Elevate Series

RESEARCH ARTICLE

Causes of death and trends in mortality from the year 2000 to 2017 in patients with acute myocardial infarction

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ABSTRACT

Objective: To investigate the most common causes of death and trends in cause-specific long-term mortality in patients hospitalized for acute myocardial infarction (AMI).

Methods: This analysis was based on 10,718 patients, aged 25–74 years, recorded by the population-based Myocardial Infarction Registry Augsburg between 2000 and 2017. All hospitalized cases of AMI occurring in the study region during this period were included. If a patient died during follow-up (median: 6.6 years, IQR: 2.8–11.2) the death certificate was obtained and coded using the ICD-10 to determine the main cause of death. Cause-specific mortality was calculated for three 6-year periods. Multivariable adjusted Cox regression models stratified by time interval were calculated.

Results: The most common cause of death was cardiovascular disease (CVD), more precisely ischemic-heart disease (IHD), followed by cancer. The proportions of CVD deaths and IHD deaths were stable over time. An increasing trend was observed in cancer mortality in post-AMI patients. In male patients, the hazard ratio for cancer mortality was 44.4% higher in 2012–2017 compared to 2000–2005, in female patients, it was more than twice as high in 2006–2012 compared to 2000–2005.

Conclusion: This study revealed consistent CVD and IHD long-term mortality and increasing trends in long-term cancer mortality in patients post-AMI. Thus, post-AMI patients should emphasize tertiary prevention of CVD by minimizing risk factors. Furthermore, patients should regularly undergo cancer screening programs. The reasons for the unfavorable development in terms of increasing cancer mortality should be investigated in further studies.
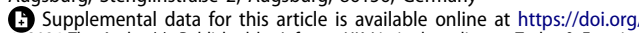
Introduction

Acute myocardial infarction (AMI) is a common disease worldwide. Approximately 3.8% of all individuals under the age of 60 years and 9.5% from the age of 60 years and above suffer from AMI [1]. The average mortality of hospitalized patients with AMI in an Iranian register study was around 5% within 28 days, 10% within 6 months, and 12% within one year [2]. Major risk factors for an increased risk of death after AMI, such as hypertension, diabetes mellitus, smoking, positive family history, and older age, are well known [3–6]. However, knowledge regarding the exact causes of long-term mortality in patients with AMI remains limited. Most previous studies on AMI patients differentiated only between cardiovascular death (CVD)

and non-cardiovascular death [7,8]. Furthermore, only a few studies have described the development of cause-specific mortality rates in patients post AMI over time and then only provided data for CVD and non-CVD mortality [9,10]. In the last 30 years, CVD-mortality in the general German population has steadily declined [11–13]. Moreover, in 2022, Stang reported that overall cancer mortality decreased from 1990 to 2019 in the general population of Hamburg, Germany [14]. This raises the question of whether these trends in cause-specific mortality also apply to AMI patients or whether they show a deviant development of mortality rates. This topic is important as recent studies on AMI patients have shown a positive association between myocardial infarction and cancer incidence [15,16]. Therefore, this study aimed to

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determine the most common causes of death among people who had suffered from hospitalized AMI between 2000 and 2017, and to detect trends in cause-specific mortality. These insights could help identify the diseases for which patients after AMI should be particularly screened and surveilled.

Materials and methods

Study population

This study was performed using data from the population-based Augsburg Myocardial Infarction Registry. This registry was part of the WHO Monitoring Trends and Determinants on Cardiovascular Diseases (MONICA) project until 1995. It was subsequently continued as the KORA Myocardial Infarction Registry and has been operating as the Augsburg Myocardial Infarction Registry since 2021. Patients who suffered from AMI and whose main residence was in the city of Augsburg, Germany, or the adjacent counties of Augsburg and Aichach-Friedberg were included in this research, totaling to ~680,000 inhabitants in the study area. From 2000 to 2008 only patients aged between 25 and 75 years have been included, from 2009 onwards, the age range has been extended to 25–84 years. During the hospital stay, standardized interviews were conducted by trained study nurses, and patient information on sociodemographic characteristics, acute symptoms, risk factors, and comorbidities was collected. To obtain as much data as possible, including diagnostics, treatment, and complications, the patients' medical files were elaborated. More details on case identification, diagnostic categorization of events, and data quality control are described elsewhere [17–19]. In this study, patients aged 25–74 years who suffered from AMI between 1 January 2000, and 31 December 2017 were included. Finally, 10,718 patients could be used for this analysis.

