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Treatment patterns and clinical outcomes of metastatic gastric cancer in South Korea: real-world evidence from retrospective electronic medical records data

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Abstract

Background Five-year survival of patients with metastatic gastric cancer (mGC) is poor. Tumor characteristics, timing of diagnosis, and treatment patterns differ between patients from Eastern and Western regions. Therefore, we aimed to evaluate treatment patterns and outcomes of patients with mGC in South Korea.

Methods This retrospective study aimed to analyze electronic medical records. Treatment patterns were evaluated in 2,229 patients, and clinical outcomes were assessed in 2,083 patients.

Results The median age of the included patients was 60 (range, 18–92) years (62.8%, male; 95.5% had Eastern Cooperative Oncology Group performance status score of 0–1). Among tested patients, HER2-positivity, microsatellite instability high/deficient mismatch repair (MSI-H/dMMR), and PD-L1 22C3 Combine Positive Score ≥ 1 rates were 16.0%, 4.7%, and 49.1%, respectively. Of the 2,353 patients, 94.7%, 68.0%, and 52.9% received first-line (1 L), second-line (2 L), third-line (3 L) therapy, respectively. Platinum doublets were used for 1 L (61.3%); paclitaxel plus ramucirumab, 2 L (50.6%); and, irinotecan-based therapy, 3 L (51.1%). The median overall survival (OS) was 3.8 and 16.3 months in the untreated and treated patients, respectively. Overall, HER2-positive patients treated with HER-2 targeted agent had a longer OS (19.1 months), and those treated with combined HER2-targeted plus immune checkpoint inhibitor (ICI) therapy (23.1 months) had the longest OS. In HER2-negative patients, OS was 15.7 months with chemotherapy, and 17.6 months with combined chemotherapy plus ICI. No survival differences were found between patients treated with oxaliplatin and cisplatin in 1 L, irinotecan and taxane in 2 L/3L, and across 2 L to 3 L sequences.

Conclusions A survival benefit was observed with multiple lines of therapy, particularly with immune checkpoint inhibitor (ICI) therapy, in both HER2-positive and HER2-negative patients. Our findings support the benefits of multiline personalized treatments in mGC.

Keywords Gastric Cancer, Metastatic, Electronic Medical Records, HER2-targeted, Immune Checkpoint Inhibitors

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Introduction

Gastric cancer is the 5th most common cancer worldwide and one of the leading causes of cancer-related deaths. In general, Asia has high incidence and mortality rates of gastric cancer, and it is the most prevalent cancer in Korea and Japan. Although the overall gastric cancer-related death rate is decreasing owing to the diagnosis of early gastric cancers (EGCs), the prognosis of advanced and metastatic gastric cancer remains poor, with a 5-year survival rate of less than 6.8% [1, 2].

There are notable differences in the diagnostic systems and treatment strategies for gastric cancer in Eastern and Western countries. In Eastern countries, the rate of EGC is higher because of the presence of the national screening system with experienced clinicians. Biological characteristics such as cancer originating from proximal locations and well-differentiated histology are less common in Eastern than in Western countries. For resectable advanced gastric cancers, the Eastern countries use a wide range of D2+α surgeries and postoperative adjuvant therapies as the standard treatment, whereas the Western countries usually perform D1 dissection ± radiotherapy and perioperative chemotherapy [3]. Unresectable or metastatic stage IV cancers characterized by distant metastases to the liver, lung, peritoneum, or multiple lesions in the abdominal cavity remain challenging to treat. Differences in treatment regimens used and outcomes achieved between Eastern and Western countries have been observed in clinical trials and real-world data [4]. A plausible explanation for this difference in oncologic outcomes is the low tumor burden due to early diagnosis of advanced or metastatic gastric cancer by experienced clinicians. An additional explanation is the early detection of peritoneal progression, which allows timely regimen changes before the deterioration of performance status. Multidisciplinary care, including stent insertion for obstruction and ascites management, may also contribute to improved outcomes in Eastern countries. Recently, the rapid turnaround time of next-generation sequencing test reports (2–3 weeks for tissue, 1 week for fluid samples) and willingness of patients to undergo biopsy have been suggested as points of support for personalized treatment after systemic therapy including immunotherapy and novel targeted treatment. Finally, awareness of and access to clinical trials with novel agents and immune checkpoint inhibitors may account for the better prognosis of patients with disease that is refractory to standard treatment [5, 6].

In gastric cancer, the established biomarkers for immunotherapy are PD-L1 and microsatellite instability high/deficient mismatch repair (MSI-H/dMMR); those for targeted therapy are HER2 and CLDN18.2; and, those for tissue agnostic treatment are NTRK, TMB, BRAF, and RET. The most recent gastric cancer treatment strategy as a first-line treatment is a personalized design based on HER2 expression for targeted treatment and PD-L1 expression for immunotherapy. For patients with HER2-negative cancer, the CheckMate-649 study which evaluated platinum-doublet chemotherapy plus nivolumab, and the KEYNOTE-859 study which evaluated pembrolizumab plus chemotherapy demonstrated improved survival compared to that of chemotherapy alone. For patients with HER2-positive cancer, the KEYNOTE-811 study with triplet therapy (trastuzumab plus chemotherapy with pembrolizumab) showed improved clinical outcomes compared to that of doublet therapy (trastuzumab plus chemotherapy). In addition, the GLOW and SPOTLIGHT studies showed that the combination of CLDN18.2-targeting agent (zolbetuximab) and chemotherapy achieved improved survival compared to that with chemotherapy alone in CLDN18.2-expressing gastric cancer. These studies drew attention to CLDN18.2 as a novel target in gastric cancer, although the co-expression of CLDN18.2 with HER2 or PD-L1 limits the decision of first-line treatment. The chemotherapy backbone in the first-line treatment is platinum-based regimens, such as FOLFOX, XELOX, SOX, FP, XP, and SP. As a second-line treatment, in patients with HER2-negative cancer, the combination of ramucirumab and paclitaxel is recommended based on the RAINBOW Study. Other docetaxel- or irinotecan-based regimens (FOLFIRI and XELIRI) are used clinically as a second-line treatment. For patients with HER2-positive cancer including HER2-low cancer, trastuzumab deruxtecan (T-DXd) is recommended as the Destiny trials showed a survival benefit. In third-line or later treatments, the drugs are generally selected regardless of HER2 status or PD-L1 expression. The TAGS Study is the only study that demonstrated the efficacy of chemotherapeutic agent monotherapy (trifluridine/tipiracil) as a third-line treatment. Four different treatment categories (chemotherapy, targeted treatment, anti-angiogenic treatment, and immunotherapy) may contribute to improved survival in patients with metastatic gastric cancer. As the optimal treatment combination and the sequential treatment regimen have not yet been established, further biomarker studies are required [7–17].

