

Original Paper

Atypical Symptoms of Acute Coronary Syndrome and Their Predictors



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Running Title Predictors of Atypical Symptoms in Acute Coronary Syndrome

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ABSTRACT

Introduction: The most important diagnostic indicator of Acute Coronary Syndrome (ACS) is typical clinical symptoms, like chest pain, but many patients may experience nonspecific (atypical) symptoms. Understanding these symptoms and their associated factors results in early diagnosis and more appropriate treatments.

Objective: We aimed to determine atypical clinical symptoms and their predictors in patients with Acute Coronary Syndrome.

Materials and Methods: This cross-sectional study was conducted on 1167 patients with ACS hospitalized at a specialized hospital in Rasht City, Iran, between December 2019 and October 2020. The research samples were selected by a consecutive sampling method. Data were collected through a researcher-made questionnaire by interview, in which sociodemographic characteristics, risk factors, disease-related factors, and symptoms of patients with ACS were collected. Data analysis was done by descriptive statistics and multiple logistic regression by the backward LR (likelihood ratio) method. The significance level was set as $P < 0.05$.

Results: In this study, 56.3% of the patients were male. The Mean \pm SD age of the patients was 60.9 \pm 11.1 years. About 28.1% of the patients experienced atypical clinical symptoms. The most common atypical symptoms were shortness of breath (29.4%), back pain (18.3%), and left shoulder pain (12.7%). The predictors of atypical symptoms were age (OR=0.98, 95% CI; 0.975 - 0.999, $P=0.047$), alcohol use (OR=1.86, 95% CI; 1.047 - 3.303, $P=0.034$), brain diseases (OR=2.36, 95% CI; 1.463 - 3.811, $P=0.001$), blood diseases (OR=1.45, 95% CI; 1.059 - 2.002, $P=0.021$), and gastroesophageal reflux (OR=1.31, 95% CI; 1.006 - 1.719, $P=0.045$)

Conclusion: Since more than a quarter of ACS patients have unusual symptoms, detecting these symptoms and related factors can help in early diagnosis and conduct more appropriate medical treatment.

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Highlights

- Acute coronary syndrome (ACS) is one of the most common causes of death in patients with cardiovascular diseases.
- ACS is associated with typical and atypical symptoms. One of the most important causes of misdiagnosis of ACS is a lack of awareness and proper understanding of the atypical symptoms.
- The most common atypical symptoms include shortness of breath, and pain in the back and left shoulder, and the most influential predictors of atypical symptoms were age, alcohol use, brain diseases, blood diseases, and esophageal reflux.

Plain Language Summary

Nowadays, cardiovascular diseases have become a social problem in Iran and the world, and their main manifestation is acute coronary syndrome (ACS). The most important diagnostic indicator of ACS is typical clinical symptoms like chest pain, but many patients may experience nonspecific (atypical) problems in gastrointestinal, respiratory, or other symptoms. We found that more than a quarter of patients with ACS had atypical symptoms, and there are interesting predictors for atypical ACS. Therefore, detecting atypical clinical symptoms of ACS and related factors can help in the early diagnosis and implementation of more appropriate medical treatment.

Introduction

Cardiovascular disease (CVD) is the leading cause of death globally, and each year, about 17.9 million people die from CVD [1]. Rezaianzadeh et al. quoted from the report of the World Health Organization (WHO) that at the end of the second millennium, a major part of the healthcare budget in developing countries will be allocated for cardiovascular diseases. These diseases have become a social problem in Iran [2], and the mortality rate due to cardiovascular diseases accounts for 43% of the total deaths [3]. Coronary artery disease (CAD) is the most important share of CVDs, and acute coronary syndrome (ACS) is the most serious manifestation of CAD [4]. Indeed, ACS is one of the most common causes of death in patients with CVD [5], during which myocardial blood supply is affected, and the symptoms appear [4]. Symptoms are the triggers that propel individuals to suspect ACS and seek emergent care for these potentially life-threatening conditions [6]. Thus, the accurate interpretation of clinical symptoms has implications for patient triage, treatment, and subsequent management [7]. One of the most important causes of errors in the diagnosis of ACS is a lack of awareness and proper understanding of the symptoms [8]. ACS is associated with typical and atypical symptoms [9]. Chest discomfort at rest is the most common presenting symptom of ACS and affects approximately 79% of men and 74% of women present-

