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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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**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 NSTE-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 (NSTE-ACS) patients received percutaneous coronary intervention (PCI).

**Design:** This observational cohort originated from the database for NSTE-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 NSTE-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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confirmed these results.

**Conclusions:** the incidence of infection is low in hospitalization, but it is associated with worse in-hospital and long-term outcomes.

**Key Words**: Non-ST-elevation acute coronary syndrome; Percutaneous coronary intervention; Infection; Outcomes.

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**Strengths and limitations of this study**

- We widely included NSTE-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.

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## Introduction

The incidence of non-ST-elevation acute coronary syndrome (NSTE-ACS) is increasing, and approximately 70% of all ACS patients are NSTE[1]. 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 outcomes[10]. 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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excluded if they were diagnosed with a malignant tumor before the index date, pregnant or presenting with cardiogenic shock. The method to search and identify appropriate NSTE-ACS patients has been outlined previously[11]. The study protocol was approved by the central ethics committee of the Guangdong Provincial People's Hospital, with a waiver of informed consent. The study was conducted in accordance with the Declaration of Helsinki.

**Data collection and procedures**

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 evidence[12].

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 prescribed[8]. Infection was classified as pulmonary, urinary tract infection (UTI) or others (including non-pulmonary/ non-urinary sepsis and cellulitis), based on the clinical records during 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 Prevention[13].

**Clinical outcomes and follow up**

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



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defined by the Bleeding Academic Research Consortium definition (grades 3-5)[14]. Secondary outcomes were: (1) major adverse clinical events (MACE), consisting of all-cause death, myocardial infarction, or major bleeding during hospitalization; and (2) all-cause death or major bleeding during follow-up.

All patients were followed-up by trained nurses via telephone interview or clinic visits from Nov 2015 to Dec 2016. Relevant information was also collected from the residence registration system and from the clinical records of the patients who were readmitted. The details of clinical events and follow-up has been previously described[11].

**Statistical analysis**

All patients were divided into groups with or without infections. Continuous variables with a normal distribution are presented as the mean ± SD, and those with an asymmetric distribution are presented as the median and interquartile range (Q25-Q75). Student's t test or Wilcoxon rank-sum test were used to compare the continuous variables. Categorical variables are presented as frequencies and were compared by the Fisher exact test or chi-square test. Univariate and multivariable analyses were performed to evaluate the relationship between infection and clinical outcomes. Variables that were significant in the univariate analysis or clinically important were included in the multivariable models. Considering the low incidence of adverse outcomes but potential high incidence of confounders, each multivariable analysis two models were developed. The first model (model 1) included infection, age, anemia, type of disease (unstable angina and non-ST-elevation acute myocardial infarction), gender, current smokers, heart failure, and estimate glomerular filtration rate (eGFR). The



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second model (model 2) included radial access, cardiac biomarker positive, time to procedure, treated multi-vessel, diabetes mellitus, hypertension, prior myocardial infarction, and prior stroke. We performed subgroup analyses by older age, gender, current smokers, diabetes mellitus, types of disease, heart failure, anemia and chronic kidney disease. Analysis based on different types of infections was reported. We also introduced the GRACE (Global Registry of Acute Coronary Events)[15] and CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines) score[16] and compared the infection outcomes among different GRACE or CRUSADE risk groups (low, medium, or high risk). All data analyses were performed with SAS (version 9.4, SAS Institute, 210 Cary, North Carolina, USA). A 2-sided $P<0.05$ was considered significant.

**Patient and public involvement**

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

**Results**

**Baseline characteristic**

From January 1, 2010, to December 31, 2014, a total of 8197 consecutive NSTE-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 a low body weight. These patients were more likely to have a



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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 of in-hospital all cause death (odd 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 independently related to the risk of the above outcomes **(Figure 1).**

**Long-term clinical outcomes**

At a median follow-up of 3.2 years, Kaplan-Meier analysis revealed that patients with in-hospital infection had a higher risk of long-term death, major bleeding, and death or major bleeding compared with those without in-hospital infection (P<.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



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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)**. Furthermore, the relationship between infection and major bleeding, and MACE was consistent among patients with different GRACE or CRUSADE scores (low, medium, or high risk) **(Figure S6, S7, S8 and S9).**

**Discussion**

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

The prevalence of infection in our study are similar to those results for the STEMI population. Data from 5,745 STEMI patients enrolled in the APEX-AMI trial



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demonstrated that the prevalence of serious infection was 2.4%, and that infection was associated with higher 90-day mortality (29%)[9]. Also, another study of 1,486 STEMI patients reported the prevalence of serious infection at 3.9% and the 30-day mortality was up to 53% in these patients[8]. The conclusions for these 2 studies paralleled our conclusion: infection is uncommon but associated with worse clinical outcomes. A recent retrospective cohort analyses of 174 octogenarians with ACS, for whom the patients with infection had a higher in-hospital, 30-day and long-term mortality than patients without infection[10]. However, that study was confined to patients older than 85 years who were admitted to the coronary care unit, the different ACS types were never specified, and the relatively liberal use of bare metal stents does not conform with the contemporary more liberal use of drug eluting stents[17, 18].

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

Although infections had a negative impact on patients with NSTE-ACS, the underlying pathophysiologic mechanism remains unclear. Corrales-Medina et al[19]



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



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paid to patients with infection when antithrombotic therapy was determined. Finally, infection can also result in worse outcomes for NSTE-ACS patients through increasing catecholamines and potentially adverse hemodynamic effects, such as coronary vasoconstriction and increased myocardial metabolic demands[27].

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

**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. In addition, all other adverse clinical events were evaluated by an independent clinical events committee that was masked to the infection details.

**Conclusions**

Infection is an uncommon complication in patients with NSTE-ACS undergoing PCI



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

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role in the study design, data collection and analysis, the decision to publish, or the preparation of the manuscript. The work was not funded by any industry sponsors. All authors agreed to submit the manuscript for publication.

**Authors' contributions**

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

**Conflict of Interest**

The authors declared no potential conflicts of interest with respect to the research, 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 hospitalisations that were already anonymised. Data were confidentially stored once the original study published according to the original protocol, but data are available upon 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

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

**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.

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

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

**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



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**Figure S9.** Subgroup analysis of in-hospital major adverse clinical events based on 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* | | | *P* 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** | | | | |



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| | All patients* | | | *P* 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(%)** | | | | |



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| | All patients* | | | *P* 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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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=angiostensin-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** | | | |



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| 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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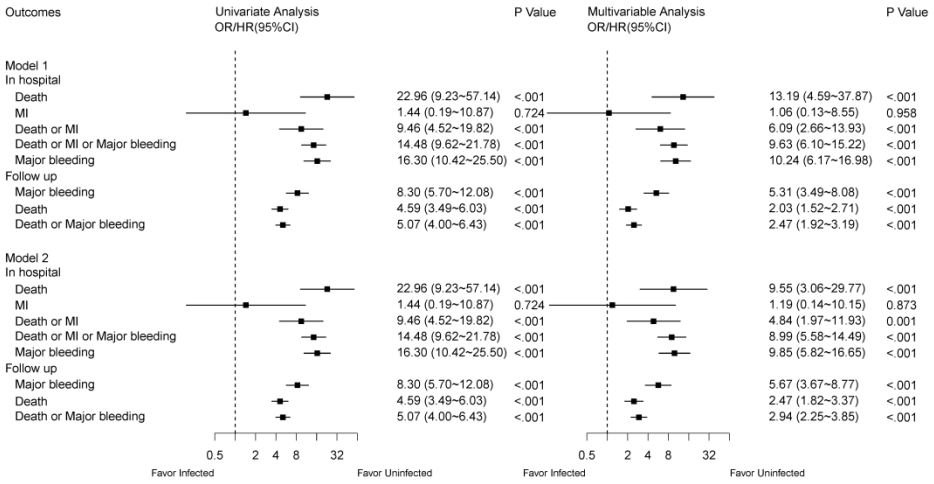


Figure 1. Univariate and multivariable logistic or Cox analysis for clinical outcomes

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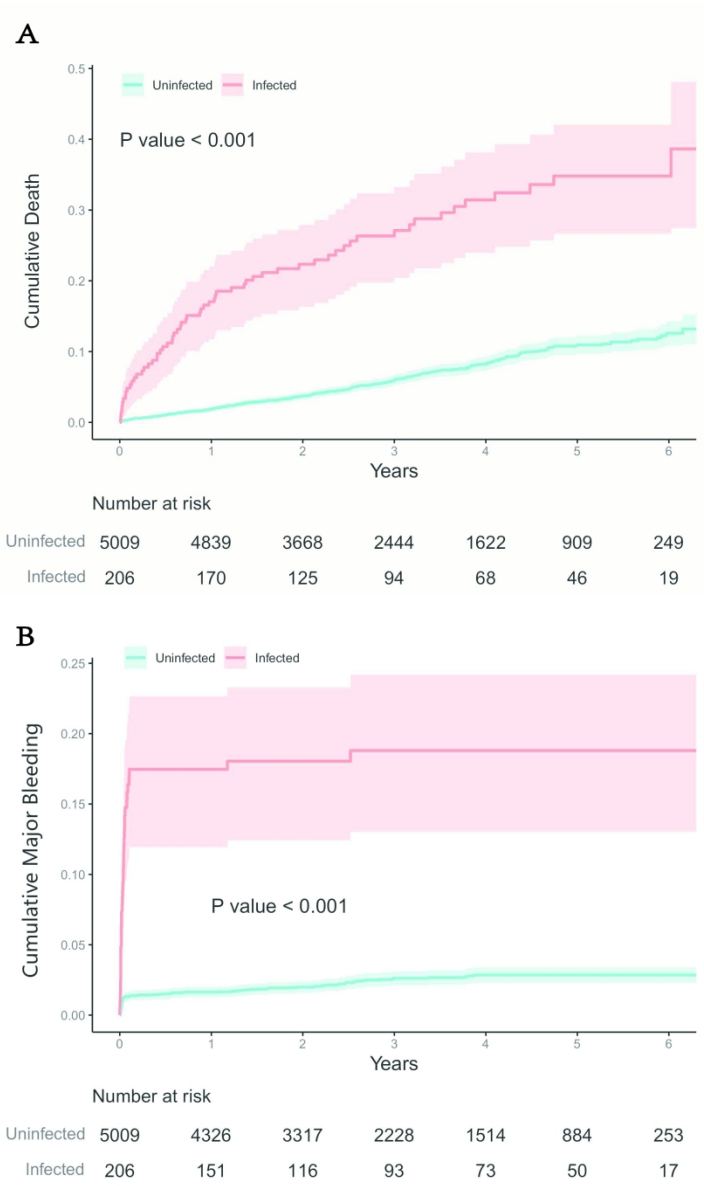


Figure 2. Kaplan-Meier estimated event rates of all cause death (A) and major bleeding (B)

# Supplementary Appendix 1

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

**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.** 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

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

| Outcomes | Univariate analysis | | | Multivariable analysis | | |
|---|---|---|---|---|---|---|
| (Compare with uninfected patients) | 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 | Univariate analysis | | | Multivariable analysis | | |
|---|---|---|---|---|---|---|
| (Compare with uninfected patients) | 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.

