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Survival of gastric cancer patients in Iran: a systematic review and meta-analysis

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ABSTRACT

Aim: This study aimed to estimate the survival rates among Iranian gastric cancer patients and to evaluate if the survival has improved during the last three decades.

Background: Gastric cancer is one of the most common cancers in Iran with high mortality.

Methods: A systematic review and meta-analysis of all published studies addressing gastric cancer survival in Iran was performed. International databases of Scopus, Web of Science, PubMed, and Iranian databases were included in the study. The study included databases from their inception till February 2022. Due to the inherent heterogeneity, we used a random effect model to pool the survivals in three categories of one, three, and five-year survivals.

Results: Thirty-three studies with total cases of 17,207 were included in the study. The overall (pooled) one, three, and five-year survivals were estimated as 58.9% (95% CI: 0.52, 0.66), 29.9% (95% CI: 0.25, 0.35), and 18.2% (95% CI: 0.15, 0.23), respectively. Results of subgroup analysis for the calendar years of study showed that the one, three, and five-year survival rates increased during the last three decades but the results were not statistically significant. There was the disparity in survival based on geographic distribution.

Conclusion: The results of our study which has pooled many studies for a long period of time clearly indicate that the survival rates of gastric cancer patients have improved. As the improvement of survival may be due to many factors, more studies is needed to understand the dynamic behind this improvement.

Keywords: Gastric cancer, Stomach cancer, Survival, Iran, Meta-analysis.

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Introduction

Globally, cancer incidence and death are increasing at an alarming rate. According to Global Cancer Observatory: CANCER TODAY (GLOBOCAN) data, gastric cancer (or stomach cancer) is the 5th most common cancer and the third leading cause of cancer-related death in many part of the world (1-3). Gastric cancer (GC) has been recognized as the 4th most common cancer in Iran and the leading cause of cancer death in Iran (4, 5). The frequency and mortality of gastric cancer are higher within the north and northwest regions of Iran than in other districts (1, 6-9). Studies have shown that the age-standardized rate (ASR) of gastric cancer from 2007 to 2017, for the global and all

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socio-demographic index (SDI) quintiles has dropped by 6% overall. One in 33 men versus 1 in 78 women in the world will suffer from gastric cancer in their lifetime (10).

Overall survival for Gastric cancer is relatively low. An important factor in predicting the low survival rate of gastric cancer patients mostly in developing countries is a delayed diagnosis, late referral, stage and morphologic type (11, 12). According to different reports, on average, the patient has a delay of 15.01 days in referral and the general practitioner has a delay of 38.83 days in diagnosis from the beginning of the symptoms to surgery with a median total delay of 96 days (13). This may be due to be similarity of symptoms in gastric diseases (14) and thus this delay in diagnosis results in late stages of cancer progression and metastasis (15). As a result, early diagnosis and screening programs are crucial to improve their prognosis (16). In Iran, the most significant barrier to GC treatment is delay in diagnosis; which results in the tumor being detected at an advanced stage based on clinic-pathological characteristics (17, 18). Treatment of gastric cancer significantly relies upon prognostic factors and survival changes over the long run (19).

There have been an increasing number of Iranian research in recent decades that have focused on the rate of GC survival. According to the findings of these researches, Iran's survival rates are comparable to those in other developing countries (20). Due to poor hospital records, negligent registration methods, disorganized patient follow-up strategies, and a lack of regional and provincial cancer centers, conducting population-based cancer research in Iran are challenging (21). The inconsistent survival rate of gastric cancer has been observed in studies in Iran, with the minimum and maximum survival rate of one year 21% (22) and 91.61% (23) and 5-year 0.83% (24) and 38% (23) respectively.

Considering the need to evaluate the survival of gastric cancer among these patients in order to provide knowledge for planning health policies, a meta-analysis that addresses the Gastric cancer survival rate in Iran has not been published in last five years. So to fill the knowledge gap, we conduct this systematic review and meta-analysis. The variations of survival in the last three decades will be evaluated.

Methods

Search strategy

This systematic review study was designed and conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA) checklist. The search included databases from inception to February 2022 with a comprehensive search strategy based on titles, abstracts, and full text of the articles in the Scopus, Web of Science, PubMed, and Iranian databases including Scientific Information Database (SID) and Magiran. The search terms included gastric cancer, stomach cancer, Iran, and survival (appendix 1 find the search strategy). End Note X9 software (Thomson Reuters, New York, NY) was used to manage the search results.

Inclusion and exclusion criteria and review process

Criteria for inclusion in the study were: Persian or English language, studies conducted on the Iranian community, and reporting survival rates among Iranian gastric cancer patients. Conference papers, posters, and letters to the editor were excluded. All the steps, screening were performed separately by two independent reviewers and disagreements regarding the inclusion or exclusion of an article in the study were resolved by holding meetings with a third reviewer. In addition to databases, the reference lists of eligible articles were evaluated for possible eligible studies.

Data extraction

The following data from each eligible study were extracted: Author and year of publication, Date of study, Setting, Type of study, Number of patients, stage, Median survival in months, and one, three, and five-year survival. We divided the studies included in this study into three categories before year 2000, between 2000 and 2010, and after 2010. To evaluate the quality of the articles reviewed in this study and to assess for the potential biases, we used a checklist provided by The Joanna Briggs Institute (JBI) (25).

