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Long-term relative survival of patients with gastric cancer from a large-scale cohort: a period-analysis

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Abstract

Background Gastric cancer poses a significant global health challenge. We aim to use period analysis to assess the changes in gastric cancer treatment at our center over the past 15 years. This study reflects the current state of gastric cancer treatment at our center and provides valuable data to support clinical advancements.

Method We used period analysis to evaluate the survival status of 3915 patients with gastric cancer at Nanfang Hospital, Southern Medical University, over a 15-year period spaning from 2008 to 2022. The 5-year relative survival rates were analyzed.

Result Our findings indicate that the 5-year relative survival rate at our center from 2018 to 2022 is 71.4%. From 2018 to 2022, the 5-year relative survival rates for patients aged < 40, 40–54, 55–69, and ≥ 70 reached 67.5%, 73.5%, 72.0%, and 67.1%, respectively. For stage IV patients, the 5-year relative survival rate reached 29% in 2018–2022. For stage I-III patients, the 5-year relative survival rate reached 89.7% in 2018–2022. The five-year relative survival rate for patients who underwent laparoscopic surgery at our center rose from 50.3% in 2008–2012 to 71.4% in 2018–2022. Overall, there has been a notable increase in the 5-year relative survival rates, regardless of age, gender, region, or tumor stage.

Conclusion Period analysis over the past 15 years shows significant improvement in the 5-year survival rate for gastric cancer at our center. This progress is due to standardized surgical techniques, perioperative management, and immunotherapy, providing robust data for evaluating the efficacy of recent treatments.

Keywords Gastric cancer, Period analysis, 5-year relative survival

Introduction

Gastric cancer poses a serious threat to humanity, representing a major challenge to global health. According to the latest report from the Global Cancer Statistics Database, gastric cancer ranks fifth in global cancer incidence and fourth in cancer mortality, highlighting its substantial impact on public health [1]. Gastric cancer incidence is significantly higher in East Asia and Eastern Europe, while lower in North America, Northern Europe, and Africa. This global disparity is likely due to a combination of environmental, genetic, and infectious factors [2]. Although the incidence of gastric cancer has declined in

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some countries in recent years, mortality rates remain high, and the survival rate has increased only slowly, even with advances in medical technology and the implementation of gastric cancer screening programs. Consequently, gastric cancer remains one of the major challenges facing global public health [3].

The increase in survival rates can be attributed to early diagnosis and timely radical surgery for gastric cancer, the standardization of gastric cancer surgeries, and more accurate staging through laparoscopic examination, among other factors. The Dutch trial, a nationwide prospective randomized clinical trial, indicates that D2 lymph node dissection offers lower local recurrence and gastric cancer-related mortality rates than D1 surgery. Thus, it has become the preferred surgical method for patients with resectable gastric cancer [4]. Multiple single-center and multicenter data have shown that D2 lymph node dissection is the most effective surgical approach for advanced gastric cancer and gastric cancer with positive lymph node metastasis [5, 6]. When patients with progressive gastric cancer underwent D1 and D2 lymph node dissection, patients who underwent D2 lymph node dissection had a higher five-year survival rate. However, more extensive lymph node dissections beyond the D2 procedure do not significantly improve 5-year survival. Randomized controlled trials conducted in Japan (JLSSG0901), Korea (KLASS-02), and China (CLASS-01) have endorsed laparoscopic D2 gastrectomy for advanced gastric cancer, drawing parallel conclusions. This technique lessens postoperative complications and reduces hospitalization durations while ensuring lymph node dissection and long-term survival rates comparable to those of open surgery [7, 8].

