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

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Keywords:	Coronary heart disease < CARDIOLOGY, Coronary intervention < CARDIOLOGY, Cardiology < INTERNAL MEDICINE





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Original article**Impact of infection for non-ST-elevation acute coronary syndrome patients undergoing percutaneous coronary intervention: insight from a multicentre observational cohort from China**

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Running Title: Infection of NSTEMI-ACS and PCI

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Abstract

Objectives: we aimed to interpret the association between in-hospital infection and the prognosis among non-ST-elevation acute coronary syndrome (NSTEMI-ACS) patients received percutaneous coronary intervention (PCI).

Design: This observational cohort originated from the database for NSTEMI-ACS underwent percutaneous coronary intervention from January 1, 2010, to December 31, 2014.

Setting: five centres from south China

Participants: This multicentre observational cohort study consecutively included 8197 NSTEMI-ACS patients 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 tumor, pregnant or cardiogenic shock at 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 hospitalization. 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%) occurred infection. Patients with infection had a higher rate of in-hospital all-cause death and major bleeding (4.4% vs. 0.2%, 16.5% vs. 1.2% respectively, $P < .001$). After adjusting for confounders, infection remained independently associated with the in-hospital and long-term all-cause death (OR, 13.19, 95% CI: 4.59-37.87; HR, 2.03, 95% CI: 1.52-2.71; $P < .001$) and major bleeding (OR, 10.24; 95% CI: 6.17-16.98; HR, 5.31, 95% CI: 3.49-8.08; $P < .001$). Subgroup analysis

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4 confirmed these results.
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6 **Conclusions:** the incidence of infection is low in hospitalization, but it is associated
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9 with worse in-hospital and long-term outcomes.
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11 **Key Words:** Non-ST-elevation acute coronary syndrome; Percutaneous coronary
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14 intervention; Infection; Outcomes.
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Strengths and limitations of this study

- We widely included NSTEMI-ACS patients who received PCI treatment from China.
- The characteristics of infection was detailed reported which included the time and infection type.
- Validation was done in different subgroups and variables which is our best effort based on the database.
- The potential bias may be neglected because of the study design.
- The etiology test of the infection is absent which limited the advanced exploration of the mechanism.

Introduction

The incidence of non-ST-elevation acute coronary syndrome (NSTE-ACS) is increasing, and approximately 70% of all ACS patients are NSTE¹. These patients typically have more comorbidities than patients with ST-segment elevation myocardial infarction (STEMI) and are associated with both worse short- and long-term outcomes^{1, 2}. Identification of patients at risk for worse outcomes could result in targeted intervention, help direct care, reduce the incidence of subsequent events, and thus optimize resource utilization.

Infection can activate platelets and the coagulation system, contributing to the 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, information about infection in patients with NSTE-ACS remains scanty. Only one study of 174 octogenarian patients with ACS evaluated the impact of infection on clinical outcomes¹⁰. Thus, we aimed to assess the incidence and association of infection on short- and long-term clinical outcomes in NSTE-ACS patients undergoing PCI.

Methods

Study design and patients

This observational cohort study consisted of consecutive NSTE-ACS patients undergoing PCI from Jan 2010 to Dec 2014 at five hospitals in China. Only patients with adequate information to diagnose or rule out infection were included. Patients were

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3 excluded if they were diagnosed with a malignant tumor before the index date, pregnant
4 or presenting with cardiogenic shock. The method to search and identify appropriate
5 NSTEMI-ACS patients has been outlined previously¹¹. The study protocol was approved
6 by the central ethics committee of the Guangdong Provincial People's Hospital, with a
7 waiver of informed consent. The study was conducted in accordance with the
8 Declaration of Helsinki.
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17 **Data collection and procedures**

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Data on demographics, patient history, laboratory tests, examinations, and medication
history were collected by investigators in the first interview after admission. The
medicines and PCI procedures were applied according to international guidelines and
clinical evidence¹².

Infection during the index hospitalization was diagnosed according to the presence
of any symptoms, signs and/or laboratory indicating infection. Once confirmed by the
infection control doctors service, appropriate antibiotics were prescribed⁸. 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
hospitalization. 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 Prevention¹³.

57 **Clinical outcomes and follow up**

The primary outcome was in-hospital all-cause death and in-hospital major bleeding as

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4 defined by the Bleeding Academic Research Consortium definition (grades 3-5)¹⁴.

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6 Secondary outcomes were: (1) major adverse clinical events (MACE), consisting of all-
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8 cause death, myocardial infarction, or major bleeding during hospitalization; and (2)
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10 all-cause death or major bleeding during follow-up.
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14 All patients were followed-up by trained nurses via telephone interview or clinic
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16 visits from Nov 2015 to Dec 2016. Relevant information was also collected from the
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18 residence registration system and from the clinical records of the patients who were
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20 readmitted. The details of clinical events and follow-up has been previously described¹¹.
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23 24 **Statistical analysis**

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26 All patients were divided into groups with or without infections. Continuous variables
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28 with a normal distribution are presented as the mean \pm SD, and those with an
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30 asymmetric distribution are presented as the median and interquartile range (Q25-Q75).
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32 Student's t test or Wilcoxon rank-sum test were used to compare the continuous
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34 variables. Categorical variables are presented as frequencies and were compared by the
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36 Fisher exact test or chi-square test. Univariate and multivariable analyses were
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38 performed to evaluate the relationship between infection and clinical outcomes.
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40 Variables that were significant in the univariate analysis or clinically important were
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42 included in the multivariable models. Considering the low incidence of adverse
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44 outcomes but potential high incidence of confounders, each multivariable analysis two
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46 models were developed. The first model (model 1) included infection, age, anemia, type
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48 of disease (unstable angina and non-ST-elevation acute myocardial infarction), gender,
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50 current smokers, heart failure, and estimate glomerular filtration rate (eGFR). The
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4 second model (model 2) included radial access, cardiac biomarker positive, time to
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6 procedure, treated multi-vessel, diabetes mellitus, hypertension, prior myocardial
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8 infarction, and prior stroke. We performed subgroup analyses by older age, gender,
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10 current smokers, diabetes mellitus, types of disease, heart failure, anemia and chronic
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12 kidney disease. Analysis based on different types of infections was reported. We also
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14 introduced the GRACE (Global Registry of Acute Coronary Events)¹⁵ and CRUSADE
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16 (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse
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18 Outcomes With Early Implementation of the ACC/AHA Guidelines) score¹⁶ and
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20 compared the infection outcomes among different GRACE or CRUSADE risk groups
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22 (low, medium, or high risk). All data analyses were performed with SAS (version 9.4,
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24 SAS Institute, 210 Cary, North Carolina, USA). A 2-sided P<0.05 was considered
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26 significant.

35 **Patient and public involvement**

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

40 **Results**

43 **Baseline characteristic**

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45 From January 1, 2010, to December 31, 2014, a total of 8197 consecutive NSTEMI-ACS
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47 patients underwent PCI at the 5 hospitals in China. Of the 5215 patients who met the
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49 final criteria, 206 (3.95%) received a diagnosis of infection, and 183 (89%) of them
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51 occurred within one week after hospital admission (**Figure S1**). **Table 1** shows the
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53 baseline characteristics of patients with and without infection. The patients with
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55 infection were older and a low body weight. These patients were more likely to have a
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4 history of myocardial infarction, stroke, hypertension and diabetes, and more often had
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6 a diagnosis of heart failure, anemia and the use of intra-aortic balloon pump and dual
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8 antiplatelet therapy. Patients with infection had lower left ventricular ejection fraction,
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10 eGFR but higher GRACE risk scores compared with those without infection. However,
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12 the CRUSADE risk score was similar between the two groups.
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16 **In-hospital clinical outcomes**

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18 Patients with infection had a higher rate of in-hospital all-cause death (4.4% vs. 0.2%),
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20 major bleeding (16.5% vs. 1.2%), and MACE (21.4% vs. 1.7%) compared with patients
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22 without infection (all $P < .001$) (**Table 2**). However, the rate of in-hospital myocardial
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24 infarction was similar between the two groups ($P = 0.726$).
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30 Univariable analyses showed that infection was a predictor of in-hospital all cause
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32 death (odds ratios [OR] 22.96; 95% confidence interval [CI], 9.23-57.14, $P < .001$),
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34 major bleeding (OR, 16.30; 95% CI, 10.42-25.50; $P < .001$), and MACE (OR, 14.48;
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36 95%CI, 9.62-21.78; $P < .001$). After adjusting for other confounding variables,
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38 multivariable logistic regression showed that infection was significantly and
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40 independently related to the risk of the above outcomes (**Figure 1**).
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45 **Long-term clinical outcomes**

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47 At a median follow-up of 3.2 years, Kaplan-Meier analysis revealed that patients with
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49 in-hospital infection had a higher risk of long-term death, major bleeding, and death or
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51 major bleeding compared with those without in-hospital infection ($P < .001$) (**Table 2**,
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53 **Figure 2 and Figure S2**). Multivariable cox analyses demonstrated that infection was
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55 independently associated with long-term adverse outcomes even after adjusting for
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4 other potential risk factors (all cause death: hazard ratio [HR], 2.03; 95% CI, 1.52-2.71;
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6 P<.001; major bleeding: HR, 5.31; 95% CI, 3.49-8.08; P<.001; death or major bleeding:
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8 HR, 2.47; 95% CI, 1.92-3.19; P<.001). The similar result was reported in the other
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10 adjusted model (**Figure 1**).

11 12 13 14 **Subgroup analyses**

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17 Subgroup analyses similarly revealed that infection was independently related to the in-
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19 hospital events (all-cause death, major bleeding, or MACE) according to different
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21 clinical status. The unadjusted and adjusted ORs for infection are presented in **Figure**
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23 **S3, Figure S4, and Figure S5**. Analysis according to the infection subtypes indicated
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25 that pulmonary infection other than UTI was independently associated with poor in-
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27 hospital and follow up clinical outcomes. However, the UTI was independently
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29 associated with all-cause death (**Table S1**). Furthermore, the relationship between
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31 infection and major bleeding, and MACE was consistent among patients with different
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33 GRACE or CRUSADE scores (low, medium, or high risk) (**Figure S6, S7, S8 and S9**).

34 35 36 37 38 39 40 **Discussion**

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43 This study demonstrates that infection was uncommon in a contemporary cohort
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45 of NSTEMI-ACS patients who underwent PCI. But still the in-hospital infection among
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47 NSTEMI-ACS patients received PCI is significant associated with higher risk of in-
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49 hospital and long-term clinical prognoses, such as all-cause death, major bleeding as
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51 well as the MACE.

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56 The prevalence of infection in our study are similar to those results for the STEMI
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58 population. Data from 5,745 STEMI patients enrolled in the APEX-AMI trial
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4 demonstrated that the prevalence of serious infection was 2.4%, and that infection was
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6 associated with higher 90-day mortality (29%)⁹. Also, another study of 1,486 STEMI
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8 patients reported the prevalence of serious infection at 3.9% and the 30-day mortality
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10 was up to 53% in these patients⁸. The conclusions for these 2 studies paralleled our
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12 conclusion: infection is uncommon but associated with worse clinical outcomes. A
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14 recent retrospective cohort analyses of 174 octogenarians with ACS, for whom the
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16 patients with infection had a higher in-hospital, 30-day and long-term mortality than
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18 patients without infection¹⁰. However, that study was confined to patients older than 85
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20 years who were admitted to the coronary care unit, the different ACS types were never
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22 specified, and the relatively liberal use of bare metal stents does not conform with the
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24 contemporary more liberal use of drug eluting stents^{17, 18}.

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27 To our knowledge, this study is the first to demonstrate the role of infection on
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29 patients with NSTEMI-ACS. Although the prevalence of infections was similar to the
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31 previous studies of STEMI^{8, 9}, the 30 and 90-day death rates were lower than those
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33 studies. These low rates might be the result of patient characteristics of our study with
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35 less patients requiring intra-aortic balloon pump support, mechanical ventilation and
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37 transfusion. However, our conclusions paralleled: patients with infections were
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39 associated with worse outcomes. This association remained consistent after the
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41 adjustment of other important potential risk factors for outcomes such as radial access,
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43 cardiac biomarker positive, time to revascularization, and treated multi-vessel.
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56 Although infections had a negative impact on patients with NSTEMI-ACS, the
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58 underlying pathophysiologic mechanism remains unclear. Corrales-Medina et al¹⁹
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4 suggested that infection increased the mortality of patients who underwent elective PCI
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6 due to change in the plaques triggered by acute inflammatory reactions. Indeed,
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8 infection has been implicated as a factor contributing to initiation, progression and
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10 rupture of an atherosclerotic plaque²⁰. Infectious vectors have been reported to induce
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12 the expression of adhesion molecules such as heat shock protein 60 and monocyte
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14 chemoattractant protein-1 on endothelial cells, which can activate the endothelium and
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16 the formation of a lipid core²¹⁻²⁴. Additionally, the SIXTUS study group²⁵ demonstrated
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18 that platelet activation and TxB₂ overproduction are related to infections via Toll-like
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20 receptor 4. Moreover, MODICA et al.²⁶ reported that aspirin non-responsiveness was
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22 often observed in patients with pneumonia. Also, increased coagulation activity has
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24 been observed in pneumonia³. Therefore, infection can activate platelets and the
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26 coagulation system, which plays a critical role in deteriorating outcomes in patients
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28 with ACS. In contrast to previous STEMI reports^{8, 9}, we did not find a significant
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30 association of infection with myocardial infarction due to the low incidence of
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32 myocardial infarction in our study. However, our results were similar to previous
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34 studies that reported major bleeding more frequent in patients with infection. Although
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36 the PLATelet inhibition and patient Outcomes (PLATO) trial demonstrated that
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38 ticagrelor, a more potent and consistent platelet P2Y₁₂ inhibitor, was associated with
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40 significantly fewer pulmonary infections and death related to infection than clopidogrel,
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42 the incidence of bleeding in patients with infection in that study was not reported⁴.
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44 Because of dysfunction of platelets and the coagulation system, patients with infection
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46 might be at higher risk of ischemia and bleeding. Therefore, more attention should be
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4 paid to patients with infection when antithrombotic therapy was determined. Finally,
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6 infection can also result in worse outcomes for NSTEMI-ACS patients through increasing
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8 catecholamines and potentially adverse hemodynamic effects, such as coronary
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10 vasoconstriction and increased myocardial metabolic demands²⁷.
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14 Although UTI was associated to some degree with in-hospital all-cause death, it
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16 was not associated with other worse outcomes. One reason why pulmonary infection is
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18 related to these worse clinical outcomes, while UTI is not, could be the lower
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20 prevalence of UTI comparing to pulmonary infection (0.3% vs. 2.6%). The prevalence
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22 of UTI was lower in our study compared with STEMI patients (0.3% vs. 7%)⁸.
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24 Therefore, when the population sample size was expanded, UTI would be similar to the
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26 pulmonary infection relating to the worse clinical outcomes.
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32 **Limitations**

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34 The study had several limitations. First, as a retrospective study a causal relationship
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36 between the infection and outcomes could not be determined. Second, despite
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38 adjustment for important confounders, we could not completely eliminate all the
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40 potential bias including selection bias. Third, although the infections were not centrally
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42 adjudicated, the infection was confirmed by the infection control services who were
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44 authorized to approve the use of antibiotic. In addition, all other adverse clinical events
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46 were evaluated by an independent clinical events committee that was masked to the
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48 infection details.
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54 **Conclusions**

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56 Infection is an uncommon complication in patients with NSTEMI-ACS undergoing PCI
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4 but is nonetheless independently associated with worse in-hospital and long-term
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6 outcomes. Future studies are indicated to identify NSTEMI-ACS patients at risk for
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8 infection which could then result in targeted intervention, help direct care, reduce the
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10 incidence of subsequent adverse events, and thus optimize resource utilization.
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7
8 authors agreed to submit the manuscript for publication.
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11 **Authors' contributions**

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14 P-C He designed and supervised the study; P-Y Chen, Y-H Liu, L Jiang, X-B Wei and
15
16 W Guo performed the study, and C-Y Duan analyzed the data; Y-H Liu and other
17
18 authors provided the samples and demographics from patients and controls; Y-H Liu
19
20 and P-Y Chen wrote the manuscript; N Tan, J-Y Chen and P-C He revised the
21
22 manuscript for important intellectual content.
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26 **Conflict of Interest**

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29
30 The authors declared no potential conflicts of interest with respect to the research,
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32 authorship, and/or publication of this article.
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35 **Ethics approval and consent to participate**

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38 The study protocol was approved by the central ethics committee of the Guangdong
39
40 Provincial People's Hospital (NO. GDREC2016210H(R1)). Patients were included
41
42 with a waiver of informed consent.
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46 This article does not contain any studies with animals performed by any of the authors.
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48 **Data availability statement**

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51 Data source for this study is a retrospective public health database with data which all
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53 hospitalisations that were already anonymised. Data were confidentially stored once the
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55 original study published according to the original protocol, but data are available upon
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57 reasonable request.
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Table legends

Table 1. The baseline characteristics at index hospitalization

Table 2. In-hospital and long-term clinical outcomes

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Figure legends

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

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

Figure S1. Time from hospital admission to the diagnosis of infection among all patients.

Figure S2. Kaplan-Meier estimated event rates of all cause death or major bleeding

Figure S3. Subgroup analysis of in-hospital all cause death

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Figure S6. Subgroup analysis of in-hospital major bleeding based on different risk of GRACE and CRUSADE adjusted by the model 1

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Figure S8. Subgroup analysis of in-hospital major adverse clinical events based on different risk of GRACE and CRUSADE adjusted by the model 1

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4 **Figure S9.** Subgroup analysis of in-hospital major adverse clinical events based on
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6 different risk of GRACE and CRUSADE adjusted by the model 2
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Table 1. The baseline characteristics at index hospitalization

	All patients*			<i>P</i> value
	Uninfected (N=5009)	Infected (N=206)	Total (N=5215)	
Demographics				
Age, y	63.61 ± 10.30	70.86 ± 9.20	63.90 ± 10.36	<.001
Age ≥ 65 y	2380(47.5%)	157(76.2%)	2537(48.6%)	<.001
Female	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, bpm	73.81 ± 10.91	77.75 ± 15.62	73.96 ± 11.16	<.001
Blood pressure, mmHg				
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%)	<.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%)	<.001
Diabetes mellitus	1509(30.1%)	96(46.6%)	1605(30.8%)	<.001
Presentation characteristics				

	All patients*			<i>P</i> value
	Uninfected (N=5009)	Infected (N=206)	Total (N=5215)	
IABP	44(0.9%)	30(14.6%)	74(1.4%)	<.001
CRUSAD	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	<.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, n(%)	489(9.8%)	66(32.0%)	555(10.6%)	<.001
LVEF, %	61.79 ± 10.77	55.99 ± 13.71	61.54 ± 10.98	<.001
eGFR, mL/min/1.73m ²	81.64 ± 24.99	60.85 ± 28.14	80.81 ± 25.45	<.001
eGFR ≤ 60, n(%)	851(17.0%)	101(49.0%)	952(18.3%)	<.001
Serum creatinine, µmol/dL	1.05 ± 0.69	1.55 ± 1.28	1.07 ± 0.73	<.001
Hematocrit, g/L	0.39 ± 0.05	0.35 ± 0.06	0.39 ± 0.05	<.001
Anemia, n(%)	1605(32.0%)	127(61.7%)	1732(33.2%)	<.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%)	<.001
β-blocker	4245(84.7%)	165(80.1%)	4410(84.6%)	0.070
Procedure characteristics, n(%)				

	All patients*			<i>P</i> value
	Uninfected (N=5009)	Infected (N=206)	Total (N=5215)	
Radial access	4470(89.2%)	154(74.8%)	4624(88.7%)	<.001
Coronary anatomy				
Any left main	690(13.8%)	49(23.8%)	739(14.2%)	<.001
Multi-vessel 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
Multi-vessel	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)	<.001
In 24 hours	2817(56.2%)	81(39.3%)	2898(55.6%)	<.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)	<.001

*Abbreviations: IABP=intra-aortic balloon pump; GRACE=Global Registry of Acute

Coronary Events; CRUSADE=Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines; NSTEMI=Non-ST elevation myocardial infarction; LVEF=left ventricular ejection fraction; eGFR=Estimate glomerular filtration rate; PTCA=Percutaneous transluminal coronary angioplasty. ACE=angiotensin-converting enzyme; ARB=angiotensin receptor blocker.

