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)	Using competing risk and multistate model to estimate the impact of nosocomial infection on length of stay and mortality in burn patients in Southeast China
AUTHORS	GUO, Hai-lei; ZHAO, Guang-ju; LING, Xiang-wei; XU, Jian-jun; LU, Cai-jiao; LIU, zhengjun

VERSION 1 – REVIEW

REVIEWER	Dr Amber Young University Hospitals Bristol NHS Foundation Trust, UK
REVIEW RETURNED	28-Nov-2017

GENERAL COMMENTS	Review: The topic is important. Diagnosis and impact of wound and other infections in patients with burns and other trauma are of key importance and any new evidence is useful and interesting. In general, the paper is well written although there are some easily correctable issues with the language and grammar, some of which are listed below. I think it would be worth expanding the introduction to include more detail on the impact of NI in general and with burn patients in particular. It would be helpful to explain the differences between the different infection types evaluated in this study ie between burn wound infection, sepsis, pneumonia and UTIs. It would also be useful to add the aim at the end of the introduction rather than what you have done and also being specific about which outcomes you planned to study. Methods: This needs more detail including detail about those patients requiring prophylactic antibiotics; the size of patient's TBSA with inhalation injury requiring prophylaxis; what prophylaxis was used; what were the first line antibiotics given for confirmed infection; were they given according to a protocol and how were the different types of infection suspected and confirmed? The authors need to separate out the impact of NIs on outcomes (the aim of this study) from the impact due to the size and depth of burn and inhalational injury (which doesn't appear to be an aim of the study and is well known).

	My main issue is with the standardisation of the use of prophylactic antibiotics and with the diagnosis of the different infection types. There is no standard for diagnosis of burn wound infection for example (ie a positive wound swab does not equate to wound infection). It would be good to know how the authors standardised this diagnosis as this is key to the results and conclusions of the study. Finally – please could the authors define mortality as used in this study. I am assuming it is in-hospital but could the authors clarify? Detailed comments: Abstract: Line 37 p2: …..and the cumulative probability of death for a patient with NI was greater than for a patient who remained free of NI after around day 7: I think this needs clarifying please. I am unclear what it means. Line 40, p2: The expected extra LOS due to NIs was 12.9 days: please clarify what 'expected' means. Line 46 p2: Considering the consequences of NIs, surveillance and prevention are required to reduce the incidence of NIs, and then improve the outcomes of burns..: I don't think this conclusion can be drawn from this study. Main text: Line 30, p4: It has been reported that 30% to 80% of burn patients were suffered from NIs: please check the grammar Line 36 p4: It should be noted that infection only can impact on LOS and outcomes after it has started: I am not sure I understand this statement? Line 11, p5: 157 burn patients were ineligible by exclusion criteria, and 986 patients were enrolled in the study. This should be in the results not methods Line 20 p5: Burn patients with acute respiratory failure or shock were admitted to the ICU, and they were transferred to the Burn Unit when the tracheal tube is removed or the hemodynamic situation of them becomes stable, according to the judgments of burn surgeon and ICU doctor. Patients without shock or acute respiratory failure were admitted to Burn Unit.: I am not sure this is necessary – as long as care was standardised according to a protocol I would have thought this detail was not necessary. Line 37 p5: Prophylactic antibiotic therapy was performed in patients with TBSA>30% or inhalation injury. In addition, patients

	with clinically suspected or confirmed infection were treated with antibiotics and adjusted according to the results of isolate's susceptibility.: This needs more detail including detail about: what TBSA with inhalation injury required prophylactic antibiotics; what prophylaxis was used, what were first line antibiotics and how was infection suspected or confirmed? Patients with a history of smoke or fire exposure in a closed space or maxillofacial burn were suspected to have inhalation injury. The diagnosis was confirmed by physical findings including changes in voice and carbonaceous sputum production or by fiberoptic bronchoscopy: please can you provide more detail; would a voice change alone cause a diagnosis of inhalation injury? Line 56 p5: burn wound infection, bloodstream infection, pneumonia, urinary tract infection: how were these diagnosed? Line 7 p6: For patients with NI at the same site, only the first episode of it was analyzed.: Is this true even if the Nis at the same site were separated temporally? Why were patients excluded? (see comments in methods above) Line 10 p8: Univariate analysis indicated that the mortality of patients with NI, TBSA more than 30%, full thickness burn, and inhalation injury were higher than patients without: Please could you clarify this statement? I am not clear what it means. Can you separate out the impact of NI and control for burn size, depth and inhalational injury? Line 12 p8: Additionally, the mortality of patients with TBSA less than 10% was lower than patients with burn injuries more than 10%. Death was rarer in burn patients with TBSA<10%, while patients with inhalation injury were more likely to die: These statements are well known and not new. They also don't seem to have relevance to NIs – the aim of this study? Line 41 p8: Based on the results of multiple linear regressions, variables associated with LOS were inhalation injury, TBSA30-50%, TBSA>50%, electric burn, flame burn, full thickness burn as well as NI: again – I am not sure if this fits the aims of the project and is relevant? Line 54 p8: severe burns: what does this mean? Line 14 p10: So, effective NI prevention and control measures may help to improve survival in burn patients.: I don't think this can be concluded from this retrospective study.

REVIEWER	Marc Jeschke RTCB and UofT, Canada
REVIEW RETURNED	29-Nov-2017

GENERAL COMMENTS	I think the authors tried to address an important point. My concern is based on how the results are presented and analyzed. i am not the impact is determined correctly. LOS is presented as absolute ignoring the burn size. it should be LOS/percent burn. additionally, what about MOF, death, etc? is there a difference between different bacteria? the discussion is superficial and does not discuss the issues around this study. i am not sure about adequate stats. i think propensity match would be better.