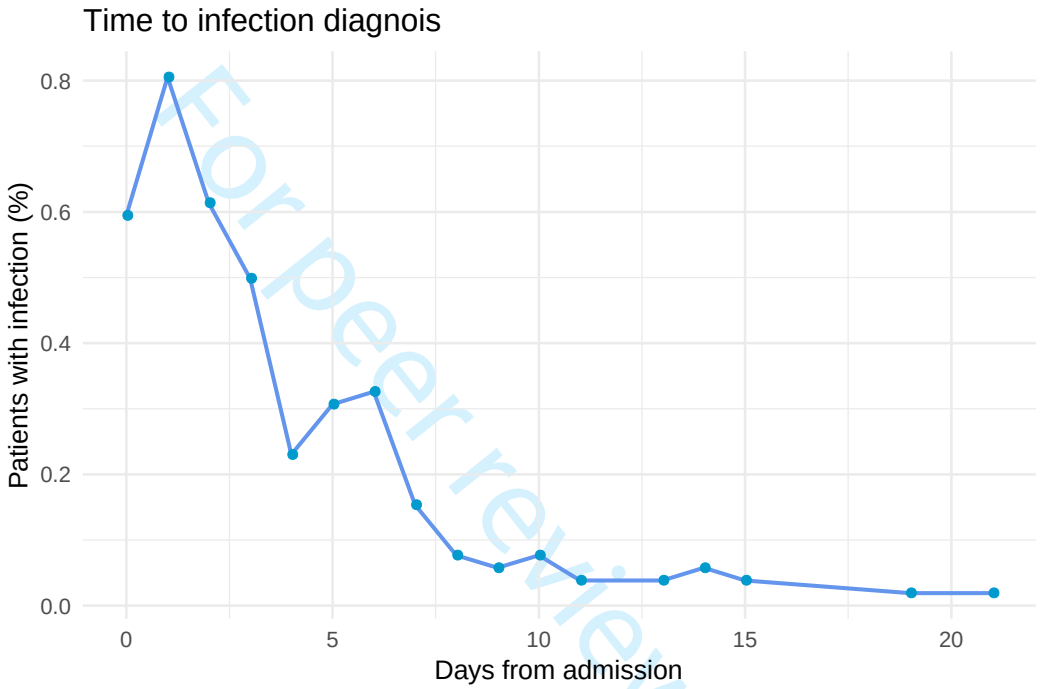


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**Figure S2.** Kaplan-Meier estimated event rates of all cause death or major bleeding

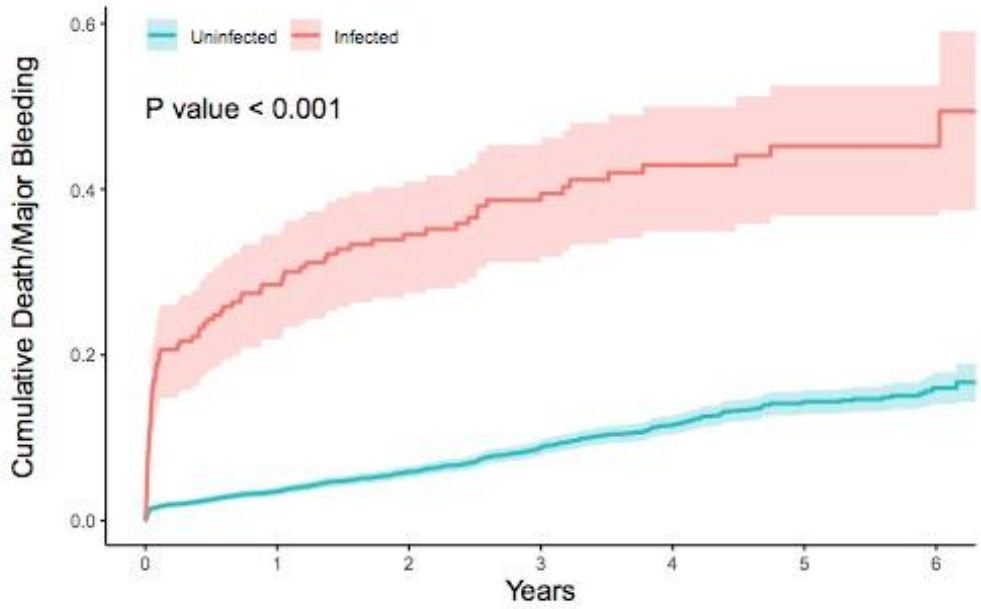
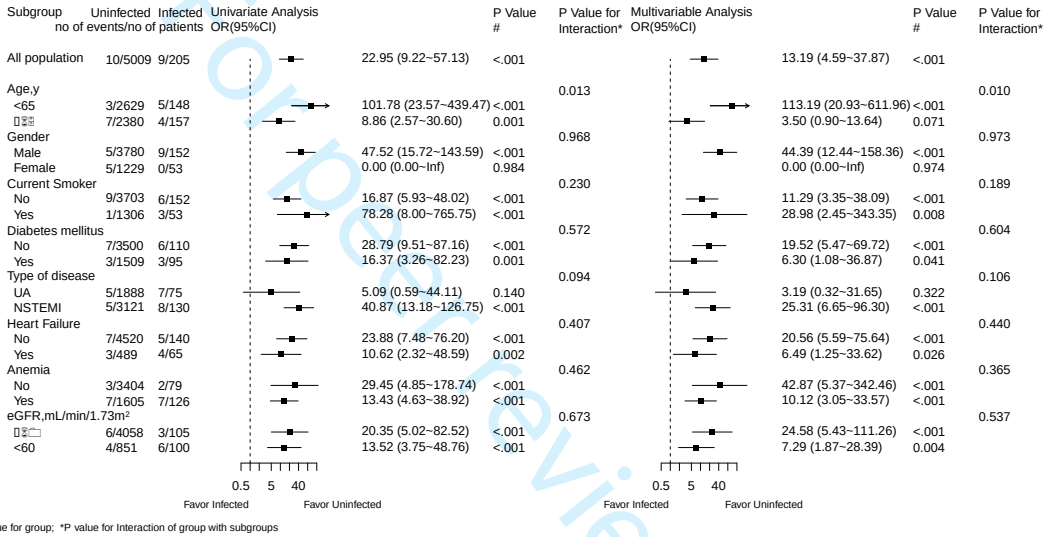


**Figure S3.** Subgroup analysis of in-hospital all cause death




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

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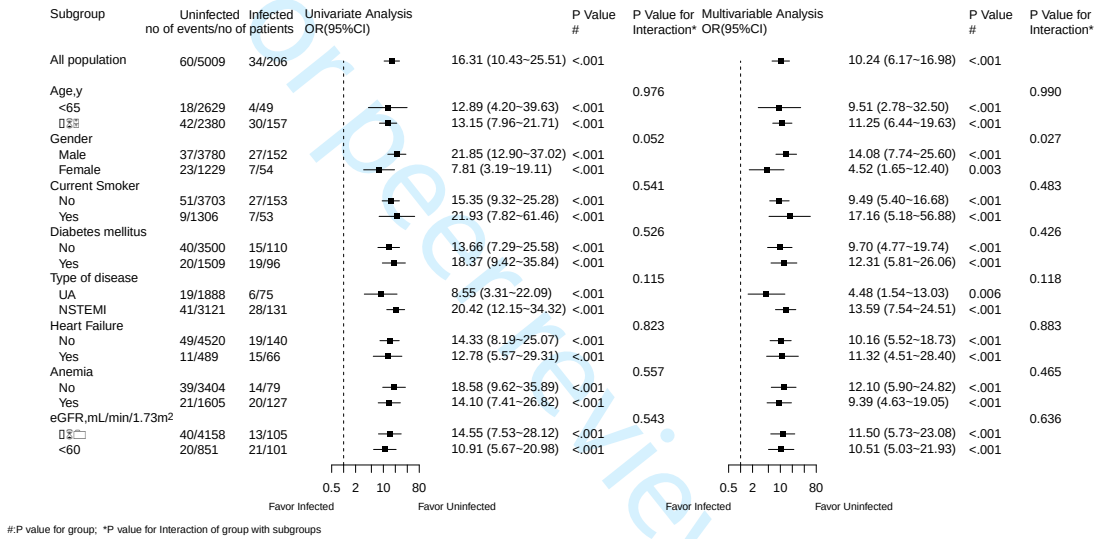
**Figure S4.** Subgroup analysis of in-hospital major bleeding




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

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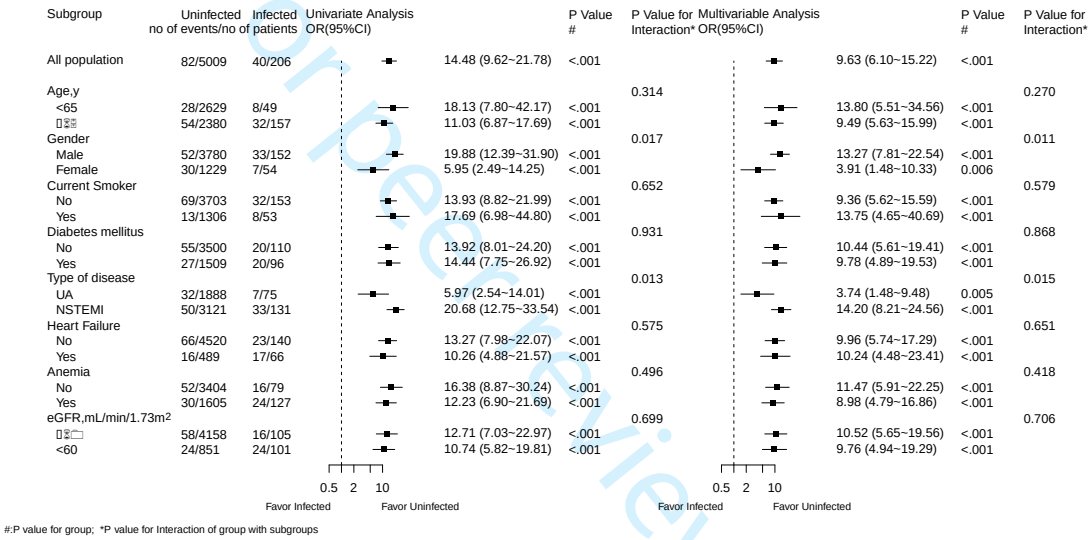
**Figure S5.** Subgroup analysis of in-hospital major adverse clinical events




