

Atypical manifestations of acute coronary syndrome – throat discomfort: a multi-center observational study

Yanqing Fang^{1,2,*}, Xiaoting Cheng^{1,2,*}, Wenhui Peng^{3,*}, Xueying Chen (✉)⁴, Chunping Tang⁵, Qiusheng Huang⁶, Sihai Wu⁷, Yibo Huang^{1,2}, Fanglu Chi^{1,2}, Matthew R. Naunheim⁸, Huawei Li^{1,2}, Bing Chen (✉)^{1,2}, Yilai Shu (✉)^{1,2}

¹ENT Institute and Department of Otorhinolaryngology, Eye & ENT Hospital, State Key Laboratory of Medical Neurobiology, Fudan University, Shanghai 200031, China; Institutes of Biomedical Sciences, Fudan University, Shanghai 200031, China; ²NHC Key Laboratory of Hearing Medicine, Fudan University, Shanghai 200031, China; ³Department of Cardiology, Shanghai Tenth People's Hospital, School of Medicine, Tongji University, Shanghai 200072, China; ⁴Department of Cardiology, Zhongshan Hospital, Fudan University, Shanghai Institute of Cardiovascular Diseases, National Clinical Research Center for Interventional Medicine, Shanghai 200032, China; ⁵Department of Cardiology, The First Affiliated Hospital, Nanjing Medical University, Nanjing 210029, China; ⁶Department of Otolaryngology, Affiliated Hospital of Jiangsu University, Zhenjiang 212001, China; ⁷Department of Otorhinolaryngology, The Second People's Hospital of Wuxi, Nanjing Medical University, Wuxi 214002, China; ⁸Department of Otolaryngology-Head and Neck Surgery, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA 02114, USA

© Higher Education Press 2021

Abstract To present the clinical characteristics and the misdiagnosis rate of acute coronary syndrome manifested primarily as throat discomfort, we conducted a multicentric and retrospective study in the cardiology and otorhinolaryngology departments. Records of patients with primary complaint of throat discomfort, absence of chest pain at onset, and an ultimate diagnosis of acute coronary syndrome, as well as patients with pharyngitis (as controls) were collected from May 2015 to April 2016. The patients' main manifestations were compared. Logistic regression results showed that chest tightness, dyspnea, perspiring, and exertional throat symptoms were significantly associated with acute coronary syndrome, with odds ratios of 8.3 (95% CI 2.2–31.5), 10.9 (95% CI 1.8–66.9), 25.4 (95% CI 3.6–179.9), and 81.2 (95% CI 13.0–506.7). A total of 25 (56.82%) out of 44 acute coronary syndrome patients, who were first admitted to the otorhinolaryngology department, were misdiagnosed, with a 12% (3/25) mortality rate. Throat discomfort can be the principal manifestation of acute coronary syndrome. Such patients exhibit high misdiagnosis and mortality rates. Exertional throat symptoms, chest tightness, perspiring, and dyspnea were important indicators of acute coronary syndrome in patients whose main complaint was throat discomfort. The awareness of this condition will result in prompt diagnosis and reduce morbidity and mortality.

Keywords acute coronary syndrome (ACS); throat discomfort (TD); throat pain; cardiology departments; non-cardiologic physicians

Introduction

Cardiovascular disease has become the leading cause of morbidity and mortality worldwide [1,2]. Acute coronary syndrome (ACS), which includes acute myocardial infarction (AMI) and unstable angina, requires immediate attention and intervention [3]. However, some ACS

patients, who do not experience chest pain, are misdiagnosed and inadequately treated [4]. Prompt treatment upon the onset of AMI symptoms decreases mortality, morbidity, and health care costs while increasing quality of life [5]. Moreover, the atypical presentation of ACS is a significant independent predictor of in-hospital mortality [6].

Chest pain is the most frequent symptom in patients with acute coronary artery disease (CAD) [7]. However, acute CAD can be manifested as chest discomfort (e.g., tightness, heaviness, squeezing, and pressure) without chest pain [8]. Approximately 25% of AMI cases were discovered during routine electrocardiograph (ECG) [9], and half of these cases are “silent” without any symptoms.

Received April 29, 2020; accepted April 8, 2021

Correspondence: Yilai Shu, yilai_shu@fudan.edu.cn;

Bing Chen, bingchen@fudan.edu.cn;

Xueying Chen, chen.xueying@zs-hospital.sh.cn

*These authors contributed equally to this work.