With the rapid advancement of immunotherapy, there have been significant shifts in the treatment strategies for advanced gastric cancer in recent years. The KEYNOTE-059 trials have shown that Pembrolizumab is both effective and exhibits manageable safety profiles in patients with advanced gastric or gastroesophageal junction cancer [9]. Furthermore, the ATTRACTION-2 study proposes Nivolumab as a novel therapeutic choice for patients with advanced gastric or gastroesophageal junction cancer who have undergone extensive pretreatment [10]. The findings from these studies mark significant advancements in immunotherapy that are poised to substantially enhance survival rates for patients with advanced gastric cancer. Recently, classification based on molecular biomarkers, such as Programmed Death Ligand 1 (PD-L1), Microsatellite Instability (MSI), and Human Epidermal Growth Factor Receptor 2 (HER2), has provided opportunities to identify patients who may benefit from immunotherapy or target therapy. Advances in molecular diagnostics have enabled the characterization of gastric cancer's genetic profile and the identification of novel potential molecular targets. Currently, systemic treatment for advanced gastric cancer (GC) patients, which includes chemotherapy, targeted therapy, and immunotherapy, has significantly evolved in recent years. For resectable GC, perioperative chemotherapy has become the standard treatment method. Current research is investigating the potential advantages of targeted or immunotherapy during the perioperative or adjuvant treatment phases. Additionally, the implementation of Multidisciplinary Team (MDT) allows patients to receive more personalized and standardized treatment plans, thereby increasing their long-term survival rates [1].

Gastric cancer has a relatively poor prognosis, with a global age-standardized 5-year net survival rate typically ranging between 20% and 40%. According to a study conducted in China, the 5-year survival rate for gastric cancer in China is approximately 35.9%, markedly lower than rates exceeding 60% seen in Japan and South Korea. In China, there is a lack of research based on hospital cohorts concerning long-term survival analysis and progress in treatment methods for patients. The Kaplan-Meier curve typically uses the complete data set from the start to the end of a study, which may include data on older treatment methods or technologies that are no longer considered best practice. It cannot sensitively reflect the impact of recent medical advancements, such as new technologies and medications, on survival rates. Period analysis, as an advanced method of survival analysis, offers a new perspective for accurately reflecting the outcomes and trends in gastric cancer treatment. It can promptly capture the impact of the latest treatment advances on survival rates [11, 12]. Employing period analysis with data from gastric cancer patients at Southern Medical University's Southern Hospital, this research recently evaluated the long-term survival rates for our gastric cancer patients between 2008 and 2022, investigating the disparities in five-year relative survival rates based on gender, age, clinical staging, surgical approaches, and residence. Our center is a founding and principal member of the CLASS research group. We aim to use period analysis to accurately assess the changes in gastric cancer treatment at our center over the past 15 years, reflecting our institution's treatment practices and providing more accurate data to support the clinical management of gastric cancer.

Patients and methods

Data source

This study is in accordance with the principles specified in the Declaration of Helsinki. The study's data collection protocol was approved by the Ethics Committee at Nanfang Hospital of Southern Medical University. Written

informed consent was acquired from all patients involved in the study.

Statistical analysis

Patient survival data over a 15-year span was categorized into three intervals based on the year of diagnosis: 2008–2012, 2013–2017, and 2018–2022. This study encompasses variables such as gender, age at diagnosis, dates of diagnosis and surgery, last follow-up, survival status during follow-up, clinical and pathological stages, surgical approach, and long-term residence. Ages were categorized into four groups: <40 years, 40–54 years, 55–69 years, and ≥70 years. To obtain more current and accurate survival estimates, we employed the period analysis method to calculate survival rates. Unlike conventional complete analysis, period analysis emphasizes follow-up experiences from more recent observation periods and excludes earlier data.

This approach concentrates on counting deaths and those at risk within a defined recent period to calculate the survival function, thus improving the relevance of survival estimates by incorporating the most recent advancements in treatment and care, making it especially applicable to cancer research. Period analysis involves truncating the survival data at the start and end of chosen date intervals, thereby allowing the results to focus on the most recent survival experiences. The objective is to precisely estimate the survival rates of a population during a designated time period. As an illustration, the five-year survival rate of gastric cancer patients between 2013 and 2017 was computed using period analysis.