Meta-analysis

The {meta} package of the R 4.1.2 software was used to do the Meta-analysis of this study. Due to the inherent heterogeneity between studies, we decided to use the random effect model to pool the effect sizes. To address the heterogeneity between the

studies we decided to conduct a subgroup analysis based on the setting of the studies and the year they have been conducted. We divided studies into two groups by their setting. Those that were conducted in the capital Tehran and those that were conducted in other cities. For the year in which studies were conducted, they were grouped into three categories: studies that the follow-up period was before 2000, between 2000 and 2011, and after 2011. The restricted maximum likelihood estimator (26) was used to calculate the heterogeneity variance τ^2. We pool the data using a generalized linear mixed model (GLMM) and logit-transformed proportions. We also used the R {dmetar} package to calculate pooled effect after removing influential studies.

Results

Study Selection

Results of search

According to PRISMA diagram shown in Figure 1,

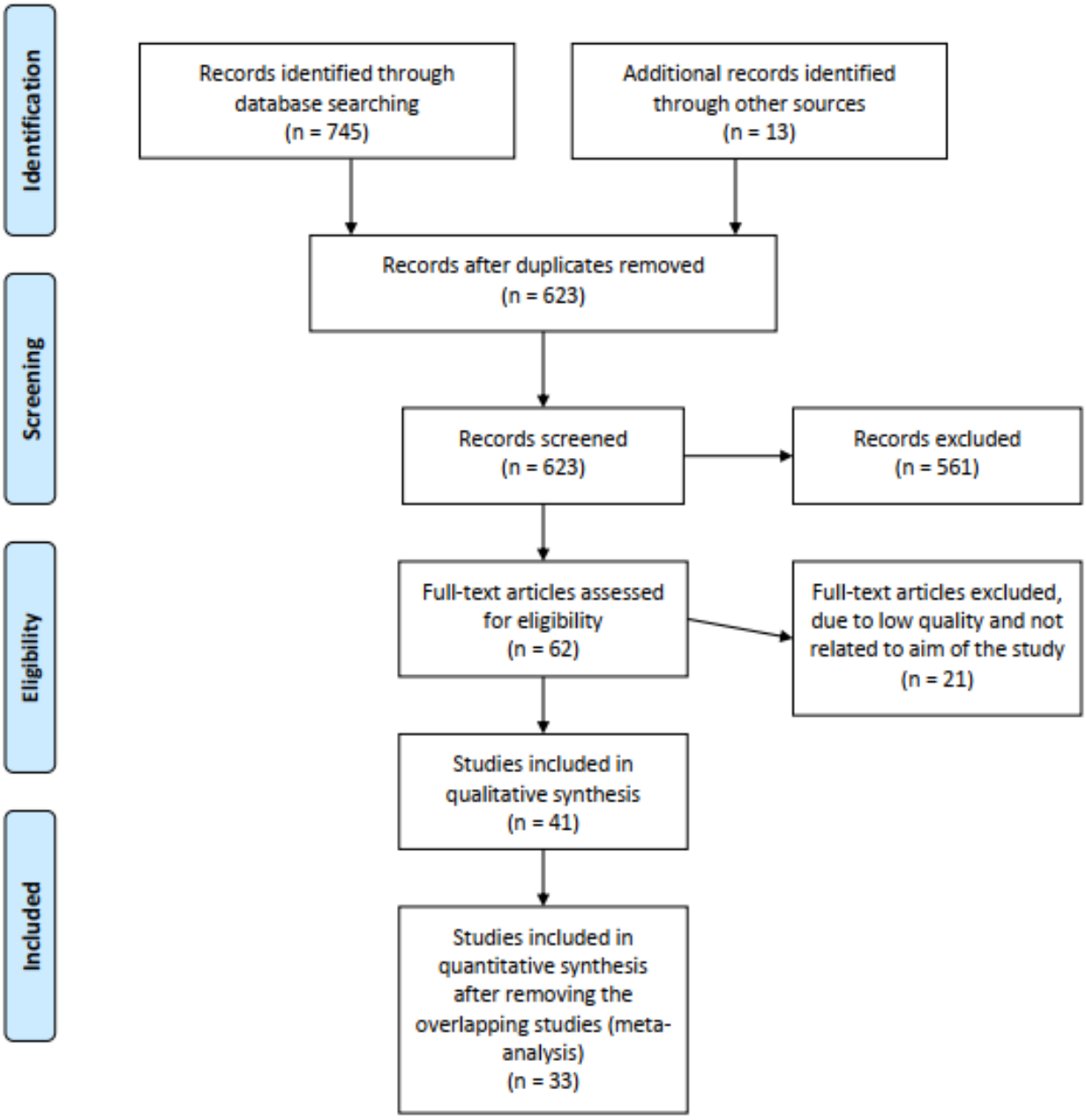

Figure 1. PRISMA flowchart shows different steps of searching for relevant studies.

at the end of the search, 758 potentially relevant articles were obtained. One hundred and thirty five articles were excluded due to duplication. After screening the title and abstract (n=623) and screening the full text of articles (excluded article due to low quality (n=5), and not related to the aim of the study (n=16)) 582 articles were excluded and 41 articles were selected as candidates for inclusion. Of these 41 studies, there are fourteen studies (18, 27-39) which their population overlapped with each other. Therefore, we included the studies with a larger population and higher quality (see appendix file). Finally, after removing 8 overlapping studies, 33 studies were included in the meta-analysis. Figure 1 shows different steps of the searching and selection procedure.

