Vasopressin versus norepinephrine for the management of septic shock: the VANCS II randomized clinical trial

Ludhmila Abrahão Hajjar[1,2], PhD; Cristiane Zambolim Capulleto[1], MD; Alessandro Belletti[3], MD; Juliano Pinheiro de Almeida[1], MD; Anthony C. Gordon[4], MD; Gisele Queiroz de Oliveira[1], MD; Clarice Hyesuk Lee Park[1], MD; Julia Tizue Fukushima[1], MSc; Stephanie Itala Rizk[1], MD; Tais Felix Szeles[1], MD; Nestor Cordeiro dos Santos[1], MD; Roberto Kalil Filho[1,2], MD; Filomena Regina Barbosa Gomes Galas[1], MD; Giovanni Landoni [3,5], MD

AFFILIATIONS

1. Instituto do Cancer, Hospital das Clinicas, Faculdade de Medicina de Universidade de São Paulo, São Paulo, Brazil.

2. Departamento de Cardiopneumologia, InCor, Faculdade de Medicina de Universidade de São Paulo, São Paulo, Brazil .

3. Department of Anesthesia and Intensive Care, IRCCS San Raffaele Scientific Institute, Milan, Italy

4. Section of Anaesthetics, Pain Medicine and Intensive Care Medicine, Faculty of Medicine, Imperial College London, London, United Kingdom

5. Vita-Salute San Raffaele University, Milan, Italy

Corresponding Author

Prof. Giovanni Landoni

Department of Anesthesia and Intensive Care

IRCCS San Raffaele Scientific Institute

Via Olgettina 60

20132 Milan

Italy

Tel: +39 02 2643 6155/6158; fax: +39 02 2643 6152; email: landoni.giovanni@hsr.it

INSTITUTION

The trial was performed at the Instituto do Câncer do Estado de São Paulo da Faculdade de Medicina da Universidade de São Paulo

REPRINTS

No reprints will be ordered

FUNDING

The study was sponsored by University of São Paulo and supported by departmental funds only.

MANUSCRIPT WORD COUNT: 2991

Copyright form disclosure: Dr. Gordon's institution received funding from the National Institutes of Health Research (NIHR) Research Professorship, and, outside of the submitted work, he has received speaker fees from Orion Corporation Orion Pharma and Amomed Pharma. He has consulted for Ferring Pharmaceuticals, Tenax Therapeutics, Baxter Healthcare, Bristol-Myers Squibb and GSK, and received grant support from Orion Corporation Orion Pharma, Tenax Therapeutics and HCA International with funds paid to his institution. The remaining authors have disclosed that they do not have any potential conflicts of interest.

ABSTRACT

Objective: Previous trials suggest that vasopressin may improve outcomes in patients with vasodilatory shock. The aim of this study was to evaluate whether vasopressin could be superior to norepinephrine to improve outcomes in cancer patients with septic shock.

Design: single-center, randomized, double-blind clinical trial and meta-analysis of randomized trials

Setting: intensive care unit of a tertiary care hospital

Patients: 250 patients aged 18 years or older with cancer and septic shock

Interventions: Patients were assigned to either vasopressin or norepinephrine as first-line vasopressor therapy. An updated meta-analysis was also conducted including randomized trials published until October 2018

Measurements and Main Results: The primary outcome was all-cause mortality at 28 day after randomization. Pre-specified secondary outcomes included 90-days all-cause mortality rate; number of days alive and free of advanced organ support at day 28; and Sequential Organ Failure Assessment score 24 hours and 96 hours after randomization. We also measure the incidence of adverse effects in 28 days. A total of 250 patients were randomized. The primary outcome was observed in 71 patients (56.8%) in the vasopressin group and 66 patients (52.8%) in the norepinephrine group (P=0.52). There were no significant differences in 90-day mortality (90 patients [72.0%] and 94 patients [75.2%], respectively; P=0.56), number of days alive and free of advanced organ support, adverse events or Sequential Organ Failure Assessment score.

Conclusions: In cancer patients with septic shock, vasopressin as first-line vasopressor therapy was not superior to norepinephrine in reducing 28-day mortality rate.

