The Effects of Ascorbic Acid Over Sepsis: Meta-analysis With Trial Sequential Analysis

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Research

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Abstract

Background: This meta-analysis is performed to evaluate the effects of AA on the mortality over sepsis patients, focusing on the courses and initiation of treatment as well as AA doses.

Methods: Randomized controlled trials concerning sepsis patients treated with intravenous AA were included when searching the database. The meta-analysis was performed using the random (M-H heterogeneity) model to produce summary odds ratio with 95% CI. Trial sequential analysis was applied to evaluated the effect of random errors.

Results: The included 12 trials enrolled a total of 1232 patients. Intravenously administration of AA could not lower 28-day mortality over sepsis patients (OR = 0.81; 95% CI (0.54-1.23); p = 0.326). Subgroup analysis demonstrated that when administrating AA alone, in a dose ≥ 10 g/d, or within 6 h of admission, the result may turn to positive (OR = 0.36; 95% CI (0.15-0.86); p = 0.020, OR = 0.50; 95% CI (0.27-0.92); p = 0.025, OR = 0.49; 95% CI (0.27-0.89); p = 0.019, relatively). The quality of evidence is moderate.

Conclusion: IV AA may have no effects to lower mortality over sepsis patients. However, when administrating AA alone, in a dose ≥ 10 g/d, or within 6 h of admission, the result may turn to positive. Due to a moderate GRADE certainty of evidence, further studies are required to fully elaborate the effectiveness of AA during the management of the sepsis patients.

PROSPERO registration number: CRD 42020170825. 24 Feb, 2020 retrospectively registered.

Background

Ascorbic acid (AA) is a water-soluble vitamin and an essential endogenous trace element that scavenges reactive oxygen species (ROS) [1,2]. Vitro experiments show that AA influence the immune system via the following major factors, inhibition of T cell apoptosis [3] and increasing NK cytotoxic activity [4]. Previous studies have demonstrated that patients in critical condition, particularly sepsis, have low levels of AA in the plasma [5-8] which holds prognostic value owing to its inverse correlation with multiple organ failure [8]. The inability for humans to synthesize AA is due to the lack of L-gulono-γ-lactone oxidase, a key enzyme that converts glucose to AA eventually [9], which makes external intake necessary. Both dosing and biodistribution data in humans suggest that pharmacological concentration of AA are only attainable through intravenous (IV) administration because of the saturation of intestinal transporters (sodium-vitamin C transporter-1) [10]. Results from involved animals and human beings have suggested that AA supplementation significantly improves the prognosis of critical ill patients in the following aspects, attenuating lipid peroxidation, reducing vascular permeability, improving microvascular dysfunction, stabilizing endothelial and microcirculatory function, promoting endogenous vasopressin synthesis, enhancing vascular sensitivity to vasopressor, maintaining hemodynamic stability, and ultimately decreasing the incidence of organ dysfunction [11-15].

Despite promising preliminary outcomes, the benefits of AA supplementation remain controversial. An observational trial via Marik and coworkers [16] stated that AA as a component of “cocktail therapy” can strikingly reduce mortality and the duration of vasopressor in severe sepsis and septic shock patients. Giladi et al. [17] reported reductions of the occurrence of abdominal compartment syndrome, postoperative infection and respiratory failure in critically ill trauma patients. Our previous meta-analysis [46] commanded an AA dose of 3-10 g/d that can significantly decreased mortality in critically ill patients. While randomized controlled trials (RCTs) published recently [18-23] failed to reach the same conclusion. Notably, the courses and the initiation of AA treatment, as well as the AA doses varied from these trials, which may account for the discrepancies.

In this meta-analysis, we recruited RCTs that AA has been intravenously administration to patients with sepsis. We aimed to identify whether the treatment course and the initiation of AA impacts mortality, furthermore, we intended to explore the other effects of AA, including length of intensive care units (ICU), duration of vasopressor requirement, acute kidney injury (AKI) and renal replacement therapy (RRT).

Materials And Methods

This study was performed and prepared according to the guidelines proposed by Cochrane Collaboration in the Cochrane Handbook for Systematic Reviews of Interventions (http://www.cochrane handbook.org) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [31,32].

