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Clinical Research

Association Between Acute Myocardial Infarction Symptoms and Short- and Long-term Mortality After the Event

Timo Schmitz, MD,[a] Eva Harmel, MD,[b] Philip Raake, MD,[b] Dennis Freuer, PhD,[a] Inge Kirchberger, PhD,[a] Margit Heier, MD,[c,d] Annette Peters, PhD,[d,e,f] Jakob Linseisen, PhD,[a] and Christa Meisinger, MD[a]

[a] *Epidemiology, Medical Faculty, University of Augsburg, Augsburg, Germany*

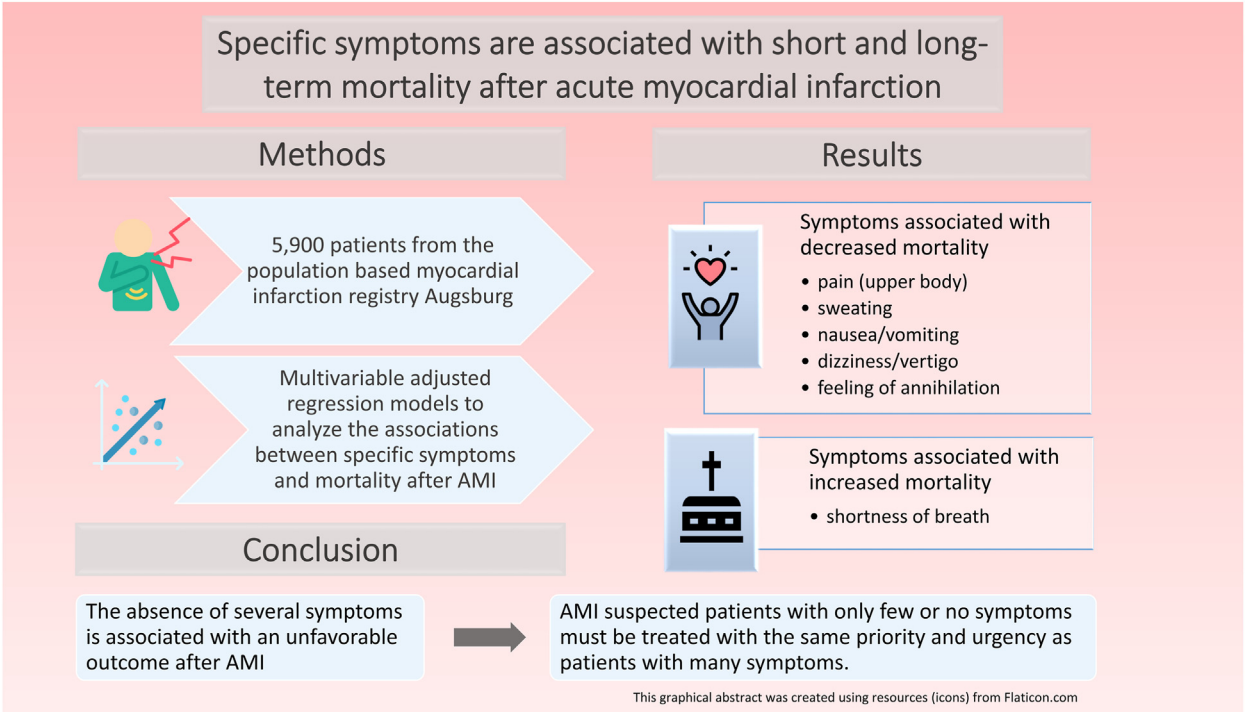
[b] *Department of Cardiology, Respiratory Medicine and Intensive Care, University Hospital Augsburg, Augsburg, Germany*

[c] *University Hospital of Augsburg, KORA Study Centre, Augsburg, Germany*

[d] *Helmholtz Zentrum München, German Research Center for Environmental Health, Institute for Epidemiology, Neuherberg, Germany*

[e] *Chair of Epidemiology, Institute for Medical Information Processing, Biometry and Epidemiology, Medical Faculty, Ludwig-Maximilians-Universität München, Munich, Germany*

[f] *German Center for Diabetes Research (DZD), Neuherberg, Germany*



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ABSTRACT

Background: In this study, we investigated various acute myocardial infarction (AMI) symptoms and their associations with short-term (28 day) and long-term mortality.

Methods: The analysis was based on 5900 patients, aged 25 to 84 years, with first-time AMI recorded by the population-based Myocardial Infarction Registry Augsburg between 2010 and 2017. Median follow-up time was 3.8 years (interquartile range: 1.1-6.3). As part of a face-to-face interview, the presence (yes/no) of 11 most common AMI symptoms at the acute event was assessed. Using multivariable-adjusted logistic regression and Cox regression models, the association between various symptoms and all-cause mortality was investigated. *P* values of the regression models were false discovery rate adjusted.

Results: Pain in various body parts (chest pain, left and right shoulder/arm/hand, between shoulder blades), sweating, nausea/vomiting, dizziness and fear of death/feeling of annihilation were significantly associated with a decreased 28-day mortality after AMI. The pain symptoms and sweating were also significantly associated with a decreased long-term mortality. Shortness of breath was significantly associated with a higher long-term mortality.

Conclusions: The absence of several symptoms, including typical chest discomfort (chest pain or retrosternal pressure/tightness), is associated with unfavourable outcomes after AMI. This finding has implications for patient management and public health measures designed to encourage appropriate and prompt medical consultation of patients with atypical AMI symptoms.

RÉSUMÉ

Contexte : Dans cette étude, nous avons évalué les divers symptômes de l'infarctus aigu du myocarde (IAM) et la mortalité à court (28 jours) et à long terme.

Méthodologie : L'analyse reposait sur 5 900 patients âgés entre 25 et 84 ans ayant subi un premier IAM d'après les données enregistrées dans le registre populationnel de l'infarctus du myocarde d'Augsburg entre 2010 et 2017. La durée médiane du suivi était de 3,8 ans (plage interquartile : 1,1 à 6,3). La présence (oui/non) de 11 des symptômes d'IAM les plus courants au moment de l'attaque a été évaluée lors d'un entretien en personne. Des modèles de régression logistique et de Cox ajustés en fonction de variables multiples ont été utilisés pour étudier le lien entre les divers symptômes et la mortalité toutes causes confondues. Les valeurs de *p* des modèles de régression ont été ajustées en fonction du taux de faux positifs.

Résultats : Un lien significatif a été établi entre la douleur dans diverses régions du corps (douleur thoracique, douleur dans la main/l'épaule/le bras gauche ou droit, entre les omoplates), l'hypersudation, les nausées/vomissements, les étourdissements et la peur de la mort/le sentiment d'anéantissement, et une réduction de la mortalité 28 jours après un IAM. Un lien significatif a également été établi entre la douleur et l'hypersudation, et une réduction de la mortalité à long terme. L'essoufflement a quant à lui été associé de manière significative à une augmentation de la mortalité à long terme.

