Original Article

Received: 2023-01-27
Accepted: 2023-04-08

BCCR
2022, No 4, Vol 14 :233-248
www.bccrjournal.com

Incidence, Prognostic Factors, and Survival of Gastric Cancer in Iran: A review of evidence

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ABSTRACT

Gastric cancer (GC) is the fifth most prevalent cancer and the fourth in terms of cancer-related death worldwide. The GC is the most commonly diagnosed and the most important cause of cancer-related death in Iranians. Due to the significant burden of stomach cancer in Iran, we aimed to review all articles that have been conducted on the Incidence, Prognostic Factors, and survival of Gastric Cancer in Iran and compare them with the global situation.

We surveyed Google Scholar, Pub Med, Scopus, Web of Science (ISI), and Science Direct databases using the keywords of Gastric Cancer, Stomach Cancer, Gastric Neoplasm, Stomach Neoplasm, and Iran and obtained English language articles. After a two-step screening of articles, 51 out of 202 remained eligible for our study (related to Incidence, Prognostic Factors, and survival of stomach Cancer in Iran).

We found that although Iran is one of the high-burden countries for GC, the incidence rate and mortality rate are very different in different provinces (up to a six-fold and thirty-fold difference in mortality rate and incidence rate have been reported respectively in reviewed articles between Northern and Southern Iran).

Considering that the initial stage is one of the most important and probably the most important prognostic factors, through upper endoscopy screening, the disease can be diagnosed in earlier stages and the survival of patients can be improved.

We recommend the Ministry of Health identify high-risk people according to their combination of risk factors (especially geographical region) and make a national cost-effective screening algorithm for Iran.

Keywords: Gastric Cancer, Incidence, Prognostic Factors, Survival, Iran

INTRODUCTION:

According to GLOBOCAN 2020, gastric cancer (GC) is the fifth most prevalent malignancy and the fourth in terms of cancer-related mortality worldwide. In men, GC is the most commonly diagnosed cancer and the most important cause of cancer-related death in many Asian countries, especially Iran [1, 2]. Additionally, a report from the national cancer registry during 1998-2001 declared that the highest prevalence of GC among Middle East countries belongs to Iran [3].

Gastric cancer was responsible for approximately one million new cases and 769,000 deaths in 2020 [2]. Similarly, the new cases of stomach cancer in Iran in 2020 were 14,656 patients and an estimated 11376 deaths [4]. The 5-year overall survival (OS5y) of gastric cancer worldwide (excluding Korea and Japan) is about 20-30% [5, 6]. In Iran, according to a meta-analysis, OS5y reaches about 18%, which has increased slightly in recent years and is almost close to the global OS5y [7].

Stomach cancer risk factors in Iran and other parts of the world are mostly similar. A very comprehensive and extensive systematic review examining all the studies conducted in the last 50 years in Iran has listed these risk factors as follows: Gender (male), older Age, Helicobacter Pylori (H.Pylori) infection, smoking, low income, food insecurity, hot tea, overconsumption of salt, red meat/fish/legumes which is processed, salty, or smoked. In addition, the most common genes involved in the pathogenesis of GC, are mRNA genes [8].

Due to the prominent burden of GC in Iran, we aimed to review all articles that have been conducted on the Incidence, Prognostic Factors, survival, and screening of GC in Iran so far (July 2022) and compare them with the global situation. We finally try to make a recommendation for improvement of the GC burden in our country based on our findings

Material and Methods:

Search strategy

The related articles were selected from valid scientific databases in July 2022. We surveyed Google Scholar, Pub Med, Scopus, Web of Science (ISI), and Science Direct databases using the keywords of Gastric Cancer, Stomach Cancer, Gastric Neoplasm, Stomach Neoplasm, and Iran using OR and AND operators.

Criteria for including/excluding articles

The title review was the first step of screening in which, unrelated, repeated, non-English-language, and animal studies were excluded. The abstract review was the second step of screening in which articles were non-relevant to the subject and purpose of our study, and the review articles were excluded. The English-language articles associated with Incidence, Prognostic Factors, and survival of GC in Iran and humans were initially included. In the next step, the inclusion criteria included study type and full-text accessibility.