Search strategy

We searched articles of all languages published from inception to September 2020 in PubMed, Embase, Ovid, Medline and Cochrane Central Register of Controlled Trials using the following keywords along with Mesh terms: “ascorbic acid” and “sepsis” (Additional file 2). We collected all RCTs in which AA has been intravenously administered to adult sepsis patients. We also searched the references manually to attain related articles.

Study selection criteria

Inclusion criteria
1. Performed on adults in condition of sepsis
2. IV AA vs. placebo or no-intervention groups
3. RCTs.

Exclusion criteria
1. Performed on children
2. AA administered orally, enterally or were permitted to change to an enteral dosage form once enteral access was established
3. Lack of mortality data
4. Lack of control group
5. The way of AA administration was unclear
6. Study design is observational studies including cohort studies and case-control studies.

Data extraction
Data were independently extracted by the first and the second authors. Extracted data consisted of the name of first author, year of publication, study population, number of patients, AA dose, AA course, initiation of treatment, co-interventions, clinical parameters and adverse events. We resolved disagreements through discussions until a consensus was reached. We didn’t contact the authors for missing data including unreported data or additional details.

Outcome measurements and definitions
The primary outcome was 28-day mortality. Secondary outcomes included ICU and in-hospital mortality, the length of ICU stay, duration of vasopressor requirement, patients suffering from AKI or demanding RRT and the change of Sequential organ failure assessment (SOFA) score. Courses of AA treatment ≤ 3 d were defined as short term, ≥ 3 d as long term. Doses < 3 g/d were defined as low, ≥ 10 g/d as high, and 3–10 g/d as medium.

Assessment of risk of bias
We applied the Cochrane Collaboration tool to assess the risk of bias in RCTs [32,33], the remaining non-RCTs were assessed via the ROBINS-I tool [34]. We rated each domain of the trials as low risk, unclear, or high risk. Trials were considered low risk when each independent domain was rated as low risk. Any domain rated as unclear or high risk increased the overall risk score. Risk were independently rated by the first and the second authors. We resolved disagreements through discussions until a consensus was reached.

Statistical analysis
Data were analyzed using Statistics/Data Analysis 15.1. The results of dichotomous data were presented as forest plots through the odds ratios (ORs) with 95% confidence intervals (CIs). Forest plots using Weighted Mean Difference (WMD) with 95% CI were performed for the assessment of continuous data. We used random (M-H heterogeneity) model to assess the effects since clinical heterogeneity including setting, AA regimen, co-interventions was high. A begger test was conducted to assess the publication bias. Subgroup analyses were pre-specified and performed to explore the correlation between mortality and the treatment course, doses, initiation of treatment, population and combination with co-interventions. A p value ≤ 0.05 was considered statistically significant, except when otherwise specified.

Assessment of the certainty of the evidence
Grading of Recommendations Assessment, Development and Evaluate system (GRADE) was used to evaluating the quality of evidence, based on the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) [35]. The first and the second authors independently rated the quality of evidence for primary outcome. The level of evidence was classified into four categories as high, moderate, low or very low. We resolved disagreements through discussions until a consensus was reached.

Trial sequential analysis (TSA)
TSA was applied to assess the robustness of the results on RCTs, and to provide sample size needed in further trials [36]. We constructed the analysis via TSA version 0.9.5.10 Beta software with a 20% relative risk reduction. The control event rate was calculated from the control group of RCTs in this meta-analysis. The type I error rate was defined as 5%, and the type II error rate was set as 20% (a statistical power of 80%). The heterogeneity correction was based on model variance.

Results

Literature search
Through database and manual search (Fig. 1), 2220 records were retrieved. We screened both titles and abstracts according to the inclusion and exclusion criteria, leaving 38 records that were deemed suitable for inclusion. After reviewing the full texts, 12 records [18-30] met the inclusion criteria and were finally included (Table 1). Studies were excluded for the following reasons: duplication (n = 24), non-RCTs (n = 1) [37].

**Study characteristics**

The characteristics of each trial are listed in Table 1. There were 8 trials exploring the effects of AA combined with co-intervention, such as thiamine [18-24], N-acetylcysteine [28], and α-tocopherol [28]. The longest intervention course of AA lasted for 10 days [18], while the shortest was only 1 day [28]. Only 1 record lacks specific data of the treatment course [28]. The articles included was published in a long span from 1997 to 2020. The sample sized ranged from 20 to 211. The included trials enrolled a total of 1232 patients of which 571 received AA administration, and 661 were controlled subjects.

