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Original Article

Neoadjuvant PD-1 inhibitor plus apatinib and chemotherapy versus apatinib plus chemotherapy versus chemotherapy alone in patients with locally advanced gastric cancer

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Abstract: Programed cell death protein-1 (PD-1) inhibitor, apatinib, and chemotherapy show synergistic antitumor effect in gastric cancer. This study aimed to evaluate this combination as a neoadjuvant therapy in locally advanced gastric cancer (LAGC). In this retrospective study, data from 179 LAGC patients who underwent neoadjuvant therapy with a PD-1 inhibitor plus apatinib and chemotherapy (PAC group, n=56), apatinib and chemotherapy (AC group, n=50), or chemotherapy alone (C group, n=73) were analyzed. The PAC group displayed a numerically higher radiologic objective response rate than the AC group (73.2% vs. 60.0%, P=0.149) and significantly higher than the C group (73.2% vs. 35.6%, P<0.001). Tumor resection rates between the PAC and AC groups were not significantly different (100.0% vs. 94.0%, P=0.102) but were higher in the PAC group compared to the C group (100.0% vs. 89.0%, P=0.010). Pathological evaluations revealed comparable R0 resection rates across all groups (P=0.873) and a non-significantly higher pathological complete response rate in the PAC group compared to the AC group (26.8% vs. 17.0%, P=0.236), while significantly higher than the C group (26.8% vs. 7.7%, P=0.005). Moreover, the PAC group exhibited a longer progression-free survival compared to the AC (P=0.036) and C (P<0.001) groups, an extended disease-free survival compared to the C group (P=0.002), and improved overall survival compared to the AC (P=0.028) and C (P=0.002) groups. Adverse events were generally comparable, with the highest incidence of peripheral neuropathy observed in the PAC group (26.8%, P=0.020). PD-1 inhibitor plus apatinib and chemotherapy may represent an effective neoadjuvant regimen for LAGC management, necessitating further validation.

Keywords: Neoadjuvant therapy, programmed cell death protein-1 inhibitor, apatinib, chemotherapy, locally advanced gastric cancer

Introduction

Gastric cancer is a leading cause of cancer-related mortality worldwide, with incidence associated with various factors, including Helicobacter pylori infection, dietary habits, genetic predisposition, and environmental pollution [1-3]. Locally advanced gastric cancer (LAGC), or stage III gastric cancer, refers to a stage where the tumor has invaded the subserosal connective tissue or serosa, metastasized to one or more regional lymph nodes, yet has not metastasized distantly [4, 5]. Neoadjuvant chemotherapy is widely recommended for LAGC, providing greater opportunity for tumor resection and increasing R0 resection rate [6-8]. Despite these measures, the prognosis for patients with LAGC remains suboptimal [9-11], necessitating the investigation of more effective neoadjuvant therapies.

Developed in China, apatinib is an antiangiogenic agent that exhibits promising efficacy and tolerable safety for the systemic treatment of advanced LAGC [12-14]. In recent years, the neoadjuvant application of apatinib in LAGC patients has been explored [15-17]. For instance, neoadjuvant apatinib combined with chemotherapy yields an objective response rate (ORR) of 80.65% and a tumor diameter

reduction from baseline of 54.32±36.11 mm in LAGC patients [15]. Another study demonstrated a radiologic response rate of 75.0% and a pathological response rate of 54.2% in patients with LAGC treated with apatinib plus chemotherapy [16], highlighting the potential efficacy of an apatinib-containing regimen as neoadjuvant therapy.

Programmed cell death protein-1 (PD-1) inhibitor suppresses binding of PD-1 with its target ligands, suppressing tumor progression [18, 19]. Given its effective antitumor properties, the combination of a PD-1 inhibitor and chemotherapy as neoadjuvant therapy in LAGC patients has attracted research interest [20-22]. Recently, two studies evaluated the efficacy of a PD-1 inhibitor plus apatinib and chemotherapy as a neoadjuvant treatment in LAGC patients [17, 23]. However, these studies were single-armed, and the superiority of a PD-1 inhibitor plus apatinib and chemotherapy against other neoadjuvant regimens remains unconfirmed. Further evidence is required to substantiate the application of neoadjuvant PD-1 inhibitor plus apatinib and chemotherapy in LAGC.

Accordingly, this study aimed to compare the efficacy and safety of PD-1 inhibitor plus apatinib and chemotherapy against apatinib plus chemotherapy and chemotherapy alone as neoadjuvant regimens in patients with LAGC.

Materials and methods

Patients

In the current retrospective study, a total of 179 LAGC patients treated with neoadjuvant therapy of either chemotherapy, apatinib plus chemotherapy, or PD-1 inhibitor plus apatinib and chemotherapy between January 2019 and February 2023 were included in the study. Inclusion criteria were as follows: 1) diagnosed with gastric cancer or gastroesophageal junction carcinoma; 2) clinically staged as cT3~cT4a/cN1~cN3/cM0; 3) age of 18 years or above; 4) receipt of chemotherapy, apatinib and chemotherapy, or PD-1 inhibitor plus apatinib and chemotherapy as neoadjuvant therapy. Exclusion criteria included: 1) co-existing malignant diseases and 2) unavailable or inaccessible clinical data for analysis. The study received approval from the Ethics Committee. Written informed consent was obtained from the patients or their families.

