

RAPID COMMUNICATION



Treatment patterns and outcomes in advanced or metastatic gastric/gastroesophageal junction adenocarcinoma in China

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ABSTRACT

Aims: Describe the characteristics, treatment patterns and outcomes of Chinese patients with unresectable advanced/metastatic (UAM) gastric/gastroesophageal junction adenocarcinoma (GA/GEJA).

Methods: This multicenter, retrospective, observational study included adults diagnosed with UAM GA/GEJA in China from 2017–2020.

Results: Among 2,745 patients, 1,902, 729, and 284 received first-, second- and third-line (1 L, 2 L and 3 L) therapy—respectively. Most patients received chemotherapy alone in 1 L (84.1%) and 2 L (63.6%), and targeted-therapy-based treatment in 3 L (49.2%). Median real-world progression-free survival (rwPFS) was 6.5, 4.2, and 3.2 months in 1 L, 2 L, and 3 L, respectively.

Conclusions: Chinese patients with UAM GA/GEJA mainly received chemotherapy alone in 1 L/2 L and targeted therapy in 3 L. Median rwPFS was short in all lines, highlighting the need for more effective treatments.

PLAIN-LANGUAGE SUMMARY

Gastric (stomach) cancer is one of the leading causes of cancer-related death globally, and nearly four-in-ten of those cases and deaths occur in China. Despite this high disease burden, real-world data on clinical outcomes and which treatments are used are lacking from Chinese patients with gastric cancer.

Therefore, we examined patient records from four large hospitals in China between 2017 and 2020, selecting adults diagnosed with gastric cancer (or a type of cancer between the stomach and esophagus), whose disease was advanced-stage or had spread. We analyzed data on the time until patients' tumors grew or spread (disease progression), the patient had to switch therapies because of disease progression, or the patient died (together called real-world progression-free survival, or rwPFS). We also tracked which treatments the patients were using and when this changed.

From the large number of patients (2,745), we found that the treatment patterns generally reflected established guidelines at the time, with the majority of initial treatments used either first or second being based on chemotherapy. We found that the median rwPFS was short, decreasing from 6.5 months, to 4.2 months, then 3.2 months each time the therapy needed to be changed.

These findings provide important real-world data that improve our understanding of current treatments and real-world outcomes in Chinese patients with this type of cancer. Our results also highlight a need for more effective and novel treatment options, with the ultimate goal of improving treatment outcomes.

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1. Introduction

Globally, gastric cancer is the fifth most common cancer and the fifth most common cause of cancer-related death [1,2]. China has the highest disease burden from gastric cancer of any other nation; Chinese gastric cancer accounts for 37.0% of new cases and 39.5% of deaths globally, making gastric cancer the fifth most common cancer and the third leading cause of cancer-related mortality in China [3–5]. Gastric and gastroesophageal junction adenocarcinomas (GA/GEJA) are often asymptomatic during the

early stages and diagnosis is typically made at a late stage [6,7]. In China, over 80% of patients already have advanced disease at the time of diagnosis and the estimated 5-year survival rate for advanced gastric cancer in this country is as low as 8.4% [8,9].

The treatment landscape and recommended treatment options in the Chinese Society for Clinical Oncology (CSCO) clinical guidelines for patients with unresectable advanced or metastatic (UAM) GA/GEJA have evolved over the years. Between 2017 and 2020, the preferred first-line (1 L) treatment was doublet chemotherapy (fluoropyrimidine combined with platinum or taxanes),

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Article highlights

- Globally, gastric cancer is the fifth most common cancer and the fifth most common cause of cancer-related deaths.
- In China, the burden of gastric cancer is particularly high, with 37.0% of all cases and 39.5% of deaths from gastric cancer occurring in China. Within China, it ranks as the fifth most common cancer and the third leading cause of cancer-related mortality.
- The treatment landscape and recommended treatment options in the Chinese Society for Clinical Oncology (CSCO) clinical guidelines for patients with unresectable advanced or metastatic (UAM) gastric and gastroesophageal junction adenocarcinomas (GA/GEJA) have evolved over the years.
- We evaluated the characteristics and treatment patterns, as well as clinical outcomes (real-world progression-free survival [rwPFS]) of 2,745 patients diagnosed with UAM GA/GEJA in China from 2017 to 2020, to better inform understanding of their treatment and associated outcomes.
- Treatment patterns generally reflected CSCO guidelines at the time, with the majority of regimens in first line (1 L) and second line (2 L) being chemotherapy-based, and targeted therapies and immunotherapies mainly used in third line (3 L).
- Median rwPFS was generally short in all lines of therapy (6.5, 4.2, and 3.2 months in 1 L, 2 L, and 3 L, respectively).
- These findings provide important real-world data that improve understanding of the current standard of care and real-world outcomes in patients with UAM GA/GEJA in China, highlighting a need for more effective and novel treatment options, with the ultimate goal of improving treatment outcomes.

in combination with trastuzumab for patients with human epidermal growth factor receptor 2 (HER2) mutations [9–12]. Since 2021, 1 L treatment with programmed cell death-1 (PD-1) inhibitors plus chemotherapy has been included as a grade I recommendation (the highest level of recommendation) [13–16]. In the second-line (2 L) setting, in 2021 and earlier, there was no consensus on the standard of care following the failure of 1 L chemotherapy [9–14]. Recommendations included mono-chemotherapy (paclitaxel, docetaxel, irinotecan), paclitaxel- or fluoropyrimidine-based doublet chemotherapy and patients were also encouraged to participate in clinical trials or receive best supportive care [9–14]. In 2022, the antiangiogenic monoclonal antibody ramucirumab combined with paclitaxel, considered the 2 L standard of care globally [17–19], was added as a grade I recommendation [15,16]. In the third-line (3 L) setting, the anti-angiogenic tyrosine kinase inhibitor (TKI), apatinib, has been a grade I recommendation since 2017 [9–16] and the PD-1 inhibitor, nivolumab, was included as a grade I recommendation in 2020 [13–16].