Final Data extraction

PTo extract the final studies, the extract forms were designed in which the first author's name, the study date, the study place, the sample size, the results, and the conclusion of the studies were included.

Results:

We found 202 articles by searching in databases, then 51 studies remained after initial (title review) and secondary (abstract review) screening. The studies were divided into three categories for ease of study (Figure 1, Table 1, Table 2, and Table 3).

Among the 51 reviewed articles, 17(33.3 %), 10(19.6%), 3(5.8%) and 3(5.8%) articles were designed and carried out in Tehran, the whole country, Ardabil, and two or more provinces, respectively.

Discussion:

Incidence

The incidence of GC varies by culture and region. According to GLOBOCAN 2020, the world age-standardized incidence rate of gastric cancer per 105 (ASIR) was 15.8 and 7 in males and females respectively and the world age-standardized mortality rate per 105 (ASMR) was 11 and 4.9 in males and females respectively [59]. Eastern Asia (Japan and Mongolia) and Eastern Europe have the highest incidence whereas

Northern Europe and Northern America have the lowest incidence of GC [59].

A retrospective study of all cancers diagnosed in Iran between 2004 and 2008 showed that GC was the second and fourth most prevalent cancer in Iranian men (ASIR = 15.02) and women (ASIR = 7.05) respectively [25]. According to a study conducted in East Azerbaijan province (northwestern Iran) during 2007-2011, GC was the most prevalent gastrointestinal cancer (ASIR of 23.1 and 7.69 for males and females respectively) [14].

Zendehdel et al. used the nationwide mortality registry to study the pattern of GC in Iran from the point of geographical differences in 2012; they found that among the northern and southern areas of Iran, there is an almost six-fold difference in GC mortality. The maximum and minimum ASMR were for Kurdistan (29.1) and Hormozgan (5), respectively. They concluded The wide geographic variation and the prominent mortality rate are probably due to differences in environmental agents predominant in each region, especially Helicobacter pylori [23].

A recently published study as a part of the Global Burden of disease 2017 (GBD 2017) evaluated the rate of GC from 1990 through 2017 and showed a decreasing trend of ASIR and ASMR (ASIR=20.5 vs 14.6 and ASMR=21.9 vs 14.9) [27].

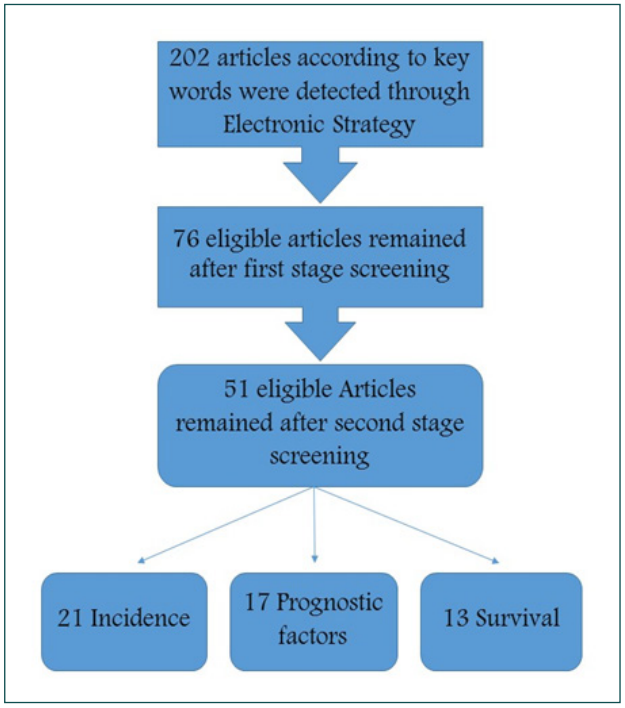

Figure 1. Flowchart for Article Screening

Moradian et al using the Iranian National Cancer Registry data from 2004 to 2014 reported the highest and lowest ASIR of GC in Iran from Ardebil Province (ASIR = 30.19) and Ghom Province (ASIR= 1.00) respectively. They also found that the most common site of GC in Iranian women and men is pylorus and fundus respectively. The more common locations of GC in northern and southern provinces are cardiac and pylorus respectively [28].