In this study, we aimed to investigate the treatment patterns and clinical outcomes of Korean patients with metastatic gastric cancer. We compared patient characteristics between untreated patients and those who received long-term subsequent treatment. We also analyzed the proportions of patients receiving each line of therapy and patient outcomes based on biomarkers, lines of treatment, regimens, and treatment composition from real-world data in patients with metastatic gastric cancer.

Methods

This is a retrospective study based on the electronic medical records (EMR) of Yonsei Cancer Center, Severance Hospital, Yonsei University College of Medicine. Patients with pathologically confirmed metastatic gastric cancer from January 2015 to December 2022 were enrolled. Out of 2,415 patients with stage IV metastatic gastric cancer, 2,353 patients were included in this study, with the exception of 62 patients (patients with neuroendocrine carcinoma [$n = 15$], double primary cancer [$n = 35$], and gastrointestinal stromal tumors [$n = 12$]) (Additional File 1). The baseline characteristics, including age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, pathological status, histological type, surgery status, metastatic status, metastatic organ involvement, HER2 status, PD-L1 expression status, Epstein–Barr virus (EBV) status, mismatch repair/microsatellite instability (MMR/MSI) status, carcinoembryonic antigen (CEA) levels, CA19-9 levels, and neutrophil-to-lymphocyte ratio, were collected. Treatment patterns were investigated by analyzing the treatment regimen and lines of therapy used in 2,229 treated patients. Excluding 117 patients who relapsed within 6 months without receiving adjuvant therapy as a standard of care, 13 patients who relapsed between 6 months and 1 year after surgery, and 16 patients who relapsed after 1 year of surgery, the line of therapy, progression-free survival (PFS), and overall survival (OS) for each treatment regimen were analyzed in 2,083 patients (Additional File 1). This study was conducted in compliance with the ethical principles of the Declaration of Helsinki and approved by the Institutional Review Board of Yonsei University (IRB No. 4-2024-0182) to ensure patient personal information protection and compliance with research ethics.

Statistical analysis

The baseline characteristics of all patients were summarized, and the differences in disease characteristics between the treated and untreated patients were compared. The median, minimum, and maximum values were used as summary statistics for continuous variables. Intergroup differences were analyzed using a two-sample t-test or the Wilcoxon rank-sum test. Categorical variables are presented as frequencies and proportions, and intergroup differences were analyzed using the Pearson chi-squared test or Fisher exact test. The proportion of treated and untreated groups was calculated based on the previous line of therapy. Subsequent treatment patterns were analyzed in patients with treatment. Among the treated patients, the regimen used for each line of therapy was classified into each proportion, and the treatment sequence from the first- to third-line treatments was figured using a Sankey plot. Total survival was calculated from the date of diagnosis and compared between patients who received and did not receive treatment, and PFS and OS for each treatment regimen was calculated from the start date of drug administration to disease progression or death with any cause and to last follow-up or death with any cause. The comparisons between treatment groups were performed using the Kaplan–Meier method and log-rank test. All analyses were performed without adjusting for the baseline characteristics. Deaths were confirmed from the medical records. If death was not confirmed, patients were censored at the date of the last follow-up. All statistical analyses were performed using the SAS software (version 9.4; SAS Institute, Inc., Cary, NC, USA) and R version 4.4.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics and overall survival in untreated patients

The baseline characteristics of the patients are summarized in Table 1. A total of 2,353 patients with gastric cancer were included in this study; the median age of the patients was 60 years (range, 18–92 years). Of all patients, 62.8% were male and 95.5% had an ECOG performance status score of 0 or 1, which was relatively good. Poorly differentiated adenocarcinoma was the most common type (46.6%), with the proportion of diffuse type adenocarcinoma being 60.2%. Synchronous metastasis, defined as the presence of distant metastases at the time of initial cancer diagnosis, was observed in 66.5% of the patients. A total of 37.9% of the patients underwent previous gastrectomy. The number of metastatic organs involved was predominantly one (67.0%), and the main metastatic sites were the peritoneum (58.9%), followed by the liver (22.1%), bone (7.3%), and lungs (6.2%). Among the tested patients, the HER2 positivity rate was 16.0%, and the dMMR/MSI-H rate was 4.7%. Further, PD-L1 expression was found in 49.1% of patients when defined as CPS ≥ 1 using the 22C3 assay and 34.2% when defined as CPS ≥ 5 using the 28 – 8 assay. For tumor marker analysis, elevated CEA and CA 19 – 9 levels were observed in 36.1% and 32.5% of the total patients, respectively.

Several characteristic differences were observed between the treated and untreated patients. The untreated patient group had a higher median age (68 years old vs. 59 years old, $p < 0.001$), and the majority of patients had poor ECOG performance statuses ($p < 0.001$). Additionally, a high proportion of patients had higher tumor volume (involvement of two or more metastatic organs), and the frequencies of hematogenous metastasis to the liver, bone, and brain were also higher. The untreated patient group had a higher HER-positivity rate (21.9%), higher dMMR/MSI-H (10.5%) rate, and elevated levels of CEA (55.4%) and CA19-9 (53.6%).

Table 1 Patient characteristics and disease status of metastatic gastric cancer ($n = 2353$)

