BMJ Open

Impact of infection in patients with non-ST elevation acute coronary syndrome undergoing percutaneous coronary intervention: insight from a multicentre observational cohort from China

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To cite: Chen P-Y, Liu Y-H, Duan C-Y, *et al*. Impact of infection in patients with non-ST elevation acute coronary syndrome undergoing percutaneous coronary intervention: insight from a multicentre observational cohort from China. *BMJ Open* 2020;**10**:e038551. doi:10.1136/bmjopen-2020-038551

► Prepublication history and additional material for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2020-038551).

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Received 16 March 2020
Revised 07 August 2020
Accepted 10 August 2020

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ABSTRACT

Objective We aimed to describe the association between in-hospital infection and prognosis among patients with non-ST elevation acute coronary syndrome (NSTE-ACS) who received percutaneous coronary intervention (PCI).

Design This observational cohort originated from a database of patients with NSTE-ACS who underwent PCI from 1 January 2010 to 31 December 2014.

Setting Five centres in South China.

Participants This multicentre observational cohort study consecutively included 8197 patients with NSTE-ACS who received PCI. Only patients with adequate information to diagnose or rule out infection were included. Patients were excluded if they were diagnosed with a malignant tumour, were pregnant or presented with cardiogenic shock at the index date. Patients were grouped by whether they had in-hospital infection or not.

Primary and secondary outcome measures The primary outcome was all-cause death and major bleeding during hospitalisation. The secondary outcomes included all-cause death and major bleeding during follow-up and in-hospital myocardial infarction.

Results Of the 5215 patients, 206 (3.95%) acquired infection. Patients with infection had a higher rate of in-hospital all-cause death and major bleeding (4.4% vs 0.2% and 16.5% vs 1.2%, respectively; p<0.001). After adjusting for confounders, infection remained independently associated with in-hospital and long-term all-cause death (OR, 13.19, 95% CI 4.59 to 37.87; HR, 2.03, 95% CI 1.52 to 2.71; p<0.001) and major bleeding (OR, 10.24, 95% CI 6.17 to 16.98; HR, 5.31, 95% CI 3.49 to 8.08; p<0.001). A subgroup analysis confirmed these results.

Conclusions The incidence of infection is low during hospitalisation, but is associated with worse in-hospital and long-term outcomes.

Strengths and limitations of this study

- We widely included patients with non-ST elevation acute coronary syndrome who received percutaneous coronary intervention in China.
- The characteristics of infection were reported in detail, including the time and type of infection.
- Validation was done in different subgroups and variables, which is the best we can do using the database.
- Potential bias may have been neglected due to study design.
- Aetiology of infection was not investigated, which may have limited further exploration of the mechanism of infection.

INTRODUCTION

Acute coronary syndrome (ACS) is a leading cause of death in China and around the world.[1] As compared with patients with ST elevation myocardial infarction (STEMI), patients with non-ST elevation acute coronary syndrome (NSTE-ACS) have shown improved outcomes after extensive use of an invasive approach, but continue to show a higher burden of comorbidities and prior cardiovascular events, which might expose them to iatrogenic and infective complications.[2] Identification of patients at risk of worse outcomes could contribute to targeted intervention, help direct care, reduce the incidence of subsequent events and thus optimise resource utilisation.

Infection can activate the platelets and the coagulation system, resulting in a prothrombotic environment.[3 4] Moreover, infection is an uncommon but important comorbidity in patients undergoing percutaneous coronary intervention (PCI).[5–7] Although the reported incidence is less than 4%, infection has been proven to be associated with an increased risk of cardiovascular events among patients with STEMI.[8 9] However, data on infection among

patients with NSTE-ACS remain scant. Only one study involving 174 octogenarian patients with ACS evaluated the impact of infection on clinical outcomes.[10] Thus, we aimed to assess the incidence of infection and its association with short-term and long-term clinical outcomes in patients with NSTE-ACS undergoing PCI.

