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Original Article

# Original Article

# Association between adjuvant chemotherapy and survival in stage I gastric cancer patients after curative resection

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## Abstract

**Background:** The efficacy of adjuvant chemotherapy (AC) on survival outcomes of patients with stage I gastric cancer (GC) after curative resection remains controversial. We aimed to determine whether these patients would benefit from AC.

**Methods:** This retrospective study included patients with pathologically confirmed stage I GC who underwent curative resection between November 2010 and December 2020. Patients were divided into AC and non-AC groups, then a 1:1 propensity score matching (PSM) analysis was performed to minimize the selection bias. Potential risk factors including age, pN stage, pT stage, lymphovascular invasion, perineural invasion, tumor size, histological type, and carcinoembryonic antigen level were used as matching covariates. The recurrence-free survival (RFS) and disease-specific survival (DSS) were compared between groups using the Kaplan–Meier method.

**Results:** A total of 902 consecutive patients were enrolled and 174 (19.3%) patients were treated with AC. PSM created 123 pairs of patients. Before PSM, patients receiving AC had lower 10-year RFS rates (90% vs 94.6%, $P = 0.035$) than those who did not receive AC; the two groups had similar 10-year DSS rates (93.8% vs 95.0%, $P = 0.240$). After PSM, there were no statistical differences in the 10-year RFS (90.9% vs 93.0%, $P = 0.507$) or DSS rates (93.5% vs 93.6%, $P = 0.811$) between the two groups. Similar results were found in the stage IA and IB subgroups. Moreover, these findings were not affected by AC cycles.

**Conclusions:** The addition of AC could not provide survival benefits for patients with stage I GC after surgery and follow-up is thus recommended. However, large-scale randomized clinical trials are required.

**Keywords:** gastric cancer; stage I; survival; adjuvant chemotherapy; propensity score matching

## Introduction

Gastric cancer (GC) is the fifth most-diagnosed malignancy and the fourth most-common cause of cancer-related deaths worldwide [1]. Despite declining incidence rates in most countries, clinicians can expect to see more GC cases in the future due to ageing populations [2]. The prevalence of endoscopic techniques associated with improved living conditions have contributed to more discoveries of early-stage GC [3, 4].

According to the eighth edition of the American Joint Committee on Cancer (AJCC) tumor-lymph node-metastasis (TNM) classification [5], stage I GC includes stage IA GC (T1N0) and stage IB GC (T1N1 and T2N0). The prognosis for patients with stage I GC after curative resection is promising, with expected 5-year survival rates of >90% [6]. Despite this relatively high survival rate, the outcome for patients who experience recurrence is poor. The post-operative recurrence rates for stage I GC have been reported to range from 2.2% to 7.6% [3, 6–8]. Some studies have identified significant risk factors for recurrence or death in stage I GC patients, such as age, pT stage, pN stage, lymphovascular invasion (LVI), perineural invasion (PNI), differentiation degree, and carcinoembryonic antigen (CEA) level [3, 6, 8–11]. They suggested that patients with risk factors should be considered candidates for adjuvant chemotherapy (AC). However, they did not further analyse whether AC had additional survival benefits for these patients. AC has become the standard treatment strategy for stage II and III GC patients after D2 resection, whereas there is no global consensus on AC for stage I GC due to a lack of randomized clinical trials with sufficient statistical power. Since the prognosis for early GC is excellent with resection alone, most clinical trials investigating the efficacy of post-operative chemotherapy for GC have excluded stage I GC patients [12–17]. According to the Japanese Gastric Cancer Association treatment

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guidelines [18] and the Korean GC guidelines [19], only follow-up is recommended for stage I GC patients who have undergone curative resection, whereas the National Comprehensive Cancer Network clinical practice guidelines [20] and the Chinese Society of Clinical Oncology (CSCO) GC treatment guidelines [21] recommend post-operative AC for high-risk stage I GC patients. Considering the treatment cost and chemotherapy-related adverse events, it is necessary to properly investigate the efficacy of AC in stage I GC patients.

