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Peripheral T Lymphocyte Predicts the Prognosis of Gastric Cancer Patients Undergoing Radical Gastrectomy: A Multicenter Retrospective Cohort Study

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Objective: The aim of this study was to investigate the predictive value of peripheral lymphocyte subsets for prognosis of gastric cancer (GC) patients following radical gastrectomy.

Methods: Consecutive GC patients received curative resection and examined peripheral lymphocyte subsets in Hunan Cancer Hospital were enrolled as training cohort (n=231), and those from Wuhan Union Hospital and Wuhan Tongji Hospital were included as external validation cohort (n=159). The optimal cutoff values of lymphocyte subsets for overall survival (OS) in training cohort were determined by X-tile. The independent predictive factors for OS were identified using univariate and multivariate Cox regression analyses. Furthermore, the predictive value of lymphocyte subsets were evaluated in validation cohort.

Results: The optimal cutoff value of T lymphocytes for OS was 0.84×10^9/L in the training cohort. Decreased T lymphocyte ($<0.84\times10^9$/L) were identified as an independent predictor for unfavorable prognosis both in the training and validation cohorts (HR:2.835, 95% CI:1.580–5.087, $P<0.001$; HR:2.470, 95% CI:1.069–5.711, $P=0.034$). In the entire cohort, stratified analyses revealed that lower T lymphocyte negatively affected the oncological outcomes in patients with stage II/III disease. A synergistic influence was confirmed in those with decreased T lymphocyte and not received adjuvant chemotherapy (AC). Further analyses revealed that AC significantly prolonged OS in stage II/III patients with decreased T lymphocyte, but not in those with relatively higher T lymphocyte.

Conclusion: Peripheral T lymphocyte numbers was a reliable predictor for OS in GC patients undergoing radical gastrectomy. Additionally, T lymphocyte might serve as an indicator for efficacy of AC in stage II/III GC patients.

Keywords: gastric cancer, gastrectomy, lymphocyte subsets, adjuvant chemotherapy, overall survival

Introduction

Gastric cancer (GC) ranks as the fifth most common and fourth leading cause of cancer-caused death globally, with gastrectomy offering the only possible curative management.[1] Although more than 80% of pathological tumor, node and

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metastasis (TNM) stage I GC patients were expected to survive for more than 5 years, about 22% to 70% of patients with stage IIA to IIIC disease die within 5 years, even after undergoing surgery and adjuvant chemotherapy (AC).[2] Unfortunately, about 70% of GC patients are diagnosed with GC at an advanced stage in Western countries and in China.[3,4] The pTNM classification system was considered to be the most promising prognostic indicator, but it is not uncommon to encounter patients with significantly different oncological outcomes, even with the same tumor stage and management strategies. On the other hand, immunosuppression is common in cancer patients and much evidence has shown that the immune status also remarkably affects the prognosis of various cancers.[5–7] The peripheral absolute lymphocyte count is considered to be a simple but reliable systemic immunity indicator.[8] Additionally, several lymphocyte-based indexes, such as the prognostic nutritional index (PNI), neutrophil to lymphocyte ratio (NLR), Co-PaL score and so on have been proposed and confirmed to be independent prognostic indicators for GC patients.[9–12]

Recent research has further investigated the predictive value of peripheral lymphocyte subsets for prognosis in a number of malignancies, such as non-small cell lung cancer (NSCLC), colon cancer and prostate cancer, etc.[13–15] However, the conclusions drawn were not consistent, possibly due to the significantly different clinicopathological characteristics of enrolled patients and the cutoff values for lymphocyte subsets. Zhang et al assessed the relationships between lymphocyte subsets, surgical outcomes and short-term survival of GC patients.[16,17] However, the sample size was relatively small and the research was conducted in a single hospital. More importantly, due to the lack of external validation, the generalizability of the conclusions still requires unequivocal evaluation.

The present retrospective study was therefore conducted to explore the predictive role of peripheral lymphocyte subsets for the prognosis of GC patients who underwent curative resection, using a relatively large sample size of patients from one tertiary hospital in China. Moreover, patients from another two tertiary hospitals in China were enrolled as the external validation cohort to strengthen our conclusions.

Study Subjects and Methods

Study Design

The medical records of consecutive patients with pathologically diagnosed GC with characterized peripheral lymphocyte subsets, in Hunan Cancer Hospital from January 2019 to December 2022, in Wuhan Union Hospital from June 2018 to November 2021 and in Wuhan Tongji Hospital from July 2020 to August 2021 were reviewed. The inclusion criteria were as follows: (1) patient age ≥ 18 years, (2) pathologically confirmed gastric adenocarcinoma, (3) examined peripheral total or T lymphocyte subsets; and (4) undergoing radical gastrectomy. The exclusion criteria were: (1) stage IV disease; (2) patient underwent only exploratory laparoscopy or palliative resections; (3) had other simultaneous malignancies; (4) active infection or autoimmune diseases; (5) missing important clinicopathological data and (6) lost follow-up or death within 30 days after surgery. Patients from Hunan Cancer Hospital were nominated as the training group, and those from Wuhan Union Hospital or Wuhan Tongji Hospital were enrolled into the validation group. This study was approved by the ethics committee of our hospitals. Written informed consent for surgery and using their clinical, pathological and follow-up data were obtained from all patients before surgery. The study complies with the Declaration of Helsinki. The retrospective cohort study was registered in the Research Registry (www.researchregistry.com) with the identifier of researchregistry10121 and described according to the STROCSS criteria.[18]

Data Collection

Data on patients' demographics, clinicopathological and follow-ups were retrospectively collected from the medical records. The main strategies for peri-operative treatment and follow-up have been described in our previous studies.[3,11,16,17] Briefly, routine blood tests, albumin concentrations, peripheral total or T lymphocyte subset numbers were generally measured on the first day after admission. The proportions of T lymphocyte (CD3+ cells), CD4+ lymphocyte (CD3+CD4+ cells), CD8+ lymphocyte (CD3+CD8+ cells), B lymphocyte (CD3-CD19+ cells), and natural killer (NK) lymphocyte (CD3-CD16+CD56+ cells) were evaluated by flow cytometry as described in one of our previous studies.[16] All surgical procedures were performed in keeping with standard guidelines and staged according to the 8th edition of the TNM classification system.[19–21] Post-operative complications were carefully documented and assigned

according to the Clavien-Dindo grading system.[22] AC was generally started about 4 weeks after surgery for pTNM stage II or III disease, using platinum- and fluorouracil-based drugs, such as S-1 and oxaliplatin (SOX) or capecitabine and oxaliplatin (CapOx) combinations.[3,11,23] Overall survival (OS) time was calculated from the day of an operation to death of the patient or the last follow-up time (December 2023), whichever occurred first.