Table 2 In-hospital and Long-term clinical outcomes

Outcomes	Uninfected (N=5009)	Infected (N=206)	P value
In-hospital outcomes			
Death*	10(0.2%)	9(4.4%)	<.001
Myocardial infarction	17(0.3%)	1(0.5%)	0.726
Death or myocardial infarction	27(0.5%)	10(4.9%)	<.001
Major bleeding	62(1.2%)	34(16.5%)	<.001
Death or Myocardial infarction or major bleeding	84(1.7%)	44(21.4%)	<.001
Long-term outcomes			
30 days			
Death	17(0.3%)	10(4.9%)	<.001
Major bleeding	61(1.2%)	31(15.0%)	<.001
Death or major bleeding	74(1.5%)	37(18.0%)	<.001
One year			
Death	93(1.9%)	35(17.0%)	<.001
Major bleeding	75(1.5%)	34(16.5%)	<.001
Death or major bleeding	161(3.2%)	56(27.2%)	<.001
Three years			

Outcomes	Uninfected (N=5009)	Infected (N=206)	P value
Death	346(6.9%)	61(29.6%)	<.001
Major bleeding	111(2.2%)	36(17.5%)	<.001
Death or major bleeding	437(8.7%)	81(39.3%)	<.001

*All cause death;

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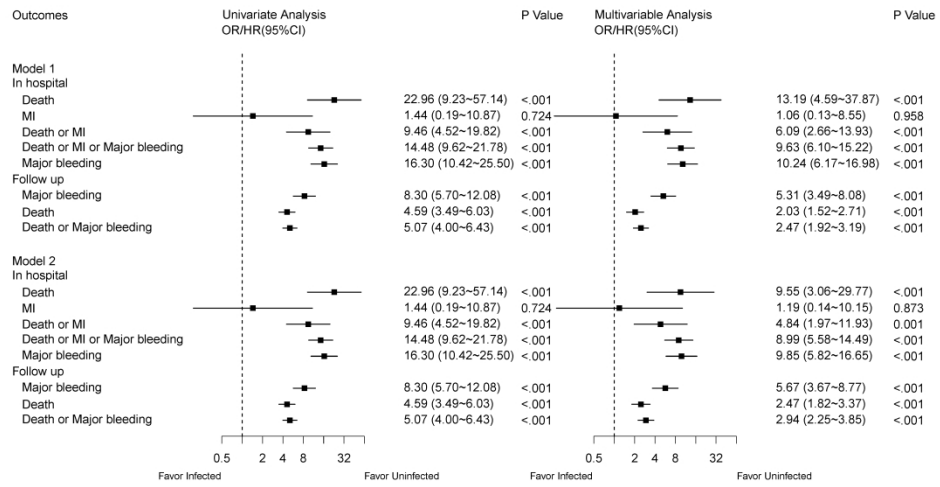


Figure 1. Univariate and multivariable logistic or Cox analysis for clinical outcomes

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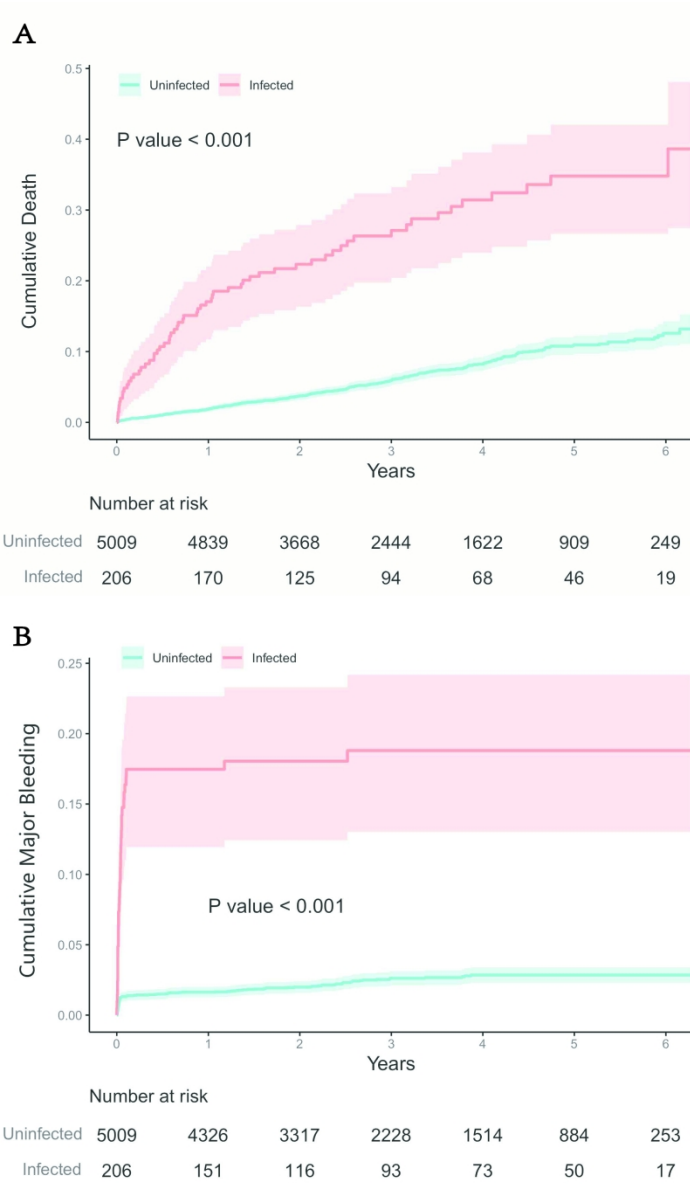


Figure 2. Kaplan-Meier estimated event rates of all cause death (A) and major bleeding (B)

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Supplementary Appendix 1

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5 **Table S1.** Univariate and multivariable logistic for clinical outcomes by stratifying infection
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10 **Figure S1.** Time from hospital admission to the diagnosis of infection among all patients.
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13 **Figure S2.** Kaplan-Meier estimated event rates of all cause death or major bleeding
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16 **Figure S3.** Subgroup analysis of in-hospital all cause death
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19 **Figure S4.** Subgroup analysis of in-hospital major bleeding
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22 **Figure S5.** Subgroup analysis of in-hospital major adverse clinical events
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25 **Figure S6.** Subgroup analysis of in-hospital major bleeding based on different risk of GRACE
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27 and CRUSADE adjusted by the model 1
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30 **Figure S7.** Subgroup analysis of in-hospital major bleeding based on different risk of GRACE
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32 and CRUSADE adjusted by the model 2
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35 **Figure S8.** Subgroup analysis of in-hospital major adverse clinical events based on different risk
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40 **Figure S9.** Subgroup analysis of in-hospital major adverse clinical events based on different risk
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Table S1 Univariate and multivariable logistic for clinical outcomes by stratifying infection subtype.

Outcomes (Compare with uninfected patients)	Univariate analysis			Multivariable analysis		
	OR	95%CI	P value	OR	95%CI	Pvalue
Model 1						
In hospital						
Death						
Community acquired pulmonary infections	17.24	4.66~63.73	<.001	8.56	2.06~35.57	0.003
Hospital acquired pulmonary infections	23.25	4.95~109.28	<.001	11.51	2.15~61.49	0.004
Urinary tract infection	31.24	3.78~258.58	0.001	21.59	2.32~200.48	0.007
Other infection	29.99	8.01~112.27	<.001	23.14	5.59~95.86	<.001
Major Bleeding						
Community acquired pulmonary infections	28.32	16.54~48.48	<.001	18.13	9.92~33.16	<.001
Hospital acquired pulmonary infections	14.80	6.37~34.43	<.001	9.04	3.63~22.49	<.001
Urinary tract infection	5.16	0.67~39.50	0.114	3.10	0.39~24.51	0.283
Other infection	4.95	1.50~16.31	0.009	3.25	0.95~11.13	0.061
Death or MI or Major Bleeding						
Community acquired pulmonary infections	21.85	13.05~36.59	<.001	14.23	8.07~25.10	<.001
Hospital acquired pulmonary infections	16.69	8.01~34.77	<.001	11.28	5.14~24.76	<.001
Urinary tract infection	3.76	0.49~28.65	0.202	2.44	0.31~19.04	0.396
Other infection	6.26	2.43~16.13	<.001	4.51	1.69~12.01	0.003
Follow up						
Death						
Community acquired pulmonary infections	5.52	3.78~8.06	<.001	2.06	1.39~3.06	<.001
Hospital acquired pulmonary infections	6.16	3.78~10.02	<.001	2.57	1.56~4.24	<.001
Urinary tract infection	3.66	1.37~9.82	0.010	2.38	0.88~6.39	0.086
Other infection	2.62	1.44~4.79	0.002	1.45	0.79~2.66	0.232
Major Bleeding						
Community acquired pulmonary infections	14.29	9.26~22.06	<.001	8.86	5.49~14.27	<.001

Outcomes (Compare with uninfected patients)	Univariate analysis			Multivariable analysis		
	OR	95%CI	P value	OR	95%CI	Pvalue
Hospital acquired pulmonary infections	7.08	3.30~15.20	<.001	4.16	1.87~9.27	<.001
Urinary tract infection	2.54	0.35~18.13	0.354	1.66	0.23~11.98	0.616
Other infection	2.49	0.79~7.83	0.119	1.83	0.57~5.85	0.307
Death or Major Bleeding						
Community acquired pulmonary infections	6.83	4.99~9.35	<.001	2.85	2.05~3.97	<.001
Hospital acquired pulmonary infections	6.32	4.08~9.79	<.001	2.93	1.87~4.61	<.001
Urinary tract infection	2.85	1.07~7.64	0.037	1.78	0.66~4.78	0.253
Other infection	2.62	1.51~4.55	0.001	1.60	0.92~2.80	0.099
Model 2						
In hospital						
Death						
Community acquired pulmonary infections	17.24	4.66~63.73	<.001	2.01	0.37~10.86	0.418
Hospital acquired pulmonary infections	23.25	4.95~109.28	<.001	6.48	0.92~45.66	0.061
Urinary tract infection	31.24	3.78~258.58	0.001	14.68	0.96~223.51	0.053
Other infection	29.99	8.01~112.27	<.001	5.02	0.98~25.62	0.052
Major Bleeding						
Community acquired pulmonary infections	28.32	16.54~48.48	<.001	11.91	6.10~23.28	<.001
Hospital acquired pulmonary infections	14.80	6.37~34.43	<.001	7.47	2.80~19.90	<.001
Urinary tract infection	5.16	0.67~39.50	0.114	1.92	0.15~25.23	0.619
Other infection	4.95	1.50~16.31	0.009	1.05	0.26~4.23	0.942
Death or MI or Major Bleeding						
Community acquired pulmonary infections	21.85	13.05~36.59	<.001	9.69	5.12~18.37	<.001
Hospital acquired pulmonary infections	16.69	8.01~34.77	<.001	10.00	4.33~23.12	<.001
Urinary tract infection	3.76	0.49~28.65	0.202	1.59	0.13~19.16	0.713
Other infection	6.26	2.43~16.13	<.001	1.71	0.54~5.35	0.360
Follow up						
Death						
Community acquired pulmonary infections	5.52	3.78~8.06	<.001	2.70	1.81~4.03	<.001
Hospital acquired pulmonary infections	6.16	3.78~10.02	<.001	3.56	2.15~5.90	<.001

Outcomes (Compare with uninfected patients)	Univariate analysis			Multivariable analysis		
	OR	95%CI	P value	OR	95%CI	Pvalue
Urinary tract infection	3.66	1.37~9.82	0.010	2.90	1.08~7.80	0.034
Other infection	2.62	1.44~4.79	0.002	1.32	0.71~2.44	0.376
Major Bleeding	14.29	9.26~22.06	<.001	6.30	3.79~10.49	<.001
Community acquired pulmonary infections	7.08	3.30~15.20	<.001	3.51	1.57~7.84	0.002
Hospital acquired pulmonary infections	2.54	0.35~18.13	0.354	1.42	0.19~10.39	0.731
Urinary tract infection	2.49	0.79~7.83	0.119	1.01	0.31~3.29	0.981
Other infection						
Death or Major Bleeding						
Community acquired pulmonary infections	6.83	4.99~9.35	<.001	3.55	2.55~4.94	<.001
Hospital acquired pulmonary infections	6.32	4.08~9.79	<.001	3.46	2.20~5.45	<.001
Urinary tract infection	2.85	1.07~7.64	0.037	1.96	0.73~5.28	0.181
Other infection	2.62	1.51~4.55	0.001	1.38	0.78~2.41	0.266

Model 1 included age, gender, current smokers, heart failure, anemia, type of disease, estimate glomerular filtration rate.

Model 2 included diabetes mellitus, hypertension, prior myocardial infarction, prior stroke, radial access, chronic kidney disease, intra-aortic balloon pump.

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Figure S1. Time from hospital admission to the diagnosis of infection among all patients.

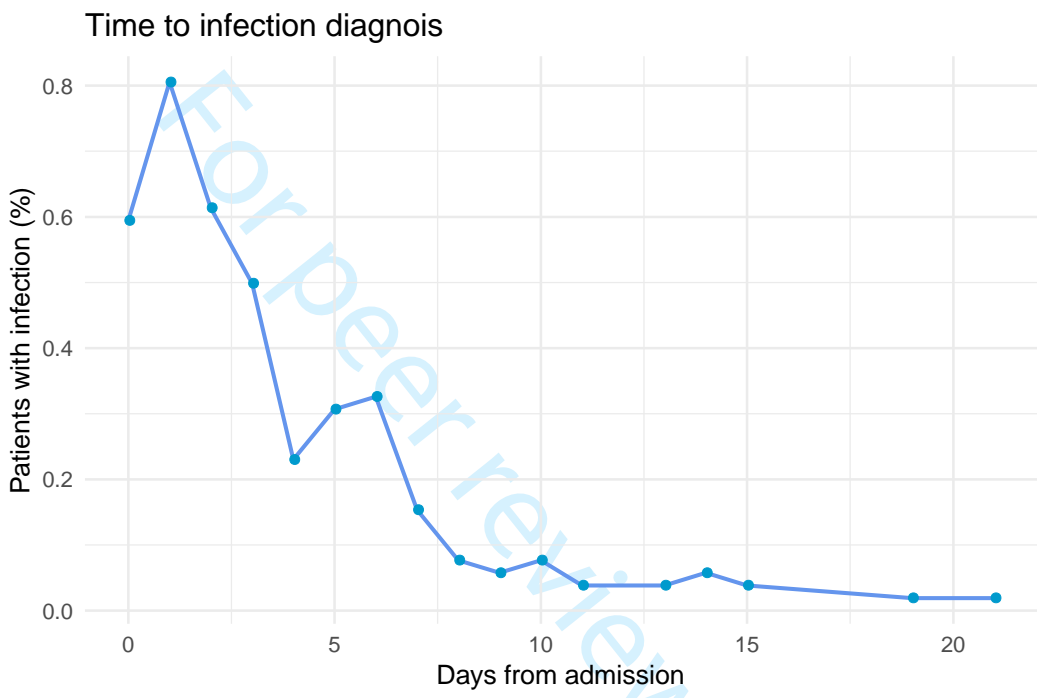


Figure S2. Kaplan-Meier estimated event rates of all cause death or major bleeding