The ethics committee of the Bavarian Medical Association (Bayerische Landesärztekammer) approved the study (ethics vote number 12057), and the study was performed in accordance with the principles of the Declaration of Helsinki. All the participants provided written informed consent.

Outcome and cause of death

Information on survival was received from the regional registration and health officers at regular time intervals. If a patient died, death certificates were obtained from local health departments and coded for the underlying causes of death by a single trained staff member using the tenth revision of the International Classification of Diseases. The last mortality follow-up date for the data collection was 30 June 2019.

This study aimed to identify trends in the mortality rates for different causes of death in post-AMI patients. Using the ICD-10 WHO code for the analysis, the causes of death were grouped as follows: all-cause mortality (A00–U85), cardiovascular disease mortality (I00–I99), ischemic heart disease mortality (I21–I25), and cancer mortality (C00–D48).

Statistical analysis

Three time periods were defined and used for subsequent statistical analyses: 2000–2005, 2006–2011, and 2012–2017.

Categorical variables are shown as total numbers and percentages, and continuous variables as medians and interquartile ranges (IQR), or means and standard deviations (SD). The chi-squared test was used to figure out differences in categorical variables, and one-way analysis of variance (ANOVA) and Kruskal–Wallis tests were performed for differences in continuous variables.

Associations between the time of infarction and cause-specific mortality were analyzed using Kaplan–Meier-curves and Cox regression models. All analyses were stratified by sex. Due to the different follow-up periods, the data was censored after 7 years (=2555 days). Kaplan–Meier-curves were stratified by the three time periods (see above), the log-rank-test was used to test for significant differences between time periods. Cox regression models were adjusted for age, type of infarction, percutaneous coronary intervention (PCI), hypertension, diabetes, and smoking status. In sensitivity analyses, the multivariable Cox regression models were additionally adjusted for eGFR (continuous, calculated according to the CKD-EPI formula). Since the data on kidney function were only available from 2005 onwards, the sex specific associations between time of infarction and cause-specific mortality were analyzed for the third time period compared to the second time period.

Cox-proportional-hazard assumptions were checked graphically (categorical variables) or by including a time-interaction term (for the continuous variable age).

Statistical analysis was conducted using SPSS statistics, version 29.0.1.0, and the significance level was set to $p < 0.05$.

Results

In total 10,718 patients (8095 males and 2623 females) were included in the analysis. Baseline characteristics of

AMI patients are displayed in Table 1 for men and Table 2 for women. Mean age of male and female participants was 60.39 (SD: 9.62) and 63.33 (SD: 9.16), respectively. Altogether, 2727 male patients and 910 female patients died until the cut-off date. The short-term mortality (i.e. mortality within 28 days after the acute event) was 5.8% in men and 6.6% in women. In the latest time period (2012–2017) PCI was used more often for the treatment of AMI than in the earliest time period, whereas coronary artery bypass graft (CABG) was used less often. It should be noted that the baseline characteristics were not censored, meaning that the cases diagnosed in the older 6-year period (2000–2005) had a longer follow-up period than the most recent period. Therefore, no false conclusions should be drawn regarding the development of mortality rates.

Table 3 shows the distribution of the causes of death in 2727 male patients and 910 female patients. The most common cause-specific deaths were CVD deaths (including ischemic-heart disease deaths), occurring in 56.3% of males and 59.0% of females. The second most common cause of death was cancer, occurring in 18.6% of males and 13.8% of females. The most common cancer type in both sexes was cancer of the bronchi and lungs, with 24.1% (males) and 26.2% (females) of all cancer deaths, followed by cancer of prostate with 9.5% in men and cancer of mammary gland with 10.3% in women, as shown in Table 4.

Figure 1 demonstrates Kaplan–Meier curves stratified by time periods and sex for the three causes of death: CVD (A, B), ischemic-heart disease (C, D), and

Table 1. Baseline characteristics of male AMI patients in total and by three 6-year time periods: categorical variables are displayed as total numbers (%).