Statistical Analyses

A χ^2 test, Fisher's exact test or a Student's *t*-test were employed to compare differences in categorical or continuous variables between groups. The optimal cut-off values of the total lymphocyte count or lymphocyte subsets were determined by X-tile (3.6.1 software 20, http://medicine.yale.edu/lab/rimm/research/software.aspx), as previously described.[12,24] Independent prognostic indicators were identified using univariate and multivariate Cox regression analyses. In addition, variance inflation factor (VIF) was calculated to assess the collinearity variables in the multivariable analysis, with VIF < 5 was considered to have insignificantly collinearity. The OS rates between groups were compared by Kaplan-Meier analyses and Log rank tests. Data analyses were performed using R version 4.0.1 or SPSS version 27.0 software. A two-tailed *P*-value < 0.05 was deemed to be statistically significant.

Results

Characteristics of Patients

A total of 231 consecutive patients from the Hunan Cancer Hospital were nominated as the training dataset and 159 consecutive patients from Wuhan Union Hospital (n = 107) or Wuhan Tongji Hospital (n = 52) as the validation dataset. The detailed flowchart of patients are shown in Supplementary Figure 1. As shown in Table 1, the 390 patients had a mean age of 58.30 years (range, 23–84), a mean body mass index (BMI) of 22.57 kg/m^2 (range, 14.53–32.05), and a mean post-operative hospital stay of 9.79 days (range, 5–52). The majority were male (65.6%), undergoing distal subtotal gastrectomy (70.5%) or through laparoscopy (74.1%). There was stage I disease in 133 patients (33.6%), stage II in 81 (20.8%) patients and stage III in 178 (45.6%) patients, according to the 8th edition of TNM classification. The mean operative time was 226.78 min (range, 60–640), and the mean intra-operative blood loss was 132.22 mL (range, 10–800). Fifty-six patients (14.4%) suffered from Clavien-Dindo stage II or higher post-operative morbidities and 217 (55.6%) patients received AC.

As listed in Table 1, individuals in the validation cohort had significantly lower rates of comorbidities, total lymphocyte counts, CD4+ lymphocytes and albumin and hemoglobin concentrations. But with a higher CD4+/CD8+ cell ratio, patients were more likely to receive a laparoscopic procedure, undergo total gastrectomy, have longer operation times, less intra-operative bleeding, and more harvested lymph nodes (all $P < 0.05$). T lymphocyte numbers seemed to decrease in the validation cohort, but the apparent difference did not reach statistical significance ($1.20 \pm 0.45 \times 10^9$/L vs $1.12 \pm 0.40 \times 10^9$/L, $P = 0.081$).

Table 1 Clinicopathological Characteristics of the Entire Cohort (n = 390)

Variables	The Entire Cohort (n = 390)	Training Group (n = 231)	Validation Group (n = 159)`	*P* value
Gender (males)	256 (65.6%)	151 (65.4%)	105 (66.0%)	0.891
Age (years)	58.30 ±10.87	57.81 ±10.85	59.01 ±10.89	0.285
Body Mass Index (kg/m^2)	22.57 ±3.08	22.67 ±3.02	22.43 ±3.16	0.441
Any comorbidities	77 (19.7%)	61 (26.4%)	16 (6.9%)	<0.001
Pre-operative lymphocyte count (×10^9/L)	1.71 ±0.61	1.77 ±0.61	1.64 ±0.60	0.042
Total T lymphocyte count (×10^9/L)	1.17 ±0.43	1.20 ±0.45	1.12 ±0.40	0.081
CD4+ lymphocyte count (×10^9/L)	0.71 ±0.28	0.70 ±0.27	0.72 ±0.29	0.363
CD8+ lymphocyte count (×10^9/L)	0.39 ±0.22	0.42 ±0.24	0.33 ±0.16	<0.001
CD4+/CD8+ cell ratio	2.18 ±1.07	1.96 ±0.95	2.49 ±1.15	<0.001
B cell count		0.18 ±0.10*	0.24 ±0.17 †	NA
NK cell count		0.37 ±0.24*	0.27 ±0.20 †	NA

(*Continued*)

Table 1 (Continued).

Variables	The Entire Cohort (n = 390)	Training Group (n = 231)	Validation Group (n = 159)`	*P* value
Pre-operative albumin concentration (g/L)	39.91 ±4.39	40.90 ±4.16	38.48 ±4.33	<0.001
Pre-operative hemoglobin (g/L)	122.33 ±25.46	125.27 ±25.53	118.04 ±24.82	0.006
Operation method				<0.001
Open	101 (25.9%)	101 (43.7%)	0	
Laparoscopy	289 (74.1%)	130 (56.3%)	159 (100.00%)	
Type of resection				<0.001
Distal subtotal gastrectomy	275 (70.5%)	184 (79.7%)	91 (57.2%)	
Proximal subtotal gastrectomy	17 (4.4%)	2 (0.9%)	15 (9.4%)	
Total gastrectomy	98 (25.1%)	45 (19.5%)	53 (33.3%)	
Harvested lymph node number	22.45 ±10.09	18.84 ±6.95	27.76 ±11.55	<0.001
T stage‡				0.110
T1	116 (29.7%)	59 (25.5%)	57 (31.6%)	
T2	57 (14.6%)	37 (16.0%)	20 (12.6%)	
T3	88 (22.6%)	51 (22.1%)	37 (23.2%)	
T4	129 (33.1%)	84 (36.4%)	45 (19.2%)	
N stage‡				0.220
N0	161 (41.3%)	86 (37.2%)	75 (47.2%)	
N1	60 (15.4%)	39 (16.9%)	21 (13.2%)	
N2	64 (16.4%)	38 (16.5%)	26 (16.4%)	
N3	105 (26.9%)	68 (29.4%)	37 (23.3%)	
pTNM stage‡				0.250
I	131 (33.6%)	70 (30.3%)	61 (38.4%)	
II	81 (20.8%)	51 (22.1%)	30 (18.7%)	
III	178 (45.6%)	110 (47.6%)	68 (42.8%)	
Intra-operative blood loss (mL)	132.22 ±101.81	180.00 ±99.56	62.80 ±53.89	<0.001
Operation time (min)	226.78 ±90.88	177.87 ±50.09	297.85 ±90.01	<0.001
Post-operative complications§				0.406
None	334 (85.6%)	195 (84.4%)	139 (87.4%)	
Yes	56 (14.4%)	36 (15.6%)	20 (12.6%)	
Post-operative hospital stays (days)	9.79 ±3.93	9.76 ±2.80	9.82 ±5.15	0.877
Adjuvant chemotherapy				0.912
None	173 (44.4%)	103 (44.6%)	70 (44.0%)	
Yes	217 (55.6%)	128 (55.4%)	89 (56.0%)	

