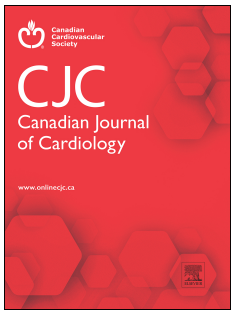

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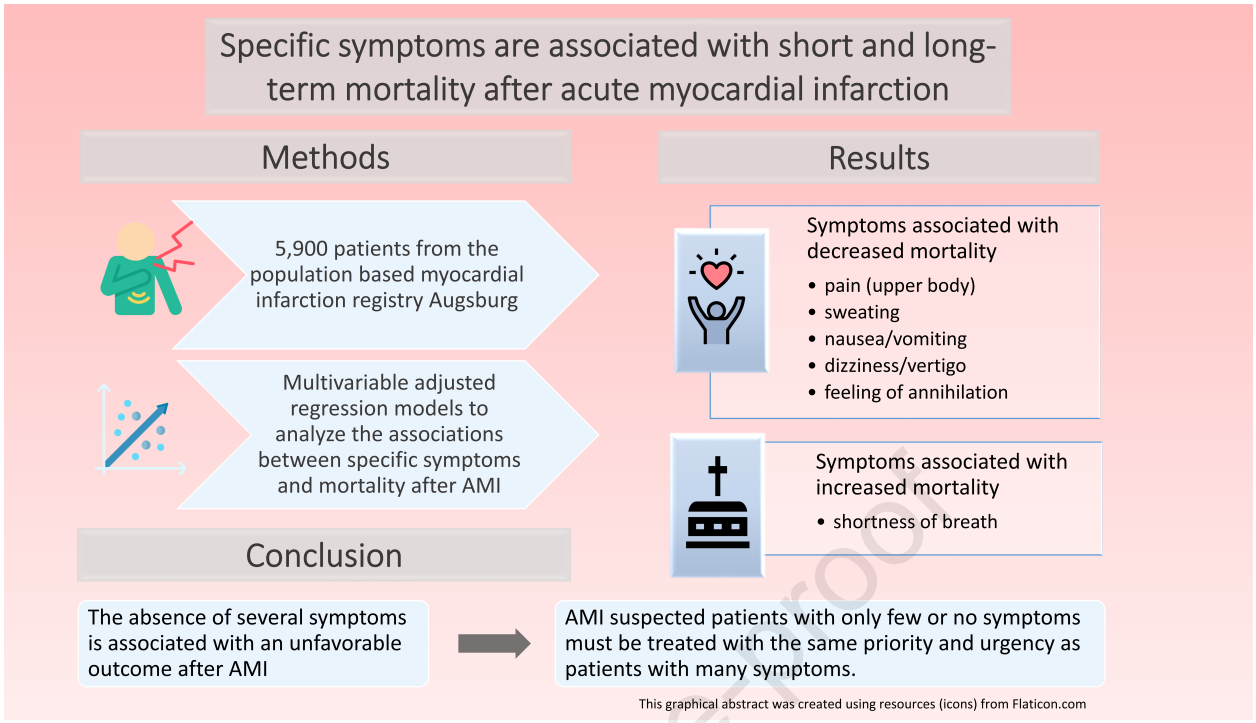

Association between acute myocardial infarction symptoms and short- and long-term mortality after the event.

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Abstract

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

Methods: The analysis was based on 5,900 patients aged 25 to 84 years with a first-time AMI recorded by the population-based Myocardial Infarction Registry Augsburg between 2010 and 2017. Median follow-up time was 3.8 years [IQR: 1.1-6.3]. As part of a face-to-face interview, the presence (yes/no) of 11 most commonly 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 FDR-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 unfavorable 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.

Keywords: Acute myocardial infarction, AMI symptoms, short-term mortality, long-term mortality