Despite the high incidence and mortality rates of gastric cancer in China, there are limited real-world data describing the treatment landscape in this population. Given this knowledge gap, the present study was conducted to improve the understanding of the patient characteristics and treatment patterns (primary objective), as well as clinical outcomes (real-world progression-free survival [rwPFS], a secondary objective) of patients with UAM GA/GEJA in China.

2. Methods

2.1. Study design and data source

This was a multicenter, retrospective, observational study using secondary data collected at four tertiary hospitals in China. Patient-level data were collected from electronic medical records (EMR), and from records from the Hospital

Information System (HIS), Laboratory Information Management System (LIS), Radiology Information System (RIS) and Picture Archiving and Communication System (PACS) at participating sites. Adult patients diagnosed for the first time with UAM GA/GEJA between 1 January 2017 and 31 December 2020 (eligibility period) were included; the date of diagnosis was designated as the index date. The individual observational period (total follow-up time) for each patient was defined as the index date to the date of the last visit on or before 31 August 2021.

2.2. Participants and data collection

Eligible patients required a histologically or cytologically confirmed first diagnosis of UAM GA/GEJA within the eligibility period. Patients who had previously been diagnosed with early-stage GA/GEJA but progressed to an advanced or metastatic stage within the eligibility period were also included. To ensure data quality and completeness, patients were required to have at least one record of UAM GA/GEJA-related inpatient admission during the observational period. Patients were excluded if they had squamous cell or undifferentiated GA/GEJA cancer, if they had other primary tumors, or had participated in any interventional clinical trials after diagnosis.

Data on the following demographic, clinical and disease characteristics were collected at the index date or within the pre-index period: age; sex; comorbidities/complications; cancer stage at initial diagnosis of UAM GA/GEJA; Eastern Cooperative Oncology Group (ECOG) performance status; HER2 status; primary tumor location; location and number of metastases and history of prior GA/GEJA cancer-related surgery. Data on treatment patterns and clinical outcomes collected during the individual observation period included the number of treatment lines received, start and end date of each treatment regimen, treatment strategy (monotherapy or combination therapy); drugs received (agent and class), reason(s) for treatment discontinuation, date of disease progression, date of death, and date of last visit.

2.3. Statistical analysis

All statistical methods were descriptive. Categorical variables were summarized as counts with percentages and continuous variables as mean with standard deviation or median with interquartile range (IQR), as appropriate. Lines of therapy were defined by the temporal relationship and sequencing of treatment regimens by using the dates of initiation and discontinuation. Treatment regimen changes due to adverse events, financial issues or reasons other than disease progression were not considered as line of therapy changes. Treatment patterns were described as counts with percentage by line of therapy. Changes in treatment patterns from 2017 to 2020 were explored by stratifying data by year of treatment initiation. Treatment sequences were mapped across three lines of therapy and a Sankey diagram was used to plot the results. Duration of therapy (DoT) was measured from the date of initiation of a treatment regimen to the date of treatment discontinuation. If there was no

information on treatment discontinuation, DoT was censored at the date of the last visit.

There was separate evaluation of rwPFS for 1 L therapy (rwPFS1), 2 L therapy (rwPFS2), and 3 L therapy (rwPFS3), which was defined as time from the initiation of one line of therapy to the subsequent earliest documented disease progression, initiation of a new treatment line, or death due to any cause, whichever occurred first. Disease progression was identified from documentation within the medical record, such as radiology reports and the statement about disease progression assessed by treating physicians. Patients without a record of disease progression, initiation of a new line of treatment, or death after one line of treatment censored at the date of the last visit prior to the end of the study. DoT and rwPFS were estimated using the Kaplan-Meier method. Median rwPFS and corresponding 95% confidence intervals (CIs) were calculated and survival curves were plotted. Rates of rwPFS at 6 and 12 months were also reported, by line of therapy.

Imputation of missing values was conducted only for variables relating to clinical outcomes as follows: where the date of discontinuation was missing, the date of initiation of the next treatment line was used. Where the day was missing from the date (of an event or censoring), the 15th was used and where the date of death was missing, the date of the last visit before the study period was used. Sensitivity analyses of rwPFS data were conducted on a subset of patients without missing data; and for patients with rwPFS censored at the date of the last imaging test or the date of the last visit if the date of the last imaging test was not known. All statistical analyses were performed using R 4.0.2 statistical software.

3. Results

3.1. Patient characteristics

A total of 2,745 patients were included in the analysis. The median age of the cohort was 62 years, and 69.2% were male. The majority of patients (97.3%) had a diagnosis of GA and had stage IV disease (95.7%). Only 30.4% of patients had previously undergone surgery of the primary tumor. The most common location of metastasis at diagnosis was the peritoneum (43.4%); 57.0% had one metastasis at diagnosis, 26.2% had two metastases, 8.5% had three and 2.4% had four or more. Among patients with known HER2 status, 82.3% were HER2 negative (Table 1).

3.2. Treatment patterns

Among the 2,745 patients, 1,902 (69.3%) received 1 L therapy; 729/1,902 (38.3%) subsequently received 2 L therapy and 284/1,902 (14.9%) went on to receive 3 L therapy during the observation period (Table 2).