Notes: Data are presented as mean ±SD or n (%). NA, not available. * 220 patients in the training cohort were examined lymphocyte subsets, the remaining 11 patients were examined T lymphocyte subsets and missing the data of B cell and NK cell count. †52 patients in the validation cohort were examined lymphocyte subsets, the remaining 107 patients were examined T lymphocyte subsets and missing the data of B cell and NK cell count. ‡Tumor stages are based on 8th edition of the Union for International Cancer Control TNM classification. §Defined as Clavien-Dindo grade II or greater.

As shown in Table 2, patients with decreased T lymphocyte numbers (< 0.84×10^9/L, n = 79) were significantly older, with a lower total lymphocyte count, lower albumin and hemoglobin concentrations, and more advanced tumor stages (all $P < 0.05$). Whereas other clinicopathological factors, such as comorbidities, resection type, post-operative complications and AC were all comparable between the two groups.

Prognosticators in the Training Group

The median OS times were not available in the training group given a relatively short follow-up time of 25.0 months (range, 1–59). A total of 56 patients (24.2%) who died were evaluated, with 1-, 2-, 3- and 4-year OS rates of 88.6%, 78.8%, 73.6% and 68.8%, respectively. The cut-off values of total lymphocytes, T lymphocytes, CD4+ lymphocytes, CD8+ lymphocytes, B cells, NK cells and CD4+/CD8+ lymphocytes ratios for OS were set at 1.33×10^9/L, 0.84×10^9/L,

Table 2 Clinicopathological Characteristics of the Patients Classified by T Cell (CD3+ Lymphocyte) Count

Variables	Training Group (n = 231)			Validation Group (n = 159)			The Entire Cohort (n = 390)		
	T Cell ≥ 0.84 $\times10^9$/L Group (n = 188)	T Cell < 0.84 $\times10^9$/L Group (n = 43)	P value	T cell ≥ 0.84 $\times10^9$/L Group (n = 123)	T cell < 0.84 $\times10^9$/L Group (n = 36)	P value	T Cell ≥ 0.84 $\times10^9$/L Group (n = 311)	T Cell < 0.84 $\times10^9$/L Group (n = 79)	P value
Gender (males)	124 (66.0%)	27 (62.8%)	0.694	76 (61.8%)	29 (80.6%)	0.037	200 (64.3%)	56 (70.9%)	0.272
Age (years)	56.82 ±10.76	62.14 ±10.31	0.004	57.76 ±10.80	63.31 ±10.20	0.007	57.19 ±10.77	62.67 ±10.21	<0.001
Body Mass Index (kg/m^2)	22.78 ±3.05	22.21 ±2.91	0.265	22.62 ±3.20	21.77 ±3.00	0.158	22.71 ±3.10	22.01 ±2.94	0.069
Any comorbidities	49 (26.1%)	12 (27.9%)	0.805	11 (8.9%)	5 (13.9%)	0.386	60 (19.3%)	17 (21.5%)	0.657
Pre-operative lymphocyte count ($\times10^9$/L)	1.92 ±0.55	1.09 ±0.30	<0.001	1.80 ±0.54	1.08 ±0.39	<0.001	1.87 ±0.55	1.09 ±0.34	<0.001
Pre-operative albumin concentration (g/L)	41.12 ±4.01	39.96 ±4.69	0.101	38.98 ±4.30	36.78 ±4.08	0.007	40.27 ±4.25	38.51 ±4.68	0.001
Pre-operative hemoglobin (g/L)	128.43 ±23.51	111.47 ±29.47	<0.001	123.00 ±22.15	101.11 ±26.28	<0.001	126.28 ±23.10	106.75 ±28.36	<0.001
Operation method			0.454			1.000			0.876
Open	80 (42.6%)	21 (48.8%)		0 (0%)	0 (0%)		80 (25.7%)	21 (26.6%)	
Laparoscopy	108 (57.4%)	22 (51.2%)		123 (100.0%)	36 (100.0%)		231 (74.3%)	58 (73.4%)	
Type of resection			0.772			0.392			0.366
Distal subtotal gastrectomy	150 (79.8%)	34 (79.1%)		72 (58.5%)	19 (52.8%)		222 (71.4%)	53 (67.1%)	
Proximal subtotal gastrectomy	2 (1.1%)	0 (0%)		13 (10.6%)	2 (5.6%)		15 (4.8%)	2 (2.5%)	
Total gastrectomy	36 (19.1%)	9 (20.9%)		38 (30.9%)	15 (41.7%)		74 (23.8%)	24 (30.4%)	
Harvested lymph node number	18.87 ±7.20	18.70 ±5.78	0.882	27.87 ±11.56	27.38 ±11.69	0.828	22.43 ±10.16	22.53 ±9.83	0.937
pTNM stage*			0.030			0.058			0.003
I	64 (34.0%)	6 (14.0%)		53 (43.1%)	8 (22.2%)		117 (37.6%)	14 (17.7%)	
II	38 (20.2%)	13 (30.2%)		20 (16.3%)	10 (27.8%)		58 (18.6%)	23 (29.1%)	
III	86 (45.7%)	24 (55.8%)		50 (40.7%)	18 (50.0%)		136 (43.7%)	42 (53.2%)	
Intra-operative blood loss (mL)	180.21 ±100.75	179.07 ± 95.36	0.946	60.69 ±47.36	70.00 ± 72.19	0.363	132.94 ±102.14	129.37 ± 101.11	0.781
Operation time (min)	180.46 ±51.56	166.56 ±41.75	0.101	294.24 ±91.41	310.17 ±85.15	0.352	225.46 ±89.43	232.00 ±96.81	0.569
Post-operative complications†			0.889			0.788			0.814
None	159 (84.6%)	36 (83.7%)		108 (87.8%)	31 (25.2%)		267 (85.9%)	67 (84.8%)	
Yes	29 (15.4%)	7 (16.3%)		15 (12.2%)	5 (24.4%)		44 (14.1%)	12 (15.2%)	
Post-operative hospital stays (days)	9.68 ±2.70	10.09 ±3.21	0.390	9.85 ±5.72	9.72 ±2.41	0.893	9.75 ±4.16	9.92 ±2.86	0.728
Adjuvant chemotherapy (yes)	106 (56.4%)	22 (51.2%)	0.534	64 (52.0%)	25 (69.4%)	0.064	170 (54.7%)	47 (59.5%)	0.440

