PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Impact of infection for non-ST-elevation acute coronary syndrome patients undergoing percutaneous coronary intervention: insight from a multicentre observational cohort from China
AUTHORS	Chen, Peng-yuan; Liu, Yuanhui; Duan, Chongyang; Jiang, Lei; Wei, Xuebiao; Guo, Wei; Chen, Jiyan; Tan, Ning; He, Pengcheng

VERSION 1 – REVIEW

REVIEWER	Stefano Savonitto Cardiovascular Department Manzoni Hospital Lecco – Italy
REVIEW RETURNED	23-Mar-2020

GENERAL COMMENTS	Journal: BMJ Open Manuscript ID bmjopen-2020-038551 The Authors describe the incidence, characteristics and impact on outcome of infection in a large population of patients with NSTEACS undergoing PCI during index admission at 5 hospitals in China. Infection was classified as either “community acquired” [diagnosis within 72h of admission] or “hospital acquired” [beyond 72 hours]. Timing and types of infection are described. Outcomes of interest are in-hospital and long-term MACE and bleeding. The excess risk of MACE and bleeding associated with infection is analysed using multivariable (logistic regression?) analysis and is confirmed across subgroups and type of infection. Main comment A useful descriptive study coming from real word practice. There are a number of supplementary tables: I would skip the analyses by GRACE and CRUSADE scores: they do not add to the information. Specific comments Abstract Objectives: “we aimed to interpret the association between in-hospital infection and the Prognosis…” Not clear: probably should be “We aimed to describe…”. Results “Subgroup analysis confirmed these results.”: meaning not clear. It should probably read “This adjusted excess risk was similar across patient subgroups and types of infection” Introduction “NSTEMI….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." This observation refers to a situation non longer real, particularly for NSTEMI patients undergoing PCI (as also shown in the present report where event rates are very low): please check Morici N, et al. Am J Med 2019;132:209-16 Methods The sentence "…all other adverse clinical events were evaluated by an independent clinical events committee that was masked to the infection details" should find place in the Methods: this increases the methodological value of the study. References - Ref 1 should be updated The manuscript needs linguistic revision

REVIEWER	Hideki Ishii Nagoya University, Japan
REVIEW RETURNED	29-Mar-2020

GENERAL COMMENTS	This paper assessed whether infection affected on short- and long-term clinical outcomes in NSTE-ACS patients undergoing PCI. The study enrolled a large number of patients, and the results seem reasonable and promising. The reviewer has some queries regarding the manuscript. Specific comments 1. It seems interesting if the authors perform landmark analysis at discharge. 2. Some patients with active infection before the onset experience ACS. Did the authors enrolled patients suffering from infection only after hospitalization in the study? Please clarify. 3. In the limitation, there are some descriptions in the present form, however, it is difficult to distinguish active infection from the results of AMI. High fever, high WBC counts, high CRP levels are induced due to myocardial necrosis. Needless to say, such signs are frequently seen in patients with large myocardial infarction who are related to high incidences of adverse events. From this point of view, data on infarction sizes or are essential. 4. Previous reports have suggested that prodromal angina, glucose levels at admission, and so on greatly affect clinical prognosis in patients with AMI. 5. Insertion of urinary catheter sometimes induces UTI. How many patients received the procedure? 6. Puncture sites may be associated with incidences of infection. 7. Were major bleedings counted only after infection? How did the authors evaluate vice-verse cases?

REVIEWER	Brent Muhlestein Intermountain Heart Institute Salt Lake City, UT USA
REVIEW RETURNED	09-Apr-2020