3.2.1. Monotherapy vs combination therapy

Across all lines of treatment, the majority of patients received combination therapy rather than monotherapy (82.7%, 73.0% and 63.6% of patients in 1 L, 2 L and 3 L settings, respectively), and doublet chemotherapy was the most common (1 L: 62.4%; 2 L: 42.5% and 3 L: 24.2%).

Table 1. Demographics and clinical characteristics of patients at initial diagnosis of UAM GA/GEJA.

Characteristic	Value
Total number of patients, n	2,745
Year of diagnosis, n (%)	
2017	760 (27.7)
2018	733 (26.7)
2019	773 (28.2)
2020	479 (17.4)
Age, years	
Mean (SD)	61.2 (11.6)
Median [IQR]	62.0 [54.0, 69.0]
<65 years, n (%)	1,659 (60.4)
≥65 years, n (%)	1,086 (39.6)
Sex, n (%)	
Male	1,899 (69.2)
Female	846 (30.8)
Comorbidities/complications^a, n (%)	
Ascites	462 (16.8)
Anemia	389 (14.2)
Hypoproteinemia	209 (7.6)
Hypertension	208 (7.6)
Gastrointestinal obstruction	140 (5.1)
Others	1,166 (42.5)
Primary tumor location, n (%)	
GA	2,671 (97.3)
GEJA	74 (2.7)
Prior surgical resection of primary tumor, n (%)	
Yes	835 (30.4)
No	1,910 (69.6)
Cancer stage^b, n (%)	
Patients with non-missing data	2,694
II	3 (0.1)
III	112 (4.2)
IV	2,579 (95.7)
Location of metastasis^{c,d}, n (%)	
Peritoneal	1,192 (43.4)
Liver	995 (36.3)
Lymph nodes	793 (28.9)
Bone	315 (11.5)
Lung	201 (7.3)
Others	434 (15.8)
Number of metastases, n (%)	
0	163 (5.9)
1	1,564 (57.0)
2	720 (26.2)
3	232 (8.5)
≥4	66 (2.4)
HER2 status^b, n (%)	
Patients with non-missing data	883
Overexpression	156 (17.7)
Negative	727 (82.3)
ECOG performance status^b, n (%)	
Patients with non-missing data	766
0–1	623 (81.3)
≥2	143 (18.7)

^aOnly displaying comorbidities/complications affecting > 5% of the study population; ^bThe denominator was calculated using the non-missing population number; ^cOnly displaying metastasis occurring in > 5% patients. ^dPatients without metastases were not included in this distribution and some patients had more than one metastatic site. Proportion=number of locations of metastasis/number of patients.

ECOG, Eastern Cooperative Oncology Group; GA/GEJA, gastric or gastroesophageal junction adenocarcinoma; HER2, human epidermal growth factor receptor 2; IQR, interquartile range, SD, standard deviation; UAM, unresectable advanced or metastatic.

3.2.2. Chemotherapy vs targeted therapy/immunotherapy

When assessing treatment use by class of agent, irrespective of whether this was given as monotherapy or combination therapy, the majority of patients received chemotherapy alone in the 1 L and 2 L settings (1 L: 84.1%; 2 L: 63.6%; 3 L: 41.4%). Fluoropyrimidine-based chemotherapy was the most common

Table 2. Number of treatment regimens by treatment strategy and treatment class in 1 L, 2 L, and 3 L.

Treatment patterns	1 L Number of regimens, n (%)	2 L Number of regimens, n (%)	3 L Number of regimens, n (%)
Total treated patients	1,902	729	284
Total regimens^a	2,023 (100.0)	758 (100.0)	297 (100.0)
Monotherapy	349 (17.3)	205 (27.0)	108 (36.4)
Chemotherapy	291 (14.4)	129 (17.0)	44 (14.8)
Targeted therapy	52 (2.6)	61 (8.0)	54 (18.2)
Immunotherapy	6 (0.3)	15 (2.0)	10 (3.4)
Combination therapy	1,674 (82.7)	553 (73.0)	189 (63.6)
Doublet chemotherapy	1,263 (62.4)	322 (42.5)	72 (24.2)
Targeted therapy + chemotherapy	206 (10.2)	146 (19.3)	63 (21.2)
Triplet chemotherapy and above	147 (7.3)	31 (4.1)	7 (2.4)
Immunotherapy + chemotherapy	38 (1.9)	31 (4.1)	18 (6.1)
Immunotherapy + targeted therapy + chemotherapy	10 (0.5)	4 (0.5)	6 (2.0)
Immunotherapy + targeted therapy	9 (0.4)	16 (2.1)	21 (7.1)
Doublet targeted therapy	1 (0.0)	3 (0.4)	2 (0.7)
Chemotherapy alone	1,701 (84.1)	482 (63.6)	123 (41.4)
Fluoropyrimidine-based	1,569 (77.6)	319 (42.1)	80 (26.9)
Taxane-based	452 (22.3)	271 (35.8)	43 (14.5)
Platinum-based	1,117 (55.2)	164 (21.6)	34 (11.4)
Others	11 (0.5)	31 (4.1)	16 (5.4)
Targeted therapy-based regimen^b	278 (13.7)	230 (30.3)	146 (49.2)
Anti-HER2 mAb-based	93 (4.6)	44 (5.8)	13 (4.4)
Anti-angiogenic based	182 (9.0)	182 (24.0)	133 (44.8)
Anti-angiogenic TKI-based	167 (8.3)	176 (23.2)	131 (44.1)
Anti-angiogenic mAb-based	15 (0.7)	7 (0.9)	3 (1.0)
Others	5 (0.2)	6 (0.8)	2 (0.7)
Immunotherapy-based regimen^b	63 (3.1)	66 (8.7)	55 (18.5)
Anti-PD-1 mAb-based	63 (3.1)	66 (8.7)	55 (18.5)

^aConsidering the missing information on drug regimens in this retrospective study, the regimens without drug information were excluded from calculations related to regimens. Some patients received more than one regimen in the same line because they changed treatment due to adverse events, financial issues or reasons other than disease progression, which resulted in the total number of regimens being higher than the total number of patients in each line of therapy. For percentage calculations, the total number of regimens in each line of therapy was used as the denominator. ^bThe treatment regimens containing both targeted therapy and immunotherapy were counted twice.