Therefore, we aimed to evaluate the potential efficacy of AC for patients with stage I GC by comparing survival outcomes between patients who received AC and those who did not. We used the propensity score matching (PSM) method to produce two comparable groups at baseline to improve exchangeability of the results and minimized the selection bias in this retrospective cohort of stage I GC patients.

# Methods

## Study population and data sources

A total of 986 consecutive GC patients between November 2010 and December 2020 at Hunan Cancer Hospital were retrospectively collected. The inclusion criteria were as follows: (i) histopathologically confirmed stage I GC; (ii) with radical (R0) resection; and (iii) complete clinical and follow-up data. Patients were excluded if they met any of the following exclusion criteria: (i) endoscopic mucosal resection or endoscopic submucosal dissection as the initial surgical intervention; (ii) concurrence of other malignancies; and (iii) with a history of gastrectomy. The study protocol was approved by the ethics committee of Hunan Cancer Hospital (KYJJ-2022–276) and informed consent from patients was waived due to the retrospective nature of the work. This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline [22].

Patients' available clinical characteristics (sex, age, smoking status, body mass index, CEA level, lymphocyte count, and type of gastrectomy) and pathological findings (LVI, PNI, pN stage, number of examined lymph nodes, pT stage, tumor size, histological type, and tumor location) were collected from their medical records. Data were input by experienced clinicians and each record was audited by trained technical and medical expert panels. Missing data were coded as unknown variables and included in the analysis. The study cohort was restaged according to the 8th edition of the AJCC staging system. Histological type was divided into the differentiated type (papillary and tubular adenocarcinomas) and the undifferentiated type (poor differentiated, signet-ring cell carcinoma, and mucinous adenocarcinomas). LVI was assessed as positive when examination of the entire periphery of the tumor on the slides revealed tumor cells within endothelium-lined spaces [23]. PNI was assessed as positive when cancer cells were seen in the perineurium or neural fascicles intramurally [24]. The histopathological diagnosis was determined by experienced pathologists.

## Treatment procedures and follow-up

All surgical procedures were performed by experienced surgeons. Curative gastrectomy with D1, D1+, or D2 lymphadenectomy was carried out in accordance with CSCO guidelines for early-stage GC [21]. Distal, proximal, or total gastrectomy depended on the location of the primary lesions using either laparoscopy or open surgery treatment. The surgeons would recommend post-operative AC for patients with high risk factors for recurrence, such as poor differentiation, LVI, and PNI [21]. However, patients were informed of the fact that there is currently lacking evidence to support AC for treating stage I GC after surgery and it was ultimately up to the patients to decide whether to receive AC. The AC regimens included monotherapy based on 5-fluorouracil and combined therapy based on 5-fluorouracil plus platinum, which was administered within 4–6 weeks after surgery. The median cycles of AC were 4 (interquartile range, 2–6).

After surgery, patients were followed up once every 3–6 months in the first 2 years, followed by once every 6–12 months until 5 years, including clinical history, physical examination, blood chemistry (whole blood count, liver–renal function test, tumor markers, etc.), chest, abdominal and pelvic computed tomography (once every 6–12 months for the first year and then once every year), and gastroscopy. Fine-needle aspiration cytology or biopsy was performed on suspected lesions to confirm locoregional or distant recurrence. The follow-up information of patients was obtained through medical record review and telephone interviews. The follow-up visits were performed up to December 2021.

## Study end points

The primary end point was recurrence-free survival (RFS), which was defined as the time from the date of surgery to locoregional or/and distant recurrence or the date of the last follow-up. The secondary end point was disease-specific survival (DSS), which was defined as the time from the date of surgery to death due to GC or the date of the last follow-up. The survival information was checked by clinicians for accuracy.

