

Comparison of Outcomes in Patients With Acute Coronary Syndrome Presenting With Typical Versus Atypical Symptoms



Yoav Hammer, MD^{a,b}, Alon Eisen, MD^{a,b}, David Hasdai, MD^{a,b}, Ilan Goldenberg, MD^{b,c,d}, Nir Shlomo, BSc^d, Tal Cohen, BSc^d, Roy Beigel, MD^{b,c,d}, Ran Kornowski, MD^{a,c}, and Zaza Iakobishvili, MD, PhD^{a,c,e,*}

Although typical chest pain is an important clinical feature required for diagnosis of acute coronary syndrome (ACS), many patients present with atypical complaints. The full extent and implication of this presentation is largely unknown. The study aim was to evaluate possible relations and temporal trends between presenting symptoms and outcomes in patients with ACS. Data was obtained from the Acute Coronary Syndrome Israeli Survey on patients presenting with typical chest pain versus atypical complaints, including dyspnea, nonspecific chest pain, palpitations or other. Temporal trends analysis examined the early (2000 to 2006) versus the late (2008 to 2016) period. During 2000 to 2016, 14,722 patients with ACS were enrolled; 11,508 (79%) presented with typical chest pain and 3,214 (21%) with atypical complaints. Patients with atypical complaints were older, majority female, and had more co-morbidities ($p < 0.001$ for each). The 30-day major adverse cardiac events, 30-day mortality, and 1-year mortality rate were significantly higher in patients presenting with atypical complaints, (18% vs 13.5%, 7.7% vs 3.6%, and 15.6% vs 7.5%, respectively, $p < 0.001$ for each). Although 1-year mortality decreased significantly over the years in patients with typical chest pain, there were no significant changes in patients who presented with atypical complaints. These results were consistent in STEMI and non-STE-ACS patients. In conclusion, ACS patients who present with atypical complaints have a less favorable outcome compared with patients who present with typical chest pain, and failed to show an improvement in mortality over the past 2 decades. Identification and utilization of guideline-recommended therapies in these high-risk patients may improve their future outcome. © 2019 Elsevier Inc. All rights reserved. (Am J Cardiol 2019;124:1851–1856)

Typical chest pain is considered a cardinal clinical feature required for ACS diagnosis.¹ However, some patients present with atypical complaints, which may result in delayed diagnosis, both due to late hospital arrival and underdiagnoses by the primary caregiver.^{2,3} This population of patients with atypical complaints is not well-characterized, although some studies suggest a higher incidence in women and older patients^{3–5} and in patients with peripheral arterial disease⁶ or cancer.⁷ The data on relations between presenting symptoms and ACS outcomes are scarce and contradictory.^{8–10} We sought to investigate whether the presenting symptoms of ACS patients are associated with their outcomes, and to examine temporal trends in the

management and outcomes of these patients in the last 2 decades.

Methods

The ACS Israel Survey (ACSIS) is a biennial prospective national registry of all patients with ACS who are hospitalized in 25 coronary care units and cardiology departments in all general hospitals in Israel, over a 2-month period (March to April).^{11,12} Clinical, historical, and demographic data were recorded on prespecified forms for all admitted patients diagnosed with ACS. Patients for whom the diagnosis of ACS was uncertain were omitted from the registry. Admission and discharge diagnoses were recorded by the attending physicians based on electrocardiographic, clinical, and biochemical criteria. Patient management was at the discretion of the attending physicians. Each participating hospital received the approval of its institutional review board, and all patients signed an informed consent for participating in the ACSIS registry.