Notes: Data are presented as mean ± standard deviation or number (percentage, %). *Tumor stages are based on 8th edition of the Union for International Cancer Control tumor-node-metastasis classification. †Defined as Clavien-Dindo grade II or greater.

Abbreviation: pTNM, pathological tumor-node-metastasis.

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0.62×10^{9}/L, 0.34×10^{9}/L, 0.18×10^{9}/L, 0.51×10^{9}/L, and 2.16 by X-tile (Supplementary Figure 2). As shown in Table 3, univariate analyses revealed that the albumin and hemoglobin concentrations, T lymphocytes, CD4+ and CD8+ lymphocytes, B cells, the CD4+/CD8+ cell ratio, pTNM stage and post-operative complications potentially affected OS (all $P < 0.05$). Further multivariate Cox regression analyses incorporating these variables showed that only T lymphocyte numbers $< 0.84 \times 10^{9}$/L, a CD4+/CD8+ cell ratio < 2.16, stage III disease and post-operative complications were independent prognostic indicators for poor survival. Collinearity analysis demonstrated no collinearity among the variables.

Oncological Outcomes in the Validation Group

With a median follow-up time of 26.0 months (range, 1–55), 23 cases of death (14.5%) were recorded among the 159 patients in the validation dataset. The 1-, 2-, 3- and 4-year OS rates were 93.7%, 87.3%, 81.9% and 81.9%, respectively.

Table 3 Univariate and Multivariate Analyses of Prognostic Factors for Overall Survival in the Training Cohort (n = 231)

Variables	N	3-year OS Rate (%)	UV P value	MV HR (95% CI)	MV P value
Gender			0.934		
Male	151	73.4%			
Female	80	72.5%			
Age (years)			0.348		
< 65	161	74.6%			
≥ 65	70	69.2%			
Body mass index (kg/m^2)			0.095		
< 18.5	14	56.3%			
18.5–24.99	168	73.5%			
≥ 25.0	49	76.7%			
Comorbidities			0.274		
Yes	61	79.3%			
No	170	70.3%			
Hemoglobin (g/L)			0.010		0.550
≥ 100	191	77.2%		Reference	
< 100	40	49.6%		1.293 (0.645–2.589)	
Albumin level (g/L)			0.045		0.705
< 35	22	46.5%		Reference	
≥ 35	209	75.2%		0.767 (0.332–1.773)	
Lymphocyte count ($\times10^{9}$/L)			0.053		
≥ 1.33	158	76.5%			
< 1.33	73	64.4%			
Total T lymphocyte count ($\times10^{9}$/L)			0.001		<0.001
≥ 0.84	188	77.8%		Reference	
< 0.84	43	52.6%		2.835 (1.580–5.087)	
CD4+ lymphocyte count ($\times10^{9}$/L)			<0.001		0.826
< 0.62	101	61.5%		Reference	
≥ 0.62	130	75.7%		0.769 (0.348–1.698)	
CD8+ lymphocyte count ($\times10^{9}$/L)			0.032		0.666
≥ 0.34	137	74.6%		Reference	
< 0.34	94	67.2%		1.202 (0.503–2.875)	
CD4+/CD8+ cell ratio			0.026		0.006
≥ 2.16	77	81.1%		Reference	
< 2.16	154	67.2%		2.416 (1.309–4.836)	

(*Continued*)

Table 3 (Continued).

Variables	N	3-year OS Rate (%)	UV P value	MV HR (95% CI)	MV P value
B cell count ($\times 10^9$/L)*			0.004		0.053
≥ 0.18	92	82.4%		Reference	
< 0.18	128	64.9%		2.069 (0.999–4.284)	
NK cell count ($\times 10^9$/L)*			0.263		
≥ 0.51	40	62.2%			
< 0.51	180	74.6%			
pTNM stage†			<0.001		<0.001
I	70	98.5%		Reference	
II	51	91.5%		3.914 (0.432–35.436)	
III	110	48.7%		33.026 (4.536–240.436)	
Post-operative complications‡			<0.001		<0.001
No	195	76.9%		Reference	
Yes	36	49.5%		3.005 (1.618–5.579)	

Notes: *220 patients in the training cohort were examined lymphocyte subsets, the remaining 11 patients were examined T lymphocyte subsets and missing the data of B cell and natural killer cell count. †Tumor stages are based on 8th edition of the Union for International Cancer Control tumor-node-metastasis classification. ‡Defined as Clavien-Dindo grade II or greater.
Abbreviations: N, number; OS, overall survival; CI, confidence interval; HR, hazard ratio; UV, univariate analysis; MV, multivariate analysis; NK, natural killer; pTNM, pathological tumor-node-metastasis.

