Diabetes mellitus promoted lymph node metastasis in gastric cancer: a 15-year single-institution experience

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Abstract

Background: Previous studies have revealed that diabetes mellitus (DM) promotes disease progress of gastric cancer (GC). This study aimed to further investigating whether DM advanced lymph nodes (LNs) metastasis in GC.

Methods: The clinicopathologic data of GC patients with >15 examined LN (ELN) between October 2004 and December 2019 from a prospectively maintained database were included. The observational outcomes included the number (N3b status) and anatomical distribution (N3 stations) of metastatic LN (MLN).

Results: A total of 2142 eligible patients were included in the study between October 2004 and December 2019. N3 stations metastasis (26.8% in DM *vs.* 19.3% in non-DM, $P = 0.026$) and N3b status (18.8% in DM *vs.* 12.8% in non-DM, $P = 0.039$) were more advanced in the DM group, and multivariate logistic regression analyses confirmed that DM was an independent factor of developing N3 stations metastasis (odds ratio [OR] = 1.771, $P = 0.011$) and N3b status (OR = 1.752, $P = 0.028$). Also, multivariate analyses determined DM was independently associated with more MLN ($\beta = 1.424$, $P = 0.047$). The preponderance of N3 stations metastasis (DM *vs.* non-DM, T1–2: 2.2% *vs.* 4.9%, T3: 29.0% *vs.* 20.3%, T4a: 38.9% *vs.* 25.8%, T4b: 50.0% *vs.* 36.6%; ELN16–29: 8.6% *vs.* 10.4%, ELN30–44: 27.9% *vs.* 20.5%, ELN ≥ 45: 37.7% *vs.* 25.3%), N3b status (DM *vs.* non-DM, T1–2: 0% *vs.* 1.7%, T3: 16.1% *vs.* 5.1%, T4a: 27.8% *vs.* 19.1%, T4b: 44.0% *vs.* 28.0%; ELN16–29: 8.6% *vs.* 7.9%, ELN30–44: 18.0% *vs.* 11.8%, ELN ≥ 45: 26.4% *vs.* 17.3%), and the number of MLN (DM *vs.* non-DM, T1–2: 0.4 *vs.* 1.1, T3: 8.6 *vs.* 5.2, T4a: 9.7 *vs.* 8.6, T4b: 17.0 *vs.* 12.8; ELN16–29: 3.6 *vs.* 4.6, ELN30–44: 5.8 *vs.* 5.5, ELN ≥ 45: 12.0 *vs.* 7.7) of DM group increased with the advancement of primary tumor depth stage and raising of ELN.

Conclusions: DM was an independent risk factor for promoting LN metastasis. The preponderance of LN involvement in the DM group was aggravated with the advancement of tumor depth.

Keywords: Diabetes mellitus; Gastric cancer; Lymph node; Metastasis

Introduction

As the most common metastasis mode and most important independent prognostic factor of gastric cancer (GC),[1-3] lymph node (LN) involvement contributes a lot to the status. GC remains one of the leading causes of cancer-related deaths worldwide.[4,5] Unfortunately, LN dissection in GC has reached a plateau in improving the prognosis since D2 lymphadenectomy been accepted as the standard surgical procedure.[1,6,7] Even more, new research progress has shown that LN is an effective gateway from lymphatics into the systemic circulation, and becoming a source of cancer cells for distant metastasis.[8,9] Thus, determining the risk of LN metastasis in GC is significant to provide guidance for investigating the mechanism of LN metastasis in basic research and for clinical diagnosis and treatments.

It has also been noted that diabetes mellitus (DM) was closely linked to cancer epidemiologically and biologically.[10,11] The association between DM and cancer has got more and more attention as a result of the alarming increases in the prevalence of DM globally. And many studies have indicated that DM is related to an increased risk in many cancer types.[11,12] Some even indicated that DM conferred an inferior prognosis for cancer patients.[13,14] It has been demonstrated that breast cancer patients with DM experienced an increased risk of death compared with the non-DM subgroup.[15,16] Similar findings have also been reported in

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colon cancer,[17] prostate cancer,[18] and pancreatic neuroendocrine tumor.[19] More importantly, our previous study has shown that DM may promote the disease progress of GC after gastrectomy.[20]

However, whether DM was associated with LN metastasis in solid tumors has not been investigated yet. Thus, we further investigated the relationship between LN metastasis and DM in GC based on 2142 GC patients in our institution to explore the potential mechanisms of LN metastasis.

Methods

Ethical approval

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the *Helsinki Declaration* of 1964 and later versions. The data collection protocol was approved by the Ethics Committee of Nanfang Hospital, Southern Medical University (No. NFEC-2018–088). Informed consent to be included in the study, or the equivalent, was obtained from all patients.

Patients selection

In the period between October 2004 and December 2019, 3213 consecutive patients were pathologically diagnosed with GC and underwent surgery at Nanfang Hospital, Southern Medical University, Guangdong, China. The analyses were based on the prospectively maintained GC database, which includes information on GC derived from electronic medical records that have been maintained in the Nanfang Hospital since 2004.[21] Data monitoring was conducted by a quality medical recorder with about 10 years of relevant work experience. The recorded variables included demographic, clinical, pathological, and surgical characteristics. Two independent surgical oncologists were requested to appraise the pathological reports and medical records of the patients retrospectively. After professional reviewing, patients who did not receive gastrectomy or lymphadenectomy and age <18 years were excluded. To make sure that the assessment for the LN status was accurate, the patients with the examined LNs (ELNs) <16 or who receive preoperative chemotherapy/radiotherapy were also excluded. After the above exclusion criteria were carried out, 2142 patients were enrolled. According to having the comorbidity of DM or not at the time of diagnosis of GC, patients were classified into two groups: non-DM group ($n = 1993$) and DM group ($n = 149$) [Figure 1].