In addition, Canto *et al.* reported that 33% of the patients diagnosed with MI did not present chest pain in the hospital [8]. The atypical presentations of AMI include back, epigastrium, throat, and jaw pain [4,6,10]. These patients may therefore visit a non-cardiac physician, including a gastroenterologist, otolaryngologist, or dentist on the first onset. AMI with throat distress may first be observed at the otolaryngologist's office. Typical AMI presenting as throat distress has been reported [10–13], and the clinical characteristics of such patients based on large-scale studies are lacking. In the present study, we will first present a multi-center study of 101 ACS patients whose symptoms manifested primarily as throat discomfort (ACS-TD) and focus on their clinical characteristics and misdiagnosis rate.

Materials and methods

This research was conducted in accordance with the ethical standards of the Internal Review Board of Eye Ear Nose and Throat (Eye & ENT) Hospital, Fudan University in Shanghai. A retrospective study of medical records from the cardiology and ENT departments at six tertiary hospitals (Department of Otorhinolaryngology in the Eye & ENT Hospital, Fudan University; Affiliated Hospital of Jiangsu University and The Second People's Hospital of Wuxi, Nanjing Medical University; Department of Cardiology in Zhongshan Hospital, Fudan University; Shanghai Tenth People's Hospital, School of Medicine, Tongji University; and The First Affiliated Hospital of Nanjing Medical University) was conducted from May 2015 to April 2016. The population of interest (ACS-TD group) included patients who appeared at the above cardiology or ENT departments during the study period with a chief complaint of throat discomfort without obvious chest pain at their first presentation and turned out to be ACS. The control (TD) group also include an equal number of patients who experienced throat discomfort that turned out to be pharyngitis diagnosed according to the criteria of Shulman *et al.* and Chiappini *et al.* [14,15]. Patients in the TD group were included by sequence during the study period to exclude possible bias. One and a half years after the study period, these patients had no diagnosis of ACS known from their follow-up. All included patients had full knowledge of the information needed. Records of these patients were reviewed for basic demographic information, clinical characteristics of the chief complaint, local findings, symptom profile, risk factors, ECG information and coronary imaging data, and treatment information. In patients with non-painful throat discomfort, if the discomfort of the throat could not be described, we noted "throat distress." The throat discomfort was classified into sore throat and non-painful throat discomfort (including throat distress that could not be clearly described, throat

burning, foreign body sensation, throat tightness, constricting or choking of throat, throat itch, dry throat, and sense of phlegm). In the present study, the severity of the throat symptoms was also studied. For the grading of the severity of the throat symptoms, we referred to previous studies associated with pain [16]. Graded pain forms were collected from all patients, with 0–10 points on a numerical scale. The severity of the throat symptoms was determined based on the degree of interference with patients' function, with ratings of 1–4 corresponding to mild degree, 5–6 to moderate degree, and 7–10 to severe degree. In addition, an exertional throat symptom was defined as throat discomfort associated with activity, including fast walking, running, biking, climbing stairs, heavy lifting, and exercise in cold weather, which could increase myocardial oxygen consumption. The history of cardiovascular disease encompasses prior myocardial infarction (MI), prior percutaneous transluminal coronary intervention (PCI), and any prior CAD. However, their history of previous cardiac events occurred at least 1.5 years before this attack.

The AMI diagnostic criteria were consistent with the guidelines of AMI in the Joint European Society of Cardiology (ESC) of 2017 [17] and ACS diagnostic criteria used in 2015 version by the ESC [18].

Statistical analysis was performed using the χ^2 test for categorical variables and the *t*-test for continuous variables in Stata 10.0 (the StataCorp, College Station, TX, USA). To evaluate the association between ACS and main symptoms of patients, we carried out logistic regression. Statistical significance level was defined at $P < 0.05$.

Results

Patient recruitment

From May 2015 to April 2016, 101 patients were included in the ACS-TD group, and 101 were included in the TD group. Among the ACS-TD patients, 44 (43.56%) were first evaluated by an otolaryngologist, and 57 (56.44%) were initially treated by a cardiologist. Among the 44 ACS-TD patients first presented at the ENT department, 25 patients received pharyngitis therapy without any relief of throat symptoms with a misdiagnosis rate of 56.82% (25/44). All the 101 TD patients were first evaluated by an otolaryngologist and received pharyngitis therapy.

Basic information of ACS-TD and TD groups

For the ACS-TD group, with an average age of 58.1 (33–81) years, 38 (37.62%) patients were female and 63 (62.38%) male. The ACS-TD group had more male than female patients. For the TD group with a mean age of 55.9 (36–77) years, 41 (40.59%) patients were female and 60 (59.41%) male. No significant difference was observed in

age ($P = 0.121$) or gender ($P = 0.665$) between the two groups (Table 1).