Treatment and grouping

Patient demographics, disease history, disease characteristics, and treatment information were collected from electronic medical records. The patients were grouped based on the different neoadjuvant regimens: chemotherapy group (C group), apatinib and chemotherapy group (AC group), and PD-1 inhibitor plus apatinib and chemotherapy group (PAC group). Neoadjuvant therapy was delivered for 4 cycles (21 days/cycle). Specifically, chemotherapy involved administration of oxaliplatin plus S-1 (SOX) or oxaliplatin plus capecitabine (CAPOX), apatinib was orally administered at 250 mg/d, and sintilimab or camrelizumab was intravenously administered at 200 mg/cycle as a PD-1 inhibitor [17, 24]. All patients intended to receive neoadjuvant treatment followed by surgery, and thus surgery was not postponed by the neoadjuvant treatment.

Assessment

Radiologic responses were evaluated based on the collected imagological examination results, utilizing Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v.1.1). Surgical data were obtained from patients deemed suitable for surgical resection (C group, n=65; AC group, n=47; PAC group, n=56). The R0 resection rate and pathological responses were assessed in surgically treated patients, following the American Joint Committee on Cancer (AJCC) criteria and Japanese classification of gastric carcinoma respectively [25, 26]. Follow-up data were also collected, with the first follow-up occurring at 3 months post-surgery and subsequent follow-ups every 3-6 months thereafter. Disease-free survival (DFS), progression-free survival (PFS), and overall survival (OS) were determined based on survival data, with DFS defined as the period from surgery to relapse or death, PFS was determined for all patients as the time from neoadjuvant therapy to progression or death, and OS was determined for all patients as the duration from neoadjuvant therapy to death. Adverse events were also documented for safety assessment.

Statistical analyses

SPSS v20.0 (IBM Corp., USA) and GraphPad Prism v7.02 (GraphPad Inc., USA) were utilized for statistical analyses and data plotting respectively. Three-group comparisons were performed using a one-way analysis of variance test, Chi-square test, or Kruskal-Wallis H rank sum test. Pairwise comparisons were evaluated using the Chi-square test or Wilcoxon rank sum test. Kaplan-Meier curves with a log-rank test illustrated correlations of treatment with survival. Factors influencing PFS, DFS, or OS were determined using Cox's proportional hazard regression analysis, with parameters showing P<0.05 in the univariate regression models included in the multivariate regression model with enter mode. A *P* value <0.05 was considered statistically significant.

Results

Patient characteristics

The mean ages of patients in the C, AC, and PAC groups were 58.9±9.7, 59.1±9.9, and 58.2±8.7 years respectively, with comparable distribution of gender (males accounting for 75.3%, 74.0%, and 66.1%, respectively). A detailed analysis indicated that the demographic characteristics, medical histories, and disease characteristics did not significantly differ among these groups (all P>0.05) (**Table 1**).

Radiologic response comparison

The count and ratio of patients with CR, PR, SD, and PD in each group are provided in **Table 2**. Overall, the PAC group demonstrated superior radiologic response, followed by the AC group, with the C group having the least favorable response (P<0.001). Pairwise analysis revealed that the radiologic response showed improvement in the PAC group compared with AC group but did not reach statistical significance (P=0.084). Radiologic response was better in the PAC group compared to the C group (P< 0.001), and the AC group also showed improvement over the C group (P=0.006).

The ORRs for the PAC, AC, and C groups were 73.2%, 60.0%, and 35.6%, respectively. Statistically significant differences were found among the three groups (P<0.001). Moreover, pairwise analysis revealed that the ORR in the PAC group compared with the AC group, while higher in the PAC group, was not statistically significant (P=0.149); the PAC (P<0.001), and AC groups (P=0.008) exhibited a higher ORR compared to the C group.

The DCRs for the PAC, AC, and C groups were 100.0%, 94.0%, and 86.3%, respectively, which also significantly varied among the groups (P=0.011). DCR showed an improvement trend in PAC compared with the AC group, albeit without significance (P=0.102). The PAC group showed a higher DCR than the C group (P= 0.005), but there was no significant difference between AC and C groups (P=0.173) (**Table 2**).

Comparison of surgical information and pathological response

Among all patients, 56 (100.0%), 47 (94.0%), and 65 (89.0%) underwent tumor resection in the PAC, AC, and C groups, respectively. Three-group comparisons showed that the tumor resection rate was significantly different among groups (P=0.037). Meanwhile, the pairwise comparison revealed that tumor resection rate was elevated in the PAC group compared with AC group (P=0.102), and it was statistically higher in the PAC group compared with the C group (P=0.010). However, resection rates between the AC and C groups were not significantly different (P=0.522).

R0 resection rates in the PAC, AC, and C groups were comparable (94.6%, 93.6%, and 92.3%, respectively) with no statistical differences among or between the groups (all P>0.05).

Detailed pathological responses from grade 0-3 for each group are given in **Table 3**. Overall, the PAC group had the best pathological response, followed by the AC group, with the C group displaying the worst response (P<0.001) In addition, general pathological response was improved in the PAC group compared with AC group but, without statistical significance (P= 0.068). PAC and AC groups showed significantly better responses than the C group (P<0.001 and P=0.004, respectively).