LN involvement was determined by two N-stage systems: the Japanese Classification of Gastric Carcinoma (JCGC, 13th edition) N-classification system[22] and Union International Cancer Control (UICC-TNM, 8th edition) N-staging system.[23] JCGC N-classification system is based on the anatomic location-based involved LNs, whereas the UICC-TNM N-staging system is based on the number of metastatic LN (MLN).[22,23] N3 stations of

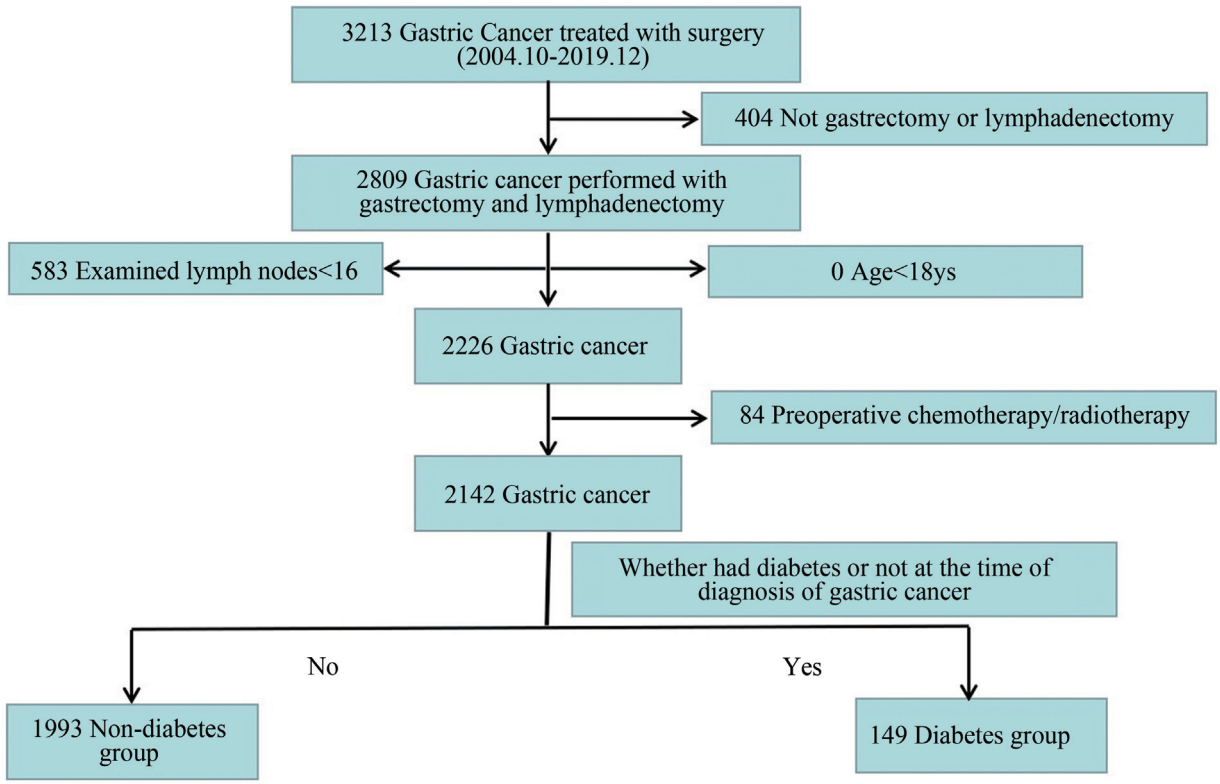

Figure 1: Study flow diagram of the study. GC: Gastric cancer; ELN: Examined LN; LN: Lymph node.

JCGC N-classification system was defined as LN involvement reached station 2, station 10, station 11 (11p and 11d), station 12 (12a, 12b, and 12p), station 13, and station 14 (LN at the root of the mesenterium) for gastric antrum cancer. And for the lesions in the body or cardia of stomach, N3 stations include station 12, station 13, and station 14, whereas N3b stage of UICC-TNM was defined >15 MLNs.

The T stage and M stage were determined based on the 8th edition of the AJCC TNM staging system.[22,23] The resection approach (laparoscopic gastrectomy [LG] or open gastrectomy [OG]) methods followed standard guidelines and our previous reports.[24-26] The LN examination approaches followed the experiences we reported.[27] The tumor location of the upper (U) 1/3, middle (M) 1/3, and lower (L) 1/3 was determined by the cancer epicenter.

Diagnosis of diabetes

The diagnosis of DM was based on the record of the prospective GC database,[21] which defined diabetes at the time of diagnosis of GC according to the following criteria: (1) Fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/ L). Fasting is defined as no caloric intake for at least 8 hours; (2) 2 hours plasma glucose 200 mg/dL (11.1 mmol/ L) during an oral glucose tolerance test (OGTT); (3) Patients with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose 200 mg/ dL (11.1 mm/L); or (4) Patients do not meet above conditions (blood test was normal before surgery) but have a specific history of diabetes with well-controlled medication. The exact time of the patients receiving the test of DM was during the process of preparation for undergoing surgery in Nanfang Hospital.

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD) (with normal distributions) or medians with interquartile ranges (IQR) (with non-normal distributions), while categorical variables were presented as counts and percentages (%). Student's *t*-test and the Mann–Whitney *U* test were used to compare continuous variables, and the χ^2 test and Fisher exact test were used to compare categorical variables, as appropriate. Risk factors for N3 stations metastasis and N3b status were evaluated by univariate analyses using the χ^2 test or Fisher exact test or Mann–Whitney *U* test, and multivariate analyses using logistic regression models. Variables with statistical significance ($P < 0.01$) in univariate analysis were entered into the multivariable model and were analyzed by using an "Enter" method. Risk factors for the number of MLN were evaluated by uni- and multi-variate analyses using linear regression models. Variables with statistical significance ($P < 0.10$) in the univariate analysis as well as the critical factor in the present analysis, diabetes, and tumor location were entered into the multivariable models and were analyzed by using an "Enter" method $P < 0.05$ (two-tailed) was considered statistically significant. The statistical software SPSS version 25.0 for Windows (IBM Corp., New York, USA) was used for all statistical analyses.

Results

Characteristics of patients

The clinical and pathological characteristics of the patients are shown in Table 1. There were more males (77.2% [115/149] *vs.* 65.4% [1304/1993], $P = 0.003$) and older patients (63.83 ± 8.50 years *vs.* 55.94 ± 12.10 years, $P < 0.001$) in the DM group than the non-DM group. Tumor location was higher in the DM group ($P = 0.016$). Besides, the DM group was more prone to develop lymphatic invasions (34.9% [52/149] *vs.* 25.7% [513/1993], $P = 0.014$) and venous invasions (32.9% [49/149] *vs.* 25.5% [508/1993], $P = 0.047$). Notably, the primary tumor depth (mean rank: 1065.28 *vs.* 1071.97, $Z = -0.132$, $P = 0.895$) and the median [IQR] number of ELN (40 (22) *vs.* 39 (27), $P = 0.735$), the most important factors affecting the detection of MLN, were very similar between the DM and non-DM groups. Other clinical and pathological characteristics were also comparable between the two groups.