METHODS

Study design and patients

This observational cohort study consisted of consecutive patients with NSTE-ACS undergoing PCI from January 2010 to December 2014 at five hospitals in China. Only patients with adequate information to diagnose or rule out infection were included. Patients were excluded if they were diagnosed with a malignant tumour or infection before the index date, were pregnant or presented with cardiogenic shock. The method used to search and identify appropriate patients with NSTE-ACS has been outlined previously.[11]

Data collection and procedures

Data on demographics, patient history, laboratory tests, examinations and medication history were collected by investigators during the first interview after admission. Medications and PCI procedures were applied according to international guidelines and clinical evidence.[12]

Infection during index hospitalisation was diagnosed according to the presence of any symptoms, signs and/or laboratory results indicating infection. Once confirmed by the infection control doctors service, appropriate antibiotics were prescribed.[8] Infection was classified as pulmonary, urinary tract infection (UTI) or others (including non-pulmonary/non-urinary sepsis and cellulitis), based on the clinical records during hospitalisation. Community-acquired pulmonary infection was defined by a diagnosis of infection within the first 72 hours of hospital admission, and hospital-acquired pulmonary infection was defined as those occurring after the first 72 hours, and were diagnosed in accordance with the criteria established by the Centers for Disease Control and Prevention.[13]

Clinical outcomes and follow up

The primary outcome was in-hospital all-cause death and in-hospital major bleeding as defined by the Bleeding Academic Research Consortium definition (grades 3–5).[14] The secondary outcomes were (1) major adverse clinical events (MACE), consisting of all-cause death, myocardial infarction or major bleeding during hospitalisation; and (2) all-cause death or major bleeding during follow-up.

All patients were followed up by trained nurses via telephone interviews or clinic visits from November 2015 to December 2016. Relevant information was also collected from the residence registration system and from the clinical records of the patients who were readmitted. The details of clinical events and follow-up have been previously described.[11] All adverse clinical events were evaluated by an independent clinical events committee that was masked to the details of infection.

Statistical analysis

All patients were divided into groups with or without infections. Continuous variables with a normal distribution are presented as mean±SD, and those with an asymmetric distribution are presented as median and IQR (Q25–Q75). Student's t-test or Wilcoxon rank-sum test was used to compare continuous variables. Categorical variables are presented as frequencies and were compared by Fisher's exact test or χ^2 test. Univariate and multivariable analyses were performed to evaluate the relationship between infection and clinical outcomes. Variables that were significant in the univariate analysis or clinically important were included in the multivariable models. Considering the low incidence of adverse outcomes but potential high incidence of confounders, two models were developed for each multivariable analysis. The first model (model 1) included infection, age, anaemia, type of disease (unstable angina and non-ST elevation acute myocardial infarction), gender, current smokers, heart failure and estimated glomerular filtration rate (eGFR). The second model (model 2) included radial access, cardiac biomarker positive, time to procedure, treated multivessel, diabetes mellitus, hypertension, prior myocardial infarction and prior stroke. We performed subgroup analyses by older age, gender, current smokers, diabetes mellitus, type of disease, heart failure, anaemia and chronic kidney disease. Analysis based on different types of infections was reported. We also introduced the GRACE (Global Registry of Acute Coronary Events)[15] and CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines)[16] scores and compared the infection outcomes among different GRACE or CRUSADE risk groups (low, medium or high risk). All data analyses were performed with SAS V.9.4. A two-sided $p<0.05$ was considered significant.

Propensity score analyses were conducted to test the robustness of the results. All factors listed in table 1 were considered in the propensity score model development. Heterogeneity analysis between the centres was conducted using meta-analysis.

Patient and public involvement

There was no patient or public involvement in any steps of this study.