Conclusions : L'absence de plusieurs symptômes, notamment ceux traduisant généralement un inconfort thoracique (douleur thoracique ou oppression/serrement rétrosternal), est associée à un pronostic défavorable après un IAM. Ce constat n'est pas sans implications pour la prise en charge des patients et les mesures de santé publique conçues pour inciter les patients qui présentent les symptômes atypiques d'un IAM à consulter un médecin rapidement et de façon appropriée.

Patients with acute myocardial infarction (AMI) may present with a wide range of symptoms of which the most common is chest pain. Some of the patients do not report the typical symptom "chest pain or a feeling of pressure or tightness behind the breastbone" at the acute event.[1-3] This phenomenon seems to occur more often in female patients, and the likelihood of not having chest pain symptoms raises with age.[4] The absence of chest pain symptoms also goes along with worse outcome and higher mortality.[2,5,6] Other symptoms such as fear of death, nausea, or syncope are also associated with mortality after AMI, as a previous publication from the population-based Augsburg Myocardial Infarction Registry showed;[5] an analysis based on AMI cases between 1998 and 2003. In the last few decades, however, percutaneous coronary intervention (PCI) was established as a routine in the acute treatment of AMI, together with major improvements in technique and material (eg, a broad availability of drug-eluting stents[7] in the first years of the new millennium or, more recently, drug-coated balloon interventions[8]), which enhanced the overall outcome.[9,10] Also, PCI is more and more used in multivessel diseases and complex coronary artery disease (CAD), with a broadening indication and improvements in outcome.[11-13] In the same time, high-sensitivity cardiac troponin measurements were added to the existing diagnostic repertoire,[14] which set new standards in accuracy and enabled a more rapid assessment of AMI.[15] In the last few decades, the consistent implementation of preventive measures (eg, long-term medication, smoking cessation) improved, and the overall level of knowledge of AMI symptoms in the general (German) population might have increased in this time (even though remaining unsatisfying in some aspects).[16] In short, in the last 20 years there were many changes regarding diagnostics and treatment of patients with AMI, and thus the question arises as to whether the overall association between presentation of symptoms and outcome after AMI is still valid today. Therefore, the main objective of this study was to analyze the association between several AMI symptoms and short- and long-term mortality in a population-based group of patients with AMI in the PCI and troponin era. A second goal of this study was to clarify whether the general results are also applicable to older age groups. This issue was not addressed by the previous study from the Augsburg Myocardial Infarction Registry, which included only patients from 25 to 74 years of

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Corresponding author: Dr Timo Schmitz, Epidemiology, Medical Faculty, University of Augsburg, Stenglinstraße 2, 86156 Augsburg, Germany. Tel.: +49 821-400-4506.

E-mail: timo.schmitz@med.uni-augsburg.de

See page 1365 for disclosure information.

age. Because of increasing life expectancy, this question gains more and more importance and therefore will be examined in the following analysis.

Material and Methods

Study population

For this study, we used data from the population-based Augsburg Myocardial Infarction Registry, which was established in 1984 as a part of the **Moni**toring Trends and Determinants in **Ca**rdiovascular (MONICA) disease project and since then operated as Cooperative Health Research in the Region of Augsburg (KORA [***Koo****perative Gesundheitsforschung in der* ***R****egion* ***A****ugsburg*]) Myocardial Infarction Registry.[17] The study area consists of the city of Augsburg, Germany and the 2 adjacent counties, comprising a total of approximately 680,000 inhabitants. For this analysis of hospitalized patients with AMI, the following inclusion criteria were applied: patient age was between 25 and 84 years, the patient survived the first 24 hours after hospital admission, and had primary residence within the study area. The definition of AMI included ST-elevation myocardial infarction (STEMI) cases as well as diagnosed non−ST-elevation myocardial infarction (NSTEMI) cases. The latter include all cases of AMI symptoms with troponin dynamic or AMI cases confirmed by percutaneous transluminal coronary angioplasty. In close cooperation with all hospitals treating patients with AMI in the study region, all patients with AMI are approached by their treating physicians or by the personnel of the registry during their hospital stay (usually in the normal care unit). Patients are informed about the registry and asked to participate. In case of participation, all patients give written informed consent and are interviewed (see point data collection). More detailed information on case identification, diagnostic classification of events, and quality control of the data can be found in previous publications.[17,18] Methods of data collection have been approved by the ethics committee of the Bavarian Medical Association (Bayerische Landesärztekammer), and the study was performed in accordance with the Declaration of Helsinki.

For the statistical analysis, only patients with a first-time AMI in the years 2010 until 2017 were considered (6327 cases). The year 2010 was chosen to analyze cases from an era with well-established PCI standards exclusively. The year 2017 was chosen as the final year of enrollment because long-term survival data were available for analyses until then. Patients with missing information on AMI symptoms or relevant covariables (n = 427) were excluded. The final study population consisted of 5900 patients with AMI.

Data collection

Intensively trained and subsequently certified medical staff (mainly nurses) performed the standardized patient interviews. The interviews were performed on the basis of standardized operating procedures. Recertification of the study nurses took place at regular intervals. The face-to-face interview included questions about specific symptoms in the context of the acute event. The presence (yes/no) of the following symptoms was interrogated: typical chest pain symptoms (defined as "chest pain or a feeling of pressure or tightness behind the breastbone"), pain in the left arm or shoulder, pain in the right arm or shoulder, pain between the shoulder blades, pain in the upper abdomen, sweating, vomiting/nausea, shortness of breath, dizziness/vertigo, syncope/unconsciousness, and fear of death/feeling of annihilation. In addition to information about symptoms, the interview also addressed further topics such as sociodemographic features, pre-existing comorbidities, use of medication, or previous infarctions. To confirm the information provided by the patients and to collect additional information, the patients' medical charts were reviewed. Demographic data, data on cardiovascular risk factors, medical history, comorbidities, laboratory values, in-hospital course, and medication was collected for each patient.

Outcomes

The endpoints used in this study were short-term (28 days) and long-term all-cause mortality. In comparison with other possible outcomes, all-cause mortality is associated with the least amount of uncertainty (eg, dependence on specific diagnoses or classifications); further outcomes or variables were not considered in this analysis. Mortality was ascertained by regularly checking the vital status of all registered persons of the myocardial infarction (MI) registry with data from the population registries. Death certificates were obtained from local health departments.

Statistical analysis

For the comparison of categorical variables, χ^2 tests were performed, and the results were presented as absolute frequencies with percentages. Continuous variables were either presented as mean (standard deviation [SD]) or as median (interquartile range [IQR]). Student's *t*-test and Mann-Whitney U test, respectively, were applied to test differences between the groups.