The pCR rates for PAC, AC, and C groups were 26.8%, 17.0%, and 7.7% respectively, which

Table 1. Clinical characteristics

Items	C group (N=73)	AC group (N=50)	PAC group (N=56)	*P* value
Age (years), mean ± SD	58.9±9.7	59.1±9.9	58.2±8.7	0.878
Gender, No. (%)				0.477
Female	18 (24.7)	13 (26.0)	19 (33.9)	
Male	55 (75.3)	37 (74.0)	37 (66.1)	
Nationality, No. (%)				0.236
Han nationality	73 (100.0)	48 (96.0)	55 (98.2)	
Others	0 (0.0)	2 (4.0)	1 (1.8)	
History of smoke, No. (%)				0.665
No	50 (68.5)	37 (74.0)	37 (66.1)	
Yes	23 (31.5)	13 (26.0)	19 (33.9)	
History of drink, No. (%)				0.857
No	45 (61.6)	29 (58.0)	32 (57.1)	
Yes	28 (38.4)	21 (42.0)	24 (42.9)	
History of hypertension, No. (%)				0.496
No	47 (64.4)	36 (72.0)	41 (73.2)	
Yes	26 (35.6)	14 (28.0)	15 (26.8)	
History of hyperlipidemia, No. (%)				0.262
No	47 (64.4)	37 (74.0)	43 (76.8)	
Yes	26 (35.6)	13 (26.0)	13 (23.2)	
History of diabetes, No. (%)				0.639
No	62 (84.9)	45 (90.0)	50 (89.3)	
Yes	11 (15.1)	5 (10.0)	6 (10.7)	
H. pylori infection, No. (%)				0.284
Negative	44 (60.3)	26 (52.0)	26 (46.4)	
Positive	29 (39.7)	24 (48.0)	30 (53.6)	
ECOG PS score, No. (%)				0.665
0	50 (68.5)	31 (62.0)	39 (69.6)	
1	23 (31.5)	19 (38.0)	17 (30.4)	
Tumor site, No. (%)				0.851
Gastric	54 (74.0)	36 (72.0)	43 (76.8)	
GEJ	19 (26.0)	14 (28.0)	13 (23.2)	
Differentiation, No. (%)				0.209
Well	2 (2.7)	6 (12.0)	4 (7.1)	
Moderate	24 (32.9)	17 (34.0)	23 (41.1)	
Poor	47 (64.4)	27 (54.0)	29 (51.8)	
cT stage, No. (%)				0.470
cT3	24 (32.9)	12 (24.0)	14 (25.0)	
cT4a	49 (67.1)	38 (76.0)	42 (75.0)	
cN stage, No. (%)				0.136
cN1	26 (35.6)	14 (28.0)	11 (19.6)	
cN2	28 (38.4)	19 (38.0)	24 (42.9)	
cN3	19 (26.0)	17 (34.0)	21 (37.5)	
cM stage, No. (%)				-
cM0	73 (100.0)	50 (100.0)	56 (100.0)	
cTNM stage, No. (%)				-
cTNM III	73 (100.0)	50 (100.0)	56 (100.0)	

C, chemotherapy; AC, apatinib and chemotherapy; PAC, PD-1 inhibitor plus apatinib and chemotherapy; SD, standard deviation; H. pylori, helicobacter pylori; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GEJ, gastroesophageal junction; cT, clinical tumor; cN, clinical node; cM, clinical metastasis; cTNM, clinical tumor-node-metastasis.

Table 2. Clinical response by RECIST v.1.1

Items	C group	AC group	PAC group	*P* value			
				Three-group	PAC group vs. AC group	PAC group vs. C group	AC group vs. C group
Assessed patients	73	50	56				
Clinical response by RECIST v.1.1, No. (%)				<0.001	0.084	<0.001	0.006
CR	0 (0.0)	1 (2.0)	3 (5.4)				
PR	26 (35.6)	29 (58.0)	38 (67.9)				
SD	37 (50.7)	17 (34.0)	15 (26.8)				
PD	10 (13.7)	3 (6.0)	0 (0.0)				
ORR, No. (%)				<0.001	0.149	<0.001	0.008
Yes	26 (35.6)	30 (60.0)	41 (73.2)				
No	47 (64.4)	20 (40.0)	15 (26.8)				
DCR, No. (%)				0.011	0.102	0.005	0.173
Yes	63 (86.3)	47 (94.0)	56 (100.0)				
No	10 (13.7)	3 (6.0)	0 (0.0)				

RECIST v.1.1, Response Evaluation Criteria for Solid Tumors version 1.1; C, chemotherapy; AC, apatinib and chemotherapy; PAC, PD-1 inhibitor plus apatinib and chemotherapy; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

Table 3. Surgery information and pathological response

Items	C group	AC group	PAC group	*P* value			
				Three-group	PAC group vs. AC group	PAC group vs. C group	AC group vs. C group
Assessed patients	73	50	56				
Surgical resection, No. (%)	65 (89.0)	47 (94.0)	56 (100.0)	0.037	0.102	0.010	0.522
Assessed patients	65	47	56				
R0 resection, No. (%)	60 (92.3)	44 (93.6)	53 (94.6)	0.873	1.000	0.724	1.000
Pathological response, No. (%)				<0.001	0.068	<0.001	0.004
Grade 0	6 (9.2)	0 (0.0)	0 (0.0)				
Grade 1	23 (35.4)	10 (21.3)	5 (8.9)				
Grade 2	31 (47.7)	29 (61.7)	36 (64.3)				
Grade 3	5 (7.7)	8 (17.0)	15 (26.8)				
pCR, No. (%)	5 (7.7)	8 (17.0)	15 (26.8)	0.019	0.236	0.005	0.128

