Title: Predictors for gram-negative monomicrobial necrotizing fasciitis in southern Taiwan

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Author’s response to reviews:

Dear Reviewer 1:

Thank you for the editorial members.

I will answer one by one for these questions you asked.

1. This study is an interesting paper but I struggled to see the importance of your aim and how this has relevance clinically:

The aim of the study is to detect more reliable predictors between gram negative and gram positive monomicrobial NF of limbs.

Please emphasise the relevance of this - usually the associations given will be associated with an outcome, good or bad, rather than an organism type - this needs to be reviewed in the context of
what the study is actually trying to do. You did mention the difference in outcome - please clarify this and express it more clearly.

Author response:

Thank you for your recognition of the importance of this study. We have removed Line 2~13 in Page 12 (Discussion section) to Line 9 ~ 19 in Page 6 and Line 1~3 in Page 7) (Introduction section). And we add Huang et al’s systemic review and reported in 2016 about V. vulnificus NSSTIs Line 18~19 in Page 6 and Line 1 in Page 7.

2. For a very rare condition, 186 patients in just over three years seems like an extremely large number, given the numbers published globally in the literature. How exactly was the diagnosis made regarding the necrosis - were superficial infections included which were in fact not NF? Please clarify this and explain the very high numbers such a short time.

I also cannot understand how you collected so many patients in this time period because in a previous paper from Taiwan (Lee et al - BMC Infect Dis. 2011 Jan 5;11:5. doi: 10.1186/1471-2334-11-5.) you collected 46 patients over 6 years - how could you collect double that number now in half the time?

Author response:

Thank you for your recognition of the larger number of this study. All patients were diagnosed with necrotizing fasciitis and not superficial infections. We have modified diagnostic criteria for NF in Materials and Methods. Lee et al retrospectively reported 46 patients with monomicrobial necrotizing fasciitis who underwent fasciectomy in conjunction with hyperbaric oxygen therapy (HBO) from November 2002 to January 2008 in 2011 (reference 8). In 2019, our VTR Group prospective corrected 186 NF admission via ED and only 118 (63.4%) patients receiving HBO from April 2015 to July 2018. There were several different points between these two studies. In Lee’s report, it was a retrospectively study performed by the HBO treatment center before 10 more years, and only monomicrobial NF who receiving HBO can be enrolled in Lee’s study. This study was performed by our VTR Group, it was a prospective study and these patients admitted skin and soft-tissue infections (SSTIs) at the ED were initially enrolled in our study and will follow up till to be discharged (Figure 1). Our VTR Group is more alert to SSTIs after ten more years later, and we also confident to improve patients lost.

3. Mortality rates are mentioned in the discussion. Please give further results of clinical outcomes - amputations and deaths resulting from NF in the current study. Please also state what treatment was given - number of debridements, number of amputations, level of amputations, mortality rate etc to emphasie the aim of your study and why this topic is so important as you seem to highlight.

Author response:
Thank you for your kind reminder. We had added clinical outcomes and surgical treatment in Results (Line 17 in Page 10 to Line 1~7 in Page 11) as your suggestions.

4. How many culture negative patients were there who were excluded despite clinical features of NF?

Author response:

There are 21 patients suspected necrotizing fasciitis initially but excluded after teamwork discussion (Figure 1). Among them, 5 patients had monomicrobial organisms, 4 had polymicrobial organisms, and 12 had no microorganism.

5. Table 4 shows Gram positive patients had an Hb of 4 - please confirm?

Author response:

There were 4 patients with Gram-positive NF with Hb < 10 g / dL (Table 4). Thank for the reviewer’s kind reminder.

6. Table 5- the CI for seawater exposure is very high - please explain this. Please also explain why seawater exposure is not a confounding factor as a result of this very wide CI.

Author response:

(1) High CI for seawater exposure may be due to still smaller patient numbers. If we can accumulate more years and more case numbers, we may improve this problem.

(2) Our hospital is situated on the western coast of southern Taiwan. In this area, patients usually had a history of handling seafood and prolonged occupational exposure to warm sea waters during oyster harvesting or fishing (reference 11). So, Vibrio spp. and Aeromonas spp. reasonable become the most fulminate gram-negative bacteria causing NF and seawater or seafood exposure became naturally a very important occupation and contact history.

7. Please clarify your diagnostic criteria for NF.

Author response:

We have modified diagnostic criteria for NF in Materials and Methods. (Line 8~12 in Page 8)
8. Please consider using more recently published articles on this subject for inclusion in your paper, especially regarding comparative data from systematic reviews.

Author response:

We have added four new recently published articles in the Reference, including two systematic reviews. The number of the references was changed subsequently.


Reviewer 2 (Reviewer 2): PEER REVIEWER ASSESSMENTS:

Dear Reviewer 2:

Thank you for the editorial members.

I will answer one by one for these questions you asked.

OBJECTIVE - Full research articles: is there a clear objective that addresses a testable research question(s) (brief or other article types: is there a clear objective)?

Yes - there is a clear objective

DESIGN - Is the current approach (including controls and analysis protocols) appropriate for the objective?

Yes - the approach is appropriate
EXECUTION - Are the experiments and analyses performed with technical rigor to allow confidence in the results?

Yes - experiments and analyses were performed appropriately

STATISTICS - Is the use of statistics in the manuscript appropriate?

Yes - appropriate statistical analyses have been used in the study

INTERPRETATION - Is the current interpretation/discussion of the results reasonable and not overstated?

Yes - the author's interpretation is reasonable

OVERALL MANUSCRIPT POTENTIAL - Is the current version of this work technically sound? If not, can revisions be made to make the work technically sound?

Yes - current version is technically sound

Author response: Thank you for your recognition of this study.

PEER REVIEWER COMMENTS:

GENERAL COMMENTS: I have reviewed the manuscript entitled "Predictors for gram-negative monomicrobial necrotizing fasciitis in southern Taiwan". Authors use multivariate logistic regression to predict risk factors in 100 patients who have developed (what seems like) NF in Taiwan and for which demographic and lab data has been collected. Interestingly, Taiwan seems to have disproportionately more cases of NF caused by Vibro sp. than elsewhere (mainly V. vulnificus) and contact with salt/seawater.

The manuscript is well written, concise and clear. Methods are appropriate, including statistics, and well explained and written too. Results were a bit concise, but precise.

Author response:

Thank you for your recognition of this study. We had added clinical outcomes and surgical treatment in Results (Line 17 in Page 10 to Line 1~7 in Page 11) as your suggestions.

REQUESTED REVISIONS:
I would add a section explaining why it's important to distinguish Gram-positive and -negative NF to the introduction. As a non-expert on NF itself, I was left to wonder the whole manuscript why you were doing this before reading it in the last sentences of the first paragraph of the discussion.

Author response:

Thank you for the reviewer’s recommendations. We have removed Line 2~13 in Page 12 (Discussion section) to Line 9 ~ 19 in Page 6 and Line 1~3 in Page 7 (Introduction section) and modified this article according to your kind suggestions.