The study subjects include two groups: one consists of patients newly diagnosed during the period 2013–2017; the other comprises patients diagnosed during 2008–2012 (before the study period) and who survived into the 2013–2017 study period. The follow-up period is from 2013 to 2017. This is achieved by examining survival within this specific time frame, rather than considering data across all time as traditional methods do. More precisely, the survival function for the k-th year (Sk) is represented by the formula below:

$$S_k = \prod_{i=1}^{k} \left(1 - \frac{d_i}{L_i - \frac{c_i}{2}}\right)$$

In this context, **d**i denotes the deaths in year i, **L**i denotes the initial population size in year i, and ci denotes the number of censored individuals in that year. To calculate the actual survival rate for the ***k***-th year (Sk), it is necessary to multiply the conditional relative survival rates for each year within ***k***. The relative survival (RS) rate is represented by the ratio of actual survival rates to expected survival rates, and is used to analyze survival trends within a specific time period. For the calculation of the five-year relative survival rate, the comparison is made between actual and expected survival, with the expected survival calculated using the Ederer II method. RS and its standard error are computed using the Greenwood method. The entire computational process is conducted using the "PeriodR" package within R software.

Results

Basic characteristics of the cohort are shown in Table 1. A total of 3,915 patients were enrolled in this study, including 2,607 men and 1,308 women. The average age at diagnosis was 56.9 years. The average Body Mass Index (BMI) was 22.2 kg/m2. According to tumor staging, there were 1,105 patients in Stage I, 913 in Stage II, 1,140 in Stage III, and 757 in Stage IV. Among the patients, 3,457 underwent laparoscopic surgery. Patients were categorized by age at diagnosis into <40 years (362 patients), 40–54 years (1,155 patients), 55–69 years (1,847 patients), and ≥70 years (551 patients). The study included 2,553 patients from urban areas and 1,362 from rural areas.

Trends in five-year relative survival rates for gastric cancer patients

It is evident that the five-year relative survival rate at our center elevated from 53.0% in the period from 2008 to 2012 to 71.4% in the period from 2018 to 2022, indicating an overall upward trend (Table 2). For males, the five-year relative survival rate grew from 56.6% in the 2008–2012 period to 70.7% in the 2018–2022 period. For Females, the five-year relative survival rate grew from 47.8% in the 2008–2012 period to 72.7% in the 2018–2022 period (Fig. 1A).

Trends in five-year relative survival rates for gastric cancer patients across different age groups and between urban and rural areas

From the period of 2008–2012 to 2018–2022, survival rates for different age groups increased from 46.5% for patients under 40, 60.4% for those aged 40–54, 53.4% for those aged 55–69, and 39.2% for those aged 70 or older, to 67.5%, 73.5%, 72.0%, and 67.1% respectively (Fig. 1B). Overall, there was an upward trend in survival rates across all age groups, with the largest increase observed in patients aged 70 and older, at 27.9%. In the 2018–2022 period, the highest five-year relative survival rate, 73.5%, was noted in patients aged 40–54. The survival rates have significantly improved between urban and rural areas. From 2018 to 2022, the five-year relative survival rate for patients in urban areas at our center increased to 74.6%, while the five-year relative survival rate for patients in rural areas rose to 66.8%. (Fig. 1C).

Table 1 Demographics and clinical characteristics of the study patients

Characteristics	Number of Cases (%)	Diagnosed time		
		2008-2012	2013-2017	2018-2022
Total	3915(100)	858	1282	1775.0
Sex				
man	2607(66.6)	582	853	1172
woman	1308(33.4)	276	429	603
Age, y				
Mean (SD)	56.9	55.7	56.4	57.7
BMI				
Mean (SD)	22.2	21.4	22.0	22.5
Histology				
Signet-ring cell	1027(26.2)	140	308	579
Other	2888(73.8)	718	974	1196
Laparoscopic	3457(88.3)	500	1190	1767
Pathologic T stage				
T1	819(20.9)	129	276	414
T2-T3	2486(63.5)	562	771	1153
T4	610(15.6)	167	235	208
Pathologic N stage				
N0	1411(36.0)	249	488	674
N1	974(24.9)	311	274	389
N2	607(15.5)	132	171	304
N3	923(23.6)	166	349	408
Pathologic M stage				
M0	3158(80.7)	658	1037	1463
M1	757(19.3)	200	245	312
Pathologic TNM stage				
Ia	629(16.1)	88	211	330
Ib	476(12.2)	55	157	264
IIa	492(12.6)	105	166	221
IIb	421(10.7)	65	103	253
IIIa	523(13.3)	195	161	167
IIIb	227(5.8)	74	92	61
IIIc	390(10.0)	76	147	167
IV	757(19.3)	200	245	312
Age at diagnosis (years)				
<40	362(9.2)	94	122	146
40~55	1155(29.5)	277	383	495
55~70	1847(47.2)	372	612	863
≥70	551(14.1)	115	165	271
Region				
Urban area	2553(65.2)	620	907	1026
Rural area	1362(34.8)	238	375	749