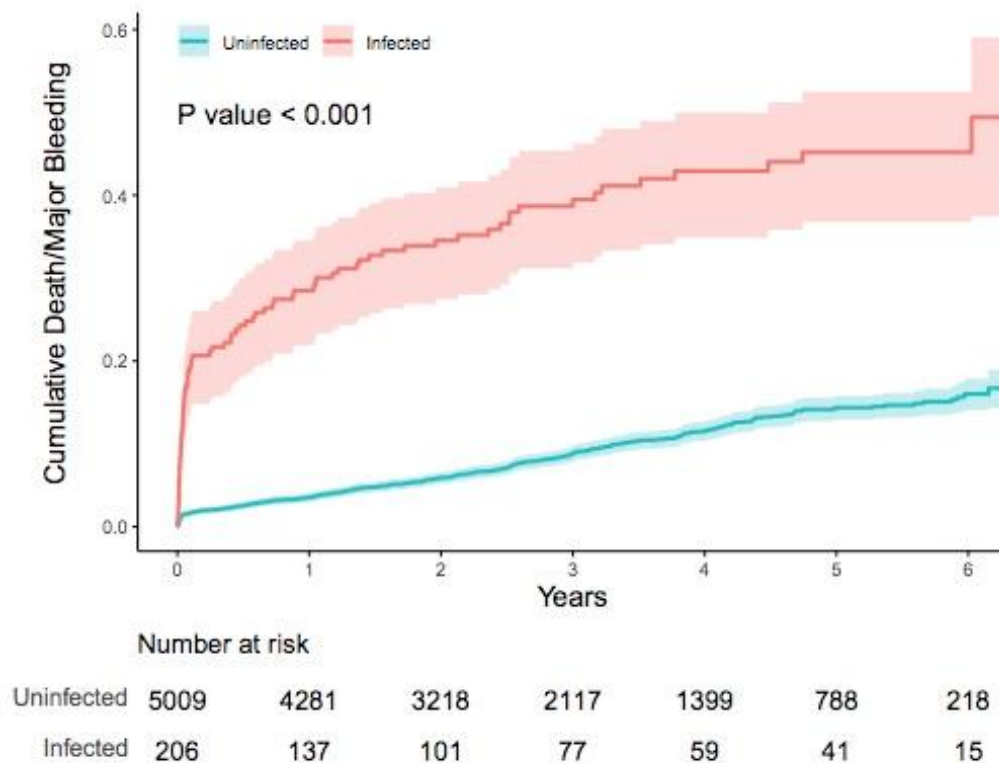


Figure S3. Subgroup analysis of in-hospital all cause death

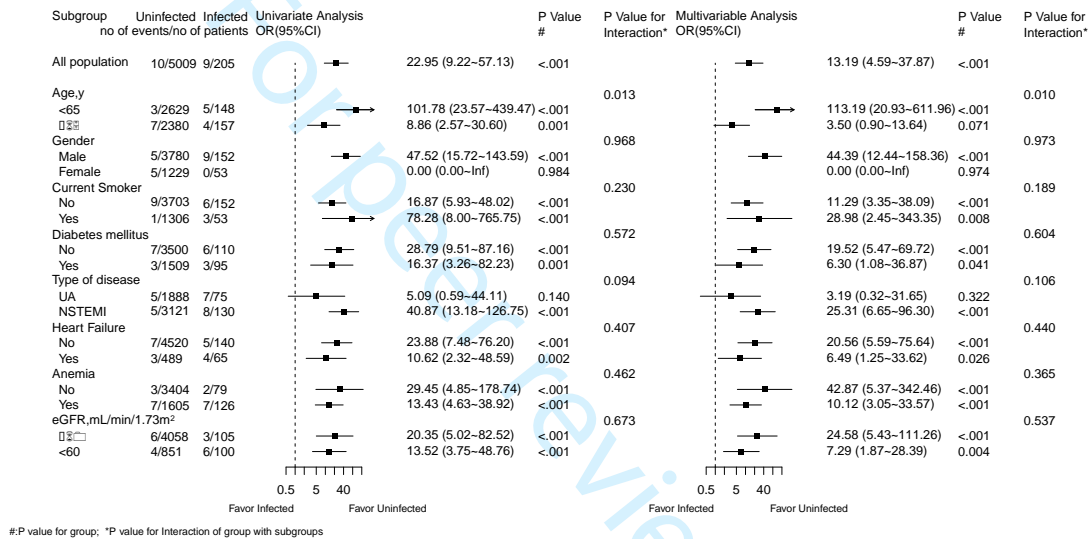


Figure S4. Subgroup analysis of in-hospital major bleeding

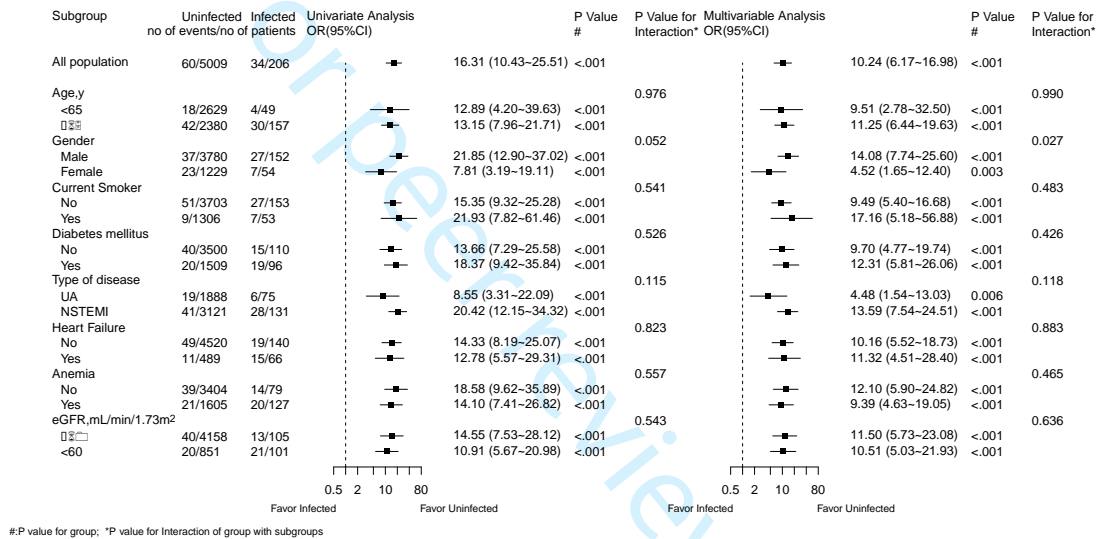
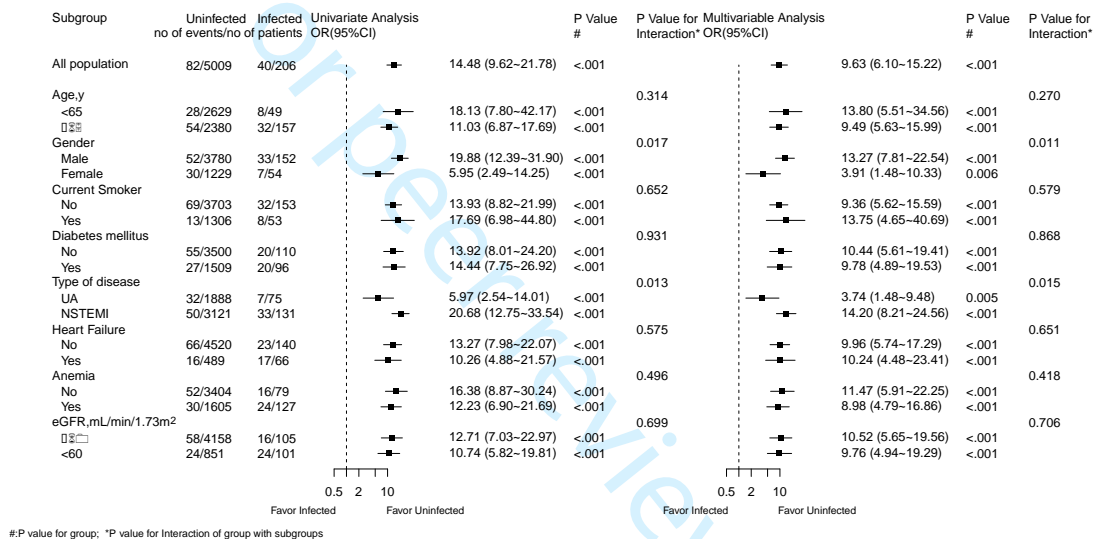


Figure S5. Subgroup analysis of in-hospital major adverse clinical events



#P value for group; *P value for Interaction of group with subgroups

Figure S6. Subgroup analysis of in-hospital major bleeding based on different risk of GRACE and CRUSADE adjusted by the model 1

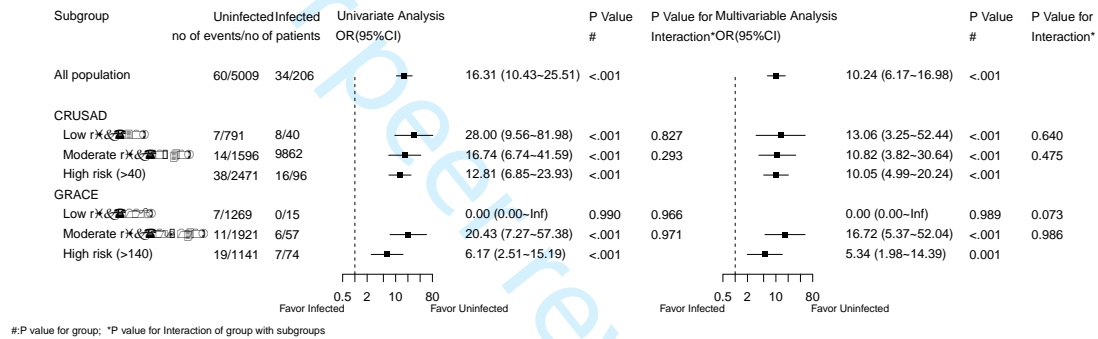


Figure S7. Subgroup analysis of in-hospital major bleeding based on different risk of GRACE and CRUSADE adjusted by the model 2

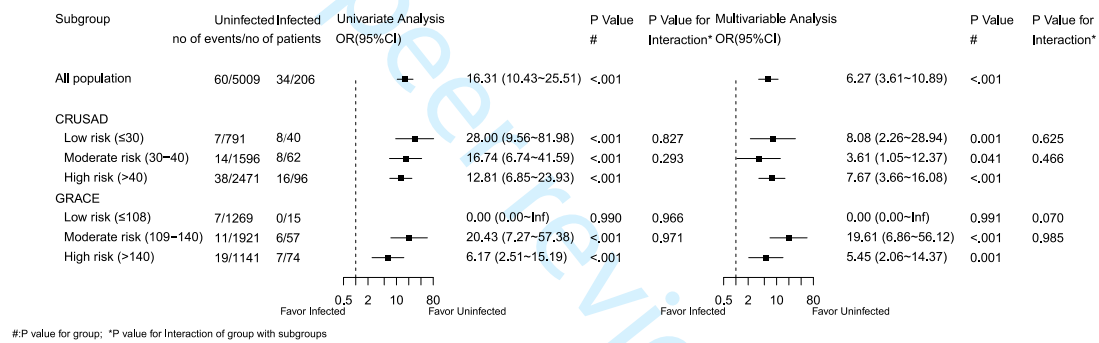


Figure S8. Subgroup analysis of in-hospital major adverse clinical events based on different risk of GRACE and CRUSADE adjusted by the model 1

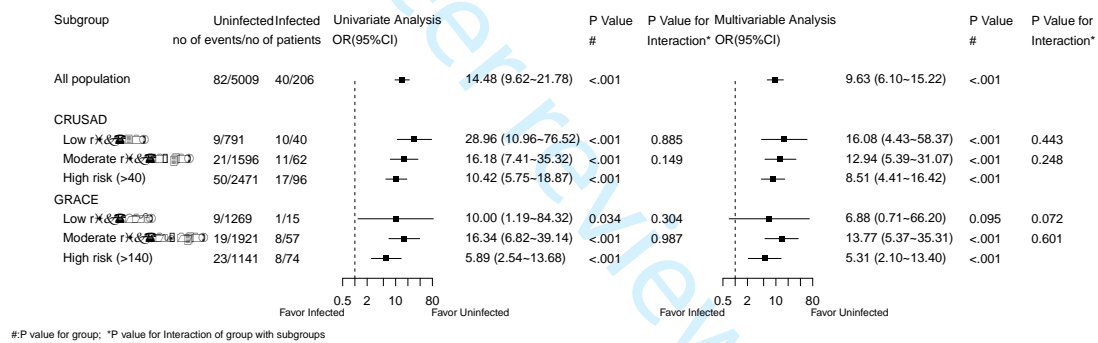
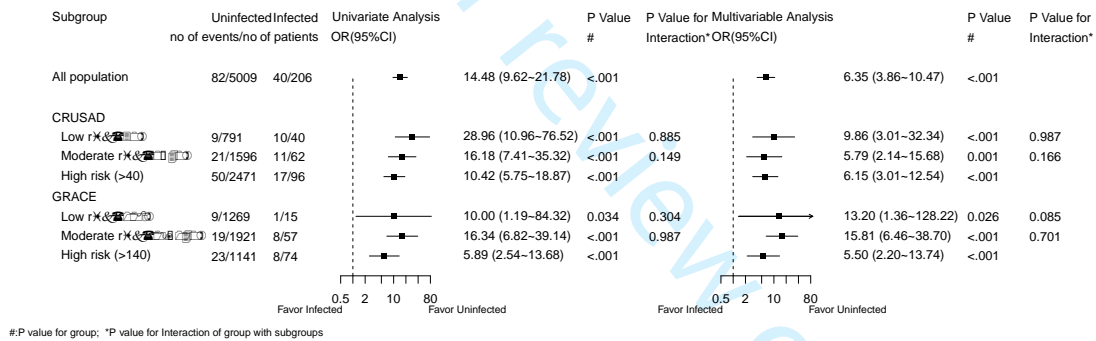


Figure S9. Subgroup analysis of in-hospital major adverse clinical events based on different risk of GRACE and CRUSADE adjusted by the model 2



STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1 3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed	7 NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8 & supplement
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	supplement
Bias	9	Describe any efforts to address potential sources of bias	8-9
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	8-9 & supplement
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	9-10
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	9-10

1	Outcome data	15*	Report numbers of outcome events or summary measures over time	9-10
2	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and	10-11 & supplement
3			their precision (eg, 95% confidence interval). Make clear which confounders were	
4			adjusted for and why they were included	
5			(b) Report category boundaries when continuous variables were categorized	
6			(c) If relevant, consider translating estimates of relative risk into absolute risk for a	
7			meaningful time period	
8	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and	11 & supplement
9			sensitivity analyses	
10	Discussion			
11	Key results	18	Summarise key results with reference to study objectives	11-12
12	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or	14
13			imprecision. Discuss both direction and magnitude of any potential bias	
14	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations,	14-15
15			multiplicity of analyses, results from similar studies, and other relevant evidence	
16	Generalisability	21	Discuss the generalisability (external validity) of the study results	14-15
17	Other information			
18	Funding	22	Give the source of funding and the role of the funders for the present study and, if	15-16
19			applicable, for the original study on which the present article is based	

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

BMJ Open

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

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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Infectious diseases
Keywords:	Coronary heart disease < CARDIOLOGY, Coronary intervention <

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	CARDIOLOGY, Cardiology < INTERNAL MEDICINE

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Original article**Impact of infection for non-ST-elevation acute coronary syndrome patients undergoing percutaneous coronary intervention: insight from a multicentre observational cohort from China**

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Running Title: Infection of NSTEMI-ACS and PCI

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For peer review only

Abstract

Objectives: we aimed to describe the association between in-hospital infection and the prognosis among non-ST-elevation acute coronary syndrome (NSTEMI) patients who received percutaneous coronary intervention (PCI).

Design: This observational cohort originated from the database for NSTEMI patients who underwent percutaneous coronary intervention from January 1, 2010, to December 31, 2014.

Setting: five centres from south China

Participants: This multicentre observational cohort study consecutively included 8197 NSTEMI patients 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 tumor, pregnant or cardiogenic shock at 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 hospitalization. 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%) occurred infection. Patients with infection had a higher rate of in-hospital all-cause death and major bleeding (4.4% vs. 0.2%, 16.5% vs. 1.2% respectively, $P < .001$). After adjusting for confounders, infection remained independently associated with in-hospital and long-term all-cause death (OR, 13.19, 95% CI: 4.59-37.87; HR, 2.03, 95% CI: 1.52-2.71; $P < .001$) and major bleeding (OR, 10.24; 95% CI: 6.17-16.98; HR, 5.31, 95% CI: 3.49-8.08; $P < .001$). Subgroup analysis

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4 confirmed these results.
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6 **Conclusions:** The incidence of infection is low in hospitalization, but it is associated
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9 with worse in-hospital and long-term outcomes.
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11 **Key Words:** Non-ST-elevation acute coronary syndrome; Percutaneous coronary
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14 intervention; Infection; Outcomes.
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For peer review only

Strengths and limitations of this study

- We widely included NSTEMI-ACS patients who received PCI treatment from China.
- The characteristics of infection was detailed reported which included the time and infection type.
- Validation was done in different subgroups and variables which is our best effort based on the database.
- The potential bias may be neglected because of the study design.
- The etiology test of the infection is absent which limited the advanced exploration of the mechanism.

Introduction

The incidence of non-ST-elevation acute coronary syndrome (NSTEMI) is increasing, and approximately 80% of all ACS patients are NSTEMI¹. Despite that there are more comorbidities in patients with ST-segment elevation myocardial infarction (STEMI), the NSTEMI patients still suffer high rate of cardiovascular events both in elder and whole population.^{1, 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 optimize resource utilization.

Infection can activate platelets and the coagulation system, resulting in the 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, information about infection in patients with NSTEMI remains scanty. Only one study of 174 octogenarian patients with ACS evaluated the impact of infection on clinical outcomes¹⁰. Thus, we aimed to assess the incidence of infection and its association with short- and long-term clinical outcomes in NSTEMI patients undergoing PCI.

Methods

Study design and patients

This observational cohort study consisted of consecutive NSTEMI patients undergoing PCI from Jan 2010 to Dec 2014 at five hospitals in China. Only patients with adequate information to diagnose or rule out infection were included. Patients were

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3 excluded if they were diagnosed with a malignant tumor before the index date, pregnant
4 or presenting with cardiogenic shock. The method to search and identify appropriate
5 NSTEMI-ACS patients has been outlined previously¹¹. The study protocol was approved
6 by the central ethics committee of the Guangdong Provincial People's Hospital, with a
7 waiver of informed consent. The study was conducted in accordance with the
8 Declaration of Helsinki.
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17 **Data collection and procedures**

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Data on demographics, patient history, laboratory tests, examinations, and medication
history were collected by investigators in the first interview after admission. The
medicines and PCI procedures were applied according to international guidelines and
clinical evidence¹².

Infection during the index hospitalization was diagnosed according to the presence
of any symptoms, signs and/or laboratory indicating infection. Once confirmed by the
infection control doctors service, appropriate antibiotics were prescribed⁸. 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
hospitalization. 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 Prevention¹³.

57 **Clinical outcomes and follow up**

The primary outcome was in-hospital all-cause death and in-hospital major bleeding as

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4 defined by the Bleeding Academic Research Consortium definition (grades 3-5)¹⁴.

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6 Secondary outcomes were: (1) major adverse clinical events (MACE), consisting of all-
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8 cause death, myocardial infarction, or major bleeding during hospitalization; and (2)
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10 all-cause death or major bleeding during follow-up.
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14 All patients were followed-up by trained nurses via telephone interview or clinic
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16 visits from Nov 2015 to Dec 2016. Relevant information was also collected from the
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18 residence registration system and from the clinical records of the patients who were
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20 readmitted. The details of clinical events and follow-up have been previously
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22 described¹¹. All adverse clinical events were evaluated by an independent clinical
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24 events committee that was masked to the infection details.
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29 30 **Statistical analysis**

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32 All patients were divided into groups with or without infections. Continuous variables
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34 with a normal distribution are presented as the mean \pm SD, and those with an
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36 asymmetric distribution are presented as the median and interquartile range (Q25-Q75).
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38 Student's t test or Wilcoxon rank-sum test were used to compare the continuous
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40 variables. Categorical variables are presented as frequencies and were compared by the
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42 Fisher exact test or chi-square test. Univariate and multivariable analyses were
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44 performed to evaluate the relationship between infection and clinical outcomes.
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46 Variables that were significant in the univariate analysis or clinically important were
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48 included in the multivariable models. Considering the low incidence of adverse
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50 outcomes but potential high incidence of confounders, two models were developed for
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52 each multivariable analysis. The first model (model 1) included infection, anemia,
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4 type of disease (unstable angina and non-ST-elevation acute myocardial infarction),
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6 gender, current smokers, heart failure, and estimate glomerular filtration rate (eGFR).
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9 The second model (model 2) included radial access, cardiac biomarker positive, time
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11 to procedure, treated multi-vessel, diabetes mellitus, hypertension, prior myocardial
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13 infarction, and prior stroke. We performed subgroup analyses by older age, gender,
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15 current smokers, diabetes mellitus, types of disease, heart failure, anemia and chronic
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17 kidney disease. Analysis based on different types of infections was reported. We also
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19 introduced the GRACE (Global Registry of Acute Coronary Events)¹⁵ and CRUSADE
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21 (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse
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23 Outcomes With Early Implementation of the ACC/AHA Guidelines) score¹⁶ and
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25 compared the infection outcomes among different GRACE or CRUSADE risk groups
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27 (low, medium, or high risk). All data analyses were performed with SAS (version 9.4,
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29 SAS Institute, 210 Cary, North Carolina, USA). A two-sided $P < 0.05$ was considered
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31 significant.
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40 Propensity score analyses were conducted to test the robustness of the results. All
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42 factors listed in **Table 1** were considered in the propensity score model development.
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45 The heterogeneity analysis between the centers was conducted using meta-analysis
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47 methods.
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50 **Patient and public involvement**

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53 There was no patient or public involvement in any step of this study.
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56 **Results**

57 **Baseline characteristic**

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4 From January 1, 2010, to December 31, 2014, a total of 8197 consecutive NSTEMI-ACS
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6 patients underwent PCI at the 5 hospitals in China. Of the 5215 patients who met the
7
8 final criteria, 206 (3.95%) received a diagnosis of infection, and 183 (89%) of them
9
10 occurred within one week after hospital admission (**Figure S1**). **Table 1** shows the
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12 baseline characteristics of patients with and without infection. The patients with
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14 infection were older and had a low body weight. These patients were more likely to
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16 have a history of myocardial infarction, stroke, hypertension and diabetes, and more
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18 often had a diagnosis of heart failure, anemia and the use of intra-aortic balloon pump
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20 and dual antiplatelet therapy. Patients with infection had lower left ventricular ejection
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22 fraction, eGFR but higher GRACE risk scores compared with those without infection.
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24 However, the CRUSADE risk score was similar between the two groups.
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33 **In-hospital clinical outcomes**

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35 Patients with infection had a higher rate of in-hospital all-cause death (4.4% vs. 0.2%),
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37 major bleeding (16.5% vs. 1.2%), and MACE (21.4% vs. 1.7%) compared with patients
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39 without infection (all $P < .001$) (**Table 2**). However, the rate of in-hospital myocardial
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41 infarction was similar between the two groups ($P = 0.726$).
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46 Univariable analyses showed that infection was a predictor for in-hospital all cause
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48 death (odds ratios [OR] 22.96; 95% confidence interval [CI], 9.23-57.14, $P < .001$),
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50 major bleeding (OR, 16.30; 95% CI, 10.42-25.50; $P < .001$), and MACE (OR, 14.48;
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52 95%CI, 9.62-21.78; $P < .001$). After adjusting for other confounding variables,
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54 multivariable logistic regression showed that infection was significantly and
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56 independently related to the risk of the above outcomes (**Figure 1**).
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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 ($P<.001$) (**Table 2, Figure 2 and 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: hazard ratio [HR], 2.03; 95% CI, 1.52-2.71; $P<.001$; major bleeding: HR, 5.31; 95% CI, 3.49-8.08; $P<.001$; death or major bleeding: HR, 2.47; 95% CI, 1.92-3.19; $P<.001$). The similar result was reported in the other adjusted model (**Figure 1**).