	Total	Treated Patients	Untreated Patients	*P*-value
	(*n* = 2353)	(*n* = 2229)	(*n* = 124)	
Median age (min – max)	60 (18–92)	59 (18–91)	68 (31–92)	< 0.001
Age (years)				< 0.001
≥65	818 (34.8%)	742 (33.3%)	76 (61.3%)	
<65	1535 (65.2%)	1487 (66.7%)	48 (38.7%)	
Sex				0.68
Male	1477 (62.8%)	1397 (62.7%)	80 (64.5%)	
Female	876 (37.2%)	832 (37.3%)	44 (35.5%)	
ECOG[a]				< 0.001
0	1673 (74.0%)	1613 (74.9%)	60 (56.6%)	
1	485 (21.5%)	455 (21.1%)	30 (28.3%)	
≥2	102 (4.5%)	86 (4.0%)	16 (15.1%)	
Unknown	93	75	18	
Pathology				0.04
Adenocarcinoma, well differentiated	80 (3.4%)	75 (3.4%)	5 (4.0%)	
Adenocarcinoma, moderately differentiated	645 (27.4%)	608 (27.3%)	37 (29.9%)	
Adenocarcinoma, poorly differentiated	1096 (46.6%)	1035 (46.4%)	61 (49.2%)	
Adenocarcinoma, undifferentiated	12 (0.5%)	9 (0.4%)	3 (2.4%)	
SRC/PCC[b]	486 (20.7%)	470 (21.1%)	16 (12.9%)	
Mucinous adenocarcinoma	22 (0.9%)	20 (0.9%)	2 (1.6%)	
Others (hepatoid adenocarcinoma, lymphoid stroma)	12 (0.5%)	12 (0.5%)	0 (0.0%)	
Histologic subtypes[c]				0.64
Intestinal	312 (32.6%)	296 (32.5%)	16 (36.4%)	
Diffuse	575 (60.2%)	550 (60.3%)	25 (56.8%)	
Mixed	69 (7.2%)	66 (7.2%)	3 (6.8%)	
Unknown	1397	1317	80	
Initial status				0.39
Synchronous	1564 (66.5%)	1486 (66.7%)	78 (62.9%)	
Metachronous	789 (33.5%)	743 (33.3%)	46 (37.1%)	
Previous gastrectomy				0.86
Yes	891 (37.9%)	845 (37.9%)	46 (37.1%)	
No	1462 (62.1%)	1384 (62.1%)	78 (62.9%)	
No. of metastatic organs				0.006
1	1577 (67.0%)	1508 (67.7%)	69 (55.6%)	
≥2	776 (33.0%)	721 (32.3%)	55 (44.4%)	
Metastasis organ[d]				
Peritoneal	1461 (58.9%)	1390 (59.4%)	71 (49.0%)	0.25
Ovary	121 (4.8%)	116 (5.0%)	5 (3.4%)	0.57
Lung	153 (6.2%)	142 (6.0%)	11 (7.6%)	0.27
Bone	181 (7.3%)	165 (7.1%)	16 (11.0%)	0.03
Liver	549 (22.1%)	510 (21.9%)	39 (26.9%)	0.03
Brain	17 (0.7%)	14 (0.6%)	3 (2.1%)	0.06
HER2[e]				0.07
Positive	372 (16.0%)	347 (15.7%)	25 (21.9%)	
Negative	1958 (84.0%)	1869 (84.3%)	89 (78.1%)	
Unknown	23	13	10	
EBV[f]				1.00
Positive	75 (3.4%)	72 (3.5%)	3 (3.0%)	
Negative	2106 (96.6%)	2009 (96.5%)	97 (97.0%)	
Unknown	172	148	24	
MMR/MSI[g]				0.01
dMMR/MSI-H	104 (4.7%)	93 (4.4%)	11 (10.5%)	
pMMR/MSS	2100 (95.3%)	2006 (95.6%)	94 (89.5%)	

Table 1 (continued)

	Total	Treated Patients	Untreated Patients	*P*-value
	(*n* = 2353)	(*n* = 2229)	(*n* = 124)	
Unknown	149	130	19	
PD-L1 22C3 CPS[h]				0.51
≥1	767 (49.1%)	735 (48.9%)	32 (54.2%)	
<1	795 (50.9%)	768 (51.1%)	27 (45.8%)	
Unknown	791	726	65	
PD-L1 28 – 8 CPS[i]				NA
≥5	13 (34.2%)	13 (34.2%)	0 (0%)	
<5	25 (65.8%)	25 (65.8%)	0 (0%)	
Unknown	2315	2191	124	
CEA [j]				< 0.001
Elevated (≥ 5)	757 (36.1%)	695 (35.0%)	62 (55.4%)	
Normal	1342 (63.9%)	1292 (65.0%)	50 (44.6%)	
Unknown	254	242	12	
CA19-9[k]				< 0.001
Elevated (≥ 34)	676 (32.5%)	616 (31.3%)	60 (53.6%)	
Normal	1403 (67.5%)	1351 (68.7%)	52 (46.4%)	
Unknown	274	262	12	
NLR[l]				0.09
Median (min-max)	2.8 (0.9–53.4)	2.8 (0.9–37.0)	3.3 (0.7–53.4)	

Percentage of patients with unknown status ([a, c, d, e, g, h, i, j]) was calculated based on 2,353 patients

[a]ECOG, Eastern Cooperative Oncology Group performance status. The ECOG performance status results of 2,260 patients (96.0%) was available

[b]SRC: signet ring cell; PCC: poorly cohesive carcinoma

[c]Histological subtypes: A total of 956 patients (40.6%) had histological subtype data

[d]Some patients had metastases at multiple sites; thus, the total number exceeded the number of patients

[e]HER2: Totally 2,330 patients (99.1%) had HER2 test results. Unknown: patients who were not tested or with missing results, and the percentage was not calculated

[f]*EBV* Epstein–Barr virus. Data were available for 2,181 patients (92.7%). Unknown: patients not tested or with missing results; percentage not calculated

[g]*MMR* Mismatch repair, *MSI* Microsatellite instability, *dMMR* Deficient mismatch repair, *MSI-H* Microsatellite instability high, *pMMR* proficient mismatch repair, *MSS* microsatellite stable. Data of 2,204 patients (93.7%) were available. Unknown: patients not tested or with missing results; percentage not calculated

[h]PD-L1 22C3 CPS: programmed cell death-ligand 1 (PD-L1) IHC 22C3 pharmaDx assay test. Data of 1,562 patients (66.4%) were available. Unknown: patients not tested or with missing results; percentage not calculated

[i]PD-L1 28 – 8 CPS: programmed cell death-ligand 1 (PD-L1) IHC 28 – 8 pharmaDx assay. Data of 38 patients (1.6%) were available. Unknown: patients not tested or with missing results; percentage not calculated

[j]*CEA* Carcinoembryonic antigen. Data of 2,099 patients (89.2%) were available. Unknown: patients not tested or with missing results; percentage not calculated

[k]*CA19-9* Carbohydrate antigen 19 – 9. Data of 2,079 patients (88.3%) were available. Unknown: patients not tested or with missing results; percentage not calculated

[l]*NLR* Neutrophil-to-lymphocyte ratio. Data of 2,159 patients (91.7%) were available. Unknown: patients not tested or with missing results; percentage not calculated

Furthermore, the difference in survival between the patient groups with and without treatment was analyzed (Fig. 3). The median overall survival (OS) of the untreated patients was 3.8 months (95% CI: 2.4–4.9). According to the HER2 status analysis, the median OS of patients with HER2-negative cancer was 4.2 months (95% CI: 2.8–5.5) and that of HER2-positive cancer was 1.7 months (95% CI: 1.5–4.0). In the untreated group, patients with HER2-positive cancer had shorter survival rates than that of patients with HER2-negative cancer, suggesting HER2 positivity to be a poor prognosis factor.