**Risk of bias and quality of evidence**

The risk of bias was summarized in Fig. 2. The trial performed by Balakrishnan [24] and Jose [21] were deemed a high risk of bias as incomplete outcome data over mortality. Studies by Fujii [18], Wani [23], and Chang [19] were not performed in a double-blinded way and were rated as high risk. In total, 7 trials were defined as an unclear risk and 5 trials were deemed high risk.

**Meta-analysis results**

**IV AA and mortality**

The meta-analysis, recruited 12 RCTs, indicated that IV AA may have no influence on 28-day mortality of sepsis patients (OR = 0.81; 95% CI (0.54-1.23); p = 0.326; I² = 44.7%, Additional files 3: Fig. 3A). A random (M-H heterogeneity) model was employed due to clinical heterogeneity. Subgroup analysis demonstrated that high (≥10 g/d) doses of AA administration was related with a lower 28-day mortality rate (OR = 0.50; 95% CI (0.27-0.92); p = 0.025; I² = 0.0%, Fig. 3B), however, the medium dose (3-10 g/d) of AA had no influence (OR = 0.92; 95% CI (0.59-1.42); p = 0.698; I² = 34.9%, Fig. 3B). Long-term course (≥3 d) of AA administration could not reduce the 28-day mortality of sepsis patients (OR = 0.75; 95% CI (0.48-1.18); p = 0.215; I² = 47.9%, Fig. 3C). Initiation of treatment within 6 hours may be associated with a lower 28-day mortality rate (OR = 0.49; 95% CI (0.27-0.89); p = 0.019; I² = 0.0%, Fig. 3D). Additional subgroup analysis suggested that IV AA alone could decrease the 28-day mortality rate compared with co-interventions (OR = 0.36; 95% CI (0.15-0.86); p = 0.020; I² = 28.6% vs. OR = 1.10; 95% CI (0.79-1.54); p = 0.572; I² = 0.0%, Fig. 3A).

Upon AA application, no decreased was found over ICU or in-hospital mortality (OR = 0.95; 95% CI (0.66-1.36); p = 0.780; I² = 0.0% vs. OR = 1.11; 95% CI (0.79-1.56); p = 0.550; I² = 0.0%, Additional file 3: Fig. S2A).

**Length of ICU stay**

Three trials [21,29,30] included compared the length of ICU stays between AA and control groups. The results suggested that AA administration did not shorten the length of ICU stay in sepsis patients (WMD = -1.52; 95% CI (-5.06-2.03); p = 0.401; I² = 79.0%, Additional file 3: Fig. S2B).

**Duration of vasopressor requirement**

Our analysis among trials [21,23,29,30] suggested that AA administration may decline the duration of vasopressor requirement (WMD = -17.41; 95% CI (-31.16- -3.65); p = 0.013; I² = 89.4%, Additional file 3: Fig. S2B).

**Change in SOFA score**

Four trials [19,21,23,27] were included to assess the influence of the change in SOFA score on which AA had no impact (WMD = 0.73; 95% CI (-0.28-1.75); P = 0.158; I² = 60.2%, Additional file 3: Fig. S2B).

**The Incidence of AKI and RRT**

From analysis among trials [20-22], AA intervention did not increase the incidence of AKI (OR = 1.28; 95% CI (0.80-2.05); p = 0.303; I² = 0.0%, Additional file 3: Fig. S2A).

No difference was observed in the incidence of RRT among trials [20,21,29] when applying AA (OR = 0.78; 95% CI (0.35-1.75); p = 0.548; I² = 39.0%, Additional file 3: Fig. S2A).

**Publication bias and sensitivity analysis**

A begger test was employed to assess the publication bias of the included trials, and the result suggested a minimal publication bias (p = 0.174).
Sensitivity analysis was performed through the removal of each individual trial and reanalysis the remaining trials. When excluding the trial performed by Wani \cite{23}, the impact of AA on change of SOFA score altered (WMD = 1.19; 95% CI (0.49-1.89); p = 0.001; $I^2 = 0.0\%$).

**Overall certainty of evidence**

The evidence for 28-day mortality was downgraded to moderate certainty, due to study limitations (including high or unclear risk of bias over studies, clinical heterogeneity), and serious concerns about imprecision (including TSA results) (Table 2). Future evidence is likely to change the estimated effect.

