Author's response to reviews

Title: The influence of statin exposure on inflammatory markers in patients with early bacterial infection: pilot prospective cohort study

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The Editor
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Dear Sir.

**Revisions for manuscript MS: 1104512291296176**

**Title: The influence of statin exposure on inflammatory markers in patients with early bacterial infection: pilot prospective cohort study.**

Many thanks for the opportunity to submit a revised version of the manuscript. Please accept our sincerest apologies the delay in resubmitting the manuscript.

Thanks you also to the reviewers for their insightful and helpful remarks. We have addressed each of their comments and we hope that they are satisfied by our changes.

All the authors have reviewed the changes and agree with the submission. None of the authors have any conflicts of interest in relation to this work.

Please do not hesitate to contact us if you need any further information or clarification.

With very best wishes,

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Response to reviewer comments

Title: The influence of statin exposure on inflammatory markers in patients with early bacterial infection: pilot prospective cohort study.

Reviewer: Erik B Kistler

Reviewer’s report:

This study by Shankar-Hari, is a prospective observational study seeking to determine risk factors for illness after infection in a low-risk hospitalized patient population, including the use of statins. As a preliminary hypothesis-generating study this prospective trial reasonably collected data and then, by regression analysis, attempted to find significant variables of interest that might be possible risk factors for inflammation and further illness. The statin angle appears to have been an afterthought, but is of some clinical interest.

Major concerns

1. The manuscript would be improved by either bringing statin use (did all patients on statins previously receive them in hospital? Were some discontinued their statins? Did patients previously not on statins have statins started in hospital?) to the forefront or decreasing the emphasis on them and then changing the title to reflect this.

Author response: Corrections made using the analysis summary presented below. Please see results section –paragraph 2.

‘7 (4.6%) patients were given statin after admission in the previously no statin group and 54 (93.1%) were administered statin in the previously statin group. Among those receiving statin after admission, the percentage days of statin is 50 (33-60) in the non-statin and 90 (75-100) in the statin group.’

2. The study population is interesting, if somewhat unusual. Subjects were enrolled based antibiotic coverage after admission and followed until admission to a high-dependency or IC unit, or for 10 days. 30 day disposition was also recorded. Although it is appreciated that a power analysis was not conducted, the result is somewhat predictable. Unless there was postulated to be a huge effect size for statins, early infection with limited mortality would likely not show a difference in this sample size.

Author response: We thank you for this comment. We also acknowledge that the study was underpowered for mortality. The inflammatory markers formed the key outcome variables.

3. What is the makeup of the 12% of patients who were given antibiotics but who did not display SIRS-like symptoms? From the inclusion criteria these patients apparently had either proven or suspected infection(?) What about those patients who may have become septic but were not given antibiotics (i.e., were missed until ICU)? Were there any patients subsequently admitted to ICU or who died who did not receive antibiotics until they reached the ICU? It is possible that this group, if statin use is a surrogate for reasonable out-patient care, contained a preponderance of non-statin users?

Author response: The additional data requested by the reviewer is provided in table 2.
4. The 30 day follow-up revealed approximately 20% morbidity/mortality with mortality at 5.7%. To this reviewer this group is more interesting than the statin result. Was there any constant in this group? (Here’s where enlarged a priori variable definition might have been helpful – but can still be done as a post hoc analysis). At present the manuscript simply reads that ‘it wasn’t the statins’ but leaves no further understanding for mechanisms of poor outcome. A sentence or two describing this subgroup would elevate considerably interest in this manuscript.

Author response: We thank the reviewer for this very interesting question. Some of these issues are addressed within the questions raised by reviewer 2 responses. We reiterate that the study focus was on inflammatory variables and as such we do not have enough data to address this question directly.

5. The sentence in Methods that reads, “..we aimed to enrol [sic] all possible study subjects during the period of availability of the data collectors.” should be explained. If this is a summer collection period this should be stated. Alternatively, if data is only collected, for example in the morning hours, this too should be noted. Sick patients have a tendency to be admitted at inopportune moments, and diurnal data collection (if this is the case) may have skewed the data towards a) less ill patients or perhaps b) better diagnosis (i.e., diagnosis not missed in the early morning hours because of staffing, etc.)