REVIEWER	Cherry Lim Mahidol-Oxford Tropical Medicine Research Unit, Bangkok, Thailand
REVIEW RETURNED	11-Jan-2018

GENERAL COMMENTS	**Minor comments:** • The authors should specify the full name of acronyms when they were mentioned at the first time to avoid confusions • Please clarify the inclusion criteria (i.e. patient age range) • Please provide details (ie. What are the variables, and how categorical variables were grouped) of the dependent and independent variables that were considered for the analysis in the methods section. • Authors should describe what are the “outcomes” clearly in details. • On Page 6 Line 32, authors mentioned “multivariate binary logistic regression” however, in the later description under the results section it seems like the authors used “multivariable logistic regression model”. Please clarify whether multivariate (multiple dependent variables) or multivariable logistic regression (multiple independent variables) was used. • Interpretation on results of logistic regression (odds ratio) should be revised (Page 7 Line 49-56). **Major comments:** • On Page 6 Line 28, authors mentioned that Spearman’s Rank correlation coefficient was calculated and if the coefficient between two variables is >0.4 then one of them will be removed. The authors should specify clearly the possible causal relationship between the covariates, the exposure variable and the outcome variable. This is because a confounder could associate with the outcome variable while having a high correlation (i.e. >0.4) with a risk factor, and a confounder should not be removed from the final analysis. When making a decision on removing variables the causal relationships between variables should also be taken into account. Also, in the results section authors should show the results on this part or specify which variables were removed from the final analysis. • The description on multistate model in the statistical analysis section on Page 6 is insufficient (i.e. What were the assumptions made? How was the impact of

	nosocomial infection on "outcomes" measured?). The results presented only partially addressed the objective specified. Impact of NIs on death (outcome) was not evaluated by multistate model. Authors should consult a statistician on multistate model. • Authors should consider the covariates to include in the analysis carefully. For example, in Table 3, it seems like the authors have included both TBSA 30-50% (binary variable) and TBSA 50% (binary variable) in the same model. This is not recommended as both are essentially of the same variables (TBSA). Authors could either include TBSA as an ordinal variables with >1 cut-offs or include TBSA as a binary variable with a single cut-off. The cut-off values should be of clinically important.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

The topic is important. Diagnosis and impact of wound and other infections in patients with burns and other trauma are of key importance and any new evidence is useful and interesting.
In general, the paper is well written although there are some easily correctable issues with the language and grammar, some of which are listed below.
I think it would be worth expanding the introduction to include more detail on the impact of NI in general and with burn patients in particular. It would be helpful to explain the differences between the different infection types evaluated in this study ie between burn wound infection, sepsis, pneumonia and UTIs. It would also be useful to add the aim at the end of the introduction rather than what you have done and also being specific about which outcomes you planned to study.
Thanks for your comments. We have improved the language and grammar, and the introduction is expanded as your suggestion. The aim of the present study has been added at the end of the introduction and the outcomes we planned to study are clarified.

Methods: This needs more detail including detail about those patients requiring prophylactic antibiotics; the size of patient's TBSA with inhalation injury requiring prophylaxis; what prophylaxis was used; what were the first line antibiotics given for confirmed infection; were they given according to a protocol and how were the different types of infection suspected and confirmed?
Thanks very much for your valuable comments. As you know, there are still some controversies in the application of antibiotic prophylaxis (BMJ. 2010 Feb 15;340:c241; J Hosp Infect. 2017 Oct;97(2):105-114). In our burn center, there are still some controversies in the application of antibiotic prophylaxis (BMJ. 2010 Feb 15;340:c241; J Hosp Infect. 2017 Oct;97(2):105-114). In our burn center, prophylactic antibiotic therapy was used in burn patients who needing surgical intervention (perioperative period of debridement or auto skin grafting) or requiring mechanical ventilation, and most of them with burns >30%TBSA and inhalation injury. In our primary manuscript, the description was inaccurate and we have corrected it. Although there were some clinical studied mentioned the prophylactic antibiotic therapy in burn patients, the results were not consistent. In our center, the strategy of antibiotic therapy was mainly based on the advice of doctors from the department of microbiology and infectious diseases and the previous antibiotic susceptibility pattern of the center. Additionally, patients with suspected infection were those who met the CDC criteria, and the infection was confirmed by detection of pathogens.

The authors need to separate out the impact of NIs on outcomes (the aim of this study) from the impact due to the size and depth of burn and inhalational injury (which doesn't appear to be an aim of the study and is well known).
Thanks very much for your comments. The size and depth of burn and inhalational injury are confounding factors, and need to be adjusted when evaluating the impact of NIs on outcomes. Nevertheless, the description of those factors has been modified in the revised manuscript.

My main issue is with the standardisation of the use of prophylactic antibiotics and with the diagnosis of the different infection types. There is no standard for diagnosis of burn wound infection for example (ie a positive wound swab does not equate to wound infection). It would be good to know how the authors standardised this diagnosis as this is key to the results and conclusions of the study.
Thanks very much for your comments. The information about how to use prophylactic antibiotics in our burn patients has been provided in the revised manuscript. As you mentioned, it is very difficult to diagnosis burn wound infection (BWI). The widely used criteria of NIs, including BWI, is the criteria of the Centers for Disease Control and Prevention (CDC) (Burns. 2007 Dec;33(8):1008-14; Ann Burns Fire Disasters. 2013 Mar 31; 26(1): 5–11; Burns. 2014 Aug;40(5):835-41). So, in the present study, NIs were diagnosed by using the criteria of CDC.

Finally – please could the authors define mortality as used in this study. I am assuming it is in hospital but could the authors clarify?
Thanks for your suggestion. The mortality of burn patients is in hospital mortality, and we have corrected it in the revised paper.

Detailed comments:
Abstract:
Line 37 p2: …..and the cumulative probability of death for a patient with NI was greater than for a patient who remained free of NI after around day 7: I think this needs clarifying please. I am unclear what it means.
Thanks for your comments. "…..and the cumulative probability of death for a patient with NI was greater than for a patient who remained free of NI after around day 7" has been corrected as " The cumulative probability of death for patients with NI was greater that for those without NI" in the revised manuscript.

Line 40, p2: The expected extra LOS due to NIs was 12.9 days: please clarify what 'expected' means.
Thanks for your comments. Previously, expected Length Of Stay (ELOS) is defined as " the length of time an individual is expected to live in a PCH, based on the person's age, sex and level of care at time of admission." The word 'expected' used in this sentence is not correct, and we have deleted it in the revised paper.

Line 46 p2: Considering the consequences of NIs, surveillance and prevention are required to reduce the incidence of NIs, and then improve the outcomes of burns..: I don't think this conclusion can be drawn from this study.
Thanks for your comments. We have modified the conclusion in the revised manuscript.