Description of studies

Of the 33 studies included in the meta-analysis, 13 were cohort studies and 20 were cross-sectional studies. In general, the lowest one-year survival was reported in Ardabil province (22) and Babol city (40) at 21%, and 28%, respectively. The highest one-year survival was reported in east Azerbaijan (91.61%) (23) and Tehran (79%) (30) provinces, respectively. The lowest five-year survival was reported in Ardabil (24), Kurdistan (41), Golestan (42), and West Azerbaijan (43) provinces at 0.83%, 5.4%, 6.1%, and 11%, respectively. The highest five-year survival was reported in Hormozgan (38%) (23), Tehran (35.3%) (28), Kerman (32%) (44), East Azerbaijan (30.14%) (45), and Yazd (24.5%) (46) provinces, respectively.

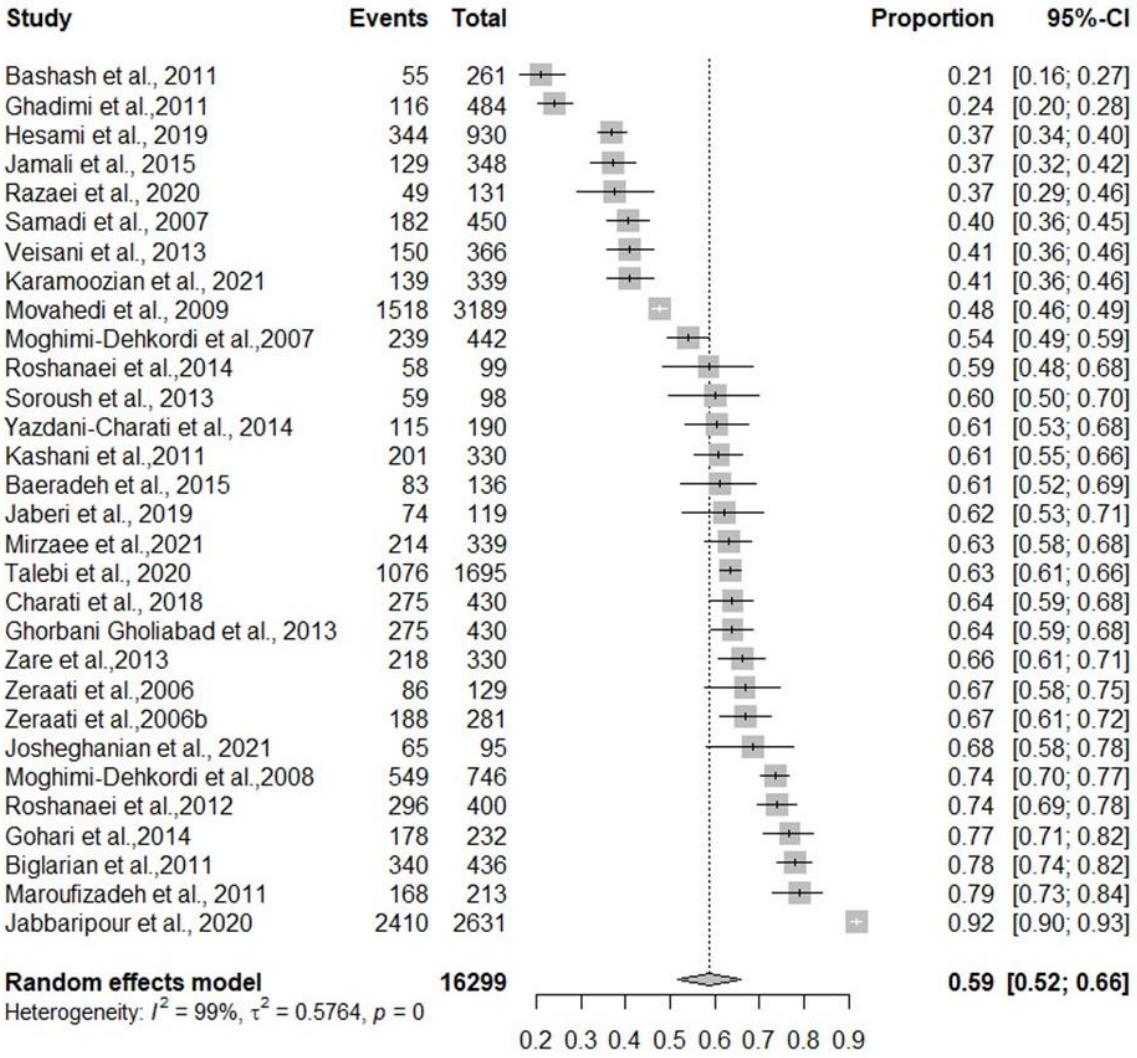

Figure 2. One-year survival rate

As shown in Table 1, eighteen studies evaluate survival of GC for all stages of the disease (I-II-III-IV). Zaraati et al. (47) have investigated only stage IV, and Roshanaei et al. (37) examined all stages except stage I. Other studies did not mention in their text which stage of the disease they were investigating for survival of GC. All studies did not provide survival of GC by stage. We divided the studies based on the calendar year into three group of pre-2000 (5 studies), 2000-2010 (20 studies), and post-2010 (8 studies). Most articles listed in Table 1 conducted before 2000 were in Tehran provience. From 2000-to 2010, there are report from more provinces than in the pre-2000 studies, but still more articles provide information about Tehran province. Since the