**Trial sequential analysis**

TSA were performed based on included RCTs using a random-effects model, and were constructed for a heterogeneity adjusted information size of 2589 patients corresponding to a relative risk reduction of 20% with an $\alpha = 0.05$ and $\beta = 0.20$ (power 80%). TSA indicated lack of solid evidence for a beneficial effect on AA for mortality and further RCTs are needed to testify the effects (Fig. 4).

**Discussion**

**Main findings**

**IV AA and in-hospital mortality**

Same as other meta-analysis \cite{38,39} which observed no significantly reduction in mortality after IV AA intervention, the major finding of this study suggested that IV AA may have no effects to lower mortality rates over sepsis patients. Notable, when administrating AA alone, in a dose $\geq 10$ g/d, or within 6 h of admission, the result may turn to positive.

AA was an essential endogenous trace element and a cofactor of biosynthetic enzymes, which plays an important role in anti-oxidative stress, maintaining the function of endothelia, enhancing the effects of immune system. For patients with COVID-19, early and high IV dose of AA alone or in combination with steroids may have a benefit, especially in a dose about 12 g/d, and at a duration of at least 7 days \cite{40}. Investigators are engaged to find out the influences of AA on COVID-19 at a dose of 24 g/d for 7 days \cite{41}.

The degradation of AA that occurs during preparation and storage, and an increased requirement may contribute to the low level of AA in critically ill patients \cite{42}. Previous study has shown that in the post-injury period, only supraphysiologic doses (3000 mg/d) for 3 or more days could approached normal plasma levels \cite{43}. A trial explores the optimal dose of AA demonstrated that 10 g/d dose was associated with supranormal plasma concentrations \cite{44}. While Jackson and colleagues \cite{45} declared that AA is insufficient to compete effectively with nitric oxide (NO) for superoxide at anything less than supraphysiologic concentrations, and a 10-100 mmol/L of AA is an efficient scavenger for preventing the interaction of NO with superoxide. According to the previous studies, we defined a dose lower than 3 g/d as low, higher than 10 g/d as high, and 3-10 g/d (inclusive of 3 and 10 g/d) as medium dose. Our analysis revealed that high doses may have an ability to reduce mortality in sepsis condition, conversely low and medium doses don't. This is different from our previous results \cite{46} in which after IV high dose of AA, no loss of mortality was observed. In a randomized pharmacokinetic trial, de Grooth and co-workers \cite{44} emphasized that high plasma concentrations require stained therapy. In this trial, after 48 h infusion of AA, a varying decline in plasma concentrations was observed even at the dose of 10 g/d. Therefore, they indicated a supplementation of AA more than 48 h, possibly as long as patients remain critically ill. Given the factors mentioned above, we defined a treatment course less than 3 days as short-term, and the others as long-term. IV AA at a long-term course ($\geq 3$ d) could not lower mortality in patients with sepsis, which is inconsistent with previous studies. Micah and co-workers \cite{47} stated that APAHCE-adjusted ICU mortality was lowest when AA was initiated within 6 hours, which is same as our outcomes but still needs further exploration.

As an antioxidant, AA plays vital parts in assisting in the recycling of other antioxidant agents \cite{67}. This seems to be inconsistent with what we have observed in this meta-analysis, of which AA alone rather than co-intervention has a better survival benefit. In view of the absence of relevant RCTs comparing the prognosis of AA monotherapy with combined-therapy, we hope the result can attract the further attentions.

**Duration of vasopressor requirement**

The result suggested that IV AA may reduce the duration of vasopressor requirement, but the quality of evidence was graded as "very low". Studies have proven that enzymes via which endogenous norepinephrine and vasopression are synthesized required AA as a cofactor for optimal activity \cite{14}. An RCT recruited 53 patients with ST-segment elevation myocardial infarction observed an amelioration of the left ventricular ejection fraction after administration of AA \cite{49}. Furthermore, in the trial performed by Galley and colleagues \cite{28}, AA reduced the systemic vascular resistance index. Sum together, all mentioned above could contribute to a decreased duration of vasopressor.