LN status of DM and non-DM groups

As shown in Supplementary Table 1, http://links.lww.com/CM9/A801, the DM group had more N3 stations metastasis than the non-DM group (26.8% [40/149] *vs.* 19.3% [385/1993], $P = 0.026$). Equally, the DM group remarkably has more N3b status patients (18.8% [28/149] *vs.* 12.8% [256/1993], $P = 0.039$). Consistently, the N stage was slightly more advanced in the DM group (mean rank: 1126.40 *vs.* 1067.40, $Z = -1.187$, $P = 0.235$), although it has not yet reached significance. The median (IQR) MLN number was 2 (10.5) in DM group whereas 2 (9.0) in non-DM group.

The independent risk factors of N3 stations metastasis

As shown in Table 2, the univariate analyses showed that DM status ($P = 0.026$), sex ($P = 0.034$), age ($P = 0.028$), ELN ($P < 0.001$), primary tumor depth ($P < 0.001$), lymphatic invasion ($P < 0.001$), venous invasion ($P < 0.001$), nerve invasion ($P < 0.001$), grade ($P < 0.001$), tumor location ($P = 0.014$), and tumor size ($P < 0.001$) were associated with the detection of N3 stations metastasis. Subsequently, the multivariate analyses confirmed that DM (odds ratio [OR] = 1.771, 95% confidence interval [CI] = 1.139–2.755, $P = 0.011$), female (OR = 1.314, 95% CI = 1.018 −1.695, $P = 0.036$), younger age (40–69 *vs.* < 40 years: OR = 0.710, 95% CI = 0.513–0.983, $P = 0.039$; >69 *vs.* < 40 years: OR = 0.505, 95% CI = 0.273–0.935, $P = 0.030$), ELN ≥ 45 (OR = 1.618, 95% CI = 1.255–2.085, $P < 0.001$), more advanced primary tumor depth (T2 *vs.* T1a: OR = 2.627, 95% CI = 1.013–6.815, $P = 0.047$; T3 *vs.* T1a: OR = 4.222, 95% CI = 1.733–10.285, $P = 0.002$; T4a *vs.* T1a: OR = 6.575, 95% CI = 2.802–15.429, $P < 0.001$; T4b *vs.* T1a: OR = 10.743, 95% CI = 4.444–25.969, $P < 0.001$), positive lymphatic invasion (OR = 2.408, 95% CI = 1.770–3.278, $P < 0.001$), positive venous invasion (OR = 1.542, 95% CI = 1.142–2.081,

Table 1: Clinicopathologic characteristics of diabetes and non-diabetes groups.

Characteristic	Non-diabetes ($n = 1993$)	Diabetes ($n = 149$)	Statistics	*P* value
Age, years	55.94 ± 12.10	63.83 ± 8.50	10.552*	<0.001
ELN	39 (27)	40 (22)	−0.338†	0.735
Gender			8.563‡	0.003
Male	1304 (65.4)	115 (77.2)		
Female	689 (34.6)	34 (22.8)		
History of abdominal surgery			0.481‡	0.488
No	1675 (84.0)	122 (81.9)		
Yes	318 (16.0)	27 (18.1)		
Primary tumor depth			−0.132†	0.895
T1a	233 (11.7)	18 (12.1)		
T1b	222 (11.1)	11 (7.4)		
T2	205 (10.3)	17 (11.4)		
T3	296 (14.9)	31 (20.8)		
T4a	805 (40.4)	54 (36.2)		
T4b	232 (11.6)	18 (12.1)		
Lymphatic invasions			5.989‡	0.014
No	1480 (74.3)	97 (65.1)		
Yes	513 (25.7)	52 (34.9)		
Venous invasions			3.942‡	0.047
No	1485 (74.5)	100 (67.1)		
Yes	508 (25.5)	49 (32.9)		
Nerve invasions			0.059‡	0.809
No	1130 (56.7)	86 (57.7)		
Yes	863 (43.3)	63 (42.3)		
Histology			2.319‡	0.128
Signet ring	499 (25.0)	29 (19.5)		
Others	1494 (75.0)	120 (80.5)		
Grade			6.091‡	0.107
G1	102 (5.1)	10 (6.7)		
G2	322 (16.2)	35 (23.5)		
G3	1553 (77.9)	103 (69.1)		
G4	16 (0.8)	1 (0.7)		
Tumor size, cm			5.154‡	0.161
<2	413 (20.7)	23 (15.4)		
2–5	698 (35.0)	49 (32.9)		
≥5	858 (43.1)	73 (49.0)		
Unknown	24 (1.2)	4 (2.7)		
Tumor location			10.292‡	0.016
Upper 1/3	424 (21.3)	48 (32.2)		
Middle 1/3	333 (16.7)	18 (12.1)		
Lower 1/3	1217 (61.1)	82 (55.0)		
Unknown	19 (1.0)	1 (0.7)		

Data are shown as *n* (%), mean ± standard deviation or median (interquartile). *Student's *t*-test. † Mann–Whitney *U* test. ‡ χ^2 test. ELN: Examined lymph node; IQR: Interquartile ranges; SD: Standard deviation.

$P = 0.014$), tumor size ≥5 cm (OR = 1.957, 95% CI = 1.145–3.344, $P = 0.005$), and tumor location in lower 1/3 (OR = 2.034,95% CI = 1.494–2.770, $P < 0.001$) were independent risk factors of developing N3 stations metastasis.

The independent risk factors of N3b status

As shown in Table 3, the univariate analyses showed that DM status ($P = 0.039$), age ($P = 0.019$), ELN ($P < 0.001$), primary tumor depth ($P < 0.001$), lymphatic invasions ($P < 0.001$), venous invasions ($P < 0.001$), nerve invasions ($P < 0.001$), grade ($P < 0.001$), and tumor size ($P < 0.001$) were associated with the detection of N3b status. Subsequently, the multivariate analyses confirmed that DM (OR = 1.752, 95% CI = 1.061–2.893, $P = 0.028$), younger age (40–69 *vs.* < 40 years: OR = 0.669, 95% CI = 0.466–0.959, $P = 0.029$; >69 *vs.* <40 years: OR = 0.362, 95% CI = 0.168–0.782, $P = 0.010$), ELN ≥45 (OR = 1.841, 95% CI = 1.369–2.475, $P < 0.001$), more advanced primary tumor depth (T3 *vs.* T1a: OR = 11.035, 95% CI = 1.411–86.297, $P = 0.022$; T4a *vs.* T1a: OR = 27.918, 95% CI = 3.687–211.372, $P = 0.001$; T4b *vs.* T1a: OR = 45.174, 95% CI = 5.888–346.601, $P < 0.001$), positive lymphatic invasion (OR = 1.870, 95% CI = 1.303–2.683, $P = 0.001$), positive venous invasion (OR = 1.993, 95% CI = 1.408–2.821,

Table 2: Univariate and multivariate analyses for the detection of N3 stations metastasis.