majority of studies before 2000 were in Tehran province, we make a comparison between the information of this period and the information of the 2000-2010 studies in Tehran. The first-year Survival range in Tehran before 2000 was between 60.8-66.8%, which increased to 60-79% from 2000-to 2010. Also, the 5-year survival has increased from 18.6-20.4% to 14.6-31%, and these promising results show that the overall Survival in Tehran is increasing.

Results of meta-analysis

Thirty studies with an overall number of 16299 patients have reported the one-year survival rate. The results of our analysis showed that the pooled estimate, assuming a random effect model, is 59% (95% CI: 0.518; 0.656). There was a significant amount of heterogeneity between studies with a τ^2=0.57 and I^2= 98.6% (95% CI 98.3%; 98.8%). Figure 2 shows the forest plot of the one-year survival rate.

The three-year survival rate was reported by 25 studies accounting for 14961 patients. The pooled estimate of survival rates, assuming a random effect model, was 30% (95% CI: 0.253; 0.349). The heterogeneity amounts were as follow τ^2=0.293 and I^2= 98.2% (95% CI: 97.9%; 98.5%) (Figure 3).

The pooled estimate of the five-year survival rate, assuming a random effect model, was 18% (95% CI: 0.146; 0.225) as individual five-year survival rates were

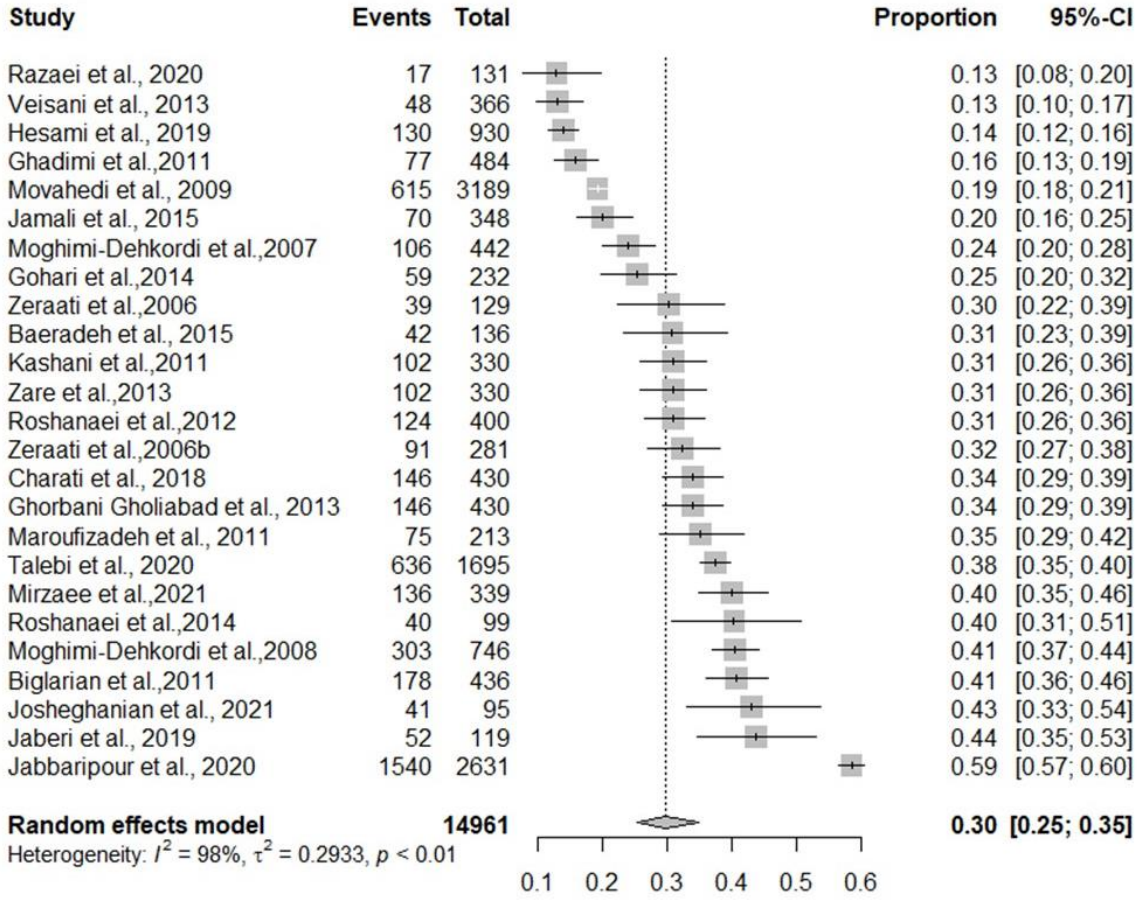

Figure 3. Three-year survival rate

reported by 30 studies with an overall number of 16524 patients. Again a great amount of heterogeneity was seen between studies τ^2=0.476 and I^2= 94.5% (95% CI 93.2%; 95.7%) (Figure 4).