Included in the present study were all patients enrolled in the ACSIS registry during 2000–2016 (9 surveys on total – 2000, 2002, 2004, 2006, 2008, 2010, 2012, 2013, and 2016). Patients were divided into 2 main groups – the first group included patients who presented with typical chest pain (for whom typical chest pain was marked as their

^aCardiology Department, Rabin Medical Center – Beilinson Hospital, Petach Tikva, Israel; ^bSackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; ^cThe Leviev Heart Center, Sheba Medical Center, Tel Hashomer, Israel; ^dIsraeli Association for Cardiovascular Trials, Sheba Medical Center, Tel Hashomer, Israel; and ^eDepartment of Community Cardiology, Clalit Health Fund, Tel Aviv, Israel. Manuscript received July 24, 2019; revised manuscript received and accepted September 16, 2019.

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*Corresponding author: Tel: +972-544918209.

E-mail address: zaza.iakobishvili@gmail.com (Z. Iakobishvili).

primary complaint) and the second group included patients who presented with a primary complaint other than typical chest pain, for whom one of the following complaints was marked – nonspecific chest pain, dyspnea, palpitations, and other. In order to create a more homogenous population, we excluded patients admitted with an initial complaint of syncope or sudden cardiac death – for whom prognosis is known to be much worse. Patients who presented with typical chest pain and an additional complaint (e.g., dyspnea or palpitations) were classified as having a typical chest pain. Clinical outcomes included 30 days major adverse cardiac events (30 days MACE) which included death, myocardial infarction, stroke, unstable angina, stent thrombosis, urgent revascularization, 30 day all-cause mortality and 1-year all-cause mortality. One-year mortality data were ascertained through the use of the Israeli National Population Registry.

Patients' baseline characteristics were recorded for the 2 study groups. The groups were tested with Chi-square for categorical variables, and with Student's *t* test or Mann-Whitney-Wilcoxon test as appropriate for normal/non-normal distributed continuous variables. Temporal trends are presented, using the Chi-square test for trend. The cumulative probabilities of 1-year mortality for the study groups are graphically displayed according to the method of Kaplan and Meier, with comparisons of cumulative events by the log-rank test. Cox proportional hazards models for 1-year survival were conducted, adjusted for other explanatory covariates that were prespecified.

To reduce bias between the 2 study groups, a propensity score matching was performed. The propensity score evaluates the chance for typical chest pain with a logistic regression, given the following variables: age, gender, marital status, current smoker, hypertension, dyslipidemia, diabetes, family history of Coronary artery disease (CAD), previous coronary artery bypass grafting (CABG), previous cerebrovascular accident/transient ischemic attack, previous congestive heart failure (CHF), killip class, and previous chronic renal failure. The area under the curve was

0.67. The propensity score matching was performed with a caliper of 0.07 and a 1:3 matching. The cumulative probabilities of 1-year mortality for the matched groups are graphically displayed according to the method of Kaplan and Meier, with comparison of cumulative events by the log-rank test.

Results

During 2000 to 2016, 14,722 ACS patients were enrolled in the ACSIS registry. Of them, 11,508 (78%) presented with typical chest pain, and 3,214 (21%) with an atypical complaint. Patient characteristics are presented in [Table 1](#). In patients who presented with atypical features, 1,883 (58.6%) presented with nonspecific chest pain, 902 (28.1%) with dyspnea, 150 (4.7%) with palpitations, and 749 (23.3%) with a complaint classified as "other."

Compared with patients with typical chest pain, those who presented with atypical complaints were more likely to be older, female, and with more comorbidities such as hypertension, diabetes mellitus (DM), renal dysfunction, and heart failure (HF); but less likely to have dyslipidemia or be an active smoker.

Patients with atypical complaints were more likely to present with a non-ST elevation acute coronary syndrome (NSTEMI-ACS), compared with patients who presented with typical chest pain and had a significant delay in primary assessment, which was expressed as longer time to first electrocardiogram and longer duration from onset of pain to an examination by a primary caregiver ([Table 2](#)). Coronary angiography was performed less frequently in patients who presented with atypical complaints, compared with patients who presented with typical chest pain, which in turn resulted in lower rates of percutaneous coronary intervention for this group ([Table 2](#)).

