PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Percutaneous Coronary Intervention in Patients with Acute Coronary Syndrome in Chinese Military Hospitals, 2011-2014, a retrospective observational study of a national registry.
AUTHORS	Zhao, Ren; Xu, Kai; Li, Yi; Qiu, Miaohan; Han, Yalin

VERSION 1 – REVIEW

REVIEWER	Raffaele Bugiardini University of Bologna
REVIEW RETURNED	12-Apr-2018

GENERAL COMMENTS	The main goal of this manuscript was to provide an updated and real-world overview of the performance of PCI in ACS patients since 2011 in China after the China PEACE study from 2001 to 2011. In the China PEACE study, Zheng et al (JAMA Intern Med. 2016) evaluated 1, 241 patients undergoing coronary catheterization and PCI at 55 urban Chinese hospitals in calendar years 2001, 2006, and 2011 using a 2-stage, random sampling strategy to create a nationally representative sample. They estimated: (a) the national rates of hospitalizations for coronary catheterization (b) the presence of nonobstructive coronary artery disease (c) the proportion of PCI procedures performed via radial approach (d) the use of drug-eluting stents (e) the median length of hospital stay (f) in-hospital mortality (g) bleedings These authors should repackage the manuscript to render comparison with China PEACE feasible. In addition the authors concluded that their “data revealed the overall interventional resources were still limited, with great disparities of interventional resources and consumptions in different geographical regions of China, and major gaps still exist in medical coverage for ACS patients. Nonetheless, our study also demonstrated notable improvements in the quality of care and major differences in the characteristics of PCI practice compared with contemporary developed countries as well as non-military hospitals in China”. I believe that conclusions do not fit the main question, i.e. what's going on China (2011 to 2018) after the China PEACE study (2001 to 2011). The current analysis should follow the same pathways of the China PEACE study and evaluate the above reported variables.

REVIEWER	Dennis Ko Institute for Clinical Evaluative Sciences
REVIEW RETURNED	12-Jun-2018

GENERAL COMMENTS	BMJ Open review: Percutaneous Coronary Intervention in Patients with Acute Coronary Syndrome in China, 2011-2014 Summary: Percutaneous Coronary Intervention (PCI) procedures are gaining popularity in China for treatment of patients with acute coronary syndrome (ACS). The authors aimed to evaluate performance of PCIs in China from 2011-2014 in this cross-sectional study. Using a national registry of 117 military hospitals containing 144,659 ACS patients, the authors found that the number of PCIs performed increased dramatically over the study period, they stated that the use of assisted devices and novel medications were relatively small. The authors concluded that interventional resources were limited, with disparities, and improvement in quality of care. Major Limitations: 1. This is a descriptive piece of the patterns of care in China. One of the major issues of this study is that amount of data that were shown. It is hard to grip the major message of the study. For example, the abstract stated improved quality of care. However, there were no data that was shown related to quality of care. What did the authors mean quality of care? Did they mean number of PCI? 2. Given a short period of time, it is actually pretty hard to depict a clear picture of trends given year to year fluctuation. 3. Comparison of mortality (without fully adjustment) over time is also difficult because there were significant changes in the characteristics. There was an overall increase in the proportion of patients with unstable angina, with a decrease of STEMI patients. Further, there is an observed overall decrease in important comorbidities including hypertension, hyperlipidemia, and smoking. Finally, the proportion of patients with heart failure, prior MI, and many other diseases have also decreased over time. This difference in baseline clinical characteristics may affect results. Any improvements in treatment pathways and subsequent outcomes may be heavily confounded by the fact that the sample population is getting healthier over time. There have been no statistical or methodological strategies used that address these potential confounding effects. 4. The other major limitation is that it is unclear how authors selected this study sample. Authors included all ACS patients undergoing interventional procedures from 2011-2014. There was no information on the timing or method of diagnosis. The only exclusion criteria mentioned: “Patients with missing data were excluded in various categorical analyses”. It is not clear what patients were excluded from what analysis and why they were excluded. There are different reported total sample sizes for each descriptive category (e.g. there are 30800 ACS patients in 2011 in table 1, but only 30651 patients analyzed when describing age distribution in table 1, and 39090 patients evaluated for artery stenosis in table 3). There is no cohort creation figure or detailed information in the methods. This lack of clarity makes the results difficult to interpret. Minor Limitations: 1. This analysis is also restricted to military hospitals, which is not

	representative of the whole Chinese ACS population (three times more males than females in this study sample). This may make it difficult to make conclusions on national trends in care. The title should be altered to reflect this key impot. 2. In the abstract, 144 659 patients were included as the total sample, but the introduction they state 11 241 ACS patients undergoing PCI procedures were included in this study. 3. When measuring for prior MI, CVD, PVD etc… in table 1, what is the lookback period? Or how did the authors determine these data? 4. There was no information in the methods on how the authors measured or defined outcomes. 5. Authors measure in-hospital event rate, are there changes in length of hospital stay? This is not reported. 6. Authors mention the regional disparities with PCI care in China, with patients in the North accounting for the majority of interventional cases. It is unclear whether there is an unmet need for care in other regions, or rather the Northern regions have more PCIs because there are more eligible patients.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:
Reviewer: 1
Reviewer Name: Raffaele Bugiardini
Institution and Country: University of Bologna, Italy
Please state any competing interests or state 'None declared': none

Please leave your comments for the authors below
The main goal of this manuscript was to provide an updated and real-world overview of the performance of PCI in ACS patients since 2011 in China after the China PEACE study from 2001 to 2011.