As shown in Supplementary Table 1, univariate analyses revealed that age, albumin and hemoglobin concentrations, total lymphocyte numbers, T lymphocytes, CD8+ lymphocytes and the pTNM stage were potential predictors for OS (all $P < 0.05$). Further multivariate Cox regression analyses were performed by analyzing the above-mentioned 7 variables; only a lower hemoglobin concentration (< 100 g/L), decreased T lymphocyte numbers (< 0.84 × 10^9/L) and an advanced pTNM stage (stage III) were confirmed negatively to influence OS. Collinearity analysis demonstrated no collinearity among the variables.

Oncological Outcomes in the Entire Cohort

Decreased T lymphocyte numbers (< 0.84 × 10^9/L), an advanced pTNM stage (stage III) and post-operative complications were independently associated with adverse prognosis in the entire cohort (Supplementary Table 2). Figure 1A shows that the prognosis of patients with lower T lymphocyte numbers (< 0.84 × 10^9/L) was significantly poorer comparing to those patients with higher T lymphocyte numbers ($P < 0.001$). After adjusting for age, albumin and hemoglobin concentrations, the total lymphocyte count, CD4+ and CD8+ lymphocytes, the pTNM stage and post-operative complications by multivariate Cox regression analyses, the difference of long-term oncological outcomes was still significant between the 2 groups (Supplementary Table 2, Figure 1B, $P = 0.001$). Further subgroup analyses revealed that there was a tendency of stage I patients with lower T lymphocyte numbers to have poorer prognosis, but the apparent difference failed to reach statistical significance (Figure 2A, n = 131, $P = 0.183$). Whereas in patients with stage II/III disease, T lymphocyte numbers significantly impacted OS times (Figure 2B, n = 259, $P = 0.017$). Collinearity analysis demonstrated no collinearity among the variables.

Associations Between T Lymphocyte, AC and Prognosis of Stage II/III GC Patients

Among the 259 patients with stage II or III diseases, decreased T lymphocyte (< 0.84 ×10^9/L) and stage III disease were confirmed to negatively impact the prognosis, while AC was a protective factor as described in Table 4. Unsurprisingly, patients with lower T lymphocyte counts and did not receive AC had the worst oncological outcomes. A synergistic influence was confirmed in these patients compared to those with T lymphocyte numbers < 0.84 × 10^9/L but who received AC (hazard ratio [HR]: 0.214, 95% CI: 0.119–0.387, $P < 0.001$). Further stratified analyses revealed that in patients with decreased pretreatment T lymphocyte numbers (n = 65), AC significantly improved the 3-year OS rate from 27.8% to 56.7% ($P < 0.001$). Whereas the 3-year OS rates were comparable among patients with relatively higher T lymphocyte numbers (≥ 0.84 × 10^9/L, n = 194) regardless of AC (72.5% vs 67.8%, $P = 0.437$) (Figure 3).

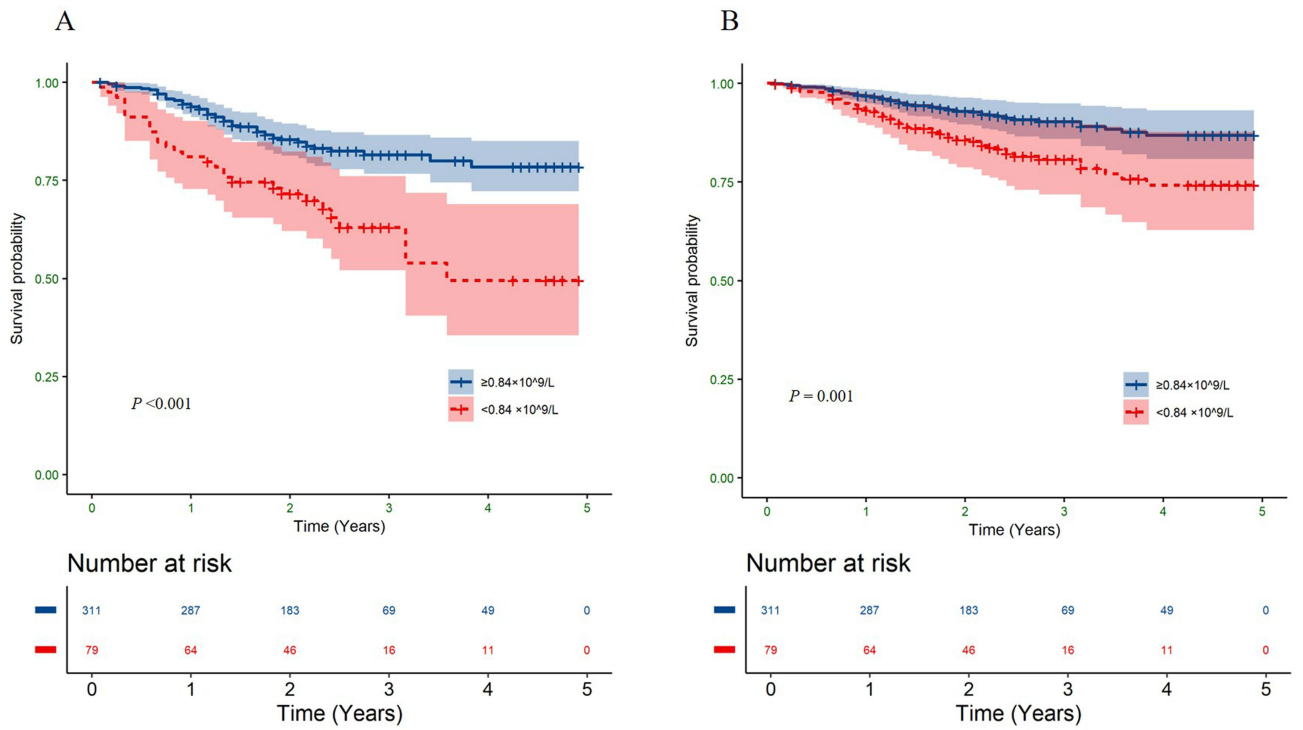

Figure 1 Over survival curves of the entire 390 gastric cancer patients who underwent curative resection stratified by peripheral T lymphocyte (< 0.84 or ≥ 0.84×10 ^{9}/L) before (**A**) and after adjusting for age, albumin and hemoglobin concentrations, total lymphocyte count, CD4+ and CD8+ lymphocyte, pTNM stage and post-operative complications (**B**).