## Statistical analysis

The patients were divided into the AC and non-AC groups. Patients from the two groups were matched using the PSM method to mitigate discrepancies in the characteristics of the study cohort that could affect the outcomes. Logistic regression was used for propensity score calculation from baseline patient characteristics including age, pT stage, pN stage, tumor size, histological type, LVI, PNI, and CEA level. Propensity score analysis with 1:1 matching was performed with the nearest-neighbor matching method. The nearest-neighbor matching was based on a greedy matching algorithm, which matched each unit in the treatment group to a unit in the control group that had the closest propensity score. For each patient receiving AC, a patient not receiving AC with a minimum distance of propensity scores was matched. Both patients were then removed from consideration for matching and the next case matching was continued until the last patient in the AC group [25]. We tested multiple caliper widths. The criterion for selecting the optimal caliper width was to simultaneously meet the requirements of preferable homogeneity and minor loss of sample size. Covariate balance was evaluated using absolute standardized difference (ASD) after PSM, and covariables were considered well balanced between the groups if the ASDs were $<0.1$ [26]. We defined the caliper as 0.1, 0.01, 0.001, or 0.0001 standard deviations of the logit of the estimated propensity score, which meant the maximum distance by which two units could be apart from each other was 0.1, 0.01, 0.001, or 0.0001 standard deviations of the logit of the estimated propensity score. Eventually, a caliper width of 0.001 resulted in the best trade-off between homogeneity and retained sample size. We performed Kaplan–Meier analysis to compare the survival outcomes between the AC and non-AC groups before and after matching.

The Mann–Whitney *U* test or the Wilcoxon rank-sum test was used for comparison of continuous variables, while the chi-square test or the Fisher's exact test was used for comparison of categorical variables. The Kaplan–Meier survival analysis was

performed to calculate the RFS and DSS rates, and the log-rank test was employed to determine the significance. All statistical analyses were conducted using R version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria) and Python version 3.6.1 (https://www.python.org/). All tests were two-sided and a *P*-value of <0.05 was considered statistically significant.

# Results

## Patient characteristics

A total of 902 patients were included in this study (Figure 1), including 571 males (63.3%) and 331 females (36.7%), with a median age of 56 years. The median follow-up time was 48 months (interquartile range, 29–72 months). Of these patients, 45 (5.0%) experienced recurrence. The median time to recurrence was 46 months (interquartile range, 25–71 months); 57.8% (26/45) of patients experienced recurrence within 2 years after surgery. The most common pattern of recurrence was distant metastasis (42.2%), followed by peritoneal metastasis (37.8%) and local recurrence (8.9%). A total of 38 (4.2%) patients died of GC; most (97.4%) of the disease-specific deaths occurred within 1 year after recurrence. The 10-year RFS and DSS rates were 92.4% and 92.7%, respectively.

## Survival outcomes in the entire cohort

In the entire cohort, 174 (19.3%) patients received AC after surgery. The patients' clinicopathological characteristics of the AC and non-AC groups are shown in Table 1. Patients in the AC group had larger tumor size ($P < 0.001$), more advanced tumor stage ($P < 0.001$), lower degree of tumor differentiation ($P < 0.001$), and higher probability of LVI ($P < 0.001$) and PNI ($P = 0.003$). Before matching, patients who received AC had a lower 10-year RFS rate than those who did not receive AC (90% vs 94.6%, $P = 0.035$; Figure 2A); the two groups had similar 10-year DSS rates (93.8% vs 95.0%; $P = 0.240$; Figure 2B).

## Survival outcomes in the propensity matched cohort

PSM created 123 pairs of patients (123 patients per group). This method was shown to be adequate based on the pairwise comparison of the matched covariates (Figure 3). The matched variables were adequately balanced after PSM, as demonstrated by an ASD of <0.1 (Table 1). In the propensity matched cohort, the median follow-up time was 55 months (interquartile range, 30–84 months). Ten patients (8.1%) experienced recurrence or death in the AC group and eight (6.5%) in the non-AC group. The Kaplan–Meier survival analysis found that the 10-year RFS (90.9% vs 93.0%, $P = 0.507$; Figure 2C) and DSS rates (93.5% vs 93.6%, $P = 0.811$; Figure 2D) were not significantly different between the AC and non-AC groups. Similar results were found in the stage IA ($P = 0.564$ for RFS and $P = 0.571$ for DSS) and stage IB ($P = 0.330$ for RFS and $P = 0.584$ for DSS) subgroups. The median cycles of AC were 4 (interquartile range, 2–6). Also, there were no significant differences in survival rates between the patients who