Treatment regimens and sequences

Of the 2,353 patients, 2,229 (94.7%) received first-line therapy. Of these, 1,515 patients (68.0%) received second-line therapy and 802 (52.9%) received third-line therapy (Fig. 1). Of 2,229 patients receiving first-line treatment, platinum doublet chemotherapy was the most common with 1,366 cases (61.3%), followed by HER2-targeted agent plus platinum agent with 268 cases (12.0%); platinum doublet plus ICI, 236 (10.6%), and fluoropyrimidine monotherapy, 113 (5.1%); HER2-targeted agent plus platinum doublet plus ICI, 59 (2.6%); triplet therapy, 35 (1.6%); and, other regimens, 152 (6.8%) (Table 2). Among the platinum doublet chemotherapy regimens, oxaliplatin-based regimens were the most common, accounting for 1,100 patients (49.3%). Of these, 778 patients (34.9%) received XELOX; 301 (13.5%), FOLFOX; and 21 (0.9%), SOX. In contrast, of the 266 patients (12.0%) treated with a cisplatin-based regimen, 220 patients (9.9%) received SP, followed by 36 (1.6%) receiving XP; 9 (0.4%), FP; and, 1 (≤0.1%), irinotecan plus cisplatin regimen. Altogether, 1,515 patients (68.0%) received second-line treatment, with paclitaxel plus ramucirumab being

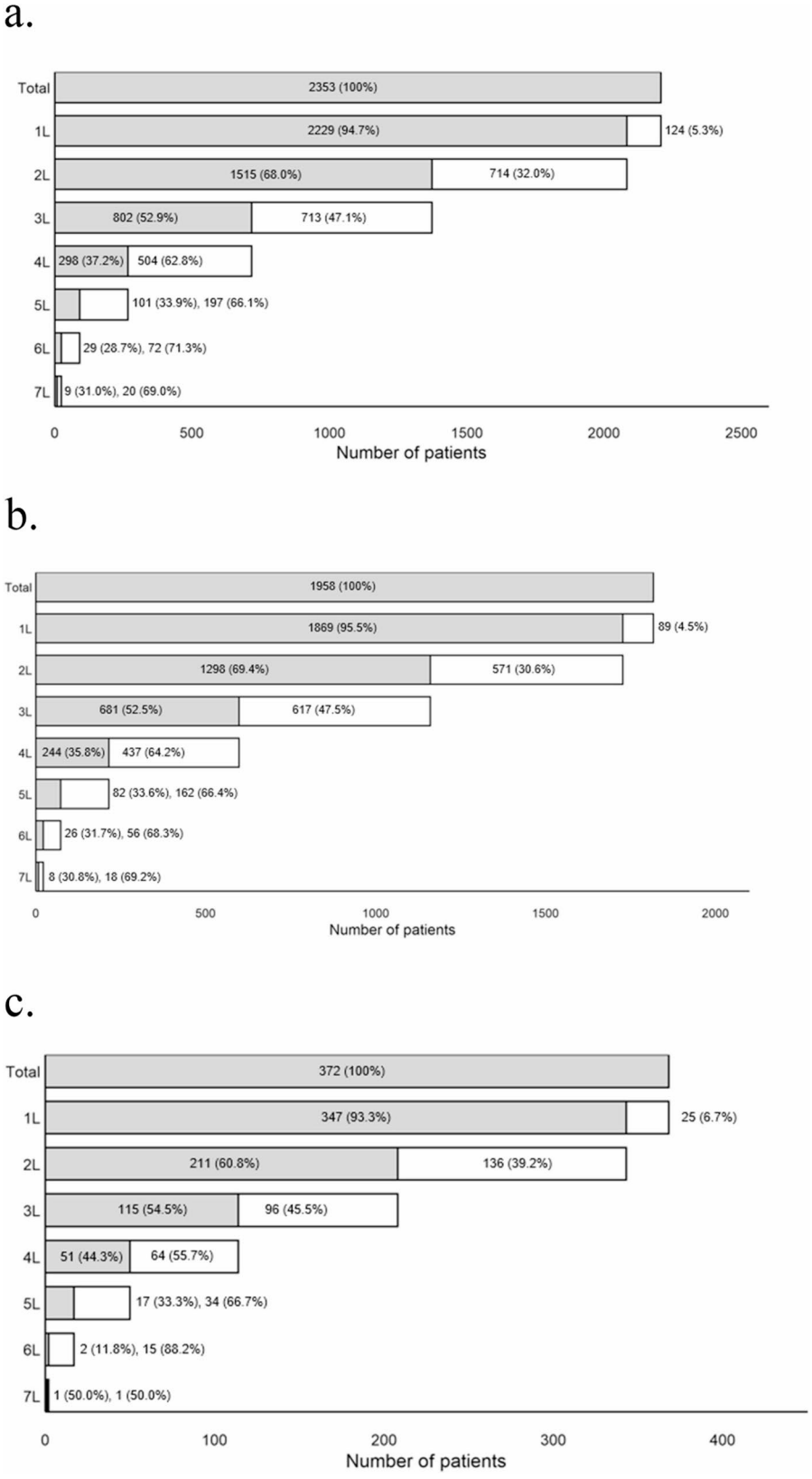

Fig. 1 Comparison of patient proportions across line of therapy; **a** Patients with metastatic gastric cancer, regardless of HER2 status; **b** Treated patients with metastatic HER2-negative gastric cancer; **c** Treated patients with metastatic HER2-positive gastric cancer. Treated (gray); Untreated (white)

Table 2 Treatment regimens for each line of therapy

Treatment	Total (*n* = 2229)
1 L Treatment Regimen	2229
Fluoropyrimidine monotherapy	113 (5.1%)
Platinum doublet	
Oxaliplatin-based	1100 (49.3%)
Cisplatin-based	266 (12.0%)
Platinum doublet + ICI	236 (10.6%)
HER2-Targeted Agent + Platinum doublet [a]	268 (12.0%)
HER2-Targeted Agent + Platinum doublet + ICI [a]	59 (2.6%)
Triplet therapy	35 (1.6%)
Others	152 (6.8%)
2 L Treatment Regimen	**1515**
Paclitaxel + Ramucirumab	767 (50.6%)
Taxane-based	251 (16.6%)
Irinotecan-based	51 (3.4%)
ICI-based	54 (3.6%)
ICI monotherapy	24 (1.6%)
HER2-Targeted Agents-based [a]	54 (3.6%)
Others	314 (20.6%)
3 L Treatment Regimen	**802**
Irinotecan-based	410 (51.1%)
Taxane-based	43 (5.4%)
ICI monotherapy	82 (10.2%)
Irinotecan + ICI	29 (3.6%)
Paclitaxel + Ramucirumab	36 (4.5%)
Trifluridine/tipiracil	8 (1.0%)
Others	194 (24.2%)
4 L ~ 7 L Treatment Regimen	**438**
Irinotecan-based	99 (22.6%)
Taxane-based	57 (13.0%)
ICI monotherapy	78 (17.8%)
ICI-based	11 (2.5%)
Trifluridine/tipiracil	12 (2.7%)
Ramucirumab-based	8 (1.8%)
Others	173 (39.6%)