As there were considerable proportions of missing values for the variable prehospital time, we conducted multiple imputations by chained equations. Because of a strong right-skewed distribution, the variable was initially square rooted. The imputation method was "predictive mean matching" with linear regression as the regression model for the square-rooted variable "prehospital time." As independent variables ("predicting variables"), we used 17 variables, including all variables included as independent variables in multivariable adjusted regression models (see following section). The number of iterations was 5, and the number of created imputed data sets was 5 as well. After the imputation, it was graphically verified that the general distribution of the square-rooted variable prehospital time did not change considerably by the imputation process (Supplemental Fig. S1). The imputation process was performed with MICE-package (R Statistic Software, R Foundation, Vienna, Austria). The subsequent regression models were calculated for each of the 5 imputed data sets, and results were pooled in the end. For more details of the imputation process, see Supplemental Fig. S1 and the following section.

Short-term mortality: logistic regression models

Multivariable logistic regression models were calculated to examine the association between AMI symptoms and short-

term mortality. According to literature review, the models were adjusted for sex, age, diabetes mellitus (yes/no), PCI (yes/no), left ventricular ejection fraction (LVEF > 30% / LVEF ≤ 30%), type of infarction (STEMI, NSTEMI, bundle branch block), renal function (according to estimated glomerular filtration rate [eGFR] group, calculated by the **C**hronic **K**idney **D**isease-**Epi**demiology [CKD-EPI] Collaboration formula[19]) and prehospital time (time between begin of the infarction/symptoms and hospital admission). The values for prehospital time were square rooted because of a strong right-skewed distribution. *P* values were false discovery rate (FDR) adjusted. Even though there were some associations between specific symptoms and the variables "peak CKMB values" and "troponin I at admission" (Table 1 and Supplemental Table S4), we did not include them into the multivariable adjusted regression models, as the results of the regression models with and without these variables were comparable.

Long-term mortality: Cox regression models

To focus on long-term mortality exclusively, only patients who survived the first 28 days after AMI were included in the following analyses. Kaplan-Meier curves and log-rank tests were used to examine the (unadjusted) associations between symptoms of AMI and long-term mortality. As the main analysis, multivariable adjusted Cox regression models were calculated. The models were adjusted in the same way as the logistic regression models. The proportional hazards assumption was checked by plotting the Schoenfeld residuals against time and searching for any visible correlation. In addition, log (log [survival]) plots were inspected for crossing curves. The proportional hazards assumptions were fulfilled sufficiently.

To evaluate whether there are interactions between sex and symptoms of AMI, we conducted formal tests for interaction. All statistical analyses were performed using R version 4.2.1.

Results

A total of 5900 cases were included in this analysis, which is approximately 75% of all patients hospitalized for AMI recorded by the registry in the time period between 2010 and 2017. Table 1 displays important baseline characteristics for the total sample and stratified by sex and AMI symptoms, respectively. A majority of 4085 (69.8%) patients were male, and the average age of the cohort was 66.3 (± 11.9) years. Median observation time was 3.8 years (IQR: 1.1-6.3]. Only 22.9% of the patients reported no chest pain or a feeling of pressure or tightness behind the breastbone at the event, which means that typical chest pain symptoms were by far the most frequently reported symptoms. All other symptoms ranged between 50.2% (shortness of breath) and only 5.6% of patients with syncope/unconsciousness.

Short-term mortality

Overall, 372 (6.3%) of the patients died within 28 days after the event. Except for syncope/unconsciousness and shortness of breath, the patients who reported any other symptoms had lower 28-term mortality compared to those patients without the specific symptoms (Fig. 1). The results of the logistic regression models mainly point in the same direction as the presence of the following symptoms was associated with a significantly better short-term survival (Table 2): chest pain or a feeling of pressure or tightness behind the breastbone (odds ratio [OR], 0.40 [0.32,0.51]; $P < 0.001$), pain in the left arm/shoulder (OR: 0.39 [0.29,0.54]; $P < 0.001$), pain in the right arm/shoulder (OR: 0.35 [0.22,0.55]; $P < 0.001$), pain between the shoulder blades (OR: 0.38 [0.28,0.52]; $P < 0.001$), sweating (OR: 0.40 [0.30,0.55]; $P < 0.001$), vomiting/nausea (OR: 0.61 [0.46,0.82]; $P = 0.002$), dizziness/vertigo (OR: 0.37 [0.24,0.55]; $P < 0.001$), and fear of death/feeling of annihilation (OR: 0.25 [0.13,0.49]; $P < 0.001$). The direction and magnitude of the associations noted in the total sample were also seen among the older patients (70 to 84 years of age; see Fig. 1 and Table 2).

Long-term mortality

A similar situation arose for the association between specific symptoms and long-term mortality. Figure 2 shows the survival curves for each specific symptom, stratified by the presence or absence of that symptom. The presence of most symptoms was associated with a lower long-term mortality risk. An exception from this was syncope/unconsciousness and shortness of breath. Most of the associations seen in Figure 2 were attenuated but remained statistically significant after multivariable adjustment in Cox regression models (Table 3). The presence of the following symptoms was significantly associated with a lower long-term mortality: chest pain or a feeling of pressure or tightness behind the breastbone (hazard ratio [HR]: 0.62 [0.55,0.71]; $P < 0.001$), pain in the left arm/shoulder (HR: 0.65 [0.57,0.74]; $P < 0.001$), pain in the right arm/shoulder (HR: 0.75 [0.64,0.88]; $P < 0.001$), pain between the shoulder blades (HR: 0.63 [0.55,0.72]; $P < 0.001$) and sweating (HR: 0.74 [0.65,0.84]; $P < 0.001$). Shortness of breath, on the other hand, was significantly associated with higher long-term mortality (HR: 1.25 [1.11,1.41]; $P < 0.001$); syncope/unconsciousness was slightly nonsignificantly associated with higher long-term mortality (HR: 1.26 [1.02,1.55]; $P = 0.053$).

Regarding the elderly group, the presence of most of the symptoms was associated with a reduced long-term mortality risk in Kaplan-Meier analyses (Fig. 3). In Cox regression models the associations were attenuated after multivariable adjustment (Table 3). The only AMI symptoms that were significantly associated with a reduced risk in the elderly group after adjustment were chest pain or a feeling of pressure or tightness behind the breastbone (HR: 0.73 [0.61, 0.87]; $P = 0.002$), left shoulder/arm/hand pain (HR: 0.65 [0.57, 0.74]; $P = 0.002$), pain between the shoulder blades (HR: 0.63 [0.55, 0.72]; $P < 0.001$) and sweating (HR: 0.81 [0.68,0.96]; $P = 0.049$). In this patient group, shortness of breath was not associated with an increased long-term mortality risk.