The rate of 30-day MACE, 30-day mortality, and 1-year mortality were significantly higher in patients presenting

Table 1
Baseline characteristics

Variable	Chest pain		p Value
	Typical (n = 11,508)	Atypical (n = 3,214)	
Age (years, mean ± SD)	62.9 ± 12.7	66.8 ± 13.3	<0.001
Women	2,454 (21.3%)	931 (29.0%)	<0.001
Dyslipidemia*	7,597 (66.3%)	1,903 (59.6%)	<0.001
Hypertension	6,567 (57.3%)	2,050 (64.1%)	<0.001
Current smoker	4,488 (39.3%)	909 (28.6%)	<0.001
Diabetes mellitus	3,947 (34.4%)	1,276 (39.9%)	<0.001
Family history of coronary artery disease	2,844 (26.4%)	634 (21.1%)	<0.001
Body mass index (kg/m ²), mean ± SD	28.1 ± 11.5	27.7 ± 9.1	0.1
Prior myocardial infarction	3,492 (30.4%)	1,010 (31.5%)	0.2
Prior coronary artery bypass graft	1,096 (9.6%)	387 (12.1%)	<0.001
Chronic kidney disease [†]	1,094 (9.5%)	491 (15.4%)	<0.001
s/p Cerebrovascular event/Transient ischemic attack	825 (7.2%)	345 (10.8%)	<0.001
Estimated glomerular filtration rate (ml/min), median [Q1,Q3]	76 [60, 92]	68 [48, 85]	<0.001
Heart failure	720 (6.3)	426 (13.3)	<0.001

Values are presented as n (%) unless otherwise specified.

* Dyslipidemia was defined if the patient had a previous history of dyslipidemia, according to his personal medical file.

[†] CKD was defined as creatinine ≥1.5 mg/dl, creatinine clearance <50 ml/min, or on dialysis.

Table 2
Characteristics of index ACS

Variable	Presenting complaint		p Value
	Typical (n = 11,508)	Atypical (n = 3,214)	
STEMI on presentation	5,595 (48%)	1,100 (34%)	<0.001
Time from symptoms onset to first medical contact (minutes)	110 [40, 360]	120 [44, 443]	0.01
Time from first medical contact to first electrocardiogram (minutes)	21 [7, 62]	51 [18, 100]	<0.001
Time from pain onset to urgent primary percutaneous coronary intervention (minutes)	329 ± 554	487 ± 668	<0.001
Coronary angiography during hospitalization	9,550 (83.0%)	2,277 (70.8%)	<0.001
Percutaneous coronary intervention during hospitalization	7,368 (64.0%)	1,563 (48.6%)	<0.001
Coronary artery bypass graft during hospitalization	557 (4.9%)	143 (4.5%)	0.4
Normal sinus rhythm on electrocardiogram	9,039 (90.0%)	2,477 (84.5%)	<0.001
Killip class III/IV on admission	431 (3.8%)	482 (14.9%)	<0.001

Values are presented as n (%), mean ± SD or median [Q1, Q3].

STEMI = ST elevation myocardial infarction.

with atypical complaints, compared with those presented with typical chest pain (18% vs 13.5%, 7.7% vs 3.6%, and 15.6% vs 7.5%, respectively, $p < 0.001$ for each), (Table 3, Figure 1). This difference was evident both in patients with ST-elevation myocardial infarction (STEMI) and in those with NSTEMI-ACS (Figure 1S).

A temporal trends analysis comparing the period of 2000 to 2006 to that of 2008 to 2016, demonstrated a significant improvement in 1-year mortality in the late period for patients who presented with typical chest pain (6.2% vs 9%, $p < 0.001$), whereas patients who presented with atypical complaints showed no improvement in 1-year mortality over time (15.6% in both early and late period) (Table S4, Figure 2). This difference was evident both in STEMI and NSTEMI-ACS patients, but more pronounced in STEMI