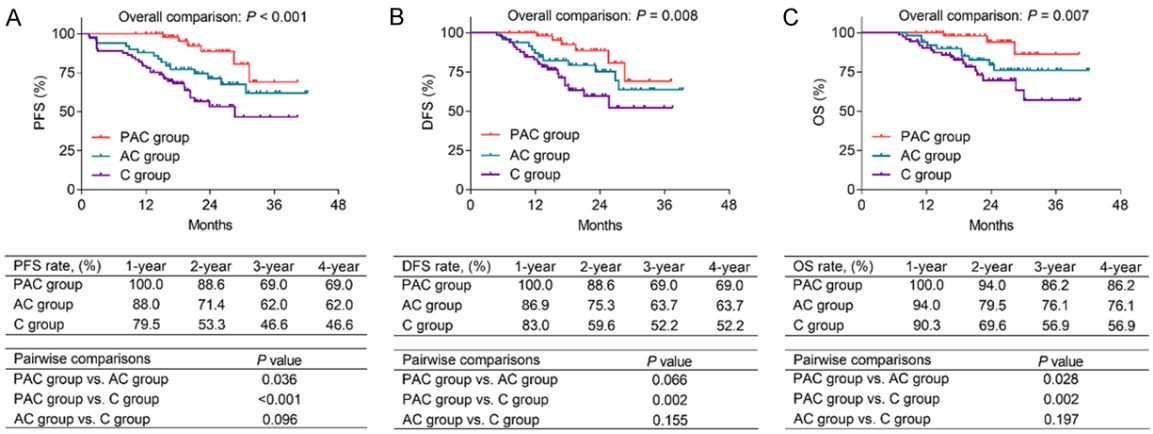
C, chemotherapy; AC, apatinib and chemotherapy; PAC, PD-1 inhibitor plus apatinib and chemotherapy; pCR, pathological complete response.

were significantly different among the three groups (P=0.019). Pairwise comparison illustrated that the pCR rates were not statistically significant between the PAC and AC groups (P=0.236), while it was elevated in the PAC group compared with the C group (P=0.005). Additionally, the pCR rates showed a non-significant increase in the AC group compared with C groups (P=0.128) (**Table 3**).

Comparison of survival

In overall survival analysis, PFS was the longest in the PAC group, followed by the AC group, and was shortest in the C group (P<0.001); it was longer in the PAC group than in the AC group (P=0.036) and C group (P<0.001). However, PFS did not significantly differ between the AC and C groups (P=0.096) (**Figure 1A**).

DFS was best in the PAC group, followed by the AC group, and worst in the C group (P=0.008). Pairwise comparisons showed that DFS was prolonged in the PAC group compared with the AC group but did not reach statistical significance (P=0.066). PAC demonstrated a significantly improved DFS compared to the C group (P=0.002). The AC group showed a non-significant prolongation compared with C group (P=0.155) (**Figure 1B**).



PFS rate, (%)	1-year	2-year	3-year	4-year
PAC group	100.0	88.6	69.0	69.0
AC group	88.0	71.4	62.0	62.0
C group	79.5	53.3	46.6	46.6

Pairwise comparisons	*P* value
PAC group vs. AC group	0.036
PAC group vs. C group	<0.001
AC group vs. C group	0.096

DFS rate, (%)	1-year	2-year	3-year	4-year
PAC group	100.0	88.6	69.0	69.0
AC group	86.9	75.3	63.7	63.7
C group	83.0	59.6	52.2	52.2

Pairwise comparisons	*P* value
PAC group vs. AC group	0.066
PAC group vs. C group	0.002
AC group vs. C group	0.155

OS rate, (%)	1-year	2-year	3-year	4-year
PAC group	100.0	94.0	86.2	86.2
AC group	94.0	79.5	76.1	76.1
C group	90.3	69.6	56.9	56.9

Pairwise comparisons	*P* value
PAC group vs. AC group	0.028
PAC group vs. C group	0.002
AC group vs. C group	0.197

Figure 1. Survival among groups in patients with LAGC. Comparison of PFS (A), DFS (B), and OS (C) among patients receiving neoadjuvant PAC, AC, and C. LAGC, locally advanced gastric cancer; PFS, progression-free survival; DFS, disease-free survival; OS, overall survival; P, programmed cell death-1 inhibitor; A, apatinib; C, chemotherapy.

OS was best in the PAC group, followed by the AC group, and worst in the C group (P=0.007). The PAC group had a longer OS than both the AC (P=0.028) and C (P=0.002) groups, while the AC and C groups did not significantly differ in OS (P=0.197) (**Figure 1C**).

Survival analysis after adjustment

Compared to the PAC neoadjuvant treatment, both AC (P=0.038, hazard ratio (HR) =2.722) and C (P<0.001, HR=4.808) treatments were associated with worse PFS (**Figure 2A**). Further, multivariate Cox regression analysis identified neoadjuvant treatment of AC (P=0.028, HR=2.903) and C (P<0.001, HR=6.586) as independently associated with shorter PFS compared to PAC (**Figure 2B**).

For DFS, neoadjuvant treatment of C (P=0.005, HR=3.691), but not of AC (P=0.136, HR=2.112), was associated with unfavorable DFS compared with PAC (**Figure 3A**). After adjustment, neoadjuvant treatment of C (P=0.004, HR=3.872), but not neoadjuvant treatment of AC (P=0.104, HR=2.258), was independently associated with worse DFS compared to PAC (**Figure 3B**).

The univariate Cox regression model revealed a shorter OS for the C group (P=0.005, HR=5.651) compared to PAC (**Figure 4A**). Multivariate adjustment confirmed the C group (P=0.001, HR=7.944) as independently associated with worse OS (**Figure 4B**). However, the AC treatment was not associated with OS in either model when compared with PAC.

Comparison of adverse events

Table 4 outlines the incidences of adverse events in each group. Hypertension incidence was highest in the AC group (48.0%), followed by the PAC group (41.1%), and lowest in the C group (26.0%) (P=0.034). Peripheral neuropathy incidence was highest in the PAC group (26.8%), followed by the AC group (12.0%), and lowest in the C group (9.6%) (P=0.020). Other adverse events and incidences of grade 3-4 events were not statistically different among the groups (all P>0.05) (**Table 4**).