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

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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

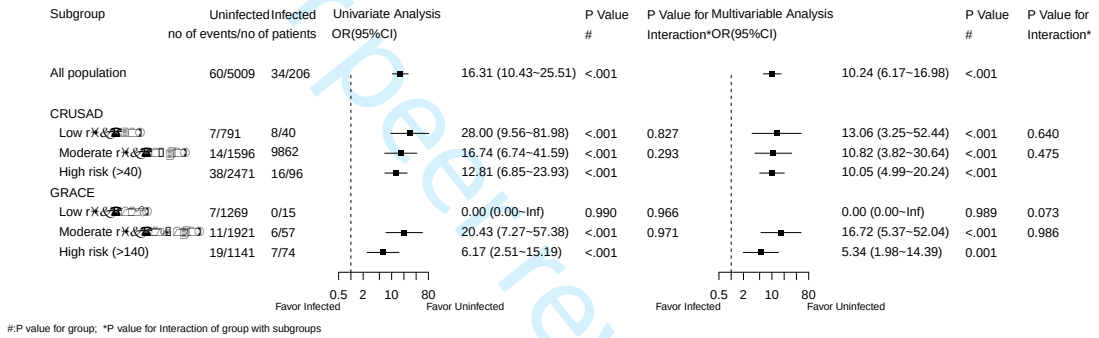


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**Figure S7.** Subgroup analysis of in-hospital major bleeding based on different risk of GRACE and CRUSADE adjusted by the model 2

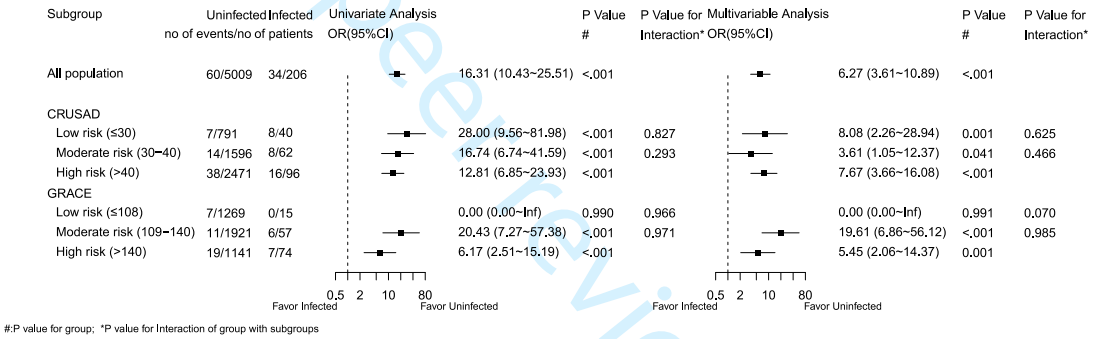


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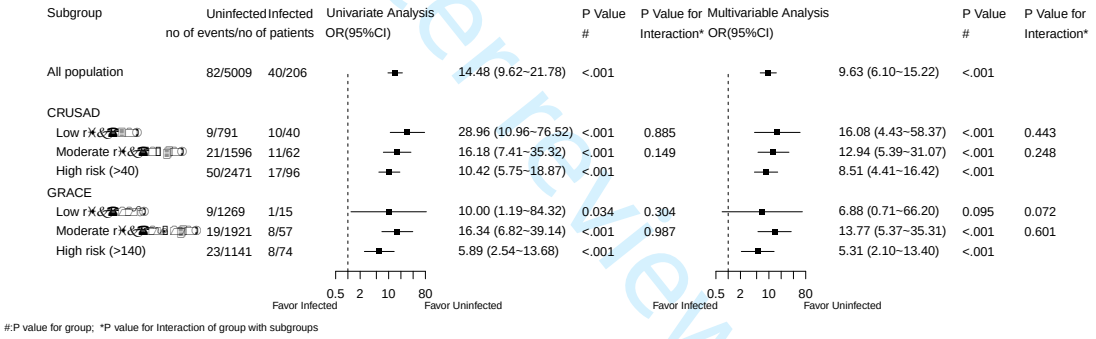
**Figure S8.** Subgroup analysis of in-hospital major adverse clinical events based on different risk of GRACE and CRUSADE adjusted by the model 1




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

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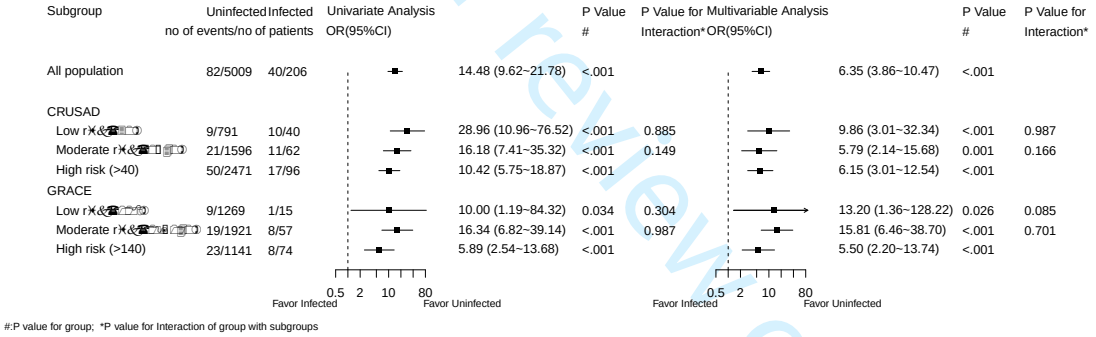
**Figure S9.** Subgroup analysis of in-hospital major adverse clinical events based on different risk of GRACE and CRUSADE adjusted by the model 2




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

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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 | 1 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 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 | 7 |
| | | (*b*) For matched studies, give matching criteria and number of exposed and unexposed | 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 | 8-9 & supplement |
| | | (*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 | |
| **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 | 9-10 |
| | | (b) Give reasons for non-participation at each stage | |
| | | (c) Consider use of a flow diagram | |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 9-10 |
| | | (b) Indicate number of participants with missing data for each variable of interest | |
| | | (c) Summarise follow-up time (eg, average and total amount) | |

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

*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.

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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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**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 NSTE-ACS and PCI

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## Abstract

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

**Design:** This observational cohort originated from the database for NSTE-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 NSTE-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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confirmed these results.

**Conclusions:** The incidence of infection is low in hospitalization, but it is associated with worse in-hospital and long-term outcomes.

**Key Words**: Non-ST-elevation acute coronary syndrome; Percutaneous coronary intervention; Infection; Outcomes.

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**Strengths and limitations of this study**

- We widely included NSTE-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.

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## Introduction

The incidence of non-ST-elevation acute coronary syndrome (NSTE-ACS) is increasing, and approximately 80% of all ACS patients are NSTE[1]. Despite that there are more comorbidities in patients with ST-segment elevation myocardial infarction (STEMI), the NSTE-ACS 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 NSTE-ACS remains scanty. Only one study of 174 octogenarian patients with ACS evaluated the impact of infection on clinical outcomes[10]. Thus, we aimed to assess the incidence of infection and its association with short- 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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excluded if they were diagnosed with a malignant tumor before the index date, pregnant or presenting with cardiogenic shock. The method to search and identify appropriate NSTE-ACS patients has been outlined previously[11]. The study protocol was approved by the central ethics committee of the Guangdong Provincial People's Hospital, with a waiver of informed consent. The study was conducted in accordance with the Declaration of Helsinki.

**Data collection and procedures**

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 evidence[12].

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 prescribed[8]. Infection was classified as pulmonary, urinary tract infection (UTI) or others (including non-pulmonary/ non-urinary sepsis and cellulitis), based on the clinical records during 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 Prevention[13].

**Clinical outcomes and follow up**

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



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defined by the Bleeding Academic Research Consortium definition (grades 3-5)[14]. Secondary outcomes were: (1) major adverse clinical events (MACE), consisting of all-cause death, myocardial infarction, or major bleeding during hospitalization; and (2) all-cause death or major bleeding during follow-up.

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

**Statistical analysis**

All patients were divided into groups with or without infections. Continuous variables with a normal distribution are presented as the mean ± SD, and those with an asymmetric distribution are presented as the median and interquartile range (Q25-Q75). Student's t test or Wilcoxon rank-sum test were used to compare the continuous variables. Categorical variables are presented as frequencies and were compared by the Fisher exact test or chi-square test. Univariate and multivariable analyses were performed to evaluate the relationship between infection and clinical outcomes. Variables that were significant in the univariate analysis or clinically important were included in the multivariable models. Considering the low incidence of adverse outcomes but potential high incidence of confounders, two models were developed for each multivariable analysis. The first model (model 1) included infection, age, anemia,



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type of disease (unstable angina and non-ST-elevation acute myocardial infarction), gender, current smokers, heart failure, and estimate glomerular filtration rate (eGFR). The second model (model 2) included radial access, cardiac biomarker positive, time to procedure, treated multi-vessel, diabetes mellitus, hypertension, prior myocardial infarction, and prior stroke. We performed subgroup analyses by older age, gender, current smokers, diabetes mellitus, types of disease, heart failure, anemia and chronic kidney disease. Analysis based on different types of infections was reported. We also introduced the GRACE (Global Registry of Acute Coronary Events)[15] and CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines) score[16] and compared the infection outcomes among different GRACE or CRUSADE risk groups (low, medium, or high risk). All data analyses were performed with SAS (version 9.4, SAS Institute, 210 Cary, North Carolina, USA). A two-sided $P<0.05$ was considered significant.

Propensity score analyses were conducted to test the robustness of the results. All factors listed in **Table 1** were considered in the propensity score model development. The heterogeneity analysis between the centers was conducted using meta-analysis methods.

**Patient and public involvement**

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

**Results**

**Baseline characteristic**



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From January 1, 2010, to December 31, 2014, a total of 8197 consecutive NSTE-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 (odd 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 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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5.33;95%CI, 1.55-18.30, P=0.007), but matched results showed an absence of a significant difference in all-cause death (in-hospital: OR, 4.01; 95%CI, 0.25-64.30; follow-up: OR, 2; 95%CI, 0.97-4.12)(**Table S3**).