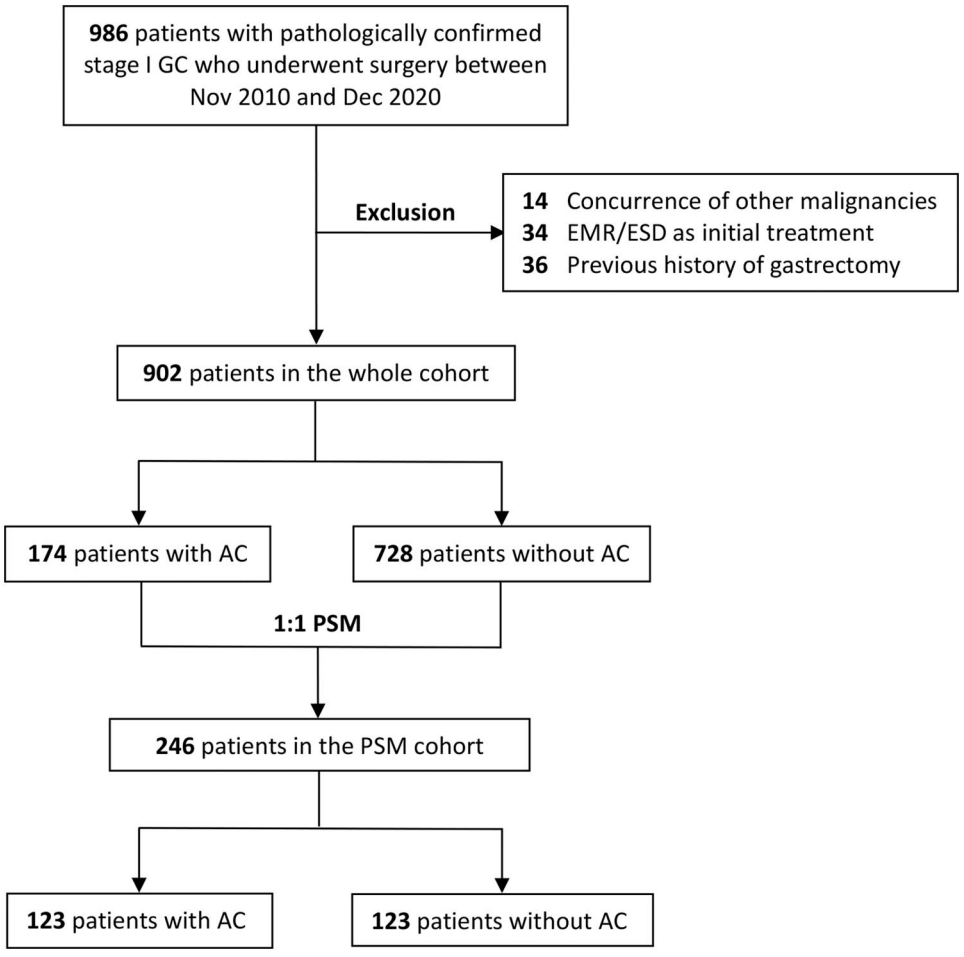


**Figure 1.** Flowchart demonstrating the inclusion and exclusion criteria of this study. GC = gastric cancer, EMR = endoscopic mucosal resection, ESD = endoscopic submucosal dissection, AC = adjuvant chemotherapy, PSM = propensity score matching.

