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Exceeding 30 ELNs is strongly recommended for pT3-4N0 patients with gastric cancer: A multicenter study of survival, recurrence, and prediction model

Lulu Zhao[1] | Weili Han[2] | Xisheng Yang[2] | Dongbing Zhao[1] | Penghui Niu[1] | Xianchun Gao[2] | Zhenkun Wu[1] | Xiaojie Zhang[1] | Zefeng Li[1] | Gang Ji[2] | Yingtai Chen[1]

[1]National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

[2]State key Laboratory of Cancer Biology and National Clinical Research Center for Digestive Diseases, Xijing Hospital of Digestive Diseases, Fourth Military Medical University, Xi'an, China

Correspondence
Gang Ji, State key Laboratory of Cancer Biology and National Clinical Research Center for Digestive Diseases, Xijing Hospital of Digestive Diseases, Fourth Military Medical University, Xi'an 710032, China.
Email: jigang@fmmu.edu.cn

Yingtai Chen, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, 17 Panjiayuan Nanli, Beijing 100021, China.
Email: yingtaichen@126.com

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Abstract

The argument concerning the exact minimum number of examined lymph nodes (ELNs) has continued for a long time among various regions, and no consensus has been reached for stratified pathological T stages for data to date. Data from 4607 pN0 patients with gastric cancer were analyzed. Kaplan-Meier analysis showed the similar overall survival (OS) outcomes among the 3 groups (ELNs ≤ 15, 16 ≤ ELNs ≤ 29 and ELNs ≥ 30, $P = .171$). However, the ELNs ≥ 30 group had a better disease-free survival (DFS) outcome compared with the others (all $P < .05$). An increased ELN group (ELNs ≥ 30) showed an improved OS only for pT3 patients (hazard ratio [HR] = 0.397, 95% confidence interval (CI): 0.182-0.866, $P = .020$), while an improved DFS for pT3 patients (HR = 0.362, 95%CI: 0.152-0.860, $P = .021$) and pT4 patients (HR = 0.484, 95%CI: 0.277-0.844, $P = .011$) in the multivariate analysis. A well discriminated and calibrated nomogram was constructed to predict the probability of the OS and DFS, with the C-index for OS and DFS prediction of 0.782 (95%CI: 0.735 to 0.829) and 0.738 (95%CI: 0.685 to 0.791), respectively. This study provides new and useful insights into the impact of ELN count on reducing stage migration and postoperative recurrence of pN0 patients with gastric cancer in 2000-2017. In conclusion, a larger number of ELNs is suggested for surgeons to prolong the prognosis of pN0 gastric cancer, especially for pT3 patients.

KEYWORDS
examined lymph nodes, gastric cancer, prediction model, stage migration, survival outcomes

Lulu Zhao, Weili Han, and Xisheng Yang are contributed equally to this work.

1 | INTRODUCTION

Despite its significant decline in incidence in the past decades, gastric cancer is still the third leading cause of cancer-related mortality worldwide.[1] As the most commonly used tool to determine pathologic T and N staging for resected gastric cancer at this time, the TNM system of the International Union for Cancer Control/American Joint Committee on Cancer (UICC/AJCC) requires 15 or more lymph nodes (ELNs) to be examined to guarantee the accurate prognosis of the pN category, especially for pN0 patients.[2,3] The latest *National Comprehensive Cancer Network Guidelines* (*NCCN Guidelines*) recommends the examination of not less than 16 regional lymph nodes when determining nodal metastatic status.[4]

Nevertheless, accumulating evidence has demonstrated that increasing the numbers of ELNs examined increases the likelihood of accurate staging, therefore stage migration could be gradually reduced or prevented (the Will Rogers phenomenon).[5-8] Ji et al demonstrated that ELNs ≥ 22 is an independent prognostic factor for pN0 population.[6] Smith et al indicated that 25 or more lymph nodes are necessary for D2 lymphadenectomy.[9] Published studies also showed that a higher number of ELNs (≥30 numbers) was associated with a better survival outcome, as nodal metastases serve as a well known prognostic factor for gastric cancer after radical treatment.[7,8,10-13] In this context, it still remains controversial how to quantitatively assess the effects of the number of ELNs on achieving an optimum reliability in stage assignment for gastric cancer. In addition, it is unknown how risk factors are associated with recurrence after gastrectomy for pN0 gastric cancer patients based on adequate ELNs.

Given these considerations, we conducted this study on 2 of the biggest Chinese gastric cancer cohorts from the China National Cancer Center, and National Clinical Research Center for Digestive Diseases and Xijing Hospital of Digestive Diseases, to investigate whether stage migration exists in pN0 gastric cancer patients, as well as the relationship between ELN count after gastrectomy and survival outcomes. In addition, a nomogram was developed to predict the probability of overall survival (OS) and disease-free survival (DFS), to directly help surgeons to formulate adjuvant therapeutic and preventive strategies for pN0 gastric cancer.

2 | MATERIALS AND METHODS

2.1 | Patient population

The study queried data from 2000 to 2017 from the 2 large gastric cancer cohorts. The first cohort, a huge bidirectional group with gastric cancer, was sourced from the China National Cancer Center, a single but large-scale institution, and included more than 19 000 patients from around China examined from 1997 to 2017. The second cohort was from a prospective database, which collected clinicopathologic data, biological specimens, and follow-up information on patients who were admitted to the Xijing Hospital of Digestive Diseases. By December 2019, this database had included more than 11 000 patients who were diagnosed with gastric or gastroesophageal cancer.

Those patients who underwent curative gastrectomy and were defined pathologically as gastric adenocarcinoma (pTanyN0M0) were included in this study. The exclusion criteria were as follows: (1) patients received neoadjuvant therapy before surgery; (2) patients with signet ring cell carcinoma; (3) patients with linitis plastica; (4) patients with pathologically positive resection margin; (5) patients with a history of other cancer or tumor; and (6) patients with any missed important data, such as surgery date, pTNM stage, and ELNs. Based on these screening criteria, 4607 gastric cancer patients with pTanyN0M0 were identified. Figure 1 showed the flow diagram for selecting the patients.

2.2 | Statistical analyses

Comparisons between the groups were tested with *t* test for continuous variables and chi-square test for categorical variables. OS and DFS analyses were performed for the entire study.