RESULTS

Baseline characteristics

From 1 January 2010 to 31 December 2014, a total of 8197 consecutive patients with NSTE-ACS underwent PCI at five hospitals in China. Of the 5215 patients who met the final criteria, 206 (3.95%) received a diagnosis of infection, of which 183 (89%) occurred within 1 week of hospital admission (see online supplemental figure S1).

Table 1 Baseline characteristics at index hospitalisation

	All patients			
	Uninfected (n=5009)	Infected (n=206)	Total (N=5215)	P value
Demographics				
Age, years	63.61±10.30	70.86±9.20	63.90±10.36	<0.001
Age ≥65 years, n (%)	2380 (47.5)	157 (76.2)	2537 (48.6)	<0.001
Female, n (%)	1229 (24.5)	54 (26.2)	1283 (24.6)	0.584
Weight, kg	65.69±11.67	63.55±12.22	65.60±11.70	0.011
Heart rate, beats per minute	73.81±10.91	77.75±15.62	73.96±11.16	<0.001
Blood pressure, mm Hg				
Systolic	133.37±19.03	136.60±22.99	133.50±19.21	0.049
Diastolic	76.99±11.27	75.81±12.56	76.95±11.32	0.188
Medical history and risk factors, n (%)				
Current smoker	1306 (26.1)	53 (25.7)	1359 (26.1)	0.912
Cardiac arrest	8 (0.2)	0 (0.0)	8 (0.2)	0.566
Myocardial infarction	784 (15.7)	53 (25.7)	837 (16.0)	<0.001
Percutaneous coronary intervention	940 (18.8)	35 (17.0)	975 (18.7)	0.522
Coronary artery bypass surgery	70 (1.4)	5 (2.4)	75 (1.4)	0.224
Stroke	302 (6.0)	23 (11.2)	325 (6.2)	0.003
Atrial fibrillation	125 (2.5)	8 (3.9)	133 (2.6)	0.216
Hypertension	3259 (65.1)	157 (76.2)	3416 (65.5)	<0.001
Diabetes mellitus	1509 (30.1)	96 (46.6)	1605 (30.8)	<0.001
Presentation characteristics				
IABP, n (%)	44 (0.9)	30 (14.6)	74 (1.4)	<0.001
CRUSADE	42.12±12.04	40.66±13.19	42.06±12.09	0.097
GRACE	124.54±27.67	143.75±29.82	125.17±27.94	<0.001
Type of disease, n (%)				
NSTEMI	3121 (62.3)	131 (63.6)	3252 (62.4)	0.709
Unstable angina	1888 (37.7)	75 (36.4)	1963 (37.6)	
Heart failure	489 (9.8)	66 (32.0)	555 (10.6)	<0.001
LVEF, %	61.79±10.77	55.99±13.71	61.54±10.98	<0.001
eGFR, mL/min/1.73 m^2	81.64±24.99	60.85±28.14	80.81±25.45	<0.001
eGFR ≤60, n (%)	851 (17.0)	101 (49.0)	952 (18.3)	<0.001
Serum creatinine, µmol/dL	1.05±0.69	1.55±1.28	1.07±0.73	<0.001
Haematocrit, g/L	0.39±0.05	0.35±0.06	0.39±0.05	<0.001
Anaemia, n (%)	1605 (32.0)	127 (61.7)	1732 (33.2)	<0.001
Cardiac biomarker positive, n (%)	2984 (62.3)	120 (61.5)	3104 (62.2)	0.836
In-hospital medication, n (%)				
Dual antiplatelet therapy	4845 (96.7)	194 (94.2)	5039 (96.6)	0.047
Statin	4909 (98.0)	202 (98.1)	5074 (97.3)	0.956
ACE inhibitor or ARB	3939 (78.6)	170 (82.5)	4109 (78.8)	0.181
Calcium-channel blocker	1066 (21.3)	72 (35.0)	1138 (21.8)	<0.001
β-blocker	4245 (84.7)	165 (80.1)	4410 (84.6)	0.07
Procedure characteristics, n (%)				
Radial access	4470 (89.2)	154 (74.8)	4624 (88.7)	<0.001
Coronary anatomy				
Any left main	690 (13.8)	49 (23.8)	739 (14.2)	<0.001