Main text:
Line 30, p4: It has been reported that 30% to 80% of burn patients were suffered from NIs: please check the grammar
Thanks for your comments. "It has been reported that 30% to 80% of burn patients were suffered from NIs" has been corrected as "It has been reported that about 30-80% of burn patients suffered from NIs".

Line 36 p4: It should be noted that infection only can impact on LOS and outcomes after it has started: I am not sure I understand this statement?
Thanks for your comments. “It should be noted that infection only can impact on LOS and outcomes after it has started” has been modified as “ It should be noted that NI is a time-varying factor, and it can develop at any time after admission. NIs can impact on length of stay (LOS) and mortality only after they have started”.

Line 11, p5: 157 burn patients were ineligible by exclusion criteria, and 986 patients were enrolled in the study. This should be in the results not methods
Thanks for your comments. We have corrected it in the revised manuscript.

Line 20 p5: Burn patients with acute respiratory failure or shock were admitted to the ICU, and they were transferred to the Burn Unit when the tracheal tube is removed or the hemodynamic situation of them becomes stable, according to the judgments of burn surgeon and ICU doctor. Patients without shock or acute respiratory failure were admitted to Burn Unit.: I am not sure this is necessary – as long as care was standardised according to a protocol I would have thought this detail was not necessary.
Thanks for your comments. As your suggestion, we have deleted it in the revised manuscript.

Line 37 p5: Prophylactic antibiotic therapy was performed in patients with TBSA>30% or inhalation injury. In addition, patients with clinically suspected or confirmed infection were treated with antibiotics and adjusted according to the results of isolate’s susceptibility.: This needs more detail including detail about: what TBSA with inhalation injury required prophylactic antibiotics; what prophylaxis was used, what were first line antibiotics and how was infection suspected or confirmed?
Thanks very much for your comments. As mentioned above, there are still some controversies in the application of antibiotic prophylaxis (BMJ. 2010 Feb 15;340:c241; J Hosp Infect. 2017 Oct;97(2):105-114). In our burn center, prophylactic antibiotic therapy was used in burn patients who needing surgical intervention (perioperative period of debridement or auto skin grafting) or requiring mechanical ventilation, and most of them with burns >30%TBSA and inhalation injury. In our primary manuscript, the description was inaccurate and we have corrected it. Although there were some clinical studied mentioned the prophylactic antibiotic therapy in burn patients, the results were not consistent. In our center, the strategy of antibiotic therapy was mainly based on the advice of doctors from the department of microbiology and infectious diseases and the previous antibiotic susceptibility pattern of the center. Additionally, patients with suspected infection were those who met the CDC criteria, and the infection was confirmed by detection of pathogens.

Patients with a history of smoke or fire exposure in a closed space or maxillofacial burn were suspected to have inhalation injury. The diagnosis was confirmed by physical findings including changes in voice and carbonaceous sputum production or by fiberoptic bronchoscopy: please can you provide more detail; would a voice change alone cause a diagnosis of inhalation injury?
Thanks very much for your comments. Until nowadays, the diagnosis of inhalational injury is a subjective assessment based largely on history of smoke exposure in an enclosed space. Physical findings, including changes in voice, singed nasal hairs, soot in the proximal airways and carbonaceous sputum production, may help support the diagnosis (Crit Care. 2015; 19: 351.). In our center, Patients with a history of smoke or fire exposure in a closed space or maxillofacial burn were suspected to have inhalation injury. The diagnosis of inhalation injury was made if suspected patients had physical finding mentioned above or had bronchoscopic evidence. We have clarified it in the revised manuscript.

Line 56 p5: burn wound infection, bloodstream infection, pneumonia, urinary tract infection: how were these diagnosed?
Thank you for your comments. The widely used criteria of NIs, including BWI, is the criteria of the Centers for Disease Control and Prevention (CDC) (Burns. 2007 Dec;33(8):1008-14; Ann Burns Fire Disasters. 2013 Mar 31; 26(1): 5–11; Burns. 2014 Aug;40(5):835-41). So, in the present study, NIs were diagnosed by using the criteria of CDC. The detail of this diagnostic criteria was added in the manuscript.

Line 7 p6: For patients with NI at the same site, only the first episode of it was analyzed.: Is this true even if the Nis at the same site were separated temporally?
Thank you for your comments. In the present study, for patients with NI at the same site, only the first episode of it was analyzed. The start time of burn patients acquired infection is based on the first episode, even if the NIs at the same site were separated temporally.

Why were patients excluded? (see comments in methods above)
Thank you for your comments. Because the aim of the present stay is to investigate the impact of NI on the outcomes, and in burn patients was defined as infection occurring 48 hours after hospital admission. So, when analysis the incidence, risk factors and impacts of NIs, patients who had an LOS <48 hours should be excluded (Emerg Infect Dis. 2004 Jan; 10(1): 76–81; Crit Care. 2006; 10(2): R66). Additionally, the time of initial treatment post-burn may influence the mortality of burn patients, and burn patients who admitted to hospital later than 3 days post-burn were usually excluded when determining the factors associated with burn complications and mortality (J Burn Care Res. 2008 Nov-Dec; 29(6): 902–906; Crit Care Med. 2015 Apr; 43(4): 808–815)

Line 10 p8: Univariate analysis indicated that the mortality of patients with NI, TBSA more than 30%, full thickness burn, and inhalation injury were higher than patients without: Please could you clarify this statement? I am not clear what it means. Can you separate out the impact of NI and control for burn size, depth and inhalational injury?
Thank you for your comments. We have separated out the impact of NI and control for confounding factors in the revised paper as your suggestion.

Line 12 p8: Additionally, the mortality of patients with TBSA less than 10% was lower than patients with burn injuries more than 10%. Death was rarer in burn patients with TBSA<10%, while patients with inhalation injury were more likely to die: These statements are well known and not new. They also don't seem to have relevance to NIs – the aim of this study?
Line 41 p8: Based on the results of multiple linear regressions, variables associated with LOS were inhalation injury, TBSA30-50%, TBSA>50%, electric burn, flame burn, full thickness burn as well as NI: again – I am not sure if this fits the aims of the project and is relevant?
Thank you for your comments. We have modified these two parts in the revised paper.

Line 54 p8: severe burns: what does this mean?
Thank you for your comments. We have corrected it in the revised manuscript.