	Total sample: n = 8095	2000–2005 n = 2849	2006–2011: n = 2632	2012–2017: n = 2614	p-Value	n
Age at AMI	60.39 (9.62)	60.33 (9.67)	60.29 (9.79)	60.54 (9.40)	0.608	8095
Total deaths	2727 (33.7%)	1442 (50.6%)	831 (31.6%)	454 (17.4%)	<0.001	8095
28-days-mortality	471 (5.8%)	199 (7.0%)	142 (5.4%)	130 (5.0%)	0.003	8095
CVD-mortality	1533 (18.9%)	826 (29.0%)	454 (17.2%)	253 (9.7%)	<0.001	8095
Ischemic heart disease-mortality	1218 (15.0%)	665 (23.3%)	348 (13.2%)	205 (7.8%)	<0.001	8095
Cancer-mortality	507 (6.3%)	271 (9.5%)	149 (5.7%)	87 (3.3%)	<0.001	8095
Type of infarction					0.073	8095
STEMI	3062 (37.8%)	1054 (37.0%)	1006 (38.2%)	1002 (38.3%)		
NSTEMI	4158 (51.4%)	1455 (51.1%)	1382 (52.5%)	1321 (50.5%)		
Bundle branch block	546 (6.7%)	213 (7.5%)	155 (5.9%)	178 (6.8%)		
Not defined	329 (4.1%)	127 (4.5%)	89 (3.4%)	113 (4.3%)		
Invasive treatment						
CABG	1289 (15.9%)	525 (18.4%)	391 (14.9%)	373 (14.3%)	<0.001	8095
PCI	5629 (69.5%)	1664 (58.4%)	1931 (73.4%)	2034 (77.8%)	<0.001	8095
Prehospital time in minutes	152.00 (80.00–480.00)	156.00 (82.00–462.00)	145.00 (82.00–430.50)	154.00 (76.00–546.00)	0.813	6177
BMI (kg/m^2)	27.69 (4.34)	27.35 (3.92)	27.84 (4.38)	27.89 (4.69)	<0.001	7469
Hypertension	5944 (73.4%)	2069 (72.6%)	2006 (76.2%)	1869 (71.5%)	<0.001	8095
Diabetes mellitus	2422 (29.9%)	847 (29.7%)	849 (32.3%)	726 (27.8%)	<0.001	8095
Previous infarction					<0.001	8095
Yes	808 (10.0%)	439 (15.4%)	231 (8.8%)	138 (5.3%)		
No	7275 (89.9%)	2400 (84.2%)	2400 (91.2%)	2475 (94.7%)		
No information	12 (0.1%)	10 (0.4%)	1 (0.0%)	1 (0.0%)		
Previous stroke					<0.001	8095
Yes	571 (7.1%)	198 (6.9%)	176 (6.7%)	197 (7.5%)		
No	6984 (86.3%)	2264 (79.5%)	2327 (88.4%)	2393 (91.5%)		
No information	540 (6.7%)	387 (13.6%)	129 (4.9%)	24 (1.0%)		
Smoking status					<0.001	8095
Current smoker	3029 (37.4%)	969 (34.0%)	995 (37.8%)	1065 (40.7%)		
Ex-smoker	2673 (33.0%)	948 (33.3%)	873 (33.2%)	852 (32.6%)		
Never-smoker	1679 (20.7%)	575 (20.2%)	542 (20.6%)	562 (21.5%)		
No information	714 (8.8%)	357 (12.5%)	222 (8.4%)	135 (5.2%)		
LVEF					<0.001	8095
≤30%	460 (5.7%)	133 (4.7%)	121 (4.6%)	206 (7.9%)		
>30%	5636 (69.6%)	1641 (57.6%)	1772 (67.3%)	2223 (85.0%)		
No information	1999 (24.7%)	1075 (37.7%)	739 (28.1%)	185 (7.1%)		
Laboratory values						
Admission troponin I (ng/ml)	0.60 (0.11–3.92)	0.57 (0.12–4.08)	0.63 (0.11–3.80)	0.56 (0.10–4.64)	0.984	5086
Peak CKMB levels (U/l)	54.00 (23.00–143.00)	37.00 (14.00–94.00)	56.00 (24.00–160.00)	78.00 (35.00–188.00)	<0.001	7237
Admission CRP (mg/dl)	0.45 (0.23–1.30)	0.46 (0.19–1.31)	0.46 (0.29–1.35)	0.41 (0.22–1.20)	<0.001	7480
Peak glucose (mg/dl)	148.00 (121.00–199.00)	155.00 (128.00–215.00)	148.00 (122.00–193.00)	139.00 (115.25–184.75)	<0.001	7873
eGFR (mL/min/1.73 m^2)	78.93 (62.09–92.98)	—	76.45 (59.96–91.64)	81.30 (64.87–93.82)	<0.001	5114

LVEF: left ventricular ejection fraction.
Numeric data is presented as mean (SD) or median (IQR).