Clinical characteristics of throat symptom, concomitant symptoms, exertional throat symptom, and the association between ACS and main symptoms and local examination

Manifestation of throat discomfort

Clearly stated pharyngeal pain was present in 48 (47.52%) patients in the ACS-TD group (Table 2). Non-painful pharyngeal symptoms included vaguely stated distress ($n = 32$; 31.68%), tightness ($n = 17$; 16.83%), choking sensation ($n = 9$; 8.91%), and itching in throat ($n = 1$; 0.99%).

The control TD group presented more often with foreign body sensation (33.66% vs. 0.00%, $P < 0.001$), throat itch (11.88% vs. 0.99%, $P < 0.01$), dry throat (12.87% vs. 0.00%, $P < 0.001$), and sense of phlegm (7.92% vs. 0.00%, $P < 0.01$) and less often with vaguely stated distress (8.91% vs. 31.68%, $P < 0.001$), tightness (4.95%

vs. 16.83%, $P < 0.01$), and compressing sensation (0.00% vs. 8.91%, $P < 0.01$) in the throat compared with the ACS-TD group. The percentage of patients with pharyngeal pain was similar to that in the ACS-TD group (45.54% vs. 47.52%, Table 2). In addition, the distribution of the degree of throat symptoms was similar between the two groups ($P > 0.05$).

In addition, we divided ACS patients into two subgroups, namely, the AMI (acute coronary infarction, $n = 59$) and unstable angina (UA, $n = 42$) groups. The throat symptoms were compared between the groups. Results showed significant differences for throat pain (55.9%, $n = 33$ in AMI subgroup vs. 35.7%, $n = 15$ in UA subgroup, $P = 0.045$) and throat tightness (10.2%, $n = 6$ in AMI subgroup vs. 26.3%, $n = 11$ in UA subgroup, $P = 0.034$), but not for other throat symptoms.

Concomitant symptoms

In the ACS-TD group, 25 (24.75%) patients manifested throat discomfort without other concomitant symptoms. Among these patients, 11 (10.89%) patients complained

Table 1 Demographic information and past medical history of patients in ACS-TD^a group and TD^b group with the P value

Demographic information		ACS-TD group ($n = 101$)	TD group ($n = 101$)	P value
Age (year, mean \pm SD)		58.1 \pm 10.1	55.9 \pm 9.3	0.121
Gender	Female	38	41	0.665
	Male	63	60	
Past medical history	Hypertension	68 (67.32%)	22 (21.78%)	<0.001
	Smoking	31 (30.69%)	21 (20.79%)	0.108
	Diabetes	17 (16.83%)	8 (7.92%)	0.054
	Prior cardiovascular disease ^c	10 (9.90%)	7 (6.93%)	0.447
	History of pharyngitis	9.90% (10/101)	32.67% (33/101)	<0.001

^aACS-TD, acute coronary syndrome patients with throat symptoms mainly. ^bTD, pharyngitis patients with throat discomfort. ^cPrior cardiovascular disease, including prior myocardial infarction (MI), prior percutaneous transluminal coronary intervention (PCI) and any prior coronary artery disease (CAD).

Table 2 Detailed information on throat symptoms between ACS-TD^a group and TD^b group (number of patients (%))

Detailed information on throat symptoms		ACS-TD group ($n = 101$)	TD group ($n = 101$)	P value
Throat symptoms	Throat pain	48 (47.52%)	46 (45.54%)	0.778
	Throat distress	32 (31.68%)	9 (8.91%)	<0.001
	Throat tightness (or constricting)	17 (16.83%)	5 (4.95%)	0.007
	Compressing of throat (i.e., obstruction, or choking)	9 (8.91%)	0 (0.00%)	0.002
	Foreign body sensation	0 (0.00%)	34 (33.66%)	<0.001
	Throat itch	1 (0.99%)	12 (11.88%)	0.002
	Dry throat	0 (0.00%)	13 (12.87%)	<0.001
	Sense of phlegm	0 (0.00%)	8 (7.92%)	0.004
	Throat burning	0 (0.00%)	1 (0.99%)	0.316

^aACS-TD, acute coronary syndrome patients with throat symptoms mainly. ^bTD, pharyngitis patients with throat discomfort.

about throat pain solely, 5 (4.95%) patients complained about throat tightness sensation solely, 6 (5.94%) patients complained about throat distress solely, 2 (1.98%) patients complained about both throat pain and tightness or choking.