Continued

Table 1 Continued

	All patients			
	Uninfected (n=5009)	Infected (n=206)	Total (N=5215)	P value
Multivessel disease	3072 (61.3)	127 (61.7)	3199 (61.3)	
Others	1247 (24.9)	30 (14.6)	1277 (24.5)	
Treated vessel				
Any left main	480 (9.6)	35 (17.0)	515 (9.9)	0.002
Multivessel	1764 (35.2)	66 (32.0)	1830 (35.1)	
Others	2765 (55.2)	105 (51.0)	2870 (55.0)	
Stent type				
Drug eluting stent	5004 (99.9)	206 (100.0)	5210 (99.9)	0.902
Bare metal stent	2 (0.0)	0 (0.0)	2 (0.0)	
PTCA or aspiration only	3 (0.1)	0 (0.0)	3 (0.1)	
Number of stents	2 (1–3)	2 (1–3)	2 (1–3)	0.048
Total length of stents	45 (27–71)	48 (31–76)	45 (27–71)	0.053
Thrombus aspiration	61 (1.2)	5 (2.4)	66 (1.3)	0.128
Time to procedure	1 (1–2)	2 (1–6)	1 (1–2)	<0.001
In 24 hours	2817 (56.2)	81 (39.3)	2898 (55.6)	<0.001
24–72 hours	1505 (30.0)	47 (22.8)	1552 (29.8)	
>72 hours	687 (13.7)	78 (37.9)	765 (14.7)	
In-hospital days	4 (3–6)	11 (7–18)	4 (3–6)	<0.001

ARB, angiotensin receptor blocker; CRUSADE, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines; eGFR, estimated glomerular filtration rate; GRACE, Global Registry of Acute Coronary Events; IABP, intra-aortic balloon pump; LVEF, left ventricular ejection fraction; NSTEMI, non-ST elevation myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty.

Table 1 shows the baseline characteristics of patients with and without infection. Patients with infection were older and had low body weight. These patients were more likely to have a history of myocardial infarction, stroke, hypertension and diabetes, and more often had a diagnosis of heart failure, anaemia, use of intra-aortic balloon pump and dual antiplatelet therapy. Patients with infection had lower left ventricular ejection fraction and eGFR but higher GRACE risk scores compared with those without infection. However, the CRUSADE risk score was similar between the two groups.

In-hospital clinical outcomes

Patients with infection had a higher rate of in-hospital all-cause death (4.4% vs 0.2%), major bleeding (16.5% vs 1.2%) and MACE (21.4% vs 1.7%) compared with patients without infection (all p<0.001) (table 2). However, the rate of in-hospital myocardial infarction was similar between the two groups (p=0.726).

Univariable analyses showed that infection was a predictor of in-hospital all-cause death (OR, 22.96, 95% CI 9.23 to 57.14, p<0.001), major bleeding (OR, 16.30, 95% CI 10.42 to 25.50, p<0.001) and MACE (OR, 14.48, 95% CI 9.62 to 21.78, p<0.001). After adjusting for other confounding variables, multivariable logistic regression showed that infection was significantly and independently related to the risk of the above outcomes (figure 1).

Long-term clinical outcomes

At a median follow-up of 3.2 years, Kaplan-Meier analysis revealed that patients with in-hospital infection had a higher risk of long-term death, major bleeding, and death or major bleeding compared with those without in-hospital infection (p<0.001) (figure 2, table 2, online supplemental figure S2). Multivariable Cox analyses demonstrated that infection was independently associated with long-term adverse outcomes even after adjusting for other potential risk factors (all-cause death: HR, 2.03, 95% CI 1.52 to 2.71, p<0.001; major bleeding: HR, 5.31, 95% CI 3.49 to 8.08, p<0.001; death or major bleeding: HR, 2.47, 95% CI 1.92 to 3.19, p<0.001). Similar results were reported in the other adjusted model (figure 1).