Table 3
Clinical outcomes

Variable	Presenting complaint		p Value
	Typical	Atypical	
	Entire cohort		
30 day rehospitalization	2,017 (17.5%)	566 (17.6%)	0.6
30 day MACE	1,549 (13.5%)	580 (18.0%)	<0.001
30 day Mortality*	409 (3.6%)	246 (7.7%)	<0.001
1-year mortality* [†]	857 (7.5%)	497 (15.5%)	<0.001
	STEMI patients		
N	5,595	1100	
30 day rehospitalization	985 (17.6%)	181 (16.5%)	0.8
30 day MACE	815 (14.6%)	232 (21.1%)	<0.001
30 day Mortality*	274 (4.9%)	129 (11.8%)	<0.001
1-year mortality* [†]	455 (8.2%)	202 (18.5%)	<0.001
	NSTEMI-ACS patients		
N	5,906	2,112	
30 day rehospitalization	1,032 (17.4%)	385 (18.2%)	0.4
30 day MACE	733 (12.4%)	348 (16.5%)	<0.001
30 day mortality*	135 (2.3%)	117 (5.6%)	<0.001
1-year mortality* [†]	400 (6.8%)	294 (14.0%)	<0.001

Values are presented as n (%). Minor discrepancies are due to missing data.

* 30 day and 1 mortality refer to all-cause mortality.

[†] Percentages are Kaplan-Meier rates.

MACE = Death/Unstable angina pectoris/MI/cerebrovascular disease (CVA)/stent thrombosis/urgent revascularization.

patients (Figure S2). Although 30 day MACE decreased significantly over the past 2 decades in both groups, the improvement was more pronounced in patients with typical chest pain (18.2% vs 9.2%) than in those with atypical complaints (19.2% vs 14.9%). In patients with atypical complaints, NSTEMI-ACS patients did not show any improvement over time (Table S4).

After adjusting for different variables using a Cox regression analysis model, factors which were inversely associated with 1-year mortality were typical chest pain (hazard ratio [HR] 0.73, 95% confidence interval [CI] 0.65 to 0.82), index event during late period (2008 to 2016) (HR 0.71, 95% CI 0.63 to 0.81), and dyslipidemia (HR 0.66, 95% CI 0.58 to 0.74), whereas those associated with 1-year mortality were chronic kidney disease (CKD) (HR 1.89, 95% CI 1.66 to 2.15), previous HF (HR 1.8, 95% CI 1.57 to 2.07), DM (HR 1.45, 95% CI 1.29 to 1.62), age (HR 1.06, 95% CI 1.06 to 1.07), and female gender (HR 1.16, 95% CI 1.03 to 1.30) (Figure 3, Figure 3S). Propensity score analysis was performed that included the following variables: age, gender, current smoking, hypertension, dyslipidemia, DM, family history of coronary artery disease, previous myocardial infarction, previous coronary artery bypass grafting, previous cerebrovascular accident/transient ischemic attack, previous congestive HF, Killip class, and previous CKD. After the matching procedure, 7,623 and 2,421 patients with typical chest pain and atypical complaints remained, respectively. One-year mortality was still significantly higher in patients who presented with atypical complaints (11.8% vs 9.2%, $p < 0.001$; Figure 4), and this difference was evident mainly in STEMI patients (Figure 4S).

Discussion

In this study of patients with ACS in a prospective biennial national registry, it is evident that patients who presented with atypical complaints had increased rates of 1-year mortality, 30-day mortality, and 30-day MACE compared with those who presented with typical chest pain. Moreover, despite the improvement in different treatment strategies over the years, only patients who presented with typical chest pain had improved outcomes in the late (2008 to 2016) compared with the early period (2000 to 2006).