Subgroup analyses

Subgroup analyses similarly revealed that infection was independently related to the 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 **Figure S3, Figure S4, and Figure 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, the UTI was independently associated with all-cause death (**Table S1**).

Propensity Score Analyses

We matched 740 patients with or without infection in a 1:4 ratio (**Table S2 and Figure S6**). The result showed a higher rate of major bleeding during the hospital stay (OR, 18; 95%CI, 2.40-134.8, $P=0.015$), and a similar result was found at follow-up (HR,

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4 5.33;95%CI, 1.55-18.30, P=0.007), but matched results showed an absence of a
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6 significant difference in all-cause death (in-hospital: OR, 4.01; 95%CI, 0.25-64.30;
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8 follow-up: OR, 2; 95%CI, 0.97-4.12)(Table S3).
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11 **Discussion**

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14 This study demonstrates that infection was uncommon in a contemporary cohort
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16 of NSTEMI-ACS patients who underwent PCI. But still the in-hospital infection among
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18 NSTEMI-ACS patients received PCI is significant associated with higher risk of in-
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20 hospital and long-term clinical prognoses, such as all-cause death, major bleeding as
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22 well as the MACE.
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27 The prevalence of infection in our study is similar to those results for the STEMI
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29 population. Data from 5,745 STEMI patients enrolled in the APEX-AMI trial
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31 demonstrated that the prevalence of serious infection was 2.4%, and that infection was
32
33 associated with higher 90-day mortality (29%)⁹. Also, another study of 1,486 STEMI
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35 patients reported the prevalence of serious infection at 3.9% and the 30-day mortality
36
37 was up to 53% in these patients⁸. The conclusions for these 2 studies paralleled our
38
39 conclusion: infection is uncommon but associated with worse clinical outcomes. A
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41 recent retrospective cohort analyses of 174 octogenarians with ACS, for whom the
42
43 patients with infection had a higher in-hospital, 30-day and long-term mortality than
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45 patients without infection¹⁰. However, that study was confined to patients older than 85
46
47 years who were admitted to the coronary care unit, the different ACS types were never
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49 specified, and the relatively liberal use of bare metal stents does not conform with the
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51 contemporary more liberal use of drug eluting stents^{17, 18}.
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4 To our acknowledge, this study is the first to demonstrate the role of infection on
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6 patients with NSTEMI-ACS. Although the prevalence of infections was similar to the
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8 previous studies of STEMI^{8, 9}, the 30 and 90-day death rates were lower than those
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10 studies. These low rates might be the result of patient characteristics of our study with
11
12 less patients requiring intra-aortic balloon pump support, mechanical ventilation and
13
14 transfusion. However, our conclusions paralleled: patients with infections were
15
16 associated with worse outcomes. This association remained consistent after the
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18 adjustment of other important potential risk factors for outcomes such as radial access,
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20 cardiac biomarker positive, time to revascularization, and treated multi-vessel.
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27 Although infections had a negative impact on patients with NSTEMI-ACS, the
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29 underlying pathophysiologic mechanism remains unclear. Corrales-Medina et al.¹⁹
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31 suggested that infection increased the mortality of patients who underwent elective PCI
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33 due to the change in plaques triggered by acute inflammatory reactions. Indeed,
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35 infection has been implicated as a factor contributing to initiation, progression and
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37 rupture of an atherosclerotic plaque²⁰. Infectious vectors have been reported to induce
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39 the expression of adhesion molecules such as heat shock protein 60 and monocyte
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41 chemoattractant protein-1 on endothelial cells, which can activate the endothelium and
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43 the formation of a lipid core²¹⁻²⁴. Additionally, the SIXTUS study group²⁵ demonstrated
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45 that platelet activation and TxB₂ overproduction are related to infections via Toll-like
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47 receptor 4. Moreover, MODICA et al.²⁶ reported that aspirin non-responsiveness was
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49 often observed in patients with pneumonia. Also, increased coagulation activity has
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51 been observed in pneumonia³. Therefore, infection can activate platelets and the
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4 coagulation system, which plays a critical role in deteriorating outcomes in patients
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6 with ACS. In contrast to previous STEMI reports^{8, 9}, we did not find a significant
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8 association of infection with myocardial infarction due to the low incidence of
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10 myocardial infarction in our study. However, our results were similar to previous
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12 studies that reported major bleeding was more frequent in patients with infection.
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14 Although the PLATelet inhibition and patient Outcomes (PLATO) trial demonstrated
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16 that ticagrelor, a more potent and consistent platelet P2Y₁₂ inhibitor, was associated
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18 with significantly fewer pulmonary infections and death related to infection than
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20 clopidogrel, the incidence of bleeding in patients with infection in that study was not
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22 reported⁴. Because of dysfunction of platelets and the coagulation system, patients with
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24 infection might be at higher risk of ischemia and bleeding. Therefore, more attention
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26 should be paid to patients with infection when antithrombotic therapy was determined.
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28 Finally, infection can also result in worse outcomes for NSTEMI-ACS patients through
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30 increasing catecholamines and potentially adverse hemodynamic effects, such as
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32 coronary vasoconstriction and increased myocardial metabolic demands²⁷.
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43 Although UTI was associated to some degree with in-hospital all-cause death, it
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45 was not associated with other worse outcomes. One reason why pulmonary infection is
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47 related to these worse clinical outcomes, while UTI is not, could be the lower
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49 prevalence of UTI comparing to pulmonary infection (0.3% vs. 2.6%). The prevalence
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51 of UTI was lower in our study compared with STEMI patients (0.3% vs. 7%)⁸.
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53 Therefore, when the population sample size was expanded, UTI would be similar to the
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55 pulmonary infection related to the worse clinical outcomes.
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Limitations

The study had several limitations. First, as a retrospective study a causal relationship between the infection and outcomes could not be determined. Second, despite adjustment for important confounders, we could not completely eliminate all the potential bias including selection bias. Third, although the infections were not centrally adjudicated, the infection was confirmed by the infection control services who were authorized to approve the use of antibiotic.

Conclusions

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

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37 **Authors' contributions**

39
40 P-C He designed and supervised the study; P-Y Chen, Y-H Liu, L Jiang, X-B Wei and
41
42 W Guo performed the study, and C-Y Duan analyzed the data; Y-H Liu and other
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44 authors provided the samples and demographics from patients and controls; Y-H Liu
45
46 and P-Y Chen wrote the manuscript; N Tan, J-Y Chen and P-C He revised the
47
48 manuscript for important intellectual content.

53 **Conflict of Interest**

55
56 The authors declared no potential conflicts of interest with respect to the research,
57
58 authorship, and/or publication of this article.

Ethics approval and consent to participate

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.

Data availability statement

Data source for this study is a retrospective public health database with data which all hospitalizations that were already anonymized. Data were confidentially stored once the original study published according to the original protocol, but data are available upon reasonable request.

Open access

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For peer review only

Table legends

Table 1. The baseline characteristics at index hospitalization

Table 2. In-hospital and long-term clinical outcomes

Table S1. Univariate and multivariable logistic for clinical outcomes by stratifying infection subtype.

Table S2 Propensity Score Analyses

Table S3 Outcomes of Propensity Score Analyses

Figure legends

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

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

Figure S1. Time from hospital admission to the diagnosis of infection among all patients.

Figure S2. Kaplan-Meier estimated event rates of all cause death or major bleeding

Figure S3. Subgroup analysis of in-hospital all cause death

Figure S4. Subgroup analysis of in-hospital major bleeding

Figure S5. Subgroup analysis of in-hospital major adverse clinical events

Figure S6. Distributions of propensity scores between the two groups before and after matching (the first row is the density plots and the second row is the QQ plots)

Table 1. The baseline characteristics at index hospitalization

	All patients*			<i>P</i> value
	Uninfected (N=5009)	Infected (N=206)	Total (N=5215)	
Demographics				
Age, y	63.61 ± 10.30	70.86 ± 9.20	63.90 ± 10.36	<.001
Age ≥ 65 y	2380(47.5%)	157(76.2%)	2537(48.6%)	<.001
Female	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, bpm	73.81 ± 10.91	77.75 ± 15.62	73.96 ± 11.16	<.001
Blood pressure, mmHg				
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%)	<.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%)	<.001
Diabetes mellitus	1509(30.1%)	96(46.6%)	1605(30.8%)	<.001
Presentation characteristics				

	All patients*			<i>P</i> value
	Uninfected (N=5009)	Infected (N=206)	Total (N=5215)	
IABP	44(0.9%)	30(14.6%)	74(1.4%)	<.001
CRUSAD	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	<.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, n(%)	489(9.8%)	66(32.0%)	555(10.6%)	<.001
LVEF, %	61.79 ± 10.77	55.99 ± 13.71	61.54 ± 10.98	<.001
eGFR, mL/min/1.73m ²	81.64 ± 24.99	60.85 ± 28.14	80.81 ± 25.45	<.001
eGFR ≤ 60, n(%)	851(17.0%)	101(49.0%)	952(18.3%)	<.001
Serum creatinine, µmol/dL	1.05 ± 0.69	1.55 ± 1.28	1.07 ± 0.73	<.001
Hematocrit, g/L	0.39 ± 0.05	0.35 ± 0.06	0.39 ± 0.05	<.001
Anemia, n(%)	1605(32.0%)	127(61.7%)	1732(33.2%)	<.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%)	<.001
β-blocker	4245(84.7%)	165(80.1%)	4410(84.6%)	0.070
Procedure characteristics, n(%)				

	All patients*			<i>P</i> value
	Uninfected (N=5009)	Infected (N=206)	Total (N=5215)	
Radial access	4470(89.2%)	154(74.8%)	4624(88.7%)	<.001
Coronary anatomy				
Any left main	690(13.8%)	49(23.8%)	739(14.2%)	<.001
Multi-vessel 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
Multi-vessel	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)	<.001
In 24 hours	2817(56.2%)	81(39.3%)	2898(55.6%)	<.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)	<.001

*Abbreviations: IABP=intra-aortic balloon pump; GRACE=Global Registry of Acute

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4 Coronary Events; CRUSADE=Can Rapid Risk Stratification of Unstable Angina
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6 Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA
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8 Guidelines; NSTEMI=Non-ST elevation myocardial infarction; LVEF=left ventricular
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10 ejection fraction; eGFR=Estimate glomerular filtration rate; PTCA=Percutaneous
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12 transluminal coronary angioplasty. ACE=angiotensin-converting enzyme;
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17 ARB=angiotensin receptor blocker.
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Table 2 In-hospital and Long-term clinical outcomes

Outcomes	Uninfected (N=5009)	Infected (N=206)	P value
In-hospital outcomes			
Death*	10(0.2%)	9(4.4%)	<.001
Myocardial infarction	17(0.3%)	1(0.5%)	0.726
Death or myocardial infarction	27(0.5%)	10(4.9%)	<.001
Major bleeding	62(1.2%)	34(16.5%)	<.001
Death or Myocardial infarction or major bleeding	84(1.7%)	44(21.4%)	<.001
Long-term outcomes			
30 days			
Death	17(0.3%)	10(4.9%)	<.001
Major bleeding	61(1.2%)	31(15.0%)	<.001
Death or major bleeding	74(1.5%)	37(18.0%)	<.001
One year			
Death	93(1.9%)	35(17.0%)	<.001
Major bleeding	75(1.5%)	34(16.5%)	<.001
Death or major bleeding	161(3.2%)	56(27.2%)	<.001
Three years			
Death	346(6.9%)	61(29.6%)	<.001
Major bleeding	111(2.2%)	36(17.5%)	<.001
Death or major bleeding	437(8.7%)	81(39.3%)	<.001

*All cause death;

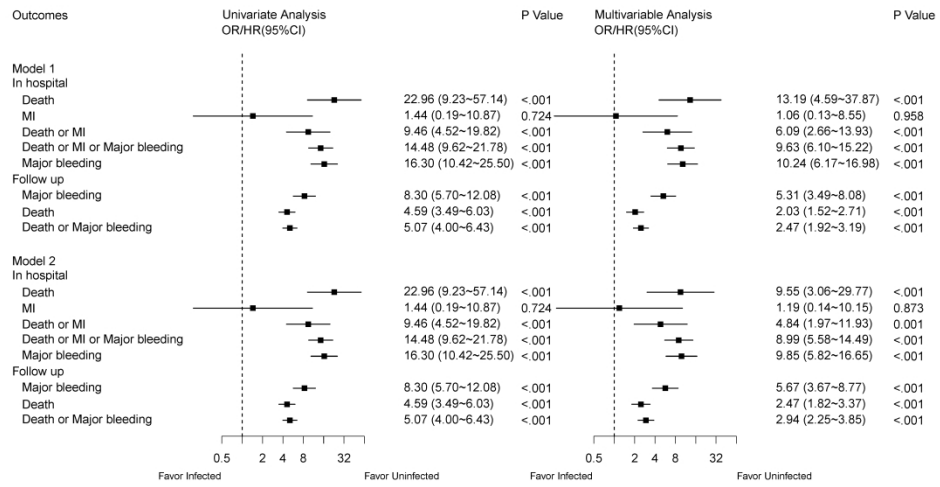


Figure 1. Univariate and multivariable logistic or Cox analysis for clinical outcomes

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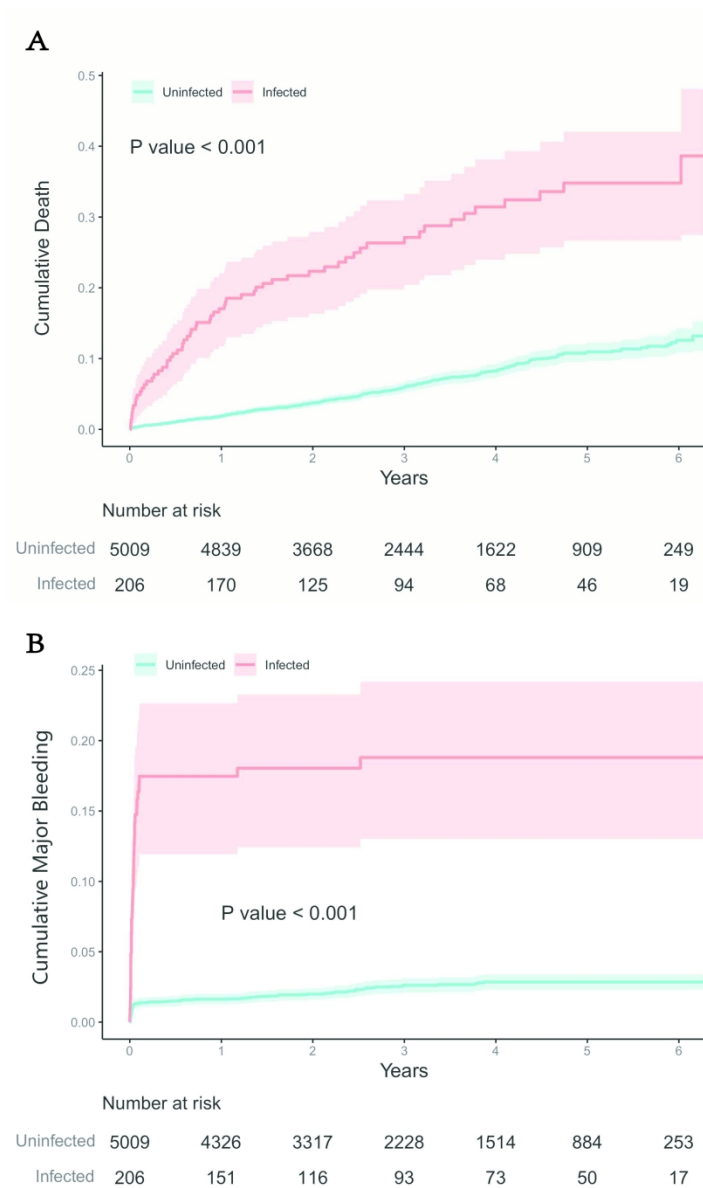


Figure 2. Kaplan-Meier estimated event rates of all cause death (A) and major bleeding (B)

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Supplementary Appendix 1

For peer review only

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Table S1 Univariate and multivariable logistic for clinical outcomes by stratifying infection subtype.

Outcomes (Compare with uninfected patients)	Univariate analysis			Multivariable analysis		
	OR	95%CI	P value	OR	95%CI	Pvalue
Model 1						
In hospital						
Death						
Community acquired pulmonary infections	17.24	4.66~63.73	<.001	8.56	2.06~35.57	0.003
Hospital acquired pulmonary infections	23.25	4.95~109.28	<.001	11.51	2.15~61.49	0.004
Urinary tract infection	31.24	3.78~258.58	0.001	21.59	2.32~200.48	0.007
Other infection	29.99	8.01~112.27	<.001	23.14	5.59~95.86	<.001
Major Bleeding						
Community acquired pulmonary infections	28.32	16.54~48.48	<.001	18.13	9.92~33.16	<.001
Hospital acquired pulmonary infections	14.80	6.37~34.43	<.001	9.04	3.63~22.49	<.001
Urinary tract infection	5.16	0.67~39.50	0.114	3.10	0.39~24.51	0.283
Other infection	4.95	1.50~16.31	0.009	3.25	0.95~11.13	0.061
Death or MI or Major Bleeding						
Community acquired pulmonary infections	21.85	13.05~36.59	<.001	14.23	8.07~25.10	<.001
Hospital acquired pulmonary infections	16.69	8.01~34.77	<.001	11.28	5.14~24.76	<.001
Urinary tract infection	3.76	0.49~28.65	0.202	2.44	0.31~19.04	0.396
Other infection	6.26	2.43~16.13	<.001	4.51	1.69~12.01	0.003
Follow up						
Death						
Community acquired pulmonary infections	5.52	3.78~8.06	<.001	2.06	1.39~3.06	<.001
Hospital acquired pulmonary infections	6.16	3.78~10.02	<.001	2.57	1.56~4.24	<.001
Urinary tract infection	3.66	1.37~9.82	0.010	2.38	0.88~6.39	0.086
Other infection	2.62	1.44~4.79	0.002	1.45	0.79~2.66	0.232
Major Bleeding						
Community acquired pulmonary infections	14.29	9.26~22.06	<.001	8.86	5.49~14.27	<.001
Hospital acquired pulmonary infections	7.08	3.30~15.20	<.001	4.16	1.87~9.27	<.001

Outcomes (Compare with uninfected patients)	Univariate analysis			Multivariable analysis		
	OR	95%CI	P value	OR	95%CI	Pvalue
Urinary tract infection	2.54	0.35~18.13	0.354	1.66	0.23~11.98	0.616
Other infection	2.49	0.79~7.83	0.119	1.83	0.57~5.85	0.307
Death or Major Bleeding						
Community acquired pulmonary infections	6.83	4.99~9.35	<.001	2.85	2.05~3.97	<.001
Hospital acquired pulmonary infections	6.32	4.08~9.79	<.001	2.93	1.87~4.61	<.001
Urinary tract infection	2.85	1.07~7.64	0.037	1.78	0.66~4.78	0.253
Other infection	2.62	1.51~4.55	0.001	1.60	0.92~2.80	0.099
Model 2						
In hospital						
Death						
Community acquired pulmonary infections	17.24	4.66~63.73	<.001	2.01	0.37~10.86	0.418
Hospital acquired pulmonary infections	23.25	4.95~109.28	<.001	6.48	0.92~45.66	0.061
Urinary tract infection	31.24	3.78~258.58	0.001	14.68	0.96~223.51	0.053
Other infection	29.99	8.01~112.27	<.001	5.02	0.98~25.62	0.052
Major Bleeding						
Community acquired pulmonary infections	28.32	16.54~48.48	<.001	11.91	6.10~23.28	<.001
Hospital acquired pulmonary infections	14.80	6.37~34.43	<.001	7.47	2.80~19.90	<.001
Urinary tract infection	5.16	0.67~39.50	0.114	1.92	0.15~25.23	0.619
Other infection	4.95	1.50~16.31	0.009	1.05	0.26~4.23	0.942
Death or MI or Major Bleeding						
Community acquired pulmonary infections	21.85	13.05~36.59	<.001	9.69	5.12~18.37	<.001
Hospital acquired pulmonary infections	16.69	8.01~34.77	<.001	10.00	4.33~23.12	<.001
Urinary tract infection	3.76	0.49~28.65	0.202	1.59	0.13~19.16	0.713
Other infection	6.26	2.43~16.13	<.001	1.71	0.54~5.35	0.360
Follow up						
Death						
Community acquired pulmonary infections	5.52	3.78~8.06	<.001	2.70	1.81~4.03	<.001
Hospital acquired pulmonary infections	6.16	3.78~10.02	<.001	3.56	2.15~5.90	<.001
Urinary tract infection	3.66	1.37~9.82	0.010	2.90	1.08~7.80	0.034

Outcomes (Compare with uninfected patients)	Univariate analysis			Multivariable analysis		
	OR	95%CI	P value	OR	95%CI	Pvalue
Other infection	2.62	1.44~4.79	0.002	1.32	0.71~2.44	0.376
Major Bleeding	14.29	9.26~22.06	<.001	6.30	3.79~10.49	<.001
Community acquired pulmonary infections	7.08	3.30~15.20	<.001	3.51	1.57~7.84	0.002
Hospital acquired pulmonary infections	2.54	0.35~18.13	0.354	1.42	0.19~10.39	0.731
Urinary tract infection	2.49	0.79~7.83	0.119	1.01	0.31~3.29	0.981
Other infection						
Death or Major Bleeding						
Community acquired pulmonary infections	6.83	4.99~9.35	<.001	3.55	2.55~4.94	<.001
Hospital acquired pulmonary infections	6.32	4.08~9.79	<.001	3.46	2.20~5.45	<.001
Urinary tract infection	2.85	1.07~7.64	0.037	1.96	0.73~5.28	0.181
Other infection	2.62	1.51~4.55	0.001	1.38	0.78~2.41	0.266

Model 1 included age, gender, current smokers, heart failure, anemia, type of disease, estimate glomerular filtration rate.

