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Original Article

Trend of Appendicitis Mortality at National and Provincial Levels in Iran from 1990 to 2015

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Abstract

Background: Appendicitis is one of the most preventable causes of death worldwide. We aimed to determine the trend of mortality due to appendicitis by sex and age at national and provincial levels in Iran during 26 years.

Methods: Data were collected from Iran Death Registration System (DRS), cemetery databanks in Tehran and Esfahan, and the national population and housing censuses of Iran. The estimated population was determined for each group from 1990 to 2015 using a growth model. Incompleteness, misalignment, and misclassification in the DRS were addressed and multiple imputation methods were used for dealing with missing data. ICD-10 codes were converted to Global Burden of Disease (GBD) codes to allow comparison of the results with the GBD study. A Spatio-Temporal model and Gaussian Process Regression were used to predict the levels and trends in child and adult mortality rates, as well as cause fractions.

Results: From 1990 to 2015, 6,982 deaths due to appendicitis were estimated in Iran. The age-standardized mortality rate per 100 000 decreased from 0.72 (95% UI: 0.46–1.12) in 1990 to 0.11 (0.07–0.16) in 2015, a reduction of 84.72% over the course of 26 years. The male: female ratio was 1.13 during the 26 years of the study with an average annual percent change of -2.31% for women and -2.63% for men. Among men and women, appendicitis mortality rate had the highest magnitude of decline in the province of Zanjan and the lowest in the province of Hormozgan. In 1990, the lowest age-standardized appendicitis-related mortality was observed in both women and men in the province of Alborz and the highest mortality rate among men were observed in the province of Lorestan. In 2015, the lowest mortality rates in women and men were in the province of Tehran. The highest mortality rates in women were in Hormozgan, and in men were in Golestan province.

Conclusion: The mortality rate due to appendicitis has declined at national and provincial levels in Iran. Understanding the causes of differences across provinces and the trend over years can be useful in priority setting for policy makers to inform preventive actions to further decrease mortality from appendicitis.

Keywords: Appendicitis, Iran, Mortality, Trend

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Introduction

Over the past two decades, in developing countries, the trend in disease burden has shifted from infectious diseases to non-communicable diseases.[1–3] Appendicitis is the most common surgical cause of acute abdominal pain around the world.[4,5] It is regarded as one of the 'avoidable' causes of death in any population.[6] Appendicitis can cause more mortality in susceptible groups such as young children,[7] older people[8-12] and people with comorbidities.[8,12,13] Also, because of the higher frequency of complications of appendicitis in men,[10] a higher mortality rate has been reported in men.

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Appendicitis-related outcomes represent the effectiveness of health care systems and national health policies[14]; therefore, an understanding of the status and change in mortality due to appendicitis in developing countries is essential for planning health care resource utilization and updating policies at national and regional levels.[15]

Although the appendicitis-related mortality rate has declined globally,[15] most studies have focused on appendicitis deaths in Western countries, and relatively few studies have focused on appendicitis and associated deaths in Asia or the Middle East.[16] Evidence is lacking for recent epidemiological study of appendicitis mortality in large populations over a long period in Iran. The study of regional and national disease trends is an essential and important step for priority setting in health research and can help authorities and policy makers to use evidence-based data for appropriate prevention and treatment of diseases.[17] The National and Sub-national Burden of Diseases, Injuries and Risk Factors (NASBOD) is a continuous project aimed at understanding the levels and trends of the burden of disease in Iran in the period from 1990 to 2015.[18,19] The goal of the NASBOD project is to show the trend of mortality across the country and describe the distribution of diseases and risk factors at the national level. This data would guide cost-effective interventions that can address the main health problems among sub-national populations.[18]

This study was designed to evaluate the trends and age-specific mortality rate of appendicitis by sex at the national and provincial levels from 1990 to 2015.

Material and Methods

The methods have been previously described in detail.[18] The NASBOD study has been the leading program for determining the burden of 290 diseases and 67 relevant risk factors from 1990 to 2015 at both national and sub-national levels in Iran.[18] For this program, the target population has been divided into 19 age groups for males and females. The age groups have 5-year intervals with the exception of neonates and children subdivided into subgroups of under 1 year and 1 to 4 years; also, people over the age of 85 are in the category of 85+. Initially, the 10th International Classification of Disease (ICD-10) coding was used to register causes of death. However, to compare the results with the Global Burden Disease (GBD) study, the ICD-10 coding were converted into GBD project standards.[20]

Death information related to appendicitis was collected from the Death Registration System (DRS) from 1995 to 2010 and cemetery databanks in Tehran and Esfahan (Data of these two cemeteries were not gathered in the DRS). The national population and housing censuses were used to estimate the population count based on age-sex groups. The estimated population was determined for each group from 1990 to 2015 using a growth model. Wealth index, average successful years of schooling, and urbanization ratio were considered as covariates which were extracted from the Household Income and Expenditure Surveys and Population and Housing Censuses datasets.[21,22]

Failure to complete the DRS due to the inability to find and record all death cases and the loss of data points in some years or in some provinces were treated as missing. After data collection, we used various statistical methods in pediatric and adult cases to estimate cause-specific mortality rates for each group by age, gender and province.

For trend analysis, we used a spatio-temporal model along with Gaussian process regression (GPR). These models were used to predict the trend at national level and predict child and adult mortality rate (AMR) independently.[23-26]

We used summary birth history (SBH) and complete birth history (CBH) methods to predict the child mortality rate (CMR). Previously, maternal age cohort (MAC) and maternal age period (MAP) methods were used to estimate the mortality rate; using the LOESS approach, these two methods were combined.[26] As the last step, the results were combined with GPR data to achieve the final estimates.