ing with ACS [10]. However, many patients may have atypical clinical symptoms at initial evaluation. Atypical clinical symptoms mean the absence of chest symptoms, and there are problems such as gastrointestinal, respiratory, or other symptoms [11]. Atypical presentation of ACS can range from non-chest pain to an epileptic seizure [12]. Approximately 40% of male and 48% of female patients present with nonspecific symptoms, such as dyspnea, either in isolation or, more commonly, in combination with chest pain [10]. Atypical presentation of ACS symptoms leads to delays in recognizing symptoms by both patients and healthcare providers and can result in misdiagnosis, delayed treatment, the start of fewer evidence-based therapies, and higher in-hospital morbidity and mortality [13, 14].

Research has shown that chest pain is more commonly observed in men, smokers, patients with a history of hypertension, hypercholesterolemia, and non-diabetics [15], and risk factors for atypical presentation include female gender, old age, comorbidities, and severe mental illness [12]. Therefore, factors such as age, sex, race, and underlying diseases can affect how symptoms appear [16]. In this case, identifying the relationship between risk factors and factors associated with early signs is crucial in the early diagnosis and initiation of appropriate treatment for patients with ACS, especially in the first 24 hours [15].

Given the diversity of ACS symptoms and limited data on atypical ACS presentation and their predictors and also considering the key role of nurses in accurate triage in the emergency department through collecting a clinical history and identifying cardiac patients, we intended to conduct this study. This research was conducted to determine atypical clinical symptoms and their predictors in patients with ACS referring to a specialized hospital in Rasht City in the north of Iran and to find what subgroups of patients are more likely to present with atypical ACS symptoms.

Materials and Methods

This research was a cross-sectional analytic study in which atypical clinical symptoms and their predictors were investigated in patients with ACS admitted to one of the specialized hospitals in Rasht City, Iran.

The required sample size was estimated as 1167 people, according to the results of a similar study [17], with 85% confidence and 80% test strength based on the odds ratio (OR) of diabetes mellitus in atypical patients (OR=1.4) and the frequency of atypical clinical symptoms equal to 8.7% in the mentioned study and considering the number of variables studied except for diabetes mellitus (K=30) and adding 10 samples per variable.

The inclusion criteria included hospitalization with a diagnosis of ACS (including ST-elevated acute myocardial infarction, non-ST-elevated acute myocardial infarction, and unstable angina) based on the diagnosis recorded in the medical record by the cardiologist, being 18 years and older, having a consent form to participate in the study, having the ability to communicate verbally and understand Persian language, having clinically stable conditions to answer questions, obtaining the minimum score in the Mini-Mental State Examination (MMSE) in patients older than 65 years, and having stable physical conditions (within the second 24 hours).

The study tool was a researcher-made checklist consisting of two parts: the patient characteristics and the file regarding ACS. The first part included three sections: demographic information (age, sex, marriage status, number of family members, female menopausal status, education, height, and weight), risk factors (hypertension, diabetes, hyperlipidemia, a history of smoking, alcohol use, drug use, hookah use, obesity, and a family history of heart disease), and disease-related factors (a history of renal failure, cardiac arrhythmia, pulmonary disease, brain disorders, blood disorders, and anemia, peripheral arterial disease, cancers, gastroesophageal reflux, pep-

tic ulcer, a history of taking sedatives and painkillers, a history of angiography, angioplasty, open-heart surgery, and a history of heart disease). The second part of the tool of study included symptoms of ACS. The symptoms of ACS inventory were used to determine the location of symptoms. In this study, the presence of pain or discomfort in the center or left side of the chest was considered the typical symptom, and pain or discomfort in other parts or the presence of other symptoms without pain or discomfort in the left side or center of the chest was considered as the atypical symptom [4]. About MMSE, we used the Persian version of the test. It seems that the Persian version of the test has good capability and reliability and can distinguish between people with dementia and healthy people. The test's total score is 30, and the difference score between people with dementia from healthy people is 22 [18].