Model 2 included diabetes mellitus, hypertension, prior myocardial infarction, prior stroke, radial access, chronic kidney disease, intra-aortic balloon pump.

Table S2 Propensity Score Analyses

	Propensity Score Analyses			
	Uninfected	Infected	Total	<i>P</i> value
	(N=592)	(N=148)	(N=740)	
Demographics				
Age, y	70.39±9.09	70.24±9.15	70.36±9.09	0.861
Age ≥ 65 y	444(75.0%)	110(74.3%)	554(74.9%)	0.865
Female	166(28.0%)	37(25.0%)	203(27.4%)	0.458
Weight, kg	63.25±12.22	63.99±12.03	63.40±12.18	0.510
Heart rate, bpm	75.01±12.30	75.37±12.80	75.08±12.40	0.751
Blood pressure, mmHg				
Systolic	137.48±21.34	137.12±21.66	137.41±21.39	0.854
Diastolic	76.07±11.68	76.00±11.13	76.06±11.56	0.944
Medical history and risk factors, n(%)				
Current Smoker	157(26.5%)	41(27.7%)	198(26.8%)	0.771
Myocardial Infarction	126(21.3%)	29(19.6%)	155(20.9%)	0.651
Percutaneous coronary intervention	100(16.9%)	25(16.9%)	125(16.9%)	1
Coronary-artery bypass surgery	10(1.7%)	4(2.7%)	14(1.9%)	0.418
Stroke	36(6.1%)	9(6.1%)	45(6.1%)	1
Atrial Fibrillation	19(3.2%)	5(3.4%)	24(3.2%)	0.917
Hypertension	445(75.2%)	111(75.0%)	556(75.1%)	0.966
Diabetes mellitus	248(41.9%)	67(45.3%)	315(42.6%)	0.457
Type of disease, n(%)				
NSTEMI	225(38.0%)	60(40.5%)	285(38.5%)	0.571
Unstable angina	367(62.0%)	88(59.5%)	455(61.5%)	NA
Heart Failure, n(%)	123(20.8%)	32(21.6%)	155(20.9%)	0.821

Propensity Score Analyses				
	Uninfected	Infected	Total	<i>P</i> value
	(N=592)	(N=148)	(N=740)	
LVEF, %	59.67±12.02	57.81±13.16	59.29±12.28	0.118
eGFR, mL/min/1.73m ²	65.65±26.10	66.66±28.13	65.85±26.50	0.678
eGFR ≤ 60, n(%)	234(39.5%)	58(39.2%)	292(39.5%)	0.940
Serum creatinine, μmol/dL	1.39±1.16	1.43±1.32	1.40±1.19	0.726
Hematocrit, g/L	0.36±0.05	0.37±0.05	0.36±0.05	0.690
Anemia, n(%)	337(56.9%)	81(54.7%)	418(56.5%)	0.630
Cardiac biomarker positive, n(%)	344(61.5%)	84(59.2%)	428(61.1%)	0.603
In hospital medication, n(%)				
Dual antiplatelet therapy	558(94.3%)	138(93.2%)	696(94.1%)	0.641
Statin	576(97.3%)	145(98.0%)	721(97.4%)	0.642
ACE inhibitor or ARB	487(82.3%)	123(83.1%)	610(82.4%)	0.809
Calcium-channel blocker	200(33.8%)	46(31.1%)	246(33.2%)	0.532
β-blocker	488(82.4%)	120(81.1%)	608(82.2%)	0.701
Procedure characteristics, n(%)				
Radial access	486(82.1%)	116(78.4%)	602(81.4%)	0.299
Coronary anatomy				
Any left main	117(19.8%)	26(17.6%)	143(19.3%)	0.786
Multi-vessel disease	363(61.3%)	95(64.2%)	458(61.9%)	
Others	112(18.9%)	27(18.2%)	139(18.8%)	
Treated vessel				
Any left main	77(13.0%)	17(11.5%)	94(12.7%)	0.708
Multi-vessel	209(35.3%)	49(33.1%)	258(34.9%)	
Others	306(51.7%)	82(55.4%)	388(52.4%)	

Propensity Score Analyses

	Uninfected	Infected	Total	<i>P</i> value
	(N=592)	(N=148)	(N=740)	
Stent type				
Drug eluting stent	592(100.0%)	148(100.0%)	740(100.0%)	1
Number of stents	2.26±1.29	2.27±1.38	2.26±1.31	0.933
Total length of stents	56.48±35.90	58.22±38.71	56.83±36.46	0.604
Thrombus aspiration	16(2.7%)	3(2.0%)	19(2.6%)	0.642
Time to procedure				
In 24 hours	253(42.7%)	59(39.9%)	312(42.2%)	0.816
24~72 hours	135(22.8%)	35(23.6%)	170(23.0%)	
> 72 hours	204(34.5%)	54(36.5%)	258(34.9%)	

*Abbreviations: NSTEMI=Non-ST elevation myocardial infarction; LVEF=left ventricular ejection fraction; eGFR=Estimate glomerular filtration rate; ACE=angiotensin-converting enzyme; ARB=angiotensin receptor blocker.

Table S3 Outcomes of Propensity Score Analyses

Outcomes	Logistics analysis		
	OR/HR	95%CI	P value
In-hospital Death	4.01	0.25~64.30	0.981
In-hospital Major bleeding	18	2.40~134.8	0.005
In-hospital MI	2.0	0.18~22.20	0.57
In-hospital Death or Major bleeding	17.24	4.66~63.73	<.001
Follow-up Death	2	0.97~4.12	0.06
Follow-up Major bleeding	5.33	1.55~18.30	0.007
Follow-up Death or Major bleeding	2.46	1.29~4.69	0.006

Figure S1. Time from hospital admission to the diagnosis of infection among all patients.

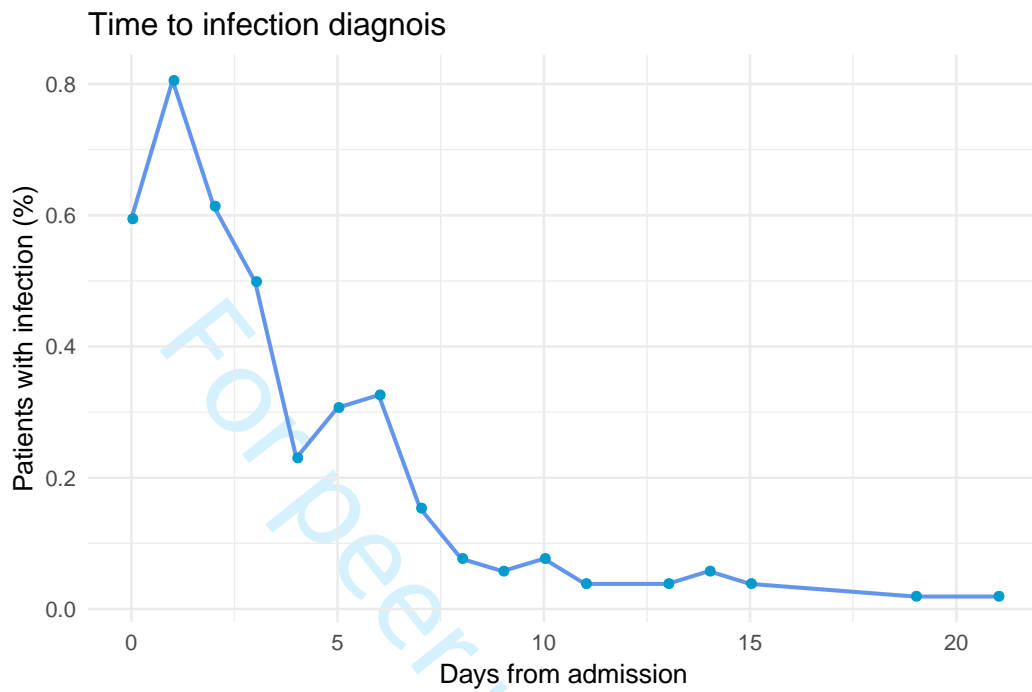
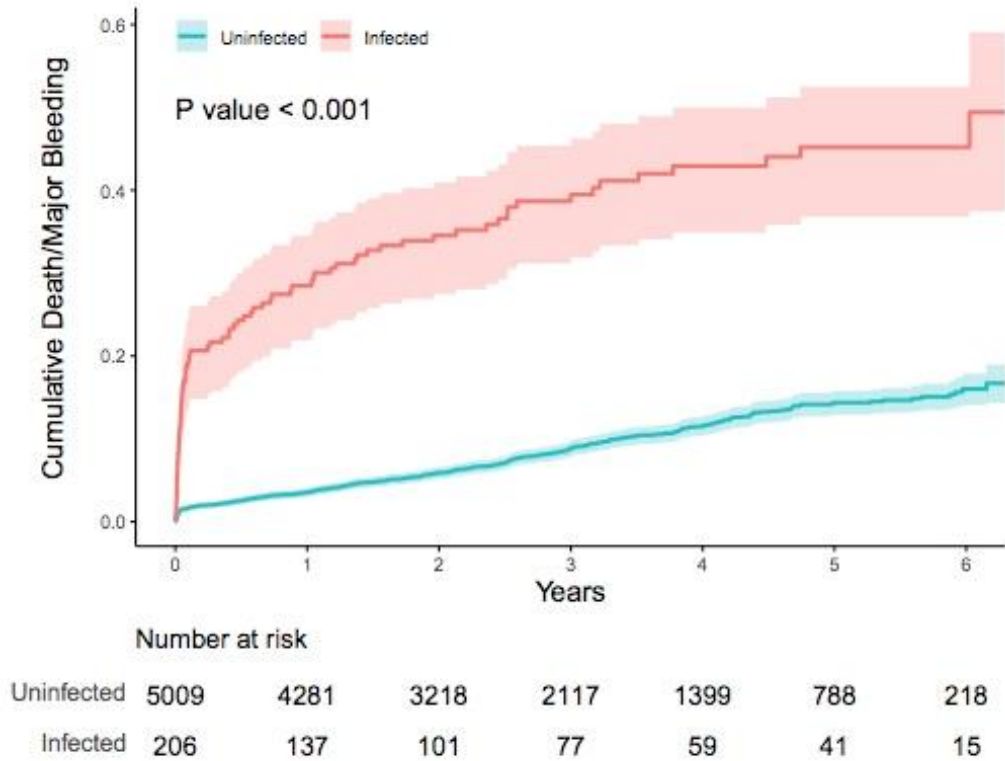


Figure S2. Kaplan-Meier estimated event rates of all cause death or major bleeding



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Figure S3. Subgroup analysis of in-hospital all cause death