The 76 other patients in the ACS-TD group complained about other non-specific concomitant symptoms. Among these conditions, chest tightness ($n = 47$, 46.53%), dyspnea ($n = 14$, 13.86%), and perspiration ($n = 34$, 33.66%) presented most frequently. In the TD group, 90 (89.10%) cases had only throat discomfort, and the 11 (10.89%) other patients complained about other atypical symptoms, such as chest tightness ($n = 5$, 4.95%), dyspnea ($n = 5$, 4.95%), and perspiration ($n = 2$, 1.98%), which presented most frequently. These main three concomitant symptoms were distributed differently in the ACS-TD group and TD groups, with statistical significance ($P < 0.05$, Table 3).

Other rare presentations accompanied by throat discomfort were pain elsewhere (tooth, shoulder, and neck), neck distress, nausea, vomiting, dizziness, weakness, fatigue, palpitations, blackouts, and syncope, with an overall occurrence rate of 7.92% (eight cases) in the ACS-TD group and 0.99% (one case) in the TD group, with significant difference ($P = 0.017$, Table 3).

Exertional throat symptoms

Exertional throat symptoms were observed in 57.42% (58 cases) of the ACS-TD group and 1.98% (2 cases) in the TD group, with significant difference ($P < 0.001$).

Logistic regression models for the analysis of the associations between main symptoms and ACS

We conducted logistic regression models to analyze the associations between the main symptoms and ACS. Chest tightness, dyspnea, perspiration, and exertional throat symptoms were positively and significantly associated with ACS with odds ratios (ORs) of 8.3 (95% CI 2.2–31.5), 10.9 (95% CI 1.8–66.9), 25.4 (95% CI 3.6–179.9), and 81.2 (95% CI 13.0–506.7), as shown in Table 4. Logistic regression was also performed for the diagnosis and number of symptoms, and the results showed that the number of the four symptoms listed above was significantly correlated with ACS ($P < 0.001$, OR = 19.3). The risk of ACS diagnosis increased by 18-fold for each additional symptom compared with the control group. Age, gender, and the severity of throat symptoms had no significant effects on the incidence of ACS.

Table 3 Information about the cardiac symptoms of ACS-TD^a group and TD^b group and *P* values (number of patients (%))

Cardiac symptoms and past medical history information		ACS-TD group ($n = 101$)	TD group ($n = 101$)	<i>P</i> value
Cardiac symptoms	Chest tightness	47 (46.53%)	5 (4.95%)	<0.001
	Dyspnea	14 (13.86%)	5 (4.95%)	0.030
	Perspiring	34 (33.66%)	2 (1.98%)	<0.001
	Rare symptoms ^c	8 (7.92%)	1 (0.99%)	0.017
	History of chest pain	3 (2.97%)	3 (2.97%)	1.00
	No cardiac symptoms	25 (24.75%)	90 (89.10%)	<0.001

^aACS-TD, acute coronary syndrome patients with throat symptoms mainly. ^bTD, pharyngitis patients with throat discomfort. ^cRare symptoms, pain elsewhere (tooth, shoulder, and neck), neck distress, nausea, vomiting, dizziness, weakness, fatigue, palpitations, blackouts, and syncope, apart from any throat pain or discomfort and any chest discomfort, perspiring and dyspnea.

Table 4 Odds ratio of the associations between main symptoms and ACS

Variables	Coefficients ^a	SE ^b	<i>P</i> value	OR ^c	95% CI
Constant value	-1.875	2.190	0.392	0.15	–
Gender	0.681	0.619	0.271	1.98	0.59–6.64
Age	0.021	0.033	0.516	1.02	0.96–1.09
Chest tightness	2.111	0.683	0.002	8.26	2.16–31.52
Dyspnea	2.395	0.923	0.009	10.97	1.80–66.90
Perspiring	3.235	0.999	0.001	25.40	3.59–179.91
Exertional throat symptoms	4.397	0.934	<0.001	81.17	13.00–506.71
Severity of throat symptoms	0.047	0.384	0.902	1.05	0.49–2.23
Usefulness of medicine for pharyngitis	-3.016	0.602	<0.001	0.05	0.02–0.16

^aCoefficients, β estimates from logistic regression models. ^bSE, standard error. ^cOR, odds ratio.

Local examinations

All ACS-TD patients mainly complained of throat discomfort. However, on local laryngology examination, no patients showed obvious acute inflammation. Among the three death cases, all patients suffered from severe throat symptoms without distinctive local acute inflammation, and this phenomenon was not consistent with their symptoms. For TD patients, throat symptoms presented with varying degrees of pharyngeal inflammation on local examination.