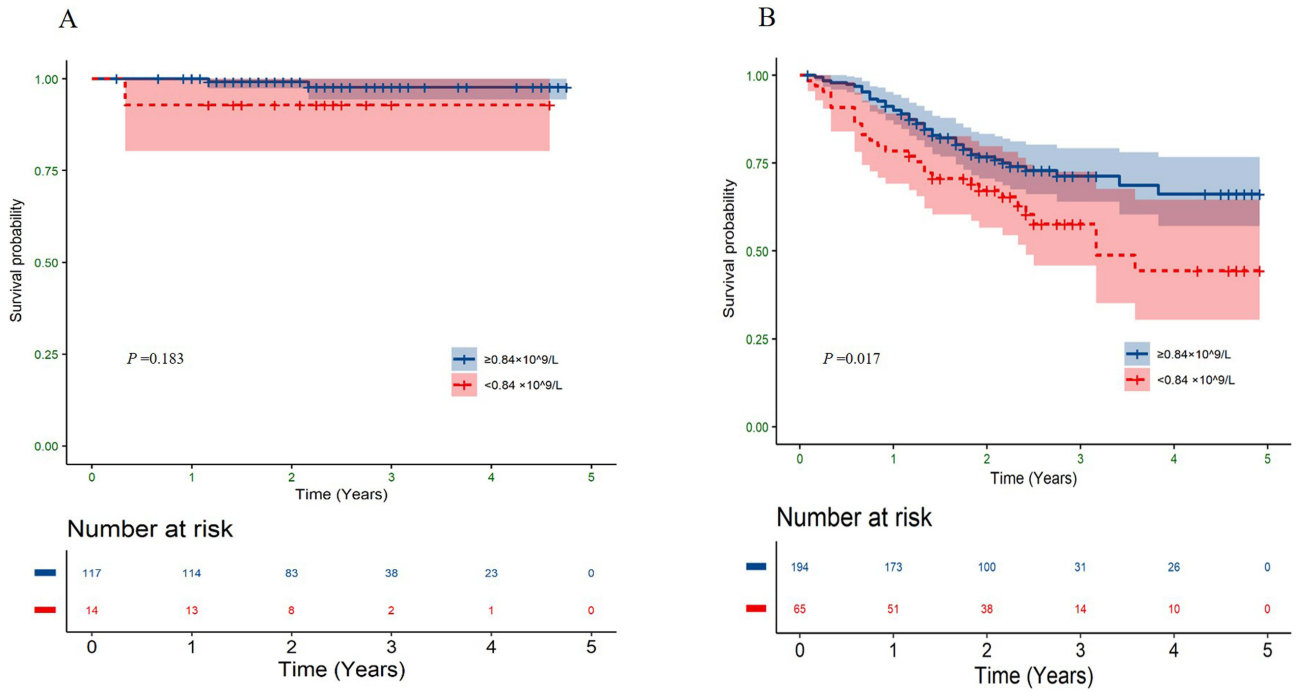

Figure 2 Over survival curves of the entire 390 gastric cancer patients who underwent curative resection stratified by peripheral T lymphocyte (< 0.84 or ≥ 0.84×10 ^{9}/L) in stage I (**A**) and stage II/III diseases (**B**).

Table 4 Univariate and Multivariate Analyses of Prognostic Factors for Overall Survival in Patients with Stage II/III Gastric Cancers (n = 259)

Variables	N	3-year OS Rate (%)	UV P value	MV HR (95% CI)	MV P value
Gender			0.559		
Male	174	63.9%			
Female	85	64.5%			
Age (years)			0.145		
< 65	177	67.3%			
≥ 65	82	57.9%			
Body mass index (kg/m^2)			0.359		
< 18.5	26	62.4%			
18.5–24.99	181	63.5%			
≥ 25.0	52	70.6%			
Comorbidities			0.255		
Yes	55	73.6%			
No	204	62.0%			
Hemoglobin (g/L)			0.027		0.134
≥ 100	197	68.1%		Reference	
< 100	62	42.2%		1.466 (0.900–2.389)	
Albumin level (g/L)			0.100		
≥ 35	219	66.7%			
< 35	40	61.2%			
Lymphocyte count (×10 ^{9}/L)			0.042		0.524
< 1.33	91	50.5%		Reference	
≥ 1.33	168	69.4%		0.670 (0.327–1.373)	
Total T lymphocyte count (×10^9/L)			0.017		0.002
≥ 0.84	194	68.7%		Reference	
< 0.84	65	48.4%		2.079 (1.301–3.324)	
CD4+ lymphocyte count (×10^9/L)			0.009		0.509
≥ 0.62	138	66.5%		Reference	
< 0.62	121	54.8%		1.413 (0.753–2.649)	
CD8+ lymphocyte count (×10^9/L)			0.059		
≥ 0.34	122	70.9%			
< 0.34	137	58.4%			
CD4+/CD8+ cell ratio			0.154		
≥ 2.16	103	69.2%			
< 2.16	156	61.4%			
pTNM stage[†]			<0.001		<0.001
II	81	88.2%		Reference	
III	178	50.9%		8.038 (3.455–18.700)	
Post-operative complication[‡]			0.006		0.079
No	215	68.6%		Reference	
Yes	44	42.4%		1.609 (0.943–2.745)	
Adjuvant chemotherapy			<0.001		<0.001
No	65	52.0%		Reference	
Yes	194	68.3%		0.394 (0.246–0.632)	

Notes: [†]Tumor stages are based on 8th edition of the Union for International Cancer Control tumor-node-metastasis classification. [‡]Defined as Clavien-Dindo grade II or greater.

Abbreviations: N, number; OS, overall survival; CI, confidence interval; HR, hazard ratio; UV, univariate analysis; MV, multivariate analysis. NA, not available; pTNM, pathological tumor-node-metastasis.