**Discussion**

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

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



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

Although infections had a negative impact on patients with NSTE-ACS, the underlying pathophysiologic mechanism remains unclear. Corrales-Medina et al.[19] suggested that infection increased the mortality of patients who underwent elective PCI due to the change in plaques triggered by acute inflammatory reactions. Indeed, infection has been implicated as a factor contributing to initiation, progression and rupture of an atherosclerotic plaque[20]. Infectious vectors have been reported to induce the expression of adhesion molecules such as heat shock protein 60 and monocyte chemoattractant protein-1 on endothelial cells, which can activate the endothelium and the formation of a lipid core[21-24]. Additionally, the SIXTUS study group[25] demonstrated that platelet activation and $TxB_2$ overproduction are related to infections via Toll-like receptor 4. Moreover, MODICA et al.[26] reported that aspirin non-responsiveness was often observed in patients with pneumonia. Also, increased coagulation activity has been observed in pneumonia[3]. Therefore, infection can activate platelets and the



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coagulation system, which plays a critical role in deteriorating outcomes in patients with ACS. In contrast to previous STEMI reports[8, 9] , we did not find a significant association of infection with myocardial infarction due to the low incidence of myocardial infarction in our study. However, our results were similar to previous studies that reported major bleeding was more frequent in patients with infection. Although the PLATelet inhibition and patient Outcomes (PLATO) trial demonstrated that ticagrelor, a more potent and consistent platelet $P2Y_{12}$ inhibitor, was associated with significantly fewer pulmonary infections and death related to infection than clopidogrel, the incidence of bleeding in patients with infection in that study was not reported[4]. Because of dysfunction of platelets and the coagulation system, patients with infection might be at higher risk of ischemia and bleeding. Therefore, more attention should be paid to patients with infection when antithrombotic therapy was determined. Finally, infection can also result in worse outcomes for NSTE-ACS patients through increasing catecholamines and potentially adverse hemodynamic effects, such as coronary vasoconstriction and increased myocardial metabolic demands[27].

Although UTI was associated to some degree with in-hospital all-cause death, it was not associated with other worse outcomes. One reason why pulmonary infection is related to these worse clinical outcomes, while UTI is not, could be the lower prevalence of UTI comparing to pulmonary infection (0.3% vs. 2.6%). The prevalence of UTI was lower in our study compared with STEMI patients (0.3% vs. 7%)[8]. Therefore, when the population sample size was expanded, UTI would be similar to the 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 NSTE-ACS undergoing PCI but is nonetheless independently associated with worse in-hospital and long-term outcomes. Future studies are indicated to identify NSTE-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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Yanyan Zhong;Liyun Wang; Jianxia He; Ruijuan Xiao; Yuanling Li; Xinrong Liu; Hui Wang; Mingyu Chen; Haiyan Xue;Xuxi Yang; Suqin Xie;). Department of Cardiology, The Second People's Hospital of Nanhai District, Guangdong General Hospital's Nanhai Hospital, Foshan, 528251, China (Wenfei He).

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**Authors' contributions**

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

**Conflict of Interest**

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



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## 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.

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**Table 1. The baseline characteristics at index hospitalization**

| | All patients* | | | *P* 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** | | | | |



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| | All patients* | | | *P* 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(%)** | | | | |



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| | All patients* | | | *P* 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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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=angiostensin-converting enzyme; 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;



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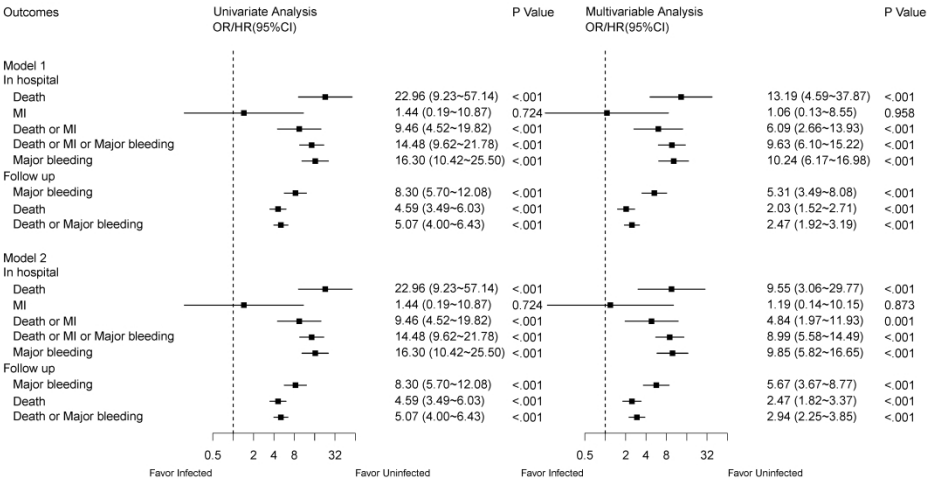


Figure 1. Univariate and multivariable logistic or Cox analysis for clinical outcomes

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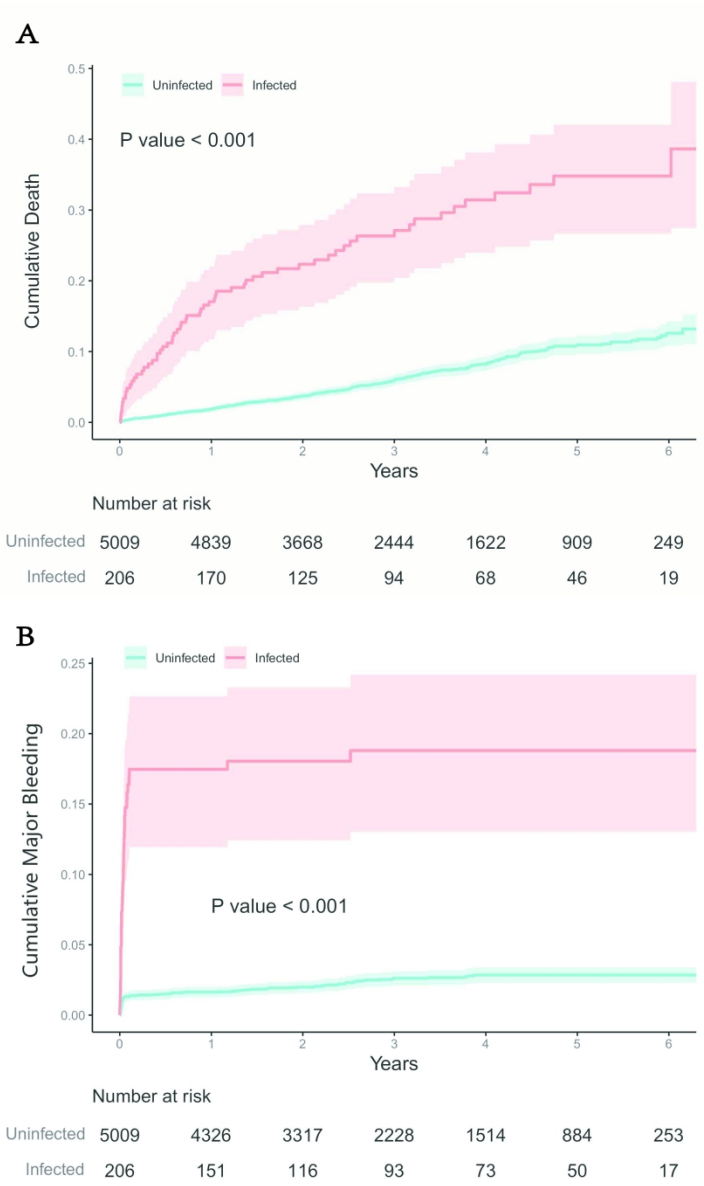


Figure 2. Kaplan-Meier estimated event rates of all cause death (A) and major bleeding (B)

# Supplementary Appendix 1

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**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 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)

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

| Outcomes | Univariate analysis | | | Multivariable analysis | | |
|---|---|---|---|---|---|---|
| (Compare with uninfected patients) | 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.

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**Table S2 Propensity Score Analyses**

| | Propensity Score Analyses | | | |
|---|---|---|---|---|
| | **Uninfected (N=592)** | **Infected (N=148)** | **Total (N=740)** | ***P* value** |
| 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 (N=592) | Infected (N=148) | Total (N=740) | *P* value |
| LVEF, % | 59.67±12.02 | 57.81±13.16 | 59.29±12.28 | 0.118 |
| eGFR, mL/min/1.73m2 | 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 (N=592)** | **Infected (N=148)** | **Total (N=740)** | ***P* value** |
| 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=angiostensin-converting enzyme; ARB=angiotensin receptor blocker.

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**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 |

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

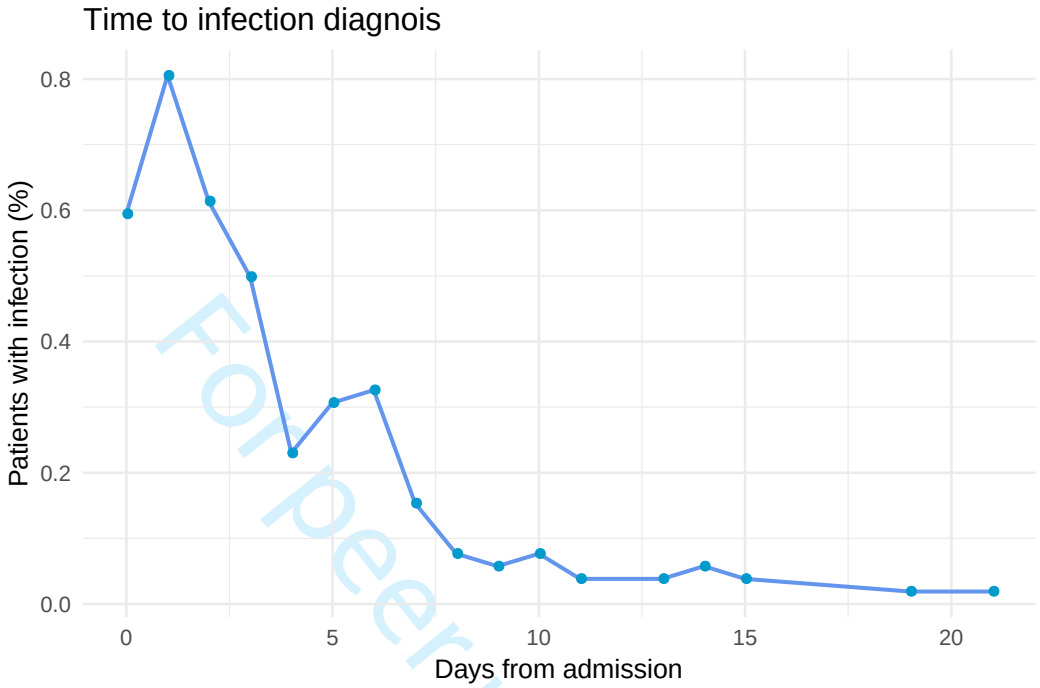


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**Figure S2.** Kaplan-Meier estimated event rates of all cause death or major bleeding