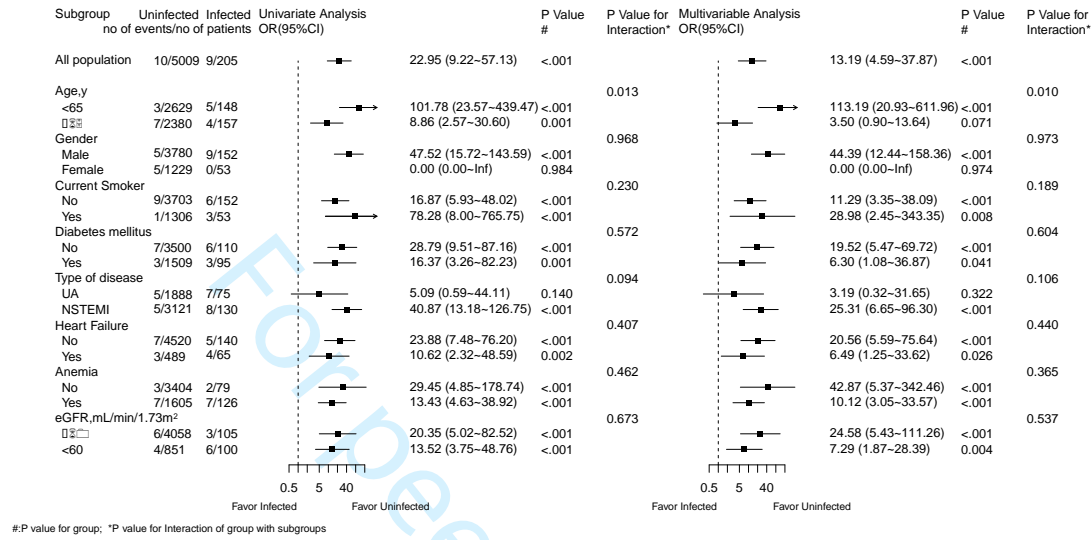


Figure S4. Subgroup analysis of in-hospital major bleeding

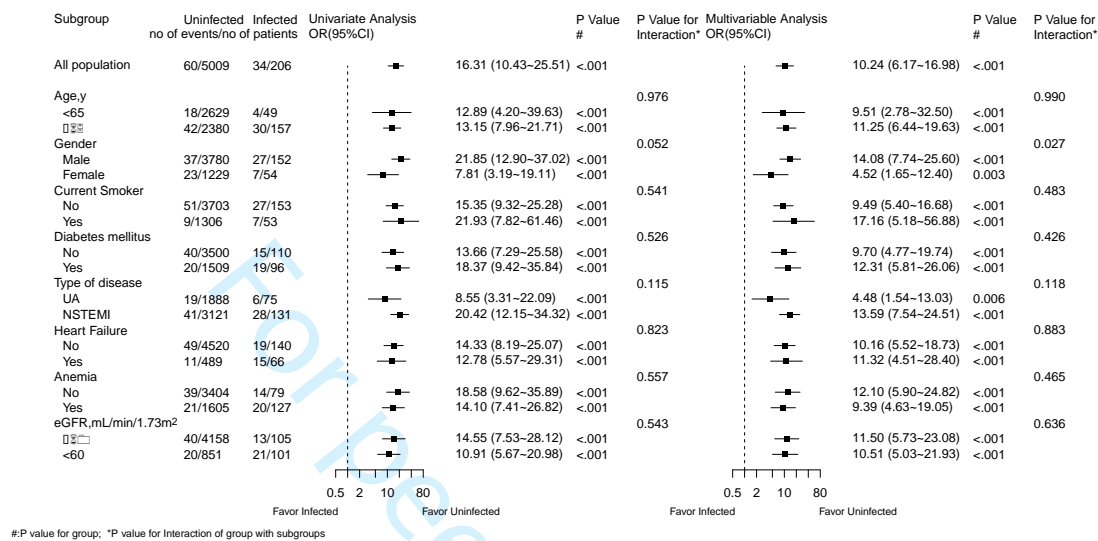


Figure S5. Subgroup analysis of in-hospital major adverse clinical events

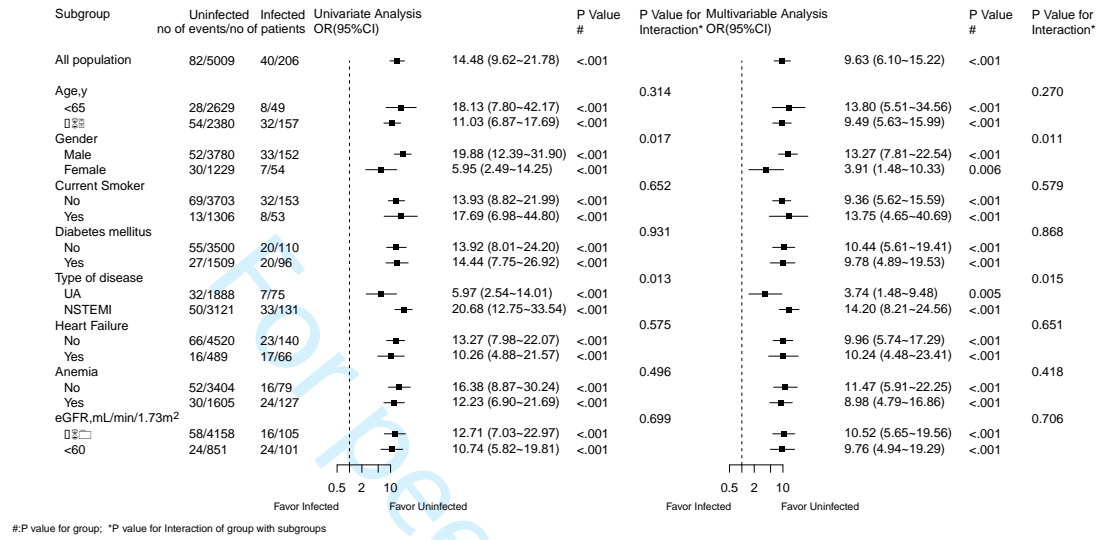
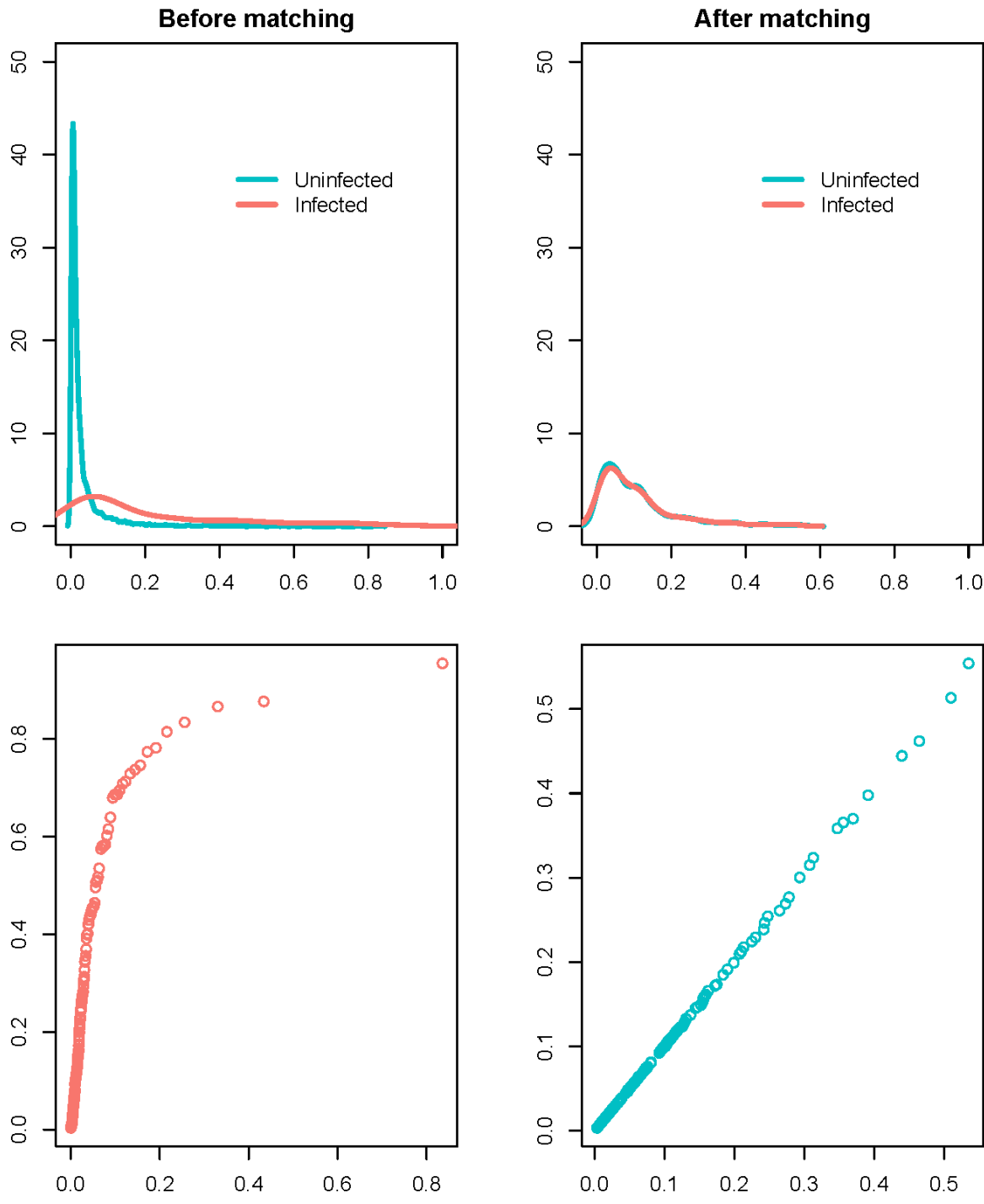


Figure S6. Distributions of propensity scores between the two groups before and after matching (the first row is the density plots and the second row is the QQ plots)



STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1 3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed	7 NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8 & supplement
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	supplement
Bias	9	Describe any efforts to address potential sources of bias	8-9
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	8-9 & supplement
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	9-10
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	9-10

1	Outcome data	15*	Report numbers of outcome events or summary measures over time	9-10
2	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and	10-11 & supplement
3			their precision (eg, 95% confidence interval). Make clear which confounders were	
4			adjusted for and why they were included	
5			(b) Report category boundaries when continuous variables were categorized	
6			(c) If relevant, consider translating estimates of relative risk into absolute risk for a	
7			meaningful time period	
8	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and	11 & supplement
9			sensitivity analyses	
10	Discussion			
11	Key results	18	Summarise key results with reference to study objectives	11-12
12	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or	14
13			imprecision. Discuss both direction and magnitude of any potential bias	
14	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations,	14-15
15			multiplicity of analyses, results from similar studies, and other relevant evidence	
16	Generalisability	21	Discuss the generalisability (external validity) of the study results	14-15
17	Other information			
18	Funding	22	Give the source of funding and the role of the funders for the present study and, if	15-16
19			applicable, for the original study on which the present article is based	

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

BMJ Open

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

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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Infectious diseases
Keywords:	Coronary heart disease < CARDIOLOGY, Coronary intervention <

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	CARDIOLOGY, Cardiology < INTERNAL MEDICINE

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Original article**Impact of infection for non-ST-elevation acute coronary syndrome patients undergoing percutaneous coronary intervention: insight from a multicentre observational cohort from China**

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Running Title: Infection of NSTEMI-ACS and PCI

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For peer review only

Abstract

Objectives: we aimed to describe the association between in-hospital infection and the prognosis among non-ST-elevation acute coronary syndrome (NSTEMI-ACS) patients received percutaneous coronary intervention (PCI).

Design: This observational cohort originated from the database for NSTEMI-ACS underwent percutaneous coronary intervention from January 1, 2010, to December 31, 2014.

Setting: five centres from south China

Participants: This multicentre observational cohort study consecutively included 8197 NSTEMI-ACS patients 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 tumor, pregnant or cardiogenic shock at 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 hospitalization. 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%) occurred infection. Patients with infection had a higher rate of in-hospital all-cause death and major bleeding (4.4% vs. 0.2%, 16.5% vs. 1.2% respectively, $P<.001$). After adjusting for confounders, infection remained independently associated with in-hospital and long-term all-cause death (OR, 13.19, 95% CI: 4.59-37.87; HR, 2.03, 95% CI: 1.52-2.71; $P<.001$) and major bleeding (OR, 10.24; 95% CI: 6.17-16.98; HR, 5.31, 95% CI: 3.49-8.08; $P<.001$). Subgroup analysis

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4 confirmed these results.
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6 **Conclusions:** The incidence of infection is low in hospitalization, but it is associated
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9 with worse in-hospital and long-term outcomes.
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11 **Key Words:** Non-ST-elevation acute coronary syndrome; Percutaneous coronary
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14 intervention; Infection; Outcomes.
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For peer review only

Strengths and limitations of this study

- We widely included NSTEMI-ACS patients who received PCI treatment from China.
- The characteristics of infection was detailed reported which included the time and infection type.
- Validation was done in different subgroups and variables which is our best effort based on the database.
- The potential bias may be neglected because of the study design.
- The etiology test of the infection is absent which limited the advanced exploration of the mechanism.

Introduction

Acute coronary syndrome (ACS) is a leading cause of death both in China and around the world¹. As compared with STEMI patients, those with non-ST elevation acute coronary syndrome (NSTEMI) have shown improved outcomes after the 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 optimize resource utilization.

Infection can activate platelets and the coagulation system, resulting in the 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, information about infection in patients with NSTEMI remains scanty. Only one study of 174 octogenarian patients with ACS evaluated the impact of infection on clinical outcomes¹⁰. Thus, we aimed to assess the incidence of infection and its association with short- and long-term clinical outcomes in NSTEMI patients undergoing PCI.

Methods

Study design and patients

This observational cohort study consisted of consecutive NSTEMI patients undergoing PCI from Jan 2010 to Dec 2014 at five hospitals in China. Only patients

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2
3 with adequate information to diagnose or rule out infection were included. Patients were
4
5 excluded if they were diagnosed with a malignant tumor or infection before the index
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7 date, pregnant or presenting with cardiogenic shock. The method to search and identify
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9 appropriate NSTEMI-ACS patients has been outlined previously¹¹. The study protocol was
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11 approved by the central ethics committee of the Guangdong Provincial People's
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13 Hospital, with a waiver of informed consent. The study was conducted in accordance
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15 with the Declaration of Helsinki.
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20 **Data collection and procedures**

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22 Data on demographics, patient history, laboratory tests, examinations, and medication
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24 history were collected by investigators in the first interview after admission. The
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26 medicines and PCI procedures were applied according to international guidelines and
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28 clinical evidence¹².
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33 Infection during the index hospitalization was diagnosed according to the presence
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35 of any symptoms, signs and/or laboratory indicating infection. Once confirmed by the
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37 infection control doctors service, appropriate antibiotics were prescribed⁸. Infection
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39 was classified as pulmonary, urinary tract infection (UTI) or others (including non-
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41 pulmonary/ non-urinary sepsis and cellulitis), based on the clinical records during
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43 hospitalization. Community-acquired pulmonary infection was defined by a diagnosis
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45 of infection within the first 72 hours of hospital admission, and hospital-acquired
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47 pulmonary infection was defined as those occurring after the first 72 hours and were
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49 diagnosed in accordance with the criteria established by the Centers for Disease Control
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51 and Prevention¹³.
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59 **Clinical outcomes and follow up**

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4 The primary outcome was in-hospital all-cause death and in-hospital major bleeding as
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6 defined by the Bleeding Academic Research Consortium definition (grades 3-5)¹⁴.
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9 Secondary outcomes were: (1) major adverse clinical events (MACE), consisting of all-
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11 cause death, myocardial infarction, or major bleeding during hospitalization; and (2)
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13 all-cause death or major bleeding during follow-up.
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17 All patients were followed-up by trained nurses via telephone interview or clinic
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19 visits from Nov 2015 to Dec 2016. Relevant information was also collected from the
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21 residence registration system and from the clinical records of the patients who were
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23 readmitted. The details of clinical events and follow-up have been previously
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25 described¹¹. All adverse clinical events were evaluated by an independent clinical
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27 events committee that was masked to the infection details.
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31 32 **Statistical analysis**

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34 All patients were divided into groups with or without infections. Continuous variables
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36 with a normal distribution are presented as the mean \pm SD, and those with an
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38 asymmetric distribution are presented as the median and interquartile range (Q25-Q75).
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40 Student's t test or Wilcoxon rank-sum test were used to compare the continuous
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42 variables. Categorical variables are presented as frequencies and were compared by the
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44 Fisher exact test or chi-square test. Univariate and multivariable analyses were
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46 performed to evaluate the relationship between infection and clinical outcomes.
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48 Variables that were significant in the univariate analysis or clinically important were
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50 included in the multivariable models. Considering the low incidence of adverse
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52 outcomes but potential high incidence of confounders, two models were developed for
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4 each multivariable analysis. The first model (model 1) included infection, age, anemia,
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6 type of disease (unstable angina and non-ST-elevation acute myocardial infarction),
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8 gender, current smokers, heart failure, and estimate glomerular filtration rate (eGFR).
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10 The second model (model 2) included radial access, cardiac biomarker positive, time
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12 to procedure, treated multi-vessel, diabetes mellitus, hypertension, prior myocardial
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14 infarction, and prior stroke. We performed subgroup analyses by older age, gender,
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16 current smokers, diabetes mellitus, types of disease, heart failure, anemia and chronic
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18 kidney disease. Analysis based on different types of infections was reported. We also
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20 introduced the GRACE (Global Registry of Acute Coronary Events)¹⁵ and CRUSADE
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22 (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse
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24 Outcomes With Early Implementation of the ACC/AHA Guidelines) score¹⁶ and
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26 compared the infection outcomes among different GRACE or CRUSADE risk groups
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28 (low, medium, or high risk). All data analyses were performed with SAS (version 9.4,
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30 SAS Institute, 210 Cary, North Carolina, USA). A two-sided $P < 0.05$ was considered
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32 significant.
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43 Propensity score analyses were conducted to test the robustness of the results. All
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45 factors listed in **Table 1** were considered in the propensity score model development.
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48 The heterogeneity analysis between the centers was conducted using meta-analysis
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50 methods.
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52 **Patient and public involvement**

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54 There was no patient or public involvement in any step of this study.
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57 **Results**

Baseline characteristic

From January 1, 2010, to December 31, 2014, a total of 8197 consecutive NSTEMI-ACS patients underwent PCI at the 5 hospitals in China. Of the 5215 patients who met the final criteria, 206 (3.95%) received a diagnosis of infection, and 183 (89%) of them occurred within one week after hospital admission (**Figure S1**). **Table 1** shows the baseline characteristics of patients with and without infection. The patients with infection were older and had a 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, anemia and the use of intra-aortic balloon pump and dual antiplatelet therapy. Patients with infection had lower left ventricular ejection fraction, 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 $P < .001$) (**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 for in-hospital all cause death (odds ratios [OR] 22.96; 95% confidence interval [CI], 9.23-57.14, $P < .001$), major bleeding (OR, 16.30; 95% CI, 10.42-25.50; $P < .001$), and MACE (OR, 14.48; 95%CI, 9.62-21.78; $P < .001$). After adjusting for other confounding variables, multivariable logistic regression showed that infection was significantly and

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4 independently related to the risk of the above outcomes (**Figure 1**).

6 **Long-term clinical outcomes**

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9 At a median follow-up of 3.2 years, Kaplan-Meier analysis revealed that patients with
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11 in-hospital infection had a higher risk of long-term death, major bleeding, and death or
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13 major bleeding compared with those without in-hospital infection ($P<.001$) (**Table 2**,
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15 **Figure 2 and Figure S2**). Multivariable cox analyses demonstrated that infection was
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17 independently associated with long-term adverse outcomes even after adjusting for
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19 other potential risk factors (all cause death: hazard ratio [HR], 2.03; 95% CI, 1.52-2.71;
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21 $P<.001$; major bleeding: HR, 5.31; 95% CI, 3.49-8.08; $P<.001$; death or major bleeding:
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23 HR, 2.47; 95% CI, 1.92-3.19; $P<.001$). The similar result was reported in the other
24
25 adjusted model (**Figure 1**).

32 **Subgroup analyses**

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35 Subgroup analyses similarly revealed that infection was independently related to the in-
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37 hospital events (all-cause death, major bleeding, or MACE) according to different
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39 clinical status. The unadjusted and adjusted ORs for infection are presented in **Figure**
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41 **S3, Figure S4, and Figure S5**. Analysis according to the infection subtypes indicated
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43 that pulmonary infection other than UTI was independently associated with poor in-
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45 hospital and follow up clinical outcomes. However, the UTI was independently
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47 associated with all-cause death (**Table S1**).

53 **Propensity Score Analyses**

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56 We matched 740 patients with or without infection in a 1:4 ratio (**Table S2 and Figure**
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58 **S6**). The result showed a higher rate of major bleeding during the hospital stay (OR,
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4 18; 95%CI, 2.40-134.8, P=0.015), and a similar result was found at follow-up (HR,
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6 5.33;95%CI, 1.55-18.30, P=0.007), but matched results showed an absence of a
7
8 significant difference in all-cause death (in-hospital: OR, 4.01; 95%CI, 0.25-64.30;
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10 follow-up: OR, 2; 95%CI, 0.97-4.12)(Table S3).

14 Discussion

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17 This study demonstrates that infection was uncommon in a contemporary cohort
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19 of NSTEMI-ACS patients who underwent PCI. But still the in-hospital infection among
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21 NSTEMI-ACS patients received PCI is significant associated with higher risk of in-
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23 hospital and long-term clinical prognoses, such as all-cause death, major bleeding as
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25 well as the MACE.
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30 The prevalence of infection in our study is similar to those results for the STEMI
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32 population. Data from 5,745 STEMI patients enrolled in the APEX-AMI trial
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34 demonstrated that the prevalence of serious infection was 2.4%, and that infection was
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36 associated with higher 90-day mortality (29%)⁹. Also, another study of 1,486 STEMI
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38 patients reported the prevalence of serious infection at 3.9% and the 30-day mortality
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40 was up to 53% in these patients⁸. The conclusions for these 2 studies paralleled our
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42 conclusion: infection is uncommon but associated with worse clinical outcomes. A
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44 recent retrospective cohort analyses of 174 octogenarians with ACS, for whom the
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46 patients with infection had a higher in-hospital, 30-day and long-term mortality than
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48 patients without infection¹⁰. However, that study was confined to patients older than 85
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50 years who were admitted to the coronary care unit, the different ACS types were never
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52 specified, and the relatively liberal use of bare metal stents does not conform with the
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4 contemporary more liberal use of drug eluting stents^{17, 18}.
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6 To our knowledge, this study is the first to demonstrate the role of infection on
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8 patients with NSTEMI-ACS. Although the prevalence of infections was similar to the
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10 previous studies of STEMI^{8, 9}, the 30 and 90-day death rates were lower than those
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12 studies. These low rates might be the result of patient characteristics of our study with
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14 less patients requiring intra-aortic balloon pump support, mechanical ventilation and
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16 transfusion. However, our conclusions paralleled: patients with infections were
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18 associated with worse outcomes. This association remained consistent after the
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20 adjustment of other important potential risk factors for outcomes such as radial access,
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22 cardiac biomarker positive, time to revascularization, and treated multi-vessel.
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30 Although infections had a negative impact on patients with NSTEMI-ACS, the
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32 underlying pathophysiologic mechanism remains unclear. Corrales-Medina et al.¹⁹
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34 suggested that infection increased the mortality of patients who underwent elective PCI
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36 due to the change in plaques triggered by acute inflammatory reactions. Indeed,
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38 infection has been implicated as a factor contributing to initiation, progression and
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40 rupture of an atherosclerotic plaque²⁰. Infectious vectors have been reported to induce
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42 the expression of adhesion molecules such as heat shock protein 60 and monocyte
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44 chemoattractant protein-1 on endothelial cells, which can activate the endothelium and
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46 the formation of a lipid core²¹⁻²⁴. Additionally, the SIXTUS study group²⁵ demonstrated
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48 that platelet activation and TxB₂ overproduction are related to infections via Toll-like
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50 receptor 4. Moreover, MODICA et al.²⁶ reported that aspirin non-responsiveness was
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52 often observed in patients with pneumonia. Also, increased coagulation activity has
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4 been observed in pneumonia³. Therefore, infection can activate platelets and the
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7 coagulation system, which plays a critical role in deteriorating outcomes in patients
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10 with ACS. In contrast to previous STEMI reports^{8, 9}, we did not find a significant
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13 association of infection with myocardial infarction due to the low incidence of
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16 myocardial infarction in our study. However, our results were similar to previous
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19 studies that reported major bleeding was more frequent in patients with infection.
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22 Although the PLATelet inhibition and patient Outcomes (PLATO) trial demonstrated
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25 that ticagrelor, a more potent and consistent platelet P2Y₁₂ inhibitor, was associated
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28 with significantly fewer pulmonary infections and death related to infection than
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31 clopidogrel, the incidence of bleeding in patients with infection in that study was not
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33
34 reported⁴. Because of dysfunction of platelets and the coagulation system, patients with
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37 infection might be at higher risk of ischemia and bleeding. Therefore, more attention
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40 should be paid to patients with infection when antithrombotic therapy was determined.
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43 Finally, infection can also result in worse outcomes for NSTEMI-ACS patients through
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46 increasing catecholamines and potentially adverse hemodynamic effects, such as
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49 coronary vasoconstriction and increased myocardial metabolic demands²⁷.