Declarations of interest: none

Introduction

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 like fear of death, nausea or syncope are also associated with mortality after AMI as a prior 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 (e.g., 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 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 (e.g., long-term medication, smoking cessation etc.) 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 AMI patients and thus the question arises, whether the overall association between symptom presentation 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 wasn´t addressed by the prior study from the Augsburg Myocardial Infarction Registry, which included only patients from 25-74 years. Due to 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 MONICA-project (Monitoring Trends and Determinants in Cardiovascular disease) and since then operated as KORA Myocardial Infarction Registry[17]. The study area consists of the city of Augsburg, Germany, and the two adjacent counties comprising a total of approximately 680,000 inhabitants. For this analysis of hospitalized AMI patients, the following inclusion criteria were applied: patients' age was between 25 and 84 years, the patient survived the first 24 hours after hospital admission and had its primary residence within the study area. The definition of AMI included ST-elevation-myocardial infarction cases (STEMI) as well as diagnosed Non-ST-elevation-myocardial infarction cases (STEMI). The latter include all cases of AMI symptoms with troponin dynamic and/or AMI cases confirmed by percutaneous transluminal coronary angioplasty. In close cooperation with all hospitals treating AMI patients in the study region, all AMI patients 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 (6,327 cases). The begin (2010) was chosen to only analyze cases from an era with well-established PCI standards. The year 2017 was chosen as the final year of enrollment because long-term survival data was available for analyses by then. Patients with missing information on AMI symptoms or relevant covariables ($n = 427$) were excluded. The final study population consisted of 5,900 patients with AMI.

Data collection

Intensively trained and subsequently certified medical staff (mainly nurses) performed the standardized patient interviews and record review. This was performed on the basis of standardized operating procedures. Re-certification 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 / shoulder, pain in the right arm / 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. Next to information about symptoms, the interview also addressed further topics like socio-demographic features, preexisting comorbidities, medication use or prior infarctions. To confirm the information provided by the patients and to collect additional information, the patients' medical chart was 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 day) and long-term all-cause mortality. In comparison to other possible outcomes, all-cause mortality is associated with the least amount of uncertainty (e.g., 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 MI registry with data from the population registries. Death certificates were obtained from local health departments.

Statistical analysis

For the comparison of categorical variables, Chi-square 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 (inter-quartiles range, IQR). Student´s t-test and Mann-Whitney U test, respectively, were applied to test differences between the groups.

Since there were considerable proportions of missing values for the variable prehospital time we conducted multiple imputation by chained equations. Due to 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 below). 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 (see Supplemental Figure 3). The imputation process was performed with MICE-package (R statistic software). 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 Figure S3 and the following.

Short-term mortality - logistic regression models

Multivariable logistic regression models were calculated in order 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% / ≤30%), type of infarction (STEMI, NSTEMI, bundle branch block), renal function (according to eGFR group, calculated by the CKD-EPI formula [19]) and prehospital time (time between begin of the infarction/symptoms and hospital admission). The values for prehospital time were square rooted due to a strong right-skewed distribution. P values were FDR (false discovery rate)-adjusted. Even though there were some associations between specific symptoms and the variables 'peak CKMB values' and 'troponin I at admission' (see 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 was very comparable.

Long-term mortality - Cox regression models

In order to focus on long-term mortality exclusively, only patients who survived the first 28 days after AMI were included into the analysis the following analyses. Kaplan-Meier curves and Log-rank tests were used to examine the (unadjusted) associations between AMI symptoms 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. Additionally, 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 AMI symptoms, we conducted formal test for interaction. All statistical analyses were performed using R version 4.2.1 (Vienna, Austria).

Results

A total of 5,900 cases was included in this analysis, which is approximately 75% of all hospitalized AMI cases 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 4,085 (69.8%) patients was 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 from 50.2% (shortness of breath) to 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 symptom had a lower 28-term mortality compared to those patients without the symptom (Figure 1). The results of the logistic regression model 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 (OR: 0.40 [0.32,0.51], p value: <0.001), pain in the left arm / shoulder (OR: 0.39 [0.29,0.54], p value: <0.001), pain in the right arm / shoulder (OR: 0.35 [0.22,0.55], p value: <0.001), pain between the shoulder blades (OR: 0.38 [0.28,0.52], p value: <0.001), sweating (OR: 0.40 [0.3,0.55], p value: <0.001), vomiting/nausea (OR: 0.61 [0.46,0.82], p value: 0.002), dizziness/ vertigo (OR: 0.37 [0.24,0.55], p value: <0.001) and fear of death / feeling of annihilation (OR: 0.25 [0.13,0.49], p value: <0.001). The direction and magnitude of the associations noted in the total sample were also seen amongst the older patients (70 to 84 years; see Figure 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/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 (HR: 0.62 [0.55,0.71], p value: <0.001), pain in the left arm / shoulder (HR: 0.65 [0.57,0.74], p value: <0.001), pain in the right arm / shoulder (HR: 0.75 [0.64,0.88], p value: <0.001), pain between the shoulder blades (HR: 0.63 [0.55,0.72], p value: <0.001) and sweating (HR: 0.74 [0.65,0.84], p value: <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 value: <0.001); syncope / unconsciousness was slightly non-significantly associated with higher long-term mortality (HR: 1.26 [1.02,1.55], p value: 0.053).