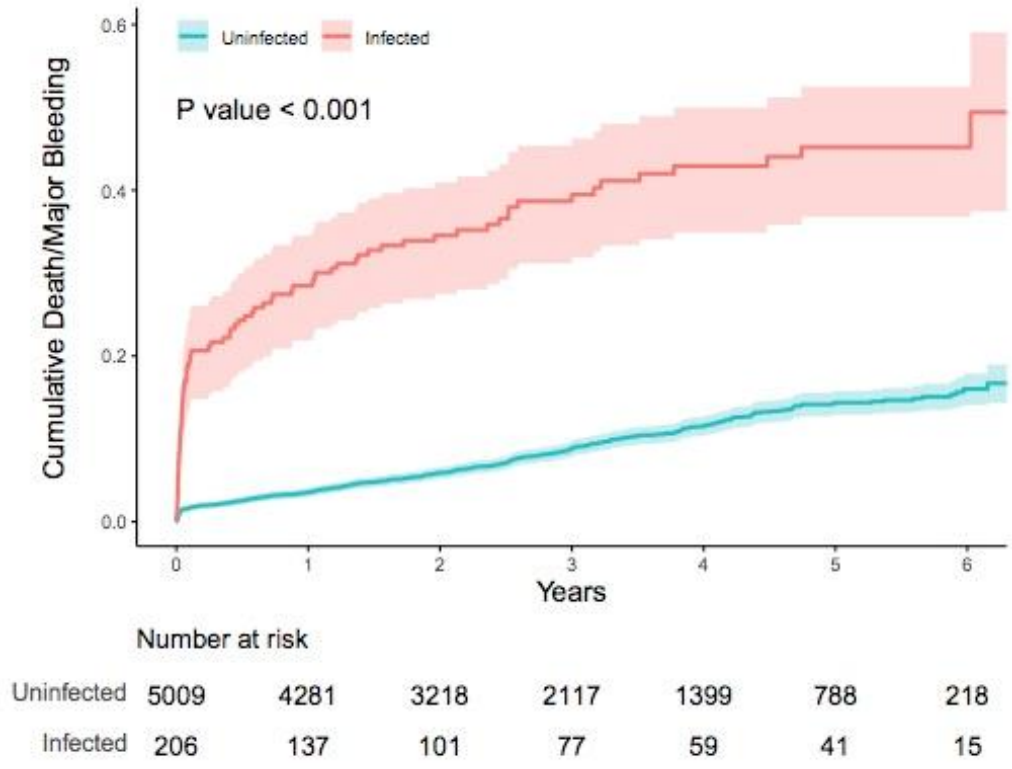


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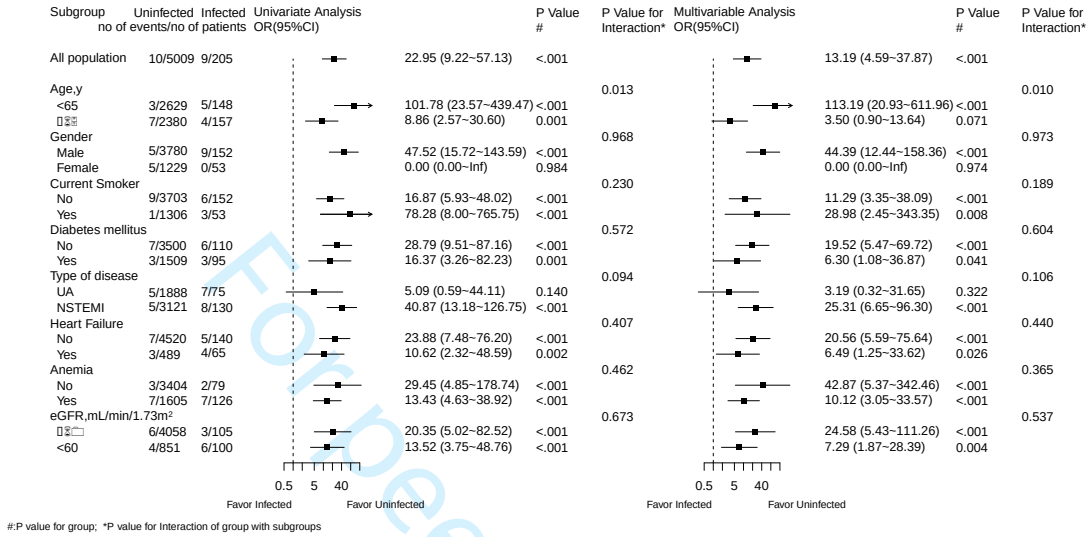
**Figure S3.** Subgroup analysis of in-hospital all cause death




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

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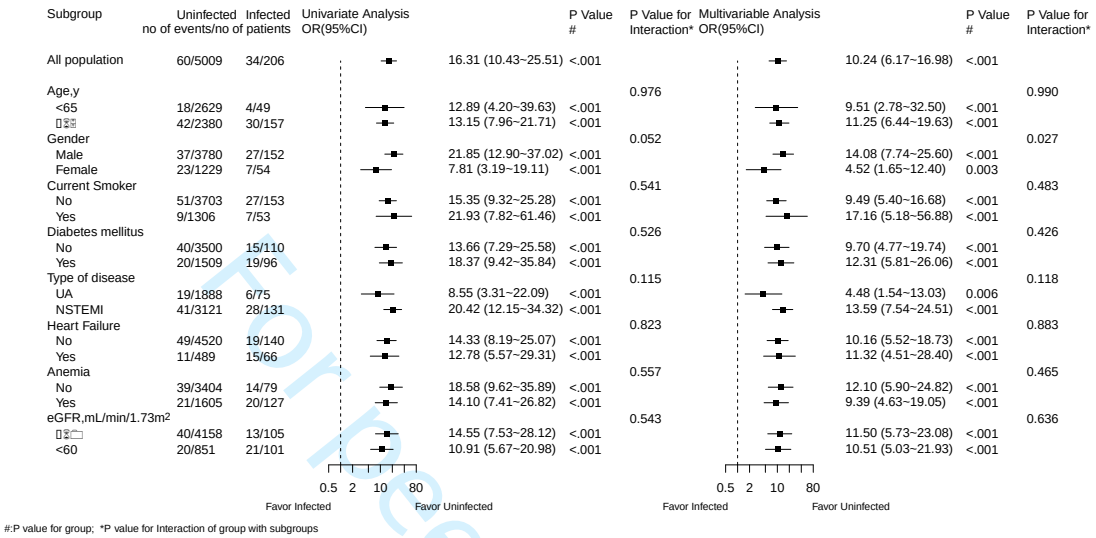
**Figure S4.** Subgroup analysis of in-hospital major bleeding