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46 Although UTI was associated to some degree with in-hospital all-cause death, it
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49 was not associated with other worse outcomes. One reason why pulmonary infection is
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52 related to these worse clinical outcomes, while UTI is not, could be the lower
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55 prevalence of UTI comparing to pulmonary infection (0.3% vs. 2.6%). The prevalence
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58 of UTI was lower in our study compared with STEMI patients (0.3% vs. 7%)⁸.
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60 Therefore, when the population sample size was expanded, UTI would be similar to the

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4 pulmonary infection related to the worse clinical outcomes.
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6 **Limitations**

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9 The study had several limitations. First, as a retrospective study a causal relationship
10 between the infection and outcomes could not be determined. Second, despite
11 adjustment for important confounders, we could not completely eliminate all the
12 potential bias including selection bias. Third, although the infections were not centrally
13 adjudicated, the infection was confirmed by the infection control services who were
14 authorized to approve the use of antibiotic. Furthermore, because there is not a general
15 screen of infection in all the patients, the infection can be underestimated. But the
16 symptom-leading diagnose of infection is more practical in real world, and can be
17 promoted easily in clinic.
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32 **Conclusions**

33 Infection is an uncommon complication in patients with NSTEMI-ACS undergoing PCI
34 but is nonetheless independently associated with worse in-hospital and long-term
35 outcomes. Future studies are indicated to identify NSTEMI-ACS patients at risk of
36 infection which could then contribute to targeted intervention, help direct care, reduce
37 the incidence of subsequent adverse events, and thus optimize resource utilization.
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37 the study design, data collection and analysis, the decision to publish, or the preparation
38
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40
41 agreed to submit the manuscript for publication.

42 43 **Authors' contributions**

44
45 P-C He designed and supervised the study; P-Y Chen, Y-H Liu, L Jiang, X-B Wei and
46
47 W Guo performed the study, and C-Y Duan analyzed the data; Y-H Liu and other
48
49 authors provided the samples and demographics from patients and controls; Y-H Liu
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51 and P-Y Chen wrote the manuscript; N Tan, J-Y Chen and P-C He revised the
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4 manuscript for important intellectual content.
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6 **Conflict of Interest**

7
8
9 The authors declared no potential conflicts of interest with respect to the research,
10 authorship, and/or publication of this article.
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13 **Ethics approval and consent to participate**

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16 The study protocol was approved by the central ethics committee of the Guangdong
17 Provincial People's Hospital (NO. GDREC2016210H(R1)). Patients were included
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19 with a waiver of informed consent.
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25 This article does not contain any studies with animals performed by any of the authors.
26

27 **Data availability statement**

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30 Data source for this study is a retrospective public health database with data which all
31 hospitalizations that were already anonymized. Data were confidentially stored once
32
33 the original study published according to the original protocol, but data are available
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35 upon reasonable request.
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39 **Open access**

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49 appropriate credit is given, any changes made indicated, and the use is non-
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51 commercial.
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Table legends

Table 1. The baseline characteristics at index hospitalization

Table 2. In-hospital and long-term clinical outcomes

Table S1. Univariate and multivariable logistic for clinical outcomes by stratifying infection subtype.

Table S2 Propensity Score Analyses

Table S3 Outcomes of Propensity Score Analyses

Figure legends

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

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

Figure S1. Time from hospital admission to the diagnosis of infection among all patients.

Figure S2. Kaplan-Meier estimated event rates of all cause death or major bleeding

Figure S3. Subgroup analysis of in-hospital all cause death

Figure S4. Subgroup analysis of in-hospital major bleeding

Figure S5. Subgroup analysis of in-hospital major adverse clinical events

Figure S6. Distributions of propensity scores between the two groups before and after matching (the first row is the density plots and the second row is the QQ plots)

Table 1. The baseline characteristics at index hospitalization

	All patients*			<i>P</i> value
	Uninfected (N=5009)	Infected (N=206)	Total (N=5215)	
Demographics				
Age, y	63.61 ± 10.30	70.86 ± 9.20	63.90 ± 10.36	<.001
Age ≥ 65 y	2380(47.5%)	157(76.2%)	2537(48.6%)	<.001
Female	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, bpm	73.81 ± 10.91	77.75 ± 15.62	73.96 ± 11.16	<.001
Blood pressure, mmHg				
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%)	<.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%)	<.001
Diabetes mellitus	1509(30.1%)	96(46.6%)	1605(30.8%)	<.001
Presentation characteristics				

	All patients*			<i>P</i> value
	Uninfected (N=5009)	Infected (N=206)	Total (N=5215)	
IABP	44(0.9%)	30(14.6%)	74(1.4%)	<.001
CRUSAD	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	<.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, n(%)	489(9.8%)	66(32.0%)	555(10.6%)	<.001
LVEF, %	61.79 ± 10.77	55.99 ± 13.71	61.54 ± 10.98	<.001
eGFR, mL/min/1.73m ²	81.64 ± 24.99	60.85 ± 28.14	80.81 ± 25.45	<.001
eGFR ≤ 60, n(%)	851(17.0%)	101(49.0%)	952(18.3%)	<.001
Serum creatinine, µmol/dL	1.05 ± 0.69	1.55 ± 1.28	1.07 ± 0.73	<.001
Hematocrit, g/L	0.39 ± 0.05	0.35 ± 0.06	0.39 ± 0.05	<.001
Anemia, n(%)	1605(32.0%)	127(61.7%)	1732(33.2%)	<.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%)	<.001
β-blocker	4245(84.7%)	165(80.1%)	4410(84.6%)	0.070
Procedure characteristics, n(%)				

	All patients*			<i>P</i> value
	Uninfected (N=5009)	Infected (N=206)	Total (N=5215)	
Radial access	4470(89.2%)	154(74.8%)	4624(88.7%)	<.001
Coronary anatomy				
Any left main	690(13.8%)	49(23.8%)	739(14.2%)	<.001
Multi-vessel 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
Multi-vessel	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)	<.001
In 24 hours	2817(56.2%)	81(39.3%)	2898(55.6%)	<.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)	<.001

*Abbreviations: IABP=intra-aortic balloon pump; GRACE=Global Registry of Acute

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4 Coronary Events; CRUSADE=Can Rapid Risk Stratification of Unstable Angina
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6 Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA
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8 Guidelines; NSTEMI=Non-ST elevation myocardial infarction; LVEF=left ventricular
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10 ejection fraction; eGFR=Estimate glomerular filtration rate; PTCA=Percutaneous
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12 transluminal coronary angioplasty. ACE=angiotensin-converting enzyme;
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17 ARB=angiotensin receptor blocker.
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Table 2 In-hospital and Long-term clinical outcomes

Outcomes	Uninfected (N=5009)	Infected (N=206)	P value
In-hospital outcomes			
Death*	10(0.2%)	9(4.4%)	<.001
Myocardial infarction	17(0.3%)	1(0.5%)	0.726
Death or myocardial infarction	27(0.5%)	10(4.9%)	<.001
Major bleeding	62(1.2%)	34(16.5%)	<.001
Death or Myocardial infarction or major bleeding	84(1.7%)	44(21.4%)	<.001
Long-term outcomes			
30 days			
Death	17(0.3%)	10(4.9%)	<.001
Major bleeding	61(1.2%)	31(15.0%)	<.001
Death or major bleeding	74(1.5%)	37(18.0%)	<.001
One year			
Death	93(1.9%)	35(17.0%)	<.001
Major bleeding	75(1.5%)	34(16.5%)	<.001
Death or major bleeding	161(3.2%)	56(27.2%)	<.001
Three years			
Death	346(6.9%)	61(29.6%)	<.001
Major bleeding	111(2.2%)	36(17.5%)	<.001
Death or major bleeding	437(8.7%)	81(39.3%)	<.001

*All cause death;

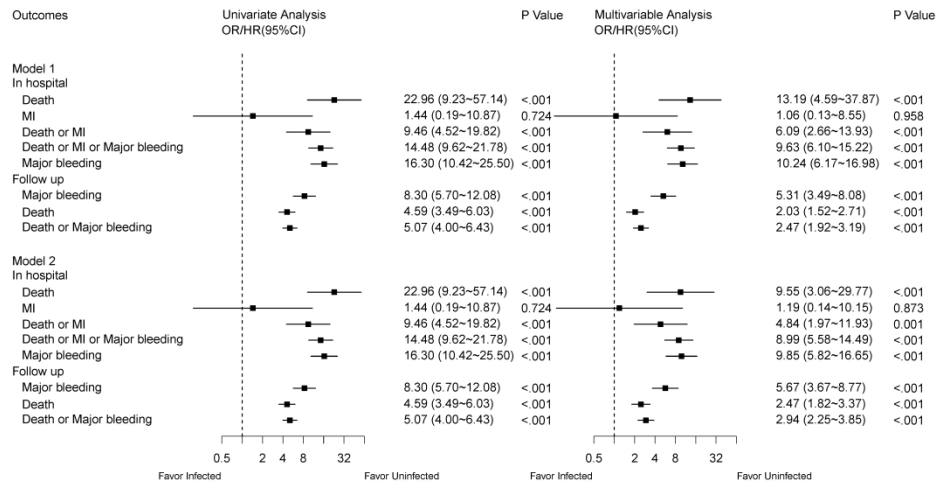


Figure 1. Univariate and multivariable logistic or Cox analysis for clinical outcomes

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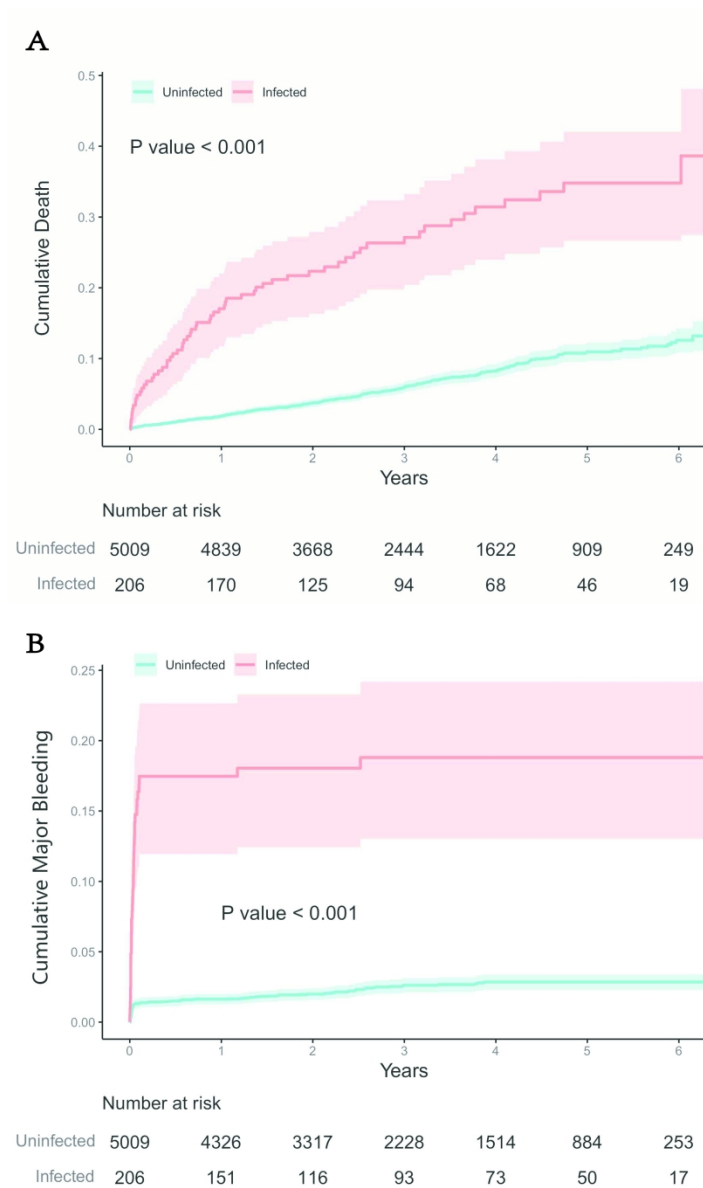


Figure 2. Kaplan-Meier estimated event rates of all cause death (A) and major bleeding (B)

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Supplementary Appendix 1

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5 **Table S1.** Univariate and multivariable logistic for clinical outcomes by stratifying infection
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7 subtype.
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10 **Table S2** Propensity Score Analyses
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13 **Table S3** Outcomes of Propensity Score Analyses
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16 **Figure S1.** Time from hospital admission to the diagnosis of infection among all patients.
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19 **Figure S2.** Kaplan-Meier estimated event rates of all cause death or major bleeding
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22 **Figure S3.** Subgroup analysis of in-hospital all cause death
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25 **Figure S4.** Subgroup analysis of in-hospital major bleeding
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28 **Figure S5.** Subgroup analysis of in-hospital major adverse clinical events
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31 **Figure S6.** Distributions of propensity scores between the two groups before and after matching
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Table S1 Univariate and multivariable logistic for clinical outcomes by stratifying infection subtype.

Outcomes (Compare with uninfected patients)	Univariate analysis			Multivariable analysis		
	OR	95%CI	P value	OR	95%CI	Pvalue
Model 1						
In hospital						
Death						
Community acquired pulmonary infections	17.24	4.66~63.73	<.001	8.56	2.06~35.57	0.003
Hospital acquired pulmonary infections	23.25	4.95~109.28	<.001	11.51	2.15~61.49	0.004
Urinary tract infection	31.24	3.78~258.58	0.001	21.59	2.32~200.48	0.007
Other infection	29.99	8.01~112.27	<.001	23.14	5.59~95.86	<.001
Major Bleeding						
Community acquired pulmonary infections	28.32	16.54~48.48	<.001	18.13	9.92~33.16	<.001
Hospital acquired pulmonary infections	14.80	6.37~34.43	<.001	9.04	3.63~22.49	<.001
Urinary tract infection	5.16	0.67~39.50	0.114	3.10	0.39~24.51	0.283
Other infection	4.95	1.50~16.31	0.009	3.25	0.95~11.13	0.061
Death or MI or Major Bleeding						
Community acquired pulmonary infections	21.85	13.05~36.59	<.001	14.23	8.07~25.10	<.001
Hospital acquired pulmonary infections	16.69	8.01~34.77	<.001	11.28	5.14~24.76	<.001
Urinary tract infection	3.76	0.49~28.65	0.202	2.44	0.31~19.04	0.396
Other infection	6.26	2.43~16.13	<.001	4.51	1.69~12.01	0.003
Follow up						
Death						
Community acquired pulmonary infections	5.52	3.78~8.06	<.001	2.06	1.39~3.06	<.001
Hospital acquired pulmonary infections	6.16	3.78~10.02	<.001	2.57	1.56~4.24	<.001
Urinary tract infection	3.66	1.37~9.82	0.010	2.38	0.88~6.39	0.086
Other infection	2.62	1.44~4.79	0.002	1.45	0.79~2.66	0.232
Major Bleeding						
Community acquired pulmonary infections	14.29	9.26~22.06	<.001	8.86	5.49~14.27	<.001
Hospital acquired pulmonary infections	7.08	3.30~15.20	<.001	4.16	1.87~9.27	<.001

Outcomes (Compare with uninfected patients)	Univariate analysis			Multivariable analysis		
	OR	95%CI	P value	OR	95%CI	Pvalue
Urinary tract infection	2.54	0.35~18.13	0.354	1.66	0.23~11.98	0.616
Other infection	2.49	0.79~7.83	0.119	1.83	0.57~5.85	0.307
Death or Major Bleeding						
Community acquired pulmonary infections	6.83	4.99~9.35	<.001	2.85	2.05~3.97	<.001
Hospital acquired pulmonary infections	6.32	4.08~9.79	<.001	2.93	1.87~4.61	<.001
Urinary tract infection	2.85	1.07~7.64	0.037	1.78	0.66~4.78	0.253
Other infection	2.62	1.51~4.55	0.001	1.60	0.92~2.80	0.099
Model 2						
In hospital						
Death						
Community acquired pulmonary infections	17.24	4.66~63.73	<.001	2.01	0.37~10.86	0.418
Hospital acquired pulmonary infections	23.25	4.95~109.28	<.001	6.48	0.92~45.66	0.061
Urinary tract infection	31.24	3.78~258.58	0.001	14.68	0.96~223.51	0.053
Other infection	29.99	8.01~112.27	<.001	5.02	0.98~25.62	0.052
Major Bleeding						
Community acquired pulmonary infections	28.32	16.54~48.48	<.001	11.91	6.10~23.28	<.001
Hospital acquired pulmonary infections	14.80	6.37~34.43	<.001	7.47	2.80~19.90	<.001
Urinary tract infection	5.16	0.67~39.50	0.114	1.92	0.15~25.23	0.619
Other infection	4.95	1.50~16.31	0.009	1.05	0.26~4.23	0.942
Death or MI or Major Bleeding						
Community acquired pulmonary infections	21.85	13.05~36.59	<.001	9.69	5.12~18.37	<.001
Hospital acquired pulmonary infections	16.69	8.01~34.77	<.001	10.00	4.33~23.12	<.001
Urinary tract infection	3.76	0.49~28.65	0.202	1.59	0.13~19.16	0.713
Other infection	6.26	2.43~16.13	<.001	1.71	0.54~5.35	0.360
Follow up						
Death						
Community acquired pulmonary infections	5.52	3.78~8.06	<.001	2.70	1.81~4.03	<.001
Hospital acquired pulmonary infections	6.16	3.78~10.02	<.001	3.56	2.15~5.90	<.001
Urinary tract infection	3.66	1.37~9.82	0.010	2.90	1.08~7.80	0.034

Outcomes (Compare with uninfected patients)	Univariate analysis			Multivariable analysis		
	OR	95%CI	P value	OR	95%CI	Pvalue
Other infection	2.62	1.44~4.79	0.002	1.32	0.71~2.44	0.376
Major Bleeding	14.29	9.26~22.06	<.001	6.30	3.79~10.49	<.001
Community acquired pulmonary infections	7.08	3.30~15.20	<.001	3.51	1.57~7.84	0.002
Hospital acquired pulmonary infections	2.54	0.35~18.13	0.354	1.42	0.19~10.39	0.731
Urinary tract infection	2.49	0.79~7.83	0.119	1.01	0.31~3.29	0.981
Other infection						
Death or Major Bleeding						
Community acquired pulmonary infections	6.83	4.99~9.35	<.001	3.55	2.55~4.94	<.001
Hospital acquired pulmonary infections	6.32	4.08~9.79	<.001	3.46	2.20~5.45	<.001
Urinary tract infection	2.85	1.07~7.64	0.037	1.96	0.73~5.28	0.181
Other infection	2.62	1.51~4.55	0.001	1.38	0.78~2.41	0.266

Model 1 included age, gender, current smokers, heart failure, anemia, type of disease, estimate glomerular filtration rate.

Model 2 included diabetes mellitus, hypertension, prior myocardial infarction, prior stroke, radial access, chronic kidney disease, intra-aortic balloon pump.