Line 14 p10: So, effective NI prevention and control measures may help to improve survival in burn patients.: I don't think this can be concluded from this retrospective study
Thank you for your comments. We have modified the conclusion as your suggestion.

3. Reviewer: 2

I think the authors tried to address an important point. My concern is based on how the results are presented and analyzed. i am not the impact is determined correctly. LOS is presented as absolute ignoring the burn size. it should be LOS/percent burn. additionally, what about MOF, death, etc?

is there a difference between different bacteria? the discussion is superficial and does not discuss the issues around this study. i am not sure about adequate stats. i think propensity match would be better.
Thanks very much for your comments. As you know, the LOS estimation is 1day per percent total body surface area burn (1day/%TBSA) in burns. This role is based on TBSA. Recent evidence illustrated that not all patients meet the 1day per percent burn rule (Burns. 2017 Mar;43(2):282-289.) . However, TBSA is an important factor associated with LOS. Although the aim of the present study was to determine the impact of NI on LOS and mortality. TBSA was adjusted as a confounding factor as well as age, sex, burn types and full thickness burn and so on. In burn patients with NI, there were usually more than one microorganism were isolated at the same site. In the present study, a total 237 microorganisms were isolated form 159 burn patients. So, it is hard to determine the difference in mortality or LOS between different bacteria. We have modified the discussion of our manuscript as your suggestion. Additionally, as you mentioned, Matched-cohort studies remain the most commonly used method for estimating LOS associated with NI. However, the matching factors used in various studies have varied and a key issue is the selection bias arising from the number of matching variables used to control for confounding. Additionally, when Matched-cohort studies was used, only a selected sample of patients initially included in the analysis. Each statistical method has its advantages and disadvantages, and the competing risk and multistate model is an appropriate model in the present study.

4. Reviewer: 3

Minor comments:

- The authors should specify the full name of acronyms when they were mentioned at the first time to avoid confusions
- Please clarify the inclusion criteria (i.e. patient age range)
- Please provide details of the dependent and independent variables (ie. what are the variables, and how categorical variables were grouped) that were considered for the analysis in the methods section.
- Authors should describe what are the “outcomes” clearly in details.
- On Page 6 Line 32, authors mentioned “multivariate binary logistic regression” however, in the later description under the results section it seems like the authors used “multivariable logistic regression model”. Please clarify whether multivariate (multiple dependent variables) or multivariable logistic regression (multiple independent variables) was used.
- Interpretation on results of logistic regression (odds ratio) should be clarified (Page 7 Line 49-56).

Thanks very much for your comments. 1) We have checked the manuscript carefully, and specified the full name of acronyms when they were mentioned at the first time. 2) The inclusion criteria has been clarified in the revised paper. 3) The potential factors which are associated with NIs, LOS and mortality were collected and the details were provided in the revised paper. 4) We have clarified the outcomes according to your suggestion. 5) In the revised paper, we used Cox regression model to analysis the factors associated with NIs and hospital mortality. We have corrected the mistake you mentioned above.

Major comments:

- On Page 6 Line 28, authors mentioned that Spearman’s Rank correlation coefficient was calculated and if the coefficient between two variables is >0.4, then one of them will be removed. The authors should specify clearly the possible causal relationship between the covariates, the exposure variable and the outcome variable. This is because a confounder could associate with the outcome variable while having a high correlation (i.e. >0.4) with a risk factor, and a confounder should not be removed from the final analysis. When making a decision on removing variables the causal

relationships between variables should also be taken into account. Also, in the results section authors should show the results on this part or specify which variables were removed from the final analysis.
Thanks for your comments. In the initial stages of the experimental design, we decided to remove one of two variables that have a high correlation (>0.4). As you mentioned, when making a decision on removing variables, the causal relationships between variables should be taken into account. In our study, we did not find two variables which have a high correlation (>0.4). So, we corrected the methods in the revised manuscript.

• The description on multistate model in the statistical analysis section on Page 6 is insufficient (i.e. What were the assumptions made? How was the impact of nosocomial infection on "outcomes" measured?). The results presented only partially addressed the objective specified. Impact of NIs on death (outcome) was not evaluated by multistate model. Authors should consult a statistician on multistate model.
Thanks for your valuable comments. We have consulted a statistics teacher as your suggestion. Cox model were used to determine the risk factors for death and NI was modeled as a time-varying covariate by the 'survival' package in R. This method is effective to determine the risk factors (including NI) for death. Additionally, competing risks model was used to calculate Cumulative incidence functions (CIF). Competing risks model is also a case of multistate model, and has been widely used to determine the impact of time-varying covariate on mortality. (Infect Control Hosp Epidemiol. 2006 May;27(5):493-9; Crit Care. 2008;12(2):R44; PLoS One. 2015 Apr 7;10(4):e0122136.
)

• Authors should consider the covariates to include in the analysis carefully. For example, in Table 3, it seems like the authors have included both TBSA 30-50% (binary variable) and TBSA 50% (binary variable) in the same model. This is not recommended as both are essentially of the same variables (TBSA). Authors could either include TBSA as an ordinal variables with >1 cut-offs or include TBSA as a binary variable with a single cut-off. The cut-off values should be of clinically important.
Thanks for your valuable comments. We have included TBSA as an ordinal variables as your suggestion. In the present study, the cutoff values were 10% and 30% TBSA. and similar cutoff values were also used in other studies (Injury. 2014 Sep;45(9):1459-64). The TBSA was included as a confounding factor in the present study. After adjusting TBSA and other confounding factors, we found that NI was associated with the LOS and mortality of burn patients.