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

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

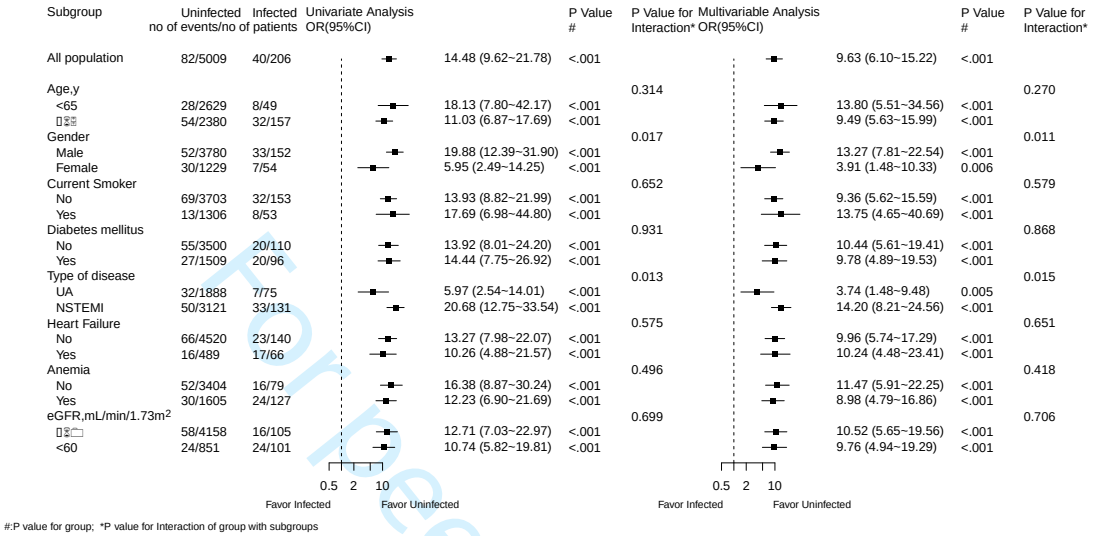


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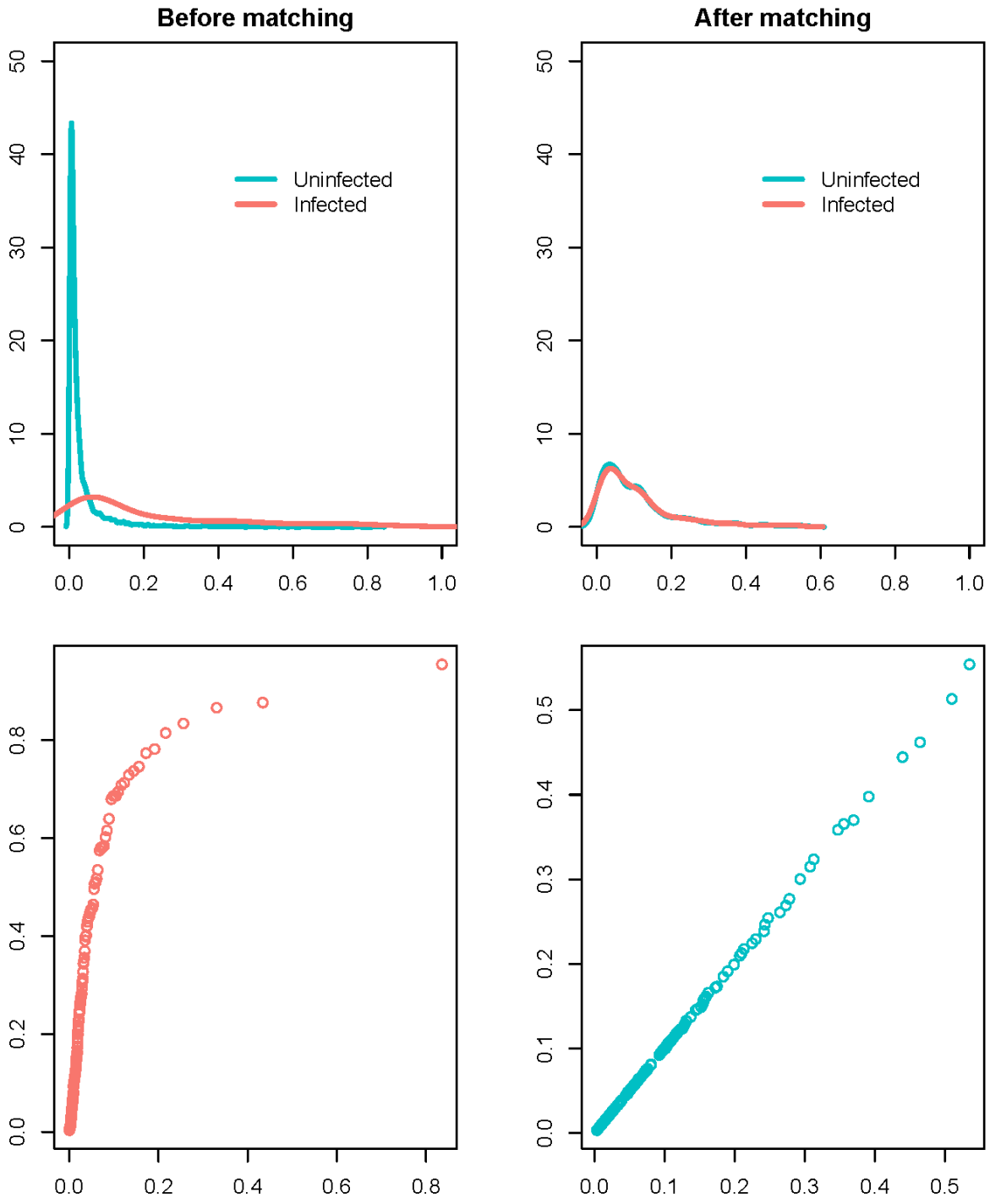
**Figure S6.** Distributions of propensity scores between the two groups before and after matching (the first row is the density plots and the second row is the QQ plots)



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 | 1 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 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 | 7 |
| | | (*b*) For matched studies, give matching criteria and number of exposed and unexposed | 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 | 8-9 & supplement |
| | | (*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 | |
| **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 | 9-10 |
| | | (b) Give reasons for non-participation at each stage | |
| | | (c) Consider use of a flow diagram | |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 9-10 |
| | | (b) Indicate number of participants with missing data for each variable of interest | |
| | | (c) Summarise follow-up time (eg, average and total amount) | |

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

*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.

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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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|---|---|
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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 NSTE-ACS and PCI

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## Abstract

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

**Design:** This observational cohort originated from the database for NSTE-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 NSTE-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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confirmed these results.

**Conclusions:** The incidence of infection is low in hospitalization, but it is associated with worse in-hospital and long-term outcomes.

**Key Words**: Non-ST-elevation acute coronary syndrome; Percutaneous coronary intervention; Infection; Outcomes.

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**Strengths and limitations of this study**

- We widely included NSTE-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.

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## Introduction

Acute coronary syndrome (ACS) is a leading cause of death both in China and around the world[1]. As compared with STEMI patients, those with non-ST elevation acute coronary syndrome (NSTEACS) 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 NSTE-ACS remains scanty. Only one study of 174 octogenarian patients with ACS evaluated the impact of infection on clinical outcomes[10]. Thus, we aimed to assess the incidence of infection and its association with short- 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



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with adequate information to diagnose or rule out infection were included. Patients were excluded if they were diagnosed with a malignant tumor or infection before the index date, pregnant or presenting with cardiogenic shock. The method to search and identify appropriate NSTE-ACS patients has been outlined previously[11]. The study protocol was approved by the central ethics committee of the Guangdong Provincial People's Hospital, with a waiver of informed consent. The study was conducted in accordance with the Declaration of Helsinki.

**Data collection and procedures**

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 evidence[12].

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 prescribed[8]. Infection was classified as pulmonary, urinary tract infection (UTI) or others (including non-pulmonary/ non-urinary sepsis and cellulitis), based on the clinical records during 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 Prevention[13].

**Clinical outcomes and follow up**



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

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

**Statistical analysis**

All patients were divided into groups with or without infections. Continuous variables with a normal distribution are presented as the mean ± SD, and those with an asymmetric distribution are presented as the median and interquartile range (Q25-Q75). Student's t test or Wilcoxon rank-sum test were used to compare the continuous variables. Categorical variables are presented as frequencies and were compared by the Fisher exact test or chi-square test. Univariate and multivariable analyses were performed to evaluate the relationship between infection and clinical outcomes. Variables that were significant in the univariate analysis or clinically important were included in the multivariable models. Considering the low incidence of adverse outcomes but potential high incidence of confounders, two models were developed for



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each multivariable analysis. The first model (model 1) included infection, age, anemia, type of disease (unstable angina and non-ST-elevation acute myocardial infarction), gender, current smokers, heart failure, and estimate glomerular filtration rate (eGFR). The second model (model 2) included radial access, cardiac biomarker positive, time to procedure, treated multi-vessel, diabetes mellitus, hypertension, prior myocardial infarction, and prior stroke. We performed subgroup analyses by older age, gender, current smokers, diabetes mellitus, types of disease, heart failure, anemia and chronic kidney disease. Analysis based on different types of infections was reported. We also introduced the GRACE (Global Registry of Acute Coronary Events)[15] and CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines) score[16] and compared the infection outcomes among different GRACE or CRUSADE risk groups (low, medium, or high risk). All data analyses were performed with SAS (version 9.4, SAS Institute, 210 Cary, North Carolina, USA). A two-sided $P<0.05$ was considered significant.

Propensity score analyses were conducted to test the robustness of the results. All factors listed in **Table 1** were considered in the propensity score model development. The heterogeneity analysis between the centers was conducted using meta-analysis methods.

**Patient and public involvement**

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

**Results**



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**Baseline characteristic**

From January 1, 2010, to December 31, 2014, a total of 8197 consecutive NSTE-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 (odd 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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independently related to the risk of the above outcomes **(Figure 1).**

**Long-term clinical outcomes**

At a median follow-up of 3.2 years, Kaplan-Meier analysis revealed that patients with in-hospital infection had a higher risk of long-term death, major bleeding, and death or major bleeding compared with those without in-hospital infection (P<.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,



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18; 95%CI, 2.40-134.8, P=0.015), and a similar result was found at follow-up (HR, 5.33;95%CI, 1.55-18.30, P=0.007), but matched results showed an absence of a significant difference in all-cause death (in-hospital: OR, 4.01; 95%CI, 0.25-64.30; follow-up: OR, 2; 95%CI, 0.97-4.12)(**Table S3**).

**Discussion**

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

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



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contemporary more liberal use of drug eluting stents[17, 18].

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

Although infections had a negative impact on patients with NSTE-ACS, the underlying pathophysiologic mechanism remains unclear. Corrales-Medina et al.[19] suggested that infection increased the mortality of patients who underwent elective PCI due to the change in plaques triggered by acute inflammatory reactions. Indeed, infection has been implicated as a factor contributing to initiation, progression and rupture of an atherosclerotic plaque[20]. Infectious vectors have been reported to induce the expression of adhesion molecules such as heat shock protein 60 and monocyte chemoattractant protein-1 on endothelial cells, which can activate the endothelium and the formation of a lipid core[21-24]. Additionally, the SIXTUS study group[25] demonstrated that platelet activation and $TxB_2$ overproduction are related to infections via Toll-like receptor 4. Moreover, MODICA et al.[26] reported that aspirin non-responsiveness was often observed in patients with pneumonia. Also, increased coagulation activity has



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been observed in pneumonia[3]. Therefore, infection can activate platelets and the coagulation system, which plays a critical role in deteriorating outcomes in patients with ACS. In contrast to previous STEMI reports[8, 9] , we did not find a significant association of infection with myocardial infarction due to the low incidence of myocardial infarction in our study. However, our results were similar to previous studies that reported major bleeding was more frequent in patients with infection. Although the PLATelet inhibition and patient Outcomes (PLATO) trial demonstrated that ticagrelor, a more potent and consistent platelet $P2Y_{12}$ inhibitor, was associated with significantly fewer pulmonary infections and death related to infection than clopidogrel, the incidence of bleeding in patients with infection in that study was not reported[4]. Because of dysfunction of platelets and the coagulation system, patients with infection might be at higher risk of ischemia and bleeding. Therefore, more attention should be paid to patients with infection when antithrombotic therapy was determined. Finally, infection can also result in worse outcomes for NSTE-ACS patients through increasing catecholamines and potentially adverse hemodynamic effects, such as coronary vasoconstriction and increased myocardial metabolic demands[27].

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



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pulmonary infection related to the worse clinical outcomes.

**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. Furthermore, because there is not a general screen of infection in all the patients, the infection can be underestimated. But the symptom-leading diagnose of infection is more practical in real world, and can be promoted easily in clinic.

**Conclusions**

Infection is an uncommon complication in patients with NSTE-ACS undergoing PCI but is nonetheless independently associated with worse in-hospital and long-term outcomes. Future studies are indicated to identify NSTE-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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**Authors' contributions**

P-C He designed and supervised the study; P-Y Chen, Y-H Liu, L Jiang, X-B Wei and W Guo performed the study, and C-Y Duan analyzed the data; Y-H Liu and other authors provided the samples and demographics from patients and controls; Y-H Liu and P-Y Chen wrote the manuscript; N Tan, J-Y Chen and P-C He revised the



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manuscript for important intellectual content.

**Conflict of Interest**

The authors declared no potential conflicts of interest with respect to the research, 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.