In Supplemental Tables S1-S3 and Supplemental Fig. S2 and S3 we present the results for the same analyses based on all cases that were recorded by the Augsburg Myocardial Infarction Registry between 2000 and 2017 (11,190 patients, median follow-up time: 6.2 years [IQR: 2.9-10.4]). The results were very similar compared with the results reported here. Like for the 2010 to 2017 sample, patients who did not report chest pain or feelings of pressure or tightness behind

Table 1. Baseline characteristics for the total sample and stratified for sex and typical chest pain symptoms (chest pain or a feeling of pressure or tightness behind the breastbone, yes/no) given by total number and % or mean and SD or median and IQR

		Stratified for sex			Stratified for typical chest pain symptoms (at the event)			
	Total sample (n = 5900)	Male (n = 4085)	Female (n = 1815)	*P* value	Typical chest pain symptoms (n = 4549)	No typical chest pain symptoms (n = 1351)	*P* value	n*
Female	1815 (30.8)	-	-	-	1375 (30.2)	440 (32.6)	-	5900
Age (mean, SD)	66.3 (11.9)	64.5 (11.7)	70.2 (11.2)	< 0.001	67 (56-75)	72 (63-79)	< 0.001	5900
Age 75-84 years	1795 (30.4)	979 (24.0)	816 (53.9)	< 0.001	1231 (27.1)	564 (41.7)	< 0.001	5900
28-day mortality (%)	372 (6.3)	221 (5.4)	151 (8.3)	< 0.001	163 (3.6)	209 (15.5)	< 0.001	5900
Symptoms at the event								
Typical chest pain symptoms	4549 (77.1)	3174 (77.7)	1375 (75.8)	0.109	-		-	5900
Any pain symptoms	5857 (99.3)	4061 (99.4)	1796 (99)	0.061	4549 (100)	1308 (96.9)	< 0.001	5899
Pain: left arm/shoulder	2438 (41.6)	1650 (40.6)	788 (43.8)	0.026	2273 (50.1)	165 (12.4)	< 0.001	5864
Pain: right arm/shoulder	1350 (23.1)	930 (22.9)	420 (23.4)	0.737	1259 (27.8)	91 (6.9)	< 0.001	5856
Pain: between shoulder blades	2438 (44.6)	1650 (43.3)	788 (47.6)	0.004	2273 (54.2)	165 (12.9)	< 0.001	5470
Pain: upper abdomen	611 (10.4)	402 (9.9)	209 (11.6)	0.051	492 (10.9)	119 (9)	0.050	5851
Sweating	2497 (42.6)	1786 (44.0)	711 (39.5)	0.002	2234 (49.4)	263 (19.7)	< 0.001	5858
Vomiting/nausea	1759 (30.0)	1058 (26.0)	701 (38.8)	< 0.001	1489 (32.8)	270 (20.2)	< 0.001	5872
Shortness of breath	2952 (50.2)	1967 (48.4)	985 (54.4)	< 0.001	2278 (50.2)	674 (50.2)	1	5877
Dizziness/vertigo	1187 (20.3)	793 (19.5)	394 (21.9)	0.042	994 (22)	193 (14.5)	< 0.001	5857
Syncope/unconsciousness	330 (5.6)	210 (5.2)	120 (6.7)	0.027	170 (3.8)	160 (12)	< 0.001	5861
Fear of death/Feeling of annihilation	742 (12.7)	490 (12.1)	252 (14)	0.045	687 (15.2)	55 (4.1)	< 0.001	5856
Comorbidities								
Hypertension	4528 (76.7)	3029 (74.1)	1499 (82.6)	< 0.001	3484 (76.6)	1044 (77.3)	0.625	5900
Diabetes mellitus	1859 (31.5)	1235 (30.2)	624 (34.4)	0.002	1327 (29.2)	532 (39.4)	< 0.001	5900
Hyperlipidemia	3107 (52.7)	2164 (53)	943 (52)	0.487	2073 (45.6)	720 (53.3)	-	5900
Smoking status				< 0.001			< 0.001	5900
Current smoker	1796 (30.4)	1393 (34.1)	403 (22.2)		1489 (32.7)	307 (22.7)		
Never smoker	1705 (28.9)	1396 (34.2)	309 (17)		1341 (29.5)	364 (26.9)		
Ex-smoker	1868 (31.7)	1019 (24.9)	849 (46.8)		1480 (32.5)	388 (28.7)		
No information	531 (9)	277 (6.8)	254 (14)		239 (5.3)	292 (21.6)		
Clinical characteristics								
Prehospital time in minutes	158 (82-530)	156 (80-521)	160 (89-540)	0.112	175.0 (90-585)	93.5 (58-291)	< 0.001	4565
Type of infarction				0.004			< 0.001	5900
STEMI	2205 (37.4)	1579 (38.7)	626 (34.5)		1860 (40.9)	345 (25.5)		
NSTEMI	3187 (54)	2148 (52.6)	1039 (57.2)		2365 (52.0)	822 (60.8)		
Bundle branch block	508 (8.6)	358 (8.8)	150 (8.3)		324 (7.1)	184 (13.6)		
Renal function according to GFR				< 0.001			< 0.001	11190
GFR ≥ 60 mL/min	3894 (66.0)	2886 (70.6)	1008 (55.5)		3261 (71.7)	633 (46.9)		5900
GFR 30- 59 mL/min	1598 (27.1)	981 (24.0)	617 (34)		1068 (23.5)	530 (39.2)		
GFR < 30 mL/min	348 (5.9)	181 (4.4)	167 (9.2)		174 (3.8)	174 (12.9)		
No information	60 (1.0)	37 (0.9)	23 (1.3)		46 (1.0)	14 (1.0)		
LVEF				< 0.001			< 0.001	5900
≤ 30%	429 (7.3)	313 (7.7)	116 (6.4)		238 (5.2)	191 (14.1)		
> 30%	4904 (83.1)	3417 (83.6)	1487 (81.9)		3961 (87.1)	943 (69.8)		
No information	567 (9.6)	355 (8.7)	212 (11.7)		350 (7.7)	217 (16.1)		
Laboratory value								
Admission troponin I (ng/mL)	0.73 (0.13-4.53)	0.765 (0.13-4.90)	0.625 (0.13-3.78)	0.146	0.65 (0.12-4.11)	1.11 (0.20-6.08)	< 0.001	2846
Peak CK-MB levels (U/l)	71 (35-171)	73 (34-173)	67 (35-167)	0.384	76 (36-178)	57 (31-136)	< 0.001	5104
Treatment								

Continued

Table 1. Continued.