The face validity method was used to determine the checklist's scientific validity so that it was given to 10 faculty members, and their opinions were applied.

After receiving ethical approval from Guilan University of Medical Sciences, the researcher attended the CCU, heart, and post-angiography wards of the specialized hospital in Rasht City, Iran. Sampling was done for 10 months, from December 6, 2019, to October 6, 2020. The samples were gradually selected and entered into the study by the researchers from those referring to the center, and data collection was done after obtaining their written informed consent.

To maintain stable conditions, all interviews were conducted within the second 24 hours after the patient's admission so that, in addition to having stable physical conditions, the problem of recalling the experienced symptoms due to a long-time stay in the hospital is minimized. The purpose of participating in the study was explained to each patient, and written consent was obtained.

The obtained data were analyzed by descriptive and inferential statistics using SPSS software version 21. For determining the factors associated with atypical clinical symptoms, a multiple logistic regression model using the backward LR (likelihood ratio) method was employed. Mean, median, standard deviation, frequency, frequency percentage, and 95% confidence interval were also used to describe the data.

Results

Based on the study results, 56.3% of the samples were male, and their Mean±SD age was 60.9±11.1 years. The 50-59 year age group (26.6%) had the highest frequency of participants. Regarding the education level, 44.4% were illiterate, and 37.8% had under-diploma education. Regarding the body mass index (BMI), 44.4% were overweight (25-29.9 kg/m²), and 34.2% were within normal weight (18.5-24.9 kg/m²) (Table 1).

In terms of risk factors and disease-related factors, obesity, hypertension, a family history of heart disease, hyperlipidemia, gastroesophageal reflux, and a history

of heart disease were detected in 64.3%, 55.1%, 52%, 50.2%, 39.6%, and 35.6% of the patients, respectively (Table 2).

The study showed that 71.9% of the samples had typical clinical symptoms of ACS, and 28.1% had atypical clinical symptoms before or during hospitalization. (It should be noted that 1.6% of the study samples had experienced both typical and atypical clinical symptoms, which due to the predominance of typical clinical symptoms, this group was considered as typical patients.)

Table 1. Demographic characteristics in patients with acute coronary syndrome (n=1167)

Variables	No. (%)	Mean±SD (Range)	
Age (y)	<50	208(17.8)	
	50-59	310(26.6)	
	60-69	391(33.5)	60.9±11.07 (28-94)
	70-79	193(16.5)	
	>80	65(5.6)	
Sex	Men	657(56.3)	
	Females	510(43.7)	
Marital Status	Single	11(0.9)	
	Married	1156(99.1)	
Number of family members	1	102(8.7)	
	2	438(37.5)	
	3-4	554(47.5)	2.79±1.14 (1- 9)
	5≤	73(6.3)	
Level of Education	Illiterate	518(44.4)	
	High school	441(37.8)	
	Diploma	161(13.8)	
	University	47(4.0)	
Body mass index (BMI)	Less than Normal	12(1.0)	
	Normal	399(34.2)	
	Overweight	514(44)	27.12±4.22 (16.61-52.44)
	Obesity	189(16.2)	
	Severe obesity	53(4.5)	

Table 2. The distribution of disease-related factors in patients with acute coronary syndrome (n=1167)