Risk factors

In the present study, the common risk factors were extracted from the medical histories of the ACS-TD patients, including prior cardiovascular disease (as stated in the section of “Materials and methods”), hypertension, smoking, and diabetes. Regarding the risk factors for cardiovascular disease, patients in the ACS-TD group more often experienced hypertension (67.32% vs. 21.78%, $P < 0.001$) and less often had smoking (30.69% vs. 20.79%, $P = 0.108$) and diabetes (16.83% vs. 7.92%, $P = 0.054$) compared with the patients in TD group (Table 3). In addition, a history of chronic laryngitis was significantly less likely observed in the ACS-TD patients compared with the TD patients (9.90% vs. 32.67%, $P < 0.001$).

Electrocardiogram (ECG) information, treatment, misdiagnosis, and mortality rate

ECG information

Among the 101 ACS-TD patients, 59 (58.42%) patients were diagnosed with AMI with 38 (37.62%) cases of ST-elevation (STE) infarction and 21 (20.79%) cases of non-ST-elevated myocardial (NSTEMI). The most common infarct location was the inferior wall (20 cases), followed by the anterior wall (14 cases), high lateral wall (2 cases), and extensive anterior wall (2 cases). Among the 21 cases with NSTEMI infarction, two cases showed normal ECG, three cases with non-fatal arrhythmia, and 16 cases of others which included mild abnormality of ST and/or T, of which neither belonged to classical AMI nor any arrhythmias.

Treatment, misdiagnosis, and mortality rate

For treatment, pharyngitis medicine did not work in all 29 ACS-TD patients (29/29, 100%) and in 13.86% (14/101) TD patients ($P < 0.001$). A total of 92 out of 101 (91.09%) ACS-TD patients underwent successful stent implantation. The six other ACS-TD patients received coronary angiography and medical therapy, in which three patients

refused stent implantation. 98 of the ACS-TD patients recovered, whereas three AMI patients died after unsuccessful cardiopulmonary resuscitation. For the three cases of death, all patients were first admitted to the ENT department and were misdiagnosed.

Referred and unreferred ACS patients first admitted to the ENT department and their results

A total of 44 ACS-TD patients were first treated by the otolaryngology team rather than by the cardiology team. Among these patients, 19 patients were immediately referred for further cardiac evaluation, while the 25 remaining patients (25/44, 56.82%) received pharyngitis treatment with a diagnosis of “chronic pharyngitis” and were inappropriately discharged from the ENT department.

By comparing the information between the two subgroups of ACS-TD patients, namely, the unreferred ($n = 25$) and the other patients ($n = 76$) that include 19 cases referred from the ENT department and 57 cases first admitted to the cardiology department, significant differences were found for symptoms of throat pain and distress and history of pharyngitis (Table 5). The number of patients (20 cases, 80%) who complained of throat pain in the unreferred group was significantly higher than those in the referred group (28 cases, 36.84%, $P < 0.001$). None of the patients in the unreferred group complained of throat distress, and this figure is significantly less than that in the referred groups (32 cases, 42.11%, $P < 0.001$). Eight (32.00%) out of 25 unreferred patients and two (2.63%) referred patients had a history of pharyngitis, with significant difference ($P < 0.001$). No significant difference was found in the demography, other throat symptoms, cardiac symptoms, and other past medical history between unreferred and referred patients ($P > 0.05$).

Discussion

AMI remains the leading cause of death worldwide [19]. The AMI mortality is 67.6 deaths/100 000 inhabitants [20]. An estimated 1.1 million people in the US experience AMI each year [21]. The atypical presentation of AMI without chest pain is more common than imagined and is associated with increased mortality, which is nearly two or three times higher in patients presenting without chest pain [8]. In the emergency department, approximately 2.1%–2.3% of the ACS patients are mistakenly discharged, mostly because of atypical symptom presentation [22]. Failure to recognize an atypical presentation of ACS can be fatal. The misdiagnosis rate of ACS was high in the present study (i.e., 56.82%) compared with the above-cited literature being worthy of increased attention.

Craniofacial pain may be the only symptom of cardiac ischemia (6%) or sole manifestation of AMI (3%) [23].