In the China PEACE study, Zheng et al (JAMA Intern Med. 2016) evaluated 1, 241 patients undergoing coronary catheterization and PCI at 55 urban Chinese hospitals in calendar years 2001, 2006, and 2011 using a 2-stage, random sampling strategy to create a nationally representative sample. They estimated:

(a) the national rates of hospitalizations for coronary catheterization
(b) the presence of nonobstructive coronary artery disease
(c) the proportion of PCI procedures performed via radial approach
(d) the use of drug-eluting stents
(e) the median length of hospital stay
(f) in-hospital mortality
(g) bleedings

These authors should repackage the manuscript to render comparison with China PEACE feasible.
Response: the manuscript has been repacked in Discussion part and comparisons with China PEACE were largely put together, or alternatively, "China PEACE" was added to make comparison feasible.

In addition the authors concluded that their “data revealed the overall interventional resources were still limited, with great disparities of interventional resources and consumptions in different geographical regions of China, and major gaps still exist in medical coverage for ACS patients. Nonetheless, our study also demonstrated notable improvements in the quality of care and major differences in the characteristics of PCI practice compared with contemporary developed countries as well as non-military hospitals in China”.

I believe that conclusions do not fit the main question, i.e. what's going on China (2011 to 2018) after the China PEACE study (2001 to 2011). The current analysis should follow the same pathways of the China PEACE study and evaluate the above reported variables.
Response: thank you for your inqury and suggestion! Due to the specific design of this registry, information regarding (a) to (g) were not all available, however, (c)(f)(g) variables were evaluated in our study as shown in Tables. Meanwhile, we revised the Conclusion as follows: This study outlined the general profiles of cardiac intervention practice in contemporary military hospital in China. Our data revealed the overall interventional resources were still limited in military hospitals, with great disparities of resources and consumptions in different geographical regions across China, and major gaps still exist in optimal medical coverage for ACS patients. Other than data from non-military hospitals, our findings can serve as an indispensable addition to a comprehensive overview of the practice of cardiac intervention in China.
We hope this conclusion would be more appropriate and objective in terms of the spectrum of this study.
Reviewer: 2
Reviewer Name: Dennis Ko
Institution and Country: Institute for Clinical Evaluative Sciences; Canada
Please state any competing interests or state ‘None declared’: None

Please leave your comments for the authors below
BMJ Open review:
Percutaneous Coronary Intervention in Patients with Acute Coronary Syndrome in China, 2011-2014
Summary:
Percutaneous Coronary Intervention (PCI) procedures are gaining popularity in China for treatment of patients with acute coronary syndrome (ACS). The authors aimed to evaluate performance of PCIs in China from 2011-2014 in this cross-sectional study. Using a national registry of 117 military hospitals containing 144,659 ACS patients, the authors found that the number of PCIs performed increased dramatically over the study period, they stated that the use of assisted devices and novel medications were relatively small. The authors concluded that interventional resources were limited, with disparities, and improvement in quality of care.
Major Limitations:
1. This is a descriptive piece of the patterns of care in China. One of the major issues of this study is that amount of data that were shown. It is hard to grip the major message of the study. For example, the abstract stated improved quality of care. However, there were no data that was shown related to quality of care. What did the authors mean quality of care? Did they mean number of PCI?
Response: We are sorry for this confusion! We’ve repacked the comparison with China-PEACE study (which is more meaningful than comparison with NCDR in US) all together to make it feasible to grip the major message in Discussion. By saying that the quality of care was improved we mainly refer to better PCI outcomes of ACS patients in 2014 than in 2013, including higher proportions of TIMI flow grade 0-1 pre-PCI (reflecting more severe lesions) and grade 3 post-PCI, lower proportions of TIMI flow grade 0 and 2 post-PCI in 2014, less residual stenosis of lesion. However, after carefully considering the reviewer’s comment, we deleted wording of “improved quality of care” in Conclusion in both the Abstract and Discussion.
2. Given a short period of time, it is actually pretty hard to depict a clear picture of trends given year to year fluctuation.

Response: we noticed that it would be better to make comparison in a longer time course such as 10 years (like the China PEACE study). However, the Quality Control Center of Intervention for Cardiovascular Diseases in military hospitals was not found until 2009 and registered data were not available until September 2010. To make an intact comparison, we included data from calendar year 2011 to 2014 with full 12 months (by the time the analysis started, data of 2015 were not complete). On the other hand, to make the comparison with statistical power, we used $\chi 2$ trend tests, which would make the results solid, reflecting the trending from 2011 to 2014.