Risk Factors	No. (%) / Mean \pm SD (Ranged)
Hypertension	643(55.1)
Diabetes mellitus	415(35.6)
Hyperlipidemia	586(50.2)
Smoking	346(29.6)
Alcohol use	58(5.0)
Drug use	207(17.7)
Hookah use	13(1.1)
Obesity	750(64.3)
Family history of heart disease	607(52.0)
Kidney failure	96(8.2)
Cardiac arrhythmia	225(19.3)
Pulmonary disease	181(15.5)
Brain disease	83(7.1)
Blood disease	233(20.0)
Peripheral arterial disease	17(1.5)
Types of cancer	21(1.8)
Gastroesophageal reflux	462(39.6)
Peptic ulcer	88(7.5)
History of heart disease	415(35.6)
Taking sedatives and painkillers	410(35.1)
History of cardiac angiography	293(25.1)
History of cardiac angioplasty	118(10.1)
History of open-heart surgery	66(5.7)
Daily smoking (No.)	6 \pm 12 (0-80)
Frequency of monthly alcohol use	0.3 \pm 2.24 (0-30)
Frequency of daily drug use	0.28 \pm 0.68 (0-5)
Frequency of weekly hookah use	0.05 \pm 0.51 (0-9)
Duration of hookah use (m)	0.09 \pm 0.95 (0-20)
Duration of heart disease (y)	2.27 \pm 4.5 (0-40)

Table 3. The most important factors related to developing atypical clinical symptoms based on logistic regression by the backward LR method

Variables	Regression Coefficient	SE	P*	OR	95% CI	
					Lower	Upper
Age	-0.012	0.006	0.047	0.988	0.975	0.999
Alcohol use	0.621	0.293	0.034	1.860	1.047	3.303
Brain disease	0.859	0.244	0.001	2.361	1.463	3.811
Blood disease	0.376	0.162	0.021	1.456	1.059	2.002
Reflux disease	0.274	0.137	0.045	1.315	1.006	1.719
Constant)	-0.398	0.386	0.303	0.672		

* Logistic regression by backward LR method

In the present study, the most atypical clinical symptoms reported by the patients were shortness of breath (29.4%), back pain (18.3%), left shoulder pain (12.7%), and left-hand pain (12.3%), respectively (Figure 1).

To determine the level of predictability of individual-social factors, risk factors, and disease-related factors associated with atypical clinical symptoms in patients with ACS, due to the large sample size, all research variables with any significant level were entered into multiple logistic regression.

The results showed that among all individual and social variables and disease-related factors, sex (OR=1.28, 95% CI; 0.995-1.662, P=0.055), history of hyperlipidemia (OR=1.3, 95% CI; 0.992-1.684, P=0.05) and alcohol use (OR=1.9, 95% CI; 1.091-3.399, P=0.02) had statistically significant associations with developing atypical clinical symptoms and increased the odds of developing atypical symptoms. Also, smoking history was found to reduce the odds of developing atypical clinical symptoms as borderline (OR=0.7, 95% CI; 0.551-1.018, P=0.06).

Also, a history of brain diseases (OR=2.1, 95% CI; 1.316-3.283, P=0.002), reflux (OR=1.3, 95% CI; 0.982-1.666, P=0.068), and blood diseases (OR=1.5, 95% CI; 1.082-2.017, P=0.014) were identified as predictors of atypical clinical symptoms in this study.

After identifying individual, social, and disease-related factors predicting the occurrence of atypical clinical symptoms separately, all the variables examined above were entered into the logistic regression model using the backward LR method (Table 3). The results showed the most important predictors of atypical clinical symptoms of ACS were age (OR=0.98, 95% CI; 0.975-0.999, P=0.047), alcohol use (OR=1.86, 95%CI= 1.047-3.303,

P=0.034), brain diseases (OR=2.36, 95% CI; 1.463-3.811, P=0.001), blood diseases (OR=1.45, 95% CI; 1.059-2.002, P=0.021), and gastroesophageal reflux (OR=1.31, 95% CI; 1.006-1.719, P=0.045). The odds of developing atypical clinical symptoms decrease with age, but increased alcohol use, the development of brain diseases, blood diseases, and gastroesophageal reflux disease increases the odds of developing atypical clinical symptoms.