Trends in five-year relative survival rates for gastric cancer patients according to clinical staging and laparoscopic approach

Surgical patients are categorized into four stages according to clinical staging. Stage I patients have maintained a five-year relative survival rate over 90%, showing negligible change between 2008 and 2022. The five-year relative survival rates for Stage II, III, and IV patients increased from 68.2%, 60.3%, and 13.8% in 2008–2012 to 85.4%, 70.2%, and 29.0% in 2018–2022, respectively (Fig. 1D). The five-year relative survival rate for patients who underwent laparoscopic surgery at our center rose from 50.3% in 2008–2012, to 52.1% in 2013–2017, and further to 71.4% in 2018–2022. From 2013 to 2022, we observed a significant increase in the survival rate for laparoscopic surgery, with an increase of 19.3% (Fig. 1E).

Discussion

In present study, through period analysis, we observed a significant elevation in the 5-year relative survival rate from 53% during 2008–2012 to 71.4% in 2018–2022. The survival rates for patients at all clinical stages have

Table 2 The five-year relative survival of gastric cancer patients during 2008 to 2022 in Nanfang Hospital, Southern Medical University

Characteristics	2008–2012	2013-2017	2018-2022
	5-year RS (% ±SE)	5-year RS(% ±SE)	5-year RS(% ±SE)
Total	53±3.6	53.7±1.7	71.4±1.3
Sex			
Male	56.6±3.4	56.2±2.1	70.7±1.6
Female	47.8±6.9	48.6±2.9	72.7±2.2
Age at diagnosis (years)			
<40	46.5±14.3	46.5±5.2	67.5±4.3
40~55	60.4±4.2	56.0±2.8	73.5±2.2
55~70	53.4±4.5	54.1±2.4	72.0±1.9
≥70	39.2±13.0	50.9±5.8	67.1±4.4
TNM stage			
I	93.1±4.3	99.8±1.7	101.0±1.1
II	68.2±11.8	79.7±3.7	85.4±3.0
III	60.3±4.9	49.2±3.4	70.2±3.3
IV	13.8±7.8	14.0±1.9	29.0±2.6
Surgery			
I-III	70.8±4.1	75.3±2.0	89.7±1.3
LADG	50.3±8.1	52.1±1.9	71.4±1.3
Region			
Urban area	56.9±4.5	53.4±1.9	74.6±1.7
Rural area	47.6±5.7	54.6±3.7	66.8±2.2

increased, with the 5-year relative survival rate for TNM stages I-III rising to 89.7% in 2018–2022. Generally speaking, there has been a significant improvement in the 5-year relative survival rate for gastric cancer patients at our center across all demographics including gender, age, and region.