Regarding the elderly group, the presence of most of the symptoms were associated with a reduced long-term mortality risk in Kaplan-Meier analyses (Figure 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 value: 0.002), left shoulder/arm/hand pain (HR: 0.65 [0.57, 0.74] p value 0.002), pain between the shoulder blades (HR: 0.63 [0.55, 0.72] p value <0.001) and sweating (HR 0.81 [0.68,0.96] p value: 0.049). In this patient group, shortness of breath was not associated with an increased long-term mortality risk.

In Supplemental Table S1/S2/S3 and Supplemental Figure S1/S2 we present the results for the same analyses based on all cases that were recorded by the Augsburg Myocardial infarction registry in the years 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 to the results reported above: like for the 2010-2017 sample, patients who didn´t report chest pain or a feeling of pressure or tightness behind 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. While 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 CKMB levels are displayed. While the unadjusted models suggested mainly positive associations between the presence of specific symptoms and CKMB levels, the adjusted models revealed a heterogeneous situation without clear associations in either way.

Supplemental Table S5 shows the frequencies of a severely restricted left ventricular ejection fraction (≤30%) stratified by the presence of each specific symptoms. Noticeably, only for shortness of breath and syncope, the patients who reported the specific symptom had a higher proportion of impaired left ventricular EF. For every other symptom, the patients without the symptom had a higher percentage of heavily impaired left ventricular EF.

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 value: 0.04). For every other regression, there was no significant interaction between symptoms and sex (see Supplemental Table S6). Thus, the results of this study and the conclusions drawn might be valid for males and females.

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 present results are basically in accordance with that of a prior publication from the Augsburg Myocardial Infarction Registry based on AMI cases between 1998 and 2003, 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 age groups up to 85 years.

In line with the present analysis a large study from the SWEDEHEART registry including almost 173,000 AMI patients between 1996 and 2010 (age 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, whether specific symptoms next to chest pain are associated with short- and long-term mortality, a topic which was rarely investigated so far. There are some deviations compared to the results from prior 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 favorable outcome. The present study indicates that the opposite may be true: the presence of some symptoms was associated with higher and some with lower CKMB values. Therefore infarct size and severity of the 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 situation but often leads to a prolonged diagnostic procedure or even an initial misdiagnosis[2,6,26,27]. Especially in STEMI cases, a delayed diagnosis and in particular a delayed start of the therapy goes along with an unfavorable 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 present results.

Another important point is that some patients have a restricted sensitivity towards symptom perception. A prominent example for this phenomenon is reduced pain perception in patients with polyneuropathy, e.g., as a consequence of a diabetes mellitus disease[31]. . In general, a reduced sensitivity towards symptom perception might be related to an overall worse health condition and in this way affect short-term as well as long-term outcome after AMI. This hypothesis is supported by the circumstance that, in the present 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 left ventricular ejection fraction. Additionally, they were less likely to report other symptoms as well. This is confirmed by the results of prior 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 analysed 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 function and thereby going along with a higher long-term mortality. This mechanism was also suggested by Goldstein et al.[21]. In the present 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 present findings, educational efforts at 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 limitation

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 to mention: 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/presence of some specific symptoms actually causes an increased mortality. Even though a wide range of variables were available in the data, unmeasured confounding or residual confounding could not be entirely excluded. In this study,

no cause-specific but only all-cause mortality could be considered. In addition, no information on other long-term outcomes following AMI (e.g. LV dysfunction, arrhythmias) or quality of life outcomes was available in this study. A further shortcoming 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 society with different symptom perception and communication.

Further research directions

Based on the limitation of the present 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, e.g. LV dysfunction, arrhythmias, impairment of renal function etc. Furthermore, future analyses should also consider the specific cause of death rather than all-cause mortality. Additionally, 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 multi-ethnic societies that exist today, it is important to increase knowledge about this issue by conducting further studies, e.g. by a collaboration of researchers around the world in a multicenter 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 in order 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, multicenter 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.

Conclusion

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

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Declarations of interest: none

Ethics approval and consent to participate: 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. All study participants have given written informed consent.

Availability of data and materials: The datasets generated during and/or analysed during the current study are not publicly available due to data protection aspects but are available in an anonymized form from the corresponding author on reasonable request.