Table 2. Baseline characteristics of female AMI patients in total and by three 6-year time periods: categorical variables are displayed as total numbers (%).

	Total sample: n = 2623	2000–2005: n = 923	2006–2011: n = 886	2012–2017: n = 814	p-Value	n
Age at AMI	63.33 (9.16)	63.82 (8.73)	63.63 (9.13)	62.45 (9.59)	0.004	2623
Total deaths	910 (34.7%)	471 (51.0%)	312 (35.2%)	127 (15.6%)	<0.001	2623
28-days-mortality	173 (6.6%)	68 (7.4%)	64 (7.2%)	41 (5.0%)	0.097	2623
CVD-mortality	537 (20.5%)	293 (31.7%)	176 (19.9%)	68 (8.4%)	<0.001	2623
Ischemic heart disease-mortality	416 (15.9%)	227 (24.6%)	134 (15.1%)	55 (6.8%)	<0.001	2623
Cancer-mortality	126 (4.8%)	56 (6.1%)	51 (5.8%)	19 (2.3%)	<0.001	2623
Type of infarction					0.184	2623
STEMI	939 (35,8%)	347 (37.6%)	316 (35.7%)	276 (33.9%)		
NSTEMI	1415 (53.9%)	493 (53.4%)	479 (54.1%)	443 (54.4%)		
Bundle branch block	158 (6.0%)	46 (5.0%)	61 (6.9%)	51 (6.3%)		
Not defined	111 (4.2%)	37 (4.0%)	30 (3.4%)	44 (5.4%)		
Invasive treatment						
CABG	320 (12.2%)	136 (14.7%)	105 (11.9%)	79 (9.7%)	0.018	2623
PCI	1669 (63.6%)	463 (50.2%)	601 (67.8%)	605 (74.3%)	<0.001	2623
Prehospital time in minutes	165.00 (90.00–511.00)	174.00 (95.00–424.00)	162.50 (90.00–473.25)	163.00 (84.25–639.00)	0.720	1931
BMI (kg/m^2)	27.97 (5.94)	27.71 (5.40)	27.94 (5.97)	28.28 (6.43)	0.165	2399
Hypertension	2083 (79.4%)	757 (82.0%)	703 (79.3%)	623 (76.5%)	0.039	2623
Diabetes mellitus	907 (34.6%)	344 (37.3%)	301 (34.0%)	262 (32.2%)	0.131	2623
Previous infarction					<0.001	2623
Yes	188 (7.2%)	105 (11.4%)	53 (6.0%)	30 (3.7%)		
No	2432 (92.7%)	816 (88.4%)	832 (93.9%)	784 (96.3%)		
No information	3 (0.1%)	2 (0.2%)	1 (0.1%)	0 (0.0%)		
Previous stroke					<0.001	2623
Yes	195 (7.4%)	94 (10.2%)	49 (5.5%)	52 (6.4%)		
No	2241 (85.4%)	707 (76.6%)	782 (88.3%)	752 (92.4%)		
No information	187 (7.1%)	122 (13.2%)	55 (6.2%)	10 (1.2%)		
Smoking status					<0.001	
Current smoker	821 (31.3%)	229 (24.8%)	304 (34.3%)	288 (35.4%)		2623
Ex-smoker	443 (16.9%)	138 (15.0%)	129 (14.6%)	176 (21.6%)		
Never-smoker	1008 (38.4%)	390 (42.3%)	329 (37.1%)	289 (35.5%)		
No information	351 (13.4%)	166 (18.0%)	124 (14.0%)	61 (7.5%)		
LVEF					<0.001	2623
≤30%	113 (4.3%)	37 (4.0%)	37 (4.2%)	39 (4.8%)		
>30%	1823 (69.5%)	519 (56.2%)	604 (68.2%)	700 (86.0%)		
No information	687 (26.2%)	369 (39.7%)	245 (27.7%)	75 (9.2%)		
Laboratory values						
Admission troponin I (ng/ml)	0.51 (0.12–3.30)	0.46 (0.12–2.60)	0.57 (0.12–4.25)	0.47 (0.09–3.09)	0.277	1668
Peak CKMB levels (U/l)	50.00 (21.00–135.50)	32.00 (12.00–94.00)	52.00 (22.00–141.75)	77.00 (36.00–185.50)	<0.001	2244
Admission CRP (mg/dl)	0.51 (0.29–1.50)	0.49 (0.23–1.37)	0.61 (0.29–1.79)	0.49 (0.29–1.45)	<0.001	2438
Peak glucose (mg/dl)	156.00 (125.00–220.00)	167.00 (130.00–256.25)	155.50 (125.00–214.75)	146.00 (118.00–198.00)	<0.001	2552
eGFR (mL/min/1.73 m^2)	71.98 (55.17–90.02)	—	68.82 (51.64–88.30)	74.70 (58.09–91.39)	<0.001	1655

Numeric data is presented as mean (SD) or median (IQR).