Subgroup analyses

Subgroup analyses similarly revealed that infection was independently related to in-hospital events (all-cause death, major bleeding or MACE) according to different clinical status. The unadjusted and adjusted ORs for infection are presented in online supplemental figures S3–S5. Analysis according to the infection subtypes indicated that pulmonary infection other than UTI was independently associated with poor in-hospital and follow-up clinical outcomes. However, UTI was independently associated with all-cause death (see online supplemental table S1).

Table 2 In-hospital and long-term clinical outcomes

Outcomes	Uninfected (n=5009)	Infected (n=206)	P value
In-hospital outcomes, n (%)			
Death*	10 (0.2)	9 (4.4)	<0.001
Myocardial infarction	17 (0.3)	1 (0.5)	0.726
Death or myocardial infarction	27 (0.5)	10 (4.9)	<0.001
Major bleeding	62 (1.2)	34 (16.5)	<0.001
Death or myocardial infarction or major bleeding	84 (1.7)	44 (21.4)	<0.001
Long-term outcomes			
30 days, n (%)			
Death	17 (0.3)	10 (4.9)	<0.001
Major bleeding	61 (1.2)	31 (15.0)	<0.001
Death or major bleeding	74 (1.5)	37 (18.0)	<0.001
One year, n (%)			
Death	93 (1.9)	35 (17.0)	<0.001
Major bleeding	75 (1.5)	34 (16.5)	<0.001
Death or major bleeding	161 (3.2)	56 (27.2)	<0.001
Three years, n (%)			
Death	346 (6.9)	61 (29.6)	<0.001
Major bleeding	111 (2.2)	36 (17.5)	<0.001
Death or major bleeding	437 (8.7)	81 (39.3)	<0.001

*All-cause death.

Propensity score analyses

We matched 740 patients with or without infection in a 1:4 ratio (see online supplemental table S2 and figure S6). The results showed a higher rate of major bleeding during hospital stay (OR, 18, 95% CI 2.40 to 134.8, p=0.015), and a similar result was found at follow-up (HR, 5.33, 95% CI 1.55 to 18.30, p=0.007), but matched results showed an absence of a significant difference in all-cause death (in-hospital: OR, 4.01, 95% CI 0.25 to 64.30; follow-up: OR, 2, 95% CI 0.97 to 4.12) (see online supplemental table S3).

DISCUSSION

This study demonstrates that infection was uncommon in a contemporary cohort of patients with NSTE-ACS who underwent PCI. However, in-hospital infection among patients with NSTE-ACS who received PCI is still significantly associated with higher risk of in-hospital and long-term clinical prognoses, such as all-cause death, major bleeding as well as MACE.

The prevalence of infection in our study is similar to the results for the STEMI population. Data from 5745 patients with STEMI enrolled in the APEX-AMI trial