		Stratified for sex			Stratified for typical chest pain symptoms (at the event)			
	Total sample (n = 5900)	Male (n = 4085)	Female (n = 1815)	*P* value	Typical chest pain symptoms (n = 4549)	No typical chest pain symptoms (n = 1351)	*P* value	n*
PCI	4274 (72.4)	3041 (74.4)	1233 (67.9)	< 0.001	3550 (78)	724 (53.6)	< 0.001	5900
Bypass therapy	776 (13.2)	583 (14.3)	193 (10.6)	< 0.001	596 (13.1)	180 (13.3)	0.868	5900
Lysis therapy	31 (0.5)	23 (0.6)	8 (0.4)	0.686	17 (0.4)	14 (1)	0.006	5900

CK-MB, creatine kinase-MB; IQR, interquartile range; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction;. NSTEMI, non−ST-elevation myocardial infarction; SD, standard deviation; STEMI, ST-elevation myocardial infarction.

* Number of cases with valid information

the breastbone were at higher risk of short-term death. The absence of most symptoms was associated with increased short-term mortality. The only exception from this was syncope/unconsciousness, as the absence of this symptom was associated with a reduced 28-day mortality risk. Although most symptoms were also associated with lower long-term mortality, the symptoms "shortness of breath" and "syncope/unconsciousness" went along with higher long-term mortality.

In Supplemental Table S4, the results of linear regression models analyzing the association between specific symptoms and peak creatine kinase (CK)-MB levels are displayed. Although the unadjusted models suggested mainly positive associations between the presence of specific symptoms and CK-MB levels, the adjusted models revealed a heterogeneous situation without clear associations in either way.

Supplemental Table S5 shows the frequencies of a severely restricted LVEF ($\leq$ 30%) stratified by the presence of each specific symptom. Notably, only for shortness of breath and syncope, the patients who reported the specific symptom had a higher proportion of impaired LVEF. For every other symptom, the patients without the symptom had higher percentages of heavily impaired LVEF.

Finally, when calculating the regression models by including an interaction term between the AMI symptoms and sex, the interaction term was only significant for chest pain or a feeling of pressure or tightness behind the breastbone and short-term mortality ($P = 0.04$). For every other regression, there was no significant interaction between symptoms and sex (Supplemental Table S6). Thus, the results of this study and the conclusions drawn might be valid for male and female patients.

Discussion

In this study, we found that the absence of several symptoms at AMI was associated with a higher short- and long-term mortality. The associations with short-term mortality were significant for most of the symptoms after multivariable adjustment in both the total sample and the age group 75 to 84 years. A few symptoms were associated with a lower long-term mortality risk after multivariable adjustment in the total sample. Shortness of breath, however, was significantly associated with a higher long-term mortality. Considering the elderly patient group, only the AMI symptoms chest pain or a feeling of pressure or tightness behind the breastbone, left shoulder/arm/hand pain, and pain between the shoulder blades were inversely associated with long-term mortality in multivariable analyses. In this patient group, shortness of breath was not associated with an increased long-term mortality risk.

The current results are basically in accordance with that of a previous publication from the Augsburg Myocardial Infarction Registry based on AMI cases between 1998 and 2003, patients aged 25 to 74 years, even though some differences were noted. Thus, the overall associations between symptoms and outcome after AMI are still valid in the current era characterized by integrating high-sensitivity cardiac troponin for diagnostics and increased PCI treatment and are also applicable to older groups of patients of up to 85 years.

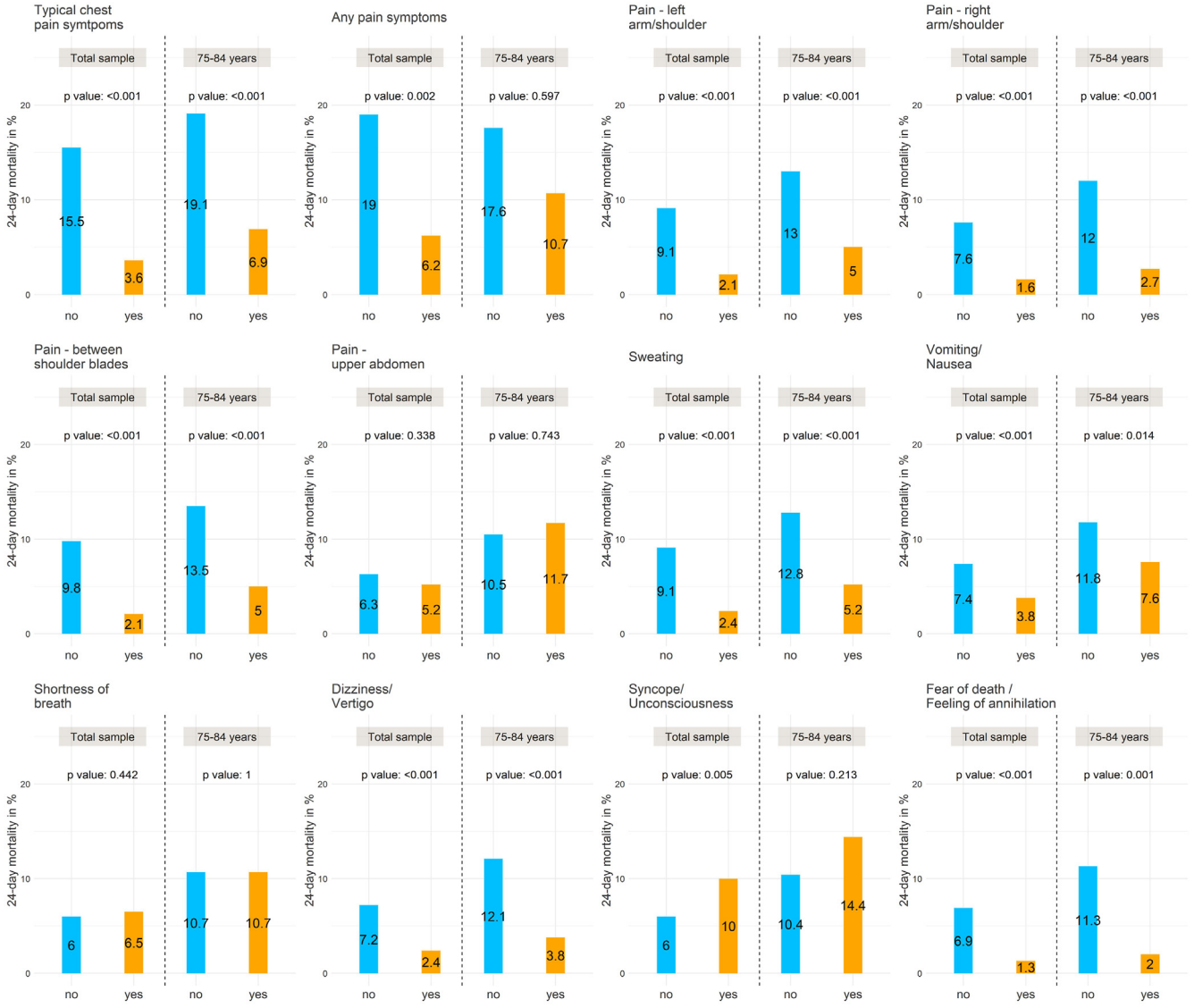

Figure 1. Presence of specific symptoms and 28-day mortality in % in the total sample and in 75- to 85-year-old patients with acute myocardial infarction (AMI). The **blue bars** represent the patients with AMI and the respective symptoms, and the **orange bars** represent patients without that symptom at the acute event. *P* values were calculated using χ^2 tests.