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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)



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**Table 1. The baseline characteristics at index hospitalization**

| | All patients* | | | *P* 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** | | | | |



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| | All patients* | | | *P* 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(%)** | | | | |



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| | All patients* | | | *P* 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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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=angiostensin-converting enzyme; 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;



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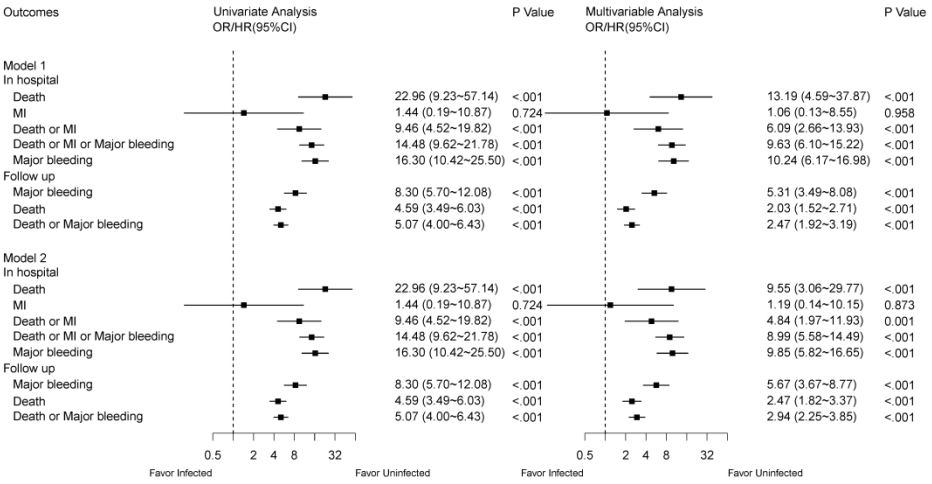


Figure 1. Univariate and multivariable logistic or Cox analysis for clinical outcomes

423x225mm (300 x 300 DPI)

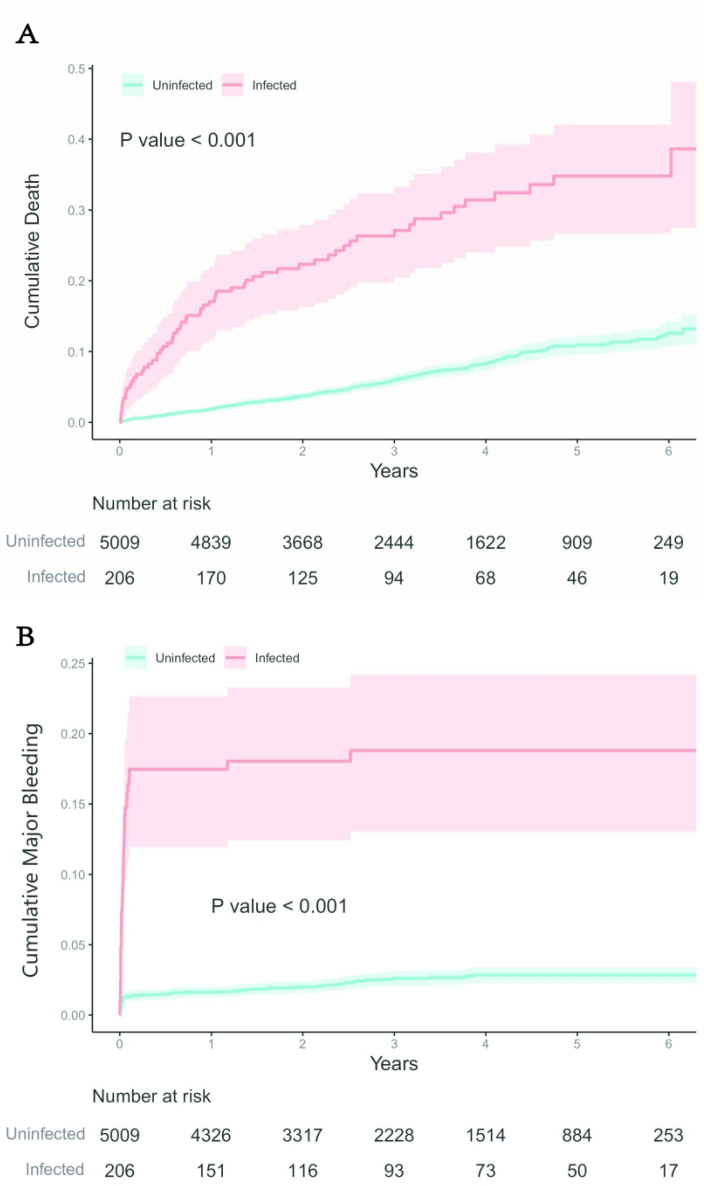


Figure 2. Kaplan-Meier estimated event rates of all cause death (A) and major bleeding (B)

# Supplementary Appendix 1

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**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 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)

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

| Outcomes | Univariate analysis | | | Multivariable analysis | | |
|---|---|---|---|---|---|---|
| (Compare with uninfected patients) | 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.

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**Table S2 Propensity Score Analyses**

| | Propensity Score Analyses | | | |
|---|---|---|---|---|
| | **Uninfected (N=592)** | **Infected (N=148)** | **Total (N=740)** | ***P* value** |
| 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 (N=592) | Infected (N=148) | Total (N=740) | *P* value |
| LVEF, % | 59.67±12.02 | 57.81±13.16 | 59.29±12.28 | 0.118 |
| eGFR, mL/min/1.73m2 | 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 (N=592)** | **Infected (N=148)** | **Total (N=740)** | ***P* value** |
| 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=angiostensin-converting enzyme; ARB=angiotensin receptor blocker.

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**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 |

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

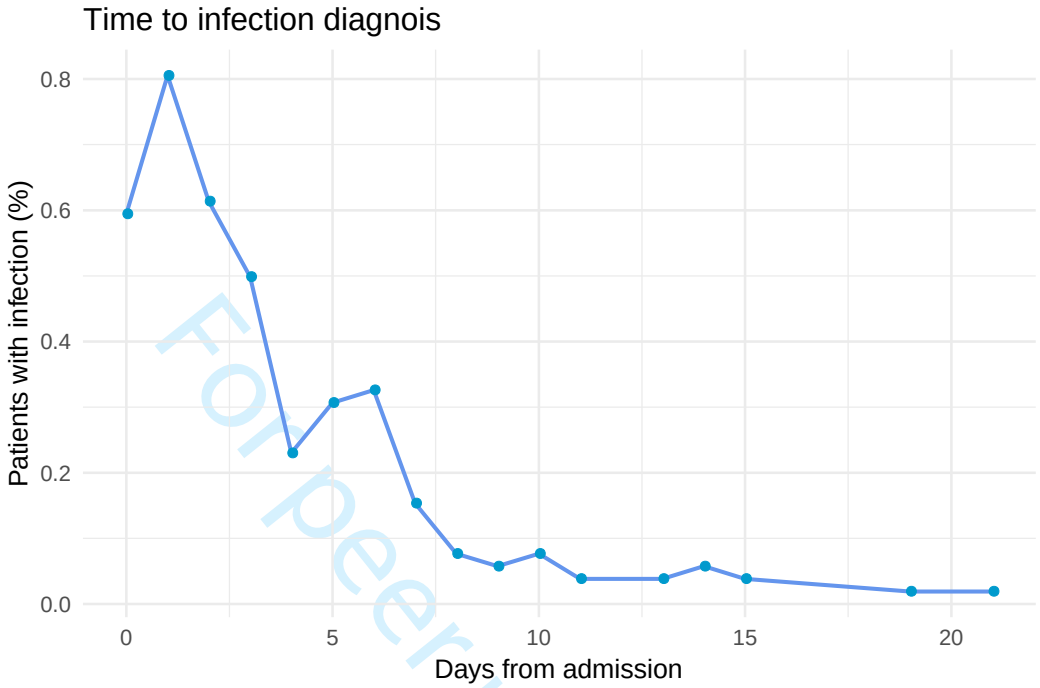


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**Figure S2.** Kaplan-Meier estimated event rates of all cause death or major bleeding