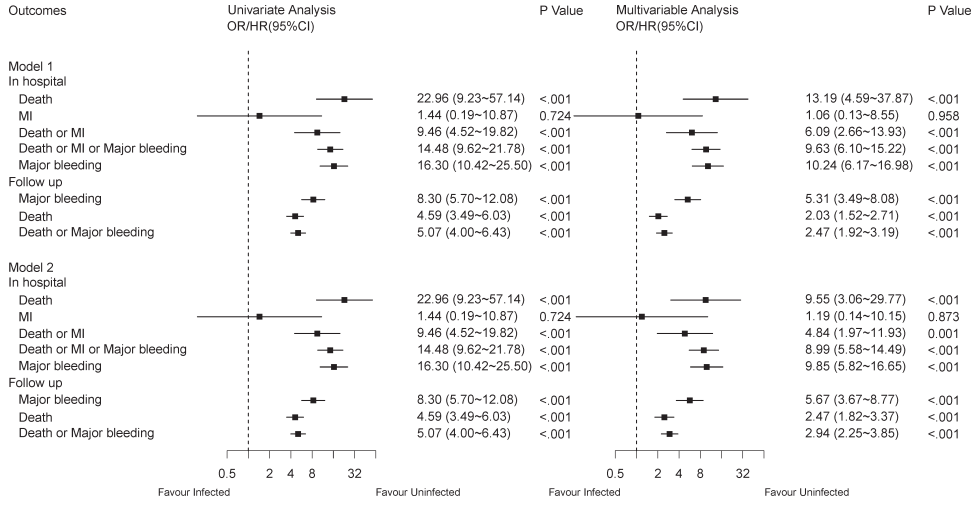

Figure 1 Univariate and multivariable logistic or Cox analysis of clinical outcomes.

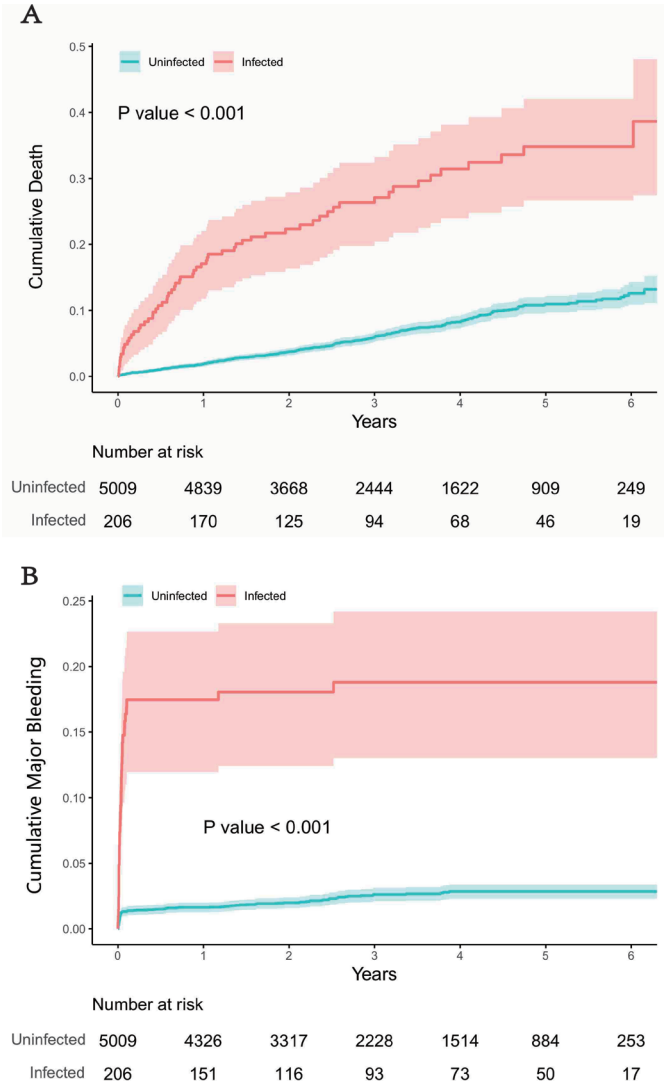

Figure 2 Kaplan-Meier estimated event rates of all-cause death (A) and major bleeding (B).

demonstrated that the prevalence of serious infection was 2.4% and that infection was associated with higher 90-day mortality (29%).[9] Also, another study of 1486 patients with STEMI reported the prevalence of serious infection at 3.9% and the 30-day mortality was up to 53% in these patients.[8] The conclusions of these two studies paralleled our conclusion: infection is uncommon but associated with worse clinical outcomes. A recent retrospective cohort analysis of 174 octogenarians with ACS showed that patients with infection had higher in-hospital, 30-day and long-term mortality than patients without infection.[10] However, the study was confined to patients older than 85 years who were admitted to the coronary care unit, the different ACS types were never specified, and the relatively liberal use of bare metal stents does not conform with the contemporary more liberal use of drug eluting stents.[17 18]