The Kaplan-Meier method was used to calculate OS, and differences between the survival curves were assessed using the log-rank test. Univariate and multivariate Cox proportional hazards models were used to determine the prognostic factors for OS and DFS. Variables with a *P*-value of <.10 in the univariate analysis were adopted for the multivariate analysis. Finally, the adjusted factors included age, gender, year of diagnosis, type of gastrectomy, vascular invasion, nerve invasion, adjuvant therapy, ELNs, and pathologic T stage. Hazard ratio (HR) and 95% confidence interval (CI) were used to measure the risk of death. A *P*-value of less than .05 was considered to be statistically significant and all the tests were two-sided. A nomogram was formulated based on the results of the multivariate analysis.[14] We then selected the pN0 patients from the last period (2013-2017) as a validated cohort to complete nomogram prediction, which was measured with a concordance index (C-index) based on the regression analysis. The larger the C-index, the more accurate the prognostic prediction.[15]

All statistical analyses were performed using SPSS v.25 (College Station, TX, USA) and R software v.3.6.3 (http://www.r-project.org/).

3 | RESULT

3.1 | Clinicopathologic characteristics

Data from 4607 pN0 gastric cancer patients were analyzed, and the clinicopathologic characteristics of the 2 cohorts are shown in Table 1. There were 1238 patients (26.9%) with ELNs ≤ 15, 2121 patients (46.0%) with 16 ≤ ELNs ≤ 29, and 1248 patients (27.1%) with ELNs ≥ 30. Compared with the ELNs ≥ 30 group, the less lymphadenectomy group (ELNs ≤ 15) was more likely to have been diagnosed in the earlier year period (2000-2004, 26.3% vs. 3.8%, $P < .001$), at

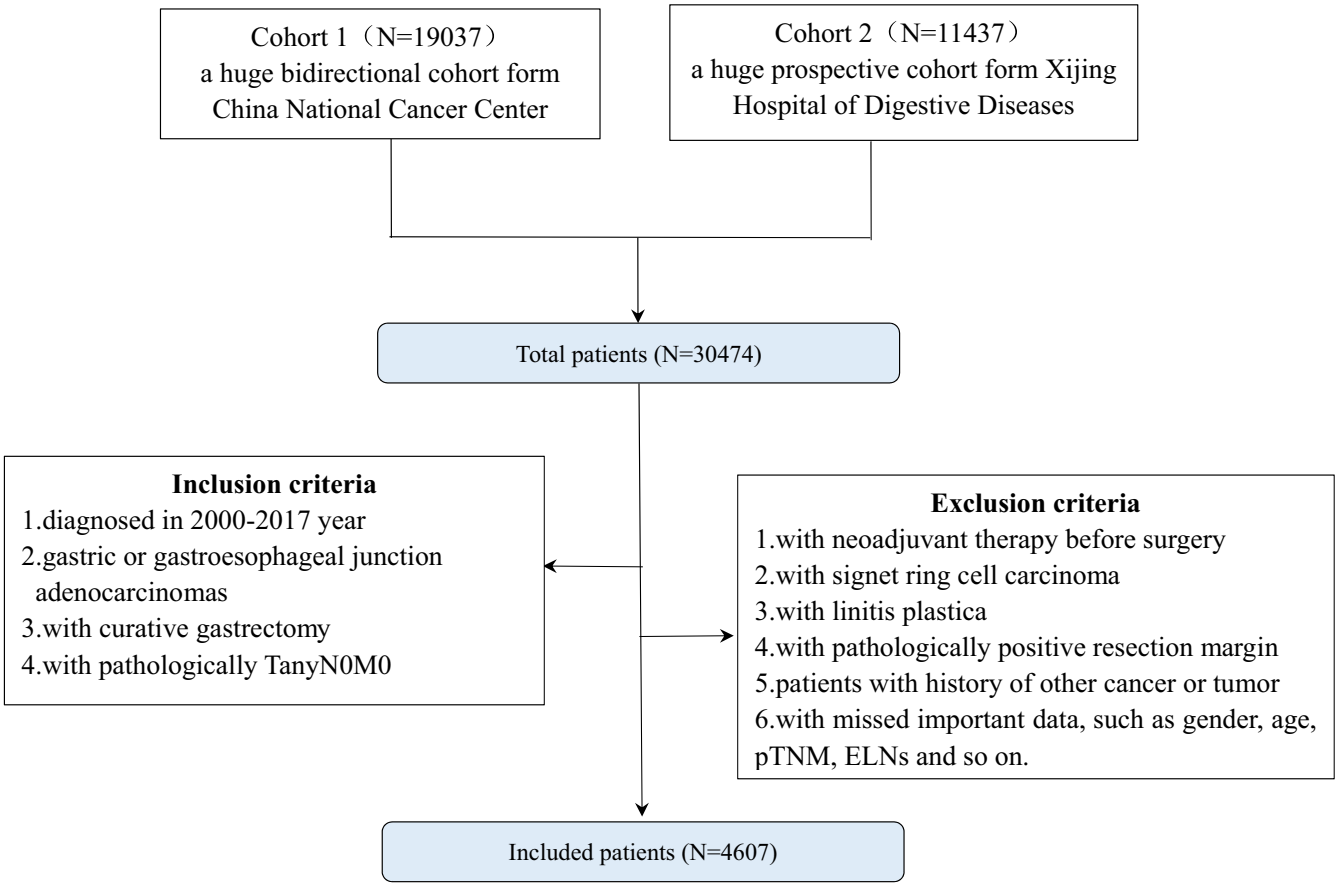

FIGURE 1 Flow diagram of the patient selection process

the earlier pT stage (T1 + Tis, 42.2% vs. 36.3%, $P < .001$), and treated with proximal gastrectomy (44.3% vs. 22.0%, $P < .001$). More patients in the 16 ≤ ELNs ≤ 29 and ELNs ≥ 30 groups underwent total gastrectomy (5.9% vs. 15.1% vs. 17.5%, $P < .001$), and were diagnosed with vascular invasion (10.1% vs. 16.9% vs. 18.6%, $P < .001$) and nerve invasion (8.6% vs. 30.9% vs. 33.3%, $P < .001$) compared with the ELNs ≤15 group.

The mean (±SD) age of the pN0 patients was 59.16 ± 10.840 in the ELNs ≤ 15 group, 58.22 ± 10.993 in the 16 ≤ ELNs ≤ 29 group, and 57.00 ± 10.46 in the ELNs ≥ 30 group, respectively. The mean (±SD) number of pathologically proven ELNs of these pN0 patients was 9.92 ± 3.880 in the ELNs ≤ 15 group, 22.15 ± 3.903 in the 16 ≤ ELNs ≤ 29 group, and 39.68 ± 11.349 in the ELNs ≥ 30 group, respectively.