Table 3. Cause-specific mortality in male and female AMI patients (n, %).

	Males (n = 2727)	Females (n = 910)
CVD	1533 (56.3%)	537 (59.0%)
Ischemic heart diseases	1218 (44.7%)	416 (45.7%)
Other CVDs	315 (11.6%)	121 (13.3%)
Cancer	507 (18.6%)	126 (13.8%)
Other causes	687 (25.2%)	247 (27.1%)

Table 4. Cancer mortality (ICD-10 codes) in male and female AMI patients (n, %).

|	Males (n = 507)	Females (n = 126)
Cancer of bronchi and lungs (C34)	122 (24.1%)	33 (26.2%)
Cancer of prostate (C61)	48 (9.5%)	0 (0.0%)
Cancer of mammary gland (C50)	0 (0.0%)	13 (10.3%)
Cancer of pancreas (C25)	39 (7.7%)	8 (6.3%)
Cancer of liver and intrahepatic bile ducts (C22)	35 (6.9%)	4 (3.2%)
Cancer of colon (C18)	35 (6.9%)	7 (5.6%)

cancer (E, F). There was a significant reduction in CVD and ischemic heart disease mortality. Regarding cancer mortality there were significant differences in women, although no constant trend was observed over the years. Cancer mortality in men did not vary significantly between time periods.

Table 5 summarizes the results of multivariable Cox regression models for the outcomes CVD, ischemic heart disease, and cancer mortality stratified by sex. The period from 2000 to 2005 was used as the reference group. In contrast to the Kaplan–Meier curves, no significant differences in CVD- and ischemic heart disease mortality over
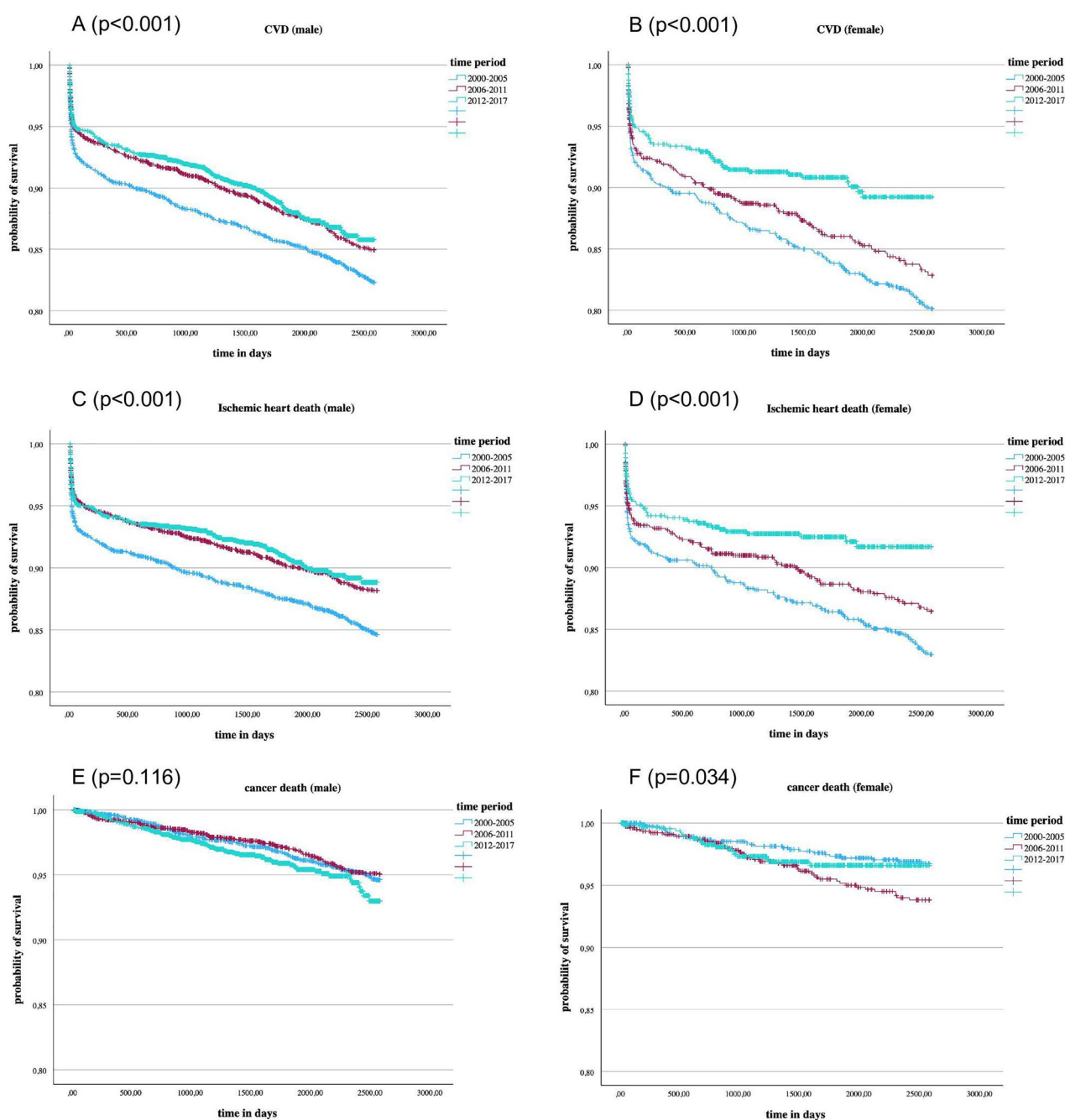
Figure 1. Kaplan Meier curves for the events CVD death (A,B), ischemic-heart disease death (C,D), and cancer death (E,F) in male and female AMI patients diagnosed in three 6-year time periods; *p*-values were calculated by log-rank tests.

