Reviewed by 00068668

The topic of the manuscript is interesting and I think that the paper must be published. However, there some concerns about the paper:

1. The comparative group is very heterogeous regarding the vasopresor used....this must be emphizased

Response: While we agree concerning the heterogeneity of the comparative group, a salient feature of this study is that the 2nd vasoactive agent used in that group was almost exclusively a second catecholaminergic agent resulting, more or less effectively, in a study comparing second-line vasopressin use vs. second-line catecholaminergic augmentation. Additionally, there are limited data as to the superiority of one vasopressor over another. We have edited our discussion to reflect this feature of the study.

2. Is clear that the patients in AVP group are more severe patients compared with the other group: MELD scores in the AVP group (32.4, 95% CI 28.6-36.2 vs. 27.1, 95% CI 23.6-30.6, p=0.041) and glomerular filtration rates were also different between the two groups (23.9 mL/min, 95% CI 18.6-29.2 in the AVP group vs. 40.0 mL/min, 95% CI 29.1-51.0 in the non-AVP group, p=0.013. These two differences clearly gives a disadvantages to the AVP group, this must be commented in the discussion section

Response: We agree that the AVP group appears to have been a sicker population and we have included a discussion of this characteristic in our Discussion section. Additionally, it may well be that the AVP group reflected a population with more profound hypertension (not responding to norepinephrine) as AVP remains the second-line vasopressor to reduce norepinephrine use as per the Surviving Sepsis guidelines. Finally, although we have included baseline GFR values for our cohort, we caution somewhat against conclusive interpretation of these data as several of these patient were already receiving renal replacement therapy at the time of first pressor administration making it difficult to interpret these values as reflective of intrinsic renal function (although the groups were evenly matched with respect to renal replacement therapy).

3. The authors says in the discussion: "After adjusting for multiple confounding factors, we report that AVP is non-inferior when compared to all other vasopressors..." this sentence must be changed and to be very careful with your aseverations. Clearly, this study cannot be considered as a "non-inferiority" study...because of that you cannot use the sentence

Response: We agree that this is not a non-inferiority trial and so we will omit such terminology from the manuscript.

4. I cannot see the conclusions

Response: We are unsure to what this reviewer is referring to.

Reviewed by 03476715

The Surviving Sepsis Guidelines suggest the vasopressin use could decrease the mortality. But such suggestion is just based on expert opinions, no further evidence was provided. The authors designed such a retrospective study, found that vasopressin is non-inferior to all other vasopressors in terms of 7-day and 28-day mortality and in the absence of significantly more deleterious effects suggest a role for vasopressin use in patients with cirrhosis admitted to the intensive care unit with septic shock, and provided further evidence on for AVP use as a second-line vasopressor in catecholamine resistant septic shock and for attention to vasopressor selection in patients with cirrhosis. Although this retrospective study has many limitations, the author has clearly stated the limitations. However, there are some minor problems the author need to clarify.

1. This research aimed to compare the efficacy of VAP in septic shock, but the author did not give us the data of blood pressure before and after the VAP use. Isn't it much more important than ALT/AST/platelet? And so did the Na level and GFR levels. The authors should add those data in table 2.

Response: While clearly, as a vasopressor, the primary clinical goal of employing AVP in this population is to augment blood pressure, this study is not prospective and so continuous blood pressure monitoring via arterial catheter was not routinely assessed. We suggest that because it is common clinical practice, and common practice at our institution, to target goal mean arterial pressures in shock patients (often MAP targets of >60 in our cirrhotic patients), that the total number of vasopressors used in each group may be viewed as a practical and clinical surrogate (although imperfect) of blood pressure response to the second vasopressor agent. Further, this variable is probably more telling than a point blood pressure at a specific moment in time (for example ~24 hours following vasopressor initiation). In other words, if a target MAP were not achieved with a second vasopressor, the clinical scenario would warrant addition of a 3rd vasopressor etc… Even so, we acknowledge that due to the high rate of withdrawal of care in our cohort, even these data must be interpreted with caution. We will include this into our discussion, but suggest that the "number of total pressors" data can be viewed as a surrogate of successful attainment of blood pressure targets in a retrospective cohort.

Additionally, we agree concerning the primacy of blood pressure augmentation clinically, however, we were also interested investigating other possible detrimental effects of AVP including platelet decline and acute-on-chronic liver failure.

Finally, we appreciate the suggestion of including post-vasopressor data regarding GFR and sodium. While we do have sodium and GFR data collected for the end of hospitalization, these data are uninterpretable given the very high rate of renal replacement therapy in our study cohort (approaching 70%) which results in values not reflective of intrinsic renal function. Accordingly, we suggest that the publication of these data would not be beneficial to increasing our understanding of AVP effects in our population.

2. In multivariable analysis, the author included 9 factors. As we know, events per variable(EPV) is recommended to be between 10-20 in such statistical analysis. When performing variable selection, these EPV rules are applied to the number of candidate variables considered, not just those in the final model. (Ojeda FM et al, Comparison of Cox Model Methods in A Low-dimensional Setting with Few Events. Genomics Proteomics Bioinformatics 2016). The number of cases of this study were only 45 and the variables in multivariable analysis were 9, the results were not robust. I suggest the authors to reduce the factors in multivariable analysis, for example, include MELD score instead of the INR, Cr or bilirubin separately.

Response: The general suggestion of observations per independent variable in regression analysis is debatable and can be as low as 5 or as many as 20. There are reports that even as few as 2 observations per variable are sufficient and that this modeling does not suffer from overfit bias and inappropriate coefficients and conclusions (Schneider A et al Dtsch Arztebl Int 2010 Nov; 107(44): 776–782). We examined each variable independent of MELD score to ensure no domination from these parameters. With that said, we have changed our analysis to limit overfitting by including MELD as a composite rather than individual variables as was previously reported. One conclusion did change with this modeling and that is initiation of renal replacement therapy in this population was associated with lower mortality. We have changed the manuscript appropriately.

3. The author should give the exact data of p values instead of NS since they said only factors with p<0.10 in the univariate analysis were included in the multivariable model.

Response: The methods state "Individual factors were included in the multivariable model if they were statistically significant to p<0.10 in the univariate analysis, were clinically important, or have been shown in the literature to be of clinical significance." Nonetheless, we have provided the requested p-values.

4. The baseline level of AST (429 vs 289) in table 1, ALT level (47 vs 206) in table 2, they looked very different. The authors should double check the data to make sure the p values were really not significant.

Response: We re-ran the statistics on this variable and the CI overlap and the p-values are not significant.

5. In method section, “Kaplan-Meier survival curves were constructed for 7-day and 28-day survival utilizing the log-rank test to determine statistical significance (log rank <0.05)”. Here the Log rank <0.05 should be corrected as P value <0.05.

Response: We have corrected this omission

6. The authors used the Student-t test, Wilcoxon sign rank test, chi-square test, or Fisher exact test for the univariate comparisons. But since it is a time-to-event data, COX regression is a better choice for univariate comparisons.

Response: We disagree respectfully and stand by our decision to utilize the current statistical methodology as the univariate analysis is cross-sectional in nature.

Reviewed by 3473431

The manuscript is well writtenn in all sections:It is a retrospective study,but the authors clearly stated this limitation in the discussion section. No need for changes.

Response: Thank you.