ICI Immune checkpoint inhibitor

[a]HER2-targeted agents + Chemotherapy and HER2-targeted agents + chemotherapy + ICI were used for HER2-positive metastatic gastric cancer. Additional details on the treatment regimens for each line of therapy are provided in Additional File 5

the most common treatment (767 patients, 50.6%). In total, 251 patients (16.6%) received taxane-based therapy (docetaxel or paclitaxel); 51 (3.4%), irinotecan-based therapy; 54 (3.6%), ICI-based therapy; 24 (1.6%), ICI monotherapy; 54 (3.6%), HER2-targeted therapy; and, 314 (20.6%), other agents. Among 802 patients receiving third-line treatment, irinotecan-based therapy was the most common (410 patients, 51.1%). Additionally, ICI monotherapy was administered in 82 patients (10.2%), followed by taxane-based therapy in 43 (5.4%); paclitaxel plus ramucirumab, 36 (4.5%); a combination of irinotecan plus ICI, 29 (3.6%); and, trifluridine/tipiracil, 8 (1.0%); and other agents, 194 (24.2%). The fourth- to seventh-line treatments were similar to those used for third-line treatment. Additional File 2 summarizes the details of each treatment regimen based on HER2-positive versus HER2-negative status in addition to that in the total population.

The proportion of patients receiving first-, second-, and third-line therapies was similar in both HER2 negative and HER2 positive groups (Fig. 1). The treatment sequence according to the HER2 status is presented in the Sankey plot in Fig. 2. In the HER2-negative patient group, the oxaliplatin-based regimen was the most common first-line treatment, and the patients were mainly switched to paclitaxel plus ramucirumab as the subsequent second-line treatment. Irinotecan-based regimens were the most common third-line treatments. In the HER2-positive group, the HER2-targeted agent plus platinum doublet regimen was predominantly used as first-line treatment. Some patients received HER2-targeted therapy in combination with ICI. After second-line treatment, the frequency of HER2-targeted therapy decreased, and the regimen was switched to paclitaxel plus ramucirumab or an irinotecan-based regimen. Both groups showed an increasing rate of stopping treatment and switching to supportive care as the lines of therapy progressed.

Real-world treatment outcomes by line of therapy and treatment regimen in treated patients

The median OS was 16.3 months in the 2,229 treated patients (overall) (95% CI: 15.4–16.9), 19.1 (95% CI: 17.5–20.5) in the HER2-positive group, and 15.7 (95% CI: 14.9–16.5) in the HER2-negative group ($p < 0.001$) (Fig. 3). The PFS and OS for each line of therapy are summarized in Table 3. As the number of lines of treatment increased, PFS and OS declined gradually across all patients. For the first- and second-line treatments, the HER2-positive group showed longer PFS and OS than the HER2-negative group, but after third-line treatment, there was no difference between the two groups. Specifically, for the first-line treatment, the median PFS and OS for all patients were 6.7 months (95% CI: 6.3–6.9) and 15.2 months (95% CI: 14.4–15.9), respectively. The HER2-negative group had a median PFS and OS of 6.4 months (95% CI: 6.1–6.6) and 14.7 months (95% CI: 14.0–15.4), and the HER2-positive group had a median PFS and OS of 8.5 months (95% CI: 7.7–9.5) and 18.1 months (95% CI: 16.7–19.6), respectively. With the second-line treatment, all patients had a median PFS and OS of 3.8 months (95% CI: 3.6-4.0) and 7.8 months (95% CI: 7.4–8.4); HER2-negative group, 3.7 months (95% CI: 3.5-4.0) and 7.6 months (95% CI: 7.1–8.0); and, HER2-positive group, 4.1 months (95% CI: 3.8–4.9) and 9.3 months (95% CI: 8.5–11.3), respectively. With third-line or later line treatment, both the HER2-positive and HER2-negative group, as well as