Variables	Univariate analysis				Multivariate analysis	
	Non-N3 stations metastasis ($n = 1717$)	N3 stations metastasis ($n = 425$)	Statistic	*P* value	OR (95% CI)	*P* value
Diabetes			4.940	0.026		0.011
No	1608 (93.7)	385 (90.6)			Ref	
Yes	109 (6.3)	40 (9.4)			1.771 (1.139–2.755)	
Gender			4.516	0.034		0.036
Male	1156 (67.3)	263 (61.9)			Ref	
Female	561 (32.7)	162 (38.1)			1.314 (1.018 -1.695)	
Age, years			−2.197	0.028		0.045
<40	256 (14.9)	82 (19.3)			Ref	
40–69	1365 (79.5)	323 (76.0)			0.710 (0.513–0.983)	0.039
>69	96 (5.6)	20 (4.7)			0.505 (0.273–0.935)	0.030
ELN			34.516	<0.001		<0.001
16–44	1080 (62.9)	201 (47.3)			Ref	
≥45	637 (37.1)	224 (52.7)			1.618 (1.255–2.085)	
Primary tumor depth			−13.114	<0.001		<0.001
T1a	244 (14.2)	7 (1.6)			Ref	
T1b	226 (13.2)	7 (1.6)			0.950 (0.324–2.783)	0.925
T2	203 (11.8)	19 (4.5)			2.627 (1.013–6.815)	0.047
T3	258 (15.0)	69 (16.2)			4.222 (1.733–10.285)	0.002
T4a	630 (36.7)	229 (53.9)			6.575 (2.802–15.429)	<0.001
T4b	156 (9.1)	94 (22.1)			10.743 (4.440–25.969)	<0.001
Lymphatic invasions			196.084	<0.001		<0.001
No	1378 (80.3)	199 (46.8)			Ref	
Yes	339 (19.7)	226 (53.2)			2.408 (1.770–3.278)	
Venous invasions			128.843	<0.001		0.005
No	1370 (79.8)	215 (50.6)			Ref	
Yes	347 (20.2)	210 (49.4)			1.542 (1.142–2.081)	
Nerve invasions			110.850	<0.001		0.783
No	1071 (62.4)	145 (34.1)			Ref	
Yes	646 (37.6)	280 (65.9)			0959 (0.713–1.291)	
Histology			2.367	0.124		–
Signet ring	411 (23.9)	117 (27.5)				
Others	1306 (76.1)	308 (72.5)				
Grade			33.865	<0.001		0.035
G1	105 (6.1)	7 (1.6)			Ref	
G2	314 (18.3)	43 (10.1)			1.135 (0.459–2.810)	0.784
G3	1284 (74.8)	372 (87.5)			1.838 (0.784–4.309)	0.162
G4	14 (0.8)	3 (0.7)			0.904 (0.191–4.287)	0.899
Tumor size, cm			132.099	<0.001		0.005
<2	411 (23.9)	25 (5.9)			Ref	
2–5	637 (37.1)	110 (25.9)			1.233 (0.720–2.112)	0.445
≥5	649 (37.7)	282 (66.4)			1.957 (1.145–3.344)	0.014
Unknown	20 (1.2)	8 (1.9)			1.597 (0.568–4.488)	0.374
Location			10.633	0.014		<0.001
Upper 1/3	393 (22.9)	79 (18.6)			Ref	
Middle 1/3	295 (17.2)	56 (13.2)			0.992 (0.654–1.502)	0.968
Lower 1/3	1012 (58.9)	287 (67.5)			2.034 (1.494–2.770)	<0.001
Unknown	17 (1.0)	3 (0.7)			0.894 (0.235–3.403)	0.870

Data are shown as *n* (%). CI: Confidence interval; ELN: Examined LN; OR: Odds ratio; –: Not applicable.

$P < 0.001$), negative nerve invasion (OR = 0.625, 95% CI = 1.408–2.821, $P = 0.008$), grade of G3 (G3 *vs.* G1: OR = 7.592, 95% CI: 1.021–56.425, $P = 0.048$), and tumor size ≥5 cm (≥5 cm *vs.* <2 cm: OR = 2.248, 95% CI = 1.152–4.784, $P = 0.019$) were independent risk factors of developing N3b status.

The independent risk factors of more number of MLN

As shown in Table 4, the univariate linear analyses showed that age (as continuous variable) ($\beta = -0.042$, $P = 0.015$), ELN ($\beta = 2.899$, $P < 0.001$), primary tumor depth ($\beta = 2.548$, $P < 0.001$), lymphatic invasion ($\beta = 7.276$,

Table 3: Univariate and multivariate analyses for the detection of N3b status.

Variables	Univariate analysis				Multivariate analysis	
	Non-N3b status ($n = 1858$)	N3b status ($n = 284$)	Statistic	*P* value	OR (95% CI)	*P* value
Diabetes			4.263	0.039		0.028
No	1737 (93.5)	256 (90.1)			Ref	
Yes	121 (6.5)	28 (9.9)			1.752 (1.061–2.893)	
Gender			<0.001	0.985		–
Male	1231 (66.3)	188 (66.2)				
Female	627 (33.7)	96 (33.8)				
Age, years			–2.343	0.019		0.016
<40	282 (15.2)	56 (19.7)			Ref	
40–69	1470 (79.1)	218 (76.8)			0.669 (0.466–0.959)	0.029
>69	106 (5.7)	10 (3.5)			0.362 (0.168–0.782)	0.010
ELN			26.807	<0.001		<0.001
16–44	1151 (61.9)	130 (45.8)				
≥45	707 (38.1)	154 (54.2)			1.841 (1.369–2.475)	
Primary tumor depth			–13.121	<0.001		<0.001
T1a	250 (13.5)	1 (0.4)			Ref	
T1b	230 (12.4)	3 (1.1)			2.961 (0.304–28.849)	0.350
T2	215 (11.6)	7 (2.5)			5.916 (0.691–50.674)	0.105
T3	296 (15.9)	31 (10.9)			11.035 (1.411–86.297)	0.022
T4a	690 (37.1)	169 (59.5)			27.918 (3.687–211.372)	0.001
T4b	177 (9.5)	73 (25.7)			45.174 (5.888–346.601)	<0.001
Lymphatic invasions			114.741	<0.001		0.001
No	1442 (77.6)	135 (47.5)			Ref	
Yes	416 (22.4)	149 (52.5)			1.870 (1.303–2.683)	
Venous invasions			128.843	<0.001		<0.001
No	1453 (78.2)	132 (46.5)			Ref	
Yes	405 (21.8)	152 (53.5)			1.993 (1.408–2.821)	
Nerve invasions			46.858	<0.001		0.008
No	1108 (59.6)	108 (38.0)			Ref	
Yes	750 (40.4)	176 (62.0)			0.625 (0.441–0.885)	
Histology			1.768	0.184		–
Signet ring	449 (24.2)	79 (27.8)				
Others	1409 (75.8)	205 (72.2)				
Grade			35.544	<0.001		0.002
G1	111 (6.0)	1 (0.4)			Ref	
G2	333 (17.9)	24 (8.5)			3.552 (0.459–27.463)	0.224
G3	1399 (75.3)	257 (90.5)			7.592 (1.021–56.425)	0.048
G4	15 (0.8)	2 (0.7)			3.490 (0.281–43.331)	0.331
Tumor size, cm			112.016	<0.001		0.010
<2	425 (22.9)	11 (3.9)			Ref	
2–5	680 (36.6)	67 (23.6)			1.462 (0.705–3.030)	0.307
≥5	731 (39.3)	200 (70.4)			2.348 (1.152–4.784)	0.019
Unknown	22 (1.2)	6 (2.1)			2.088 (0.641–6.798)	0.222
Location			0.719	0.873		–
Upper 1/3	413 (22.2)	59 (20.8)				
Middle 1/3	306 (16.5)	45 (15.8)				
Lower 1/3	1121 (60.3)	178 (62.7)				
Unknown	18 (1.0)	2 (0.7)				