3.2 | Stage migration

For analysis of stage migration, the pN0 gastric cancer patients with ELNs ≤ 15 (n = 1239) and pN1 patients with ELNs ≥ 16 (n = 1176) were included using long-rank test. We hypothesized that an increasing number of ELNs may transform the pN0 patients to pN1 patients at the same pT stage. Based on this definition, we compared several groups (Figure 2A-D): (A) pT1N1M0 (ELNs ≥ 16) vs. pT1N0M0 (ELNs ≤ 15), $P = .889$; (B) pT2N1M0 (ELNs ≥ 16) vs. pT2N0M0 (ELNs ≤ 15), $P = .691$; (C) pT3N1M0 (ELNs ≥ 16) vs. pT3N0M0 (ELNs ≤ 15), $P = .570$; and (D) pT4N1M0 (ELNs ≥ 16) vs. pT4N0M0 (ELNs ≤ 15), $P = .889$. There was no significant difference between these groups. Therefore, stage migration may be proven and the pT1N0M0 patients were classified as Stage pT1N1M0 with an increased number of ELNs. Similarly, pT2N0M0 may migrate to pT2N1M0 with an increased number of ELNs, pT3N0M0 may migrate to pT3N1M0 with an increased number of ELNs, and pT4N0M0 may migrate to pT4N1M0 with an increased number of ELNs.

3.3 | OS and DFS analysis

Figure 3 shows the Kaplan-Meier curves for OS (Figure 3A) and DFS (Figure 3B) of 2 large population-based cohorts with different ELNs groups. The analysis showed the similar OS outcomes among the 3 groups (ELNs ≤ 15, 16 ≤ ELNs ≤ 29 and ELNs ≥ 30, $P = .171$). However, the ELNs ≥ 30 group had a better DFS outcome compared with both the ELNs ≤ 15 and 16 ≤ ELNs ≤ 29 groups ($P = .029$).

Considering the clinicopathological differences among the groups, we conducted subgroup analysis based on pT stage. In the stratified analysis of patients with Stages pT1-2 and pT4, the OS and DFS of the gastric cancer patients were comparable in these 3

TABLE 1 Characteristics of pN0 patients with different ELNs

Characteristics	Total		ELNs ≤ 15		16 ≤ ELNs ≤ 29		ELNs ≥ 30		*P*-value
	Number	%	Number	%	Number	%	Number	%	
Total	4607	100	1238	26.87	2121	46.04	1248	27.09	
Age at diagnosis (y)									
Mean (SD)	58.14	10.837	59.16	10.840	58.22	10.993	57.00	10.46	<.001
Younger (≤35)	139	3.0	26	2.1	72	3.4	41	3.3	<.001
Middle-aged (36-65)	3258	70.7	831	67.1	1484	70	943	75.6	
Older (≥66)	1210	26.3	381	30.8	565	26.6	264	21.2	
Gender									
Male	3467	75.3	970	78.4	1601	75.5	896	71.8	.001
Female	1140	24.7	268	21.6	520	24.5	352	28.2	
Year at diagnosis									
2000-2004	550	11.9	326	26.3	176	8.3	48	3.8	<.001
2005-2009	959	20.8	489	39.5	365	17.2	105	8.4	
2010-2013	1494	32.4	288	23.3	767	36.2	439	35.2	
2014-2017	1604	34.8	135	10.9	813	38.3	656	62.6	
Type of gastrectomy									
Proximal	1528	33.2	549	44.3	704	33.2	275	22.0	<.001
Distal	2467	53.5	616	49.8	1097	51.7	754	60.4	
Total	612	13.3	73	5.9	320	15.1	219	17.5	
Grade									
Well	318	7.3	95	8.4	163	8.0	60	5.0	<.001
Well-Moderately	294	6.8	68	6.0	146	7.2	80	6.7	
Moderately	1107	25.4	314	27.9	536	26.5	257	21.4	
Poorly-Moderately	1038	23.8	241	21.4	493	24.3	304	25.3	
Poorly	1596	36.7	408	36.2	688	34.0	500	41.6	
Vascular invasion									
Yes	693	15.7	114	10.1	350	16.9	229	18.6	<.001
No	3734	84.3	1014	89.9	1719	83.1	1001	81.4	
Nerve invasion	4427								
Yes	1144	25.9	96	8.6	639	30.9	409	33.3	<.001
No	3276	74.1	1025	91.4	1432	69.1	819	66.7	
Pathologic T stage									
T1 + Tis	1670	36.2	523	42.2	694	32.7	453	36.3	<.001
T2	939	20.4	250	20.2	449	21.2	240	19.2	
T3	862	18.7	125	10.1	447	21.1	290	23.2	
T4	1136	24.7	340	27.5	531	25.0	265	21.2	
Adjuvant therapy									
Yes	1510	59.2	335	58.5	759	60.6	416	57.5	.352
No	1039	40.8	238	41.5	493	39.4	308	42.5	
ELNs									
Mean (SD)	23.61	12.935	9.92	3.880	22.15	3.903	39.68	11.349	<.001

groups ($P > .05$) (Figure 4A-D,G,H). For the gastric cancer patients with Stage pT3 (Figure 4E,F), the ELNs ≥ 30 group had better OS and DFS results compared with the other 2 groups, respectively ($P = .031$ and $P = .019$, respectively).

A linear ELN count-to-survival correlation model provided the best fit in each pT stage subgroup (Figure 5A-D). A superior 5-y survival rate is depicted in the higher ELNs groups (31 ≤ ELNs ≤ 44, or ELNs ≥ 45) for all 4 stage subgroups.