Discussion

The present study examined atypical clinical symptoms and their predictors in patients with ACS. The results showed that more than a quarter of patients experienced atypical clinical symptoms of ACS before or during referring to the hospital, and it is time to pay more attention to atypical clinical symptoms of ACS when evaluating patients. The most common atypical clinical symptoms experienced by the patients were shortness of breath, back pain, and left shoulder pain, in this order. In Coventry et al.'s study [19], a quarter of the study participants experienced atypical clinical symptoms, and the most common atypical clinical symptom was shortness of breath, and our study is consistent with this study. In Björck et al.'s study, 12.7% of patients presented without chest pain [20]. In King-Shier et al.'s study [13], 10.7% of the study participants experienced atypical clinical symptoms, and the most common atypical clinical symptom was shortness of breath. In another study [21], it was shown that only 41.2% of patients aged 75 years or older were referred to the emergency department with chest pain, and other referred patients had symptoms such as shortness of breath, weakness, indigestion, a disturbance in the general conditions, and delirium. Although the results of our study were different from the frequency of develop-

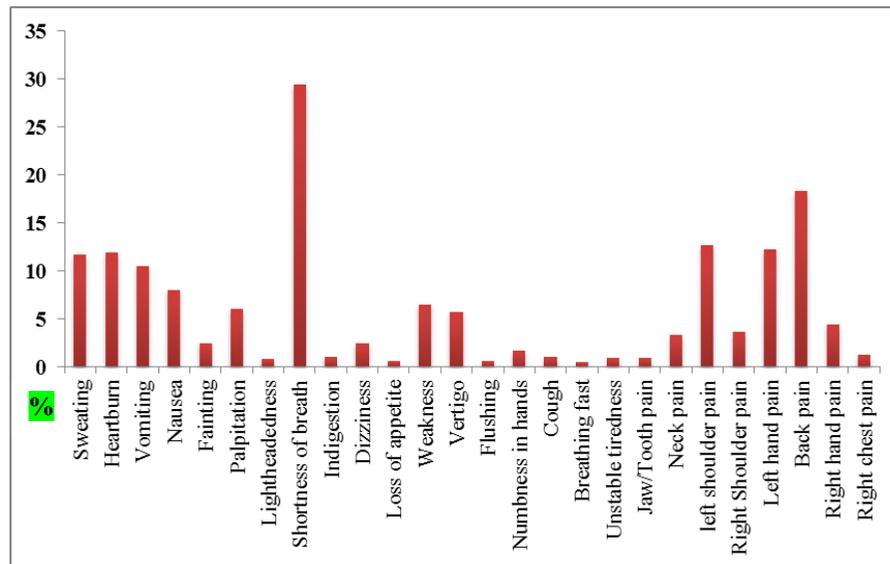


Figure 1. The frequency of atypical clinical symptoms in patients with acute coronary syndrome

ing atypical clinical symptoms in the mentioned studies but similar to our research, shortness of breath was the most common atypical clinical symptom experienced among the study participants. Perhaps the reason can be attributed to the lack of a history of heart disease, on the one hand, and anxiety due to the lack of a specific symptom in the chest, on the other hand. This condition emphasizes the importance of paying attention to the shortness of breath in patients referring to hospital triage units. Shortness of breath is a common symptom in a wide range of pulmonary diseases. Therefore, paying more attention to this and other symptoms and taking an accurate patient history is crucial in diagnosing and starting appropriate treatment.

In our study, age was recognized as one of the most important predictors of atypical clinical symptoms, so the odds of developing atypical clinical symptoms decreased with age. According to Chien et al.'s study [22], although the most common symptom of acute myocardial infarction in all age groups was chest pain, the odds of developing atypical clinical symptoms increase with age, so developing atypical symptoms in the elderly patient group (65 years of age and older) was more than younger patients. In many studies, it was shown that old age (mean age = 70 years of age and older) was identified as the predictor of atypical clinical symptoms [23, 24]. The findings of our study are inconsistent with the results of these studies, the reason may be attributed to the greater awareness of young and middle-aged people in the study population to atypical clinical symptoms and their further follow-up, and this issue further re-

veals the importance of promoting the elderly's awareness of atypical clinical symptoms.