Data are shown as *n* (%). CI: Confidence interval; ELN: Examined LN; OR: Odds ratio; –: Not applicable.

$P < 0.001$), venous invasions ($\beta = 7.009$, $P < 0.001$), nerve invasions ($\beta = 4.365$, $P < 0.001$), grade ($\beta = 2.776$, $P < 0.001$), and tumor size ($\beta = 4.078$, $P < 0.001$) were associated with the detecting more number of MLN. Subsequently, the multivariate linear analyses (Durbin–Watson = 1.924) confirmed that DM ($\beta = 1.424$, $P = 0.047$), younger age (scale) ($\beta = -0.059$, $P < 0.001$), ELN ≥45 ($\beta = 2.212$, $P < 0.001$), more advanced primary tumor depth ($\beta = 1.951$, $P < 0.001$), positive lymphatic invasion ($\beta = 3.855$, $P < 0.001$), positive venous invasion ($\beta = 2.844$, $P < 0.001$), negative nerve invasion ($\beta = -1.975$, $P < 0.001$), grade of G3 ($\beta = 0.854$, $P = 0.011$), and tumor size ≥5 cm ($\beta = 1.246$, < 0.001) were independent risk factors of detection of more number of MLN. The histogram of regression standardized residual [Supplementary Figure 1, http://links.lww.com/CM9/

Table 4: Univariate and multiple linear regression analyses for the detection of the number of MLNs.

	Univariate linear regression analysis					Multiple linear regression analysis*				
			95% CI for β					95% CI for β		
Variables	Durbin–Watson	β	Lower bound	Upper bound	*P* value	VIF	β	Lower bound	Upper bound	*P* value
Diabetes (yes *vs.* no)	1.949	1.377	−0.236	2.990	0.094	1.037	1.424	0.019	2.829	0.047
Gender (female *vs.* male)	1.952	0.031	−0.838	0.899	0.945	Not included	–	–	–	–
Age (scale)	1.956	−0.042	−0.077	−0.008	0.015	1.007	−0.059	−0.089	−0.028	<0.001
No. of ELN (≥45 *vs.*16–44)	1.939	2.899	2.070	3.727	<0.001	1.110	2.212	1.457	2.966	<0.001
Primary tumor depth (T4b *vs.* T4a *vs.* T3 *vs.* T2 *vs.* T1b *vs.* T1a)	1.946	2.548	2.309	2.786	<0.001	1.824	1.951	1.648	2.253	<0.001
Lymphatic invasions (yes *vs.* no)	1.862	7.276	6.396	8.155	<0.001	1.753	3.855	2.800	4.910	<0.001
Venous invasions (yes *vs.* no)	1.920	7.009	6.121	7.897	<0.001	1.647	2.844	1.817	3.871	<0.001
Nerve invasions (yes *vs.* no)	1.923	4.365	3.558	5.173	<0.001	1.574	−1.975	−0.284	−1.086	<0.001
Histology (others *vs.* signet ring)	1.951	0.387	−0.565	1.340	0.425	Not included	–	–	–	–
Grade (G4 *vs.* G3 *vs.* G2 *vs.* G1)	1.944	2.776	2.053	3.498	<0.001	1.097	0.854	0.198	1.510	0.011
Tumor size (≥5 cm *vs.* 2–5 cm *vs.* <2 cm)	1.979	4.078	3.588	4.568	<0.001	1.711	1.246	0.664	1.827	<0.001
Location (lower 1/3 *vs.* middle 1/3 *vs.* upper 1/3)	1.951	0.256	−0.234	0.747	0.306	1.057	1.038	0.607	1.469	<0.001

* Durbin-Watson: 1.924. CI: Confidence interval; ELN: Examined LN; LNs: Lymph nodes; MLNs: Metastatic LNs; VIF: Variance inflation factor.

A784] and normal P-P plot of regression standardized residual [Supplementary Figure 2, http://links.lww.com/CM9/A784] for linear regression model showed the residual is an approximate normal distribution.