1 L, first line; 2 L, second line; 3 L, third line; mAb, monoclonal antibody; PD-1, Programmed cell death-1; PD-L1, Programmed cell death ligand 1; TKI, tyrosine kinase inhibitor.

class of chemotherapy (1 L: 77.6%; 2 L: 42.1%; 3 L: 26.9%), followed by platinum-based (1 L: 55.2%; 2 L: 21.6%; 3 L: 11.4%) and taxane-based (1 L: 22.3%; 2 L: 35.8%; 3 L: 14.5%). Both targeted-therapy-based (1 L: 13.7%; 2 L: 30.3%; 3 L: 49.2%) and immunotherapy-based regimens (1 L: 3.1%; 2 L: 8.7%; 3 L: 18.5%) were given more often in the 3 L setting than in earlier lines. Anti-angiogenic TKIs were the most commonly used targeted agents (1 L: 8.3%; 2 L: 23.2%; 3 L: 44.1%), followed by anti-HER2 monoclonal antibodies (1 L: 4.6%; 2 L: 5.8%; 3 L: 4.4%). All immunologic agents were anti-PD-1 monoclonal antibodies (Table 2).

Between 2017 and 2020, the use of chemotherapy alone decreased year on year, and this trend was particularly marked in the 1 L and 2 L settings. In parallel, the use of targeted therapies and immunotherapy increased across all treatment lines over the study period, with a noticeable rise in the use of immune-based therapy observed in the 3 L setting (Figure 1).

3.2.3. Most common regimens received

Overall, almost 80 different treatment regimens were used in the 1 L setting, nearly 70 in 2 L, and over 50 in 3 L (Supplementary Tables S1-S3). The most frequently used treatment regimens differed by line of therapy. In 1 L, the three most common regimens were fluoropyrimidine plus platinum (44.5%), fluoropyrimidine monotherapy (11.9%), and fluoropyrimidine plus taxanes (10.9%). In 2 L, the three most common regimens were fluoropyrimidine plus taxanes

(16.5%), fluoropyrimidine plus platinum (9.2%), and anti-angiogenic TKI monotherapy (7.7%) (Supplementary Table S2). In 3 L, anti-angiogenic TKI monotherapy was the most common (18.2%). Other frequently used regimens were an anti-angiogenic TKI plus an anti-PD-1 monoclonal antibody (6.7%); fluoropyrimidine monotherapy or in combination with irinotecan or taxanes (6.7% each); and an anti-angiogenic TKI plus fluoropyrimidine (6.4%) (Supplementary Table S3).

Treatment sequences across the three lines of therapy were complex. While fluoropyrimidine-based regimens predominated in 1 L, a diverse range of regimens were used in 2 L and 3 L, with no clear trend for patients as they proceeded from 1 L to 2 L and 3 L (Figure 2).

3.2.4. Duration of therapy

The median (95% CI) DoT decreased progressively with each advancing line of therapy; from 4.4 (4.2, 4.8) months in 1 L therapy to 3.1 (2.7, 3.6) months in the 2 L setting, and 2.4 (2.0, 2.9) months in the 3 L setting. DoT of the most frequently used regimens by line of therapy is shown in Supplementary Tables S4-S6.

3.3. Clinical outcomes

Median (95% CI) rwPFS declined progressively with each advancing line of therapy, from 6.5 (6.1, 6.9) months for rwPFS1, to 4.2 (3.7, 4.5) months for rwPFS2 and 3.2 (2.8, 3.7) months for rwPFS3