To our knowledge, this study is the first to demonstrate the role of infection in patients with NSTE-ACS. Although the prevalence of infections is similar to previous studies of STEMI,[8 9] the 30-day and 90-day death rates are lower than those studies. These low rates might be due to the characteristics of the patients in our study, with fewer patients requiring intra-aortic balloon pump support, mechanical ventilation and transfusion. However, our conclusion paralleled those of previous studies: patients with infections are associated with worse outcomes. This association remained consistent after adjustment for other important potential risk factors for outcomes, such as radial access, cardiac biomarker positive, time to revascularisation and treated multivessel.

Although infections had a negative impact on patients with NSTE-ACS, the underlying pathophysiological mechanism remains unclear. Corrales-Medina *et al*[19] suggested that infection increased the mortality of patients who underwent elective PCI due to the change in plaques triggered by acute inflammatory reactions. Indeed, infection has been implicated as a factor contributing to initiation, progression and rupture of an atherosclerotic plaque.[20] Infectious vectors have been reported to induce the expression of adhesion molecules, such as heat shock protein 60 and monocyte chemoattractant protein-1 on endothelial cells, which can activate the endothelium and the formation of a lipid core.[21–24] Additionally, the SIXTUS study group[25] demonstrated that platelet activation and TxB_2 overproduction are related to infections via Toll-like receptor 4. Moreover, Modica *et al*[26] reported that aspirin non-responsiveness was often observed in patients with pneumonia. Also, increased coagulation activity has been observed in pneumonia.[3] Therefore, infection can activate the platelets and the coagulation system, which plays a critical role in deteriorating outcomes in patients with ACS. In contrast to previous STEMI reports,[8 9] we did not find a significant association of infection with myocardial infarction due to the low incidence of myocardial infarction in our study. However, our results were similar to previous studies that reported major bleeding was more frequent in patients with infection. Although the PLATO (PLATelet inhibition and patient Outcomes) trial demonstrated that ticagrelor, a more potent and consistent platelet $P2Y_{12}$ inhibitor, was associated with significantly fewer pulmonary infections and death related to infection than clopidogrel, the incidence of bleeding in patients with infection in that study was not reported.[4] Due to dysfunction of the platelets and the coagulation system, patients with infection might be at higher risk of ischaemia and bleeding. Therefore, more attention should be paid to patients with infection when antithrombotic therapy is determined. Finally, infection can also result in worse outcomes for patients with NSTE-ACS through increasing catecholamines and potentially adverse haemodynamic effects, such as coronary vasoconstriction and increased myocardial metabolic demands.[27]

Although UTI was associated to some degree with in-hospital all-cause death, it was not associated with other worse outcomes. One reason why pulmonary infection is related to these worse clinical outcomes, while UTI is not, could be the lower prevalence of UTI compared with pulmonary infection (0.3% vs 2.6%). The prevalence

of UTI was lower in our study compared with patients with STEMI (0.3% vs 7%).[8] Therefore, if the population sample size is expanded, UTI would be similar to the pulmonary infection related to worse clinical outcomes.

Limitations

The study had several limitations. First, as a retrospective study a causal relationship between infections and outcomes could not be determined. Second, despite adjustment for important confounders, we could not completely eliminate all potential bias, including selection bias. Third, although infections were not centrally adjudicated, the infections were confirmed by the infection control services who were authorised to approve the use of antibiotics. Furthermore, because there is not a general screening of infection for all patients, the infection can be underestimated. However, the symptom-leading diagnosis of infection is more practical in the real world and can be promoted easily in clinical setting.