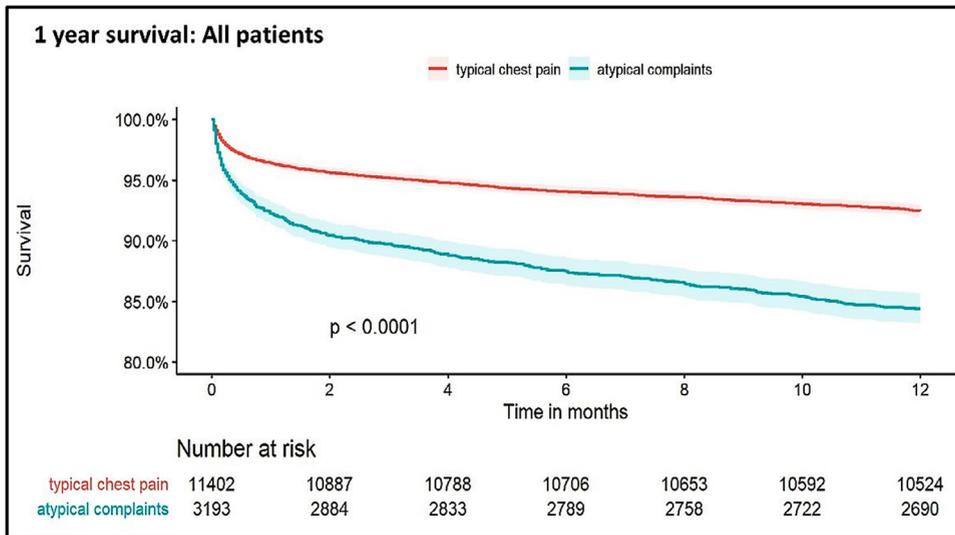


Figure 1. Kaplan-Meier curves for 1-year all-cause mortality according to symptoms at presentation.

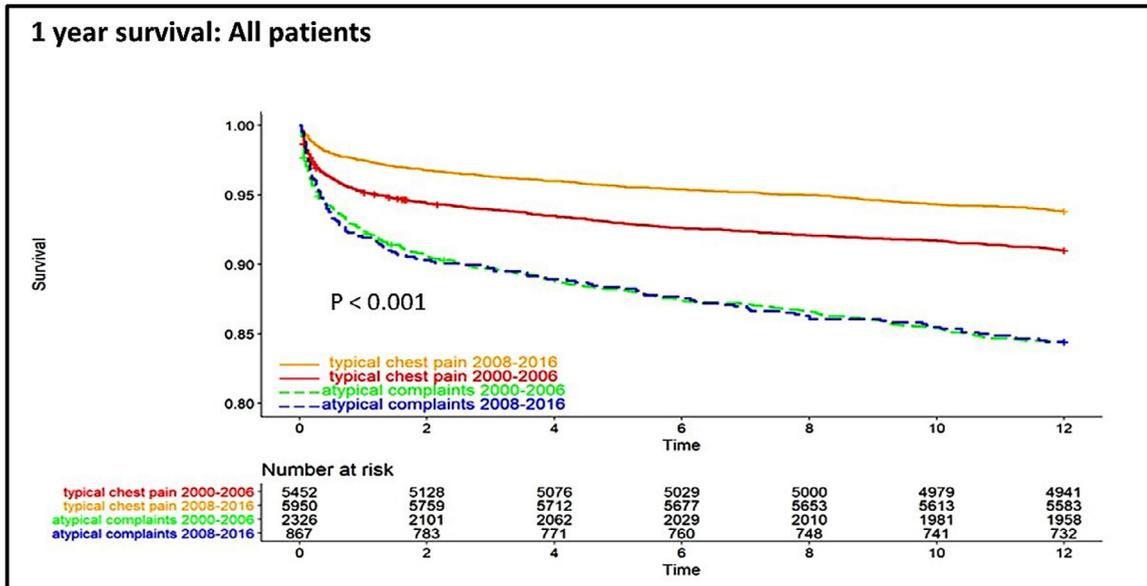


Figure 2. Temporal trends analysis for 1-year all-cause mortality according to symptoms at presentation during the early period (2000 to 2006) compared with late period (2008 to 2016).

Outcomes of patients who initially presented with atypical complaints did not seem to change over the years.