**Table 1.** Baseline clinicopathological characteristics of patients treated with or without adjuvant chemotherapy before and after matching

| Clinicopathological variable | Before PSM | | | | After PSM | | | |
|---|---|---|---|---|---|---|---|---|
| | Non-AC ($n = 728$) | AC ($n = 174$) | *P*-value | ASD | Non-AC ($n = 123$) | AC ($n = 123$) | *P*-value | ASD |
| Sex | | | 0.211 | 0.105 | | | 0.793 | 0.033 |
| Male | 468 (64.3) | 103 (59.2) | | | 77 (62.6) | 75 (61.0) | | |
| Female | 260 (35.7) | 71 (40.8) | | | 46 (37.4) | 48 (39.0) | | |
| Age (years) | | | 0.157 | 0.123 | | | 0.858 | 0.022 |
| <65 | 567 (77.9) | 144 (82.8) | | | 104 (84.6) | 105 (85.4) | | |
| ≥65 | 161 (22.1) | 30 (17.2) | | | 19 (15.4) | 18 (14.6) | | |
| Smoking | | | 0.181 | 0.114 | | | 0.604 | 0.067 |
| No | 407 (55.9) | 107 (61.5) | | | 71 (57.7) | 75 (61.0) | | |
| Yes | 321 (44.1) | 67 (38.5) | | | 52 (42.3) | 48 (39.0) | | |
| CEA level (ng/mL) | | | 0.287 | 0.119 | | | 1.000 | 0 |
| ≤5 | 606 (83.2) | 153 (87.9) | | | 109 (88.6) | 1098.6) | | |
| >5 | 29 (4.0) | 4 (2.3) | | | 2 (1.6) | 2 (1.6) | | |
| Unknown | 93 (12.8) | 17 (9.8) | | | 12 (9.8) | 12 (9.8) | | |
| BMI ($kg/m^2$) | 22.3 ± 3.0 | 22.4 ± 3.2 | 0.952 | 0.026 | 22.5 ± 3.0 | 22.5 ± 3.2 | 0.893 | 0.010 |
| Lymphocyte ($\times 10^9$/L) | 1.9 ± 0.7 | 1.9 ± 0.6 | 0.662 | 0.027 | 1.9 ± 0.6 | 1.9 ± 0.7 | 0.789 | 0.076 |
| Type of gastrectomy | | | 0.122 | 0.152 | | | 0.653 | 0.115 |
| Proximal | 14 (1.9) | 3 (1.7) | | | 4 (3.3) | 3 (2.4) | | |
| Distal | 664 (91.2) | 151 (86.8) | | | 109 (88.6) | 106 (86.2) | | |
| Total | 50 (6.9) | 20 (11.5) | | | 10 (8.1) | 14 (11.4) | | |
| Lymphovascular invasion | | | <0.001 | 0.264 | | | 0.734 | 0.042 |
| No | 704 (96.7) | 157 (90.2) | | | 118 (95.9) | 119 (96.7) | | |
| Yes | 24 (3.3) | 17 (9.8) | | | 5 (4.1) | 4 (3.3) | | |
| Perineural invasion | | | 0.003 | 0.218 | | | 0.790 | 0.033 |
| No | 708 (97.3) | 161 (92.5) | | | 115 (93.5) | 116 (94.3) | | |
| Yes | 20 (2.7) | 13 (7.5) | | | 8 (6.5) | 7 (5.7) | | |
| pN stage | | | <0.001 | 0.762 | | | 1.000 | 0 |
| N0 | 710 (97.5) | 125 (71.8) | | | 107 (87.0) | 107 (87.0) | | |
| N1 | 18 (2.5) | 49 (28.2) | | | 16 (13.0) | 16 (13.0) | | |
| No. of examined LNs | | | 0.057 | 0.161 | | | 0.055 | 0.245 |
| ≤15 | 330 (45.3) | 65 (37.4) | | | 64 (52.0) | 49 (39.8) | | |
| >15 | 398 (54.7) | 109 (62.6) | | | 59 (48.0) | 74 (60.2) | | |
| pT stage | | | <0.001 | 0.586 | | | 1.000 | 0 |
| T1 | 561 (77.1) | 87 (50.0) | | | 53 (43.1) | 53 (43.1) | | |
| T2 | 167 (22.9) | 87 (50.0) | | | 70 (56.9) | 70 (56.9) | | |
| Tumor size (cm) | | | <0.001 | 0.411 | | | 0.974 | 0.025 |
| ≤2 | 435 (59.8) | 72 (41.4) | | | 58 (47.2) | 57 (46.3) | | |
| 2–5 | 257 (35.3) | 80 (46.0) | | | 54 (43.9) | 54 (43.9) | | |
| ≥5 | 36 (4.9) | 22 (12.6) | | | 11 (8.9) | 12 (9.8) | | |
| Histological type | | | <0.001 | 0.378 | | | 1.000 | 0 |
| Differentiated type | 506 (69.5) | 148 (85.1) | | | 104 (84.6) | 104 (84.6) | | |
| Undifferentiated type | 222 (30.5) | 26 (14.9) | | | 19 (15.4) | 19 (15.4) | | |
| Tumor location | | | 0.438 | 0.127 | | | 0.557 | 0.148 |
| Upper third | 28 (3.8) | 11 (6.3) | | | 6 (4.9) | 10 (8.1) | | |
| Middle third | 111 (15.2) | 30 (17.2) | | | 19 (15.4) | 20 (16.3) | | |
| Lower third | 584 (80.2) | 132 (75.9) | | | 95 (77.2) | 92 (74.8) | | |
| Multiple | 5 (0.6) | 1 (0.6) | | | 3 (2.4) | 1 (0.8) | | |
| AC cycles | | | NA | NA | | | NA | NA |
| <6 | NA | 122 (70.1) | | | NA | 87 (70.7) | | |
| ≥6 | NA | 52 (29.9) | | | NA | 36 (29.3) | | |