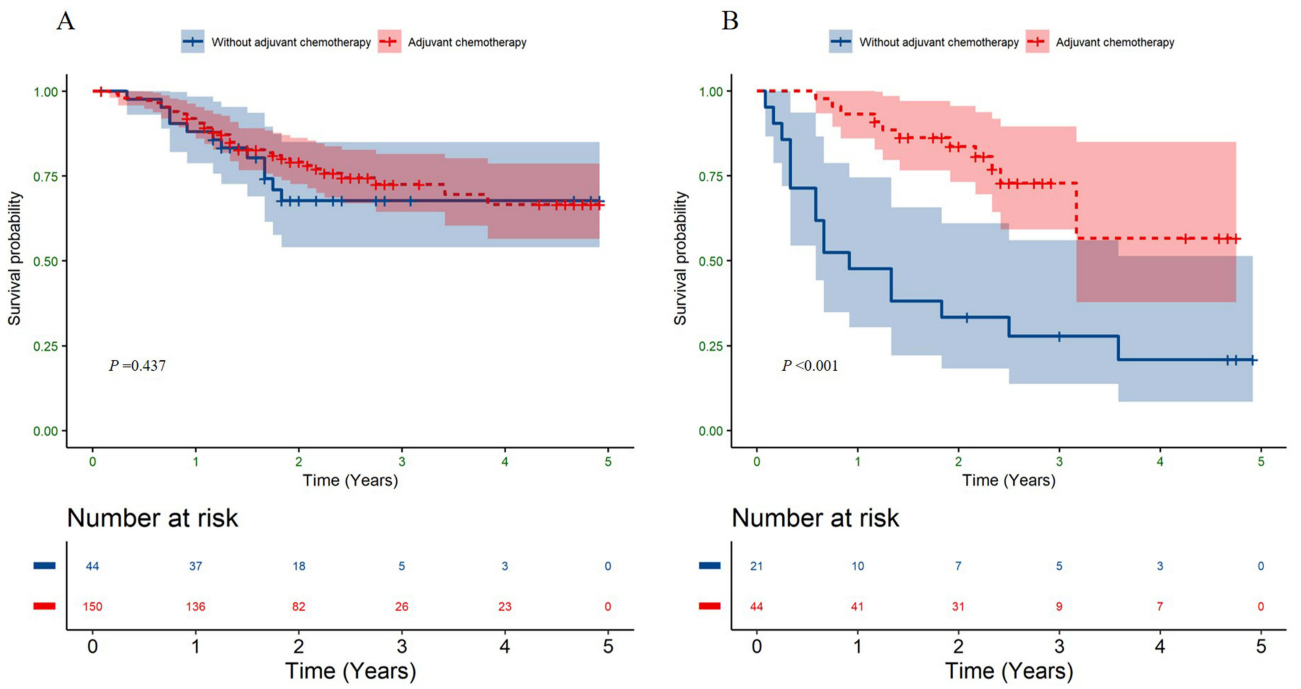

Figure 3 Over survival curves of the 259 stage II/III gastric cancer patients who underwent curative resection stratified by with or without adjuvant chemotherapy in those with peripheral T lymphocyte ≥ 0.84×10 ^{9}/L (**A**) and with peripheral T lymphocyte < 0.84×10 ^{9}/L (**B**).

Discussion

In this retrospective study based on a relatively large sample size of patients in three tertiary hospitals in China, decreased T lymphocyte numbers was revealed to be significantly associated with poorer patients' conditions, a more advanced tumor stage and unsatisfactory prognosis of GC patients following curative resection. In the external validation dataset of 159 patients, a T lymphocyte count < 0.84 × 10^9/L was also confirmed to influence negatively long-term outcomes. In the entire cohort and those with stage II or III disease, multivariate Cox regression analyses results lead to the same conclusion. Further analyses revealed that AC significantly improved the oncological outcomes of stage II/III patients with lower pretreatment T lymphocyte numbers, but the influence was not significant in those patients with T lymphocyte numbers ≥ 0.84 × 10^9/L. Taken together, these results of the present study confirmed that T lymphocytes were a valuable prognostic indicator for GC patients who underwent curative surgical resection. Further external, independent validation enhanced the reliability and generalizability of our findings. In addition, T lymphocyte numbers might serve as an indicator for the efficacy of AC in stage II/III GC patients.

Peripheral total lymphocyte count is a simple and commonly used index for assessing immunity. Lymphocytopaenia usually indicates an immunosuppressed condition attacking and eliminating cancer cells, and thus adversely affecting oncological outcomes.[8,12,25] In an observational study involving 791 patients with oropharyngeal cancer, Price et al[8] reported that the pretreatment absolute lymphocyte count was prognostic for OS and the predicted benefit of adding chemotherapy with cisplatin to radiotherapy. Further external validation from another hospital confirmed these conclusions. In one of our previous studies[12] and a study reported by Joseph et al,[26] pretreatment lymphocyte numbers < 1.5 × 10^9/L were identified as an independent adverse prognostic indicator for both GC and bladder cancer patients. The cutoff value for peripheral total lymphocyte count was set at 1.33 × 10^9/L in the training cohort in the present study and lymphocytopaenia was not found to be an independent prognostic indicator for OS in the training or validation cohorts (Table 3 and Supplementary Table 1). The possible explanations for the inconsistency of conclusions include different clinicopathological characteristics of enrolled patients and the cut-off values of lymphocyte numbers.

In recent years, increasingly studies have explored the association between lymphocyte subsets with oncological outcomes of various cancers. In a retrospective study involving 158 patients with metastatic colon cancer, circulating NK

cell numbers was found to be an independent prognostic indicator for OS, whereas T lymphocytes, CD4+ lymphocytes and B cells were not significantly related to the prognosis.[13] In another retrospective study of 136 stage IV NSCLC patients receiving immune checkpoint inhibitors, peripheral blood $CD4^{+}CD45RA^{-}$ T lymphocyte was found to be associated with the prognosis.[27] Zhang et al[28] analyzed the influence of lymphocyte subsets on 32,731 patients with liver cancer, rectal cancer or GC, etc. Multivariate analyses revealed that CD19+ lymphocytes had the most significant influence on OS of the total cohort. Whereas the exact lymphocyte subsets affecting prognosis for different types of cancers were not identical. For example, CD19+ and CD127+ lymphocytes were positive predictors for liver cancer. But for esophageal cancer, CD3+ and CD19+ lymphocytes were independent prognostic indicators. Significant differences in the inclusion criteria, the underlining diseases and management strategies might be responsible for the inconsistency of conclusions among different studies. Thus, conclusions must be cited with careful explanations in patients with GC.