Most descriptive or cross-sectional studies conducted between 2003 and 2010 have identified northern and northwestern provinces such as Gilan, Mazandaran, Ardabil, East Azerbaijan, West Azerbaijan, Kurdistan, Zanjan, and Qazvin as the regions with the high rate of GC in Iran [10, 18, 19, 26].

Significant differences in the distribution of GC in terms of geographical location, tumor site, and gender may indicate different etiologies including variations in dietary patterns and certain cooking methods.

Prognostic factors

Several factors (patient-related and treatment-related) influence survival. Age, gender, TNM stage, treatment method, tumor site, and histopathology, are the prognostic factors frequently mentioned in many studies around the world; cardia tumors are significantly worse compared to distal tumors [60]. According to these findings, a special treatment method (for example, neoadjuvant chemotherapy or chemoradiation) may be considered for proximal stomach tumors.

Elderly people generally have more comorbidities than younger people, their nutritional status is more inappropriate, and their tolerance to multimodality treatments is less, which can be the reason for their poorer prognosis [61, 62].

As expected, the pathological stage is one of the most important prognostic factors. Especially, the Lymph node involvement deeply affects the long-term results of treatment.[62-64].

Table 1. Articles related to the Incidence of GC in Iran

Ref	Author & year/ City	City	Date	Sample size	Results	Conclusion
[1]	Farid Zayeri.	Iran	2000-2010	The cases of GCb (49,917 cases) were registered for 31 provinces.	The incidence rate of GCb was ascending (1.53 and 0.75 persons every year for males and females, respectively).	ASIRa is significantly differences between different districts of Iran.
[9]	Bahareh Yazdizadeh	Shiraz, Tehran	1972-1995	The publications related to cancer patients referred to the Tehran and the Shiraz cancer centers were utilized.	The GCb had an increasing trend by 35% and 13% in Shiraz and Tehran respectively.	During the last three decades, the incidence of GCb had a slight to moderate increase.
[10]	Reza Pakzad.	Iran	2009	The previously reported incidence rate of GCb in different provinces were gathered and normalized to the world population rate.	A total of 6,886 GCb patients were reported (ASIRa of 19.2 and 10.0 per 105 men and women, respectively). The northwest of the country had the highest incidence.	Further investigations are needed to clarify the reasons for this geographical concentration.
[11]	Abozar Solimay	Kermanshah	2009 - 2014	All newly diagnosed patients of GCb were studied. The spatially and temporally high burden locations were recognized by saTScan and GIS.	The total GCb patients were 1040. 11 districts showed a high incidence pattern (hot spots) and 5 districts showed a lower incidence (cold spots, $P<0.05$).	All attempts should be focused on the recognition of hot/cold spots and the risk factors.
[12]	M.Norouzinia 2012	Iran	2010-2011	The GCb patients diagnosed in eight provinces were evaluated.	The ASIRa was 40.6 per 105 populations per year. Regarding tumor location; 63%, 34%, and 3% were located in the distal, cardia, and fundus respectively. There was a significant association between poor differentiation and distal tumors.	Distally located tumors are more common in Iran.
[13]	Zeinab Almasi	Iran	2003-2008	The article is about collected retrospective data at the Cancer Registry Center of Iran	35,171 cases of GCb were registered. The average ASRa for males and females were 15.1 and 7.1 per 105 population, respectively. ASIRa was increased in both males and females at 9.2 (CI: 5.2 to 13.4) and 11.1 (CI: 4.3 to 18.3), annually.	Because of the increase in GC incident in Iran further studies about epidemiology, etiology, and early detection is important.
[14]	Mohammad Hossein Somi	Tabriz	2007-2011	All referral and lab centers were gathered and reviewed in East Azerbaijan.	6889 GC registered and it was the most prevalent GI cancer. ASIR of 7.69 for females and 23.1 for males reported.	East Azerbaijan is one of the highly prevalent regions for GC