In the present study, it was shown that smoking reduced the odds of developing atypical clinical symptoms as borderline, which is in line with the findings of Manfrini et al.'s study [17].

Coventry et al.'s study [19] showed an association between a history of brain stroke and developing acute myocardial infarction without chest pain. Also, Wu et al. [25], in their study, noted an association between atypical clinical symptoms and cerebrovascular events. In Manfrini et al.'s study [17], stroke was also found as a predictor of atypical clinical symptoms. The findings of our study are consistent with the results of the mentioned studies.

Regarding blood diseases and developing atypical clinical symptoms of ACS, no significant relationship was found in any of the reviewed studies. It can be mentioned as a new finding which shows the necessity of further studies and investigations in this field. In Manfrini et al.'s study [17], gastroesophageal reflux was more common in atypical patients than in typical patients, but this finding was not statistically significant. However, in our study, gastroesophageal reflux was found to be a predictor of atypical clinical symptoms. This difference may be attributed to differences in lifestyles, eating, and social habits of different societies, such as high-fat diets, alcohol use, and obesity. Also, the habit of lying on the back when the stomach is full varies from person to person, which can affect gastroesophageal reflux. In ad-

dition, some endocrine disorders, such as diabetes and hypothyroidism, can also cause delayed gastric motility and, therefore, reflux. So, these stated issues can introduce gastroesophageal reflux in our studied population as a predictor of atypical clinical symptoms.

Given cultural issues, the rarity of alcohol use in our society, and the unwillingness to respond correctly, many alcohol users may refuse to express it, and the statistics obtained in this field are incomplete. In any case, based on the results of our study, alcohol use was a predictor of atypical clinical symptoms. Most reviewed studies have not addressed the history of participants regarding alcohol use, which may be due to cultural differences in various societies. In the Sohn study [26], it was reported that current alcohol users were associated with chest pain and worse angiographic findings than those who had previously used alcohol. However, the findings of our study are not consistent with the results of the mentioned study because, in our study, alcohol use is associated with atypical symptoms.

This study had some limitations. Patients may not recall the pre-hospitalization signs and symptoms correctly, which is one of the questionnaire's limitations. To ease this limitation, all interviews were performed during the second 24 hours after patients' hospitalization so that patients reach a stable condition on the one hand, and to reduce the problem of recalling the experienced symptoms due to the long-time hospitalization.

Given that an atypical presentation of symptoms is not rare in patients with ACS, early presentation to hospitals for life-saving treatments among ACS patients, recognizing typical as well as atypical ACS symptoms, and educating people for appropriate care-seeking action comprise an important nursing intervention. In this study, more than a quarter of patients with ACS had atypical clinical symptoms; in addition, the study found that age, smoking, alcohol use, brain disease, blood disease, and reflux disease are the most important predictors of atypical clinical symptoms of ACS. Therefore, diagnosing atypical clinical symptoms of ACS and related factors with them can help in early diagnosis and more appropriate medical treatment.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of [Guilan University of Medical Sciences](#) with a code number of IR.GUMS.REC.1398.381.

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Authors' contributions

Study design and conceptualization: Masoumeh Rezvani, Majid Pourshaikhian, Mohammad-Taghi Moghadamnia, and Hojjat Houshyari Khah; Data collection: Masoumeh Rezvani; Data analysis: Ehsan Kazemnezhad Leili, Majid Pourshaikhian, and Mohammad-Taghi Moghadamnia; Initial draft preparation: Masoumeh Rezvani, Majid Pourshaikhian, Mohammad-Taghi Moghadamnia, and Hojjat Houshyari Khah; Final approval: All authors.

Conflict of interest

The authors declared no conflict of interest.

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