The LN status of DM and non-DM in subgroup divided by primary tumor depth

The variations of N3 stations metastasis divided by primary tumor depth in the DM and the non-DM groups were shown in Figure 2A. The proportion of N3 stations metastasis in each primary tumor depth stage was as follows (DM *vs.* non-DM): T1–2: 2.2% *vs.* 4.9%, T3: 29.0% *vs.* 20.3%, T4a: 38.9% *vs.* 25.8%, T4b: 50.0% *vs.* 36.6%. The variations of N3b status divided by primary tumor depth in the DM and non-DM groups were shown in Figure 2B. The proportion of N3b status in each primary tumor depth stage was as follows (DM *vs.* non-DM): T1–2: 0% *vs.* 1.7%, T3: 16.1% *vs.* 5.1%, T4a: 27.8% *vs.* 19.1%, T4b: 44.0% *vs.* 28.0%. The variations of the number of MLN divided by primary tumor depth in the DM and non-DM groups were shown in Figure 2C. The mean number of MLN in each primary tumor depth stage was as follows (DM *vs.* non-DM): T1–2: 0.4 *vs.* 1.1, T3: 8.6 *vs.* 5.2, T4a: 9.7 *vs.* 8.6, T4b: 17.0 *vs.* 12.8. The above result indicated that the percentage of N3 stations metastasis, N3b status, and the number of MLN increased with the advanced primary tumor depth stage. Thus, the subgroup analysis of T3+T4 was conducted to show the role of DM on tumor cells and tumor microenvironment with enough time. As shown in Supplementary Table 2, http://links.lww.com/CM9/A801 in the subgroup of T3 +T4, the DM group has more N3 stations metastasis (DM *vs.* non-DM: 37.9% [39/103] *vs.* 26.5% [353/1333], $P = 0.012$). Equally, the DM group has more N3b status patients (DM *vs.* non-DM: 27.2% [28/ 103] *vs.* 18.4% [245/1333], $P = 0.028$). Similarly, the N stage was more advanced in the DM group (mean rank [DM *vs.* non-DM]: 782.1 *vs.* 713.6, $Z = -1.710$, $P = 0.087$) but has not yet reached significance. The number of MLN in the DM group was more than that in the non-DM group (median [IQR], 7 (14) *vs.* 5 (12), $P = 0.066$). Furthermore, the multivariate analyses confirmed that DM was an independent risk factor of N3 stations metastasis (b = 1.951, 95% CI: 1.226–3.104, $P = 0.005$) [Supplementary Table 3, http://links.lww.com/CM9/A801], N3b status (b = 1.930, 95% CI: 1.155–3.224, $P = 0.012$) [Supplementary Table 4, http://links.lww.com/CM9/A801], and more number of MLN (b = 2.082, Durbin–Watson = 1.918, Variance Inflation Factor [VIF] = 1.050, $P = 0.040$) [Supplementary Table 5, http://links.lww.com/CM9/A801] in the subgroup of T3+T4.

The LN status of DM and non-DM in subgroup divided by ELN

The variations of N3 stations metastasis divided by ELN in the DM and the non-DM groups were shown in Figure 2D. The proportion of N3 stations metastasis in each ELN was as follows (DM *vs.* non-DM): ELN16–29: 8.6% *vs.* 10.4%, ELN30–44: 27.9% *vs.* 20.5%, ELN≥45: 37.7% *vs.* 25.3%. The variations of N3b status divided by ELN in the DM and non-DM groups were shown in Figure 2E. The proportion of N3b status in each ELN was as follows (DM *vs.* non-DM): ELN16–29: 8.6% *vs.* 7.9%, ELN30–44: 18.0% *vs.* 11.8%, ELN≥45: 26.4% *vs.* 17.3%. The mean number of MLN in each ELN was as follows (DM *vs.* non-DM): ELN16–29: 3.6 *vs.* 4.6, ELN30–44: 5.8 *vs.* 5.8, ELN≥45: 12.0 *vs.* 7.7. The above results indicated that the percentage of N3 stations metastasis, N3b status, and the number of MLN increased with the raising of ELN. Thus, the analyses for the subgroup of ELN ≥45 were conducted to reflect the work of DM on LN status with the most

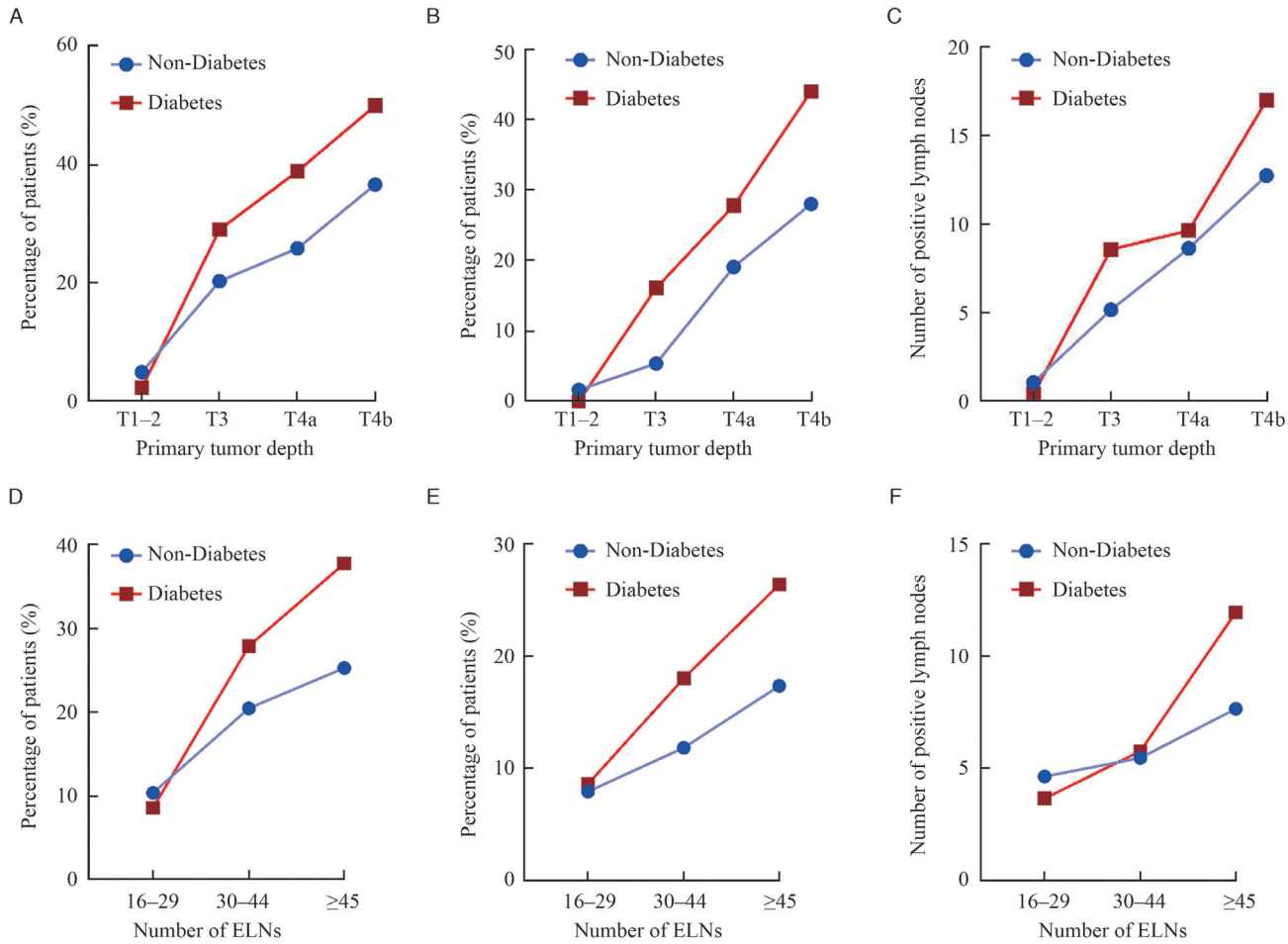

Figure 2: (A) The N3 stations metastasis is divided by primary tumor depth in diabetes and non-diabetes groups. (B) The N3b status in the diabetes and non-diabetes groups is divided by primary tumor depth. (C)The number of MLNs is divided by primary tumor depth in the diabetes and non-diabetes groups. (D) The N3 stations metastasis is divided by the number of ELNs in the diabetes and non-diabetes groups. (E) The N3b status is divided by the number of ELNs in diabetes and non-diabetes groups. (F) The number of MLNs is divided by the number of ELNs in the diabetes and non-diabetes groups. ELNs: Examined lymph nodes; MLNs: Metastatic lymph nodes.