[15]	Reza Ghadimi /	Babol	2007	From 130 patients from Babol in 2004 UBT, IgG antibodies of helicobacter pylori and pepsinogen test collected,	Male mortality rate was lower than Japanese male but female mortality was higher. UBT and H.P antibodies in both males and females were higher than Japanese	Higher H.P infection rates and chronic atrophic gastritis were associated with higher mortality in GC at Babol
[16]	Mehdi Babaei	Semnan	1998-2002	all patients that have cancer registered in Semnan province	1732 patients recorded, GC is the most prevalent cancer and has an incidence rate of 19.7 per 10,000 persons. (ASIR=27.5)	GC was 17 percent of all cancers in Semnan
[17]	F. Amani.	Ardabil	2003-2011	1056 patients were recorded at Ardebil.	672 patients were male with a 3:1 ratio. Namin has the highest incident. (137.5 pet 10000)	Sablan volcanic province has a significantly higher incidence rate.
[18]	Amir Kavousi	Iran	2004-2009	SatScan app is used to analyze high-risk populations.	The most likely populations were found in Gilan, Zanjan, Ardabil, Qazvin, east and west Azerbaijan, Tehran, Kurdistan, Mazandaran, and Hamedan.	More screening should be performed in these cities.
[19]	Sedigheh Rastaghi	Iran	2005-2010	It is a cross-sectional study with the use of Bayesian hierarchical space-time model. They measured temporal trends and the relative risk of GC in 30 regions.	Ardabil, west Azerbaijan, Zanjan, Khoroasan Razavi, and Mazandaran had the highest incidence rates. However, during the time of the study, overall trend of GC significantly decreased.	Northern and northwestern Iran has a high risk of GC.
[20]	Abdoljalal Marjani	Golestn	2007	56 new GC cases were recorded.	The overall incidence was 11.23 per 10000, 80-84 years has the highest rate and 40-44 years had the lowest rate. In males, GC was the second most common.	Golestan province is among the high-risk areas.
[21]	Abdoljalal Marjani	Golestan, Mazandaran, Kerman, and Ardabil	1996-2000	The data gathered from Golestan, Mazandaran, Kerman and Ardabil	The most common cancer in males (by ASIRa) is GCb (26.1) and the third most common in females is GCb (11.1).	With comparing these data with past data, the incidence of GC increased by 100 percent
[22]	Parviz Haghighi	Shiraz	1963-1968	483 patients were recorded with GI cancers.	GCb was the most prevalent cancer of the Gastrointestinal tract including 47.8% of all patients.	The reason for the high prevalence of GC is not clear. It may be due to environmental and genetically factors
[23]	Kazem Zendehdel	Iran	2012	The nationwide mortality registry was used to study the geographical pattern of GCb in Iran.	The average ASMRc of males and females was 15 and 8.1 respectively. The highest and lowest mortality was for Kurdistan and Hormozgan (29.1 and 5 per 105 respectively). Men had 100 percent higher ASMR, H.P infection rate was 90% in Ardabil and 27% in Sistan Baluchestan	The wide variation in GC cancer rate in Iran province may due to environmental risk factors and H.pyloir incidence.

[24]	Mehdi Darabi	Tehran	2001 to 2010	Cancer incidence data gathered from MOH. All rates are adjusted by age.	The GC incidence rises from 2.41 and 4.18 per 10000 in females and males to 8.85 and 17.06 respectively. The rise was seen more in 80-year-old and older patients.	Screening and monitoring the trends of rise in incidence rate help to cancer prevention.
[25]	N. Amori	Iran	2004–2008	a retrospective study performed on all cases of cancer diagnosed in Iran	301055 cases of cancer were established. GCb was the second and fourth most common cancer in males (ASIRa = 15.02) and females (ASIR= 7.05) respectively.	Screening with the help of early diagnosis is a necessity concerning these significant increases in the incident of cancer.
[26]	Naeimehossadat Asmarian	Tabriz	2003-2010	Data gathered, analyzed with BYM spatial model and standardized incidence rates of GC in 373 province	Meshkinshahr has the highest SIR based in Poisson Kriging in the northwest of Iran. Based on BYM Ardabil has the Highest SIR	GC incidents are high in the north and northwest of Iran based on both models.
[27]	Nima Fattahi	Tehran	1990 to 2017	burden of GC measured in this study	ASIRa and ASMRc in 2017 were 22.9 and 14.6 per 100,000 population, respectively.	The ASIRa of GCb showed a decreasing trend from 1990 to 2017.
[28]	Farid Moradian	Tehran	2004 to 2014	Data gathered from the Iranian national cancer registry and in each county measured the ASIR and crude of GC.	Cardia and pylori is the frequent location of GC. In Iran in 2014 incidence of GC was higher than the worldwide rate.	The data showed variations in the incidence of GC in the province and the location and type of the neoplasm.