While specific survival rate data may show slight variations across different studies, it is widely acknowledged that the five-year survival rate for gastric cancer patients in China following surgery typically falls within the range of 40–45%.[13] Japan and South Korea show a more significant declining trend in gastric cancer incidence and mortality rates compared to China [14]. Both Korea and Japan have nationwide gastric cancer screening programs, which contribute to early diagnosis and treatment, significantly improving survival rates. A primary cause of gastric cancer in these Asian countries is the high prevalence of Helicobacter pylori infections [15]. In Western countries, the primary risk factors for gastric cancer include smoking, high-salt diets, and obesity [16]. However, the absence of comprehensive gastric cancer screening results in many patients being diagnosed in advanced stages, leading to a five-year survival rate of approximately 30% for those undergoing radical surgery in these regions [17]. Our research found that the five-year relative survival rate for gastric cancer at our center increased from 53% in 2008–2012 to 53.7% in 2013–2017, and subsequently rose to 71.4% in 2018–2022. This represents a significant improvement over the national average five-year survival rate, and the gap with Japan and South Korea is narrowing. Additionally, we observed that there are still survival rate disparities between urban and rural patients, which may be related to differences in regular postoperative follow-up and treatment adherence between the two groups [13]. We aim to improve postoperative management to contribute to the homogenization of treatment outcomes for both urban and rural patients.