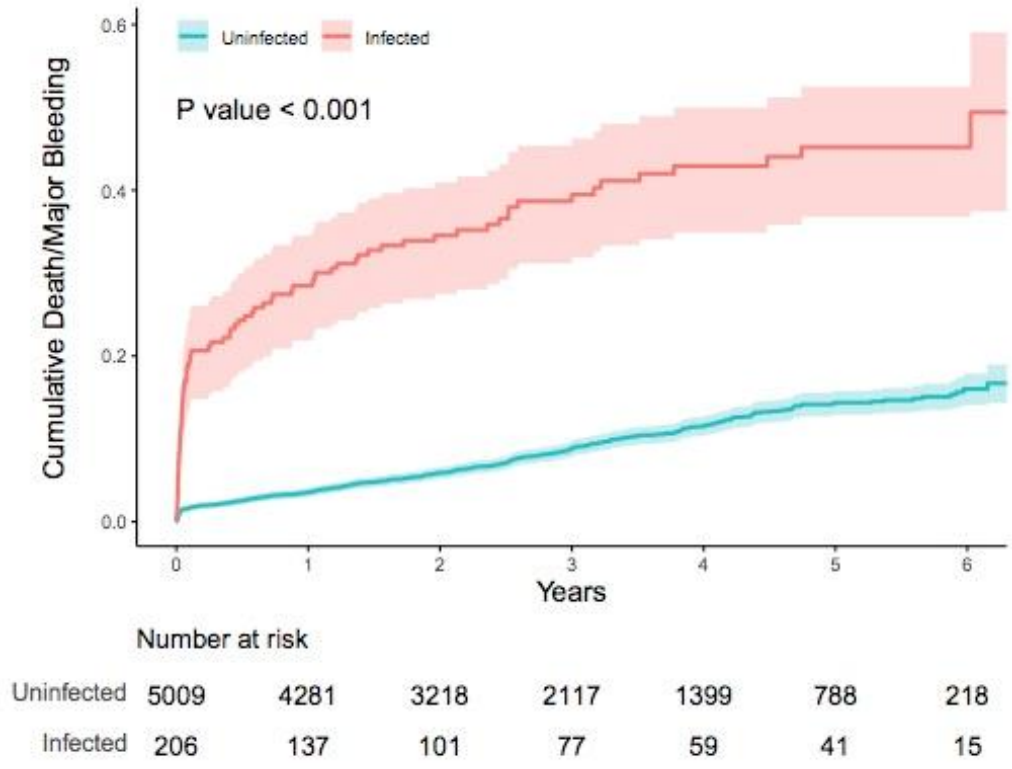


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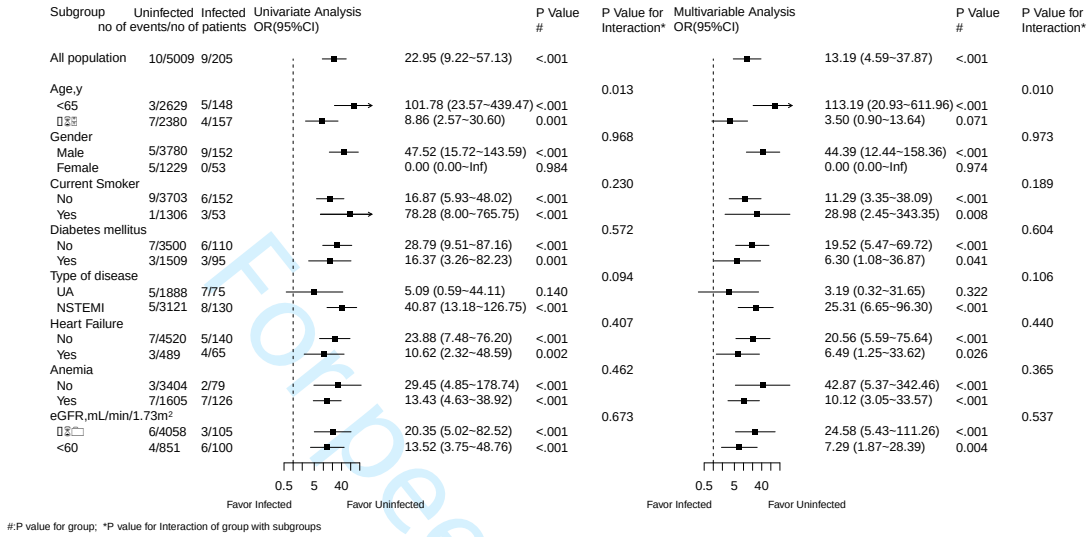
**Figure S3.** Subgroup analysis of in-hospital all cause death




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

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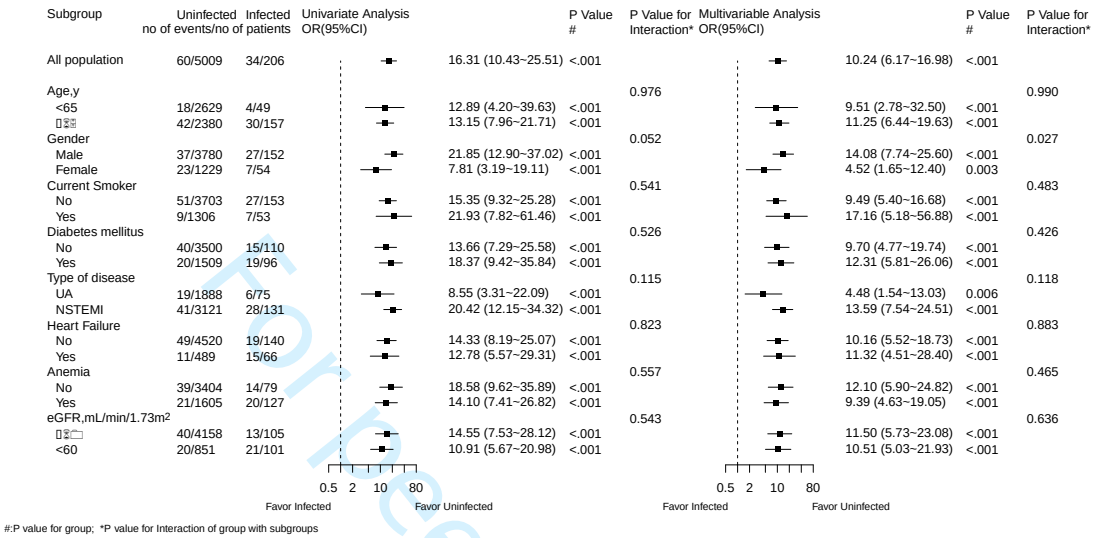
**Figure S4.** Subgroup analysis of in-hospital major bleeding




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

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

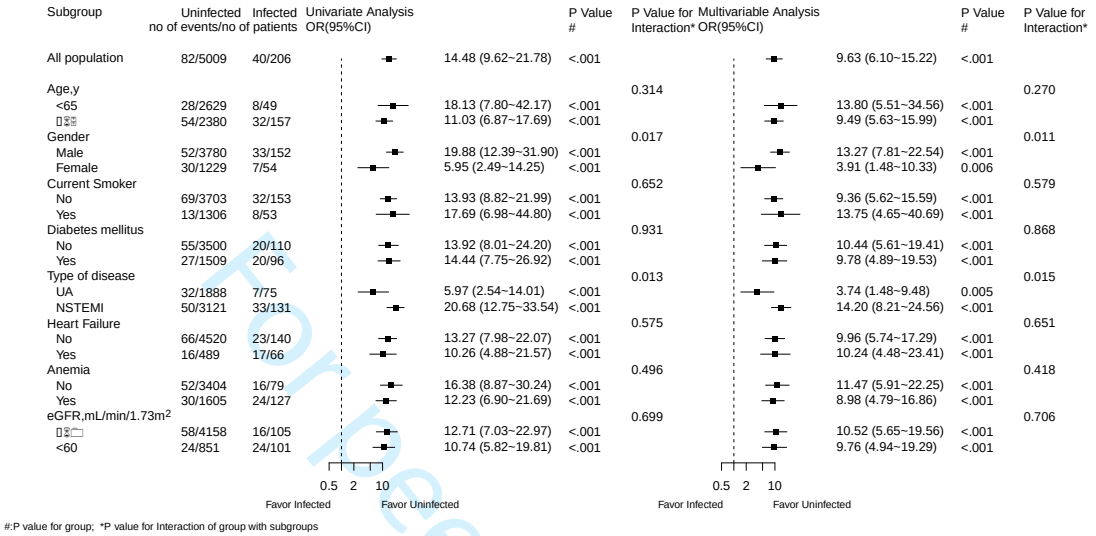


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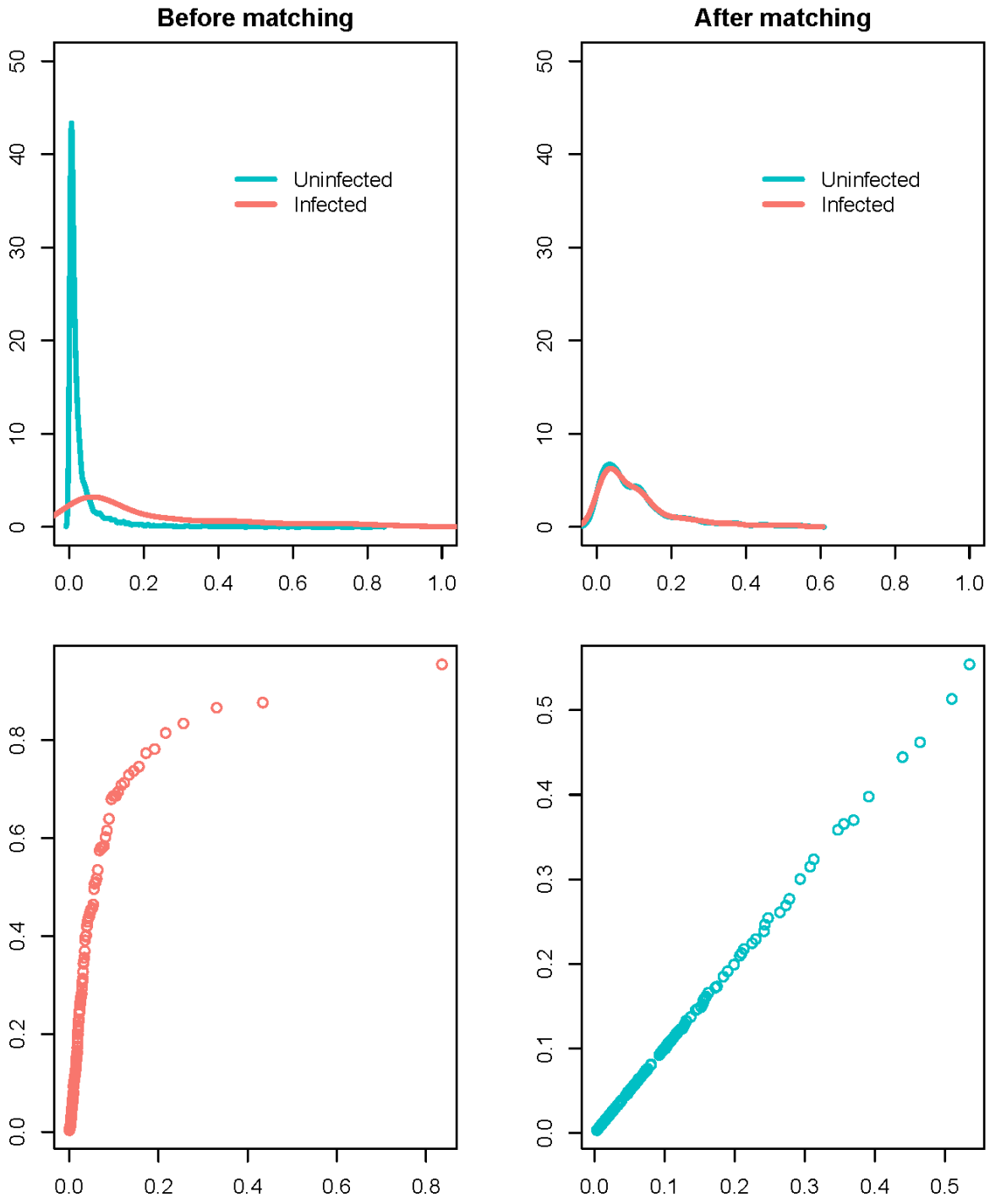
**Figure S6.** Distributions of propensity scores between the two groups before and after matching (the first row is the density plots and the second row is the QQ plots)



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 | 1 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 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 | 7 |
| | | (*b*) For matched studies, give matching criteria and number of exposed and unexposed | 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 | 8-9 & supplement |
| | | (*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 | |
| **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 | 9-10 |
| | | (b) Give reasons for non-participation at each stage | |
| | | (c) Consider use of a flow diagram | |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 9-10 |
| | | (b) Indicate number of participants with missing data for each variable of interest | |
| | | (c) Summarise follow-up time (eg, average and total amount) | |

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

*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.

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