To address the heterogeneity between the studies we decided to conduct a subgroup analysis based on the setting of the studies and the year they have been conducted. We divided studies into two groups by their setting. Those that were conducted in the capital Tehran and those that were conducted in other cities. For the year in which studies were conducted, they were grouped into three categories: studies that the follow-up period was before 2000, between 2000 and 2011, and after 2011.

The one-year survival rate was statistically significantly higher in Tehran than in other cities. Although the third and the fifth year survival rate were also higher in Tehran compared with other settings the difference did not reach a significant level (Table 2).

As shown in Table 3, results of subgroup analysis for the year of study showed improve in one, three, and five-year survival rates. Although the difference did not reach a significant level. The only exception to this is that the five-year survival rate decreased between 2000 and 2010 in comparison with previous years (Table 3). Also, Figure 5 shows the time trend of one year and five year survival rate of Gastric cancer in Iran.

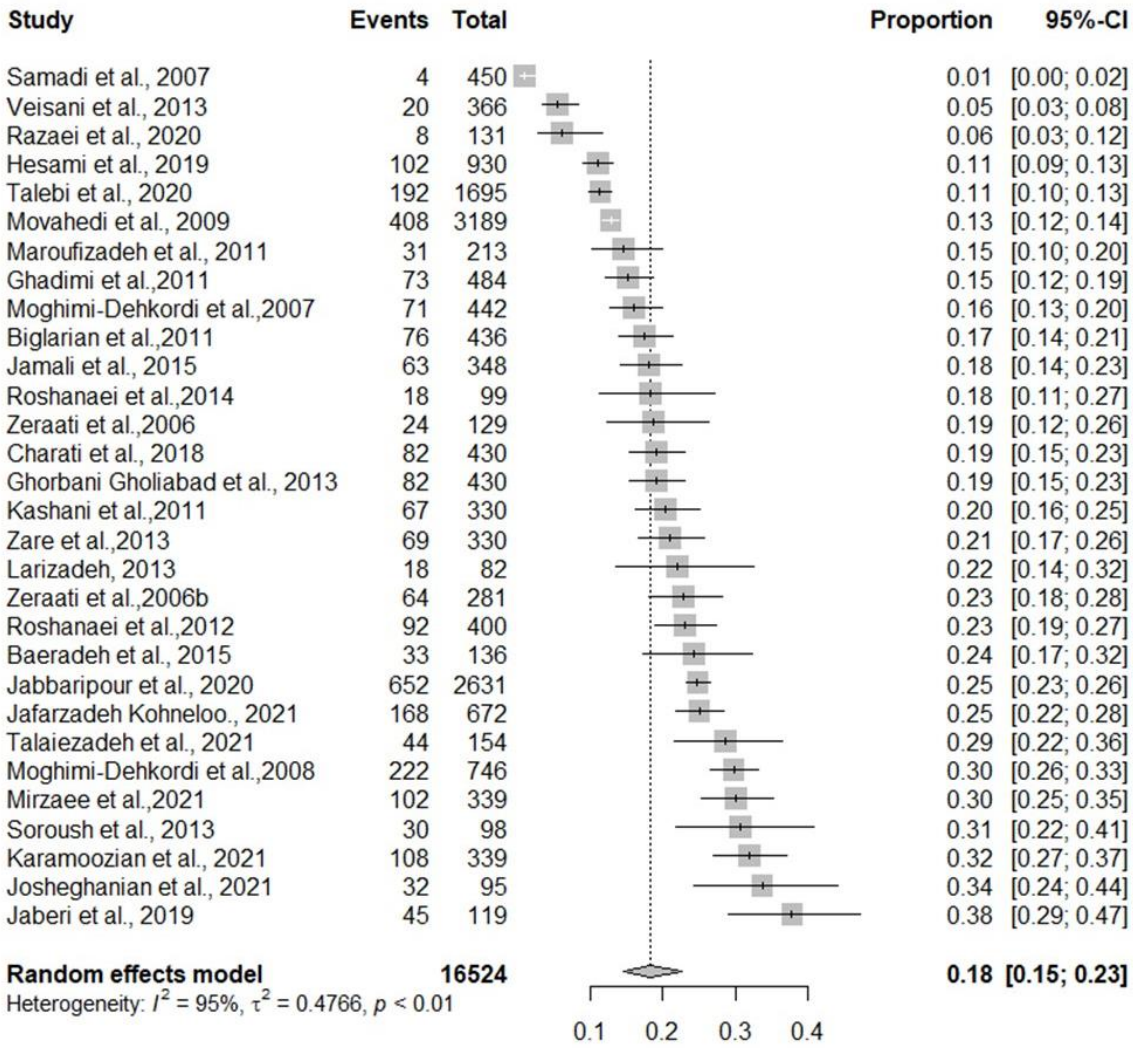

Figure 4. Five-year survival rate

Table 1. Eligible studies that entered the review study

First author	Date of study	Setting	Type of study	NO. of patients	stage	Median survival months	First year survival	Two-year survival	Three-year survival	Four-year survival	Five-year survival	quality
Studies before 2000												
Kashani (29)	1995-1999	Tehran	Cross-sectional study	330 (228 male, 102 female)	I-II-III-IV	-	60.8%	41.4%	30.8%	24.4%	20.4%	Medium
Zeraati (61)	1995-1999	Tehran	Analytical cross-sectional study -sectional	129 (77.5% male)	IV	18.9	66.7%	-	30.6%	-	18.6%	Medium
Zare (62)	1995-1999	National	Cross-sectional study	330 (228 male, 102 female)	I-II-III-IV	16.33	66%	42%	31%	26%	21%	High
Zeraati (47)	1995-1999	Tehran	Analytical cross-sectional study	281 (71.2 % male)	I- II-III-IV	19	66.8%	-	32.5%	-	22.6%	Medium
Ghadimi (40)	1990-1991	Babol	Analytical cross-sectional study	484 (321 male, 163 female) (359 GC)	-	9.1	24%	-	16%	-	15%	High
Studies between 2000-2010												
Jamali (54)	2005-2011	Kohgiluyeh & Boyerahmad	Analytical cross-sectional study	348 (75.6%men.24.4% women)	-	12.4	37%	27%	20%	19%	18%	High
Baeradeh (46)	2006-2010	Yazd	Analytical cross-sectional study	136 (66.9%men,33.1% women)	-	19	61.3%	-	31.2%	-	24.5%	Low
Razaei (42)	2007-2009	Golestan	Cohort study	131 (77.9% men and 22.1% women)	-	-	37.4%	-	13%	-	6.1%	Low
Samadi (24)	2000-2004	Ardabil	Analytical cross-sectional study	450 (141 esophagus, and 279 stomach)	-	11.8 for GC	40.5% (esophagus & stomach)	-	-	-	0.83% (esophagus & stomach)	Medium
Charati (14)	2006-2013	Mazandaran	historical cohort study	430 (296 (68.6%) male and 134 (31.4%) female)	I-II-III-IV	19±2.04	64%	44%	34%	24%	19%	High
Yazdani-Charati (63)	2007-2010	Sari	historical cohort study	190	I-II-III-IV	19.95	60.3%	-	-	27.7%	-	High