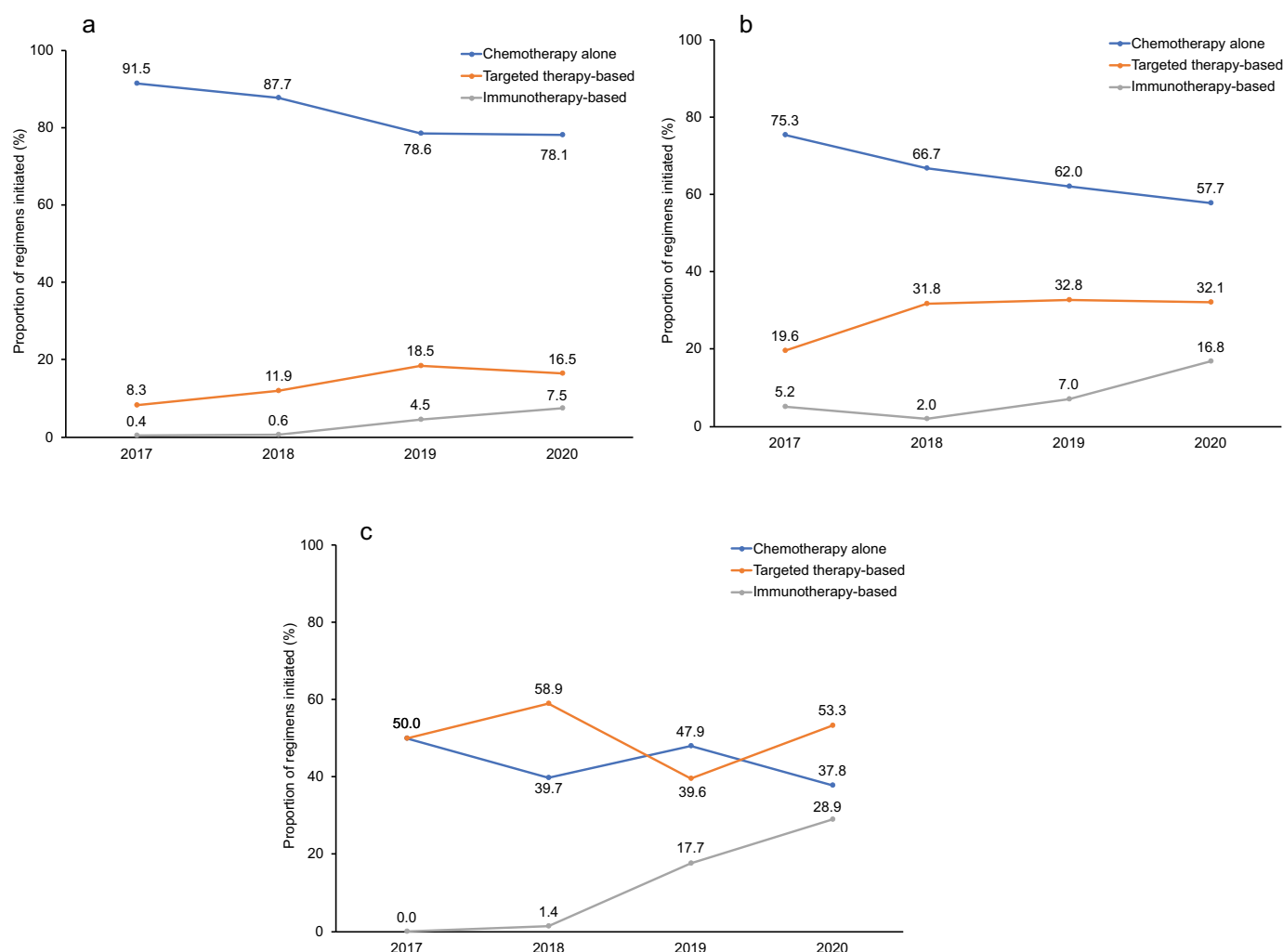


Figure 1. Evolution of treatment regimens utilized over the study period in (a) 1 L, (b) 2 L, and (c) 3 L therapy.

The number of regimens initiated per year in the: (a) 1 L setting; (b) 2 L setting; (c) 3 L setting. 2021 not shown due to low numbers of regimens initiated. For percentage calculations, the total number of regimens initiated per year was used as denominator. The treatment regimens containing both targeted therapy and immunotherapy were counted twice.

(Figure 3). At 6 months, the rwPFS1 rate was 53.5% and at 12 months, 26.9%. With later-line treatment, rwPFS rates were lower at each timepoint (35.5% and 15.0% in 2 L; 28.4% and 17.3% in 3 L). Between 2017 and 2020, median rwPFS1 fluctuated, median rwPFS2 was relatively constant, and median rwPFS3 numerically increased in 2020 (Table 3 ; Supplementary Figure S1). The results of the rwPFS sensitivity analyses were consistent with the main analysis (Supplementary Figures S2–S3).

4. Discussion

To the authors' knowledge, this study represents the largest retrospective observational study of gastric cancer conducted in China to date, providing real-world data from over 2,700 patients with UAM GA/GEJA. These data provide valuable insights into the characteristics, treatment patterns and outcomes of this patient population and facilitate a deeper understanding of their unmet medical needs. The short median rwPFS values observed across all lines of treatment highlight the importance of developing novel treatments and new therapeutic approaches for patients with UAM GA/GEJA in China.

The clinical characteristics of this patient cohort were similar to those reported in other real-world studies of UAM GA/GEJA; patients were predominantly male and aged around 60 years, typically with GA tumor location and peritoneal metastases [20–24]. Only 69.3% of patients had received treatment for UAM GA/GEJA and only 38.3% of these individuals received subsequent treatment after progression on 1 L therapy. The proportion of patients receiving 1 L therapy was consistent with one previous retrospective real-world study conducted in China, in which 69.3% of patients with UAM GC received 1 L therapy [25]. Another prospective real-world study conducted in China reported a slightly higher proportion of patients receiving 1 L therapy (80.3%) and a similar proportion of patients receiving 2 L and later lines of therapy (38.5%) [26].

In our study, most patients received fluoropyrimidine plus platinum chemotherapy as a 1 L treatment, which is consistent with the CSCO guideline recommendations during the study period [9–13] and also with the findings of previous real-world studies conducted in China and other regions, in which the most frequently used 1 L therapies were also fluoropyrimidine- and platinum-based regimens [22–29]. However, the results of the present study found no predominant