time were detected in the adjusted models. For cancer death, significant differences in both sexes were found. In male patients, the hazard ratio for cancer mortality was 44.4% higher in the time period 2012–2017 compared to the time period 2000–2005 (HR 1.44; 95%-CI: 1.08–1.93; *p*-value: 0.013). In female patients, the risk of cancer mortality was more than double (HR 2.01; 95%-CI: 1.20–3.36; *p*-value: 0.008) in the period 2006–2012 compared to the period 2000–2005.

Sensitivity analysis

The results of the sex-specific multivariable Cox regression models comparing the third time period with the second time period with regard to different mortality endpoints are shown in Supplementary Material, Table S1. After including eGFR in addition to the other confounders in the Cox regression models the effect estimates were quite similar to the models without adjustment for kidney function in both males and females.

Table 5. Hazard ratios (HR) and 95% confidence intervals (95%CI) of the Cox-regression analyses for the outcomes CVD death, ischemic-heart disease death and cancer death in male and female AMI patients diagnosed in three 6-year time periods.

	Male, HR (95% CI)	p-Value	Female, HR (95% CI)	p-Value
CVD death				
2000–2005	1		1	
2006–2011	1.018 (0.855–1.171)	0.801	1.089 (0.864–1.374)	0.469
2012–2017	1.080 (0.920–1.267)	0.345	0.918 (0.683–1.233)	0.568
Ischemic-heart disease death				
2000–2005	1		1	
2006–2011	0.920 (0.788–1.075)	0.294	0.999 (0.771–1.293)	0.991
2012–2017	0.991 (0.831–1.180)	0.915	0.860 (0.620–1.192)	0.365
Cancer death				
2000–2005	1		1	
2006–2011	1.060 (0.812–1.383)	0.670	2.010 (1.203–3.357)	0.008
2012–2017	1.444 (1.082–1.926)	0.013	1.425 (0.761–2.672)	0.269

Models were adjusted for age, type of infarction, PCI, hypertension, diabetes and smoking status.

Supplementary Figure 1 shows the distribution of the eGFR values for the years 2005–2017. It can be seen that the kidney function values did not significantly change over time.