exact and optimal effect. As shown in Supplementary Table 6, http://links.lww.com/CM9/A801 in the subgroup of ELN≥45, the DM group has more N3 stations metastasis (DM *vs.* non-DM: 37.7% [20/53] *vs.* 25.2% [204/808], $P = 0.045$). Equally, the N stage was significantly more advanced in the diabetes group (mean rank [DM *vs.* non-DM]: 507.5 *vs.* 425.9, $Z = -2.458$, $P = 0.014$). Similarly, the diabetes group has more N3b status (DM *vs.* non-DM: 26.4% [14/53] *vs.* 17.3% [140/808], $P = 0.094$) patients but has not yet reached significance. The number of MLN in the DM group was significantly more than that in the non-DM group (median [IQR], 8 [18.50] *vs.* 2 [10.75], $P = 0.017$). Furthermore, the multivariate analyses confirmed that DM was an independent risk factor of N3 stations metastasis (OR = 2.115, 95% CI: 1.063–4.209, $P = 0.033$), N3b status (OR = 1.647, 95% CI: 0.783–3.464, $P = 0.189$), and more MLN number (b = 3.529, Durbin–Watson = 1.913, VIF = 1.050, $P = 0.021$) in the subgroup of ELN≥45 [Supplementary Tables 7–9, http://links.lww.com/CM9/A801].

Discussion

Our study implied that DM promotes the LN metastasis in GC based on the analysis of 2142 GC patients between October 2004 and December 2019 in our institution. On the ground that the most important factors affecting the LN status, the status of ELM ($P = 0.735$), and the primary tumor depth ($P = 0.895$) were roughly equal between two groups, DM was still significantly associated with detecting more N3 stations metastasis and N3b status and more number of MLN. More importantly, the subsequent multivariate analyses confirmed that DM was a dependent factor of N3 stations metastasis and N3b status and more number of MLN. Furthermore, since primary tumor depth and ELN have been suggested as the most important factors affecting the LN status, thus the LN status in subgroups divided by primary tumor depth and ELN were performed. And the subgroups analyses showed the preponderance of N3 stations metastasis, N3b status, and the number of MLN in the DM group aggravated with the advancement of the primary tumor depth and the increase of ELN. The finding in our study

indicated that DM promoted LN metastasis, which was revealed rarely.

As the most important independent prognostic factor for GC,[1-3] great emphasis was put on the LN involvement assessing, and currently, two N-stage systems were most recognized: the Japanese Classification of Gastric Carcinoma (JCGC, 13th edition) N-classification system and Union International Cancer Control (UICC-TNM, 8th edition) N-staging system. JCGC N-classification system is based on the anatomic location-based involved node stations, whereas the UICC-TNM N-staging system is based on the number of MLNs.[2,22,23] The JCGC defined N stage by the site of LN metastasis relative to the primary tumor and this classification of LN metastasis can reflect the metastatic pathways of cancer cells from the primary tumor. Although the TNM N-staging system is based on the number of MLN and could provide an accurate prognostic evaluation for GC patients. Our study evaluating not only the exact number of MLN but also the N3 stations metastasis with JCGC N-classification system and N3b status with UICC-TNM N-staging system. Thus, this study assessed the node status not only in LN burdens but also the metastatic extent, in other words, assessing both dimensions of LN burdens and involved distance and pathways. The multiple dimensions assessment in our study is much more comprehensively than the previous studies, which could only evaluate one dimension.

The novelty of evaluating the LN status by assessing the N3 stations metastasis, N3b status, and the number of MLN are as followed: (1) N3b status was first put forward by the 7th AJCC TNM staging system in 2014 and was incorporated into the 8th TNM stage in 2017 for the first time. According to the result of the International Gastric Cancer Association Project which reported the good prognostic discrimination of N3b from N3a, the 8th edition AJCC set a high value to the impact of N3b on the TNM stage. Even for early GC, the N3b node status (T1N3b) could upgrade patients into stage IIIB. There is no doubt that the N3b node status could have a great impact on the disease stage. Thus, the N3b status should be particularly evaluated to investigate the effect of DM on LN metastasis. (2) N3 stations metastasis assesses the LN status from another dimension that is different from N3b and the number of MLN and makes the evaluation more comprehensive. N3 stations metastasis reflects the extent of cancer cells from the primary tumor. Previous studies have demonstrated that insufficiency of ELN could result in inadequate detection of MLN in all stations. However, ELN in many centers was not satisfying that resulted in their relevant research could not present the exact LN status, especially the evaluation of each station and N3 stations was not accurate. Sano *et al*[3] collected data from 59 institutions present that the mean/median number of LNs examined in Japan, Korea, selected advantaged other Asian centers, and selected advantaged Western centers was 39.4/36, 33.0/31, 24.8/22, and 29.5/27, respectively. While the mean number of ELN of 2142 patients in our studies reached 42, which evaluate N3 stations metastasis more accurately and appropriately than most previous studies. (3) Previous studies assessing the risk factors of LN involvement almost roughly defined the LN metastasis as a bivariate variable (negative *vs*. positive) which may neglect important information of LN metastasis burden. Although our study defined one of the primary points as the number of MLN, which could comprehensively measure the burden of LN. The change was more accurate, specific, and reasonable to investigate the impact of DM on the progress of LNs metastasis in GC.