Discussion

The innovative strategy of combining a PD-1 inhibitor with apatinib as neoadjuvant therapy has shown promise in cancer treatment [17, 23, 27, 28]. For instance, this combination has achieved a major pathological response rate of 40% in patients with locally advanced resectable oral squamous cell carcinoma [27]. Furthermore, a phase II clinical trial demonstrated a major pathological response rate of 57% and a pCR rate of 23% in patients with resectable non-small cell lung cancer [28]. In the context of LAGC, a phase II pilot trial reported complete and major pathological response rates of 15.8% and 26.3%, respectively, using neoadjuvant PD-1 inhibitor plus apatinib and chemotherapy [17]. Another prospective cohort study

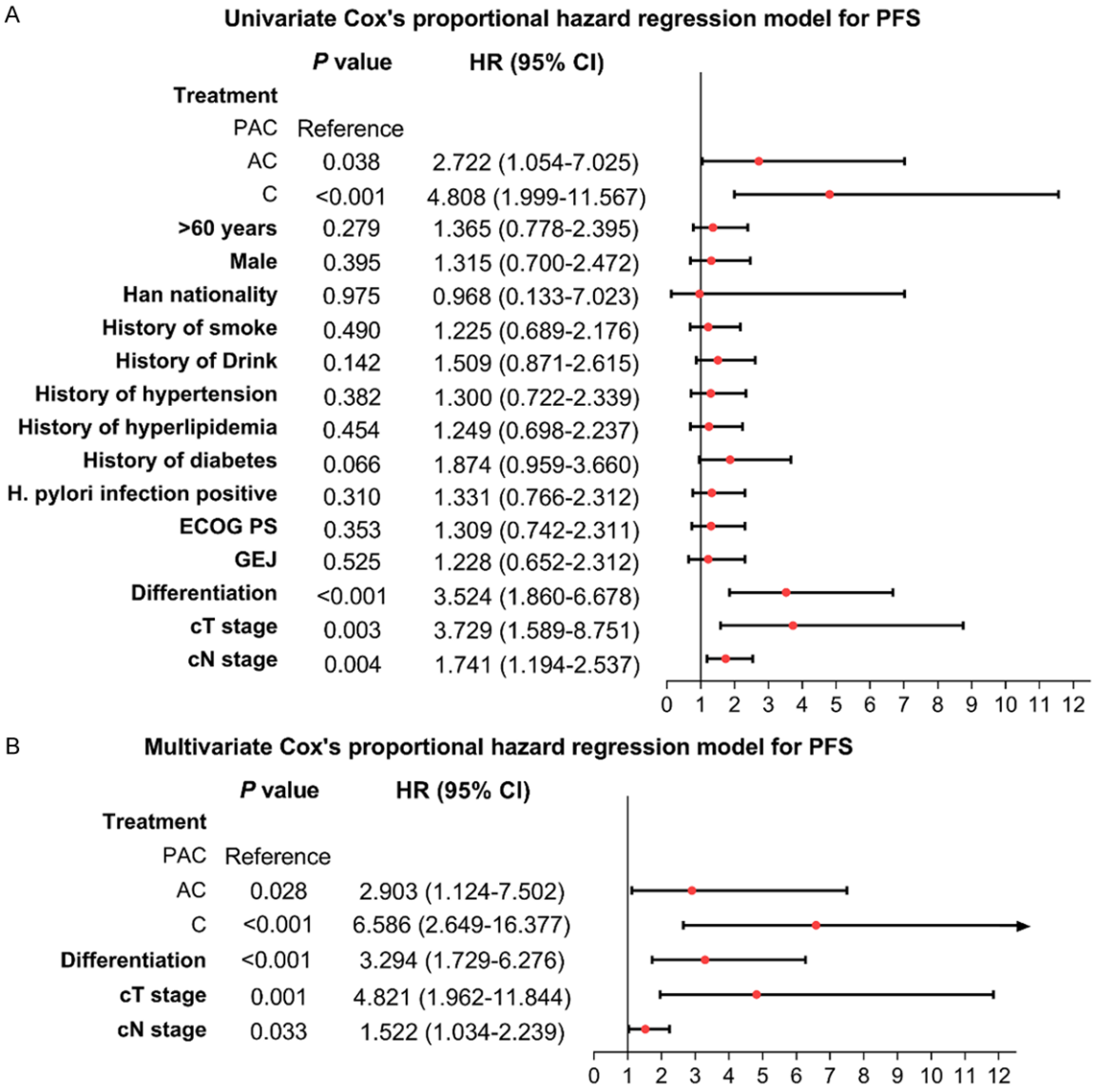
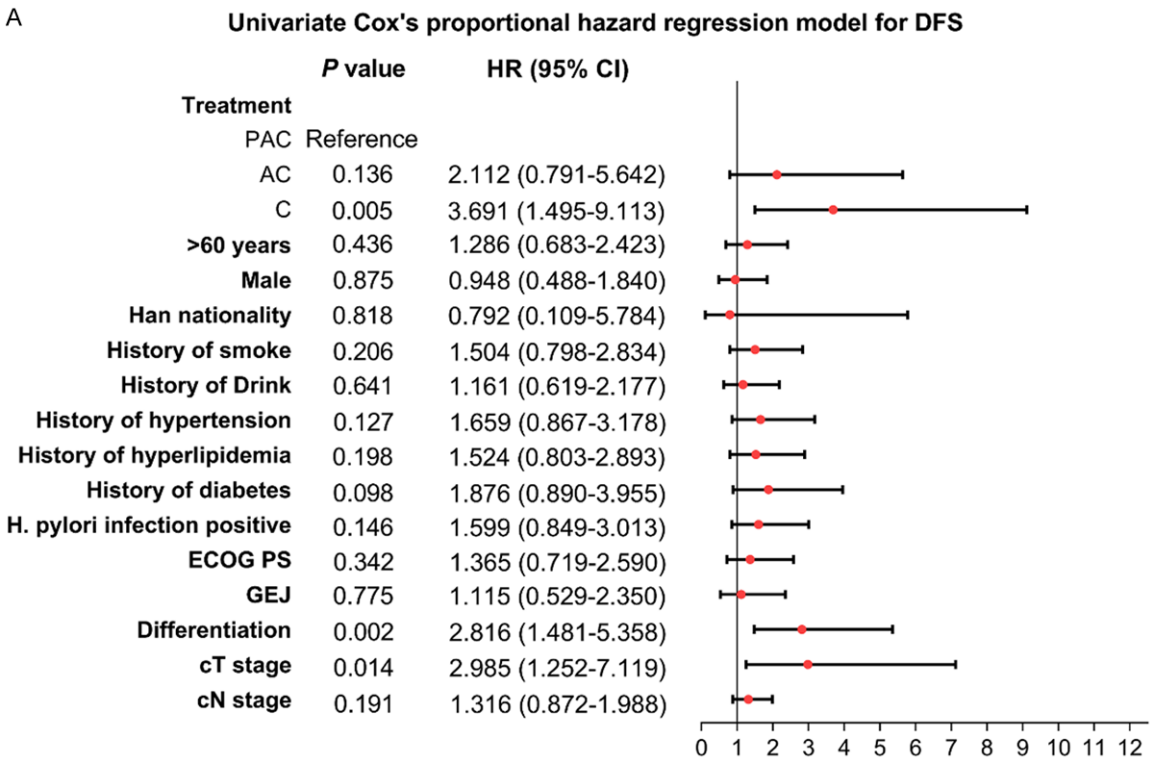