Author response: Thank you for pointing out this potentially lack of clarity. The methodology used in patient recruitment are fully explained on page 5.

6. Although it is appreciated that the a priori selected predictors are appropriate, there are several others, including race, type of infection (i.e. PNA vs urologic infection), APACHEII/SOFA (or some scale attesting to acuity of illness not included in Charlson score), that since this study was a hypothesis-generating one might have included (and presumably one has the data available for at least some of these predictors).

Author response: The study was conducted in ward patients and as such to the best of our knowledge none of the severity scores are neither commonly measured nor validated. We do not have any additional data to provide. Table 1 does contain some of the variables that form part of commonly measured severity of illness score. We did not have a specific hypothesis on other predictors highlighted by the reviewer – given that we were primarily interested in inflammatory markers.

Minor points:

7. It is noted that data was collected in 2008. Not that 6 year-old data is invalid, but this gives the flavor of an after-thought of a study, not one that was designed to answer a particular research question.

Author response: As we highlight in the introduction, the principal hypothesis behind the study was to identify a group of patients who have a high chance of deteriorating following hospital admission with infection to inform a future RCT. Unfortunately, we acknowledge that the time for such an RCT may well have passed.

8. Idle question: is it routine for the institution where the study was conducted to obtain a daily CRP on all patients admitted with routine or suspected infection? Or is this data-set part of a larger interventional trial that specifically collected CRPs? If so, this aspect of study design should be acknowledged.
Author response: Yes; CRP measurement is part of routine care.

9. Figures 1, 2 and 3 need a legend

Author response: Addressed

10. Overview: The result that statin use did not alter CRP or WCC or results of any kind is of some interest. However, as this was a hypothesis-generating study there was no a priori hypothesis and thus no power analysis, and it is not possible to make a definitive statement from this manuscript, only state that in the convenience sample collected there was no difference in outcome between groups. As it stands, the manuscript is relatively superficial and of limited interest in its bird’s eye view of patients with low-acuity infection. It is suspected, however, that there may be some genuinely interesting outcomes from this study (already collected and presumably not already published) that would at least inform to a hypothesis-driven RCT; it would be of great interest to see these results, inconclusive though they may be (what kinds of infections pre-disposed to long hospital stay? Any commonality in mortality or ICU admission? Any particular SIRS component that seemed more or less predictive in this population? Etc.).

Author response: Please see answers to reviewer 2 comments that directly address some of the concerns highlighted by the reviewer in this ‘overview’.
Reviewer: Peter Kruger

Reviewer's report:

The authors describe an interesting and well performed prospective observational study to evaluate the progression (or regression) of clinical and laboratory markers of systemic inflammation in a cohort of non surgical patients admitted to hospital with presumed infection. In addition to the description of laboratory and clinical outcomes the investigators assessed the influence of prior statin use, age, gender and coexisting disease.

Markers of systemic inflammation tended to fall away over time in most patients with progression or deterioration (defined as more SIRS criteria that present on day 1) seen in about 30% of the cohort. The authors comment that larger studies would be required to identify patients at a high risk of deterioration.

I think the methodology is appropriate and the study has been conducted to a high standard and the report well written.

**Major comments to be addressed:**

Several issues warrant some clarification

11. The manuscript should reflect these are non surgical patients and this could also be mentioned in the discussion.

Author response: corrections made in discussion and in methods

12. Given the slight increase in SIRS over time in prior statin users do the authors have any information on what happened with continued vs. discontinued statin use in these patients during their hospital stay - perhaps this could be included in the text.

Author response: Corrections made using the analysis summary presented below. Please see results section - paragraph 2.

‘7 (4.6%) patients were given statin after admission in the previously no statin group and 54 (93.1%) were administered statin in the previously statin group. Among those receiving statin after admission, the percentage days of statin is 50 (33-60) in the non-statin and 90 (75-100) in the statin group.’