**The Incidence of AKI and RRT**
AA was reported to promotes the incidence of acute renal failure [50]. A randomized, crossover and controlled design trial observed an increased urinary oxalate and Tiselius Risk Index for calcium oxalate kidney stones [51]. Contrarily, this meta-analysis observed that the incidence of AKI and RRT did not grow after AA treatments (a maximum dose of 66 mg/kg/h), indicating that IV high dose of AA in sepsis patients may be safe. However, reports over the safety of AA in the condition of critical illness are scare in the literature. Cautions should be paid when IV high doses of AA in patients with hemochromatosis, glucose-6-phosphate dehydrogenase deficiency, renal dysfunction, kidney stone, oxaluria and pediatrics [52].

**Comparison with other studies**

The major strength of this meta-analysis was to investigate the effects over different AA treatment course and initiation as well as doses contribute to mortality in patients with sepsis. In addition, we focused on the adverse consequences of AA, such as the incidence of AKI and RRT.

**Limitation**

This meta-analysis had several weaknesses that should be noted. Firstly, 5 trials are under high risks, which may lead to a bias. Secondly, except for 5 multicenter studies [18,20-22,27], 7 of the included studies were single-center background. Thirdly, the initiation of AA treatment, the treatment courses and doses, and the role of single versus co-intervention therapy still requires clarification in future studies. Lastly, the missing data handling remained major limitations for this paper.

**Conclusion**

Based on the current available evidence, IV AA may have no effects to lower mortality over sepsis patients, the quality of evidence was graded as moderate. However, when administrating AA alone, in a dose ≥ 10 g/d, or within 6 h of admission, the result may turn to positive. In view of the limitations of the primary literature and a moderate GRADE certainty of evidence, further studies are required to fully elaborate the effectiveness of AA during the management of sepsis patients.

**Abbreviations**

AA: ascorbic acid

GRADE: Grading of Recommendations, Assessment, Development and Evaluation

ROS: reactive oxygen species

IV: intravenous

ICU: Intensive care units

AKI: acute kidney injury

RRT: acute kidney injury

RCT: randomized controlled trial

OR: odds ratios

CI: confidence interval

TSA: trial sequential analysis

WMD: Weighted Mean Difference

SOFA: sequential organ failure assessment

**Declarations**

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

Not applicable.

**Availability of data and materials**
All data generated or analyzed during this study are included in this published article and its supplementary information files.

Competing interests

The authors declare that they have no competing interests.

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None.

Author contributions

WY/ ZHC developed the search strategy and performed the literature search. WY/ZHC did the study selection and data extraction for the systematic review. WY wrote the first draft of the manuscript. All authors contributed to the interpretation of data and critical revision of the manuscript, and approved the final manuscript. All authors confirm to the accuracy or integrity of the work.