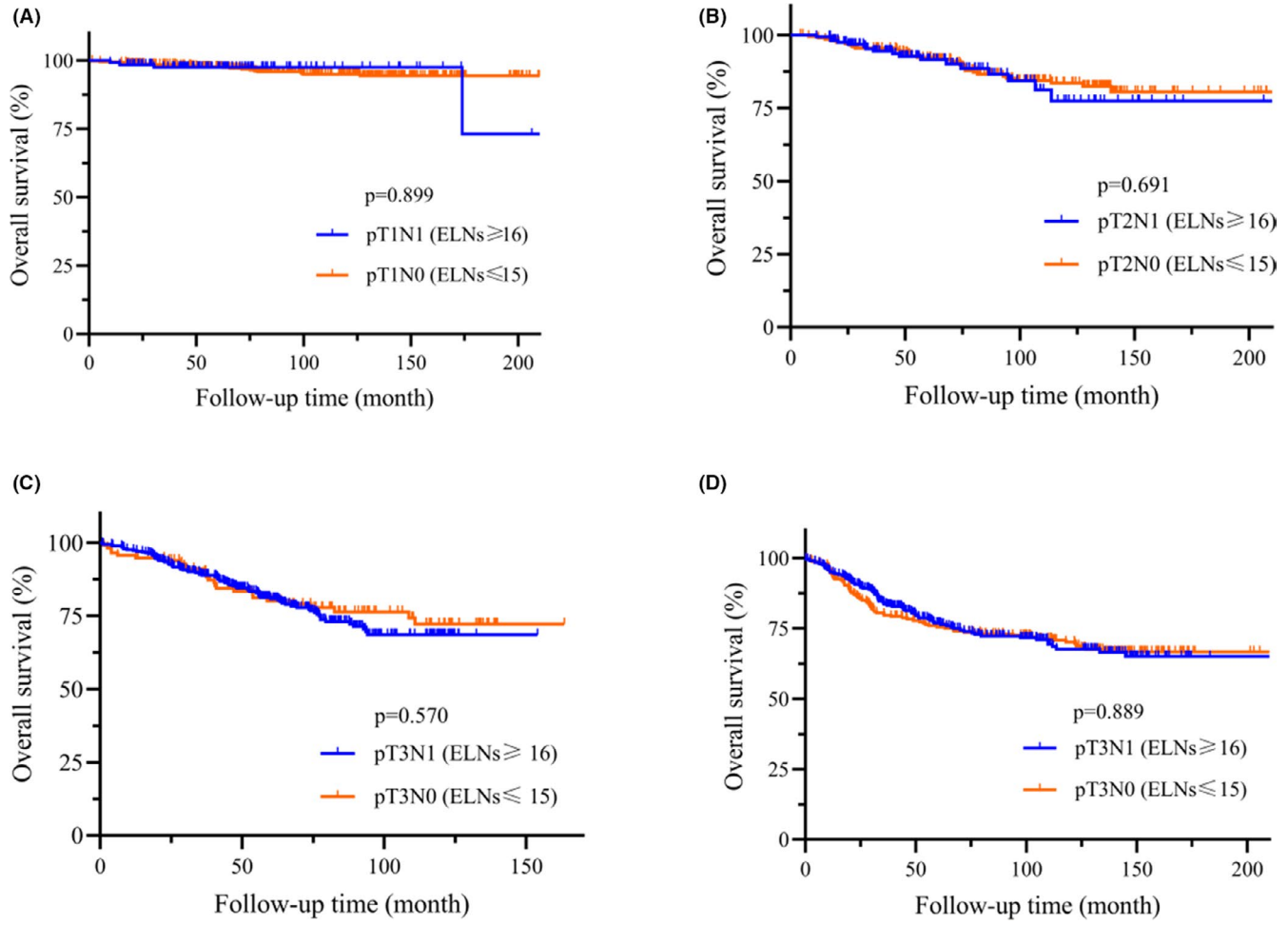

FIGURE 2 OS of pN0 vs. pN1. A, pT1N0 (ELNs ≤ 15, n = 523) vs. pT1N1 (ELNs ≥ 16, n = 144). B, pT2N0 (ELNs ≤ 15, n = 250) vs. pT2N1 (ELNs ≥ 16, n = 189). C, pT3N0 (ELNs ≤ 15, n = 862) vs. pT3N1 (ELNs ≥ 16, n = 390). D, pT4N0 (ELNs ≤ 15, n = 1136) vs. pT4N1 (ELNs ≥ 16, n = 454)

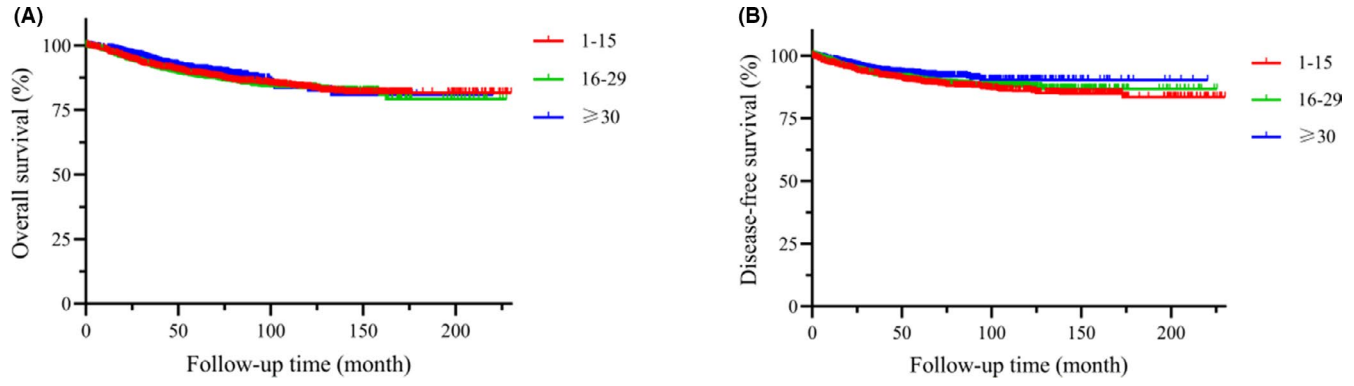

FIGURE 3 OS and DFS of the total pN0 patients in different ELN group. A, OS, *P* = .171. B, DFS, *P* = .029

Furthermore, the univariate and multivariate Cox proportional hazards models were used to determine the prognostic factors for OS and DFS (Tables 2 and 3). Variables with a *P*-value of less than .10 in the univariate analysis were involved in the multivariate analysis, including age, gender, year of diagnosis, type of gastrectomy, vascular invasion, nerve invasion, adjuvant therapy, pT stage, and ELNs. For all the patients, the independent predictor for OS included distal gastrectomy (HR = 0.632, 95%CI: 0.469-0.853, *P* = .003), nerve invasion (HR = 0.614, 95%CI: 0.455-0.828, *P* = .001), and increasing pT stage (*P* < .05). However, the increased ELNs group