a: Age Standardized Incidence Rate
b: Gastric Cancer
c: Age Standardized Mortality Rate
d: Ministry Of Health
e: Annual Percent Change
f: Standardized Incidence Rate

Table 2. Articles related to prognostic factors of GC in Iran

Ref	Author	City	Date	Sample size	Results	Conclusion
[29]	Hajiani Eskandar. 2006	Khuzestan	1996-2002	186 GCa patients were studied.	Men to women ratio was 2.6:1. The mean age recorded was 60.6 years. Intestinal type was more common in adenocarcinomas. The most common localization was distal third (88.4%). Thirty-one patients (17%) had a family history of GCa.	In Khuzestan, GCa has more frequency in young patients. Probably family history is an important problem in this area.
[30]	Majid Boreiri 2013	Ardabil	2000-2013	1011 Ardabil residents underwent endoscopy; those without GI illnesses were followed up until 2013.	3.95% died of GC; HRb was 7.4 for atrophic gastritis and 23.6 for intestinal metaplasia. Age, FH, smoking, and gastric ulcer were independent risk factors.	Identifying people at risk of GC with multiple risk factors can help provide timely surveillance for early diagnosis.
[31]	F. Mohammadzadeh 2015	Tehran	2015	216 GC patients were split into dead and alive groups, and a decision tree model was built using 80% of them.	Multiple factors such as tobacco, t size, surgery type, age, stage, diabetes, and… impact GC mortality. Decision tree accuracy was 0.74 with 0.72 sensitivity and 0.75 specificity.	Clinicians can use a simple decision tree to predict GC mortality probability, aiding diagnosis and treatment decisions.
[32]	Najmeh Karami. 2013	Tehran	2013	H. pylori was evaluated in gastric specimens and patient sera in a study comparing 102 GC and 122 dyspeptic patients.	In both groups, H. pylori seropositivity was high. Protective antibodies to 35kDc protein and higher seroreactivity to VacA and CagA were found. Double-positive subjects had a higher risk of GC.	Seroreactivity to low and high molecular weight H. pylori antigens were respectively protective and risky for GC
[33]	Seyedeh Habibeh Mirmajidi. 2015	Mazandaran	2015	PCRd was used to assay bcl2 gene expression after DNA extraction from 10 normal and 10 GC tissue samples.	The Bcl2 gene was expressed more in normal tissues than in cancer and marginal cancer tissues.	Both tumoral and non-tumoral groups had lower expression than controls (P>0.05), and BCL-2 affects the prognostic outcome
[34]	Ghodratollah Roshanaei 2012	Hamadan	2003-2007	This study collected data on GC patients' characteristics, stage, grade, site, and size.	Eighty-two patients with GC had recurrence with mean and median time at 25.5 and 21.5 months. Recurrence was affected by stage, grade, and site.	The study suggests that pathologic stage, tumor grade, and tumor site have a positive prognostic value and can aid follow-up