As the first step in calculating the AMR, we assessed the completeness of the DRS data using death distribution methods. The second step involved use of three distinct models including generalized growth balance (GGB), synthetic extinct generation (SEG), and GGB-SEG models. After analysis of the completeness of data, the LOESS approach was used to merge the results. The AMR was then estimated with extracting life tables. As the last step in AMR estimation, the GPR model was applied to the data.

After estimating the CMR and AMR, key variables including age, sex, cause of death, and residential area were extracted from the data. In order to impute missing values for causes of death, we used multinomial imputation in STATA 11.[27] Also, the Amelia package in R programming language was used to impute missing values for age and sex variables.[28] By considering combinations of age and sex, the effect of covariates on the cause fraction of death by logit link function was adjusted using mixed effect models. In this model, random effect related to each province was considered to handle the correlation between cause fractions of death in each province separately.

We incorporated a spatio-temporal model to further expand the results from the period of 1995–2010 to 1990–2015. Uncertainty Intervals (UIs) were calculated using the spatio-temporal model on thousand simulated value and the 2.5th and 97.5th percentiles were used as the lower and upper bounds, respectively.

Rates were calculated for the age and sex groups mentioned above at national and sub-national levels over the 26 years of the study. We computed age-standardized rates by direct method of standardization utilizing the Iranian population in 2015. We used tables and figures to visualize the data; all calculations of the data demonstration

were performed by STATA 11 and R programming language version 3.0.2. Average annual percent changes (APC) were estimated by the package 'segmented' in R programming language.[29] The socio-demographic index (SDI) was used to assess the status of Iran among other countries. SDI is a summary measure that identifies where countries or other geographic areas sit on the spectrum of development. Expressed on a scale of 0 to 1, SDI is a composite average of the rankings of the incomes per capita, average educational attainment, and fertility rates of all areas in the GBD study.[30] Since SDI is a national index, we used the HDI index at the level of provinces, consisting of the statistic composite index of life expectancy, education, and per capita income indicators.[31] For assessing gains on personal health-care access and quality and nationwide comparisons between countries, we used health-care access and quality index (HAQ).[32] The HAQ Index encompasses 32 causes of death considered to be avoidable provided that quality healthcare is available. These causes include a range of health service areas: vaccine-preventable diseases; infectious diseases and maternal and child health; non-communicable diseases, including cancers, cardiovascular diseases, and diabetes; and gastrointestinal conditions for which surgery can easily avert death, such as appendicitis.[33]

Results

The study estimated that from 1990 to 2015, there were 6982 deaths due to appendicitis across the country. The records of appendicitis-related deaths increased from 1990 to 1995 in both sexes, and then decreased from 1995 to 2015. The highest number of appendicitis deaths was in 1995: 197 cases (95% UI: 126–311) in women and 226 (151–339) cases in men. The male to female ratios were 1.16 and 1.04 in 1990 and 2015, respectively. The majority of deaths were in the age group of 1 to 9 years from 1990 to 2015 (Figure 1).

The age-standardized mortality rate per 100 000 decreased from 0.72 (0.46–1.12) in 1990 to 0.11 (0.07–0.16) in 2015, a reduction of approximately 84.72% over the study period. The age-standardized mortality rate of appendicitis was 0.67 (0.42–1.08) and 0.75 (0.49–1.15) per 100 000 among women and men, respectively in 1990. This rate declined to 0.11 (0.07–0.16) in women and 0.11 (0.08–0.16) in men in 2015 (Figure 2).

Children (1 to 4 years), as well as the elderly population (over 85 years), had higher mortality rates during the study period (Figure 3). In 1990, with the exception of two age groups of 5 to 9 years and 10 to 14 years old, the appendicitis mortality rate was higher in men than women in all age groups. In 2015, the appendicitis mortality rate in women was higher than men, in the age group of 1 to 4 years and over 85 years of age in addition to the two previously mentioned age groups (5 to 9 years and 10 to 14 years old) (Figure 3).

The average APC (AAPC) of the age-standardized mortality rate was -2.45% overall at national level and -2.31% and -2.63% for women and men between 1990 and 2015 at national level, respectively. The APC of the age-standardized mortality rate in estimated break-point years at national level is shown in Table 1.

The rate of decline in the appendicitis mortality rate was not similar in all provinces across the country (Figure 4, Table 2). The highest and the lowest APC magnitude between 1990 and 2015 in provincial levels were seen in women in Zanjan (-13.2%) and Hormozgan (-1.7%), respectively. Among men, Zanjan (-12.9%) and Hormozgan (-3.0%) had the highest and lowest magnitude of decline, respectively (Table 2 and Figure 4). In 1990,

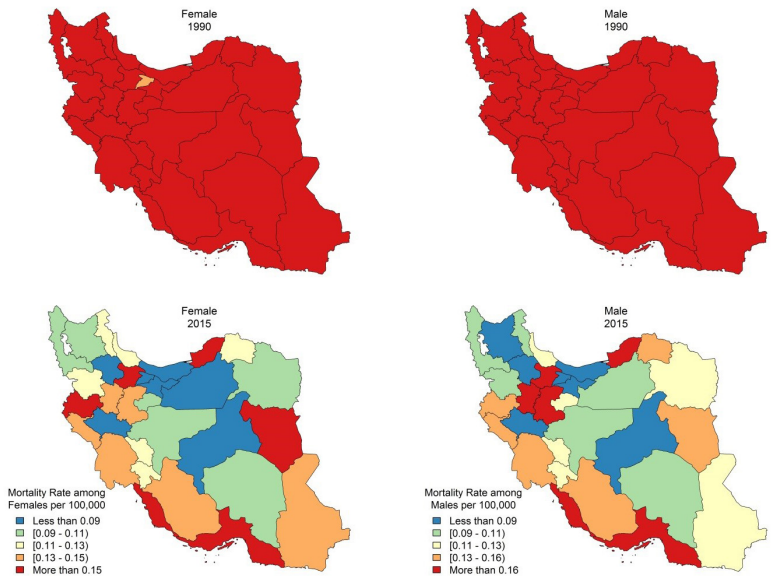

Figure 1. Time Trend of Appendicitis Death Number at National Level Based on Age Groups and Sex from 1990 to 2015.