Discussion

Causes of death

This study found that most patients who have suffered from AMI died from CVD during a follow-up period of seven years. The second common cause of death was cancer. This was the case for both the men and women. These findings are consistent with the most common causes of death in the general German population [20]. Lung cancer was the leading cause of cancer death in the general German population, accounting for 19.5% of all cancer deaths in 2022 [21]. In the present sample of AMI patients, lung cancer was responsible for 24.1% of deaths in men and 26.2% of deaths in women, which is much higher than in the general population. This indicates an association between myocardial infarction and lung cancer death. Other studies displayed an increased risk of tobacco-related cancers in patients hospitalized for first AMI [10,22], which is probably caused by overlapping risk factors, first of all smoking, but possibly also hypertension, diabetes, advanced age, and obesity [23].

CVD and ischemic-heart disease mortality

In contrast to the Kaplan–Meier curves, the multivariable-adjusted Cox regression analyses showed no significant differences in CVD and ischemic-heart disease mortality stratified by the three time periods. This means that between 2000 and 2017 CVD mortality remained at a stable level in AMI-patients. Few other studies have reported trends in CVD-mortality rates in patients after myocardial infarction. In 2015,

Sulo et al. found opposing trends in Norway: they detected a decline in one-year-CVD-mortality rates during the period from 2001 to 2014 in AMI patients [9]. The divergent results as compared to our study may be explained due to different follow-up time periods (1 and 7 years).

As mentioned above, previous studies found a decrease in CVD-mortality in the general German population [11–13], which means that post-AMI patients in Germany have different development of mortality rates compared to the general population. This finding can be explained by various factors.

Looking at intake rates for cardio-preventive medications between 2010 and 2018 other studies determined that antithrombotic medication, particularly low dose aspirin, has been used less in Europe, probably due to concerns about bleeding, whereas statin use has been shown to be consistent or has increased gradually. The use of oral anticoagulants increased but did not fully account for the decrease in aspirin [24]. Protty et al. found similar results for the use of aspirin in the time between 2005 and 2016 in Wales [25]. Aspirin has a significant benefit in secondary prevention after AMI [26,27]. In 2014, data from the same register from 2000 to 2008 was analyzed regarding the use of cardio preventive medication after AMI. Of all patients, only 70.3% were prescribed the recommended combination of four active ingredients, whereas in Cox regression analysis, the study detected that the combination of the four drugs revealed significant survival benefits [19].

Another reason for stable CVD mortality over time could be found in different risk factor profiles: Leosdottir et al. looked at the development of risk factors from 2006 to 2019 in post-AMI patients in Sweden: secondary preventive objectives for blood pressure and LDL-cholesterol were achieved by a higher percentage of patients one year after hospitalization. In contrast, the percentage of patients with obesity and diabetes has increased and fewer patients were sufficiently

physically active [5]. According to Timmis et al. blood pressure, levels of low-density-lipoprotein (LDL) cholesterol, smoking, and alcohol consumption showed positive developments in European post-AMI patients from 2006 to 2019, while the prevalence of obesity and diabetes at least doubled during the past 30 years [6]. Our data did not entirely match with the two studies mentioned above: we detected no increase in the prevalence of diabetes in AMI patients over time, but a decrease. The percentage of hospitalized AMI-patients with diabetes decreased from 29.7% in men and 37.3% in women in the period from 2000 to 2005 to 27.8 and 32.2% in the period from 2012 to 2017, respectively. For obesity, we observed an increase in BMI over time, which could account for the present findings. Additionally, the proportion of current smokers in our study increased over time. As smoking increases the risk of cardiovascular diseases, this could also contribute to the explanation of our findings [28–31].

Moreover, the development of depression is a common comorbidity after AMI [32,33]. The prevalence of depression in Germany increased by 26% between 2009 and 2017 [34]. Various studies have revealed that depression is an independent risk factor for mortality after acute myocardial infarction [35–38].

Consequently, changes in medication, particularly for low-dose-aspirin, changes in the prevalence of overlapping risk factors, and changes in the frequencies of diagnosed depression could be responsible for unchanged and non-decreasing CVD mortality, as observed in AMI-patients in our study.

Cancer-mortality

Over the observed period, our study revealed an increasing cancer mortality in both sexes. To date, no previous studies have investigated trends in cancer mortality in patients with AMI.

In the general population, studies have reported different results, displaying that overall cancer mortality has decreased in the last two decades in men and women. In 2015, Bertuccio et al. showed that since 2006 cancer mortality in Europe has declined every year by 1.5% in men and since 2007 by 0.8% in women [39]. According to Shelton et al., all type cancer mortality in the UK decreased between 1993 and 2018 by 20% in men and 17% in women among people aged between 35 and 69 years [40]. In contrast, our study found increasing mortality rates for all type cancer mortality, which suggests that patients who have suffered from myocardial infarction are at higher risk for cancer compared to the general population.