[35]	Ghodratollh Roshanaei 2011	Tehran	2003-2007	This is a retrospective study analyzing 408 cases of GC referred to the Tehran Cancer Institute.	Tumor size and pathologic stage significantly impacted recurrence in both analyses, while tumor site and grade only had significance in univariate analysis.	Semi-competing risk methods are effective in identifying disease recurrence risk factors, according to the study.
[36]	Sakineh Amoueian 2014	Mashhad	2004-2008	Fifty patients with non-metastatic intestinal-type gastric adenocarcinoma underwent curative gastrectomy and were stratified by immune cell counts determined by IHCe staining.	Certain immune cell types such as NK cells, mast cells, and Langerhans impacted positive survival rates and macrophages had a negative impact for certain gastric cancer patients, as did location, stage, and certain tumor markers.	The impact of natural killer and mast cells on prognosis depends on Langerhans cell count, supporting their role in immunocyte activity.
[37]	Bijan Moghimi-Dehkordi 2008	Tehran	2001-2006	The study is a retrospective analysis of early gastric cancer patients diagnosed to identify prognostic factors.	The study included early gastric cancer patients with a mean age of 57.9±11.9 years. Tumor size (>35mm) and lymph node metastasis were significant survival factors.	Independent prognostic factors in early gastric cancer patients are tumor size >35mm and lymph node metastasis
[38]	Ahmad Farajzadeh Sheikh 2018	Ahvaz	2018	The study analyzed 301 biopsy specimens from patients suspected of gastrointestinal disorders with molecular and phenotypical methods to detect H. pylori.	Out of 201 patients with H. pylori, 22 had gastric cancer. The most virulent allelic combination was vacA s1/m1. The cagA gene was present in 66.7% of isolates and was associated with GC and PUD.	Study shows the cagA, vacA s1m1 combinations as the dominant H. pylori genotype associated with an increased risk of GC.
[39]	Hossein Khedmat 2011	Tehran	1991-2007	367 GC patients were obtained in the Baqyiatallah Hospital. They studied international variations in 5-year survival stage distribution and GC.	Stomach cancer has a low 5-year survival; stage, tumor size, age, and gender are significant factors, with global variation in survival.	Because of the late diagnosis of gastric cancer, the prognosis is not good
[40]	Seyed Navid Latifi 2013	Iran	2013	They studied international variations in 5-year survival stage distribution and GC.	Stomach cancer has a low 5-year survival; stage, tumor size, age, and gender are significant factors, with global variation in survival.	Because of the late diagnosis of gastric cancer, the prognosis is not good
[41]	H. Zeraati 2006	Iran	1995 and 1999	The study involved 281 adenocarcinomatous GC patients who underwent surgery in Iran, identifying H. pylori genetic differentiation related to GC incidence.	A study involving 281 GC patients who surgery in Iran between 1995-1999 found that survival was influenced by age, lymph node metastasis, recurrence, and disease stage.	Gastric cancer prognosis due to late diagnosis is low in Iran.

[42]	Amin Talebi Bezmin Abadi 2011	Mazandaran	2011	PCR genotyping of 138 H. pylori strains obtained from dyspeptic patients (35 gastritis, 62 peptic ulcer, and 41 gastric cancer patients).	The prevalence rates of cagA, homA, and homB were 58%, 54%, and 43%, with homB higher in GC patients	HomB is more prevalent in patients with gastric cancer, and its presence may indicate more virulent H. pylori strains.
[43]	Siadati Sepideh 2012	Tehran	2001-2007	A study analyzed 33 gastric and 66 colonic cancers showing the MDM2 protein expression in tissue sections.	82.4% of GC had high MDM2 expression, and MDM2 immunoreactivity had a significant correlation with tumor size.	MDM2's role in cell growth and positive correlation with tumor size suggests its importance as a prognostic factor.
[44]	Moradi G. 2016	Sanandaj	2009-2013	The study examined survival rates for 202 GC patients considering age, gender, education, weight, and clinical variables.	GC patients' survival rate was 43.9% after one year and 7% after five years. Age, education, disease stage, and weight were significant predictors.	Early detection methods and prompt access to effective treatment are essential to improve the poor prognosis of GC patients.
[45]	Kambiz Sotoudeh. 2012	Tehran	2008-2009	The study examined c-MET expression in 130 GC patients who underwent curative gastrectomy.	High c-MET expression was found in 71% of studied GC tumors and associated with advanced stages and invasive characteristics (pT3, pT4, PNI, stage 3 or 4). the c-MET expression has a lesser association with lymph node metastasis and LVI	The c-MET oncogene protein was associated with characteristics like tumor type, depth of invasion, neural invasion, and staging

a: Gastric Cancer
b: Hazard Ratio
c: Kilo Dalton
d: Polymerase Chain Reaction
e: Immunohistochemistry