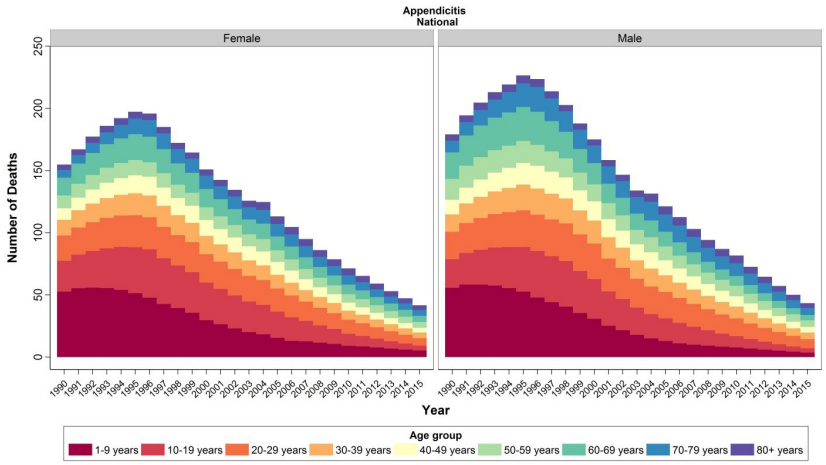

Figure 2. Time Trend of Appendicitis Age-Standardized Mortality Rate Per 100 000 at National Level by Sex from 1990 to 2015.

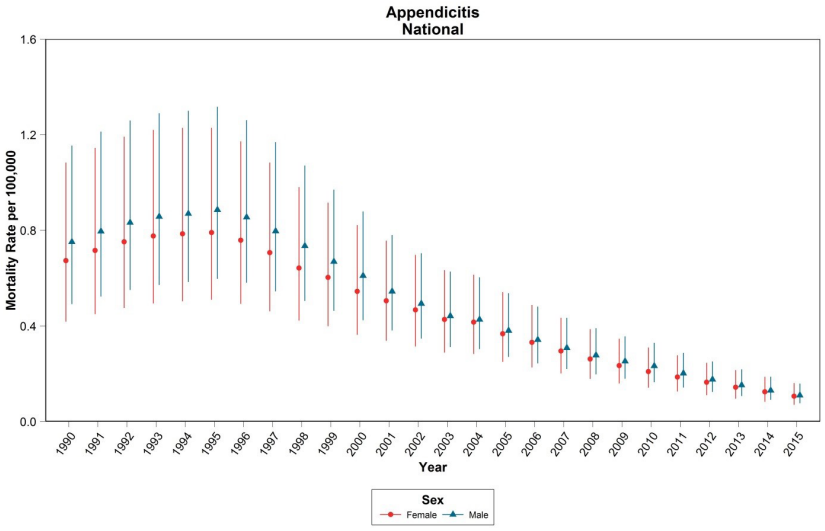

Figure 3. Comparison of Mortality Rate Per 100 000 Due to Appendicitis by Age Groups and Sex, in 1990 and 2015.

the lowest age-standardized appendicitis-related mortality was observed in both women and men in the province of Alborz: 0.13 (0.08–0.22) in women and 0.23 (0.15–0.37) in men. Also, the highest mortality rate among men was observed in the province of Lorestan [2.12 (1.40–3.17)] and Zanjan for women [2.07 (1.22–3.43)]. In 2015, the lowest mortality rates in women [0.04 (0.02–0.07)] and men [0.06 (0.04–0.10)] occurred in the province of Tehran. The highest mortality rates in women were in Hormozgan [0.23 (0.15–0.37)], and in men were in Golestan province [0.22 (0.16 – 0.31)].

Discussion

This is the first study in Iran examining the appendicitis-related mortality rate by regions/provinces. Appendicitis is considered amenable to health care; surgery can easily prevent death.[34] We have examined differences in the appendicitis mortality rate by sex and age as well as provincial differences in order to examine the differences between health access and quality and effects on the mortality of appendicitis. The findings help in reducing the burden of appendicitis death by informing managers about high-risk regions and population to target interventions and improve population health.