In order to provide the patient with prompt and adequate treatment, timely recognition of patients with ACS is crucial. One of 5 patients in our cohort presented with atypical complaints, an incidence that emphasizes the prevalence of these patients in our day to day routine. The evidence regarding the relation between presenting symptoms and outcomes in ACS patients is scarce, and few studies have examined this issue. King-Shier et al reported an increased incidence of atypical complaints in Chinese patients which led to worse outcomes, and Kirchberger et al reported an increased incidence of atypical complaints in patients with a previous diagnosis of peripheral arterial disease, which in turn led to longer prehospital delay and worse outcomes.^{6,13}

Patients who presented with atypical complaints tended to have more co-morbidity (e.g., CKD, HF, and DM). This

higher prevalence of different comorbidities might reflect a worse prognosis to begin with, but on the other hand might blunt typical anginal pain. Moreover, patients with atypical complaints waited a longer time for a first electrocardiogram to be performed (Table 2), a finding that was previously described by Alnsasra et al,¹⁴ that probably reflects the difficulties in recognizing these patients and providing them with appropriate treatment. The increased incidence of atypical complaints in females warrants a higher index of suspicion in this population.

Despite the inherent differences between our 2 cohorts, both a Cox regression analysis with multiple adjustments and a propensity score matching demonstrated that a first presentation without typical chest pain results in a worse prognosis (Figures 3 and 4). This worse prognosis is probably related to a delay in diagnosis, to an undertreatment because of uncertainty regarding the exact diagnosis and

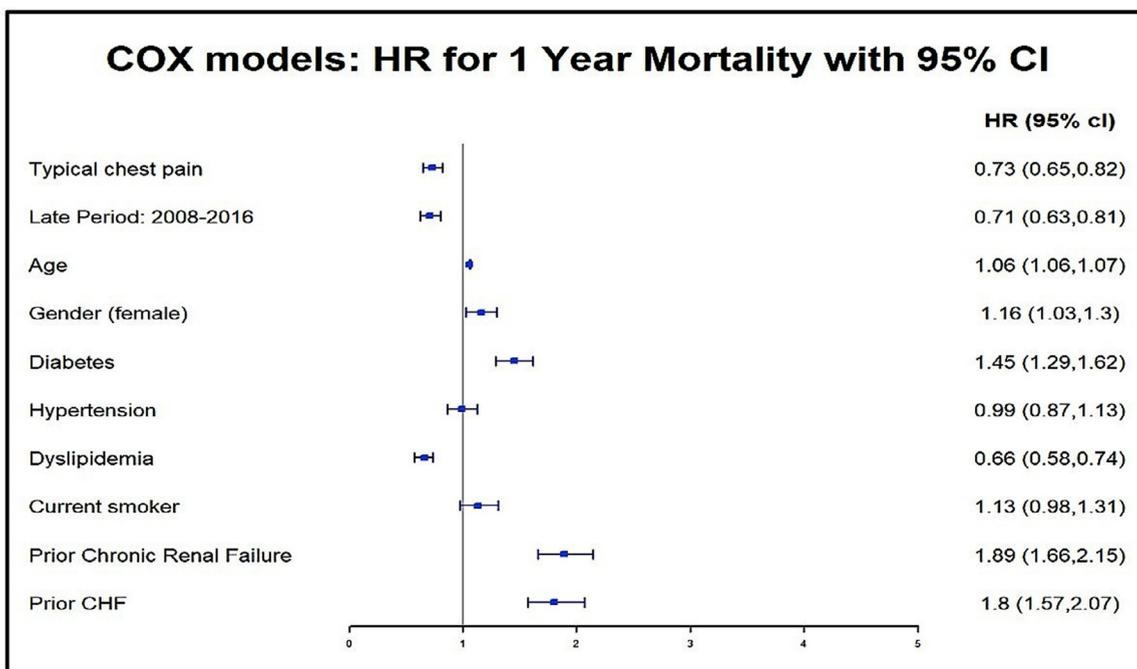


Figure 3. Cox regression analysis and hazard ratios (HR) for 1-year all-cause mortality according to different co-variables.