Table 5 Detailed information of comparison between the unreferred and the other patients including 19 cases referred from the ENT department and 57 cases first admitted to cardiology of ACS-TD^a patients (number of patients (%))

		Unreferred patients (<i>n</i> = 25)	19 cases referred from ENT department and 57 cases first admitted to cardiology department (<i>n</i> = 76)	<i>P</i> value
Age (year, mean±SD)		55.24±8.54	59.00±10.46	0.107
Gender	Female	8 (32.00%)	30 (39.47%)	0.503
	Male	17 (68.00%)	46 (60.53%)	
Throat symptoms	Throat pain	20 (80.00%)	28 (36.84%)	<0.001
	Throat distress	0 (0.00%)	32 (42.11%)	<0.001
	Throat tightness (or constricting)	5 (20.00%)	12 (15.79%)	0.625
	Compressing of throat (i.e., obstruction or choking)	2 (8.00%)	7 (9.21%)	0.854
	Foreign body sensation	0 (0.00%)	0 (0.00%)	1.00
	Throat itch	0 (0.00%)	1 (1.325)	0.654
	Dry throat	0 (0.00%)	0 (0.00%)	1.00
	Sense of phlegm	0 (0.00%)	0 (0.00%)	1.00
	Throat burning	0 (0.00%)	0 (0.00%)	1.00
Cardiac symptoms	Chest tightness	9 (36.00%)	38 (50.00%)	0.223
	Dyspnea	4 (16.00%)	10 (13.16%)	0.721
	Perspiring	10 (40.00%)	24 (31.58%)	0.440
	Rare symptoms ^b	2 (8.00%)	6 (7.89%)	0.987
	History of chest pain	0 (0.00%)	3 (3.95%)	0.313
	No cardiac symptoms	6 (24.00%)	19 (25.00%)	0.920
Past medical history	Hypertension	16 (64.00%)	52 (68.42%)	0.683
	Smoking	5 (20.00%)	26 (34.21%)	0.181
	Diabetes	3 (12.00%)	14 (18.42%)	0.457
	Prior cardiovascular disease ^c	0 (0.00%)	10 (13.16%)	0.056
	History of pharyngitis	8 (32.00%)	2 (2.63%)	<0.001

^aACS-TD, acute coronary syndrome patients with throat symptoms mainly. ^bRare symptoms, pain elsewhere (tooth, shoulder, neck), neck distress, nausea, vomiting, dizziness, weakness, fatigue, palpitation, blackouts, and syncope, apart from any throat pain or discomfort and any chest discomfort, perspiring and dyspnea. ^cPrior cardiovascular disease, including prior myocardial infarction (MI), prior percutaneous transluminal coronary intervention (PCI), and any prior coronary artery disease (CAD).

The most common site of pain reported in this region is the throat, followed by the jaw, neck, teeth, and ear [24]. However, throat pain has rarely been studied. In the present study, 25 (24.75%) patients manifested throat discomfort without other concomitant symptoms. Among these symptoms, a special throat symptom, i.e., throat tightness or choking sensation as the only manifestation, presented on five (4.95%) ACS patients, which had not been reported. Symptom recognition at onset is paramount to the successful management and early treatment and improvement of the care quality of such patients. To our knowledge, this analysis represents the largest observational study that compares the detailed characteristics, treatments, and outcomes of ACS patients presenting primarily with throat symptoms and those of common pharyngitis.

All ACS-TD patients in the present study complained mainly of throat symptoms, and the main complaint of throat discomfort was not alleviated by conventional drugs for pharyngitis, but all symptoms were alleviated by

cardiac treatment, including cardiac medications and stent implantation apart from the three death cases. In Schelbert *et al.*'s study, pressure and burning were the two pain quality descriptors frequently used by patients when describing the facial pain from cardiac origin [25]. In the present study, however, throat burning was not an indicator for distinguishing ACS from TD. A total of 25 (24.75%) patients manifested throat discomfort without other concomitant symptoms. Among these symptoms, a special throat symptom called throat tightness or choking sensation is the only manifestation presented on five (4.95%) ACS patients, and this condition has not been reported. The symptoms of throat distress, tightness, and compressing sensation were highly suggestive of ACS other than TD.

In the current analysis, the most frequent concomitant symptoms with throat discomfort in ACS patients was chest tightness (46.53%), followed by perspiration (33.66%) and dyspnea (13.86%). These symptoms along with exertional throat symptoms (57.42%) were

significantly associated with the risk of ACS, thus supporting previous reports on the symptoms linked with ACS. For example, a study by Milner *et al.* found a relationship between perspiration and dyspnea and ACS [26]. Moreover, chest pressure is a significant predictor for the diagnosis of ACS [27]. Further throat pain on exertion indicates cardiac events [11]. These symptoms could not reasonably be explained by ordinary pharyngitis but rather by cardiovascular disease [28]. Moreover, these symptoms along with other rare cardiac symptoms of ACS (Table 3) were probably not well-appreciated by non-cardiac physicians. The lack of chest pain at the onset of the disease and ignoring or misinterpreting other concurrent symptoms could lead to misdiagnosis.