Figure 2. Factors related to PFS in patients with LAGC. Univariate (A) and multivariate (B) Cox regression models for PFS. Treatment refers to neoadjuvant regimens. LAGC, locally advanced gastric cancer; PFS, progression-free survival; P, programmed cell death-1 inhibitor; A, apatinib; C, chemotherapy; HR, hazard ratio; H. pylori, helicobacter pylori; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GEJ, gastroesophageal junction; cT, clinical tumor; cN, clinical node.

revealed an ORR of 66.7, DCR of 100.0%, and pCR rate of 20.0% [23]. These studies underscore the potential benefits of this neoadjuvant regimen in LAGC patients. However, a direct comparison of its efficacy with neoadjuvant apatinib plus chemotherapy and neoadjuvant chemotherapy alone, which is of high clinical relevance, has not been made.

This study found that the neoadjuvant PD-1 inhibitor plus apatinib and chemotherapy regimen improved radiologic and pathological responses in LAGC patients compared to the neoadjuvant chemotherapy regimen. It also showed some improvement over the neoadjuvant apatinib and chemotherapy regimen. These findings can be attributed to the different mechanisms through which PD-1 inhibitor plus apatinib and chemotherapy suppress tumors, such as restoration of CD8+ T-cell cytotoxicity, suppression of angiogenesis, and direct cytotoxicity, which may exert synergistic

A



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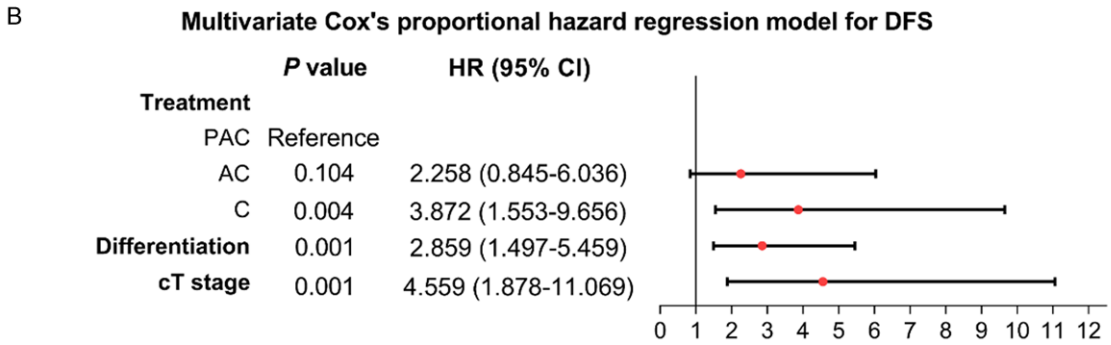

Figure 3. Factors related to DFS in patients with LAGC. Univariate (A) and multivariate (B) Cox regression models for DFS. Treatment refers to neoadjuvant regimens. LAGC, locally advanced gastric cancer; DFS, disease-free survival; P, programmed cell death-1 inhibitor; A, apatinib; C, chemotherapy; HR, hazard ratio; H. pylori, helicobacter pylori; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GEJ, gastroesophageal junction; cT, clinical tumor; cN, clinical node.

antitumor effects [29-31]. However, the small sample size of this study could affect the statistical power, and the superiority of the treatment response by the neoadjuvant PD-1 inhibitor plus apatinib and chemotherapy regimen did not reach statistical significance.