In this study, we showed that the appendicitis-related mortality rate has declined by an average of -2.5% during the study period. Appendicitis constitutes 0.065% of all death causes in Iran with an APC of -1.4% reported previously.[35] This finding is similar to the other countries in the Middle East and North Africa.[35] According to the interactive global map of the incidence of appendicitis, Iran was among the countries with the highest incidence of appendicitis (≥150 per 100 000) between 1990 and 2014.[15] The appendicitis death rate in Iran at national level declined from 1.37 to 0.13 and from 1.42 to 0.10 in women and men between 1990 and 2015, respectively. The mortality rate in Iran from appendicitis was higher than the global death rate in 1990, but in 2015, Iran's

Table 1. Annual Percent Change of Age-Standardized Mortality Rate in Estimated Break-Points by Sex at National Level

Sex	Estimated Break-Point	APC
Female	1990 to 1992	4.0 (3.1 to 4.8)
	1992 to 1995	0.9 (0.1 to 1.8)
	1995 to 2000	-5.3 (-5.7 to -4.9)
	2000 to 2009	-3.5 (-3.7 to -3.3)
	2009 to 2015	-2.1 (-2.4 to -1.9)
Male	1990 to 1995	2.6 (2.2 to 3.0)
	1995 to 2002	-6.2 (-6.6 to -5.8)
	2002 to 2007	-3.6 (-4.0 to -3.2)
	2007 to 2013	-2.5 (-2.9 to -2.1)
	2013 to 2015	-2.0 (-4.4 to 0.3)
Both	1990 to 1995	2.9 (2.3 to 3.4)
	1995 to 2002	-5.4 (-5.8 to -5.1)
	2002 to 2008	-3.5 (-3.9 to -3.1)
	2008 to 2012	-2.5 (-3.0 to -1.9)
	2012 to 2015	-2.0 (-3.2 to -0.8)

* Data in parenthesis are 95% confidence intervals.

appendicitis death rate was similar to the global rates (0.09,[36] 0.08[37]) at a rate of 0.11 (0.07–0.16) in 2015. Some studies have reported a slight decrease in the incidence of appendicitis, especially in women, which may have been due to improved diagnostic methods with reduced cases of negative appendectomy[38] and reduction in the misdiagnosis of gynecological pathology.[39]

Over the course of 26 years, the overall trend of appendicitis deaths in Iran has declined in a fashion similar to the global trend. According to the GBD study, the worldwide age-standardized mortality rate declined by -24.11% from 1990 to 2015, while the decline in Iran was about -31.87%.[40]

According to SDI groupings by geography, based on 2015 values, Iran was among countries of the High-middle SDI group.[40] A reduction in the mortality of appendicitis may be attributed to the incremental trend of SDI values from 1990 to 2015 in Iran (0.46 in 1990 and 0.71 in 2015) with the percent change of 55.51% and APC of 1.78% from 1990 to 2015.[40]

Another important reason for mortality from appendicitis is lack of access to high quality health care. In Iran, the HAQ index increased from 49.3 in 1990 to 71.8 in 2016 which is higher than the average global rate.[41] Improvement in the HAQ Index has a strong relationship with overall development and improvement in the health care delivery systems.[34] Other factors contributing to reduction in appendicitis-related mortality rate include the increasing availability of diagnostic modalities and surgical teams over the time period.[42] The advancement of antibiotic therapy strategies has also reduced deaths from appendicitis.[43,44] Studies have shown that the use of antibiotics in the treatment of appendicitis has been able to reduce the hospitalization and mortality rate of appendicitis.[45]

The longitudinal trend in data indicated an increase in the death rate during the five-year period between 1990 and 1995 in Iran. Financial crises can be a threat to health[46]; this finding may be linked to the economic depression after the Iraq-Iran war.[47] Increasing construction budgets and reducing health budgets could be amongst the other causes for this period of increasing appendicitis-related mortality.

As shown in the figures, one of the most vulnerable age groups is the elderly group. Despite the reduction in the mortality of patients, appendicitis is still a diagnostic problem among the elderly.[8–10] This is due to the unusual presentation of appendicitis in the elderly and more complications associated with it.[8,12] The combination of delayed referral, diagnostic problems, delay in surgical intervention, comorbidities and possible differences in the pathophysiology of appendicitis development in the elderly plays a role in the complications of acute appendicitis in this group of patients.[12,48] Comorbidities and general

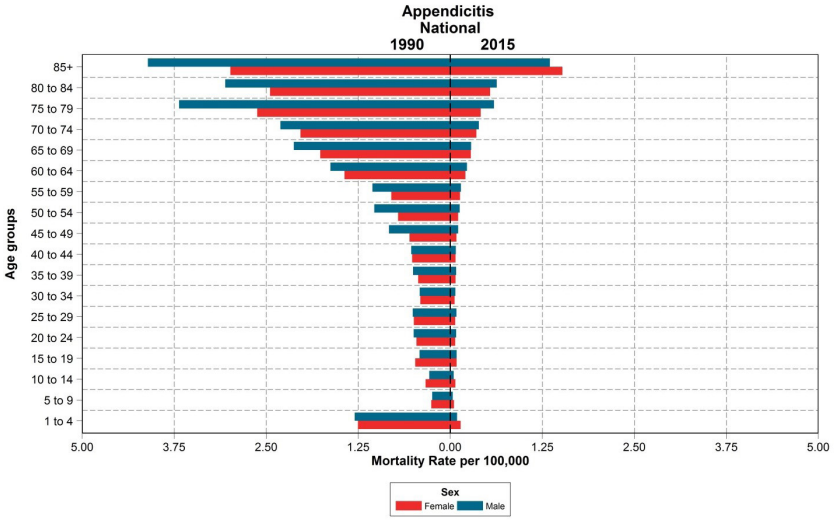

Figure 4. The Appendicitis Age-Standardized Mortality Rate Per 100 000 at Provincial Level in 1990 and 2015, by Sex.