GENERAL COMMENTS	Bmjopen-2020-038551 Impact of infection for non-ST-elevation acute coronary syndrome patients undergoing percutaneous coronary intervention: Insight from a multicentre observational cohort from China. Comments to the authors: This manuscript reports the results of the multicenter observational cohort study of 8,197 patients admitted to any one of several hospitals in China with a diagnosis of non-ST elevation acute coronary syndrome who received a percutaneous coronary intervention. By query of electronic health records, the investigators divided the patients into two groups; those who diagnosed with or without concurrent acute infection. Of the 5,215 qualifying patients, only 206 (3.95%) were diagnosed with an acute infection. The investigators followed both groups for in-hospital all-cause death, and major bleeding and post-discharge all-cause death and major bleeding and myocardial infarction. The authors reported that after adjusting for confounders, the infection was a strong independent predictor of both in-hospital and out of hospital death and major bleeding. In general, the manuscript is well written and of an appropriate length. It addresses an important question as to what may be the contribution of a concomitant acute infection in the setting of ACS. The dramatic increase in the risk of both hospital death and long-term follow-up death among the patients diagnosed with acute infection during initial hospitalization is impressive. It would be nice if the investigators could offer some potential explanations for their findings. Some specific comments are as follows: 1. Since there was such a small number (206 out of 5,215) of patients diagnosed with an infection, presumably, these acute infections were severe. It would be good to clarify exactly how they identified patients to have an acute infection and what the acuity was. A minor upper respiratory infection caused by a cold virus is very different from severe bi-lobar pneumococcal pneumonia. Understanding the severity of the infections could be very helpful. 2. When reviewing the baseline characteristics at initial index hospitalization, as shown in Table 1, it can be easily seen that many baseline characteristics are different between those with and without an acute infection. For example, the infected patients were much older and more likely to have had prior myocardial infarction, be diabetic, present with heart failure, require intra-aortic balloon pump therapy, have renal failure, and be anemic. All of these baseline clinical differences, though unrelated to the presence or absence of infection, would tend to increase the likelihood of in-hospital and follow-up death. The authors did report that the presence of a concurrent infection remained an independent predictor of mortality, even after multivariable adjustment. However, because of the substantial differences in the baseline characteristics of the two groups, a standard multivariable analysis may not be adequate to adjust for all of these differences. I recommend the investigators also perform a confirmatory nested-control statistical analysis. This can be done by matching each infected patient to five or so uninfected patients who are the same age and gender, and also have the same clinical history regarding

	prior MI or the presentation with heart or renal failure, or anemia, or the use of IABP therapy.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1:
1. Response to comment: (A useful descriptive study coming from real word practice. There are a number of supplementary tables: I would skip the analyses by GRACE and CRUSADE scores: they do not add to the information.)
Response: We appreciated the suggestions of review. Since the baseline characteristics differ a lot between patients with infection and without, we would like to introduce PS analyses instead. So, we decided to delete the supplemental tables 6-9 in the initial version to make the manuscript more concisely and accurate.

2. Response to comment: (Abstract Objectives: "we aimed to interpret the association between in-hospital infection and the Prognosis…" Not clear: probably should be "We aimed to describe…")
Response: We are sorry for unclear indication of the word. We replaced "interpret" by "describe". We also checked again so that no other similar content. See the change in the modification version.

3. Response to comment: ("NSTEMI….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." This observation refers to a situation non longer real, particularly for NSTEMI patients undergoing PCI (as also shown in the present report where event rates are very low): please check Morici N, et al. Am J Med 2019;132:209-16)
Response: We are sorry for the outdate references. After reading the recommended paper we decided to rewrote this part in the introduction. Despite the fact that STEMI patients suffered more comorbidities, the NSTEMI patients still suffer high rate of cardiovascular events both in elder patients and whole population. And we replaced the second reference by the recommended one.

4. Response to comment: (The sentence "…all other adverse clinical events were evaluated by an independent clinical events committee that was masked to the infection details" should find place in the Methods: this increases the methodological value of the study.)
Response: We changed the position of this sentence to method so that there is an increase about the methodological value.

5. Response to comment: (- Ref 1 should be updated)
Response: We have updated the reference to 2019 version, and we also updated the data in the main text. We are sorry for outdate reference during drafting the manuscript. Modifications were made in reference part as well as the text.

6. Response to comment: (The manuscript needs linguistic revision)
Response: We have rechecked the linguistic mistakes, and the related changes were trackable in the modification version.

Reviewer #2:
1. Response to comment: (It seems interesting if the authors perform landmark analysis at discharge.)
Response: We performed the landmark analysis at discharge, and the results were shown in the figure appendix. We performed the COX regression (Appendix 1) as well as the K-M plots (death: Appendix 2A; major bleeding: Appendix 2B) of follow-up by landmark analysis. We found that infection is still a robust factor for predicting death and major bleeding both by COX regression and K-M analysis. Since none differences were seen compared with our previous submitted results, we prefer to show them in the appendix of respond letter rather than add them in the manuscript.