Table 3. Articles related to the survival of GC in Iran

Ref	Author	City	Date	Sample size	Result	Conclusion
[46]	Ghodratollah Roshanaei 2011	Tehran	2003-2007	471 patients followed.	The median age at diagnosis was 60.7 and the mean was 58.5. Mean survival and median survival were 41.8 and 27 months. Stage, gender, treatment types, and differentiation degree related significantly to survival	Early diagnosis at a younger age can reduce the death risk.
[47]	Hamideh Salimzadeh 2018	Tehran, Isfahan	Isfahan (2007 to 2010) and 2 big cemeteries in Tehran (1995 to 2010).	334160 gastric cancer-related death reported	GC is the leading cause of mortality among GI cancers, with an ASMRa of 20.5 per 105 persons-years from 1990 and 2015. A decreasing trend revealed in the mortality of GCa in the recent decade. The ASMRb was enhanced by advancing age (more common in adults aged 50 or older). Higher mortality rates were detected in men versus women.	Cancer prevention, early detection, and high quality treatment strategies are needed.
[48]	Ali Zare 2013	Tehran	1995-1999	330 patients with GC undergone surgery at the Iran Cancer Institute were recorded.	Factors impacting the survival and relapse of cancer patients include age, metastases, surgery type/extent, and number of treatments. Median survival =16.3 months 5-year survival rate = 21.6%.	Cancer studies focus on death factors, disregarding events that affect the natural process of the disease.
[49]	S.Sadighi 2005	Tehran	1998 - 2003	The Cancer Institute's Medical Oncology Department treated 413 patients in a retrospective study of GC.	Most patients were diagnosed at stage 4 and had a tumor in the cardia; median survival was 10 months. Surgery and chemotherapy led to 20 months of survival. Better prognosis correlated with less extensive disease, free surgical margins, and chemotherapy.	Survival benefit was observed only with curative resection and free margins in the study
[50]	Saman Maroufizadeh 2011	Tehran	2011	The study reviewed the medical registry of 213 GC patients in a referral cancer center in Tehran, Iran, retrospectively.	The study found a 14.6% 5-year survival rate and 29.6 months median life expectancy. Age, tumor size, and stage were independent prognostic factors.	Early detection of GC in younger patients and primary stages is crucial for improving survival rates, according to the study.

[51]	Bijan Moghimi-Dehkordi 2010	Tehran	2001-2006	The cancer center reviewed 742 GC patient records, registered to analyze risk factors for disease recurrence.	Non-elderly patients had higher rates of lymph node metastasis and differentiated type and better 5-year survival rates than elderly patients.	Age is a significant factor in predicting survival rates, with non-elderly patients showing better outcomes than elderly patients.
[52]	Pourhoseingholi MA 2011	Tehran	1995 - 2003	This study includes Ministry of Health death statistics, categorized by age, sex, and cause of death	The overall mortality rates for GC increased significantly from 1.68 to 9.67 per 10,000 over the studied years	The study recommends primary prevention and early detection programs due to the rising mortality rates of GC.
[53]	Morteza Bashash 2010	Ardabil	2010	Population-based cancer registries for BCb and Ardabil were used to obtain data for gastric cancer patients.	1-year age-standardized relative survival rates were higher in BC than in Ardabil for gastric cancer patients in all categories analyzed.	Differences in disease characteristics and patient factors, not just healthcare systems were found to contribute to gastric cancer survival disparities.
[54]	Hojjat Zeraati	Hamadan	2003-2007	760 Iranian gastric cancer patients who had surgery were analyzed for H. pylori,	The median survival time for 760 GC patients was 25.69 months and the 5-year survival rate was 28%. Age and disease stage negatively impacted 5-year survival. (P<0.001).	The 5-year survival GC patients seem to be low in Iran. It may be due to late referral of patients for diagnosis and treatment.
[55]	Fatemeh Samadi	Ardabil	2000 to 2004	279 patients with gastric cancer were included in the prospective study	Patients who had surgery and chemotherapy survived longer. Smoking was identified as the only independent risk factor in stomach cancer (between tumor pathology, age, radiation, alcohol, & opium)	In Ardabil survival rate of GC is low so the diagnostic test should be performed sooner to increase survival
[56]	B Moghimi-Dehkordi 2009	Tehran	2001-2006	Study of 746 GC patients at the Research Center for Gastroenterology Cancer Registry Center.	The study found a mean survival of 42.45 months, median survival of 22.8 months, and 5-year survival rate of 25.3%. Several prognostic factors were identified such as age, size, histology, stage, surgery, and first treatment type.	Early diagnosis of GC in the low stage is important for increasing survival
[57]	Zahra Yousefli 2021	Mashhad	2012 - 2016	This was a cross-sectional study conducted on 308 patients with GC	Univariate analysis showed that ethnicity, addiction, positive family history, past medical history, and education level had a significant effect on survival rate.	Survival in GC can be negatively impacted by older age, male sex, positive family history, CAD, diabetes, and hypertension.