There have also been several studies that investigated the influence of lymphocyte subsets on the prognosis of GC patients. In 2020, research revealed that the proportion of peripheral NK cells was significantly higher in 122 cases of GC than that in 80 healthy controls. Further analyses found that NK cells were independently related to the T stage and oncological outcomes of GC patients.[29] The conclusions were echoed by Sun et al,[30] who retrospectively probed the impact of lymphocyte subsets on the prognosis of 291 GC patients following surgery. In their study, T lymphocytes, CD8+ and NK lymphocyte numbers were found to be negatively associated with prognosis but CD19+ B cells positively associated with prognosis. Zhang et al[16] reported that decreased preoperative B cell numbers was an independent predictive marker for a prolonged postoperative hospital stay and complications in a prospective cohort study involving 137 GC patients who underwent laparoscopic D2 gastrectomy. In another study of 171 GC patients following curative resection, T lymphocyte and B cell counts and the regulatory T cell percentage were identified as significant predictors for disease free survival (DFS).[17] In contrast, Li et al[31] argued that peripheral CD4+ and CD8+ lymphocytes had no impact on OS and were just associated with the tumor size of 99 GC patients. One should bear in mind that previous similar studies were generally single-center, with relatively small sample sizes, and more important, lacking external validation. Thus, the association between lymphocyte subsets and the prognosis of GC remains controversial and deserves further investigation.

As far as we are aware, this was the first multicenter study to investigate the predictive value of lymphocyte subsets on the prognosis of GC, having the largest sample size to date. More importantly, this was the only study with external validation. Independent, external validation utilizing a cohort with significantly different clinicopathological characteristics from two other tertiary hospitals unequivocally established the promising predictive value of T lymphocyte numbers for prognosis. The T lymphocyte number, instead of B or NK cells, was confirmed as an independent predictor for OS of GC patients in the present study. The potential underlying mechanism may be that the capacity of the antigen-directed cytotoxicity of T lymphocytes played a crucial role in the human cellular adaptive immunity fight against cancer.[32] In retrospective research involving 598 lung cancer patients, a higher proportion of CD3+ cells ($\geq$ 67.25%) was proved to be a positive predictor for OS.[33] Liu et al[34] constructed a clinical nomogram based on 10 variables including the absolute count of T lymphocytes to predict OS in 1,685 NSCLC patients. The nomogram showed good discriminating ability between both the training and validation cohorts.

The mean number of T lymphocytes was significantly decreased in patients with stage II/III disease compared to those patients with stage I disease (1.12×10^9/L vs 1.25×10^9/L, $P = 0.004$). This finding indicated that the immune function was partially weakened by the advanced stage of cancer, as a result, favoring proliferation and metastasis.[35] Further stratified analyses revealed that the benefits of AC were limited to patients with decreased T lymphocyte numbers. Our findings are echoed by Tulyte et al,[36] who reported that gemcitabine produced better survival times for advanced pancreatic cancer patients with extremely low baseline CD8+CD57- lymphocyte counts. Wang et al[37] established a complex immune scoring system (ISS_{GC}) using 6 immunosuppressive ligands (CD44, CD155, etc.) in GC patients. Further analyses revealed that in stage II or III GC patients with high-ISS_{GC}, the difference of prognosis was not significant regardless of chemotherapy. Additionally, oropharyngeal cancer patients with decreased pretreatment absolute lymphocyte counts derived additional benefits from concurrent cisplatin chemotherapy plus radiotherapy, while those with a high lymphocyte count did not.[8] Although the underlining mechanisms have not been unequivocally clarified, increasing evidence suggests that the efficacy of conventional chemotherapy not only depends on direct cytotoxic effects but is also affected by the activation of tumor-targeting immune responses.[36] Another feasible explanation is that in patients with T lymphocyte numbers $\geq 0.84 \times 10^9$/L, the immune-stimulatory tumor environment itself could act as

a favorable predictor for patients undergoing curative resection, so they could not get further benefit from AC. Given that the immune micro-environment was not investigated in the present study, prospective evaluations are still needed.

Several limitations of the present study should be addressed. First, selective biases were inevitable because of their retrospective nature. Second, although AC was recommended as standard management for stage II or III GC, about a quarter of these patients did not receive AC. In addition, several chemotherapy regimen combinations were used during the study, which might also have influenced efficacy and thus acting as a confounding factor. Last, but by no means least, the median follow-up time of 26 months seemed too short to collect subsequent disease recurrence and deaths of patients, especially those with stage I disease. But 80% of recurrence of stage II/III GC occurred within three years after surgery.[38]

Conclusion

The present study found that decreased pretreatment peripheral T lymphocyte numbers ($< 0.84 \times 10^9$/L) was an independent prognostic indicator for unfavorable prognosis in GC patients who underwent curative resection surgery. The relatively large sample size of patients from multicenter tertiary hospitals and external validation improved the reliability of our findings. Further analyses revealed that T lymphocyte numbers can serve as an indicator for the efficacy of AC in stage II/III GC patients. But further studies are still needed to validate this conjecture and to investigate the exact underlying mechanisms.

Abbreviations

AC, Adjuvant chemotherapy; BMI, body mass index; CapOx, Capecitabine and oxaliplatin combination; CI, confidence interval; GC, Gastric cancer; HR, Hazard ratio; NLR, the neutrophil to lymphocyte ratio; NK, natural killer; NSCLC, non-small cell lung cancer; OS, overall survival; PNI, prognostic nutritional index; SOX, oxaliplatin and S-1 combination; TNM, tumor-node-metastasis.

Data Sharing Statement

The data used or analyzed during this study are included in this article and available from the corresponding author (J.L.) upon reasonable request.

Ethics Approval

This study was approved by the Clinical Research Ethics Committee of Hunan Cancer Hospital (No. 49 in 2024), Wuhan Union Hospital (2024 (0984)) and Wuhan Tongji Hospital (TJH20210109). Written informed consent for surgery and using their clinical, pathological and follow-up data were obtained from all patients before surgery. The study complies with the Declaration of Helsinki.

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Disclosure

The authors have no conflicts of interest directly relevant to this work.

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