2. Response to comment: (Some patients with active infection before the onset experience ACS. Did the authors enrolled patients suffering from infection only after hospitalization in the study? Please clarify.")
Response: Thanks. The current research included patients with diagnose of infection during index hospitalization, which was indicated in the method part. Thus, it is certain that all the infection was confirmed after hospitalization. And the infections were divided into the community-acquired and hospital-acquired pulmonary infection according to the criteria established by the Centers for Disease Control and Prevention.

3. Response to comment: (In the limitation, there are some descriptions in the present form, however, it is difficult to distinguish active infection from the results of AMI. High fever, high WBC counts, high CRP levels are induced due to myocardial necrosis. Needless to say, such signs are frequently seen in patients with large myocardial infarction who are related to high incidences of adverse events. From this point of view, data on infarction sizes or are essential.)
Response: Thank you. We agree with you that infection may share the same symptoms and lab examination with AMI, but the current diagnose is far more than that, and can reach a very strict diagnose criteria. In the current study, the diagnose of infection based on symptoms and lab examination. Additionally, all the infections come to the criteria of antibiotic application, which is under surveillance in responsible infection control doctor.

4. Response to comment: (Previous reports have suggested that prodromal angina, glucose levels at admission, and so on greatly affect clinical prognosis in patients with AMI.)
Response: Thanks. We agree with you that glucose levels at admission might affect the clinical prognosis in patients with AMI and we adjusted it in our multivariate model 1. However, we did not collect the data about the prodromal angina. As an observational study, despite adjustment for important confounders, we could not completely eliminate all the potential bias including selection bias. We reported this limitation in the manuscript.

5. Response to comment: (Insertion of urinary catheter sometimes induces UTI. How many patients received the procedure?)
Response: We reviewed all the in-hospital documents of the infectious patients again to confirm the proportion of urinary catheter among UTI. We found that 2 in 18 UTI patients (11.1%) received urinary catheter insertion. One received the procedure before the confirmation of UTI, and another after the UTI. Additionally, we found 49 in 344 without UTI patients (14.2%) received urinary catheter insertion, and 13 of them received the procedure after the confirmation of infection. However, the present study cannot confirm the association between the catheter insertion and the UTI because of the current limited infectious population.

6. Response to comment: (Puncture sites may be associated with incidences of infection.)
Response: Thanks. We agree with you that puncture sites might be associated with incidences of infection. Our result also showed that the infectious patients are more likely to receive the femoral puncture site. And we adjusted the access site in the multivariate analysis to find the infection as an independent factor for increased risk of death and bleeding. Additionally, we performed the propensity score analysis in our revision version, which also matched the access site. And the results were similar as main text in bleeding.

7. Response to comment: (Were major bleedings counted only after infection? How did the authors evaluate vice-verse cases?)
Response: We are here to confirm that all the clinical outcomes, including all-cause death, major bleeding and MACE, were all counted after infection.

Reviewer #3:
1. Response to comment: (It would be nice if the investigators could offer some potential explanations for their findings.)
Response: Actually, the mechanism of infection's negative impact on NSTE-ACS patients is still unknown. According to the previous research the potential mechanism can be interpreted briefly as follows. Firstly, inflammatory factors can trigger the change of plaques. Secondly, the infectious vector is an activator of lipid core formation. Thirdly, the infection activates the platelet, so that may result in the aspirin non-responsiveness. And the three points and related references are presented detailly in our discussion part.

2. Response to comment: (Since there was such a small number (206 out of 5,215) of patients diagnosed with an infection, presumably, these acute infections were severe. It would be good to clarify exactly how they identified patients to have an acute infection and what the acuity was. A minor upper respiratory infection caused by a cold virus is very different from severe bi-lobar pneumococcal pneumonia. Understanding the severity of the infections could be very helpful.)
Response: We agree with you that it is necessary to clarify the severity of the infections. As we mentioned in the method, the infection was confirmed by both symptoms and positive lab examination, and all the patients come to the indication of antibiotics. All the procedures above were under the surveillance of the infection control doctors. Notably, the upper respiratory infections caused by the cold virus were not included in the infectious group.