Karamoozian (44)	2001-2015	Kerman	Analytical cross-sectional study	339 (216 men, 123 female)	I-II-III-IV	25.46	41%	-	-	-	32%	High
Biglarian (64)	2002-2007	Tehran	historical cohort	436 (315 men, 121 female)	I-II-III-IV	28.3	77.9%,	53.1%	40.8%	32%	17.4%	High
Larizadeh (57)	2003-2011	Kerman	Analytical cross-sectional study	82 (53male, 29 female)	I-II-III-IV	37	-	53%	-	-	22%	Low
Veisani (41)	2006-2011	Sanandaj city, Kurdistan province	concurrent (prospective) cohort study	366 (239 GC, 125 esophageal cancer)	-	11 ± 0.46	41%	17%	13%	10%	5.4%	High
Moghimi-Dehkordiet (32)	2001-2006	Tehran	Historical cohort study	746	I-II-III-IV	24.2	73.6%	50.2%	40.6%	33.2%	29.7%	High
Maroufizadeh (30)	2003-2008	Tehran	Analytical cross-sectional study	213 (154 male, 59 female)	I-II-III-IV	29.6	79.0%	-	35.1%	-	14.6%	High
Bashash (22)	2004	Ardabil	Cross sectional study	261	-	-	21%	-	-	-	-	High
Moghimi dehkordi (65)	2001-2005	Fars	Analytical cross-sectional study	442 (303 male, 139 female)	-	12.6	54%	30%	24%	18%	16%	Medium
Soroush (66)	2008-2010	Tehran	Analytical cross-sectional study	98	I-II-III-IV	17	60%	-	-	-	31%	High

Continued												
Ghorbani Gholiabad (67)	2007-2012	Mazandaran	Analytical cross-sectional study	430 (68.8% male, 31.2% female)	I-II-III-IV	19	64%	44%	34%	28%	19%	High
Movahedi (33)	2001-2005	National	Cohort study	3189 (2541 male, 898 female)	-	11.53	47.6%	27.2%	19.3%	15.7%	12.8%	High
Roshanaei (37)	2003-2007	Tehran	Historical cohort	400 (303 male, 97 female)	II-III-IV	26	74%	54%	31%	26%	23%	Medium
Barfei (53)	2007-2008	Tehran	Analytical cross-sectional study	99 (69 male, 30 female)	-	14.5	59%	-	40%	-	18%	Low
Gohari (68)	2002-2007,	Tehran	Historical cohort study	232	I-II-III-IV	25.1	76.9%	-	25.6%	-	-	Medium
Studies from 2011												
Hesami (43)	2011-2013	West Azerbaijan	Analytical cross-sectional study	930	-	9	37%	-	14%	-	11%	High
Talebi (60)	2001-2018	Rasoul Akram Hospital (2013–2018), Taleghani Hospital (2003–2007), and Fars province in southern Iran (2001–2006)	Historical cohort study	1695 (56% men, 44% women)	-	13.2	63.5%	-	37.5%	-	11.3%	High
Jabbaripour (45)	2015-2017	East Azerbaijan	Analytical cross-sectional study	2,631 (1847 male, 784 female)	I-II-III-IV	-	91.61%	64.21%	58.53%	30.14%	24.77%	High
Jaberi (23)	2008-2013	Hormozgan	Analytical cross-sectional study	119 (86 male, 33 female)	I-II-III-IV	24	62.2%	49.4%	43.7%	39.7%	38%	High
Talaiezadeh (69)	2010 to 2017	Ahvaz	Analytical cross-sectional study	154 patients including 101 males (65.6%)	I-II-III-IV	28	-	57.7%	-	-	28.5%	Medium
Josheghanian (70)	2005-2017	Hamadan	Retrospective cohort study	95 patients, including 66 (71%) male, and 27 (29%) female	I-II-III-IV	24±6.99	68%	49%	43%	39%	34%	Low
Jafarzadeh Kohneloo (71)	1995–2012	-	Cohort study	672 who were undergone total or partial gastrectomy	I-II-III-IV	24.5	-	-	-	-	25%	High
Moghadam (72)	2001-2016	Kerman	Retrospective cohort study	339 (Male 216 (63.7%))	-	25.5 male, 24.5 female	63%	-	40%	-	30%	Medium