13. I think the authors should reconsider the use of the word “low” when describing the mortality outcomes – This may be better framed with some sort of comparison – I agree it is low compared to that seen in critically ill patients but I suspect a 1:20 chance may not be universally regarded as low (it is, for example higher than often seen with hospital admission for myocardial infarction).

Author response: corrections made as highlighted in comment 11

14. How was vital status at 30 days verified? Could the authors provide further detail. Discharge from hospital alive prior to 30 days is not always equivalent to still alive at 30 days unless some specific additional enquiries are made.

Author response: This was assessed by noting the status at hospital discharge, with maximum 30 day follow up. Corrections made in methods section.
15. It would be worth mentioning in the methods that the blood tests described were not part of a study protocol and results were only available if these were collected as part of usual patient care. This introduces the fact that the data presented for these is incomplete. I think the results would be enhanced if the authors present the number of patients that remained in the study on each subsequent day so we have a denominator for the number of CRP / WCC results – so figure 3 might have 48/58 and 138/151 at study entry and then go on to detail the number of patients still in hospital at each of the subsequent time point.

Author response: Corrections made in methods section and Figure 3 is altered in response to reviewer comments.

16. Please clarify in Figure 1 if the “numbers of patients with data” is the total cohort – did any patients have missing data for this, the primary outcome measure?

Author response: Corrections made using the analysis summary presented below.

Figure 1 is altered in response to reviewer comments.

‘Out of 341 patient-days coded as no SIRS there are 35 days for which values are missing for all variables in the SIRS criteria. In the event of missing data, then variables were considered to be within normal limits.’

17. I think the paper would be enhanced with a little more detail around the “progression” definitions. Did the additional SIRS criteria occur in the subsequent days (so really progression of this illness) or “pop up” a few days later (raising the possibility of some new process).

18. Similarly – perhaps some more details around ICU/HDU and death. How many patients that died went via the ICU? or were these mutually exclusive groups? As a composite end point (Died or care escalated to ICU/HDU might increase the frequency of events?). Similarly are any details available on cause of death – was it thought to be related to the infection progression or a new problem?

Author response to comments 7&8: Corrections made using the analysis summary presented below. Please refer to paragraph 3 of results section.

‘Although for the SIRS (Y/N) we used all patients day for the score SIRS if the data was missing on a certain day for all variables than we considered it missing for that day. That was mainly due to the fact that for the last day if they were admitted to ICU or died the SIRS was considered 1 but there was no way to evaluate the actual score as they might be all missing. We have 2 patients with missing score on day 1.

The day of follow up where the SIRS score increased was not significantly different between the statin user and non-user groups. Statin group: median [IQR]2 (2-3) and non-statin: 2 (2-3); p=0.5725 based on Wilcoxon rank-sum test). There were 13 deaths with 1 death occurring after 30 days and among 12 deaths who occur in the first 30 days, one death is after a readmission. None of these patients were admitted to ICU and they all die on ward.’

19. Some of the literature in the progression of disease reflects that in some patients it is “failure to improve” rather a deterioration that results in their poor outcome. Do the authors have information if a subset “failed to improve” so SIRS persisted rather than declined and if so did that group have any different outcomes from those patients where SIRS resolved?
20. Along these same lines did the people who died or went to ICU/HDU actually deteriorate to achieve the SIRS definition they applied. This might be a very useful additional analysis to better inform the larger question behind this study “why patients die, deteriorate or fail to get better from infections”.

Author response to comments 9 & 10: corrections made using the analysis summary presented below. Please refer to paragraph 4 of results section.

‘We evaluated SIRS criteria on the final day and compared it to admission day SIRS criteria. Out of 184 who had at least one SIRS criteria on day 1, 112 (60.9%) still have one SIRS on the last day. And out of 25 who do not have SIRS on day 1, 13 (52%) have SIRS on last day. Out of the 7 patients who are admitted to ICU/HDU in the first 10 days only 2 have a score that can be calculated (i.e. have non-missing data for at least one of the SIRS criteria). One patient has a score of 0 on the first day and the day of ICU admission a score of 1 and a second patient had a score of 2 on the first day and a score of 3 on the day of ICU admission.’