3. Response to comment: (When reviewing the baseline characteristics at initial index hospitalization, as shown in Table 1, it can be easily seen that many baseline characteristics are different between those with and without an acute infection. For example, the infected patients were much older and more likely to have had prior myocardial infarction, be diabetic, present with heart failure, require intra-aortic balloon pump therapy, have renal failure, and be anemic. All of these baseline clinical differences, though unrelated to the presence or absence of infection, would tend to increase the likelihood of in-hospital and follow-up death. The authors did report that the presence of a concurrent infection remained an independent predictor of mortality, even after multivariable adjustment. However, because of the substantial differences in the baseline characteristics of the two groups, a standard multivariable analysis may not be adequate to adjust for all of these differences. I recommend the investigators also perform a confirmatory nested-control statistical analysis. This can be done by matching each infected patient to five or so uninfected patients who are the same age and gender, and also have the same clinical history regarding prior MI or the presentation with heart or renal failure, or anemia, or the use of IABP therapy.)
Response: We appreciated the suggestions from the reviewer. 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. We matched 740 patients with or without infection in a 1:4 ratio (Table S2 and Figure S10). The result showed a higher risk 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, 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). All the contents were added in our latest submitted files, such as manuscript and supplemental materials.

We appreciate for Editors/Reviewers' warm work earnestly, and hope that the correction will meet with approval.
Once again, thank you very much for your comments and suggestions. We look forward to hearing from you.

Sincerely
PengCheng He
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VERSION 2 – REVIEW

REVIEWER	Stefano Savonitto Manzoni Hospital Lecco Italy
REVIEW RETURNED	17-Jun-2020

GENERAL COMMENTS	In the Introduction, the following sentence “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 should be rephrased as follows: “As compared with STEMI patients, those with 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 events2 which might expose them to iatrogenic and infective complications.”

REVIEWER	Hideki Ishii Fujita Health University Bantane Hospital, Japan
REVIEW RETURNED	12-Jun-2020

GENERAL COMMENTS	Thank you for changings. The reviewer is satisfied with most of them. The reviewer has only a few comments. 1. As to the previous query 2: Some patients with active infection before the onset experience ACS. The response from the authors indicated that patients who had active infection before the onset experience ACS but was diagnosed after admission were enrolled into the study. Is it OK? If so, please state clearly. Once again, infections may be masked particularly in ACS cases. WBC and/or CRP levels are increasing or high fever may be seen only due to myocardial infarction. It is really difficult to distinguish etiologies. The reviewer thinks that there might be over-diagnose or under-diagnose. This seems a limitation of the study. 2. The first sentence: ‘The incidence of non-ST-elevation acute coronary syndrome (NSTE-ACS) is increasing, and approximately 80% of all ACS patients are NSTE.’ In the US, a number of NSTE-ACS may be increasing. In other words, the phenomena may be adapted to particular countries. However, the paper is from China. Please modify.

VERSION 2 – AUTHOR RESPONSE

Reviewer #1:
1. Response to comment: (In the Introduction, the following sentence “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” should be rephrased as follows: “As compared with STEMI patients, those with 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.”)
Response: Thank you for your suggestion. We replaced this sentence as recommended. The modification may be tracked in our latest submitted manuscript.

Reviewer #2:
1. Response to comment: (As to the previous query 2: Some patients with active infection before the onset experience ACS. The response from the authors indicated that patients who had active infection before the onset experience ACS but was diagnosed after admission were enrolled into the study. Is it OK? If so, please state clearly. Once again, infections may be masked particularly in ACS cases. WBC and/or CRP levels are increasing or high fever may be seen only due to myocardial infarction. It is really difficult to distinguish etiologies. The reviewer thinks that there might be over-diagnose or under-diagnose. This seems a limitation of the study.)
Response: Thank you. We added the exception criterion of infection that was diagnosed before index in the method so that it can be clarified. We also added the limitation of underestimated infection in the newly submitted manuscript.

2. Response to comment: (The first sentence: ‘The incidence of non-ST-elevation acute coronary syndrome (NSTE-ACS) is increasing, and approximately 80% of all ACS patients are NSTE.’ In the US, a number of NSTE-ACS may be increasing. In other words, the phenomena may be adapted to particular countries. However, the paper is from China. Please modify.)
Response: Thank you. We have rewritten this sentence according to the data from Asian-Pacific region. Also, we updated the first reference. And hope the modification may not cause any more misunderstand.

We appreciate for Editors/Reviewers’ warm work earnestly, and hope that the correction will meet with approval.
Once again, thank you very much for your comments and suggestions. We look forward to hear from you.

Sincerely
PengCheng He
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