Authors´ contribution: TS and CM conceived the study. TS performed the statistical analysis and drafted the manuscript. CM was responsible for the acquisition of the data and supervised the analysis. EH, PR, DF, IK, MH, AP and JL contributed to data acquisition and revised the manuscript. All authors approved the final manuscript.

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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*

	Total sample (n=5900)	***Stratified for sex***			***Stratified for typical chest pain symptoms (at the event)***			***N****
		male (n=4085)	***female (n=1815)***	***P-value***	***Typical chest pain symptoms (n=4549)***	***No typical chest pain symptoms (n=1351)***	***P-value***	
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)	711 (39.5)	0.002	2234 (49.4)	263 (19.7)	<0.001	5858
Vomiting/Nausea	1759 (30)	1058 (26)	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)	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 ≥ 60ml/min	3894 (66)	2886 (70.6)	1008 (55.5)		3261 (71.7)	633 (46.9)		5900
GFR 30-59ml/min	1598 (27.1)	981 (24)	617 (34)		1068 (23.5)	530 (39.2)		
GFR < 30ml/min	348 (5.9)	181 (4.4)	167 (9.2)		174 (3.8)	174 (12.9)		
No information	60 (1)	37 (0.9)	23 (1.3)		46 (1)	14 (1)		
Left ventricular ejection fraction				<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 CKMB levels (U/l)	71 (35 - 171)	73 (34 - 173)	67 (35 - 167)	0.384	76 (36 - 178)	57 (31 - 136)	<0.001	5104
Treatment								
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

* Number of cases with valid information

Table 2: *Results of the logistic regression models for the association between different symptoms and 28-day mortality. All models were adjusted for sex, age, diabetes mellitus, PCI,*

left-ventricular ejection fraction, type of infarction, renal function (eGFR group) and prehospital time. P values were FDR-adjusted.

	Total sample		Age 75-84 years	
Symptom	Odds ratio [95%CI]	p value	Odds ratio [95%CI]	p value
Typical chest pain symptoms*	0.40 [0.32,0.51]	<0.001	0.54 [0.38,0.76]	0.002
Pain - left shoulder/arm/hand	0.39 [0.29,0.54]	<0.001	0.51 [0.32,0.81]	0.009
Pain - right shoulder/arm/hand	0.35 [0.22,0.55]	<0.001	0.32 [0.15,0.71]	0.009
Pain - between shoulder blades	0.38 [0.28,0.52]	<0.001	0.50 [0.32,0.8]	0.009
Pain - upper abdomen	1.06 [0.71,1.59]	0.765	1.33 [0.76,2.32]	0.354
Sweating	0.40 [0.3,0.55]	<0.001	0.51 [0.32,0.79]	0.009
Nausea / vomiting	0.61 [0.46,0.82]	0.002	0.79 [0.53,1.2]	0.334
Shortness of breath	0.83 [0.65,1.05]	0.139	0.82 [0.59,1.15]	0.334
Dizziness / vertigo	0.37 [0.24,0.55]	<0.001	0.32 [0.17,0.6]	0.002
Syncope / unconsciousness	1.09 [0.72,1.65]	0.764	1.01 [0.57,1.79]	0.976
Fear of death/ feeling of annihilation	0.25 [0.13,0.49]	<0.001	0.2 [0.06,0.66]	0.013

* *chest pain or a feeling of pressure or tightness behind the breastbone*

Table 3: *Results of the COX regression models examining the impact of different symptoms on long-term mortality of AMI patients. All models were adjusted for sex, age, diabetes mellitus, PCI,* left-ventricular ejection fraction*, type of infarction, renal function (eGFR group) and prehospital time. P values were FDR-adjusted.*

	Total sample		Age 75-84 years	
Symptom	**Hazard ratio [95%CI]**	**p value**	**Hazard ratio [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	1.2 [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

** chest pain or a feeling of pressure or tightness behind the breastbone*

Figure 1: *Presence of specific symptoms and 28-day mortality in % in the total sample and in 75-85 year old AMI patients. The blue bars represent the AMI patients with the respective symptoms and orange bars those without that symptom at the acute event. P values were calculated using chi-squared tests.*

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 AMI patients with the respective symptoms and orange lines those without that symptom at the acute event. P values are derived from log rank tests (unadjusted for multiple testing).*

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 AMI patients with the respective symptoms and orange lines those without that symptom at the acute event. Only older patients aged 75-84 years were included. P values are derived from log rank tests (unadjusted for multiple testing).*