VERSION 2 – REVIEW

REVIEWER	Dr Amber Young University Hospitals Bristol NHS Foundation Trust, UK
REVIEW RETURNED	07-Mar-2018

GENERAL COMMENTS	The aim of this study was to evaluate using a retrospective cohort of patients the impacts of NI on length of stay (LOS) and hospital mortality in burn patients using a multistate model. The paper is interesting and presents important results. The English needs improvement especially in the discussion section. I have not commented on all the English that needs correction. The definition section of the methods requires some clarification as per the more detailed comments below. The limitation section of the discussion should include more detail on the effect of differing hospital protocols (how and why did they differ) and on the use of prophylactic antibiotics especially in ventilated patients (see

	comments below). Abstract: • Data were obtained from 1143 records of patients admitted with burn between 1 January 2013 to 31 December 2016. Were the patients sequential?? • Perhaps add detail about the type of NIs and the effect of TBSA on NIs to the abstract?? Main text: • "It has been reported that about 30-80% of burn patients suffered from NIs": in what context? What type of patients? • "NIs can impact on length of stay (LOS) and mortality only after they have started": I am not clear what this means? • "Blood culture not done or no organisms or antigen detected in blood": I don't think this makes sense for blood stream infections?? Am I mis-reading this? Please kindly clarify. • p6, line 3: "….the following: 1) positive dipstick for leukocyte esterase and/or nitrate; 2) physician diagnosis of urinary tract infection".: this should include a positive urine microscopy and not 'physician diagnosis' as this is not objective. Please clarify. • P6 line 42: "requiring mechanical ventilation". Are all ventilated patients given antibiotics? How long for? Can you add this to the limitation section and kindly explain the impact of this on the study findings. What was the impact of ventilation on the incidence of NIs? • Demographics: what was the median and IQR of the burn size in total (not just full thickness)? • P7 line 38: ….the hospital mortality of patients with and without NI were 16.0% and 3.5%, respectively.: is there a significance associated with this? • P8 line 32: full thickness burn: was this the presence or size of full thickness burn? • P9 line 34: In patients who have > 20% TBSA burn and need for surgical intervention, the incidence of NI was 70%.: this needs some context from the paper. • "In the present study, overall burn patients during the study period were enrolled": I am not clear what this means • P10 line 40: "The associated between TBSA and mortality was observed in the present study which was consist with the results of other studies": this is difficult to be clear about in Table 1 without the overall median or mean TBSA (total) in each group and significance. • P11 line 7: "Nevertheless, NI can only impact LOS after it has started and the duration of hospitalization prior to the infection should be controlled".: I am unclear what this means?

REVIEWER	M JESCHKE UofT, Toronto Canada
REVIEW RETURNED	14-Feb-2018

GENERAL COMMENTS	I think this single center retrospective analysis of infections is important and good, but it really is limited to a lot of subjective interventions and single center and retrospective. in addition, this information is not novel and has been shown before. infections are important and need to be cared for. i also would recommend for the authors to consider a burn specific journal.

REVIEWER	Cherry Lim Mahidol-Oxford Tropical Medicine Research Unit, Thailand
REVIEW RETURNED	02-Mar-2018

GENERAL COMMENTS	1. In the analysis (Table 2) for impact of NI on mortality (assuming NI is time-dependent), authors should consider adjusting for age and gender, as both could be potential confounder for the effect of NI on mortality (especially age). 2. It is not clear why 65 years was used as a single cutoff for age. Please justify. 3. Authors should revise the tenses used in the manuscript and sentence structure. For example the section under "Definitions and data collection" is difficult to read. Also Line 55 of page 6 needs clarification. 4. Sentence 40-42 on page 4 citing Reference 12, 13, should be elaborated further. The authors should explain more on why multistate model would be the "appropriate" statistical methods for this situation. 5. More discussions are needed on the estimated extra length of stay due to NI. What are the estimates reported in other studies? If the estimate in the current study differed largely from that in the other studies, what would be the possible reasons? 6. More description on multistate model is needed.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name
Dr Amber Young
The aim of this study was to evaluate using a retrospective cohort of patients the impacts of NI on length of stay (LOS) and hospital mortality in burn patients using a multistate model.
The paper is interesting and presents important results. The English needs improvement especially in the discussion section. I have not commented on all the English that needs correction. The definition section of the methods requires some clarification as per the more detailed comments below. The limitation section of the discussion should include more detail on the effect of differing hospital protocols (how and why did they differ) and on the use of prophylactic antibiotics especially in ventilated patients (see comments below).
Thanks for your comments. We have improved the English of the manuscript.

Abstract:
• Data were obtained from 1143 records of patients admitted with burn between 1 January 2013 to 31 December 2016. Were the patients sequential??
Thanks for your comment. The patients of the present study were sequential.

• Perhaps add detail about the type of NIs and the effect of TBSA on NIs to the abstract??
Thanks for your suggestion. The information you mentioned above has been described in the main text. Nevertheless, BMJ OPEN sets a maximum word count for Abstract. Additionally, the aim of this

study is to investigate the impact of NIs on LOS and mortality in burns. So, the detail about the type of NIs and the effect of TBSA on NIs were not added.

Main text:
• “It has been reported that about 30-80% of burn patients suffered from NIs”: in what context? What type of patients?
Thanks for your comments. The incidence of NIs in burn patients varied from one study to another. We chose three independent studies. Burn patients needing ICU care or not, and the different types of burns were included in these studies. Based on these studies, we provided an approximate incidence of NIs in burns.

• “NIs can impact on length of stay (LOS) and mortality only after they have started”: I am not clear what this means?
Thanks for your comments. This sentence has been modified in the revised paper.

• “Blood culture not done or no organisms or antigen detected in blood”: I don’t think this makes sense for blood stream infections?? Am I mis-reading this? Please kindly clarify.
Sorry for our negligence. Bloodstream infection includes laboratory-confirmed BSI and clinical sepsis. Patient with laboratory-confirmed BSI must have a recognized pathogen cultured from one or more blood cultures and organism cultured from blood is not related to an infection at another site. Clinical sepsis must meet the following clinical signs or symptoms with no other recognized cause: Fever (T>38°C), hypotension (systolic pressure ≤90 mm Hg), or oliguria (<20 cm3/h); blood culture not done or no organisms or antigen detected in blood; and no apparent infection at another site and physician instituted treatment for sepsis.

• p6, line 3: “….the following: 1) positive dipstick for leukocyte esterase and/or nitrate; 2) physician diagnosis of urinary tract infection”.: this should include a positive urine microscopy and not ‘physician diagnosis’ as this is not objective. Please clarify.
Thanks for your comments. The criteria used in the present study is based on CDC criteria. There are four criteria for the diagnosis of urinary tract infections according to CDC criteria. We described some parts of the criteria, but missed the urine microscopy and urine culture. We have modified this part in the revised manuscript.

