to select the optimal surgical strategy.

Patients and Methods

Clinical data

This study was approved by the ethics committee of our hospital (approval No. HMCH201802003), and written informed consent was obtained from all the patients who participated. The sample size of study was determined based on our pre-experiments. A total of 187 elderly patients pathologically diagnosed as EGC and receiving radical gastrostomy in our hospital during March 2018-March 2021 were enrolled. All the subjects underwent partial or total gastrectomy and D1, D1+ or D2 lymph node dissection.

The inclusion criteria were set as follows: (i) patients with the age ≥60 years old; (ii) those receiving no chemotherapy before surgery; (iii) those with no exact distant metastasis detected in preoperative auxiliary examination; (iv) those with localized mucosal or submucosal gastric cancer confirmed by postoperative pathology; and (v) those with complete clinical and pathological data.

The exclusion criteria were as follows: (i) patients receiving adjuvant chemoradiotherapy before operation or had a recent history of chemoradio-therapy due to other malignancies; (ii) those undergoing gastric surgery or ESD; (iii) those with rare pathological types of GC, such as papillary adeno-carcinoma, mucinous adenocarcinoma, lympho-epithelial carcinoma and hepatoid adenocarcinoma; (iv) those complicated with other malignancies (such as lung cancer and liver cancer); (v) those with advanced GC; or (vi) those with incomplete clinical data.

Among the enrolled 187 patients, 110 were males and 77 were females, aged 60-85 years old, with the mean of (65.31±6.82) years. In terms of tumor position, there were 20 cases of the upper part, 61 cases of the middle part, and 106 cases of the lower part.

Observation indices

The clinicopathological characteristics, including gender, age, tumor location, number of tumors, tumor diameter, underlying disease, depth of invasion, gross morphology of tumor, vascular invasion and local ulcer, were collected using a pre-established questionnaire by specific personnel.

Statistical analysis

SPSS21.0 software was used for statistical analysis. Shapiro-Wilk test was performed for normal distribution of measurement data, and the results suggested that all data were normally distributed. The measurement data were expressed as (x±s), and compared using '*t*' test between the two groups. Numerical data were represented as percentage (%) and compared by χ^2 between groups. The independent risk factors for lymph node metastasis were identified by multivariate logistic regression analysis. The difference was considered statistically significant at P <0.05.

Results and Discussion

Incidence rate of lymph node metastasis

Lymph node metastasis occurred in 32 out of the 187 elderly patients with undifferentiated EGC, with an incidence rate of 17.11%.

Univariate analysis results of lymph node metastasis

The lymph node metastasis of undifferentiated EGCs in the elderly was not associated with gender, age, tumor location, cross-sectional perimeter, number of tumors, underlying disease and gross morphology (P >0.05), but was correlated with tumor diameter, depth of invasion, vascular invasion and local ulcer (P <0.05). Besides, undifferentiated EGC in the elderly had a higher lymph node metastasis rate (Table 1).

Multivariate logistic regression analysis results of lymph node metastasis

The factors with a statistically significant difference in univariate analysis were included in multivariate logistic regression analysis, and the results demonstrated that tumor diameter, depth of invasion, vascular tumor thrombus and local ulcer were independent risk factors for lymph node metastasis in undifferentiated EGC in the elderly (OR=2.080, 5.202, 2.406 and 2.738, P <0.05) (Table 2).

Establishment of model for predicting risk of lymph node metastasis

The nomogram model was constructed based on the influencing factors for lymph node metastasis in undifferentiated EGC in the elderly, and a recurrence risk prediction model was built using the R software. The sum of the score on the ruler corresponding to each index was the total score, and the corresponding value on the axis indicated the risk of lymph node metastasis in undifferentiated EGC in the elderly (Fig. 1).