In line with the current analysis, a large study from the **S**wedish **W**eb-System for **E**nhancement and **D**evelopment of **E**vidence-Based Care in **H**eart Disease **E**valuated **A**ccording to **R**ecommended **T**herapies (SWEDEHEART) registry including almost 173,000 patients with AMI between 1996 and 2010 (aged 18 to 84 years), reported that the absence of chest-pain symptoms was associated with higher short- and long-term mortality.[6] This and other studies[2,20-25] only investigated the associations between chest pain symptoms and mortality but considered no other AMI symptoms. Therefore, it is of interest as to whether specific symptoms next to chest pain are associated with short- and long-term mortality, a topic that has been rarely investigated so far. There are some deviations compared with the results from previous studies.[5] Especially new diagnostic measurements (troponin values) and therapeutic standards (PCI) may be responsible for these discrepancies. In addition to this, comprehensive preventive measures and an increased overall knowledge on the topic could have influenced the associations.

It could be assumed that less symptoms and a weaker clinical presentation may be associated with less severe infarction and consequently a more favourable outcome. The current study indicates that the opposite may be true: The presence of some symptoms was associated with higher and some with lower CK-MB values. Therefore, infarct size and severity of AMI might not be the driving explanatory factors for the associations between symptoms and mortality.

A clinical presentation without chest pain or a feeling of pressure or tightness behind the breastbone may not only cause uncertainty of the patients about their situations but often leads to a prolonged diagnostic procedure or even an initial misdiagnosis.[2,6,26,27] Especially in cases of STEMI, a

Table 2. Results of the logistic regression models for the association among different symptoms and 28-day mortality

Symptom	Total sample		Age 75-84 years	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Typical chest pain symptoms*	0.40 (0.32, 0.51)	< 0.001	0.40 (0.32, 0.51)	< 0.001
Pain: left shoulder/arm/hand	0.39 (0.29, 0.54)	< 0.001	0.39 (0.29, 0.54)	< 0.001
Pain: right shoulder/arm/hand	0.35 (0.22, 0.55)	< 0.001	0.35 (0.22, 0.55)	< 0.001
Pain: between shoulder blades	0.38 (0.28, 0.52)	< 0.001	0.38 (0.28, 0.52)	< 0.001
Pain: upper abdomen	1.06 (0.71, 1.59)	0.765	1.06 (0.71, 1.59)	0.765
Sweating	0.40 (0.3, 0.55)	< 0.001	0.40 (0.3, 0.55)	< 0.001
Nausea/vomiting	0.61 (0.46, 0.82)	0.002	0.61 (0.46, 0.82)	0.002
Shortness of breath	0.83 (0.65, 1.05)	0.139	0.83 (0.65, 1.05)	0.139
Dizziness/vertigo	0.37 (0.24, 0.55)	< 0.001	0.37 (0.24, 0.55)	< 0.001
Syncope/unconsciousness	1.09 (0.72, 1.65)	0.764	1.09 (0.72, 1.65)	0.764
Fear of death/feeling of annihilation	0.25 (0.13, 0.49)	< 0.001	0.25 (0.13, 0.49)	< 0.001

All models were adjusted for sex, age, diabetes mellitus, PCI, LVEF, type of infarction, renal function (eGFR group), and prehospital time. *P* values were FDR adjusted.

AMI, acute myocardial infarction; CI, confidence interval; eGFR, estimated glomerular filtration rate; FDR, false discovery rate; LVEF, left ventricular ejection fraction; OR, odds ratio; PCI, percutaneous coronary intervention.

*Chest pain or a feeling of pressure or tightness behind the breastbone.

delayed diagnosis and, in particular, a delayed start of the therapy goes along with an unfavourable outcome.[28-30] In this study, we considered prehospital delay, PCI, and bypass therapy in the regression models. Despite all these, the associations remained significant for many symptoms, leading to the conclusion that delayed diagnosis and therapy are unlikely to be the main factors for the current results.

Another important point is that some patients have restricted sensitivity toward perception of symptoms. A prominent example for this phenomenon is reduced pain perception in patients with polyneuropathy, a typical consequence of a diabetes mellitus.[31] In general, a reduced sensitivity towards symptom perception might be related to an overall worse health condition and, in this way, affects short-term as well as long-term outcomes after AMI. This hypothesis is supported by the circumstance that, in the current study, patients without chest pain or a feeling of pressure or tightness behind the breastbone were older and more likely to have diabetes mellitus, an impaired renal function, or a reduced LVEF. In addition, they were less likely to report other symptoms. This is confirmed by the results of previous studies, which also found that patients without chest pain were older and had more comorbidities.[6,20] It could be assumed that the overall health condition is not the only factor driving the association between symptoms and outcome after AMI but still might contribute substantially to the relationships we found in this study. Consequently, a broader understanding of AMI symptoms that can occur in the absence of chest pain—regardless of age, sex, or comorbidities—is needed.[32]

A last point for discussion is the observed association of shortness of breath with a higher long-term mortality and thereby differing from all other symptoms analyzed in this study. Shortness of breath is a very subjective symptom, strongly influenced by psychological mechanisms, perhaps more than any other symptoms examined in this study. Furthermore, shortness of breath possibly indicates a greater impairment of left ventricular (LV) function, thereby going along with higher long-term mortality. This mechanism was also suggested by Goldstein et al.[21] In the current study, patients reporting shortness of breath at the event were more than twice as likely to have a heavily impaired ventricular ejection fraction than patients without this symptom (Supplemental Table S5), a major factor possibly explaining the positive association between shortness of breath and increased long-term mortality.

As a consequence of the current findings, educational efforts at the population level seems necessary to raise awareness of the various but possible symptoms of AMI. In particular, this should also aim to educate the population regarding ischemic symptoms without chest pain in AMI.[33] Considerable efforts should be made to empower patients to take appropriate action to seek medical care early. Taking advantage of emergency medical transport is often life saving if symptoms occur. Medical staff should also be repeatedly made aware of the fact that, in addition to acute chest pain, a number of other symptoms could indicate AMI.

Strengths and limitations

This study is characterized by a large sample size derived from a population-based registry with consecutive enrollment, which minimizes the risk of selection bias and a considerably long follow-up time. Standardized data collection was performed by trained and certified medical staff. The large amount of collected data provided the opportunity for extensive adjustment of the regression models.