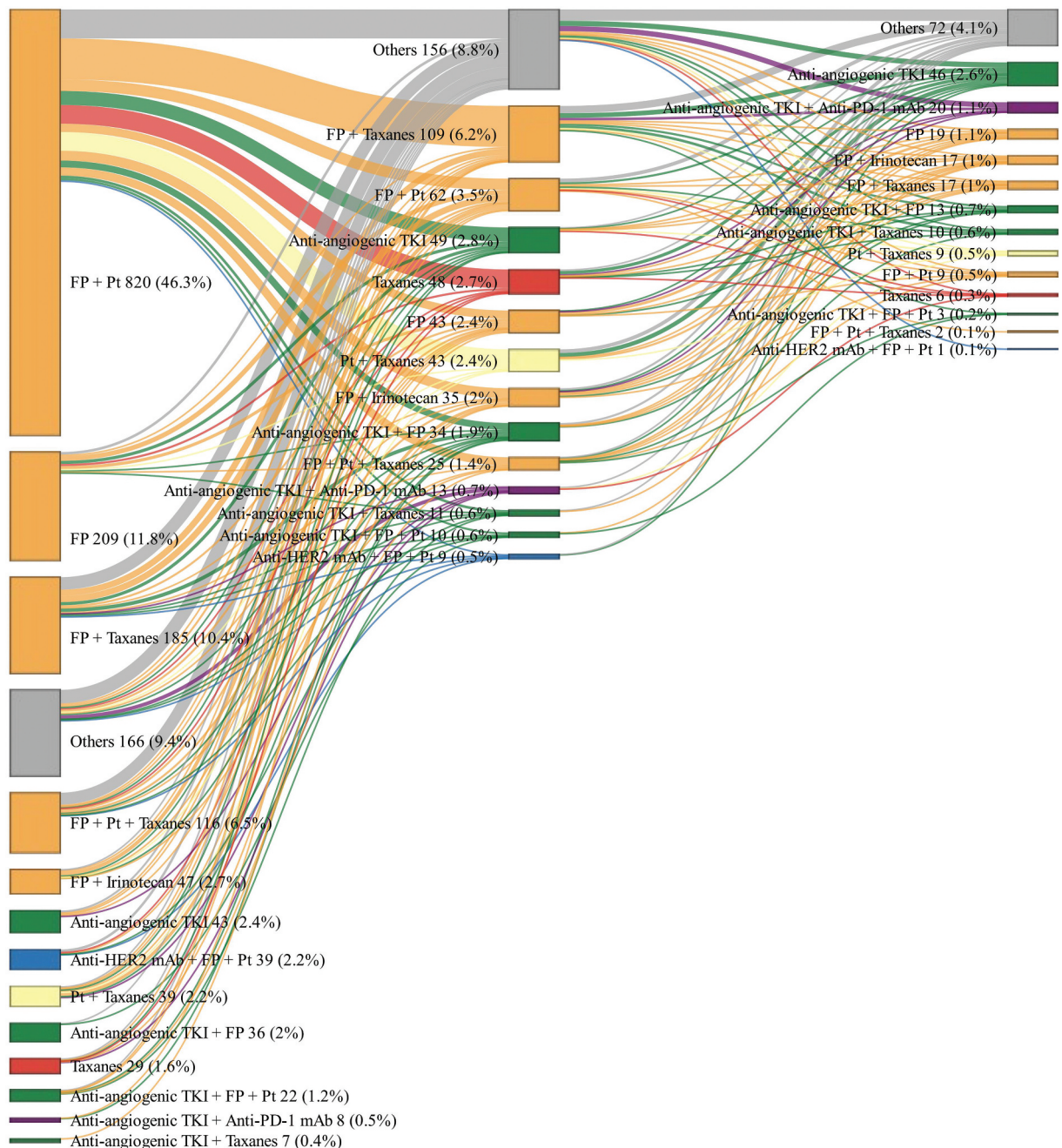


Figure 2. Sankey diagram illustrating treatment sequences across first- to third-line therapy.

Considering that patients may have changed regimen because of adverse events, financial issues or other reasons (other than disease progression), patients who received more than one regimen in the same line were excluded from this Sankey diagram; 1,772 patients with treatment pattern information were included. Among these patients, 1766 received 1 L therapy, 647 received 2 L therapy, and 244 received 3 L therapy. The regimen was classified as "other" when the percentage (of the total number of regimens among all lines) was $\leq 1\%$. The color of combination therapy was marked according to this priority: anti-PD-1 mAb (purple) > anti-angiogenic TKI (green) > anti-HER2 mAb (blue) > fluoropyrimidine (orange) > platinum (yellow) > taxanes (red). Others groups were marked in gray. 1 L, first-line; 2 L, second-line; 3 L, third-line; FP, fluoropyrimidine; HER2, human epidermal growth factor receptor 2; mAb, monoclonal antibody; Pt, platinum; PD-1, programmed cell death-1; TKI, tyrosine kinase inhibitor.

treatments in the 2L and 3L settings. In the 2L setting, chemotherapy was typically given, although treatment regimens were very diverse, reflecting the lack of consensus on the standard of care following failure of 1L treatment during the study period [9–11,13]. It should be noted that ramucirumab plus taxane was also commonly used in the 2L setting in Japan and other Western countries [22,23,29,30]. However, our study was conducted before the approval of ramucirumab in China as a 2L treatment. In 3L, the most commonly used therapy was anti-angiogenic TKIs, which is consistent

with the CSCO guideline recommendations during the study period [9–13]. In previous real-world studies conducted in the USA and Japan, paclitaxel plus ramucirumab and nivolumab were the most common 3L regimens, respectively [22,23].

An analysis of our data by year of treatment initiation revealed a progressive increase in the use of targeted therapy-based and immunotherapy-based regimens from 2017 to 2020. The increase in the use of targeted therapy (mostly anti-angiogenic TKIs) in 2L was inconsistent with the Chinese guidelines at the time of the study, but likely reflects the lack of treatment options