Table 1 — Univariate analysis results of lymph node metastasis [n (%)]

Factor	n	Lymph node metastasis (n=32)	Non-lymph node metastasis (n=155)	χ^2	P
Gender				1.54	0.204
Male	110	22	88		
Female	77	10	67		
Age (year)				0.03	0.870
≥70	78	15	63		
<70	109	17	92		
Tumor location				1.80	0.160
Upper 1/3	20	5	15		
Middle 1/3	61	8	53		
Lower 1/3	106	19	87		
Cross-section perimeter				2.78	0.249
Anterior wall	19	2	17		
Posterior wall	18	3	15		
Lesser curvature	95	19	76		
Greater curvature	30	6	24		
Circumference	25	2	23		
Number of tumors				0.26	0.584
Multiple tumors	39	9	30		
Single tumor	148	23	125		
Tumor diameter				4.08	0.019
>2 cm	40	9	31		
≤2 cm	147	23	124		
Underlying disease				1.64	0.441
Yes	86	18	68		
No	101	14	87		
Depth of invasion				54.64	0.001
Mucous layer	154	13	141		
Submucosa	33	19	14		
Gross morphology				0.37	0.520
Elevated type	45	13	32		
Superficial type	58	8	50		
Depressed type	84	11	73		
Vascular tumor thrombus				5.17	0.012
Yes	27	10	17		
No	160	22	138		
Local ulcer				4.98	0.034
Yes	104	24	80		
No	83	8	75		

Assessment of nomogram model for predicting lymph node metastasis

The discrimination of the model was assessed by Harrell concordance index (C-index) and the receiver operating characteristic (ROC) curve. Both the area under the ROC curve (AUC) and the C-index can be used to estimate the probability that a model correctly identifies the risk of a disease. The C-index and AUC were 0.756 (95% CI: 0.684-0.830) and 0.758 (95% CI: 0.701-0.815), respectively, suggesting moderate discrimination of the risk prediction model (Fig. 2).

Bootstrap re-sampling was adopted for internal verification, and the calibration curve results displayed that the incidence rate of metastasis in EGC predicted by the nomogram model was highly consistent with the observed one, with an average error of 0.014 and a good accuracy. It can be seen that

Table 2 — Multivariate logistic regression analysis results of lymph node metastasis

Factor	*β*	*SE*	*Waldx*^{2}	*OR*	*95% CI*	*P*
Tumor diameter	0.697	0.234	8.821	2.080	(1.190,2.541)	0.022
Depth of invasion	1.649	0.773	8.553	5.202	(1.187,9.313)	0.001
Vasc. tumor thrombus	0.837	0.287	8.624	2.406	(1.074,6.459)	0.009
Local ulcer	0.914	0.325	8.269	2.738	(1.141~7.528)	0.001

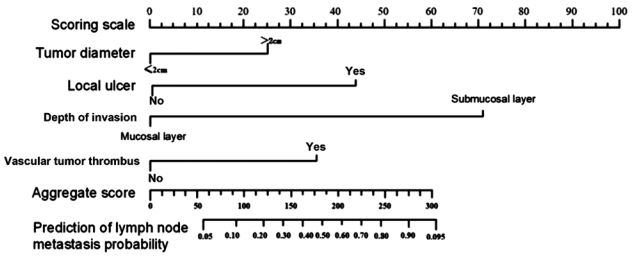

Fig. 1 — Establishment of the nomogram model for predicting lymph node metastasis. [The sum of the score on the ruler corresponding to each index was the total score, and the corresponding value on the axis indicated the risk of lymph node metastasis]