21. I found the 3rd paragraph of the discussion confusing. Several papers have looked at progression / regression of SIRS over time, mainly in ICU patients as the authors point out. Please clarify that the “prognostic value” they refer to is for detecting culture +ve sepsis rather than other clinical outcomes. The authors may wish to review the paper by Lai N.A et al (The predictive ability of a weighted systemic inflammatory response syndrome score for microbiologically confirmed infection in hospitalised patients with suspected sepsis. Critical Care and Resuscitation, 2011: 13 (3) – 146- 150 ) as this follows a similar cohort and shows a clear increase in mortality for increased numbers of SIRS criteria at baseline – so perhaps some prognostic value exists for outcome / illness severity if not for predicting positive microbiology.

Author response: corrections made as below

In our study cohort consisting of medical [non-surgical] patients, approximately one-third of patients had progression of illness defined by an increase in number of SIRS criteria. Compared to ward patients, the prevalence of SIRS in a critically ill population is high. ICU-based studies have evaluated the utility of SIRS progression either as a risk factor for more severe illness or as risk factor for mortality often related to number of SIRS criteria [4-6, 18, 19]. Rangel-Frausto et al found a higher incidence of culture-positive sepsis with increase in number of SIRS criteria [4], but other studies have found that SIRS criteria have little value in detecting culture positive sepsis [19]. Similarly, patients with SIRS have a mortality rate of 10% [18] and increase in number of SIRS has been shown to be associated with increase in risk of death [19], this relationship has not been replicated in other studies [6]. These inconsistent observations suggest that SIRS criteria lack specificity and sensitivity to predict progression of illness due to infection [2, 6, 18, 19]. Finally, the overall mortality in the study cohort was a limiting factor that precluded modelling the influence of SIRS criteria [2, 4-6], CRP trends [20, 21], or pneumonia [2, 22] on mortality.

Minor comments to be addressed:

22. opening paragraph background – 3rd sentence , after ref 4-6 ? should this be a full stop

Author response: correction made

23. The following sentence could be reworded to improve clarity – “ minimal treatment effects of harm... “ ?
Author response: Re-written to address the concerns as below.

‘Given this risk of organ dysfunction [8, 9], the reported minimal treatment effects and potential for harm with interventions for established organ failure [10, 11], an alternative approach is to evaluate drugs with pleotropic effects to prevent progressive organ dysfunction in a pre-ICU population of patients with infection.’

24. The authors describe the primary outcome as “evolution of systemic inflammatory response syndrome” – perhaps this should be clarified a little as evolution is often associated with progression / increases?

Author response: Re-written to address the concerns as below.

‘Our primary outcome measures were the evolution changes in of the systemic inflammatory response syndrome (SIRS) during the follow-up period, defined as the proportion of patients who had at least one SIRS criterion on each day of follow-up, and the evolution of inflammation, as defined by trends in CRP and WCC.’

25. Could the investigators comment on the choice of 38.3 as the upper temperature criteria – while this is listed in the cited 2003 levy paper the original SIRS criteria used 38 (as is also mentioned in this paper)

Author response: The case-definition used was to be consistent with the updated consensus definitions for sepsis by Levy et al.

26. In the discussion 2nd paragraph – “hospitalised patients with infection” maybe preferable to use “infected hospitalised patients”. (? and perhaps even non-surgical hospitalised patients.)

Author response: correction made

27. Caption for figure 2 and 3 and the mention in the text of changes in WCC or CRP. I think would be clearer and more correct if “over time” were added to the complete the eg. .... change in WCC or CRP “over time”.

Author response: correction made

28. Table 1 might be clearer with a slight format change – the AVPU section could put the n= in each column along that row to better reflect the totals below are a cumulative subsection

Author response: correction made

29. Please clarify that in Table 2 – the supplemental oxygen, days 2-10 row is “at anytime in this time period” ie. yes / no

Author response: correction made