TABLE 2 Multivariate analyses in OS of pN0 patients with gastric cancer

	Total (n = 4607)			pT1 (n = 1670)			pT2 (n = 939)			pT3 (n = 862)			pT4 (n = 1136)		
Prognostic factors	**HR**	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**
Age at diagnosis (y)															
Younger (≤35)	1			–			1			–			1		
Middle-aged (36-65)	1.293	0.570-2.933	.539				1.339	0.180-9.942	.775				0.961	0.383-2.413	.932
Older (≥66)	2.236	0.974-5.131	.058				4.140	0.548-31.271	.169				1.299	0.500-3.371	.591
Gender															
Male	1			1			1			1			1		
Female	0.973	0.745-1.270	.838	0.363	0.077-1.706	.199	0.937	0.456-1.925	.858	0.914	0.514-1.626	.759	1.156	0.815-1.640	.415
Year at diagnosis															
2000-2004	1			1			–			1			–		
2005-2009	1.349	0.684-2.663	.388	0.984	0.166-5.817	.985				0.674	0.299-1.517	.341			
2010-2013	1.502	0.764-2.953	.238	0.698	0.101-4.800	.698				0.488	0.199-1.197	.488			
2014-2017	1.088	0.536-1.376	.815	0.352	0.031-4.022	.352									
Type of gastrectomy															
Proximal	1			1			1			1			1		
Distal	0.632	0.469-0.853	.003	0.787	0.247-2.508	.685	0.449	0.249-0.811	.008	0.633	0.341-1.175	.147	0.757	0.467-1.126	.257
Total	1.268	0.926-1.736	.139	–			0.500	0.22-1.135	.098	1.366	0.768-2.431	.288	1.760	1.080-2.869	.023
Vascular invasion															
Yes	1			1			1			1			1		
No	0.992	0.760-1.293	.951	0.211	0.049-0.915	.038	0.874	0.450-1.698	.691	0.974	0.575-1.650	.922	1.111	0.775-1.591	.568
Nerve invasion															
Yes	1			–			1			1			1		
No	0.614	0.455-0.828	.001				0.753	0.412-1.377	.357	0.642	0.363-1.133	.126	0.621	0.391-0.986	.043
Adjuvant therapy															
Yes	1			1			1			1			1		
No	1.105	0.833-1.465	.489	3.312	1.050-10.449	.041	1.051	0.601-1.836	.862	1.136	0.648-1.990	.656	1.488	0.977-2.265	.064
ELNs															
ELNs ≤ 15	1			1			1			1			1		
16 ≤ ELNs ≤ 29	0.985	0.697-1.393	.933	1.992	0.596-6.663	.264	1.634	0.686-3.889	.267	0.576	0.289-1.148	.117	0.879	0.534-1.447	.613
ELNs≥30	0.820	0.560-1.199	.306	0.609	0.060-6.617	.675	2.092	0.798-5.482	.133	0.397	0.182-0.866	.020	0.772	0.453-1.316	.342
Pathologic T stage															
T1 + Tis	1			–											
T2	3.384	1.867-6.135	<.001												
T3	4.119	2.254-7.528	<.001												
T4	8.644	4.829-15.473	<.001												

Adjusted factors: age, gender, year at diagnosis, type of gastrectomy, vascular invasion, nerve invasion, adjuvant therapy, ELNs, pathologic T stage.

TABLE 3 Multivariate analyses in DFS of pN0 patients with gastric cancer

	Total (n = 4607)			pT1 (n = 1670)			pT2 (n = 939)			pT3 (n = 862)			pT4 (n = 1136)		
Prognostic factors	**HR**	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**
Age at diagnosis (y)															
Younger (≤35)	1			–			–			–			1		
Middle-aged (36-65)	1.286	0.567-2.918	.548										0.716	0.307-1.670	.439
Older (≥66)	2.041	0.886-4.699	.094										1.069	0.441-2.592	.882
Gender															
Male	1			1			1			1			1		
Female	0.999	0.759-1.316	.995	0.355	0.132-0.952	.040	1.166	0.559-2.430	.682	0.704	0.355-1.396	.315	1.289	0.896-1.856	.172
Year at diagnosis															
2000-2004	1			1			1			–			–		
2005-2009	0.362	0.222-0.589	<.001	0.166	0.051-0.544	.003	0.347	0.097-1.237	.103						
2010-2013	0.452	0.291-0.700	<.001	0.174	0.059-0.510	.001	0.275	0.078-0.971	.045						
2014-2017	0.357	0.221-0.578	<.001	0.212	0.062-0.733	.014	0.145	0.037-0.562	.005						
Type of gastrectomy															
Proximal	1			1			1			1			1		
Distal	0.571	0.428-0.763	<.001	0.504	0.233-1.091	.082	0.300	0.158-0.569	<.001	0.391	0.196-0.778	.007	0.843	0.523-1.359	.483
Total	0.892	0.639-1.243	.499	–			0.341	0.127-0.916	.033	0.841	0.456-1.552	.580	1.347	0.801-2.266	.262
Vascular invasion															
Yes	1			1			1			1			1		
No	1.054	0.792-1.402	.72	0.755	0.238-2.392	.633	0.875	0.423-1.810	.719	1.157	0.645-2.075	.626	1.229	0.829-1.823	.305
Nerve invasion															
Yes	1			1			1			1			1		
No	0.676	0.499-0.915	.011	0.433	0.088-2.132	.304	1.053	0.532-2.085	.882	0.874	0.481-1.588	.658	0.451	0.274-0.742	.002
Adjuvant therapy															
Yes	1			1			1			1			1		
No	1.610	1.177-2.203	.003	4.761	2.252-10.065	<.001	1.603	0.862-2.982	.136	2.470	1.102-5.536	.028	1.053	0.639-1.744	.841
ELNs															
ELNs≤15	1			1			1			1			1		
16 ≤ ELNs ≤ 29	0.870	0.624-1.214	.413	1.839	0.797-4.244	.153	0.593	0.555-2.802	.593	0.582	0.274-1.238	.160	0.689	0.423-1.120	.133
ELNs ≥ 30	0.635	0.431-0.935	.021	1.130	0.344-3.716	.841	1.590	0.612-4.133	.341	0.362	0.152-0.860	.021	0.484	0.277-0.844	.011
Pathologic T stage															
T1 + Tis	1														
T2	0.986	0.609-1.597	.955												
T3	1.142	0.698-1.868	.597												
T4	2.303	1.464-3.623	<.001												

Adjusted factors: age, gender, year at diagnosis, type of gastrectomy, vascular invasion, nerve invasion, adjuvant therapy, ELNs, pathologic T stage.

(ELNs ≥ 30) showed an improved survival only for pT3 patients (HR = 0.397, 95%CI: 0.182-0.866, $P = .020$) (Table 2). For the DFS analysis in the multivariate analysis (Table 3), there were significant differences among the different ELNs groups for all the patients (HR = 0.635, 95%CI: 0.431-0.935, $P = .021$), pT3 patients (HR = 0.362, 95%CI: 0.152-0.860, $P = .021$), and pT4 patients (HR = 0.484, 95%CI: 0.277-0.844, $P = .011$).