Table 2. National and Provincial Age Standardized Mortality Rate Due to Appendicitis Per 100000 at 5 Years Intervals with Annual Percentage Change of Death (APC) between 1990 and 2015 by Sex

Location	Female							Male						
	Year						APC 1990 - 2015 (%)	Year						APC 1990 - 2015 (%)
	1990	1995	2000	2005	2010	2015		1990	1995	2000	2005	2010	2015	
Alborz	0.13 (0.08 - 0.22)	0.17 (0.10 - 0.27)	0.15 (0.09 - 0.23)	0.12 (0.08 - 0.18)	0.1 (0.06 - 0.15)	0.06 (0.04 - 0.09)	-3.23	0.23 (0.15 - 0.37)	0.29 (0.19 - 0.44)	0.23 (0.15 - 0.34)	0.16 (0.11 - 0.23)	0.12 (0.08 - 0.17)	0.06 (0.04 - 0.1)	-5.01
Ardebil	0.91 (0.57 - 1.45)	1.04 (0.68 - 1.6)	0.55 (0.37 - 0.8)	0.5 (0.35 - 0.7)	0.28 (0.2 - 0.39)	0.12 (0.09 - 0.18)	-7.62	1.27 (0.86 - 1.86)	1.4 (0.98 - 1.98)	0.97 (0.7 - 1.34)	0.46 (0.34 - 0.61)	0.26 (0.19 - 0.35)	0.11 (0.08 - 0.14)	-9.48
Bushehr	0.73 (0.46 - 1.16)	0.97 (0.64 - 1.47)	0.59 (0.4 - 0.85)	0.49 (0.34 - 0.7)	0.32 (0.22 - 0.47)	0.19 (0.13 - 0.29)	-5.19	0.47 (0.31 - 0.71)	0.64 (0.44 - 0.93)	0.57 (0.4 - 0.8)	0.42 (0.31 - 0.58)	0.3 (0.22 - 0.43)	0.16 (0.11 - 0.23)	-4.29
Chahar Mahall and Bakhtiari	1.1 (0.72 - 1.69)	1.16 (0.78 - 1.73)	0.65 (0.45 - 0.95)	0.41 (0.29 - 0.59)	0.22 (0.15 - 0.31)	0.12 (0.08 - 0.17)	-8.64	0.99 (0.67 - 1.45)	1.1 (0.76 - 1.57)	0.78 (0.56 - 1.1)	0.44 (0.32 - 0.61)	0.25 (0.18 - 0.34)	0.12 (0.09 - 0.17)	-8
East Azarbaijan	0.74 (0.48 - 1.15)	0.93 (0.62 - 1.4)	0.68 (0.47 - 0.98)	0.4 (0.28 - 0.57)	0.23 (0.16 - 0.33)	0.11 (0.07 - 0.16)	-7.44	0.51 (0.35 - 0.74)	0.69 (0.48 - 0.98)	0.55 (0.4 - 0.76)	0.33 (0.24 - 0.46)	0.22 (0.16 - 0.3)	0.09 (0.07 - 0.13)	-6.51
Esfahan	0.58 (0.36 - 0.95)	0.64 (0.41 - 1.02)	0.45 (0.3 - 0.7)	0.27 (0.18 - 0.41)	0.17 (0.11 - 0.26)	0.1 (0.06 - 0.15)	-6.95	0.39 (0.26 - 0.61)	0.53 (0.35 - 0.79)	0.41 (0.28 - 0.6)	0.28 (0.2 - 0.41)	0.18 (0.13 - 0.26)	0.1 (0.07 - 0.15)	-5.21
Fars	0.52 (0.33 - 0.82)	0.71 (0.47 - 1.07)	0.49 (0.33 - 0.72)	0.37 (0.26 - 0.53)	0.25 (0.17 - 0.36)	0.14 (0.09 - 0.21)	-5.19	0.52 (0.35 - 0.76)	0.7 (0.49 - 1)	0.51 (0.36 - 0.71)	0.35 (0.26 - 0.49)	0.25 (0.18 - 0.35)	0.13 (0.09 - 0.18)	-5.45
Gilan	0.66 (0.42 - 1.03)	0.74 (0.49 - 1.11)	0.52 (0.35 - 0.76)	0.35 (0.24 - 0.5)	0.22 (0.15 - 0.33)	0.12 (0.08 - 0.18)	-6.64	0.83 (0.56 - 1.22)	0.9 (0.63 - 1.28)	0.63 (0.45 - 0.87)	0.34 (0.25 - 0.47)	0.25 (0.18 - 0.35)	0.12 (0.09 - 0.17)	-7.47