There are also some limitations: Only patients between 25 and 84 years were included; consequently, results cannot be applied to older age groups and may not be generalized to all ethnic groups. Therefore, physicians around the world, and especially in countries outside of Western Europe, must be cautious about the validity of these results in their surroundings. As this is an observational study, causality cannot be proven, and results cannot be interpreted in a way that the absence or presence of some specific symptoms actually causes increased mortality. Even though a wide range of variables was available in the data, unmeasured confounding or residual confounding could not be entirely excluded. In this study, no cause-specific but

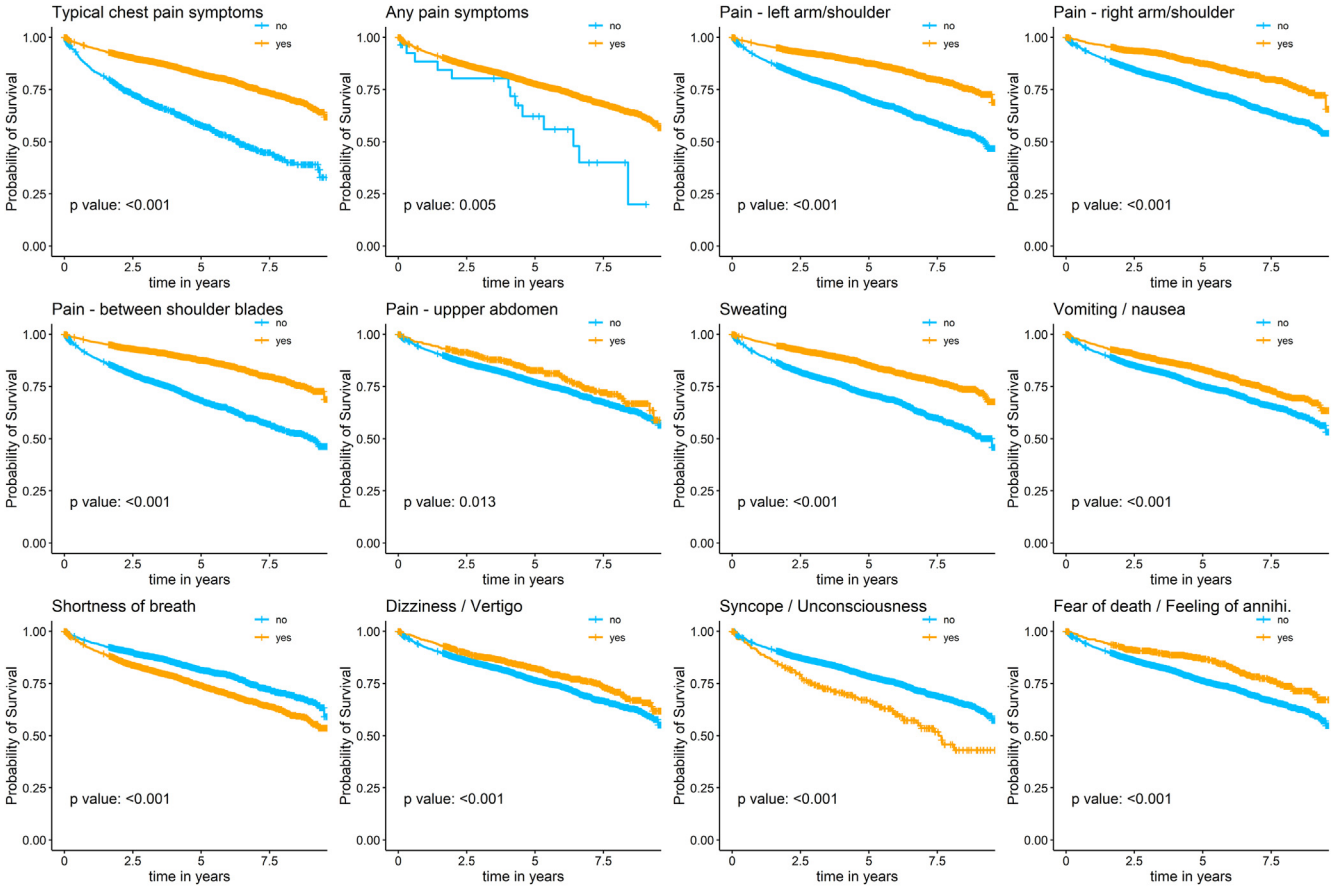

Figure 2. Kaplan-Meier curves displaying the long-term mortality stratified for the presence of specific symptoms at the acute event. The **blue lines** represent the patients with acute myocardial infarction (AMI) and the respective symptoms, and the **orange lines** represent patients without that symptom at the acute event. *P* values are derived from log-rank tests (unadjusted for multiple testing).

only all-cause mortality was considered. In addition, no information on other long-term outcomes following AMI (eg, LV dysfunction, arrhythmias) or quality-of-life outcomes were available in this study. A further limitation is that the symptoms were self-reported by the patients and thus based on a highly subjective experience, making objectification difficult. This further implies that the association might not be applicable to other cultures and societies with different perceptions of symptoms and communication.

Table 3. Results of the Cox regression models examining the impact of different symptoms on long-term mortality of patients with AMI

	Total sample		Age 75-84 years	
Symptom	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Typical chest pain symptoms*	0.62 (0.55, 0.71)	< 0.001	0.73 (0.61, 0.87)	0.002
Pain: left shoulder/arm/hand	0.65 (0.57, 0.74)	< 0.001	0.72 (0.59, 0.86)	0.002
Pain: right shoulder/arm/hand	0.75 (0.64, 0.88)	< 0.001	0.84 (0.67, 1.06)	0.200
Pain: between shoulder blades	0.63 (0.55, 0.72)	< 0.001	0.68 (0.56, 0.82)	< 0.001
Pain: upper abdomen	0.94 (0.77, 1.15)	0.579	0.88 (0.66, 1.18)	0.413
Sweating	0.74 (0.65, 0.84)	< 0.001	0.81 (0.68, 0.96)	0.049
Nausea/vomiting	0.87 (0.76, 0.99)	0.054	0.81 (0.67, 0.97)	0.057
Shortness of breath	1.25 (1.11, 1.41)	< 0.001	1.20 (1.02, 1.41)	0.059
Dizziness/vertigo	0.87 (0.75, 1.02)	0.087	0.89 (0.73,1.09)	0.315
Syncope/unconsciousness	1.26 (1.02, 1.55)	0.053	1.13 (0.85, 1.5)	0.413
Fear of death/feeling of annihilation	0.84 (0.69, 1.01)	0.082	0.8 (0.61, 1.05)	0.164

All models were adjusted for sex, age, diabetes mellitus, PCI, LVEF, type of infarction, renal function (eGFR group) and prehospital time. *P* values were FDR-adjusted.