• P6 line 42: “requiring mechanical ventilation”. Are all ventilated patients given antibiotics? How long for? Can you add this to the limitation section and kindly explain the impact of this on the study findings. What was the impact of ventilation on the incidence of NIs?
Thanks for your suggestion. All ventilated patients are given antibiotics in our patients. As a retrospective study, the duration of antibiotics was not available. We have added this to the limitation section in the revised paper.

• Demographics: what was the median and IQR of the burn size in total (not just full thickness)?
Thanks for your comments. Full thickness burn is the burns that destroy both layers of skin and penetrate more deeply into underlying structures. The information of burn size in present study was based on ICD codes. Our method may be sufficient to illustrate the relationship between BSA and mortality.

• P7 line 38: ….the hospital mortality of patients with and without NI were 16.0% and 3.5%, respectively.: is there a significance associated with this?
Thanks for your comments. As shown in Table S1, univariate analysis indicated that the hospital mortality of patients with NIs were higher than those without NIs.

• P8 line 32: full thickness burn: was this the presence or size of full thickness burn?

Thanks for your comments. Full thickness burn is the burns that destroy both layers of skin and penetrate more deeply into underlying structures.

• P9 line 34: In patients who have > 20% TBSA burn and need for surgical intervention, the incidence of NI was 70%.: this needs some context from the paper.
Thanks for your suggestion. Some context from the paper were added.

• “In the present study, overall burn patients during the study period were enrolled”: I am not clear what this means
Thanks for your comments. This sentence was deleted in the revised paper.

• P10 line 40: “The associated between TBSA and mortality was observed in the present study which was consist with the results of other studies”: this is difficult to be clear about in Table 1 without the overall median or mean TBSA (total) in each group and significance.
Thanks for your comments. “The associated between TBSA and mortality was observed in the present study which was consist with the results of other studies” has been corrected as “ In the present study, we found that TBSA is a risk factor for hospital death in burn patients”.

• P11 line 7: “Nevertheless, NI can only impact LOS after it has started and the duration of hospitalization prior to the infection should be controlled”.: I am unclear what this means?
Thanks for your comments. We have modified this sentence in the revised paper.

We sincerely hope that the revised manuscript meets your approval and the approval of the reviewers, and that it is now acceptable for publication in your esteemed journal.

Reviewer: 2

Reviewer Name
M JESCHKE
i think this single center retrospective analysis of infections is important and good, but it really is limited to a lot of subjective interventions and single center and retrospective. in addition, this information is not novel and has been shown before. infections are important and need to be cared for. i also would recommend for the authors to consider a burn specific journal.
Thanks for your comments. As you mentioned above, infection is one of the most common adverse events that occur with hospitalized patients, and need to be cared for.
Although few studies illustrated the relationship between NI and LOS and mortality in burn patients, there were no studies that assessed the exact impact of NIs on LOS. The findings of the present study would be helpful in making medical decisions and developing policy.

Reviewer: 3

Reviewer Name
Cherry Lim
1. In the analysis (Table 2) for impact of NI on mortality (assuming NI is time-dependent), authors should consider adjusting for age and gender, as both could be potential confounder for the effect of NI on mortality (especially age).
Thanks for your comments. According to your suggestion, in the revised paper, analyses were adjusted for age, gender, TBSA and inhalation injury.

2. It is not clear why 65 years was used as a single cutoff for age. Please justify.

Thanks for your comments. As you mentioned above, age potential confounder for the effect of NI on mortality. In the revised paper, this cutoff for age was not used, and analyses were adjusted for age.

3. Authors should revise the tenses used in the manuscript and sentence structure. For example the section under "Definitions and data collection" is difficult to read. Also Line 55 of page 6 needs clarification.
Thanks for your suggestions. We have corrected it in the revised manuscript.

4. Sentence 40-42 on page 4 citing Reference 12, 13, should be elaborated further. The authors should explain more on why multistate model would be the "appropriate" statistical methods for this situation.
Thanks for your comments. The reason why multistate model was used in the present study has been further explained in the revised study.

5. More discussions are needed on the estimated extra length of stay due to NI. What are the estimates reported in other studies? If the estimate in the current study differed largely from that in the other studies, what would be the possible reasons?
Thanks for your comments. Although few studies illustrated the relationship between NI and LOS in burns, there were no studies that assessed the exact impact of NIs on LOS. In the revised manuscript, this information was added.

6. More description on multistate model is needed.
Thanks for your suggestion. More description on multistate model was added in the revised paper.

VERSION 3 – REVIEW

REVIEWER	Dr Amber Young University of Bristol, UK
REVIEW RETURNED	16-May-2018

GENERAL COMMENTS	This retrospective observational study aims to assess the impact of nosocomial infections (NIs) on mortality and length of hospital stay in patients with burns. Data were obtained from 1143 records of patients admitted with burn between 1 January 2013 to 31 December 2016. The topic will be of interest to burn clinicians and will also impact on future health economic analyses related to new technology to prevent or treat NIs in this area. The paper is much better written now, although the English still needs some improvement. I cannot comment on the statistics as discussed before. My only issues remaining are with the criteria for the diagnosis of burn wound infection and sepsis as detailed below. I think both need more clarity esp burn wound infection. I also think the relevance of inhalation injury to the main objectives of the study needs to be clearer in the discussion. I am disappointed that there was no patient involvement at all and although I understand that this was a retrospective study, I think some explanation or defence of the lack of PPI input should be added briefly. Detailed comments: Abstract: ‘were suffered’ should be ‘suffered’

	Intro: p4: A recent study reported an incidence density of 14.7 infections/1000 patient days in burn patients and NIs was not the most significant risk factors for mortality [11].: I do not think the second part of the sentence follows from the first and isn't worded well. I am not sure what the second part means? P4: Matched-cohort study: could this be briefly explained P4: difficult to identify appropriate matching factors for NIs: why? P5: line 40: methods: please describe why you defined burn wound infection as you have – will simply a change in wound appearance be enough to diagnose this? P6: blood culture not done or no organisms or antigen detected in blood: I don't understand this in your diagnostic criteria for sepsis? P7: Why were patients on mechanical ventilation given prophylactic antibiotics and for how long? P7: Additionally, patients met CDC criteria or with identified pathogens were treated with antibiotics and adjusted according to the results of isolate's susceptibility.: Please could this be re-worded – if patients had 'identified pathogens but did not fulfil CDC criteria – were they given antibiotics? Patient and public involvement: please explain why there was no involvement P9: …… NI in patients with age: does this mean increasing age? P9, line 46: NI was associated with LOS in burn patients: does this mean incidence of NIs was associated with increased LOS? P10, line 42: Foxp3+T cells: it might be helpful to explain the relevance of these cells P10: Nevertheless, some evidence illustrated that NIs were not the main cause of death in overall burn patients.: what evidence? P11, line 7: The different severity of burn injury and statistical method may contribute to the different results: are these two parts of the sentence connected – could you clarify please. P11, line 22: Inhalation injury usually cause pulmonary and systemic complications which greatly increases the risk of death after burn and the results of our study confirmed this: How is this linked to the previous sentence?