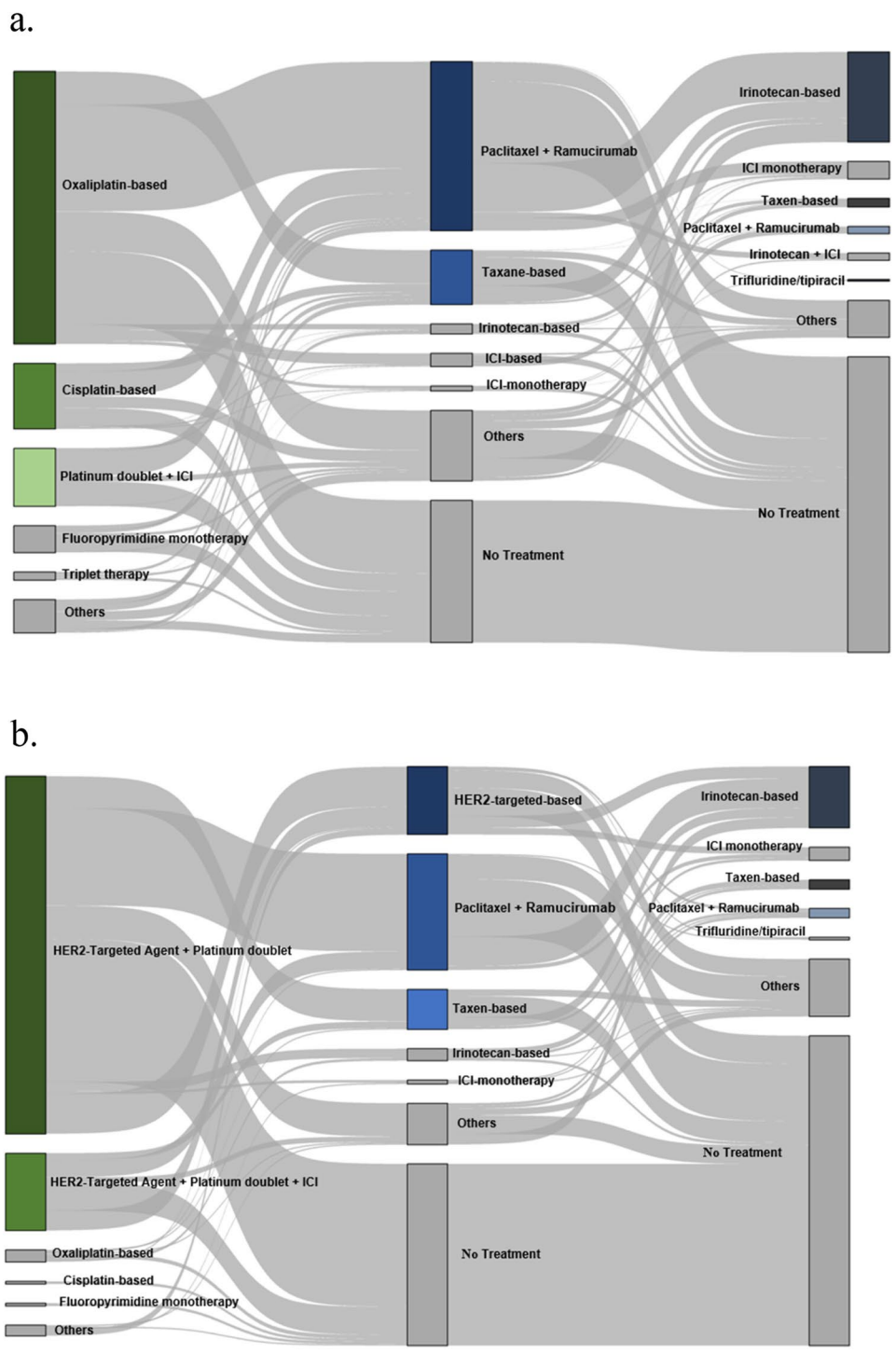

Fig. 2 Sankey diagrams depicting treatment sequences across 1L, 2L, and 3L according to HER2 status; **a** HER2-negative group; **b** HER2-positive group. ICI, immune checkpoint inhibitor

the overall population, showed similar median PFS and OS.

In the first-line treatment in the HER2-negative group, the PFS and OS were compared among the monotherapy, platinum doublet, and platinum doublet plus ICI groups (Additional File 3a). The median PFS was 4.5 months (95% CI: 3.7–6.5), 6.1 months (95% CI: 5.8–6.4), and 8.5 months (95% CI: 7.2–9.8) ($p < 0.001$), whereas the median OS was 9.6 months (95% CI: 6.6–13.6), 14.3 months (95% CI: 13.4–15.1), and 17.6 months (95% CI: 15.9–21.0), respectively, and all the three groups were significantly different ($p < 0.001$). There was no difference

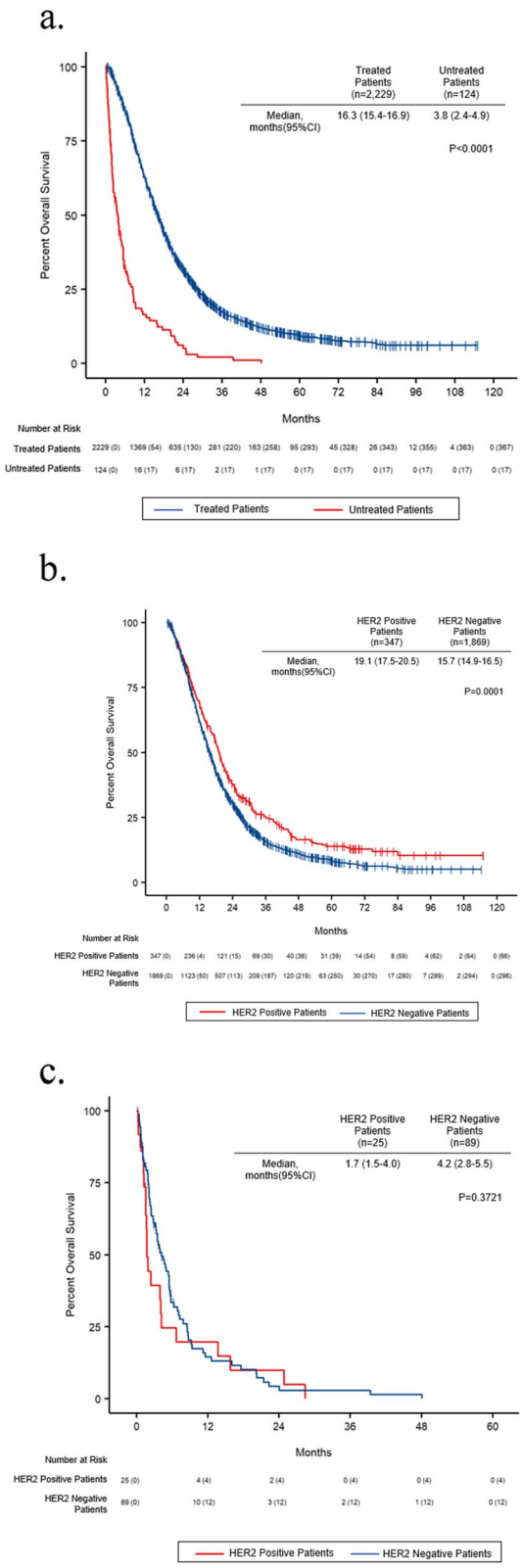

Fig. 3 Overall survival according to the treatment status for all patients, patients with HER2-negative cancer, and patients with HER2-positive cancer; **a** Overall survival for treated vs. untreated patients, regardless of HER2 status; **b** Overall survival for treated patients according to HER2 status (HER2-positive vs. HER2-negative); **c** Overall survival for untreated patients according to HER2 status (HER2-positive vs. HER2-negative)

in the median PFS and OS between the patients undergoing the oxaliplatin- and cisplatin-based regimens, and both the treatment groups showed similar treatment outcomes (Additional File 3b). The treatment outcomes of the HER2-positive group were compared between those who received a combination of HER2-targeted therapy plus a platinum doublet and those who received the same combination with an ICI. The median PFS was 8.5 months (95% CI: 7.4–9.3) in the HER2-targeted plus platinum doublet group and 10.4 months (95% CI: 7.9–17.6) in the ICI combination group, showing a significant improvement in the latter group ($p = 0.02$). Furthermore, the median OS was 17.3 months (95% CI: 15.1–19.3) and 23.1 months (95% CI: 18.3–28.1), respectively, with a trend toward prolonged survival in the ICI combination group ($p = 0.07$) (Additional File 3c). Within the ICI combination group, patients with PD-L1 CPS ≥ 1 exhibited numerically longer median PFS (10.5 months; 95% CI, 8.0–18.3) and median OS (24.5 months; 95% CI, 18.4–30.1) than did those with CPS < 1 (median PFS, 7.7 months; 95% CI, 5.5–21.5; median OS, 18.1 months; 95% CI, 7.9–73.1), although the difference was not statistically significant (Additional File 5). The PFS in second-line treatment showed significant differences between the irinotecan-based regimen, taxane monotherapy, and paclitaxel plus ramucirumab combination therapy ($p < 0.001$), but OS did not ($p = 0.23$) (Additional File 3d). In the third-line treatment, both the irinotecan-based and taxane-based regimens showed no differences in PFS and OS ($p = 0.82$ and $p = 0.17$) (Additional File 3e).