3. Comparison of mortality (without fully adjustment) over time is also difficult because there were significant changes in the characteristics. There was an overall increase in the proportion of patients with unstable angina, with a decrease of STEMI patients. Further, there is an observed overall decrease in important comorbidities including hypertension, hyperlipidemia, and smoking. Finally, the proportion of patients with heart failure, prior MI, and many other diseases have also decreased over time. This difference in baseline clinical characteristics may affect results. Any improvements in treatment pathways and subsequent outcomes may be heavily confounded by the fact that the sample population is getting healthier over time. There have been no statistical or methodological strategies used that address these potential confounding effects.

Response: multilevel logistic regression analysis was done. We constructed three indicator variables representing years 2012, 2013, and 2014, leaving 2011 as the reference. We did logistic regressions including these indicators for time as key explanatory variables, while adjusting for patients' ACS types (unstable angina, NSTEMI, STEMI), demographics (age and sex), comorbidities (hypertension, hyperlipidemia, diabetes mellitus, COPD, current smoking, heart failure, renal failure, under dialysis, prior cerebrovascular disease, prior peripheral vascular disease, prior PCI, prior cardiac valve surgery, prior CABG). The dependent variable was in-hospital death. Our result shows mortality also decreased significantly over time ($P_{trend} < 0.0001$). And these information were updated in Methods and Results, the result was shown as Figure 2.

4. The other major limitation is that it is unclear how authors selected this study sample. Authors included all ACS patients undergoing interventional procedures from 2011-2014. There was no information on the timing or method of diagnosis. The only exclusion criteria mentioned: "Patients with missing data were excluded in various categorical analyses". It is not clear what patients were excluded from what analysis and why they were excluded. There are different reported total sample sizes for each descriptive category (e.g. there are 30800 ACS patients in 2011 in table 1, but only 30651 patients analyzed when describing age distribution in table 1, and 39090 patients evaluated for artery stenosis in table 3). There is no cohort creation figure or detailed information in the methods. This lack of clarity makes the results difficult to interpret.

Responses: we are really sorry for the confusion in understanding due to the lack of information. The timing (discharge diagnosis) and criteria (Diagnoses were made according to the China National Guidelines for ACS, which are consistent with guidelines in the US.) of diagnosis were added into Methods. Due to the large-volume information inputed into this Registry, patients with missing data (which is inevitable) were excluded in specific categorical analyses, including age, gender, region of hospital, access artery, contrast type, lesion vessel, target vessel. For measured categories like artery stenosis and lesion category, their sum exceed the total number of patients enrolled in each study year is because each patient usually had more than one stenosed/lesioned vessel. For the sake of clarity, the sum for each measured variable category was listed in the column of each category unless otherwise specified. However, data integrity was not less than 91.8% in this study. The above explanation was also added into Methods.

Minor Limitations:

1. This analysis is also restricted to military hospitals, which is not representative of the whole Chinese ACS population (three times more males than females in this study sample). This may make it difficult to make conclusions on national trends in care. The title should be altered to reflect this key impot.

Responses: thank you for your advice! We've corrected our title as "Percutaneous Coronary

Intervention in Patients with Acute Coronary Syndrome in Chinese Military Hospitals, 2011-2014, a retrospective observational study of a national registry"
2. In the abstract, 144 659 patients were included as the total sample, but the introduction they state 11 241 ACS patients undergoing PCI procedures were included in this study.
Response: we are sorry for the mistake. 144 659 is the right number of ACS patients undergoing PCI during 2011-2014 in this study. This mistake has been corrected in Introduction.
3. When measuring for prior MI, CVD, PVD etc… in table 1, what is the lookback period? Or how did the authors determine these data?
Response: medical histories including histories of myocardial infarction, cerebrovascular disease, peripheral vascular disease, cardiac valve surgery, CABG, and PCI were collected by physicians in charge of that patient (mainly via patient's own statement and further verified, if any, by documentation in previous admission notes, discharge diagnoses, or corroborating laboratory test results) and were uploaded into the registry database. These information were added in Methods.
4. There was no information in the methods on how the authors measured or defined outcomes.
Response: complications such as slow flow, acute/subacute stent thrombosis, major bleeding, postoperative myocardial infarction, and death were defined or explained in Methods.
5. Authors measure in-hospital event rate, are there changes in length of hospital stay? This is not reported.
Response: unfortunately there was no data input regarding length of hospital stay in this registry database. However, we would be glad to update the registration form to include that information for further study.
6. Authors mention the regional disparities with PCI care in China, with patients in the North accounting for the majority of interventional cases. It is unclear whether there is an unmet need for care in other regions, or rather the Northern regions have more PCIs because there are more eligible patients.
Response: we would speculate that the Northern regions have more PCIs because there are more eligible patients. And we've mentioned that in Discussion (paragraph1): "Out data also suggest great regional disparities of PCI procedures performed on ACS patients, with patients in the north region of China (North China, Northwest, and Northeast) consumed the majority of interventional resources (65.5%-67.2% of all PCI cases for ACS patients, Table1). This also reflects pandemic state of unstable coronary artery disease in these regions."

VERSION 2 – REVIEW

REVIEWER	Raffaele Bugiardini University of Bologna Italy
REVIEW RETURNED	31-Jul-2018

GENERAL COMMENTS	The authors have answered to my issues. The quality of the paper has improved.