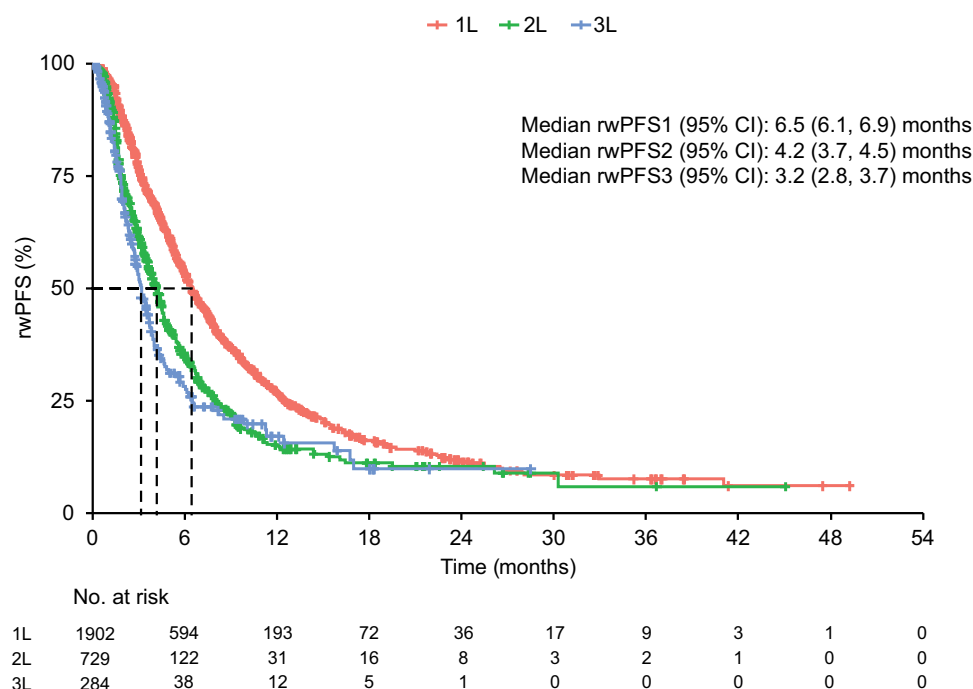


Figure 3. Kaplan-Meier estimates of rwPFS in patients with UAM GA/GEJA in 1 L, 2 L, and 3 L treatment.

1 L, first line; 2 L, second line; 3 L, third line; CI, confidence interval; GA/GEJA gastric/gastroesophageal junction adenocarcinoma; rwPFS1, first-line real-world progression-free survival; rwPFS2, second-line real-world progression-free survival; rwPFS3, third-line real-world progression-free survival; UAM, unresectable advanced or metastatic.

Table 3. Real-world progression-free survival in patients with UAM GA/GEJA.

Line of therapy	Number of patients	Median rwPFS (95% CI), months
rwPFS1		
Total	1,902	6.5 (6.1, 6.9)
2017 ^a	494	6.5 (5.9, 7.5)
2018	492	7.9 (6.8, 9.0)
2019	543	6.4 (5.7, 7.4)
2020	365	5.5 (4.9, 6.2)
rwPFS2		
Total	729	4.2 (3.7, 4.5)
2017 ^a	95	4.8 (3.5, 5.8)
2018	189	3.8 (3.3, 4.4)
2019	220	3.9 (3.5, 5.5)
2020	187	4.0 (3.0, 6.1)
rwPFS3		
Total	284	3.2 (2.8, 3.7)
2017 ^a	10	2.9 (1.0, NR)
2018	66	3.2 (2.3, 4.6)
2019	92	2.7 (2.1, 3.7)
2020	88	4.2 (3.4, 7.9)

^aPatients initiated 1 L therapy in 2017. 2021 not shown due to low numbers of patients initiating 1 L/2 L/3 L therapy during this year.

1 L, first line; 2 L, second line; 3 L, third line; rwPFS1, first-line rwPFS; rwPFS2, second-line rwPFS; rwPFS3, third-line rwPFS; GA/GEJA gastric/gastroesophageal junction adenocarcinoma; NR, not reached; rwPFS, real-world progression-free survival; UAM, unresectable advanced or metastatic.

in this setting. However, the increase in the use of immunotherapy (PD-1 inhibitors) in 3 L was in accordance with CSCO recommendations [10]. Our results also show that median rwPFS declines progressively with each advancing line of therapy, from 6.5 months in patients receiving 1 L therapy, through 4.2 months for second line to 3.2 months in 3 L therapy. Despite the evolving treatment patterns from 2017 to 2020, rwPFS1 and rwPFS2 did not show noticeable improvements over this time period. Our data also show that the DoT was generally short in all

lines of therapy, ranging from 4.4 months in 1 L therapy to 2.4 months in the 3 L setting. The short DoT and poor rwPFS in all lines of therapy in this patient population clearly highlight the need for more effective treatment options.

A number of prior real-world studies have investigated rwPFS in patients with advanced gastric cancer. For example, one study of 1,556 patients with gastric cancer in China conducted between 2013 and 2018 reported similar rwPFS findings to the present study [24]. This earlier study found the median rwPFS to be between 6.2 and 8.2 months for 1 L treatment in patients with metastatic disease, depending on HER2 status and treatment. As in the present study, rwPFS dropped to 2.7–4.8 months for 2 L treatment, and 3.1–5.4 months for 3 L treatment [24]. However, our results add to the findings of this prior study by providing estimates of rwPFS for Chinese patients with UAM GA/GEJA regardless of HER2 status and also cover a time period following that of the prior study. Real-world studies of UAM GC/GEJA in Western countries also reported similar median rwPFS data to the present study (5.3 months for 1 L treatment in the USA; 3.1 months for 2 L treatment in Australia, Canada, Italy and UK) [21,28]. The findings of our analysis are also similar to the results of randomized clinical trials in Chinese patients with UAM GA/GEJA. Among clinical trials of 1 L therapies for UAM GA/GEJA that included a chemotherapy treatment arm, median PFS ranged from 5.0 to 5.7 months, compared with a median rwPFS of 6.5 months in the present study [31–33]. In the 2 L setting, clinical trial results show median PFS for chemotherapy ranging from 3.15 to 5.0 months, compared with a median rwPFS of 4.2 months in the present study [34,35]. Finally, in 3 L the median PFS was 2.6 months for apatinib monotherapy and 1.61 months for nivolumab monotherapy, compared with a median rwPFS of 3.2 months in our study [36,37]. These median rwPFS values of

around 6 months or less are relatively short, regardless of the type of tumor, as seen in reports of other real-world studies [38,39], highlighting the need for more effective and novel treatment options for patients with UAM GA/GEJA.