Based on the analysis of the referred and unreferred ACS-TD patients, who presented at the ENT department initially (Table 5), patients with a history of pharyngitis were more likely to be misdiagnosed with chronic pharyngitis rather than referred to the cardiology department. Although a history of pharyngitis was presented more in the TD group than in the ACS-TD groups with significant difference ($P < 0.001$), the history of previous pharyngitis causes misdiagnosis of ACS patients with such history. However, regarding that the distribution of the degree or severity of throat symptoms was similar between the two groups, the severity of the throat symptoms is not an indicator for distinguishing ACS from TD, but could be the reason for unreferred cases, delaying the correct diagnosis.

Regarding the local examination of ACS patients, no obvious acute inflammation existed during their local examinations, consistent with previous reports [10–13]. For the infarction site of ACS patients in the present study, throat discomfort of cardiac origin was mostly associated with inferior wall ischemia, and this condition was the same as those in previous reports regarding craniofacial pain of cardiac origin [29]. This condition is associated with the function of vagal nerve [29]. The vagus and sympathetic nerve supplies both the heart and throat. The terminal end of the cervical sympathetic ganglion is located at the pharynx. When ACS occurs, pain or discomfort may be experienced in the throat, manifested as radiating or referred pain.

Overall, our study provided new methods for the prompt screening out of the possible at-risk patients of ACS by clinical manifestation. Notably, the presentation of chest tightness, perspiration, and dyspnea in patients who complain of throat discomfort and patients with exertional throat symptoms should lead to exploration of possible cardiac problems. This information should be noted by cardiac physicians, as well as non-cardiac doctors, especially ENT doctors. Further examinations, including ECG, myocardial enzyme detection, and laboratory microbiologic testing [15,17,18] could help distinguish ACS from common pharyngitis.

The study is naturally limited by its retrospective nature. Further prospective studies enrolling all patients with throat pain could potentially elucidate the prevalence of cardiac causes of throat pain. A potential ramification of our study for clinical practice is to educate patients and clinicians of the ACS presentation as throat discomfort. Physicians should have a high index of suspicion in patients with throat discomfort associated with ACS features. ECG and cardiac testing can be of help in such cases where alternate diagnoses are suspected.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (Nos. 81822011 and 81771013) and Clinical Research Plan of SHDC (No. SHDC2020CR4083).

Compliance with ethics guidelines

Yanqing Fang, Xiaoting Cheng, Wenhui Peng, Xueying Chen, Chunping Tang, Qiusheng Huang, Sihai Wu, Yibo Huang, Fanglu Chi, Matthew R. Naunheim, Huawei Li, Bing Chen, and Yilai Shu declare that they have no competing interests. This research was conducted in accordance with the ethical standards of the Internal Review Board of Eye & ENT Hospital, Fudan University.

References

1. Joseph P, Leong D, McKee M, Anand SS, Schwalm JD, Teo K, Mente A, Yusuf S. Reducing the global burden of cardiovascular disease, part 1: the epidemiology and risk factors. *Circ Res* 2017; 121(6): 677–694
2. GBD 2015 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016; 388(10053): 1603–1658
3. Grech ED, Ramsdale DR. Acute coronary syndrome: unstable angina and non-ST segment elevation myocardial infarction. *BMJ* 2003; 326(7401): 1259–1261
4. Ryan CJ, DeVon HA, Zerwic JJ. Typical and atypical symptoms: diagnosing acute coronary syndromes accurately. *Am J Nurs* 2005; 105(2): 34–36
5. Li PW, Yu DS. Predictors of pre-hospital delay in Hong Kong Chinese patients with acute myocardial infarction. *Eur J Cardiovasc Nurs* 2018; 17(1): 75–84
6. El-Menyar A, Zubaid M, Sulaiman K, AlMahmeed W, Singh R, Alsheikh-Ali AA, Al Suwaidi J; Gulf Registry of Acute Coronary Events (Gulf RACE) Investigators. Atypical presentation of acute coronary syndrome: a significant independent predictor of in-hospital mortality. *J Cardiol* 2011; 57(2): 165–171
7. Khafaji HA, Suwaidi JM. Atypical presentation of acute and chronic coronary artery disease in diabetics. *World J Cardiol* 2014; 6(8): 802–813
8. Canto JG, Shlipak MG, Rogers WJ, Malmgren JA, Frederick PD,