Table 2. Results of subgroup analysis in comparison of Tehran and other settings

	Geographic distribution	Number of studies	Survival rate	95% CI	I^2	P-value for subgroup analysis
First year survival rate	Tehran	11	0.696	0.646-0.742	88.5%	0.0006
	Others Settings	19	0.523	0.425-0.619	99.0%	
Third year survival rate	Tehran	10	0.345	0.310-0.382	75.2%	0.062
	Others Settings	15	0.272	0.205-0.350	99.0%	
Fifth year survival rate	Tehran	10	0.199	0.158-0.246	93.4%	0.455
	Others Settings	20	0.173	0.123-0.238	95.2%	

Table 3. Results of subgroup analysis for the date of study

	Number of studies	Setting	Survival rate	95% CI	I^2	P-value for subgroup analysis
One year survival rate	5	Before 2000	0.566	[0.346; 0.763]	98.0%	0.712
	22	2000-2010	0.576	[0.503; 0.646]	97.1%	
	3	After 2010	0.707	[0.107; 0.979]	99.8%	
Three year survival rate	5	Before 2000	0.273	[0.194; 0.370]	89.7%	0.709
	17	2000-2010	0.297	[0.247; 0.353]	96.1%	
	3	After 2010	0.357	[0.053; 0.845]	99.6%	
Five year survival rate	6	Before 2000	0.204	[0.168; 0.245]	71.6%	0.414
	20	2000-2010	0.167	[0.119; 0.230]	95.1%	
	4	After 2010	0.227	[0.110; 0.410]	96.4%	