Golestan	1.03 (0.65 - 1.6)	1.3 (0.85 - 1.94)	0.94 (0.65 - 1.36)	0.67 (0.47 - 0.95)	0.35 (0.25 - 0.5)	0.21 (0.14 - 0.3)	-6.2	1 (0.69 - 1.45)	1.47 (1.05 - 2.08)	1.02 (0.74 - 1.41)	0.76 (0.56 - 1.03)	0.47 (0.34 - 0.65)	0.22 (0.16 - 0.31)	-5.8
Hamadan	0.73 (0.48 - 1.1)	0.93 (0.63 - 1.36)	0.72 (0.51 - 1.03)	0.48 (0.35 - 0.68)	0.26 (0.19 - 0.37)	0.14 (0.1 - 0.19)	-6.5	0.75 (0.53 - 1.08)	1.01 (0.72 - 1.41)	0.78 (0.57 - 1.05)	0.54 (0.41 - 0.73)	0.32 (0.24 - 0.44)	0.16 (0.11 - 0.22)	-6.08
Hormozgan	0.35 (0.22 - 0.58)	0.53 (0.34 - 0.82)	0.5 (0.34 - 0.76)	0.49 (0.33 - 0.72)	0.36 (0.24 - 0.54)	0.23 (0.15 - 0.37)	-1.66	0.43 (0.28 - 0.65)	0.66 (0.45 - 0.96)	0.69 (0.48 - 0.97)	0.52 (0.37 - 0.72)	0.3 (0.21 - 0.43)	0.2 (0.13 - 0.3)	-3
Ilam	0.82 (0.52 - 1.31)	0.99 (0.64 - 1.52)	0.68 (0.46 - 1.02)	0.49 (0.33 - 0.73)	0.28 (0.19 - 0.41)	0.14 (0.09 - 0.21)	-6.85	0.72 (0.48 - 1.07)	0.92 (0.63 - 1.33)	0.69 (0.48 - 0.98)	0.51 (0.36 - 0.71)	0.32 (0.22 - 0.45)	0.16 (0.11 - 0.23)	-5.93
Kerman	0.73 (0.48 - 1.11)	0.92 (0.63 - 1.35)	0.68 (0.47 - 0.97)	0.41 (0.29 - 0.57)	0.21 (0.15 - 0.3)	0.1 (0.07 - 0.15)	-7.63	0.82 (0.57 - 1.18)	1.03 (0.74 - 1.44)	0.68 (0.5 - 0.93)	0.43 (0.32 - 0.57)	0.26 (0.19 - 0.35)	0.11 (0.08 - 0.15)	-7.79
Kermanshah	0.91 (0.59 - 1.4)	1.22 (0.82 - 1.82)	1.01 (0.69 - 1.48)	0.6 (0.42 - 0.86)	0.36 (0.25 - 0.51)	0.18 (0.12 - 0.26)	-6.3	0.93 (0.65 - 1.34)	1.16 (0.83 - 1.63)	0.86 (0.62 - 1.18)	0.52 (0.39 - 0.71)	0.33 (0.25 - 0.45)	0.16 (0.11 - 0.22)	-6.89
Khuzestan	0.4 (0.27 - 0.61)	0.56 (0.38 - 0.83)	0.4 (0.28 - 0.59)	0.39 (0.27 - 0.55)	0.24 (0.17 - 0.35)	0.14 (0.09 - 0.2)	-4.24	0.56 (0.38 - 0.82)	0.79 (0.55 - 1.13)	0.66 (0.47 - 0.94)	0.48 (0.35 - 0.66)	0.27 (0.2 - 0.37)	0.14 (0.1 - 0.19)	-5.43
Kohgiluyeh and Buyer Ahmad	0.96 (0.59 - 1.58)	1.05 (0.65 - 1.66)	0.58 (0.38 - 0.89)	0.45 (0.3 - 0.67)	0.24 (0.16 - 0.36)	0.11 (0.07 - 0.17)	-8.29	1.25 (0.8 - 1.96)	1.52 (0.99 - 2.33)	0.73 (0.49 - 1.08)	0.46 (0.32 - 0.67)	0.29 (0.2 - 0.42)	0.12 (0.08 - 0.17)	-9.1
Kordestan	1.37 (0.83 - 2.24)	1.52 (0.98 - 2.38)	1.09 (0.73 - 1.63)	0.61 (0.42 - 0.88)	0.31 (0.22 - 0.45)	0.13 (0.09 - 0.19)	-9.04	1.42 (0.92 - 2.19)	1.56 (1.06 - 2.29)	1.07 (0.75 - 1.51)	0.51 (0.38 - 0.7)	0.26 (0.2 - 0.36)	0.1 (0.07 - 0.14)	-10.14