Values are expressed as *n* (%) or mean ± standard deviation. PSM = propensity score matching, AC = adjuvant chemotherapy, CEA = carcinoembryonic antigen, BMI = body mass index, PNI = prognostic nutritional index, LNs = lymph nodes, ASD = absolute standardized differences, NA = not applicable.

completed six cycles of AC and those who did not ($P = 0.305$ for RFS and $P = 0.957$ for DSS).

## Discussion

To date, no clinical trials have been completed to confirm the therapeutic benefit of AC in stage I GC patients. We performed PSM to balance baseline patient characteristics and found that patients in the non-AC group had similar survival outcomes when compared with patients in the AC group. In the absence of a randomized prospective clinical trial, these results suggest that only follow-up is enough for stage I GC patients after curative resection.

Some studies have investigated the prognosis for stage I GC patients [3, 6–11, 23, 27–29]. Consistently with the results of previous studies [3, 6, 8, 11], our results demonstrated that stage I GC patients had a good prognosis with survival rates of >90%. However, some patients experienced recurrence within 5 years of curative resection [30]. In most studies [3, 6, 8, 9, 11, 27, 28], advanced age, pT stage, pN stage, LVI, and PNI were identified as independent risk factors for recurrence or death in stage I GC patients. In this study, by comparing basic characteristics between AC and non-AC groups in the entire cohort, we found that variables that showed significant difference were previously reported prognostic risk factors. Biased distribution of prognostic risk factors between groups would have significantly affected the