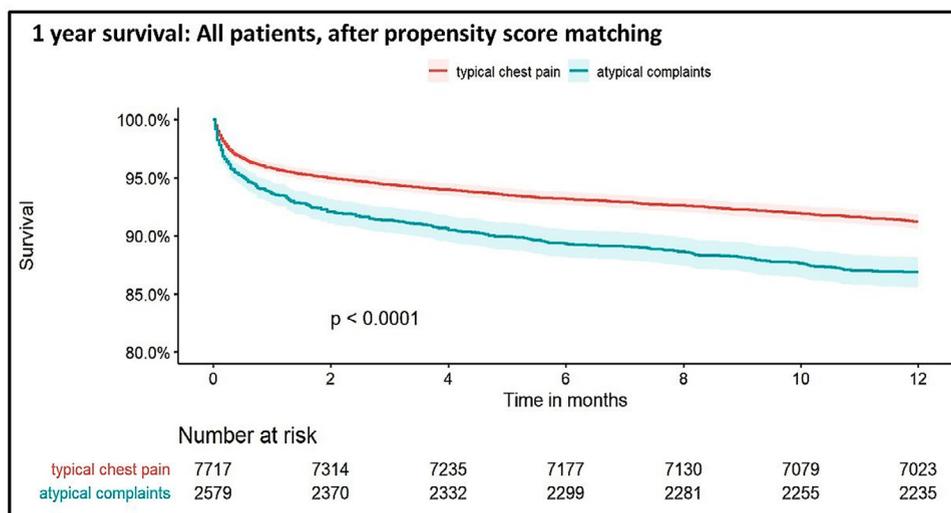


Figure 4. Kaplan-Meier curves for 1-year all-cause mortality after propensity score matching according to symptoms at presentation.

to an increased rate of other cardiac and noncardiac comorbidities.

Because STEMI and NSTEMI-ACS patients do not always share the same population characteristics (STEMI patients tend to be younger, more often male, and have fewer comorbidities), a separate analysis was performed for STEMI and NSTEMI-ACS patients. Although worse outcomes were found in both STEMI and NSTEMI-ACS patients who presented with atypical complaints, STEMI patients who presented with atypical features had worse outcomes compared with NSTEMI-ACS patients (Figure S2).

Despite continuous efforts to improve diagnostic and treatment strategies in ACS, a temporal trends analysis revealed that for patients who presented with atypical

complaints, outcomes have not significantly improved over the past 2 decades. This finding emphasizes that these patients might “slip under our radar” and not be treated properly. An effort should be made to timely identify these patients by careful history taking, a proper physical examination, and the use of highly sensitive biomarkers and different imaging modalities.

Our study has several limitations. Results are derived from the ACSIS registry, which is comprised of a population admitted to cardiology wards and intensive cardiac care units nationwide with the diagnosis of ACS, therefore patients who were admitted to an internal medicine ward might not be represented in this study. In addition, the ACSIS registry has limited follow-up data beyond the

index hospitalization with respect to long-term medical treatment, adherence to treatment, cause of death, and additional interventions. Therefore, the long-term outcomes may be significantly influenced by these and other postdischarge intervening factors. In addition, our study is an observational study, and therefore a definite causal relation between the natures of the initial complaint of the patient to their outcomes cannot be ascertained. Last, despite existence of clear definitions of “typical” and “atypical” in the ACSIS operating manual, our data collection may be susceptible to ascertainment bias.

In conclusion, ACS patients who present with atypical complaints have a less favorable outcome compared with patients who present with typical chest pain. Moreover, ACS patients who presented with atypical complaints failed to show an improvement in mortality over the past 2 decades. Identification and utilization of guideline-recommended therapies in these high-risk patients may improve their future outcome.

Disclosures

The authors have no conflicts of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.amjcard.2019.09.007>.

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