The OS by treatment sequence of irinotecan-based regimen and taxane-based regimen was compared between the second-line and third-line treatments. In the second-line setting, the median OS for taxane followed by irinotecan was 11.3 months (95% CI: 8.4–12.3), whereas that for irinotecan followed by taxane was 6.1 months (95% CI: 3.9–16.3), showing numerical differences ($p = 0.80$). In the third-line setting, the median OS for irinotecan followed by taxane was 3.0 months (95% CI: 1.4–6.7) and that for taxane followed by irinotecan was 6.9 months (95% CI: 3.5–8.9). No significant difference was observed between the two groups ($p = 0.71$) (Additional File 4).

Table 3 Progression-free survival (PFS) and overall survival (OS) for each line of therapy in each subgroup: total patients, patients with HER2-negative cancer, and patients with HER2-positive cancer

Line of Therapy	No of Patients	Median PFS (months, 95% CI)	Median OS (months, 95% CI)
1 L Treatment	2083	6.7 (6.3–6.9)	15.2 (14.4–15.9)
HER2-negative	1728	6.4 (6.1–6.6)	14.7 (14.0–15.4)
HER2-positive	343	8.5 (7.7–9.5)	18.1 (16.7–19.6)
2 L Treatment	1374	3.8 (3.6–4.0)	7.8 (7.4–8.4)
HER2-negative	1161	3.7 (3.5–4.0)	7.6 (7.1–8.0)
HER2-positive	207	4.1 (3.8–4.9)	9.3 (8.5–11.3)
3 L Treatment	717	2.2 (1.9–2.4)	5.2 (4.8–5.7)
HER2-negative	555	2.2 (1.9–2.4)	5.1 (4.7–5.7)
HER2-positive	111	2.3 (1.7–2.7)	5.6 (4.4–7.2)
4 L Treatment	267	2.0 (1.7–2.3)	4.6 (4.1–5.2)
HER2-negative	210	1.9 (1.7–2.2)	4.6 (4.1–5.3)
HER2-positive	49	2.3 (1.6–2.9)	4.9 (2.6–6.0)
5 L Treatment	91	2.1 (1.8–2.6)	4.7 (3.4–5.9)
HER2-negative	69	2.1 (1.8–3.0)	5.3 (3.6–6.7)
HER2-positive	17	1.9 (1.2–3.0)	2.9 (1.8–4.6)
6 L Treatment*	24	1.6 (1.2–2.4)	4.5 (1.7–5.2)
7 L Treatment*	9	2.0 (0.4–3.6)	3.6 (1.2–6.3)

1 L; 1st line, 2 L; 2nd line, 3 L; 3rd line, 4 L; 4th line, 5 L; 5th line, 6 L; 6th line, 7 L; 7th line

NR Not reached, *OS* Overall survival, *PFS* Progression-free survival

*OS and PFS according to HER2 status were not reported for 6 L and 7 L treatments due to insufficient data

Discussion

This study reflected the disease characteristics of metastatic gastric cancer in a wide range of ages, disease conditions, treatment patterns, and outcomes in a real-world setting, based on data from a high-volume hospital in Korea.

The median age of the patients diagnosed with metastatic gastric cancer was 60 years (range, 18–92), which was relatively higher than the median age (57 years) reported in a Korean real-world study approximately 10 years ago. In contrast, the patient characteristics aligned with previous studies in that the proportion of patients aged < 65 years among all patients was still high, the majority of the patients were male, a high proportion of patients had a good ECOG performance status, a high proportion of patients did not undergo gastrectomy in the past, and many patients had < 2 organs involved in metastasis [18]. In this study, the untreated patient group was older and had a poor ECOG performance status, a high proportion of patients with metastases to various organs, and a short median OS of 3.8 months (95% CI, 2.4–4.9). In contrast, 94.7% of patients received anticancer therapy, and the median OS of the treated patients was 16.3 months (95% CI, 15.4–16.9), which showed remarkable survival improvement. According to the US real-world data, approximately 75% of the total patients received first-line treatment, with a median OS of 10.7 months (95% CI, 10.2–11.2). The majority of treated patients were predominantly younger men, and proactive treatment trends were observed [19]. In a German real-world study, 49.8% of all patients were treated with anticancer therapy, and the median OS of the treated patients was 12.7 months (95% CI, 12.1–13.3). Moreover, male, younger patients, and those with fewer comorbidities tended to receive more treatment [20]. In contrast, the current study showed that most Korean patients with metastatic gastric cancer received anticancer therapy, and the survival outcomes of the treated patients were more favorable than that of those in the US and Germany. Compared to Western countries, the differences in treatment rates and survival outcomes observed in this study supported the hypothesis that the diagnosis and treatment strategies for gastric cancer differ between Western and Eastern countries on top of biological differences [3].

Regarding the treatment patterns observed in this study, more than 50% of the patients received first-line to third-line treatment, but the treatment rate declined dramatically after the fourth-line treatment. Platinum doublet chemotherapy was used for patients with HER-negative cancer as the first-line treatment, and HER2-targeted therapy was used for patients with HER2-positive cancer. A combination of ICI was administered to some patients in both groups. However, the available medicines for third-line and later treatments were limited, resulting in a majority of the patients participating in clinical trials. This finding is consistent with those of previous studies, which have indicated that effective treatment options for patients with gastric cancer beyond the third-line setting remain lacking. Despite these limitations, the treatment strategies used in this study largely adhered to the latest clinical guidelines in real-world practice [4, 7, 17, 21].