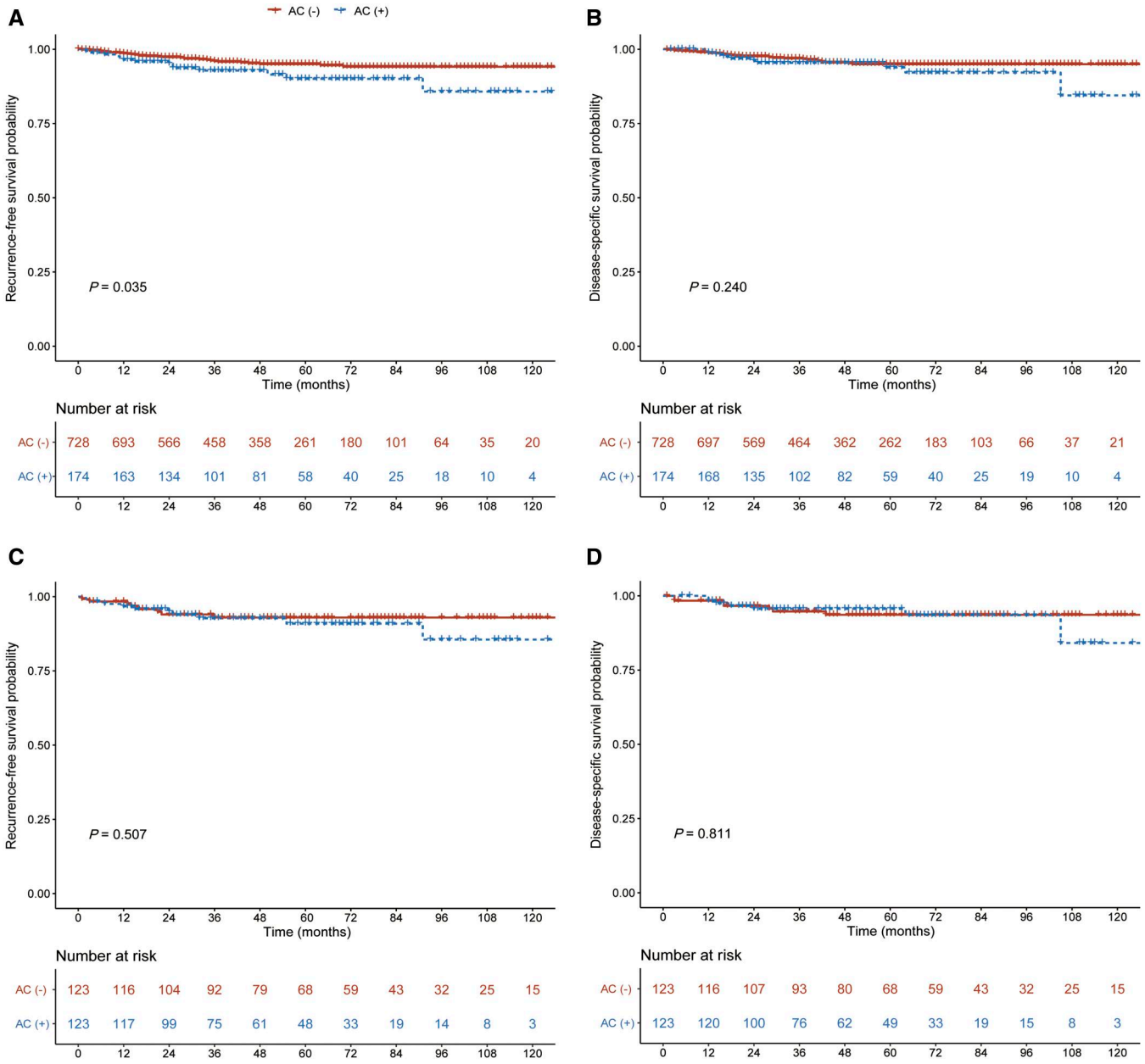


**Figure 2.** Comparisons of survival outcomes between patients treated with and without adjuvant chemotherapy in the unmatched (A and B) and matched (C and D) cohorts.

outcomes, thereby they needed to be controlled regardless of their relevance to AC. Hence, we leveraged the PSM to eliminate the influence of potential confounding factors. This way of analysis offers researchers the ability to balance two groups across all putative risk factors and allows easy inspection of achieved balance across the observed variables [25, 31]. After matching, AC was no longer associated with a lower RFS that showed before matching. Consequently, the survival difference between the two groups in the entire cohort may be due to the biased distribution of baseline characteristics rather than AC itself.