CI, confidence interval; eGFR, estimated glomerular filtration rate; FDR, false discovery rate; HR, hazard ratio; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.

*Chest pain or a feeling of pressure or tightness behind the breastbone.

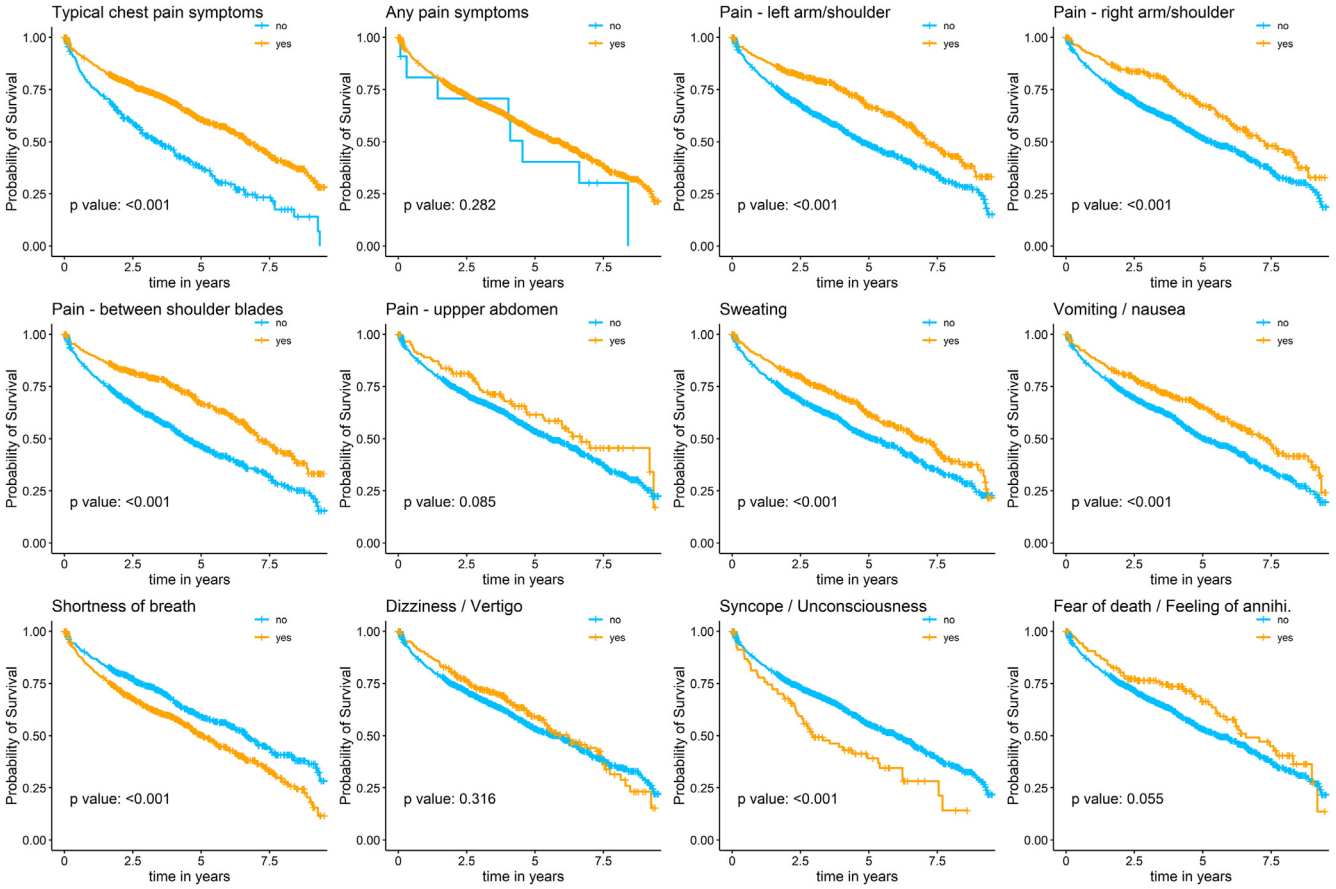

Figure 3. Kaplan-Meier curves displaying the long-term mortality stratified for the presence of specific symptoms at the acute event. The **blue lines** represent the patients with acute myocardial infarction (AMI) and the respective symptoms, and the **orange lines** represent patients without that symptom at the acute event. Only older patients, aged 75 to 84 years, were included. *P* values are derived from log-rank tests (unadjusted for multiple testing).

Further research directions

Based on the limitations of the current study, future research is necessary to close relevant knowledge gaps. First, it has to be examined what outcome parameters other than death are associated with specific symptoms such as LV dysfunction, arrhythmias, and impairment of renal function. Furthermore, future analyses should also consider the specific cause of death rather than all-cause mortality. In addition, future research is supposed to identify specific patient subgroups with particularly strong associations between (atypical) symptoms and outcome after AMI. One important aspect in this regard might be that there are racial differences in the perception of symptoms. In view of the multiethnic societies that exist today, it is important to increase knowledge about this issue by conducting further studies, such as by a collaboration of researchers around the world in a multicentre study, including patients with different cultural backgrounds and habits. This requires a more precise recording of the symptoms, which can only be achieved by providing refined and standardized measuring instruments.[34] Routine clinical use of medical decision support systems would be desirable to achieve a fast, efficient and reliable diagnosis in patients with suspected MI. The introduction of refined symptom assessment and associated potential risk stratification requires careful training of emergency department staff and emergency physicians. To raise the knowledge about atypical symptoms in connection with an AMI, it is also important to educate cardiac patients, other vulnerable groups, and the general population. The effectiveness of the measures and the associated improvements in patient care or outcomes must be examined in randomized, controlled intervention studies. To summarize, in the future, larger comprehensive, prospective, multicentre studies are needed to identify subgroups at risk and to perform in-depth stratification of outcomes by symptoms. The use of a machine-learning approach to estimate the individual probability of AMI in patients with symptoms suggestive of AMI could significantly enhance research methods in this area.

Conclusions

The absence of a variety of symptoms at AMI is significantly associated with unfavourable short- and long-term outcomes. In contrast, the presence of shortness of breath is significantly associated with worse long-term outcomes. This

finding has implications for patient management and public health measures designed to encourage appropriate and prompt medical consultation of patients with atypical symptoms of AMI.

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Data Availability

The datasets generated during or analyzed during the current study are not publicly available because of data-protection aspects but are available in an anonymized form from the corresponding author on reasonable request.

Ethics Statement

Data collection of the MONICA/KORA MI registry has been approved by the Ethics Committee of the Bavarian Medical Association (Bayerische Landesärztekammer), and the study was performed in accordance with the Declaration of Helsinki.

Patient Consent

All study participants have given written informed consent.

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2024.01.019.