[58]	Abdolhassan Talaiezadeh 2022	Ahvaz	2010 - 2017	In a prospective study, curative or palliative surgery was performed on 154 GC patients.	The overall survival of patients at two and five years was 57.7% and 28.5%, respectively.	Patients with GC undergoing surgery have low survival rates, especially with high-grade tumors, metastasis, and recurrence.

a: Age Standardized Mortality Rate
b: British Columbia

Most studies regarding prognostic factors of GC are compatible with the aforementioned international studies, although a few studies have highlighted some prognostic factors; for instance, a study conducted in Kerman (southern Iran) by Korhani Kangi et al. introduced age as the most important factor for predicting survival [65] and another study declared that age (over or under 70) is an important predictor of survival [51]. In a prospective study on 100 patients who were treated and followed by Khetmat et al., they stated that the only determining factor of 6-month survival of the patients was age older than 68 (P=0.039) [66].

A retrospective study of 161 early-stage GC (including T1 and T2) indicated that involved lymph nodes and tumor size (>35mm) are the most independent prognostic factors[37]. Also in another study, Tumor size >35mm was recognized as a poor prognostic factor in all stages [56].

A retrospective survey including 760 patients who underwent gastrectomy concluded that the pathologic type, cancer site, and gender had no significant effect on patient survival based on univariate analysis. [54]; However, we did not find any further study to support this.

Diabetes mellitus, hypertension, and coronary artery disease are comorbidities supposed to have adverse effects on the survival rate of GC patients [57].

Survival

GC overall survival (OS) is highly variable by geographical region and several studies have been conducted in various countries in this regard. Survival is highly variable based on the pathological stage. The OS5y in the United States for stage IA and IB tumors with surgical treatment are 94% and 88%, respectively. In contrast, stage IIIC tumors with surgical treatment had an OS5y of 18%. The average OS5y in Europe is 26%, lower than that of the United States [67].

Due to the heterogeneous studies regarding the overall and median survival of GC patients in Iran and the heterogeneity of patients enrolled in these studies, it is difficult to estimate the survival rate precisely. We found three retrospective studies conducted in Iran Cancer Institute from 1993 to 2006 including 281, 330, and 760 participants respectively who underwent curative surgery regardless of adjuvant or neoadjuvant treatments and a recently published prospective study on 151 patients with GC who underwent curative or palliative surgery from 2010 to 2017 in Khuzestan province; these studies reported the OS5y and median OS in the range of 22.6 to 28.5 percent and 16.3 to 25.6 months respectively [41, 48, 54, 58].

A few studies have specifically examined the effect of some factors; A retrospective study by Khedmat et al. on 367 gastric cancer patients showed that the stage IV to stage IA mortality ratio is 9.9 [39]. Another retrospective study including 742 patients in all stages, focused on age and showed that five-year overall survival is significantly lower in elderly (over 70 years old) patients compared to non-elderly (15% vs. 27%) [51].

Conclusion:

Due to the heavy mortality of GC in the advanced stages all around the world, diagnosis in earlier stages is critical for longer survival. Only limited Asian countries (South Korea and Japan) have organized screening programs but it seems that other high-burden countries for GC (e.g. Iran) necessitate a national screening program too. The Ministry of Health can use the aforementioned studies to prioritize people according to their combina-

tion of risk factors (geographical region, Helicobacter. pylori infection, family history of GC, age over 50 years, atrophic gastritis, smoking, intestinal metaplasia, and in particular, an undiagnosed gastric ulcer) and make a national cost-effective screening algorithm.

Conflict of Interest

The authors declare that they have no conflict of interest.

Data Availability

The data relating to this study is available if necessary.

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