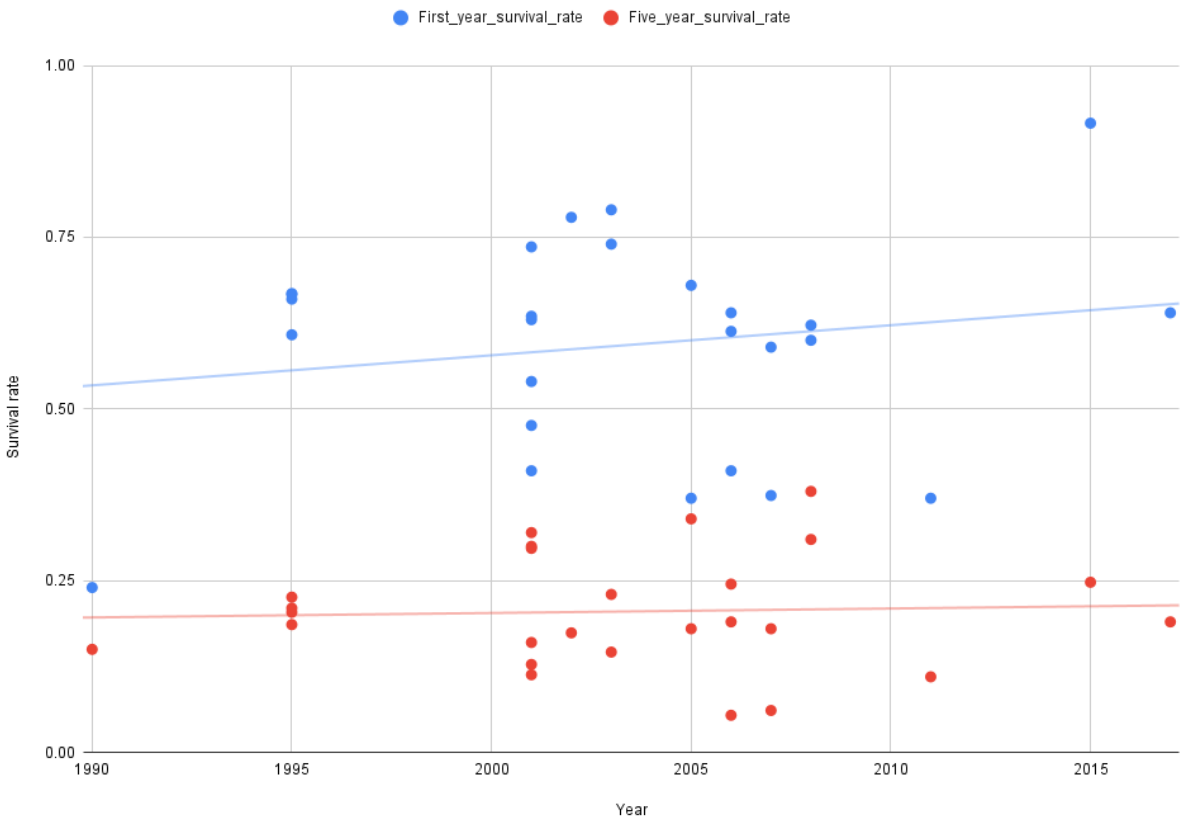

Figure 5. Scatter plot for the first and five-year survival rate based on the starting year of patients follow up

Discussion

In the present study, we investigated numerous studies conducted in Iran and to provide a pooled estimate for the survival of gastric cancer in Iran, We report that survival among gastric cancer patients improved over the last three decades.

The results of our meta-analysis show a considerable heterogeneity between included studies regarding one, three, and five-year survival rates of Gastric cancer. We try to clarify several of the factors that have played a role to this heterogeneity.

Treatment modality is a potential cause of heterogeneity as several studies only included post-operative patients, whereas in other studies other modalities such as radiotherapy and chemotherapy were considered. In the study of Razaei et al., in spite of 34% of patients refusal of any treatment, the five-year survival rate in their study (0.06) was less than the lower limit of the overall five-year survival confidence interval of this meta-analysis (42). Hesami et al.s study indicates that the five-year survival rate of gastric cancer in west Azerbaijan is 0.11 and almost 40% of patients did not receive any treatment. Surgery is associated with a higher survival rate than other treatment modalities (43). Age at diagnosis is a prognostic factor for gastric cancer and older ages are associated with poorer prognosis (48). Age at diagnosis of 60 and more was associated with lower survival, which considered as another source of heterogenesity in this meta-analysis. The age of patients was unevenly distributed in the studies thereupon subgroup analysis could not be conducted on studies on specific age group. Several studies state the anatomical site of the tumor mass in the belly as a prognostic factor. (24, 33), whereas the majority of the studies did not report any data regarding the site of the tumor mass. Movahedi et al reported that stomach cancers that arise from cardia are associated with better survival; in contrast, Samadi et al. reported that these tumors are correlated with lower survival (24, 33). Other conceivable sources of heterogeneity include a patient's

information source that is in case it comes from a cancer registry system or hospital records, stage at diagnosis, presence of distant metastasis, histological type, and, biomarkers and genes (21).

In general, by evaluating Table 3, we see an increase in the survival rate of gastric cancer in Iran during the last three decades, although this is not significant, which can be attributed to heterogeneity between studies. The higher survival rate in Tehran may be due to the inequality in the distribution of health care services in Iran. Healthcare services are well distributed in Iran based on the population level, rather it is not the case when we consider health need indexes (49). Shahabi et al (50) argued that the distribution of nurses, specialist physicians, and hospital beds is fair in Iran's public hospitals based on population concentration. Rezaei et al (49) reported that physicians and hospital beds are better distributed according to population-level than the health need index.

One-year and three-year survival of gastric cancer in Iran according to the present study were 58.9% and 29.9%, respectively. Results of this analysis show that the estimated five-year gastric cancer survival rate in Iran is 18.2%, which is similar to the results of Veisani's study (15%) (21). Overall, the survival rate of gastric cancer patients worldwide varies greatly and is very low. Except for Japan (60.3%) and South Korea (68.9%), the average five-year survival of gastric cancer in most countries is between 20-30% (51, 52), which is lower in Iran (18.2%). The lower gastric cancer survival rate in Iran can be attributed to the late diagnosis of the disease and the lack of necessary facilities in some areas of Iran (21, 35, 38, 42, 43, 46, 53-60). According to Table 3, the five-year survival rate of gastric cancer in Iran after 2010 is 22.7%, which is close to this amount in 2010-2014 in Malta (23.8%), Kuwait (22.4%), Argentina (21.5%), Slovakia (21.1%) and Russia (21%). Comparing the 5-year survival of Iran after 2010 (22.7%) with its neighboring middle eastern countries during the years 2010-2014, the 5-year survival of gastric cancer in Iran is higher than Kuwait (22.4%) and Qatar (17.5%) and less than Jordan (50.7%) and Turkey (24.6%) (51).

The most important limitation of this study is the considerable heterogeneity between included studies, which is unavoidable due to the inherent characteristics of observational studies. As the other limitation of our study, none of the studies included in the meta-analysis provided survival of gastric cancer by stage. Therefore, it is necessary to conduct a comprehensive study with maximum coverage of GC patients to determine the survival of gastric cancer because the data on gastric cancer patterns can be a guide for setting up cancer prevention programs.

Conclusion

The results of our study which has pooled many studies for a long period of time clearly indicate that the survival rates of gastric cancer patients have improved. As the improvement of survival may be due to many factors, more studies is needed to understand the dynamic behind this improvement.

Acknowledgment

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Conflict of interests

The authors declare that there is no conflict of interest.

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