Looking at cancer type specific mortality in the general population, there are also some cancer types with rising mortality: lung cancer mortality in females, which is responsible for more than a quarter of all cancer deaths in our study, shows an increasing trend during the last two decades in Europe [39,41,42]. Furthermore, liver cancer mortality in Europe has increased in both sexes [39,40]. This unfavorable development of mortality of lung cancer in females and cancer of the liver may partially explain our findings.

Other than that, the total cancer mortality for patients after AMI increases, probably due to the higher prevalences of overlapping risk factors. The prevalence of obesity has increased in recent decades [6,43]. Additionally, the proportion of current smokers among the patients included in the analyses increased over time. Smoking is one of the leading preventable causes of death associated with cancer [44–47]. The growing proportion of smokers in AMI patients could be a driving factor for rising cancer mortality.

Furthermore, medical radiation exposure in patients hospitalized for CVD shows an increasing trend [48] and is associated with a higher risk of cancer and cancer mortality [49,50].

Previous studies have shown that the use of low-dose aspirin for secondary prevention in Europe decreased from 2010 to 2018 [24]. Besides, the use of aspirin three or more times per week is associated with a reduction in cancer mortality [51–53]. Thus, post-AMI patients taking less aspirin may have an increased risk of dying from cancer.

In summary, the increased incidence of lung and liver cancer, higher prevalence of obesity and smoking, higher radiation exposure, and patients taking less aspirin could explain the rising trend in cancer mortality for patients who had suffered from myocardial infarction. However, further studies are required to investigate these possible associations. Any biological mechanisms, potential confounders, or biases that might underlie the observed trends must be elucidated.

Strengths and limitations

The strength of this study is the high number of AMI patients included from a population-based registry with consecutive enrollment and a long follow-up period, which diminishes the risk of selection bias. Moreover, a lot of additional data was collected in a standardized manner for every patient, such as sociodemographic data, treatment, and risk factors, which made multivariable adjustment in Cox regression models possible. In addition, the analysis was performed

stratified by sex, and cause-specific mortality was investigated.

However, our study has certain limitations. The techniques and standards used in the diagnosis and management of AMI patients have changed significantly from 2000 to 2017, which may have impacted our findings. Besides, there were only patients included aged 25–74 years, and no data was collected regarding the ethnicity of the patients. Therefore, the results cannot be extended to older patients and may not be valid for all ethnicities. Additionally, data regarding kidney function were only recorded from 2005 onwards; thus, this risk factor associated with mortality could not be considered in the analyses for the whole time period. Moreover, the registry does not record patients' serum albumin concentrations, so that these could not be included in the analyses.

Finally, we cannot rule out the possibility of reverse causality and may not have considered all confounders.

Conclusions

The main cause of death for patients who have suffered from myocardial infarction was CVD, more precisely ischemic heart disease, followed by cancer. Moreover, this study revealed consistent CVD and ischemic heart disease long-term mortality and rising trends in long-term cancer mortality in patients post-AMI. Therefore, in the future, physicians must put more emphasis on tertiary prevention of CVD: they should make sure that patients take their medication regularly and ensure that risk factors, such as hypertension or obesity, are minimized or well controlled. Furthermore, post-AMI patients should undergo regular cancer screening programs and be informed about possible early cancer symptoms. The reasons for the rising cancer mortality rate in post-AMI patients should be investigated in further studies.

Ethical approval

Data collection of the MONICA/KORA MI registry has been approved by the ethics committee of the Bavarian Medical Association (Bayerische Landesärztekammer) (ethics vote number 12057) and the study was performed in accordance with the Declaration of Helsinki. All study participants have given written informed consent.

Author contributions

Formal analysis: D.S. Conception and design: D.S., T.S., C.M. Supervision: T.S., C.M. Methodology: T.S., C.M. Funding acquisition: T.S., J.L., C.M. Writing–original draft: D.S. Writing–review and editing: T.S, P.R., J.L., C.M. All authors have read and approved the manuscript.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Data availability statement

The datasets generated during and/or analyzed in the current study are not publicly available due to data protection aspects but are available in an anonymized form from the Chair of Epidemiology on reasonable request. Requests to access these datasets should be directed to Dr. Timo Schmitz, timo.schmitz@med.uni-augsburg.de.

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