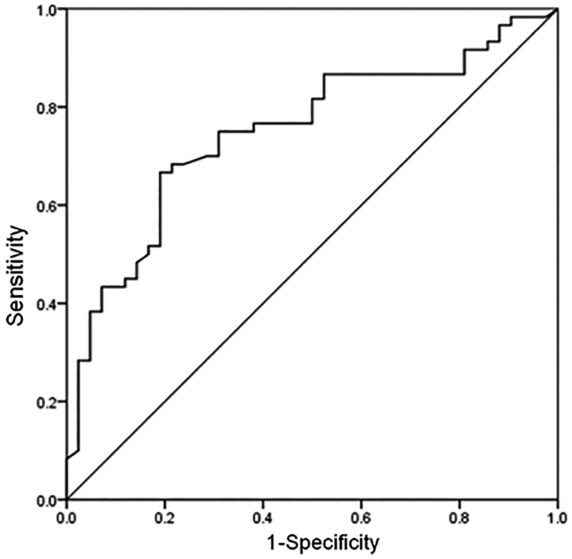

Fig. 2 — ROC curve of nomogram prediction model. [The C-index and the area under the ROC curve were 0.756 (95%CI: 0.684-0.830) and 0.758 (95%CI: 0.701-0.815), respectively, suggesting moderate discrimination of the model]

the nomogram prediction model has a good value in predicting lymph node metastasis in undifferentiated EGC in the elderly (Fig. 3).

Gastric cancer is generally caused by factors such as diet, *Helicobacter pylori* infection, heredity and precancerous lesions[7]. EGC usually exhibits no specific clinical manifestations, and symptoms including belching, upper abdominal distension and discomfort

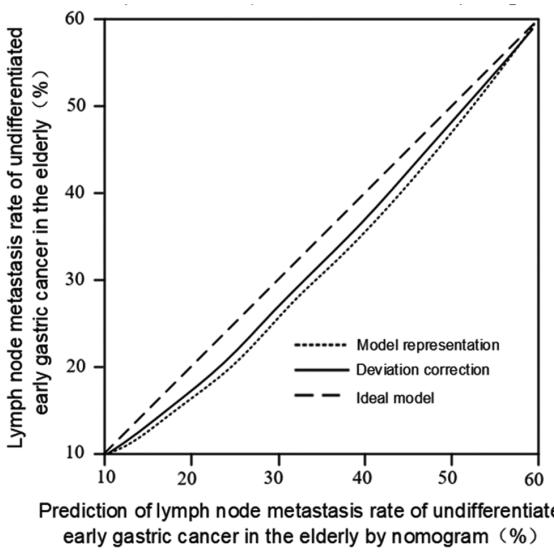

Fig. 3 — Calibration curve of the nomogram model for predicting risk of lymph node metastasis. [The incidence rate of metastasis in EGC predicted by the nomogram model was highly consistent with the observed one]

after meals are easily confused with diseases such as gastritis. Even if the symptoms occur, most of them can be relieved with acid inhibitors, thus losing the best treatment opportunity[8,9]. Therefore, early diagnosis and treatment are of great clinical significance.

The prognosis of EGC patients is good. As endoscopic minimally invasive technology develops, ESD has become a new choice for the treatment of EGC. However, no lymph node metastasis is an important prerequisite for endoscopic therapy[10,11]. Therefore, accurate preoperative assessment of lymph node metastasis is vital for the selection of treatment methods. The sensitivity and specificity of endoscopic ultrasonography and multi-slice CT are not satisfactory in the diagnosis of lymph node metastasis in EGC[12,13]. As a result, it is necessary to analyze the factors related to lymph node metastasis in EGC.

In this study, tumor diameter >2 cm, invasion to submucosa, tumor thrombus and local ulcer were independent risk factors for lymph node metastasis in undifferentiated EGC in the elderly. Lymph node metastasis has been correlated with tumor diameter in EGC[14]. The maximum tumor diameter of >2 cm is a high-risk factor for lymph node metastasis. With rising tumor diameter, the difficulty of operation increases, and the incidence rate of lymph node metastasis soars[15]. We herein also found that tumor diameter >2 cm was a risk factor for lymph node metastasis. Nomura *et al.* reported that the lymph node metastasis rate of submucosal cancer was 14-25%, which was significantly higher than that of intramucosal cancer (1-6%)[16]. The this study revealed that the lymph node metastasis rate under submucosal invasion was significantly higher than that under inner layer (27.58% *vs.* 8.44%), being consistent with the results of previous literatures[17,18]. As tumor invades more deeply in the submucosa, the tumor cells invade the lymphatic capillaries and microvessels, and the lymph node metastasis rate rises markedly. Probably, the submucosa of the gastric wall is rich in capillaries and lymphatic vessels, and the space between lymphatic endothelial cells is large. When the tumor infiltrates into the submucosa, the tumor cells can easily invade the lymphatic capillaries through the space between endothelial cells, ultimately leading to the metastasis of surrounding lymph nodes.