Post-operative AC has been established as a standard treatment for advanced GC to decrease the risk of recurrence [32, 33]. The efficacy of AC in stage I GC has been preliminarily explored in several studies, with inconsistent conclusions. Mei *et al.* [34] found no significant difference in 5-year overall survival (OS) or DSS between surgery plus AC and surgery alone groups in patients with pT1N0 and pT1N1 GC. Zheng *et al.* [6] and Yang *et al.* [35] revealed that stage IB GC patients who received AC did not have prolonged survival. However, in a retrospective analysis of 1,687 patients, In *et al.* [36] demonstrated a significant survival benefit of AC in T2N0 GC patients (hazard ratio for OS, 0.71; $P = 0.043$). Jin *et al.* [37] reported that patients with <15 lymph nodes examined and tumor size of >3 cm could achieve DSS benefit from AC with marginal significance ($P = 0.049$). Lu *et al.* [38] revealed that patients with systemic immune score = 2 may benefit from AC for stage I GC. Notably, all the above studies did not control the potential confounding factors of prognosis that showed as unbalanced between the AC and non-AC groups, thus their conclusions should be interpreted with caution.

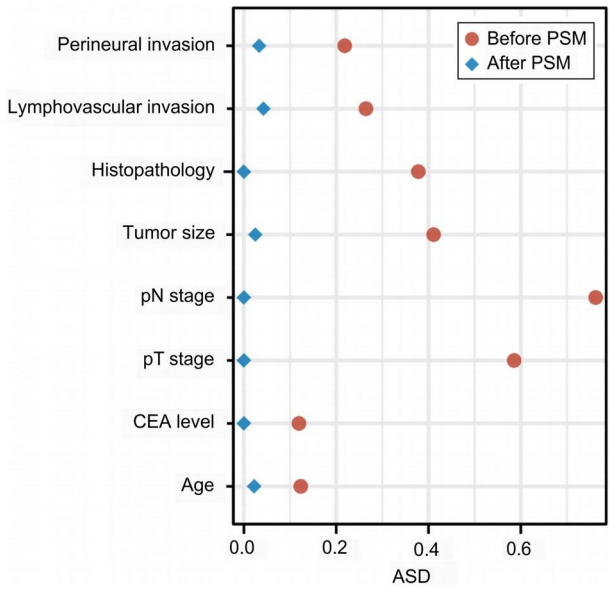


**Figure 3.** Absolute standardized differences before and after propensity score matching. CEA = carcinoembryonic antigen, ASD = absolute standardized differences, PSM = propensity score matching.

Our study has some limitations. First, selection bias may have been introduced due to the retrospective nature of this study. Although we applied PSM to minimize such bias, this method can only balance known covariates, and statistical inferences may still be subject to bias from unmeasured confounding variables. A large, multicenter randomized clinical trial may be needed to confirm our findings. Second, it is impossible to conduct an intent-to-treat comparison between AC and non-AC groups, which would introduce immortal time bias. Third, this study was performed at a single center and the study population may not represent the general patient population with stage I GC. The marked differences in ethnicity, diet, and living habits between Chinese and Caucasian populations may influence clinical management [39]. However, the patient characteristics of the present study were similar to those of other previous studies [3, 6, 11]. Finally, we included patients who underwent different chemotherapy regimens; the potential effect of different schemes on survival should not be neglected.

## Conclusions

Our study demonstrates that stage I GC patients have an excellent prognosis after curative surgical resection, with 10-year survival rates of >90%. For stage I GC patients, surgery alone offers similar survival outcomes as compared with surgery followed by AC. Therefore, only follow-up is recommended for these patients. However, prospective randomized–controlled studies are necessary to confirm our findings.

## Authors' Contributions

Q.Y.C. and H.X. contributed to the conception and design of the study, the interpretation of data, and the work draft. L.Z. participated in the data extraction. J.J.Y. and Z.J. participated in the data analysis. B.Z. offered guidance in study design and revised the article critically for important intellectual content. All authors read and approved the final version of the manuscript.

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The institutional review board of Hunan Cancer Hospital approved this retrospective study and waived the need for informed consent. The study was performed in accordance with the Declaration of Helsinki.

## Conflict of Interest

None declared.

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