Table 2. Continued

Location	Female							Male						
	Year						APC 1990 - 2015 (%)	Year						APC 1990 - 2015 (%)
	1990	1995	2000	2005	2010	2015		1990	1995	2000	2005	2010	2015	
Lorestan	1.43 (0.9 - 2.27)	1.57 (1.04 - 2.39)	0.95 (0.65 - 1.38)	0.48 (0.35 - 0.68)	0.21 (0.15 - 0.3)	0.09 (0.06 - 0.12)	-10.68	2.12 (1.4 - 3.17)	2.21 (1.53 - 3.18)	1.16 (0.83 - 1.62)	0.57 (0.42 - 0.76)	0.22 (0.16 - 0.3)	0.09 (0.06 - 0.12)	-11.96
Markazi	0.51 (0.32 - 0.79)	0.66 (0.44 - 0.98)	0.56 (0.39 - 0.82)	0.45 (0.32 - 0.64)	0.28 (0.2 - 0.41)	0.15 (0.1 - 0.22)	-4.74	0.65 (0.43 - 0.96)	0.87 (0.61 - 1.25)	0.76 (0.54 - 1.06)	0.54 (0.4 - 0.74)	0.35 (0.26 - 0.48)	0.18 (0.13 - 0.26)	-4.91
Mazandaran	0.77 (0.49 - 1.23)	0.79 (0.51 - 1.23)	0.45 (0.29 - 0.68)	0.27 (0.18 - 0.41)	0.14 (0.09 - 0.21)	0.07 (0.04 - 0.1)	-9.42	0.78 (0.52 - 1.18)	0.8 (0.54 - 1.17)	0.47 (0.32 - 0.69)	0.26 (0.18 - 0.38)	0.13 (0.09 - 0.19)	0.06 (0.04 - 0.09)	-9.74
North Khorasan	0.88 (0.54 - 1.4)	1.01 (0.65 - 1.55)	0.71 (0.47 - 1.06)	0.51 (0.35 - 0.75)	0.28 (0.19 - 0.41)	0.13 (0.08 - 0.19)	-7.47	1.26 (0.83 - 1.93)	1.32 (0.9 - 1.95)	0.97 (0.68 - 1.39)	0.6 (0.43 - 0.85)	0.35 (0.25 - 0.49)	0.14 (0.1 - 0.2)	-8.47
Qazvin	0.94 (0.61 - 1.44)	1.04 (0.7 - 1.54)	0.93 (0.65 - 1.34)	0.65 (0.46 - 0.91)	0.37 (0.26 - 0.52)	0.2 (0.14 - 0.29)	-6	0.88 (0.6 - 1.27)	1.08 (0.77 - 1.52)	0.92 (0.67 - 1.26)	0.68 (0.51 - 0.92)	0.44 (0.33 - 0.6)	0.21 (0.15 - 0.29)	-5.51
Qom	0.4 (0.23 - 0.69)	0.49 (0.29 - 0.82)	0.42 (0.26 - 0.69)	0.32 (0.2 - 0.51)	0.17 (0.11 - 0.28)	0.09 (0.06 - 0.15)	-5.6	0.56 (0.34 - 0.92)	0.72 (0.45 - 1.16)	0.55 (0.35 - 0.85)	0.39 (0.25 - 0.59)	0.24 (0.16 - 0.36)	0.11 (0.07 - 0.17)	-6.36
Razavi Khorasan	0.64 (0.4 - 1.01)	0.8 (0.52 - 1.23)	0.5 (0.33 - 0.74)	0.42(0.28 - 0.61)	0.21 (0.14 - 0.3)	0.09 (0.06 - 0.14)	-7.49	0.58 (0.39 - 0.88)	0.73 (0.49 - 1.08)	0.59 (0.41 - 0.85)	0.43 (0.31 - 0.61)	0.27 (0.19 - 0.38)	0.12 (0.08 - 0.17)	-6.14
Semnan	0.41 (0.24 - 0.68)	0.48 (0.3 - 0.78)	0.39 (0.25 - 0.61)	0.28 (0.18 - 0.42)	0.16 (0.11 - 0.25)	0.09 (0.06 - 0.14)	-5.96	0.41 (0.25 - 0.64)	0.53 (0.35 - 0.82)	0.39 (0.26 - 0.59)	0.3 (0.21 - 0.44)	0.2 (0.14 - 0.29)	0.1 (0.07 - 0.15)	-5.34
Sistan and Baluchestan	1.29 (0.72 - 2.33)	1.5 (0.85 - 2.63)	1.13 (0.66 - 1.91)	0.64 (0.39 - 1.04)	0.3 (0.19 - 0.48)	0.15 (0.09 - 0.24)	-8.23	1.82 (1.08 - 3.06)	1.87 (1.14 - 3.05)	0.96 (0.61 - 1.51)	0.49 (0.32 - 0.74)	0.25 (0.17 - 0.38)	0.13 (0.08 - 0.19)	-10.11
South Khorasan	0.6 (0.36 - 0.97)	0.72 (0.46 - 1.15)	0.58 (0.37 - 0.88)	0.49 (0.32 - 0.73)	0.3 (0.2 - 0.46)	0.16 (0.1 - 0.24)	-5.2	0.89 (0.56 - 1.4)	1.02 (0.67 - 1.56)	0.78 (0.53 - 1.14)	0.54 (0.37 - 0.77)	0.35 (0.24 - 0.5)	0.15 (0.1 - 0.22)	-6.81
Tehran	0.31 (0.17 - 0.57)	0.33 (0.18 - 0.6)	0.2 (0.11 - 0.35)	0.13 (0.07 - 0.22)	0.08 (0.05 - 0.14)	0.04 (0.02 - 0.07)	-7.68	0.55 (0.31 - 0.97)	0.61 (0.36 - 1.05)	0.33 (0.2 - 0.56)	0.19 (0.12 - 0.32)	0.12 (0.08 - 0.2)	0.06 (0.04 - 0.1)	-8.45
West Azarbaijan	0.77 (0.48 - 1.22)	0.87 (0.57 - 1.32)	0.63 (0.43 - 0.94)	0.43 (0.3 - 0.61)	0.24 (0.17 - 0.34)	0.11 (0.07 - 0.15)	-7.61	0.89 (0.59 - 1.34)	1.01 (0.7 - 1.47)	0.68 (0.49 - 0.94)	0.39 (0.29 - 0.52)	0.25 (0.18 - 0.34)	0.1 (0.07 - 0.14)	-8.44
Yazd	0.39 (0.25 - 0.6)	0.44 (0.29 - 0.68)	0.34 (0.23 - 0.51)	0.26 (0.17 - 0.38)	0.17 (0.11 - 0.25)	0.08 (0.06 - 0.13)	-5.91	0.64 (0.43 - 0.95)	0.72 (0.49 - 1.05)	0.45 (0.31 - 0.64)	0.3 (0.22 - 0.43)	0.2 (0.14 - 0.28)	0.09 (0.07 - 0.14)	-7.36
Zanjan	2.07 (1.22 - 3.43)	1.89 (1.22 - 2.92)	1.01 (0.68 - 1.5)	0.44 (0.29 - 0.66)	0.18 (0.11 - 0.29)	0.06 (0.03 - 0.11)	-13.17	2.03 (1.29 - 3.19)	1.83 (1.25 - 2.66)	1.04 (0.74 - 1.45)	0.45 (0.32 - 0.64)	0.23 (0.15 - 0.35)	0.07 (0.04 - 0.11)	-12.85
National	0.67 (0.42 - 1.08)	0.79 (0.51 - 1.23)	0.54 (0.36 - 0.82)	0.37 (0.25 - 0.54)	0.21 (0.14 - 0.31)	0.11 (0.07 - 0.16)	-7.14	0.75 (0.49 - 1.15)	0.89 (0.6 - 1.32)	0.61 (0.42 - 0.88)	0.38 (0.27 - 0.54)	0.23 (0.16 - 0.33)	0.11 (0.08 - 0.16)	-7.41