Vascular tumor thrombus is a high-risk factor for lymph node metastasis in GC, and the incidence rate of lymph node metastasis is obviously elevated when there is vascular tumor thrombus. The incidence rate of lymph node metastasis in EGC patients with vascular tumor thrombus is dramatically higher than that in those without vascular cancer thrombus[19]. Similar results were also found in this study. Probably, the lymphatic capillary wall is composed of endothelial cells mostly in an imbricate shape, without basement membrane or pericytes, which are more permeable than capillaries and more prone to invasion by cancer cells. Ulcer has been related to the lymph node metastasis of EGC[20]. In this study, the lymph node metastasis rate in EGC patients with ulcer was significantly higher than that in those without ulcer (23.08 *vs.* 9.64%). Hence, ulcer is an important factor affecting the lymph node metastasis in EGC, which can provide a theoretical basis for the evaluation of preoperative lymph node metastasis status and the selection of treatment methods.

On the basis of the independent risk factors for lymph node metastasis, a nomogram risk prediction model was established, and the differentiation and accuracy of the model were evaluated. The C-index was 0.756 (95% CI: 0.684-0.830), and AUC was 0.758 (95% CI: 0.701-0.815), indicating that the model had a relatively high predictive value and can accurately differentiate whether the patients had lymph node metastasis. The calibration curve suggested the model had a preferable accuracy.

Conclusion

Our above observations clearly suggest that tumor diameter >2 cm, infiltration into the submucosal layer, and the presence of vascular cancer thrombosis and local ulcers are independent risk factors affecting lymph node metastasis in early gastric cancer (EGC) in the elderly. Individualized programs can be developed for the treatment options of EGCs on the basis of the above high-risk factors. The limitations of this study included single-center retrospective analysis and a small sample size. In addition, the AUC-ROC curve was lower than 0.8. Large scale high quality studies involving more clinico-pathological characteristics are thus needed to improve our model studied here.

Conflict of interest

Authors declare no competing interests.

References

1 Siegel RL, Miller KD, Wagle NS & Jemal A, Cancer statistics, 2023. *CA Cancer J Clin*, 73 (2023) 17.

2 *American Cancer Society. Cancer Facts & Figures 2023*. (American Cancer Society, Atlanta), 2023.

3 Fujiyoshi MR, Inoue H, Fujiyoshi Y, Nishikawa Y, Toshimori A, Shimamura Y, Tanabe M, Ikeda H & Onimaru M, Endoscopic classifications of early gastric cancer: A literature review. *Cancers*, 14 (2021) 100.

4 Machlowska J, Baj J, Sitarz M, Maciejewski R & Sitarz R, Gastric Cancer: Epidemiology, Risk Factors, Classification, Genomic Characteristics and Treatment Strategies. *Int J Mol Sci*, 21 (2020) 4012.

5 Waddingham W, Nieuwenburg SA, Carlson S, Rodriguez-Justo M, Spaander M, Kuipers EJ, Jansen M, Graham DG & Banks M, Recent advances in the detection and management of early gastric cancer and its precursors. *Frontline Gastroenterol*, 12 (2021) 322.

6 Kook MC, Risk factors for lymph node metastasis in undifferentiated-type gastric carcinoma. *Clin Endosc*, 52 (2019) 15.