Despite the current guideline-recommended neoadjuvant chemotherapy, the survival rates of LAGC patients remain suboptimal [32, 33]. For example, the median DFS and OS are 28 months and 59 months, respectively, in LAGC patients who receive doublet neoadjuvant chemotherapy, and 34 months and 56 months in those who receive triplet neoadjuvant chemotherapy [32]. The CRITICS trial reported a median OS of 43 months in LAGC patients who receive neoadjuvant chemotherapy [33]. Our study observed improved survival in LAGC patients treated with the neoadjuvant PD-1 inhibitor plus apatinib and chemotherapy regimen, compared to those treated with neoadjuvant apatinib and chemotherapy or chemotherapy alone. This improvement was partly

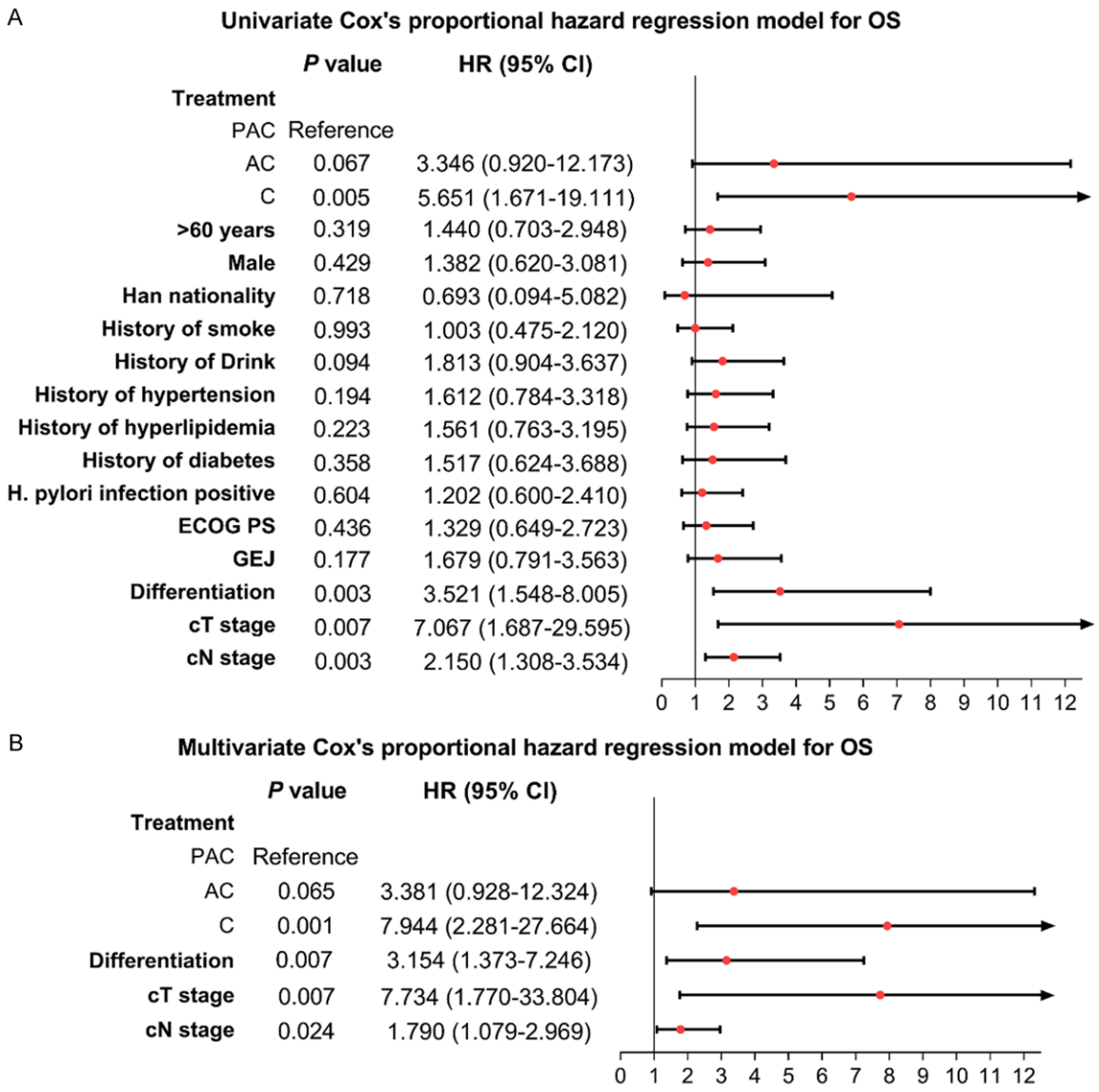

Figure 4. Factors related to OS in patients with LAGC. Univariate (A) and multivariate (B) Cox regression models for OS. Treatment refers to neoadjuvant regimens. LAGC, locally advanced gastric cancer; OS, overall survival; P, programmed cell death-1 inhibitor; A, apatinib; C, chemotherapy; HR, hazard ratio; H. pylori, helicobacter pylori; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GEJ, gastroesophageal junction; cT, clinical tumor; cN, clinical node.

confirmed by multivariate Cox regression models. The better treatment response achieved by the neoadjuvant PD-1 inhibitor plus apatinib and chemotherapy regimen could explain these results. However, the addition of PD-1 inhibitor to the neoadjuvant apatinib plus chemotherapy regimen only numerically improved DFS in LAGC patients. Therefore, future studies should explore the necessity and benefits of adding a PD-1 inhibitor to the neoadjuvant apatinib plus chemotherapy regimen in LAGC patients.