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Tables

Table 1: The main characteristics of the studies included

| Author               | Country     | Patients                          | AA dose          | Treatment courses | Initiation of treatment | Co-interventions                                      | Outcomes                                      | Adverse events                  |
|----------------------|-------------|-----------------------------------|------------------|-------------------|-------------------------|-------------------------------------------------------|---------------------------------------------|----------------------------------|
| Fujii 2020 [18]      | Australia   | Septic shock (n = 211)            | 1.5g q6h         | 10 days           | Unavailable             | Thiamine and hydrocortisone                           | Change in SOFA score at day 3á          | Hyperglycemia                    |
| Ferron-Celma 2009 [23] | Spain      | Septic abdominal surgery patients (n = 20) | 450 mg qd        | 6 days            | Within 12 h             | None                                                   | Caspase-3á, PARPá, Bcl-2á          | -                               |
| Wani 2020 [23]       | India       | Sepsis/ septic shock (n = 100)    | 1.5g q6h         | 4 days            | Unavailable             | Thiamine and hydrocortisone                           | Duration of vasopressorá, Lactate clearance á | -                               |
| Zabet 2016 [30]      | Iran        | Septic shock (n = 28)             | 25 mg/kg q6h     | 3 days            | Unavailable             | None                                                   | Dose and duration of NE á, 28-day mortality á    | None                            |
| Fowler III 2019 [27] | USA         | Patients with sepsis and ARDS (n = 167) | 50mg/kg q6h      | 4 days            | Within 6 h              | None                                                   | Reduction in SOFA score á, PCT and CRP á, 28-day mortality á | None                            |
| Fowler III 2014 [26] | USA         | Severe sepsis (n = 24)            | 50 or 200 mg/kg/d | 4 days            | Within 6 h              | None                                                   | CRPá, PCT (only in high-dose)á          | None                            |
| Galley 1997 [28]     | UK          | Septic shock (n = 30)             | 1 g/d            | 1 day             | Unavailable             | N-acetylcysteine, α-tocopherol                         | HRá, Clá, SVRIá                         | -                               |
| Moskowitz 2020 [22]  | USA         | Septic shock (n = 200)            | 1.5g q6h         | 4 days            | Unavailable             | Thiamine and hydrocortisone                           | Fail to reduce mortality                | Hyperglycemia, hypematremia      |
| Jose 2020 [21]       | USA         | Sepsis/ septic shock (n = 137)    | 1.5g q6h         | 4 days            | Unavailable             | Thiamine and hydrocortisone                           | Duration of vasopressorá                | None                            |
| Chang 2020 [19]      | China       | Sepsis/ septic shock (n = 80)     | 1.5g q6h         | 4 days            | Unavailable             | Thiamine and hydrocortisone                           | Duration of vasopressorá                | Sever hypematremia               |
| Hwang 2020 [20]      | Korea       | Septic shock (n = 111)            | 50mg/kg q12h     | 2 days            | Unavailable             | Thiamine                                              | Fail to reduce mortality              | None                            |
| Balakrishnan 2019 [24] | India     | Septic cardiac surgery patients (n = 24) | 1.5g q6h         | 4 days            | Unavailable             | Thiamine and hydrocortisone                           | PCT level at day 3 and 4 á, dose of vasopressor á, SOFA score á | -                               |
| Nabil 2017 [29]      | Egypt       | Septic shock (n = 100)            | 1.5g q6h         | Until ICU discharge | Within 24 h             | None                                                   | Duration of vasopressor á, Length of ICU stayá | -                               |

*AA: Ascorbic acid; RCT: randomized controlled trial; ARDS: acute respiratory distress syndrome; SOFA score: Sequential organ failure assessment score; CRP: C-reactive protein; NE: norepinephrine; PCT: procalcitonin; ICU: Intensive care unit; HR: heart rate; CI: cardiac index; SVRI: systemic
vascular resistance index.

Table 2: Quality of evidence using GRADE approach.

| Outcomes                  | Studies (participants) | Quality assessment | Summary of findings |
|---------------------------|------------------------|--------------------|---------------------|
|                           |                        | Risk of bias       | Inconsistency       | Indirectness | Impression | Publication bias | Overall quality of evidence | WMD or OR (95%CI) | Heterogeneity | P value |
| 28-day mortality          | 8 (918)                | Serious            | No serious          | No serious    | Serious     | No serious     | ÂÂOO Moderate             | 0.81 (0.54,1.23)   | 44.7          | 0.326   |
| ICU mortality             | 6 (776)                | Serious            | No serious          | No serious    | Serious     | No serious     | ÂÂOO Moderate             | 0.95 (0.66,1.36)   | 0.0           | 0.780   |
| In-hospital mortality     | 5 (758)                | Very serious       | No serious          | No serious    | Serious     | No serious     | ÂOOO Low                  | 1.11 (0.79,1.56)   | 0.0           | 0.550   |
| AKI                       | 3 (419)                | Serious            | No serious          | No serious    | Serious     | No serious     | ÂÂOO Moderate             | 1.28 (0.80,2.05)   | 0.0           | 0.303   |
| RRT                       | 3 (347)                | Very serious       | No serious          | No serious    | Serious     | No serious     | ÂÂOO Moderate             | 0.78 (0.35,1.75)   | 39.0          | 0.548   |
| Duration of VR            | 4 (365)                | Very serious       | Serious            | No serious    | Serious     | No serious     | OOOO Very low             | -17.41 (-31.16, -3.65) | 89.4          | 0.013   |
| Change in SOFA score      | 4 (484)                | Very serious       | Serious            | No serious    | Serious     | No serious     | OOOO Very low             | 0.73 (-0.28, 1.75)  | 60.2          | 0.158   |
| ICU stay                  | 3 (265)                | Very serious       | Serious            | No serious    | Serious     | No serious     | OOOO Very low             | -1.52 (-5.06, 2.03) | 79.0          | 0.401   |

*VR: vasopressor requirement