3.4 | Nomogram analysis of gastric cancer patients with pN0 stage

To predict the OS and DFS of pN0 patients with gastric cancer, a nomogram was established for predicting 3-y and 5-y OS and DFS by incorporating the following parameters: age, gender, year of diagnosis, type of gastrectomy, vascular invasion, nerve invasion, adjuvant therapy, pT stage, and ELNs (Figure 6A,B). The C-index for OS and DFS prediction was 0.782 (95CI: 0.735 to 0.829) and 0.738 (95CI: 0.685 to 0.791), respectively.

This result was similar to the multivariate outcome that adjuvant therapy was an independent factor for DFS but not for OS in patients with pN0 gastric cancer. We can see that adjuvant therapy had a longer line in the DFS nomogram compared with the OS nomogram.

4 | DISCUSSION

This multicenter study investigated systematically how ELNs following gastrectomy affected the prognosis in patients with gastric cancer. To the best of our knowledge, our analysis represents the largest evaluation of ELN count-to-survival outcomes in patients with gastric cancer. A primary finding was that the higher the number of ELNs following gastrectomy, the better the possibility of long-term survival in pN0 patients. The effect was also observed in the pT3 stage subgroup in the multivariate analysis, in which the ELNs ≥ 30 group had improved OS and DFS outcomes. Therefore, the exact minimum number of ELNs deserves further discussion before a considered conclusion is given.

Notably, there were 1238 patients (26.87%) with the minimum of 16 ELNs in our study, which meant that more than 1/4 gastric cancer patients received inappropriate lymphadenectomy based on the AJCC TNM stage. The main reasons for this phenomenon are as follows. Firstly, the ELNs ≤ 15 group had a greater proportion of earlier year diagnosis (during 2000-2004), while the D2 lymphadenectomy of gastric cancer is not yet fully mature then.[16] Secondly, the ELNs ≤ 15 group presented to be more frequent in proximal gastrectomy compared with the ELNs ≥ 30 group, while total gastrectomy did enable a more complete nodal dissection as previously reported than proximal gastrectomy.[17]

However, gastric cancer could be staged incorrectly because of an insufficient number of ELNs, which is called "stage migration."[2] To confirm the aforementioned speculation, we initially designed the study to investigate whether stage migration existed by examining those subgroups: pT1N1M0 (ELNs ≥ 16) vs. pT1N0M0 (ELNs ≤ 15), pT2N1M0 (ELNs ≥ 16) vs. pT2N0M0 (ELNs ≤ 15), pT3N1M0 (ELNs ≥ 16) vs. pT3N0M0 (ELNs ≤ 15), and pT4N1M0 (ELNs ≥ 16) vs. pT4N0M0 (ELNs ≤ 15), which indicated that a significant portion of patients classified as pN0 had been understaged in the ELNs ≤ 15 group. Because the number of ELNs could be controlled by surgeons with pathological diagnostic biases, it is necessary for surgeons to perform standard lymphadenectomy during surgery. Luckily, the stage migration of pN0 patients has been gradually reduced as most Chinese medical centers can achieve D2 lymphadenectomy successfully.[18]

In the analysis of survival trend and ELNs, a better 5-y survival rate was depicted in the higher ELNs group for all 4 stage subgroups in Figure 5. However, the lessening of the curve with pT3 and pT4 patients was possibly because the number of patients with ELNs ≥ 45 was limited. This result is similar to that of 1 published study, namely, a significant 5-y OS improvement for pT3 patients by up to 11% for every 10 extra ELNs.[9] Both studies indicated than more ELNs were strongly recommended for pN0 patients.

In addition, a superior OS in pT3 patients was showed in the multivariate analysis based on ELNs ≥ 30. This is possibly not just because of a low probability of stage migration in the ELNs ≥ 30 group, and regional disease control is another important factor. In our study, the ELNs ≥ 30 patients showed a better DFS outcome compared with the other groups (ELNs ≤ 15 and 16 ≤ ELNs ≤ 29 groups). Based on the stratification by prognostic factors, ELNs ≥ 30 was defined as an independent predictor for improved DFS in pT3 and pT4 patients. Given these findings, pT3 patients with gastric cancer may constitute a special population attracting attention for the optimal number of ELNs following gastrectomy. In addition, Smith et al reported that 20 or 25 ELNs were advised for the examination for gastrectomy for pT3 and pT4 patients.[9] A recent published study indicated that 31 ELNs are required for an accurate evaluation of pT4bN0 patients.[13] This was comparable with our research. Therefore, we concluded that ELNs ≥ 30 is a prerequisite for reducing the postoperative recurrence of pT3-4N0 gastric cancer patients. The present results still need to be validated in the future with larger prospective studies.

Nomograms have been widely used as a visualization tool for predicting the prognosis of patients with various types of cancers.[19] To the best of our knowledge, the present study is the first one to construct a nomogram for predicting OS and DFS following gastrectomy based on the risk factors of survival and recurrence. The C-index (0.782 for OS and 0.738 for DFS) demonstrated that the nomogram developed in the present study was a reliable prognostic prediction model. More importantly, the DFS nomogram showed that adjuvant therapy plays an important role in preventing recurrence following gastrectomy in pN0 patients. As Haejin et al reported, the addition of adjuvant therapy may be beneficial even for pN0 patients.[20]

Several limitations need to be considered in this study. Firstly, it was not just a total prospective study, and furthermore clinical trials are needed to clarify our conclusion in the future. Secondly, we included patients monitored over a long time period of 17 y, and significant differences in OS and DFS were observed between different