7 Zhang M, Ding C, Xu L, Feng S, Ling Y, Guo J, Liang Y, Zhou Z, Chen Y & Qiu H, A nomogram to predict risk of lymph node metastasis in early gastric cancer. *Sci Rep*, 11 (2021) 22873.

8 Charalampakis N, Tsakatikas S, Schizas D, Kykalos S, Tolia M, Fioretzaki R, Papageorgiou G, Katsaros I, Abdelhakeem AA, Sewastjanow-Silva M & Rogers JE, Trimodality treatment in gastric and gastroesophageal junction cancers: Current approach and future perspectives. *World J Gastrointest Oncol*, 14 (2022) 181.

9 Bhandari P, Abdelrahim M, Alkandari A, Galtieri PA, Spadaccini M, Groth S, Pilonis N, Subramaniam S, Kandiah K, Hossain E & Arndtz S, Predictors of Long-term Outcomes of Endoscopic Submucosal Dissection of Early Gastric Neoplasia in the West: A Multicentre Study. *Endoscopy*, (2023) doi: 10.1055/a-2100-2258.

10 Milhomem LM, Milhomem-Cardoso DM, da Mota OM, Mota ED, Kagan A & Filho JB, Risk of lymph node metastasis in early gastric cancer and indications for endoscopic resection: is it worth applying the east rules to the west? *Surg Endosc*, 35 (2021) 4380.

11 Zhang P, Xu T, Feng H, Zhu Z, Wang J & Wang Y, Risk of lymph node metastasis and feasibility of endoscopic submucosal dissection in undifferentiated-type early gastric cancer. *BMC Gastroenterol*, 23 (2023) 175.

12 Lee KG, Shin CI, Kim SG, Choi J, Oh SY, Son YG, Suh YS, Kong SH, Lee HJ, Kim SH & Lee KU, Can endoscopic ultrasonography (EUS) improve the accuracy of clinical T staging by computed tomography (CT) for gastric cancer? *Eur J Surg Oncol*, 47 (2021) 1969.

13 Li X, Zhu M, Wang Y, Niu Y, Ji M, Li P & Zhang S, Diagnostic efficacy and decision-making role of preoperative endoscopic ultrasonography in early gastric cancer. *Front Med*, 8 (2021) 761295.

14 Theiss L & Contreras CM, Gastrointestinal Stromal Tumors of the Stomach and Esophagus. *Surg Clin North Am*, 99 (2019) 543.

15 Liang Y, Liu L, Xie X, Xia L, Meng J, Xu R & He D, Tumor Size Improves the Accuracy of the Prognostic Prediction of Lymph Node-Negative Gastric Cancer. *J Surg Res*, 240 (2019) 89.

16 Wang S, Ling T, Zhao E & Cao H, The surgical treatment of gastric cancer in the era of minimally invasive surgery. *Minerva Chir*, 72 (2017) 334.

17 Yang P, Zheng XD, Wang JM, Geng WB & Wang X, Undifferentiated-predominant mixed-type early gastric cancer is more aggressive than pure undifferentiated type: a systematic review and meta-analysis. *BMJ Open*, 12 (2022): e054473.

18 Kim DH, Yun HY, Ryu DH, Han HS, Han JH, Kim KB, Choi H & Lee TG, Clinical significance of the number of retrieved lymph nodes in early gastric cancer with submucosal invasion. *Medicine*, 101 (2022) e31721.

19 Li L, Liu P, Wang J, Niu X & He C, Clinicopathologic Characteristics and Risk Factors of Lymph Node Metastasis in Patients with Early Gastric Cancer in the Wannan Region. *Med Sci Monit*, 26 (2020) e923525.

20 Ren MH, Qi XS, Chu YN, Yu YN, Chen YQ, Zhang P, Mao T & Tian ZB, Risk of lymph node metastasis and feasibility of endoscopic treatment in ulcerative early gastric cancer. *Ann Surg Oncol*, 28 (2021) 2407.