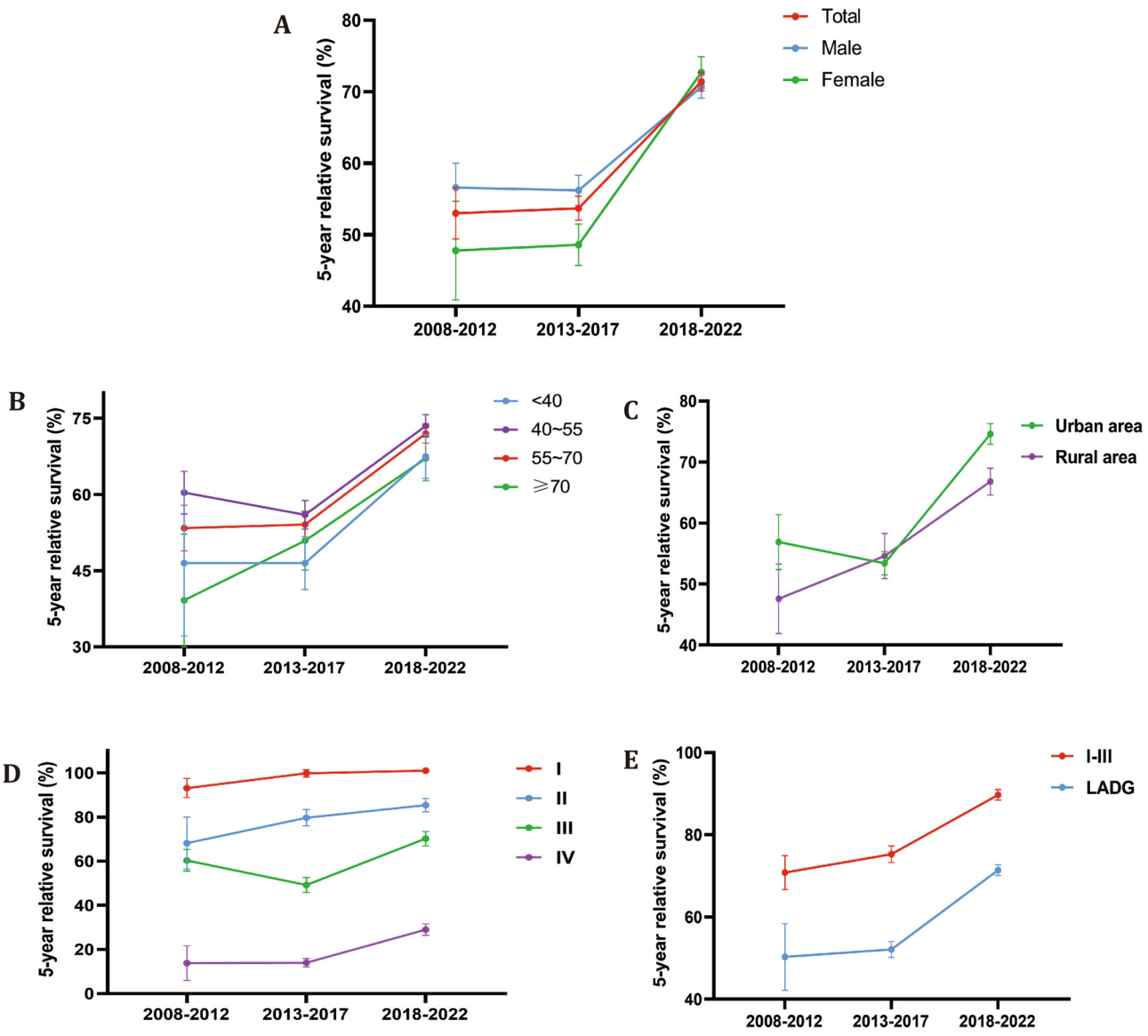

Fig. 1 (**A**) Five-year relative survival for patients with gastric cancer by sex during 2008–2022. (**B**) Five-year relative survival for patients with gastric cancer by age during 2008–2022. (**C**) Five-year relative survival for patients with gastric cancer by regions during 2008–2022. (**D**) Five-year relative survival for patients with gastric cancer by TNM stage(I-IV) during 2008–2022. (**E**) Five-year relative survival for patients with gastric cancer by TNM stage(I-III) and laparoscopic surgery during 2008–2022

Using period analysis to examine the latest survival data, we have concluded that significant progress has been made in the treatment of gastric cancer at our center. The reasons can be attributed to the following: firstly, our center has been implementing D2 lymph node dissection since 2004, and we have accumulated extensive clinical experience in laparoscopic lymph node dissection for advanced gastric cancer. In 2012 the Chinese Laparoscopic Gastrointestinal Surgery Study (CLASS) group conducted a multicenter randomized trial (CLASS-01 trial) which standardized the surgical procedures [18]. Laparoscopic distal gastrectomy involves the use of five trocars for tumor staging and lymph node dissection, and has established its own standard procedure for laparoscopic D2 lymph node dissection in treating distal gastric cancer. Data published by similar international research institutions show that in the KLASS-02 trial, the 5-year overall survival (OS) rates for patients who underwent laparoscopic and open distal gastrectomy were 88.9% and 88.7%, respectively [19]. All their patients were staged between I and III phases. Comparing our data, we found that the five-year survival rate for patients in stages I to III who underwent surgery at our center from 2018 to 2022 was 89.7%, similar to the results of the KLASS study group. The trends are also similar to the results of the JLSSG0901 Randomized Clinical Trial recently published

by the Japanese Gastric Cancer Study Group (JLSSG). In the JLSSG0901 FAS analysis, the 5-year OS was 79.8% and 81.7% in the ODG and LADG groups, respectively [20]. The CLASS01 trial At 5 years, the overall survival rates were 72.6% in the laparoscopic distal gastrectomy group and 76.3% in the open distal gastrectomy group [21]. Moreover, Staging laparoscopy has proven to be highly accurate for detecting peritoneal metastases and serves as an essential diagnostic tool in gastric cancer staging [22]. The invasion depth determined by laparoscopy aligns well with surgical pathology standards, making our staging more accurate through laparoscopic exploration [23, 24].

Furthermore, the utilization of MDT has a vital impact on gastric cancer treatment. Perioperative studies have confirmed their findings, as shown in the early European MAGIC study, where perioperative chemotherapy offered a survival benefit compared to surgery alone, with an estimated increase in 5-year survival rates by 13% [25]. In the Japanese ACTS-GC study, patients who received the effective adjuvant chemotherapy showed a 5-year overall survival rate of 71.7%, compared to 61.1% for the surgery-only group. According to 5-year follow-up data, postoperative adjuvant therapy has been confirmed to improve overall and recurrence-free survival for stage II or III gastric cancer patients undergoing D2 gastrectomy [26]. Our research also demonstrates a similar trend: the 5-year relative survival rates for patients in stages II and III increased from 68.2% to 60.3% in 2008–2012 to 85.4% and 70.2% in 2018–2022, respectively. In the American INT-0116 study, data on overall survival (OS) and recurrence-free survival (RFS) showed continuous strong benefits of postoperative chemoradiotherapy, with a 5-year overall survival rate of 44% [27]. Specifically, neoadjuvant chemotherapy can effectively reduce the TNM stage of gastric cancer, eliminate potential micro-metastases through systemic treatment, and reduce the risk of postoperative recurrence. However, neoadjuvant treatment 's impact on tissue can complicate surgical procedures, increasing the risk of postoperative infections, anastomotic leakage, and extended recovery times. The potential benefits of this treatment must be carefully balanced against the heightened risk of complications. Similar increases in postoperative complications have been observed in multicenter studies involving Western populations, underscoring the need for further evaluation of these risks across diverse populations [28, 29].