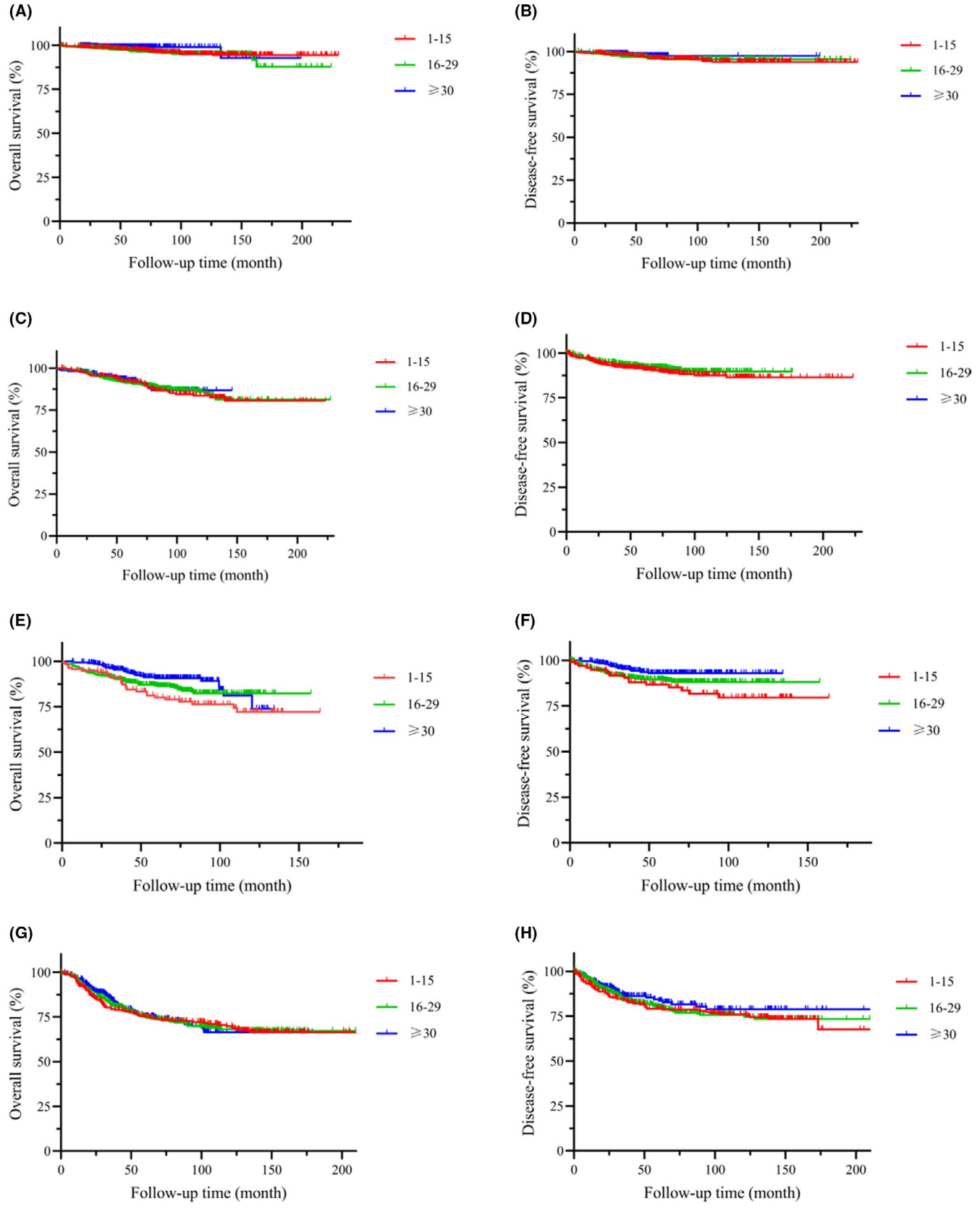

FIGURE 4 OS and DFS of pN0 patients in different ELN groups. A, OS of pT1 and pTis patients, $P = .156$. B, DFS of pT1 and pTis patients, $P = .927$. C, OS of pT2 patients, $P = .930$. D, DFS of pT2 patients, $P = .154$. E, OS of pT3 patients, $P = .031$. F, DFS of pT3 patients, $P = .019$. G, OS of pT4 patients, $P = .970$. H, DFS of pT4 patients, $P = .458$