REVIEWER	Cherry Lim Mahidol-Oxford Tropical Medicine Research Unit, Bangkok, Thailand
REVIEW RETURNED	01-Jun-2018

GENERAL COMMENTS	Many thanks to the authors for the changes made. The design study described by the authors is appropriate for the research question asked. The authors are well aware that nosocomial infection is a time-varying covariate, and appropriate statistical methods should be used. However, I have one major concern on the estimated excess length of hospital stay. In the descriptive analysis (Table 1) the crude difference in LOS between NI and non-NI group is around 14 days, and the estimated excess LOS from the multistate model is around 17.7 days (abstract and last paragraph of 'Results' section). It seems quite unlikely that the estimated LOS could be longer than the crude difference. Beyersmann and the group published a detailed description on multistate model for assessing excess LOS (Beyersmann, J., et al. 2006. Infection Control & Hospital Epidemiology, 27(5), 493-499. doi:10.1086/503375). It is more preferable if the authors could attach their R codes that were used to perform the analysis in the appendix. This could ensure that readers could fully understand

	how the excess LOS, using multistate model, was estimated in this study. A minor point is that the authors mentioned in the response letter that age and gender were added into the model to evaluate factors associated with death (Table 2), however, those two covariates were not presented in Table 2 in the current version. Another minor point is that the authors should be consistent with the way p-value is presented (i.e. write the actual p-value, rather than 'p-value<0.05' in Table 1). Also, the estimate parameters (i.e HR) can be present with just 1 decimal place. Please also be consistent with the number of decimal places to present for p-values.

VERSION 3 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name
Dr Amber Young

Institution and Country
University of Bristol, UK

Please state any competing interests or state ‘None declared’:
None declared

Please leave your comments for the authors below
This retrospective observational study aims to assess the impact of nosocomial infections (NIs) on mortality and length of hospital stay in patients with burns. Data were obtained from 1143 records of patients admitted with burn between 1 January 2013 to 31 December 2016.
The topic will be of interest to burn clinicians and will also impact on future health economic analyses related to new technology to prevent or treat NIs in this area. The paper is much better written now, although the English still needs some improvement. I cannot comment on the statistics as discussed before. My only issues remaining are with the criteria for the diagnosis of burn wound infection and sepsis as detailed below. I think both need more clarity esp burn wound infection. I also think the relevance of inhalation injury to the main objectives of the study needs to be clearer in the discussion. I am disappointed that there was no patient involvement at all and although I understand that this was a retrospective study, I think some explanation or defence of the lack of PPI input should be added briefly.
Thanks for your comments. The detailed responses to the comments are listed as below.

Detailed comments:
Abstract: ‘were suffered’ should be ‘suffered’
“were suffered” has been corrected as “suffered” in the revised manuscript.

Intro: p4: A recent study reported an incidence density of 14.7 infections/1000 patient days in burn patients and NIs was not the most significant risk factors for mortality [11].: I do not think the second part of the sentence follows from the first and isn’t worded well. I am not sure what the second part means?

This sentence was modified as “A recent study reported an incidence density of 14.7 infections/1000 patient days in burn patients [11]. Nevertheless, the study illustrated that NIs was not a risk factor for mortality, using logistic regression, after adjusting for confound variables [11]” in the revised paper.

P4: Matched-cohort study: could this be briefly explained
P4: difficult to identify appropriate matching factors for NIs: why?

Matched-cohort study is a type of cohort study. Such studies ‘match’ controls to account for factors unrelated to research endpoints. Because there is no objective standard, it is difficult to determine which factors should be included. More importantly, Vrijens et al showed that the more matching factors included, the smaller the increase in LOS. The detailed information about why it is difficult to identify appropriated matching factors for NIs was described in reference [12].

P5: line 40: methods: please describe why you defined burn wound infection as you have – will simply a change in wound appearance be enough to diagnose this?
We are very sorry for our negligence. The diagnosis of BWI was based on the criteria of CDC. Burn patient only has change in burn wound appearance was not enough to diagnose BWI. Burn wound infection was defined as a patient has change in burn wound appearance or character (rapid eschar separation; dark brown, black, or violaceous discoloration of eschar) and at least one of the following: histologic examination of burn biopsy shows invasion of organisms into adjacent viable tissue or positive blood culture without other identifiable infection.
The previous reviewers suggested us to provide the detailed diagnosis criteria of NIs. However, the diagnosis criteria too complex to be fully described in one paper. For example, there are three different criteria used to diagnosis BWI, and there are more than two parts in each criteria. So, we try our best to describe the criteria briefly. When we summarized the key points of the criteria, some mistakes were made. Sorry again for my negligence. We have modified this part in the revised manuscript.

P6: blood culture not done or no organisms or antigen detected in blood: I don’t understand this in your diagnostic criteria for sepsis?
Bloodstream infection (BSI) includes laboratory-confirmed BSI and clinical sepsis. To distinguish clinical sepsis (suspected infection) from laboratory-confirmed BSI (infection), clinical sepsis must be met the criteria that blood culture not done, or no organisms or antigen detected in blood. These diagnostic criteria for BSIs is based on CDC criteria.
P7: Why were patients on mechanical ventilation given prophylactic antibiotics and for how long?
Although There is still controversy about the use of prophylactic antibiotics in burn patients, several small sample studies and systematic reviews have found reduced incidence of pneumonia in burn patients to be associated with systemic antibiotic regimens (J Trauma 1998; 45:383–7; Ann Surg 2005; 241:424–30; BMJ 2010; 340:c241; Cochrane Database Syst Rev 2013; 6:CD008738.); . So, all ventilated patients are given antibiotics in our patients. More importantly, a recent study indicated that Prophylactic antibiotics use may result in improved 28-day in-hospital mortality in mechanically ventilated patients with severe burns but not in those who do not receive mechanical ventilation (Clin Infect Dis. 2016 Jan 1;62(1):60-6). The duration of antibiotics is decided by the treating physician based on clinical symptoms, blood culture results as well as other infection markers. We have described it in the revised paper.