In this study, the first-line treatment with the longest OS was the combination of HER2-targeted agent plus platinum doublet plus ICI for the treatment of patients with HER2-positive cancer, and the median OS was 23.1 months (95% CI, 18.3–28.1). Within this ICI-containing regimen in HER2-positive patients, those with PD-L1 CPS ≥ 1 tended to have more favorable survival outcomes than did those with CPS < 1. The difference was not statistically significant, possibly due to the limited sample size. This real-world observation is consistent with existing clinical evidence. Additionally, the median OS of the combination of platinum doublet and ICI in patients with HER2-negative cancer was 17.6 months (95% CI, 15.9–21.0). This result corroborated real-world data: the addition of ICI to the conventional standard of care, platinum doublet or trastuzumab-based regimens, improved OS, as reported by the KEYNOTE-811, KEYNOTE-859,

and CheckMate-649 studies [8–10]. Of the most widely used doublet chemotherapies in the first-line treatment, oxaliplatin- and cisplatin-based regimens had a median OS of 14.4 months (95% CI, 13.3–15.4) and 14.2 months (95% CI, 12.9–15.9), respectively, showing no observed difference between the two regimens. These findings are consistent with those of previous studies that reported similar treatment outcomes for oxaliplatin- and cisplatin-based regimens [22–25]. The median OS of the combination of paclitaxel plus ramucirumab in the second-line treatment was 7.5 months (95% CI, 7.0–8.2), which was relatively shorter than the median OS of 9.6 months (95% CI: 8.5–10.8) in the RAINBOW trial and 10.03 months (95% CI: 9.33–10.73) in Korean real-world data [14, 26]. In this study, as the data on treatment duration, dose intensity, and toxicities were not analyzed, it is necessary to carefully interpret the clinical outcomes of paclitaxel plus ramucirumab that might be induced from different patient population. In second-line treatment, the median OS of taxane monotherapy was 6.5 months (95% CI, 5.5–7.7). In the third-line treatment, the median OS of irinotecan-based regimens was 5.1 months (95% CI, 4.7–5.6), and the median OS of taxane-based regimens was 6.7 months (95% CI, 4.3–8.1), which showed no significant differences. Additionally, the survival outcomes related to the treatment sequence of irinotecan-based and taxane-based regimens did not differ significantly. The finding of no difference in OS between the two regimens in the later-line treatments was consistent with the report of Kang et al. [27].

This study had several strengths and limitations. In terms of strengths, this study reflected the real-world setting well by including patients with metastatic gastric cancer with a wide range of ages, disease statuses, and treatment phases from a high-volume hospital in Korea, which could lead to greater representativeness. Additionally, information that is difficult to obtain from claims data-based studies, such as PFS, lines of therapy, treatment regimen, and treatment transition, could be collected relatively precisely from EMR. The limitations of this study include the possibility of selection and information bias owing to its retrospective nature. Furthermore, detailed clinical information, such as treatment duration, dose intensity, and toxicities, was not collected, and an accurate causal relationship with treatment outcomes could not be confirmed. Additionally, trastuzumab deruxtecan (T-DXd) for patients with HER2-positive cancer and zolbetuximab for patients with HER2-negative cancer were not approved in Korea during the study period. Further research is needed to assess the clinical impact with these agents.

Conclusion

This study shows that treatment strategies adopted in real-world settings are consistent with International and Korean guidelines, and relatively improved treatment outcomes were observed through the analysis of treatment patterns and changes in the characteristics of patients with metastatic gastric cancer in Korea.

Abbreviations

PFS	Progression-free survival
OS	Overall survival
MSI-H/dMMR	Microsatellite instability high/deficient mismatch repair
ICI	Immune checkpoint inhibitor
ECOG	Eastern Cooperative Oncology Group
EGC	Early gastric cancers
CEA	Carcinoembryonic antigen
EBV	Epstein–Barr virus
CPS	Combined Positive Score
HER2	Human epidermal growth factor receptor 2

Supplementary Information

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Additional file 1. Study flow diagram for patient selection and analysis.

Additional file 2. Comprehensive overview of treatment regimens: total patients, patients with HER2-negative cancer, patients with HER2-positive cancer, and patients with HER2 status unknown.

Additional file 3. PFS and OS by treatment regimen across the 1L, 2L, and 3L therapies.

Additional file 4. OS according to treatment sequence of irinotecan-based and taxane monotherapy regimens in 2L and 3L treatments.

Additional file 5. PFS and OS according to PD-L1 CPS (≥1 vs <1) in the HER2-positive patients treated with HER2 targeted agent, chemotherapy, and ICI.

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Authors' contributions

E.K.:Conceptualization, Methodology, Validation, Formal analysis, Writing – original draft; J-Y.S.: Methodology, Supervision, Writing-Review & Editing; S.P.: Methodology, Data Curation, Investigation, Formal analysis. Writing-Review & Editing; J.H.Y: Investigation, Data Curation; W.S.Kwon: Investigation, Data Curation, Writing-Review & Editing; C-k.L.: Investigation, Data Curation, Writing-Review & Editing; M.J.: Investigation, Data Curation, Writing-Review & Editing; H.S.K.: Investigation, Data Curation, Writing-Review & Editing; H.C.C.: Investigation, Data Curation, Writing-Review & Editing; S.Y.R.: Conceptualization, Methodology, Validation, Supervision, Writing-Review & Editing. All authors read and approved the final manuscript.

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Data availability

The datasets generated and/or analysed during the current study are not publicly available due to institutional confidentiality policies but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Yonsei University (IRB No.4-2024-0182). This study was a retrospective analysis, and the need for obtaining informed consent was waived by the institutional review board.

Consent for publication

Not applicable.

Competing interests

C-k.L. received honoraria from Astellas Pharma, AstraZeneca, Servier, Dong-A ST, Boryung Pharmaceuticals, and Roche; consulting fees from MSD, Roche, and Daiichi Sankyo; and research grants or support from Ono Pharmaceuticals, Celltrion, Boryung Pharmaceuticals, and Lunit Inc (outside the submitted work). S.Y.R. received honoraria from Amgen, Astellas, Astra Zeneca, MSD, Daiichi Sankyo, BMS, and Ono; consulting fees from Amgen, Astellas, Arcus, Astra Zeneca, BeiGine, Beringer Ingelheim, BMS, Ono, Daiichi Sankyo, Gilead, Indivumed, LG Biochemical, MSD, and Qureator; and research grants or support from Amgen, Astellas, Beigine, Beringer Ingelheim, BMS, Ono, Daiichi Sankyo, Eli Lilly, Ipsen, Roche, MSD, Merck, Jazz, Sanofi-Aventis, Gilead, and Taiho. The other authors declare that they have no conflict of interest.

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