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Association between comorbidities and absence of chest pain in acute coronary syndrome with in-hospital outcome

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ABSTRACT

Background: To evaluate the impact of comorbidities on the management and outcomes of acute coronary syndrome (ACS) patients without chest pain/discomfort (i.e. ACS without typical presentation).
Methods: Of the 11,458 ACS patients, enrolled by the International Survey of Acute Coronary Syndrome in Transitional Countries (ISACS-TC; ClinicalTrials.gov: NCT01218776), 8.7% did not have typical presentation at the initial evaluation, and 40.2% had comorbidities. The odds of atypical presentation increased proportionally with the number of comorbidities (odds ratio [OR]: 1, no-comorbid; OR: 1.64, 1 comorbidity; OR: 2.52, 2 comorbidities; OR: 4.57, ≥3 comorbidities).
Results: Stratifying the study population by the presence/absence of comorbidities and typical presentation, we found a decreasing trend for use of medications and percutaneous intervention (OR: 1, typical presentation and no-comorbidities; OR: 0.70, typical presentation and comorbidities; OR: 0.23, atypical presentation and no-comorbidities; OR: 0.18, atypical presentation and comorbidities). On the opposite, compared with patients with typical presentation and no-comorbidities (OR: 1, referent), there was an increasing trend ($p < 0.001$) in the risk of death (OR: 2.00, OR: 2.52 and OR: 4.83) in the above subgroups. However, after adjusting for comorbidities, medications and invasive procedures, atypical presentation was not a predictor of in-hospital death. Independent predictors of poor outcome were history of stroke (OR: 2.04), chronic kidney disease (OR: 1.57), diabetes mellitus (OR: 1.49) and underuse of invasive procedures.
Conclusions: In the ISACS-TC, atypical ACS presentation was often associated with comorbidities. Atypical presentation and comorbidities influenced underuse of in-hospital treatments. The latter and comorbidities are related with poor in-hospital outcome, but not atypical presentation, per se.

1. Introduction

One of the great achievements of the last decades has been the reduction in mortality from acute coronary syndromes (ACS) [1]. Unfortunately, this progress, attributable to advances in medical and percutaneous treatments, is not complete. ACS patients without typical chest pain still have very high in-hospital mortality [2,3], mostly due to late hospital arrival and low use of intensive treatments [2–4]. The problem is particularly relevant for the large number of patients involved [2–10]. Understanding the factors associated with atypical ACS presentation may be of help to educate patients and clinicians for a more rapid identification and cure [11,12]. Although old age, female gender, and diabetes mellitus are clinical factors frequently accompanying atypical presentation of myocardial ischemia [2–5,13,14], the population of patients with atypical ACS presentation is still not well characterized.

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Previous stroke, heart failure, chronic kidney disease (CKD) and chronic obstructive pulmonary disease (COPD) have been reported to be associated with acute myocardial ischemia without typical presentation (i.e. chest pain/discomfort) [3–10]. However, data on typical versus atypical ACS presentation and comorbidities are limited. Whether these patients are also less likely to receive treatments and to have favorable outcomes in the management of ACS is unclear. We hypothesized that the rate of patients with comorbidities would have been prevalent among patients with atypical ACS presentation compared to those with the typical one, and that the interaction between atypical presentation and comorbidities would have influenced ACS patient's treatment and outcome.

2. Methods

2.1. Study population

The International Survey of Acute Coronary Syndrome in Transitional Countries (ISACS-TC) is a large, prospective, multinational registry of patients who have been hospitalized with the entire spectrum of ACSs in 57 hospitals in the East Europe. Details of the ISACS-TC registry have been reported previously (ClinicalTrials.gov Identifier: NCT01218776) [15–22]. Patients included in this analysis were enrolled between 2010 and 2015. In the ISACS-TC, the diagnosis of ACS was determined by trained physician at each local hospital, taking into account clinical history, physical examination, electrocardiogram (ECG), cardiac biomarkers, angiography, and/or postmortem findings [23]. Demographic and medical data were collected for all patients during hospitalization. Patients with contraindications to class I evidence-base-drugs for ACS treatment [24,25] (aspirin, ACE-inhibitors, beta-blockers, heparin, and reperfusion) were excluded from our analysis. The study was approved by the local research ethics committee from each hospital. Patients provided written consent for evaluation of their medical notes and monitoring of their health status. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

2.2. Study design and study variables

The study aims to examine the relationship among patients hospitalized with ACS between presence/absence of typical presentation and comorbidities (primary objective) and presence/absence of typical presentation, comorbidities and outcome (secondary objective). Measure of outcome was in-hospital death.

Among patient presenting with ACS, the typical presentation was defined by the presence of typical chest pain. Typical chest pain was defined as any symptom of chest pain/discomfort (pressure, heaviness, tightness, or sensation); or arm, neck, jaw or epigastria pain preceding the diagnosis of ACS. Typical presentation may have included, but not limited, other symptoms (dyspnea, diaphoresis, nausea/vomiting, palpitation). Specific symptoms, other than presence/absence of typical chest pain, were not abstracted from medical records.

Comorbidity was defined as any distinct clinical condition characterized by organ damage, ascertained before the index ACS and existing simultaneously, but independently of ACS. Specifically, we predefined to investigate the presence of: diabetes mellitus, heart failure (NYHA class II, III and IV), chronic kidney disease (CKD, glomerular filtration rate < 90 mL/1.73 m^2 for ≥3 months), chronic obstructive pulmonary disease (COPD), peripheral artery disease (PAD), gastro-esophageal reflux disease (GERD), active cancer (disease still active or documented active in the last 6 months), and stroke. Hypertension without history of organ damage was not considered comorbidity. Behavioral (i.e., drugs abuse) or mental disorder was not abstracted from medical records.