* Data in parenthesis are 95% uncertainty intervals.

health problems in older people with late diagnoses and complications such as perforation and abdominal sepsis have led to more deaths in this age group.[12,49]

The next vulnerable group among the different age groups in Iran is the 1 to 4-year-old group. Appendicitis in young children is a diagnostic challenge. Appendicitis can be mimicked by other medical conditions like gastroenteritis and urinary tract infection[7] and ultimately, it might be misdiagnosed. An increase in mortality and complications after perforation has been previously demonstrated.[38] Studies show that perforation is more common in young children than adults, which may contribute to their high mortality rate; the mean perforation rate in children was 46% while it was 5% in older patients.[7,50] A study conducted by Andreu-Ballester et al[38] notes that the cause of the high mortality rate in this age group can be in part related to the limited access to the health care facilities that provide pediatric care. Thus, the transfer of these patients to other hospitals can delay treatment and increase complications. In addition to the above, vulnerable groups carry a large share of the burden of diseases due to poverty, malnutrition, homelessness, poor housing and poor health services.[51]

The mortality rate at the national level was higher in men than women over the years from 1990 to 2014, although the M/F ratio was approximately the same as in 2015. In other studies, in Taiwan and Spain, the incidence of appendicitis in men has been reported to be higher than women.[52–54] On the other hand, Augustin *et al*.[10] stated that men are at higher risk of perforation than women even within similar timeline of symptoms. This fact leads to the hypothesis that the higher incidence in men due to increased complications can increase the rate of death. In 1990, in both upper (over 85 years) and lower (1 to 4 years) age groups, the mortality rate was higher in men than women, while the trend was reversed in 2015. This may be related to women's greater life expectancy based on the latest census results in Iran.[55,56] According to the latest WHO data published in 2017, life expectancy in Iran is 74.5 and 76.6 years in men and women, respectively, with an overall life expectancy of 75.5 years. In our study, in the age group of 10 to 20 years, female mortality rates were higher; while some studies confirm our findings,[57] other studies do not agree.[58]

In 1990, the lowest age-standardized mortality rates due to appendicitis were observed in both women and men in Alborz; the highest mortality rates in both women and men were observed in the province of Lorestan. In 2015, the lowest mortality rates were observed in both women and men in the province of Tehran. The highest mortality rates in women were in Hormozgan and in men were in Qazvin province. These findings are in line with the ranking of provinces in terms of human development index; the province of Tehran is ranked first in terms of development indices whereas Hormozgan and Lorestan provinces have lower development indices – 18th and 20th, respectively.[59]

Looking at Figure 4 in 1990, all provinces in the country had a death rate (from appendicitis) of more than 0.15 per 100 000 in both sexes, but by 2015, this death rate had declined in many provinces, such as Zanjan province which had the greatest decrease in appendicitis-related mortality. This might be due to some background factors such as socioeconomic status and access to health services.[60]

The majority of provinces with an undesirable situation in controlling the mortality rate of appendicitis are among the deprived provinces based on the HDI.[55,61]

Limitations

The DRS system in Iran is incomplete. This may lead to wider uncertainty intervals and reduced precision of available data. The administrative boundary divisions in Iran in 1990 changed from 24 provinces to 31 provinces in 2015, so the data are adjusted according to the new divisions of 31 provinces. Also, there have been incorrect categorizations regarding age and sex groups, geographical locations and causes of death in the raw datasets.

In addition, lack of access to all related causes of appendicitis deaths, can pose restrictions to this study. Because of the retrospective nature of our study, we were unable to provide additional hospitalization information; it seems that crude statistical data cannot solely reflect the full extent of the status of appendicitis mortality rate. Also, it is difficult to find relationships between the higher mortality rate of appendicitis in some provinces and their social factor indicators. Further studies are needed to evaluate these factors. Changes in diagnostic codes and therapeutic categories could have effected appendicitis mortality rate and its trend in our study.[45] However, we have used appropriate measures to minimize this effect.

In conclusion, efforts to reduce preventable diseases at the national and provincial level will improve the mortality rate and incidence and outbreak. Precise health plans on prevention and treatment and improving population access to fair financial participation can increase the effectiveness of the health system in preventing death. Knowing variations at different ages and in both sexes by identifying vulnerable groups will lead to special interventions and specific health programs in these groups.

The trend of death from appendicitis in this study in many provinces indicated an improvement in Iran's healthcare system. Also, some provinces have been more successful in reducing appendicitis mortality. Implementing the health programs of successful provinces in the other provinces can reduce mortality and the burden of the disease. It is essential to implement preventive programs and target these regions. These findings in the context of declining mortality across the country and provinces should be the basis for future health policy discussions and goals.

Authors' Contribution

SMP and ZG have written study concept and design, and conducted the first to final drafting of the manuscript. SSM was involved in analysis of statistical data. MY, NR, AM and AKi were involved in collecting and sending data to the Collaborative Center. SS at was the Project consultant. PS and MSA were involved in reviewing and modifying the text and commenting on it. AHM, GO, SBJ and MML have conducted critical revision of the manuscript for important intellectual content. VRM was involved in reviewing and & editing the study design and he is also the corresponding author.

Conflict of Interest Disclosures

The authors declare that they have no conflict of interest.

Ethical Statement

The Ethics Committee of Tehran University of Medical Sciences, approved the study, and the reference number is IR.TUMS.EMRI.REC.1396.00175.

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