Since 2018, treatment for advanced gastric cancer has seen significant advancements, particularly in immunotherapy. Nivolumab was launched in China in 2018, and since then, we have benefited from immunotherapy in frontline advanced gastric cancer. In our study, we observed a significant increase in the five-year relative survival rate from 2018 to 2022, primarily due to the effective application of immunotherapy at our center, the initiation of MDT post-2018, and the formation of specialized comprehensive treatment teams for managing and treating advanced gastric cancer. The development of large-scale clinical trials has provided more options for our treatment, for example, in a large Phase III clinical trial (ATTRACTION-2) conducted in Asia with nivolumab, there was a significant improvement in survival rates for patients with advanced gastric cancer. The nivolumab group observed higher OS rates compared to the placebo group, with 1-year survival rates of 27.3% vs. 11.6% and 2-year rates of 10.6% vs. 3.2%. Moreover, in the largest global Phase III gastric cancer trial, CheckMate-649, nivolumab combined with chemotherapy showed superior OS compared to chemotherapy alone, reducing the risk of death by 20%. The combination therapy performed slightly better in patients with higher PD-L1 scores [30]. In the ToGA research, Trastuzumab in combination with chemotherapy can be considered as a new standard option for patients with HER2-positive advanced gastric or gastroesophageal junction cancer. Provides new hope for patients with HER2-positive [31]. By comparing the 5-year relative survival rates for stage IV gastric cancer derived from this study, it is evident that this series of studies has been highly effective for patients with advanced gastric cancer, corroborated by a 15% increase in the 5-year relative survival rates from 2013 to 2017 to 2018–2022 at our center. With advances in molecular biology and personalized medicine, future treatments for gastric cancer will become more precise, and the indications and effectiveness of immunotherapy will be further optimized. These therapeutic advances have not only increased the survival rates of patients with advanced gastric cancer but have also significantly improved their quality of life, demonstrating the new hopes and directions of modern medicine in combating gastric cancer.

There several limitations in our study: (1) Although the use of period analysis can provide the latest insights into survival rate changes, it may not be sufficient to capture all the complex factors that influence the outcomes. (2) As data were collected from a single center, our findings may not be generalizable to other regions or populations with different healthcare systems or demographic characteristics. (3) For some rural patients, we are sometimes unable to obtain timely information on their regular postoperative follow-up, treatment, and monitoring, which prevents us from conducting a detailed analysis of the reasons behind their lower survival rates. (4) The resources and technological capabilities of our center, which may impact the quality of diagnosis and treatment, are not necessarily reflective of those available in other settings.

In conclusion, the overall enhancement in gastric cancer outcomes at our center can be credited to standardized surgical procedures, standardized treatment guidelines, and perioperative management. Our study has timely identified that, over the past 15 years, with ongoing improvements in treatment methods, the 5-year survival rate of gastric cancer patients has been rising annually. This provides a robust data foundation for gastric cancer monitoring and treatment efficacy assessment.

Abbreviations

MDT	Multidisciplinary team
GC	Gastric cancer
OS	Overall survival
RS	Relative survival
RFS	Recurrence free survival
BMI	Body mass index

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Author contributions
Study conception and design: HZ, WY, HL, LZ and GL; Data collection: HZ, WY, XT and WH; Data analyses: HZ, WY, WH and XT; Results interpretations: all authors; Manuscript drafting: HZ, HL, LZ, GL; Manuscript proofing: HZ, WY, HL, LZ and GL. The 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 protect study participant privacy, but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the Declaration of Helsinki and was approved by the ethical committee of Nanfang Hospital, Southern Medical University.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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