2.3. Statistical analysis

The descriptive results were displayed by the presence or absence of typical ACS presentation and by the presence or absence of comorbidities. Comparisons between groups were made either by χ^2 test for categorical variables, the *t*-test for continuous and the nonparametric Wilcoxon rank sum test for median comparison, as appropriate. Logistic regression analysis was used to assess the factors associated with atypical ACS presentation (i.e. absence of chest pain/discomfort). Baseline characteristics, cardiovascular risk factors and medical history were analyzed, reporting the odds ratio (OR) for atypical ACS presentation. Multiple stepwise logistic regression ($p < 0.02$) analysis was performed by introducing all variables that in the univariate analysis presented a level of significance ≤0.05. In multiple regression analysis, all variables were dichotomized except for age, which was handled as a continuous variable. To assess the interaction of comorbidities and symptoms presentation, the following 4 dummy variables were created: patients with typical ACS presentation and comorbidities, patients with typical ACS presentation and no-comorbidities, patients with atypical ACS presentation and comorbidities, and patients with atypical ACS presentation and no-comorbidities. Score test for trend of odds was used in order to examine trend across ordered groups for the use of evidence-based medication and invasive procedures. Multiple stepwise logistic regression ($p < 0.02$) analysis was also used to identify independent predictors of mortality (in-hospital death), introducing all variables that in univariate analysis presented a level of significance ≤0.05; for excluding possible bias caused by early death, individuals who died within 24 h since hospital admission were excluded. Statistical evaluation was performed using the STATA 11 (Stata Corporation, TX, USA). Values for $p \leq 0.05$ were regarded significant.

3. Results

ISACS-TC enrolled 14,701 patients between 2010 and 2015. After the exclusion of 3243 patients with missing data on symptom presentation or presence of comorbidities, the final study population was 11,458 ACS patients. The mean (SD) age was 63.4 (12.1) years; 7778 (67.9%) subjects were men. There were 7203 (62.9%) with ST-segment elevation myocardial infarction (STEMI), 2855 (24.9%) patients with non STEMI (NSTEMI), and 1394 (12.2%) patients with unstable angina. Patients with atypical ACS presentation at the initial evaluation were 995 (8.7%).

Patients with comorbidities (diabetes mellitus, heart failure, CKD, COPD, stroke, PAD, GERD or active cancer) represented the 40.2% of the overall study population. The prevalence of 0, 1, 2 and ≥3 comorbidities was 59.8%, 30.1%, 7.7% and 2.4%, respectively. Patients with comorbidities were 38.7% and 55.2% of those with and without typical presentation, respectively ($p < 0.001$).

3.1. Baseline characteristics

Comparisons of demographic and clinical variables between patients with typical ACS presentation and those with atypical ACS presentation are shown in Table 1. More women (10.5%) than men (7.8%) presented

Table 1
Baseline characteristics of patients presenting with and without typical chest pain/discomfort and diagnosed with ACS; The ISACS-TC 2010–2015.

Variable	Typical presentation n = 10463	Atypical presentation n = 995	p-value
Age, year	62.9 ± 12.1	67.8 ± 12.2	<0.001
Age ≥ 80 years	888 (8.6)	174 (17.7)	<0.001
Male	7170 (68.5)	608 (61.1)	<0.001
Hypertension	7156 (70.0)	702 (74.1)	0.008
Smoking	4750 (47.2)	321 (34.7)	<0.001
Hypercholesterolemia	4050 (46.2)	309 (40.2)	0.002
Family history of CAD	3621 (38.7)	310 (36.9)	0.288
Diabetes mellitus	2602 (25.8)	336 (35.6)	<0.001
Prior ACS	1791 (17.1)	201 (20.2)	0.014
Prior unstable angina	119 (1.1)	5 (0.5)	0.064
Prior myocardial infarction	1699 (16.2)	198 (19.9)	0.003
Prior stable angina	1122 (10.7)	124 (12.5)	0.092
Prior PCI	1464 (14.0)	111 (11.2)	0.013
Prior CABG	322 (3.1)	39 (3.9)	0.15
History of congestive HF	516 (4.9)	91 (9.8)	<0.001
History of stroke	428 (4.1)	94 (9.4)	<0.001
History of PAD	282 (2.7)	54 (5.4)	<0.001
History of COPD	402 (3.8)	65 (6.5)	<0.001
History of CKD	542 (5.2)	123 (12.4)	<0.001
History of GERD	285 (2.7)	34 (3.4)	0.20
History of active cancer	186 (1.8)	24 (2.4)	0.15
Prior medications			
Aspirin	1979 (28.1)	203 (33.3)	0.007
Beta blockers	2198 (31.0)	216 (34.4)	0.071
ACE-inhibitors	2987 (41.8)	266 (42.2)	0.82
Statins	1466 (20.6)	129 (20.9)	0.87
>12 h from onset to hospital	2800 (28.6)	416 (47.0)	<0.001
Clinical findings at initial evaluation			
ST-segment elevation	6787 (64.9)	416 (41.9)	<0.001
Killip class ≥ 2	1581 (15.1)	298 (29.9)	<0.001

Values are means ± SD or numbers (%) of observations.
ACE, angiotensin converting enzyme; CABG, coronary artery by-pass graft; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; GERD, gastro-esophageal reflux disease; HF, heart failure; PAD, peripheral artery disease; PCI, percutaneous coronary intervention.