The safety of neoadjuvant treatment is a significant concern as it can impact the timing of tumor resection and patient outcomes [34-36]. Previous studies have reported mostly mild adverse events in LAGC patients receiving neoadjuvant PD-1 inhibitor plus apatinib and chemotherapy, including nausea and vomiting, fatigue, and neutropenia [17, 23]. In this study, the data revealed that the addition of PD-1 inhibitor to neoadjuvant apatinib plus chemotherapy regimen induced a higher peripheral neuropathy

Table 4. Adverse events

Adverse events	C group (N=73)			AC group (N=50)			PAC group (N=56)			P_1 value	P_2 value
	Total	Grade 1-2	Grade 3-4	Total	Grade 1-2	Grade 3-4	Total	Grade 1-2	Grade 3-4		
Hematological adverse events											
Leukopenia, No. (%)	30 (41.1)	28 (38.4)	2 (2.7)	24 (48.0)	24 (48.0)	0 (0.0)	26 (46.4)	23 (41.1)	3 (5.4)	0.715	0.247
Anemia, No. (%)	23 (31.5)	20 (27.4)	3 (4.1)	20 (40.0)	18 (36.0)	2 (4.0)	24 (42.9)	21 (37.5)	3 (5.4)	0.379	0.927
Neutropenia, No. (%)	20 (27.4)	18 (24.7)	2 (2.7)	14 (28.0)	12 (24.0)	2 (4.0)	17 (30.4)	15 (26.8)	2 (3.6)	0.930	0.924
Thrombocytopenia, No. (%)	22 (30.1)	22 (30.1)	0 (0.0)	11 (22.0)	11 (22.0)	0 (0.0)	11 (19.6)	11 (19.6)	0 (0.0)	0.344	-
Non-hematological adverse events											
Fatigue, No. (%)	28 (38.4)	26 (35.6)	2 (2.7)	22 (44.0)	21 (42.0)	1 (2.0)	33 (58.9)	31 (55.4)	2 (3.6)	0.062	0.886
Hypertension, No. (%)	19 (26.0)	19 (26.0)	0 (0.0)	24 (48.0)	20 (40.0)	4 (8.0)	23 (41.1)	21 (37.5)	2 (3.6)	0.034	0.053
Elevated transaminase, No. (%)	20 (27.4)	18 (24.7)	2 (2.7)	12 (24.0)	11 (22.0)	1 (2.0)	20 (35.7)	17 (30.4)	3 (5.4)	0.382	0.588
Hand-foot syndrome, No. (%)	20 (27.4)	20 (27.4)	0 (0.0)	22 (44.0)	21 (42.0)	1 (2.0)	18 (32.1)	18 (32.1)	0 (0.0)	0.154	0.273
Pruritus, No. (%)	18 (24.7)	18 (24.7)	0 (0.0)	11 (22.0)	11 (22.0)	0 (0.0)	16 (28.6)	16 (28.6)	0 (0.0)	0.733	-
Peripheral neuropathy, No. (%)	7 (9.6)	7 (9.6)	0 (0.0)	6 (12.0)	6 (12.0)	0 (0.0)	15 (26.8)	15 (26.8)	0 (0.0)	0.020	-
Nausea and vomiting, No. (%)	17 (23.3)	15 (20.5)	2 (2.7)	14 (28.0)	14 (28.0)	0 (0.0)	14 (25.0)	11 (19.6)	3 (5.4)	0.839	0.247
Diarrhea, No. (%)	10 (13.7)	10 (13.7)	0 (0.0)	10 (20.0)	10 (20.0)	0 (0.0)	14 (25.0)	13 (23.2)	1 (1.8)	0.262	0.331
Fever, No. (%)	6 (8.2)	5 (6.8)	1 (1.4)	8 (16.0)	6 (12.0)	2 (4.0)	12 (21.4)	10 (17.9)	2 (3.6)	0.102	0.626
Anorexia, No. (%)	8 (11.0)	8 (11.0)	0 (0.0)	7 (14.0)	7 (14.0)	0 (0.0)	7 (12.5)	7 (12.5)	0 (0.0)	0.879	-
Elevated bilirubin, No. (%)	6 (8.2)	6 (8.2)	0 (0.0)	4 (8.0)	4 (8.0)	0 (0.0)	7 (12.5)	7 (12.5)	0 (0.0)	0.652	-

P_1, comparisons for the occurrence rate of each adverse events among three groups; P_2, comparisons for the occurrence rate of grade 3-4 adverse events among three groups. C, chemotherapy; AC, apatinib and chemotherapy; PAC, PD-1 inhibitor plus apatinib and chemotherapy.

incidence, and the addition of apatinib to neoadjuvant chemotherapy regimen elevated hypertension incidence in patients with LAGC. The possible explanations include PD-1 inhibitor-induced autoreactive antibodies, cytotoxic T cells, and inflammatory cytokines that affect neurological integrity [37], and apatinib-induced activation of endothelin-1 and oxidative stress [38]. However, the adverse events were generally mild, suggesting that the benefits of the neoadjuvant PD-1 inhibitor plus apatinib and chemotherapy regimen may outweigh its toxicity in LAGC patients.

There were several limitations in this study that should be acknowledged. The small sample size may affect the statistical power, and the efficacy and safety of the neoadjuvant PD-1 inhibitor plus apatinib and chemotherapy regimen in LAGC patients should be validated in larger studies. Additionally, longer follow-up durations are needed to confirm the survival benefit of this regimen.

In conclusion, neoadjuvant administration of PD-1 inhibitor plus apatinib and chemotherapy shows a higher efficacy than neoadjuvant apatinib and chemotherapy or chemotherapy alone in patients with LAGC, but it also increases peripheral neuropathy risk to some extent. Application of this treatment regimen in LAGC patients shows promise and should be further validated by additional studies.

Disclosure of conflict of interest

None.

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