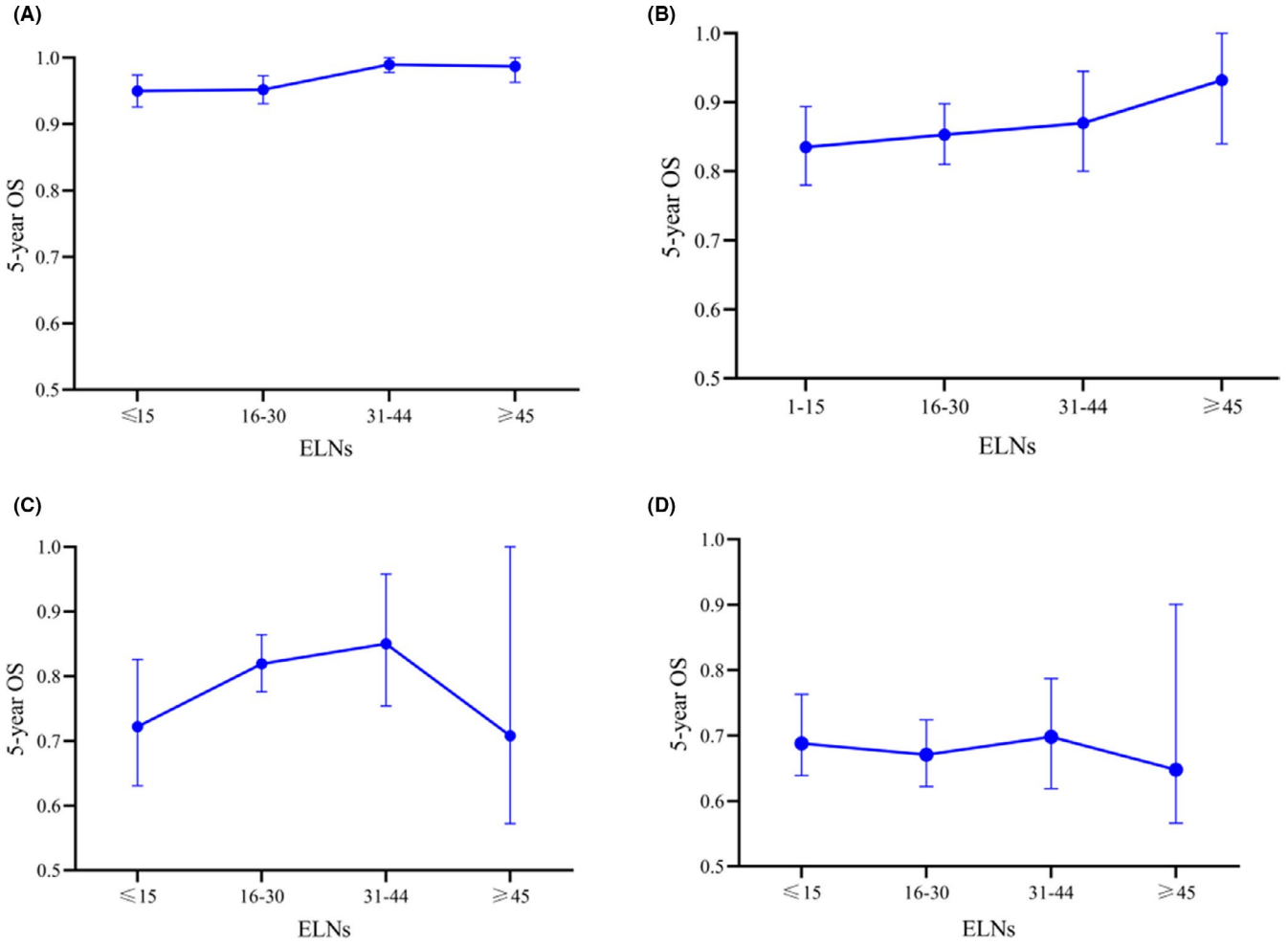

FIGURE 5 A linear ELNs to survival correlation model for each pT stage subgroup. A, pT1 and pTis. B, pT2. C, pT3. D, pT4

operative periods. Thirdly, the number of lymph nodes removed during surgery for gastric cancer cannot be controllable by the surgeon's intent, and various background factors in the patient may affect the number of lymph nodes removed. It may be a challenge during the surgical process. However, it is an advantage that should not be ignored that the volume of pN0 patients was large and the source of patients usually came from northern and eastern China in the China National Cancer Center, while another medical center, the National Clinical Research Center for Digestive Diseases, was the biggest gastric cancer center in northwestern China. Therefore, the data in our study could serve as a reference for a large population-based study in China.

The present study provides new and useful insights into the impact of ELNs count on reducing stage migration and postoperative recurrence of pN0 patients with gastric cancer during 2000-2017. ELNs ≥ 30 is an independent predictor for improved DFS in pT3 and pT4 patients, as well as OS in pT3 patients with gastric cancer. Giving these findings, a larger number of ELNs is expected for surgeons to prolong the prognosis on gastric cancer, especially for pT3 patients.

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CONFLICT OF INTEREST

The authors have declared no conflicts of interest.

ETHICAL APPROVAL

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the ethics committee of National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (No. 17-156/1412).

DATA AVAILABILITY

The data used to support this findings of this study are include in tables within the article.

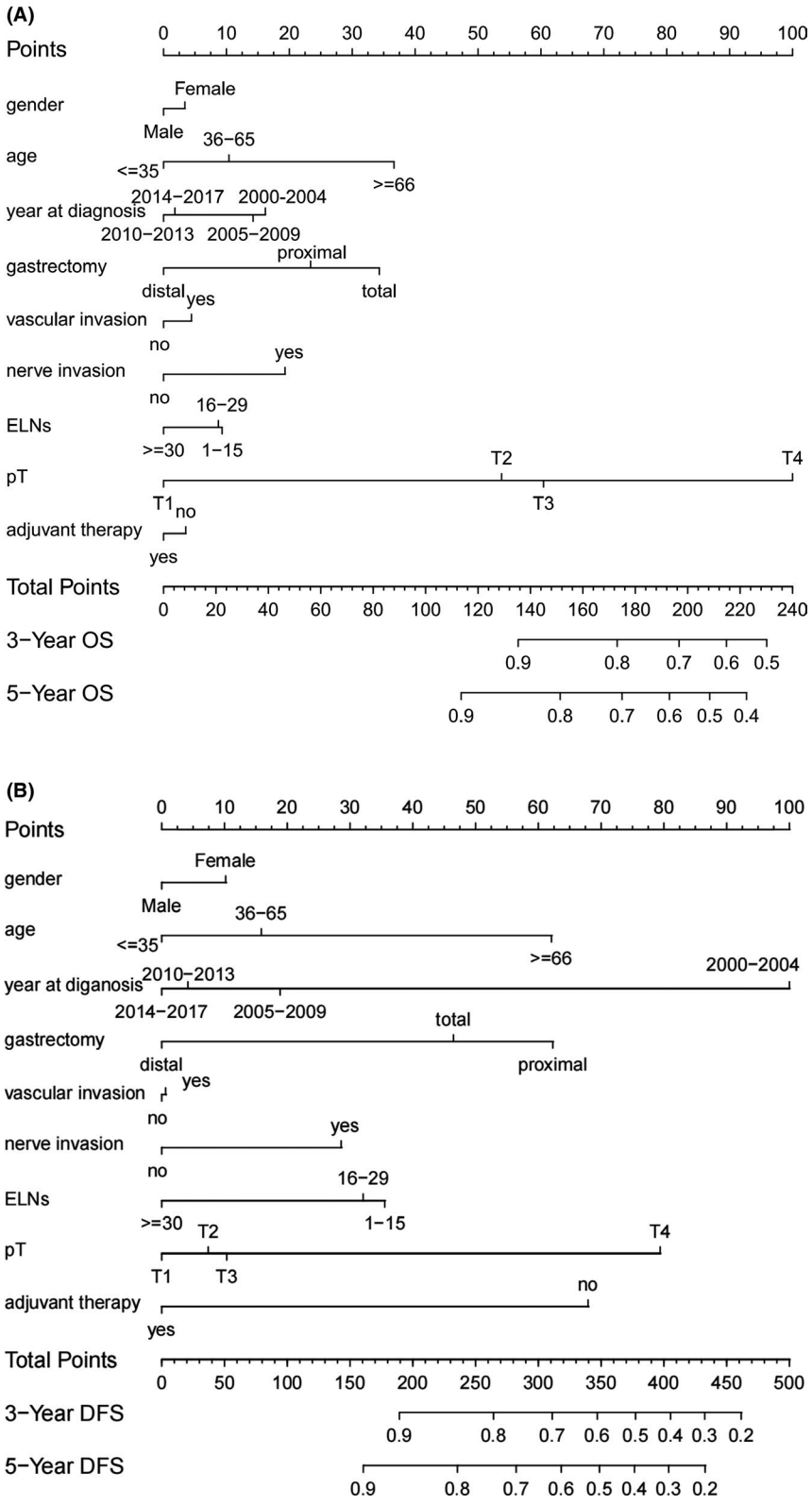

FIGURE 6 Prognostic nomogram for pN0 gastric cancer patients. A, OS nomogram. B, DFS nomogram

ORCID

Lulu Zhao https://orcid.org/0000-0001-8344-0498
Weili Han https://orcid.org/0000-0002-0708-5268
Yingtai Chen https://orcid.org/0000-0002-4342-4335

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