Another encouraging finding in this study is that the preponderance of N3 stations metastasis, N3b status, and the number of MLN in the DM group was aggravated with the advancement of the primary tumor depth. The mechanisms behind this phenomenon may include the following reasons. First, the longer process of developing a more advanced primary tumor stage allows the biological function of DM to act on tumor cells and tumor microenvironment with enough time. And some basic research has revealed some potential mechanisms that were consistent with the finding in this study. First, it has been found that multiple factors associated with DM, such as hyperglycemia, hyperinsulinemia and insulin-like growth factor I, dyslipidemia, adipokines and cytokines, and the gut microbiome, potentially give rise to the progression of cancer.[28] Hyperglycemia, the hallmark of DM, could provide tumor cells with more glucose and add to tumor proliferation and migration as a result that cancer cells are glucose avid and generate more energy from glycolysis and lactate production compared with oxidative phos$_{[2}$p$_9$h$_]$orylation than noncancerous cells. Besides, Lin *et al*[29] suggested that hyperglycemia may account for the impairment of the immune system. Of course, the suppression of the immune system may result in the progress of LN metastasis. Furthermore, Wu *et al*[30] recently reveal the pathway linking diabetes to cancer via glucose-regulated phosphorylation of ten-eleven translocation-2 (TET2) by AMP-activated kinase (AMPK). They identify the tumor suppressor TET2 as a substrate of the AMPK and thereby stabilizing the tumor suppressor. Sustained hyperglycemia caused by DM destabilizes the tumor suppressor TET2 and deregulates levels of 5–hydroxymethylcytosine (5hmC), and ultimately diabetes to cancer. This study presented a new sight of how DM contributed to cancer, as well as offering the potential mechanism of how DM promoted LN metastasis of GC. Likewise, hyperinsulinemia and insulin receptor signaling could also drive tumor growth and thus may potentially activate the migration of GC cells to LNs. Although dyslipidemia, which is common in patients with DM, has also been found to affect the growth and progression of cancers.[30] It is also noted that adipose tissue is a vital organ for the production of adipokines, inflammatory cytokines, and enzymes that potentially lead to tumor promotion.[28] Thus, the changes in adipose tissue resulted from DM might contribute to the release of tumor progressing factors into the circulation. Also, changes in the gut microbiome caused by DM were indicated to have a link between cancer.[31] It is worth noting that the relationship between bacteria and cancer is also being revealed. It has been found that bacterial biofilms in the colon change the cancer metabolome to produce a regulator of cellular proliferation and colon cancer development potentially influencing cancer progression.[32] Likewise, recently, it has also been demonstrated that the tumor microbiome diversity, which cross-talks to

the gut microbiome, significantly affected the prognosis of pancreatic cancer patients by modulating the tumor microbiome and affecting tumor development and host immune response.[33] Thus, the subgroup with T3–4 allows the greatest biological effect of DM on LN metastasis.

Another key issue is the superiority of LN involvement in the DM group was enhanced with the increase of ELN in our study. The leading superiority of N3 stations metastasis in the DM group increased with the adding of ELN. The consistent trend was discovered in the mean number of MLN. These amazing phenomenon may be attributed as following reasons: (1) as our previous study has shown that increase of ELN significantly improve the detection of more MLN and screen more patients with N3b node status; (2) for the subgroups with insufficient ELN, some N3 stations could even have not any ELN at all, not to mention investigating the LN involvement in N3 stations. Thus, deficient ELN hinders assessing the exact N3 stations metastasis to some extent. Therefore, the increase of ELN could reflect a more exact LN burden. Thus, the subgroup with ELN≥45 could show the effect of DM on LN metastasis more comprehensive and exact.

Considering the above reasons, the subgroups of T3–4 and ELN ≥ 45 were conducted to show the work of DM on MLN with minimal confounding factors. And consistent with the above hypothesis, the subgroup analysis showed DM patients have more heavily LN status burdens and widen LN involvement extent in the T3–4 and ELN ≥ 45 subgroups than the whole group.

As for other variables that were also commonly assessed in other studies, the results in our study were consistent with those in other studies. A single institutional experience from China also shown that large tumor size, undifferentiated type, and lymphovascular invasion were independent risk factors for LNs metastasis in early GC.[34] Another multivariate logistic regression analysis also showed that tumor size, depth of invasion, and macroscopic types were independent factors that affect the LN metastasis.[35] Similarly, Li *et al*[36] recently showed that the depth of invasion, vascular tumor thrombus, and neural invasion were independent predictive risk factors for LN metastasis in GC patients. Except for the clinical characteristics, the number of ELN has also been confirmed to be associated with the detecting of the number of metastasis LN in GC.[27] The consistency of our results with that in the previous studies[37] indicated that the design of our study was reasonable, our data were reliable and the analysis of the general linear regression model was calculable. Thus, the results in our study that DM significantly promoted the LN metastasis in GC was also credible and worth subsequent exploring.

Encouragingly, the finding that DM significantly promoted LN metastasis in GC may provide a reference for subsequent clinical researches and treatments for GC. As we knew, postoperative adjuvant chemotherapy based on histological and biological characteristics to determine tailored treatment for specific subgroups could further improve the prognosis of GC patients.[38] Although LN metastasis has been demonstrated to be the strongest predictor of disease recurrence for GC[1-3] and even might be the active hubs for systemic tumor cell spread.[8,9] At the same time, it has been demonstrated that more intensive adjuvant chemotherapy was safe and could significantly improve prognosis for the subgroup GC patients with an indication for intense adjuvant chemotherapy in serious trials in Japan, including the Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer study,[39] the Japan Clinical Oncology Group 1104 trial,[40] and the Japan Clinical Cancer Research Organization GC-07 trial.[41] Thus, since GC patients with DM are more prone to develop high-LN-burden and involve widen extent, the tailored perioperative management for them specifically may be worth being explored.

Also, the specific mechanisms that DM could promote LN metastasis should be specific and exactly studied so that corresponding target drugs could be used to relieved LN metastasis. Furthermore, the finding in this study gives clues for the orientation of the mechanisms of LN metastasis.

There are still some limitations to our study. Although the data in our study were prospectively collected,[21] our study was not prospectively designed but retrospectively analyzed. And as a result of the nonprospective design, the clinical characteristic was not comparable, such as age and sex. Also, to make sure the assessment for the LN status is more accurate to compensate for the inherent limitations of retrospective analysis, our study excluded the patients with the number of ELN < 16 or receive preoperative chemotherapy/radiotherapy. In addition, the size of the metastasis LN in each group was not registered in our database, so we could not investigate whether DM affects the size of metastasis LN, which may be a variable to reflect the metastasis LN burden. Therefore, the size of the metastasis LNs should be taken into consideration in the design of subsequent randomized control trials.

Conclusions

DM was an independent risk factor for promoting LN metastasis, especially for subgroups of T3–4 and ELN ≥ 45, which allow the biological function of DM to act on tumor cell and tumor microenvironment with enough period and reflect the exact LN status. The preponderance of N3 stations metastasis, N3b status, and MLN in the DM group was aggravated with the advancement of primary tumor depth and the increase of ELN. This finding provides a reference for subsequent clinical researches and treatments for GC and gives clues for the orientation of the mechanisms of LN metastasis in basic research.

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Conflicts of interests

None.

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