CONCLUSIONS

Infection is an uncommon complication in patients with NSTE-ACS undergoing PCI but is nonetheless independently associated with worse in-hospital and long-term outcomes. Future studies are indicated to identify patients with NSTE-ACS at risk of infection, which could then contribute to targeted intervention, help direct care, reduce the incidence of subsequent adverse events and thus optimise resource utilisation.

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Acknowledgements We appreciate the efforts of the following in revising the manuscript: Scott J Denardo, MD, Reid Heart Center/First Health of Carolinas Cardiac and Vascular Institute, Pinehurst, North Carolina, USA. We thank the patients who participated in this trial and their relatives, the clinical and research teams, and the nursing teams in our hospital for their work on the study: Department of Cardiology, Guangdong Cardiovascular Institute, Guangdong Provincial Key Laboratory of Coronary Heart Disease Prevention, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China (Danqing Yu, Jianfang Luo, Zhonghan Ni, Peixia Huo, Qiong Ren, Yanyan Zhong, Liyun Wang, Jianxia He, Ruijuan Xiao, Yuanling Li, Xinrong Liu, Hui Wang, Mingyu Chen, Haiyan Xue, Xuxi Yang and Suqin Xie); and Department of Cardiology, The Second People's Hospital of Nanhai District, Guangdong General Hospital's Nanhai Hospital, Foshan, China (Wenfei He).

Collaborators Pattern group and the members (Investigator members included): Jiyan Chen, Pengcheng He, Yuanhui Liu, Xuebiao Wei, Lei Jiang, Wei Guo, Yinlin Zhou, Zhujun Chen, Jianfang Luo, Danqing Yu, Qingshan Geng and Ning Tan (Department of Cardiology, Guangdong Cardiovascular Institute, Guangdong Provincial Key Laboratory of Coronary Heart Disease Prevention, Guangdong General Hospital, Guangdong Academic of Medical Sciences, Guangzhou, China); Chunying Lin and Zhiqiang Guo (Department of Cardiology, The Second People's Hospital of Nanhai District, Guangdong General Hospital's Nanhai Hospital, Foshan, China); Chongyang Duan (Department of Biostatistics, School of Public Health, Southern Medical University, Guangzhou, China); Yansong Guo and Wei Chen (Department of Cardiology, Fujian Provincial Clinical College of Fujian Medical University, Fujian Provincial Hospital, Fujian Institute of Cardiovascular Disease, Fuzhou, China); Yiyue Chen (Department of Cardiology, Fuwai Hospital Chinese Academy of Medical Sciences, Shenzhen 518000, China); Jun Li (Department of Cardiovascular Medicine, Zhuhai People's Hospital, Zhuhai, China); Wensheng Li (Department of Cardiology, Shunde Hospital, Southern Medical University, Foshan, China).

Contributors P-YC designed and supervised the study. P-YC, Y-HL, LJ, X-BW and WG performed the study. C-YD analysed the data. Y-HL and the other authors provided the samples and demographics from patients and controls. Y-HL and P-YC wrote the manuscript. NT, J-YC and P-CH revised the manuscript for important intellectual content.

Funding This study was supported by a grant from the Outstanding Young Talent Program of Guangdong Provincial People's Hospital (grant number: KJ012019084), National Science Foundation for Young Scientists of China (grant number 81800325), Science and Technology Planning Project of Guangzhou City (201906010089, 201707010002), and China Youth Research Funding (2017-CCA-VG-02). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The work was not funded by any industry sponsors. All authors agreed to submit the manuscript for publication.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study protocol was approved by the central ethics committee of the Guangdong Provincial People's Hospital (no. GDREC2016210H(R1)). Patients were included with a waiver of informed consent. This article does not contain any studies with animals performed by any of the authors. The study was conducted in accordance with the Declaration of Helsinki.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data source for this study is a retrospective public health database with anonymised data on all hospitalisations. Data are confidentially stored when the original study has been published according to the original protocol.

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