P7: Additionally, patients met CDC criteria or with identified pathogens were treated with antibiotics and adjusted according to the results of isolate’s susceptibility.: Please could this be re-worded – if patients had ‘identified pathogens but did not fulfil CDC criteria – were they given antibiotics?
In theory, if suspected infectious disease patients had ‘identified pathogens’ but did not fulfil CDC criteria, they also need to be treated with antibiotics. Nevertheless, we recognize that this sentence of our manuscript is ambiguous, and it has been modified as “Additionally, patients met CDC criteria

were treated with antibiotics. When a pathogen was identified, antibiotics were adjusted according to the results of isolate's susceptibility" in the revised manuscript.

Patient and public involvement: please explain why there was no involvement
Patient and public involvement (PPI) in research is increasingly required, although evidence to inform its implementation is limited (BMJ Open, 2014, 4 (12):e006400). From 1 June 2015 to 31 May 2016, the BMJ published 152 research papers of which 16 (11%) reported PPI activity (BMJ Open 8(3):e020452). When we designed this study, we did not know the importance of PPI and how to do it. Now, we know that, PPI is distinct from public engagement and being a participant in a research study. In PPI, the public become active partners in one or multiple aspects of the research. Involving the public and patients can improve the quality and the value of health research to end users. (BMJ Open 8(3):e020452). Although the present study is a retrospective observational study, no patients involved is a limitation, and we have mentioned it in the revised paper.

P9: …… NI in patients with age: does this mean increasing age?
We are very sorry for our negligence. We have corrected this part in the revised paper.

P9, line 46: NI was associated with LOS in burn patients: does this mean incidence of NIs was associated with increased LOS?
"NI was associated with LOS in burn patients" has been corrected as "NI was associated with increased LOS in burn patients" in the revised manuscript.

P10, line 42: Foxp3+T cells: it might be helpful to explain the relevance of these cells
The function of Foxp3+T cells has been added in the revised paper.

P10: Nevertheless, some evidence illustrated that NIs were not the main cause of death in overall burn patients.: what evidence?
P11, line 7: The different severity of burn injury and statistical method may contribute to the different results: are these two parts of the sentence connected – could you clarify please.
This part has been modified as "Nevertheless, a study illustrated that NI was a risk factor for mortality in univariate analysis, but it was not found as a risk factor for mortality in the stepwise forward logistic regression undertaken to control effect of confound variables [11]. The different statistical method may contribute to the different results. In the present study, NI was modeled as a time-varying factor in a competing risk model." in the revised paper.

P11, line 22: Inhalation injury usually cause pulmonary and systemic complications which greatly increases the risk of death after burn and the results of our study confirmed this: How is this linked to the previous sentence?
The main content of this paragraph is about the risk factors for mortality in burn patients. So, in addition to NIs, other factors associated with mortality were also described.

Reviewer: 3

Reviewer Name
Cherry Lim

Institution and Country
Mahidol-Oxford Tropical Medicine Research Unit, Bangkok, Thailand

Please state any competing interests or state 'None declared':
None declared

Please leave your comments for the authors below
Many thanks to the authors for the changes made.

The design study described by the authors is appropriate for the research question asked. The authors are well aware that nosocomial infection is a time-varying covariate, and appropriate statistical methods should be used. However, I have one major concern on the estimated excess length of hospital stay. In the descriptive analysis (Table 1) the crude difference in LOS between NI and non-NI group is around 14 days, and the estimated excess LOS from the multistate model is around 17.7 days (abstract and last paragraph of 'Results' section). It seems quite unlikely that the estimated LOS could be longer than the crude difference. Beyersmann and the group published a detailed description on multistate model for assessing excess LOS (Beyersmann, J., et al. 2006. Infection Control & Hospital Epidemiology, 27(5), 493-499. doi:10.1086/503375). It is more preferable if the authors could attach their R codes that were used to perform the analysis in the appendix. This could ensure that readers could fully understand how the excess LOS, using multistate model, was estimated in this study.
Thanks very much for your comments. Due to the confound factors and the competing factors, the crude difference in LOS between NI and non-NI group cannot reflect the effect of NIs on LOS exactly. Additionally, the crude analysis has the potential to produce misleading results (either underestimate or overestimate) . So, the medium LOS of patients with NIs and without NIs was provided in our paper, and we did not calculate the crude difference in LOS between NI and non-NI group. In addition to the medium LOS, multiple-linear regression analysis was applied to detect the variables associated with LOS. Finally, the multistate model was used to estimate the extra LOS. The ‘etm’ package in R was performed to calculate the difference in length of stay between patients with and without infection (J Hosp Infect. 2014 Dec;88(4):213-7.). In addition, COX model and CIF were also performed with The R Project for Statistical Computing which is an open-source language for statistical computing and graphics. The code used in the present study was available at: https://CRAN.R-project.org/ and this information has been mentioned in the revised paper.

A minor point is that the authors mentioned in the response letter that age and gender were added into the model to evaluate factors associated with death (Table 2), however, those two covariates were not presented in Table 2 in the current version.
Thanks for your comments. Age and gender were added into the model to evaluate factors associated with death. Age and gender are not the risk factors associated with death. Nevertheless, all covariates, including age and gender, were added in the revised paper.

Another minor point is that the authors should be consistent with the way p-value is presented (i.e. write the actual p-value, rather than 'p-value<0.05' in Table 1). Also, the estimate parameters (i.e HR) can be present with just 1 decimal place. Please also be consistent with the number of decimal places to present for p-values.
Thanks for your suggestion, we have provided actual p-values which are present with 3 decimal places, and to be consistent with the number of decimal places of present for p-values, the estimate parameters are present with 3 decimal places.