Strengths: Despite China having the highest disease burden from gastric cancer of any nation [3–5], this is a previously under-researched population. Previous observational studies conducted in China mainly focused on first-line treatment patterns [25] or reported clinical outcomes by HER2 status [24] or treatment [26]. In contrast, our study is the first retrospective observational study, with the largest sample size to date, to provide real-world data on patient characteristics, treatment patterns, DoT, and rwPFS for Chinese patients with UAM GA/GEJA across first- to third-line, regardless of HER2 status or treatment. Our study enrolled from four participating sites, with two located in North China and the others located in South China. Liaoning Cancer Hospital & Institute is located in Liaoning province and the First Affiliated Hospital of Fujian Medical University is located in Fujian province. Liaoning and Fujian are regions that have a high incidence of gastric cancer in China [40]. Therefore, combined with the large sample size included, we believe the selected sample has good representativeness of Chinese patients with advanced gastric cancer. Our findings highlight the need for more effective and novel treatment options in this difficult-to-treat population. In recent years, the treatment of advanced gastric cancer in China has entered the era of immunotherapy, with the approval of nivolumab plus chemotherapy as first-line therapy in China in August 2021. Real-world data from Chinese patients with UAM GA/GEJA treated with first-line immunotherapy are emerging and indicate favorable survival outcomes that exceed those reported in the present study; however, cohort sizes remain small and treatment pattern data are lacking [41–45]. To date, no studies have comprehensively investigated treatment patterns and clinical outcomes in Chinese patients with UAM GA/GEJA in the era of immunotherapy. Our study could provide valuable information and a benchmark for future studies evaluating the real-world impact of the introduction of immunotherapy for Chinese patients with UAM GA/GEJA.

Limitations of the present study include the potential for missing values, which is inherent to observational studies, and imputation of clinical outcomes. However, sensitivity analyses conducted in the subset of patients without missing data were consistent with the main analyses. Moreover, the findings may not be generalizable to the entire UAM GA/GEJA population in China since our study population comprised patients treated in Grade-A tertiary general hospitals or top oncology hospitals. Furthermore, this study mainly focused on describing patient characteristics and treatment patterns, and did not explore the associations between specific treatments/other factors and clinical outcomes, or suggest treatment regimens. Additionally, the relationship between ECOG PS or medication cost and rwPFS by treatment line and the distribution of clinicopathological characteristics of the population between different therapy patterns could not be analyzed due to a lack of data availability or a sample size too small for meaningful conclusions. Similarly, while we were able to report DoT in months, we were unable to report DoT by cycle, because even

drugs in the same class may have different treatment cycles, meaning this would require further subdivision of the treatment regimens by generic name, limiting the accuracy of any estimates drawn from these data. These all may be valuable areas for future research. Finally, we were unable to collect survival information if patients did not die at the participating hospitals. Therefore, no overall survival data were reported in this study as the high censoring rate prevented robust estimation of this clinical outcome.

5. Conclusion

The results of this study highlight that Chinese patients with UAM GA/GEJA were mainly treated with chemotherapy alone in 1 L and 2 L during 2017–2020 and rwPFS was generally short (around 6 months or less) in all lines of therapy. Our findings in this difficult-to-treat population provide important real-world data that will help to improve the understanding of recent treatment patterns and real-world outcomes in patients with UAM GA/GEJA in China. Overall, our findings highlight a need for more effective and novel treatment options, with the ultimate goal of improving treatment outcomes.

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Author contributions

Yanqiao Zhang was responsible for study conception and design. Jingdong Zhang, Guangyu Wang, Li Zhou, Chan Zhou, and Grace Segall made substantial contributions to study design. Yanqiao Zhang, Jingdong Zhang, Xianhe Xie, Wensheng Pan, Guangyu Wang, Qian Dong, Nianhai Zhang, and Jie Dong were responsible for data acquisition. All authors contributed to data analysis, data interpretation, drafting, and revising the manuscript. All authors approved the final version to be published and agree to be accountable for all aspects of the work.

Disclosure statement

Li Zhou, Chan Zhou, Jinnan Li, and Grace Segall are employees and stockholders of Eli Lilly and Company. Yanqiao Zhang, Jingdong Zhang, Guangyu Wang, Xianhe Xie, Wensheng Pan, Qian Dong, Nianhai Zhang, and Jie Dong have no competing interests to declare. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Ethical declaration

This study was conducted in accordance with the Declaration of Helsinki using procedures consistent with Good Pharmacoepidemiology Practices (GPPs) and applicable laws and regulations in China and received approval from the Ethics Committees of all participating sites which include Liaoning Cancer Hospital & Institute, Harbin Medical University Cancer Hospital, The First Affiliated Hospital of Fujian Medical University, and Zhejiang Provincial People's Hospital (Affiliated People's Hospital). As a retrospective, observational study, a waiver of informed consent was

sought and granted by all participating sites for the following reasons: 1) patients have signed the informed consent upon admission which allows their medical records or specimens to be used in other research studies, and this study complies with the conditions of the original informed consent; 2) the privacy and identity of patients can be strictly protected, to ensure that personal information will not be disclosed during the study; 3) waiving informed consent will not have any negative impact on the rights and health of patients, and the study does not involve personal privacy or commercial interests.

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