Table S2 Propensity Score Analyses

	Propensity Score Analyses			
	Uninfected	Infected	Total	<i>P</i> value
	(N=592)	(N=148)	(N=740)	
Demographics				
Age, y	70.39±9.09	70.24±9.15	70.36±9.09	0.861
Age ≥ 65 y	444(75.0%)	110(74.3%)	554(74.9%)	0.865
Female	166(28.0%)	37(25.0%)	203(27.4%)	0.458
Weight, kg	63.25±12.22	63.99±12.03	63.40±12.18	0.510
Heart rate, bpm	75.01±12.30	75.37±12.80	75.08±12.40	0.751
Blood pressure, mmHg				
Systolic	137.48±21.34	137.12±21.66	137.41±21.39	0.854
Diastolic	76.07±11.68	76.00±11.13	76.06±11.56	0.944
Medical history and risk factors, n(%)				
Current Smoker	157(26.5%)	41(27.7%)	198(26.8%)	0.771
Myocardial Infarction	126(21.3%)	29(19.6%)	155(20.9%)	0.651
Percutaneous coronary intervention	100(16.9%)	25(16.9%)	125(16.9%)	1
Coronary-artery bypass surgery	10(1.7%)	4(2.7%)	14(1.9%)	0.418
Stroke	36(6.1%)	9(6.1%)	45(6.1%)	1
Atrial Fibrillation	19(3.2%)	5(3.4%)	24(3.2%)	0.917
Hypertension	445(75.2%)	111(75.0%)	556(75.1%)	0.966
Diabetes mellitus	248(41.9%)	67(45.3%)	315(42.6%)	0.457
Type of disease, n(%)				
NSTEMI	225(38.0%)	60(40.5%)	285(38.5%)	0.571
Unstable angina	367(62.0%)	88(59.5%)	455(61.5%)	NA
Heart Failure, n(%)	123(20.8%)	32(21.6%)	155(20.9%)	0.821

Propensity Score Analyses				
	Uninfected	Infected	Total	<i>P</i> value
	(N=592)	(N=148)	(N=740)	
LVEF, %	59.67±12.02	57.81±13.16	59.29±12.28	0.118
eGFR, mL/min/1.73m ²	65.65±26.10	66.66±28.13	65.85±26.50	0.678
eGFR ≤ 60, n(%)	234(39.5%)	58(39.2%)	292(39.5%)	0.940
Serum creatinine, μmol/dL	1.39±1.16	1.43±1.32	1.40±1.19	0.726
Hematocrit, g/L	0.36±0.05	0.37±0.05	0.36±0.05	0.690
Anemia, n(%)	337(56.9%)	81(54.7%)	418(56.5%)	0.630
Cardiac biomarker positive, n(%)	344(61.5%)	84(59.2%)	428(61.1%)	0.603
In hospital medication, n(%)				
Dual antiplatelet therapy	558(94.3%)	138(93.2%)	696(94.1%)	0.641
Statin	576(97.3%)	145(98.0%)	721(97.4%)	0.642
ACE inhibitor or ARB	487(82.3%)	123(83.1%)	610(82.4%)	0.809
Calcium-channel blocker	200(33.8%)	46(31.1%)	246(33.2%)	0.532
β-blocker	488(82.4%)	120(81.1%)	608(82.2%)	0.701
Procedure characteristics, n(%)				
Radial access	486(82.1%)	116(78.4%)	602(81.4%)	0.299
Coronary anatomy				
Any left main	117(19.8%)	26(17.6%)	143(19.3%)	0.786
Multi-vessel disease	363(61.3%)	95(64.2%)	458(61.9%)	
Others	112(18.9%)	27(18.2%)	139(18.8%)	
Treated vessel				
Any left main	77(13.0%)	17(11.5%)	94(12.7%)	0.708
Multi-vessel	209(35.3%)	49(33.1%)	258(34.9%)	
Others	306(51.7%)	82(55.4%)	388(52.4%)	

Propensity Score Analyses

	Uninfected	Infected	Total	<i>P</i> value
	(N=592)	(N=148)	(N=740)	
Stent type				
Drug eluting stent	592(100.0%)	148(100.0%)	740(100.0%)	1
Number of stents	2.26±1.29	2.27±1.38	2.26±1.31	0.933
Total length of stents	56.48±35.90	58.22±38.71	56.83±36.46	0.604
Thrombus aspiration	16(2.7%)	3(2.0%)	19(2.6%)	0.642
Time to procedure				
In 24 hours	253(42.7%)	59(39.9%)	312(42.2%)	0.816
24~72 hours	135(22.8%)	35(23.6%)	170(23.0%)	
> 72 hours	204(34.5%)	54(36.5%)	258(34.9%)	

*Abbreviations: NSTEMI=Non-ST elevation myocardial infarction; LVEF=left ventricular ejection fraction; eGFR=Estimate glomerular filtration rate; ACE=angiotensin-converting enzyme; ARB=angiotensin receptor blocker.

Table S3 Outcomes of Propensity Score Analyses

Outcomes	Logistics analysis		
	OR/HR	95%CI	P value
In-hospital Death	4.01	0.25~64.30	0.981
In-hospital Major bleeding	18	2.40~134.8	0.005
In-hospital MI	2.0	0.18~22.20	0.57
In-hospital Death or Major bleeding	17.24	4.66~63.73	<.001
Follow-up Death	2	0.97~4.12	0.06
Follow-up Major bleeding	5.33	1.55~18.30	0.007
Follow-up Death or Major bleeding	2.46	1.29~4.69	0.006

Figure S1. Time from hospital admission to the diagnosis of infection among all patients.

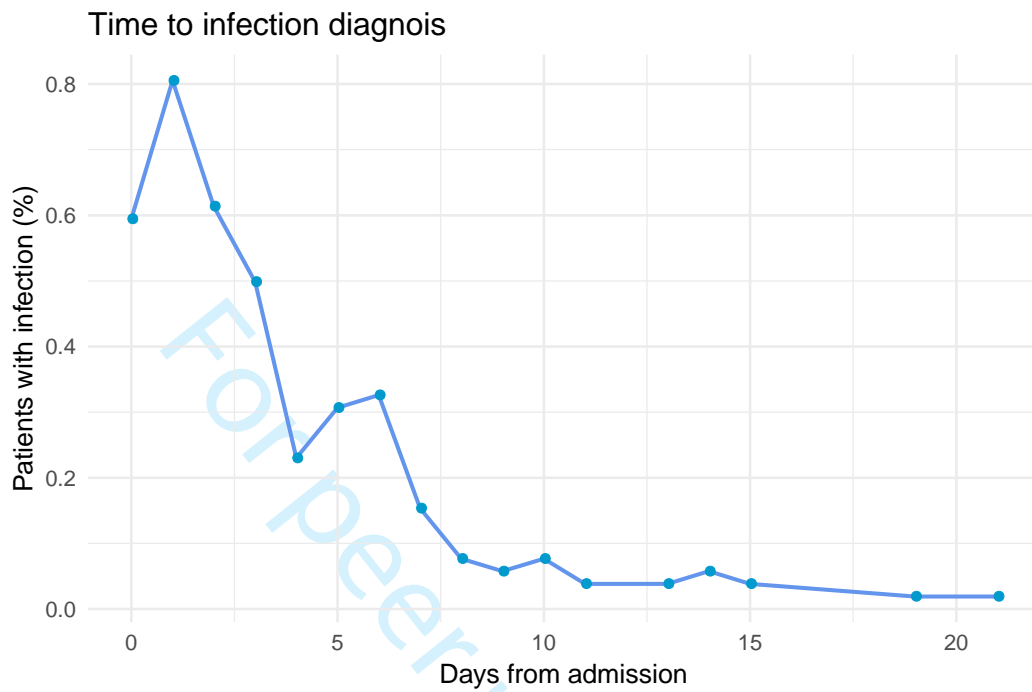


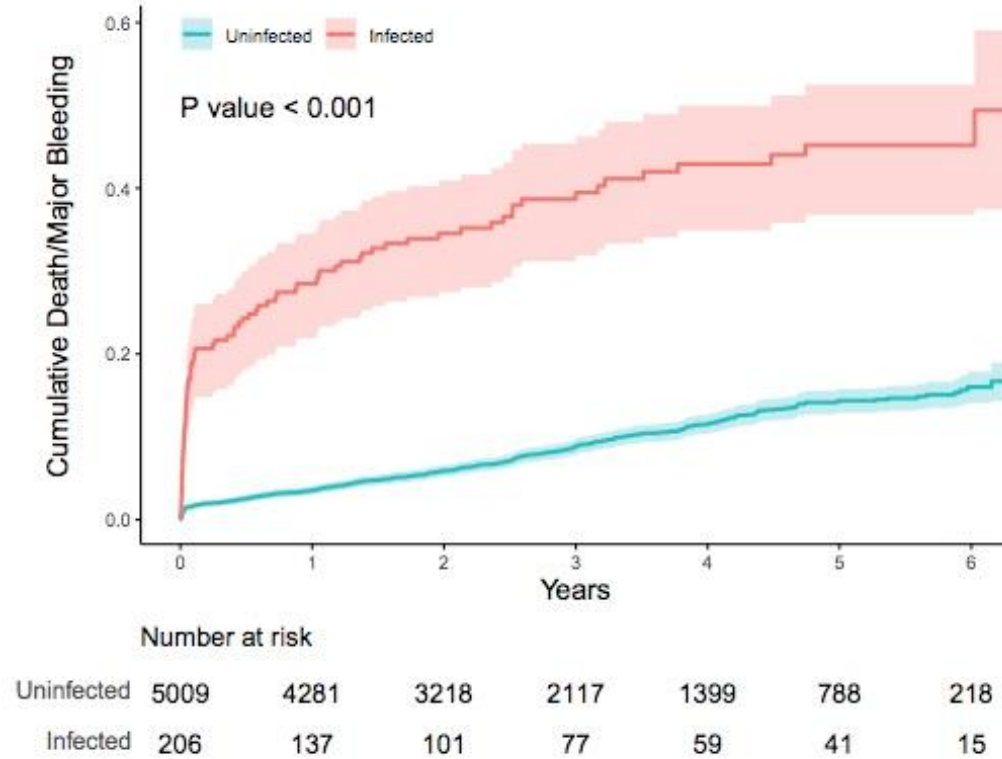
Figure S2. Kaplan-Meier estimated event rates of all cause death or major bleeding

Figure S3. Subgroup analysis of in-hospital all cause death

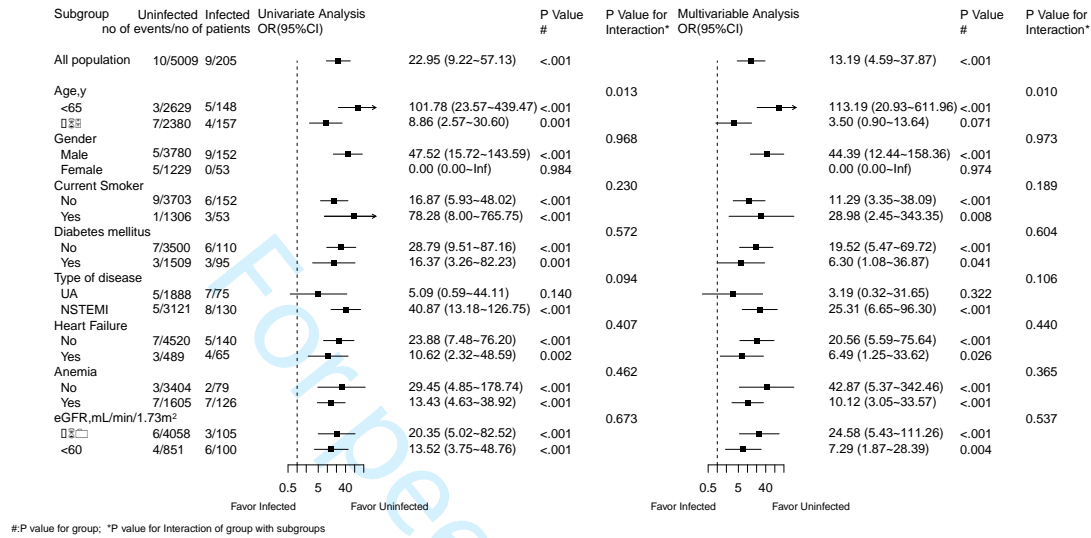


Figure S4. Subgroup analysis of in-hospital major bleeding

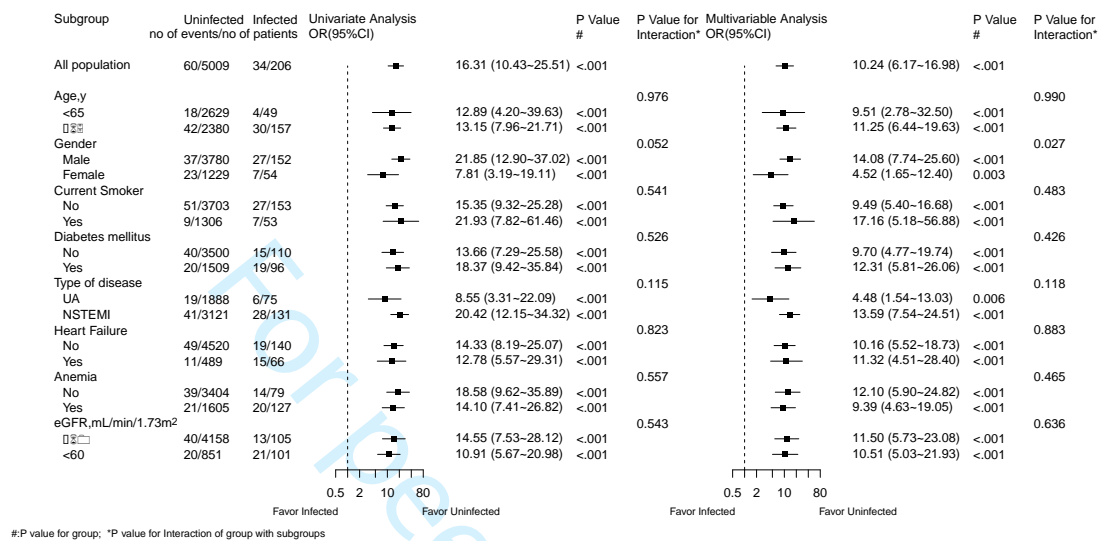


Figure S5. Subgroup analysis of in-hospital major adverse clinical events

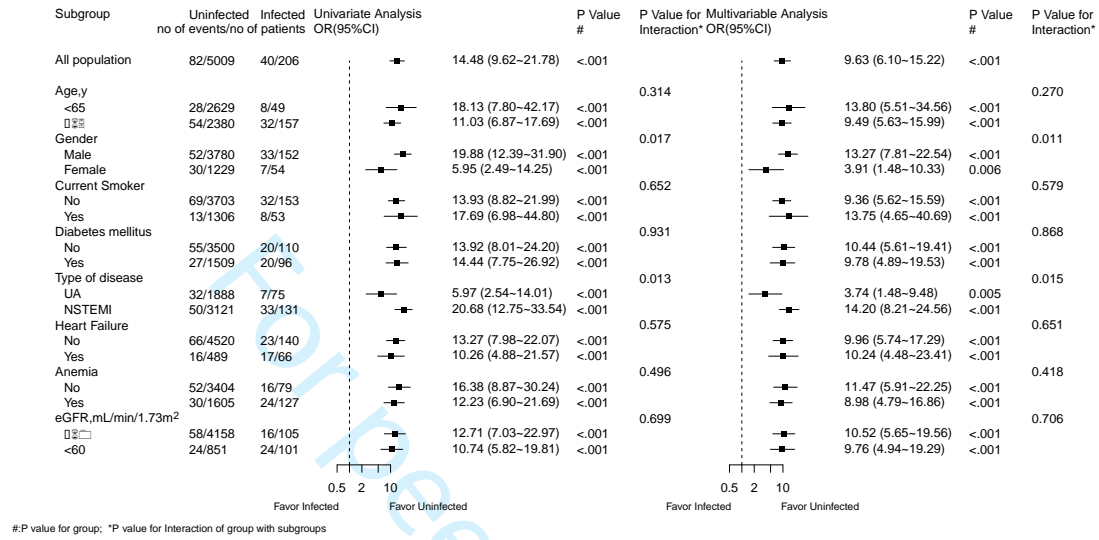
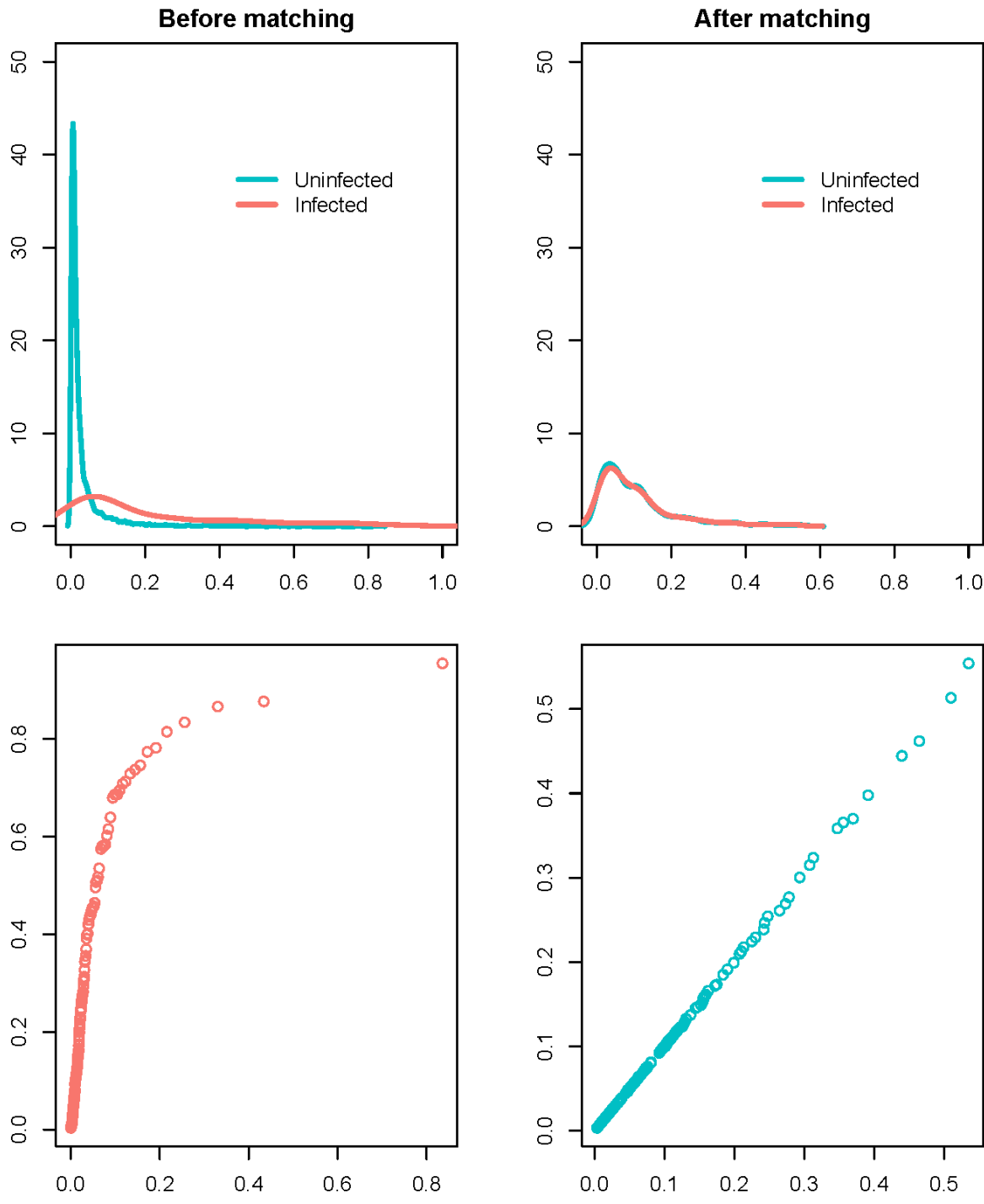


Figure S6. Distributions of propensity scores between the two groups before and after matching (the first row is the density plots and the second row is the QQ plots)



STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1 3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed	7 NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8 & supplement
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	supplement
Bias	9	Describe any efforts to address potential sources of bias	8-9
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	8-9 & supplement
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	9-10
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	9-10

1	Outcome data	15*	Report numbers of outcome events or summary measures over time	9-10
2	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and	10-11 & supplement
3			their precision (eg, 95% confidence interval). Make clear which confounders were	
4			adjusted for and why they were included	
5			(b) Report category boundaries when continuous variables were categorized	
6			(c) If relevant, consider translating estimates of relative risk into absolute risk for a	
7			meaningful time period	
8	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and	11 & supplement
9			sensitivity analyses	
10	Discussion			
11	Key results	18	Summarise key results with reference to study objectives	11-12
12	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or	14
13			imprecision. Discuss both direction and magnitude of any potential bias	
14	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations,	14-15
15			multiplicity of analyses, results from similar studies, and other relevant evidence	
16	Generalisability	21	Discuss the generalisability (external validity) of the study results	14-15
17	Other information			
18	Funding	22	Give the source of funding and the role of the funders for the present study and, if	15-16
19			applicable, for the original study on which the present article is based	

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.