- Lambrew CT, Ornato JP, Barron HV, Kiefe CI. Prevalence, clinical characteristics, and mortality among patients with myocardial infarction presenting without chest pain. *JAMA* 2000; 283(24): 3223–3229
9. Kannel WB, Abbott RD. Incidence and prognosis of unrecognized myocardial infarction. An update on the Framingham study. *N Engl J Med* 1984; 311(18): 1144–1147
 10. Yanagawa Y, Nishimura M, Ohkawara J, Hasegawa K, Yamane M. Acute myocardial infarction presenting with pharyngeal pain alone. *J Emerg Med* 2012; 43(5): e287–e288
 11. Sone M, Koizumi A, Tamiya E, Inoue K, Ebihara I, Koide H, Okazaki S, Kato Y, Suzuki J, Daida H. Angina pectoris with pharyngeal pain alone: a case report. *Angiology* 2009; 60(2): 259–261
 12. Ocak U, Avsarogullari L, Kaya MG, Ozmen Y, Taslidere B, Guldeste EA, Yakar S. Acute coronary syndrome presenting with earache and sore throat. *Am J Emerg Med* 2014; 32(5): 487.e5–6
 13. Amirhaeri S, Spencer D. Myocardial infarction with unusual presentation of otalgia: a case report. *Int J Emerg Med* 2010; 3(4): 459–460
 14. Shulman ST, Bisno AL, Clegg HW, Gerber MA, Kaplan EL, Lee G, Martin JM, Van Beneden C; Infectious Diseases Society of America. Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: 2012 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2012; 55(10): e86–e102
 15. Chiappini E, Regoli M, Bonsignori F, Sollai S, Parretti A, Galli L, de Martino M. Analysis of different recommendations from international guidelines for the management of acute pharyngitis in adults and children. *Clin Ther* 2011; 33(1): 48–58
 16. Serlin RC, Mendoza TR, Nakamura Y, Edwards KR, Cleeland CS. When is cancer pain mild, moderate or severe? Grading pain severity by its interference with function. *Pain* 1995; 61(2): 277–284
 17. Ibáñez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimský P. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Rev Esp Cardiol (Engl Ed)* 2017; 70(12): 1082
 18. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S; ESC Scientific Document Group. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016; 37(3): 267–315
 19. Reed GW, Rossi JE, Cannon CP. Acute myocardial infarction. *Lancet* 2017; 389(10065): 197–210
 20. Meza JS. Mortality caused by acute myocardial infarction in Chile in the period 1990–2001. *Rev Med Chil* 2004; 132(10): 1227–1233 (in Spanish)
 21. Mahmoud AN, Elgendy IY, Mojadidi MK, Wayangankar SA, Bavry AA, Anderson RD, Jneid H, Pepine CJ. Prevalence, causes, and predictors of 30-day readmissions following hospitalization with acute myocardial infarction complicated by cardiogenic shock: findings from the 2013–2014 national readmissions database. *J Am Heart Assoc* 2018; 7(6): e008235
 22. Pope JH, Aufderheide TP, Ruthazer R, Woolard RH, Feldman JA, Beshansky JR, Griffith JL, Selker HP. Missed diagnoses of acute cardiac ischemia in the emergency department. *N Engl J Med* 2000; 342(16): 1163–1170
 23. Kreiner M, Okeson JP, Michelis V, Lujambio M, Isberg A. Craniofacial pain as the sole symptom of cardiac ischemia: a prospective multicenter study. *J Am Dent Assoc* 2007; 138(1): 74–79
 24. Myers DE. Vagus nerve pain referred to the craniofacial region. A case report and literature review with implications for referred cardiac pain. *Br Dent J* 2008; 204(4): 187–189
 25. Schelbert EB, Rumsfeld JS, Krumholz HM, Canto JG, Magid DJ, Masoudi FA, Reid KJ, Spertus JA. Ischaemic symptoms, quality of care and mortality during myocardial infarction. *Heart* 2008; 94(2): e2
 26. Milner KA, Funk M, Arnold A, Vaccarino V. Typical symptoms are predictive of acute coronary syndromes in women. *Am Heart J* 2002; 143(2): 283–288
 27. Mirzaei S, Steffen A, Vuckovic K, Ryan C, Bronas U, Zegre-Hemsey J, DeVon HA. The quality of symptoms in women and men presenting to the emergency department with suspected acute coronary syndrome. *J Emerg Nurs* 2019; 45(4): 357–365
 28. Kreiner M, Falace D, Michelis V, Okeson JP, Isberg A. Quality difference in craniofacial pain of cardiac vs. dental origin. *J Dent Res* 2010; 89(9): 965–969
 29. Kreiner M, Alvarez R, Waldenström A, Michelis V, Muñoz R, Isberg A. Craniofacial pain of cardiac origin is associated with inferior wall ischemia. *J Oral Facial Pain Headache* 2014; 28(4): 317–321