Trial registration number: ClinicalTrials.gov NCT01718613

KEY WORDS

septic shock; neoplasm; vasopressin; norepinephrine, meta-analysis; morbidity; mortality; randomized controlled trial

INTRODUCTION

Septic shock is the most severe subset of sepsis , with mortality rates up to 50%.[1,2]

The number of patients with cancer admitted to the ICU is increasing, and cancer patients now account for up to 20% of ICU patients, and 10% of patients with sepsis.[3-5] Overall, immunocompromised patients account for about 40% of patients with septic shock.[4,6] Accordingly, research focusing on this specific subpopulation has been identified as a priority by a consensus of experts in septic shock management.[5,7] Immunocompromised patients present high rates of mortality in septic shock, and early aggressive treatment is important in these patients.[6,8] Cancer is frequently associated with immune response defects, and alteration in coagulation system and endothelial function.[9,10]

Vasopressor therapy is essential to maintain an adequate mean arterial pressure (MAP) in septic shock.[11] Norepinephrine is the most commonly used drug, but has significant adverse events, including potential cardiotoxicity, excessive vasoconstriction leading to bowel and peripheral ischemia, alteration of immune response and coagulation.[12-14]Notably, a substantial number of patients become refractory to norepinephrine, thus requiring increasing doses and hence increasing the risk of side effects.[15,16]

In recent years, vasopressin emerged as a potential alternative to norepinephrine as a vasopressor agent.[17-20] Previous meta-analyses suggested that vasopressin administration may reduce atrial fibrillation (AF), acute kidney injury (AKI), renal-replacement therapy (RRT) and duration of vasopressor therapy in vasoplegic shock patients.[21-24] Vasopressin has multiple mechanisms of action, including direct vasoconstrictor effects, stimulation of V1b receptors in the anterior pituitary gland that increase adrenocorticotropic hormone producing cortisol, in addition of effects on purinergic and oxytocin receptors, which block endothelial-mediated vasodilation.[25-27]

Vasopressin mechanisms of action in septic shock may include a decrease of norepinephrine and norepinephrine adverse effects on the macro- and microcirculation, altered immunity, and a potentially beneficial interaction with corticosteroids.[28] Notably, norepinephrine has immunomodulating effects, while vasopressin may have a greater effect on reducing inflammatory cytokines compared with norepinephrine.[14,29] In patients with cancer who develop septic shock, early use of vasopressin appears particularly attractive. Accordingly, we hypothesized that vasopressin was superior to norepinephrine to improve outcomes in cancer patients with septic shock, and we designed the Vasopressin versus Norepinephrine for the Management of Septic Shock in Cancer Patients (VANCS) II randomized controlled trial (RCT) to test this hypothesis. In addition, we also performed an updated systematic review focusing on vasopressin administration in cancer patients with septic shock.

MATERIALS AND METHODS

Trial Design

We performed a single center, double-blind, RCT. The original study protocol was approved by the Comitê de Ética em Pesquisa da Faculdade de Medicina da Universidade de São Paulo, Brazil. Patients with septic shock were randomized to receive either vasopressin or norepinephrine as first-line vasopressor therapy. Written informed consent was obtained from all participants or their legally authorized next of kin. The trial was registered before initiation (NCT01718613).

Participants

Eligible patients were adults (≥18 y) with cancer admitted to ICU with a documented or strong clinical suspicion of infection, associated with ≥2 criteria of the systemic

inflammatory response syndrome, and with vasopressor therapy.[11] The trial was performed at a quaternary hospital in Brazil. Exclusion criteria were pregnancy, Raynaud's phenomenon, systemic sclerosis, vasospastic diathesis, severe hyponatremia (Na^+ <130mmol/L), acute mesenteric ischemia, acute myocardial infarction, cardiogenic shock, ongoing use of vasopressor before randomization, enrollment in another study and refusal to consent.

Randomization and Masking

Randomization was performed with a computer-generated list in a 1:1 ratio, generated on-line by a web-based program that ensured allocation concealment. After informed consent, randomization was performed and the patient assigned to the intervention. The information about the intervention assignment of each patient was sent only to the ICU pharmacists. The patients, treating clinicians, and trial personnel including outcome assessors were unaware of trial-group assignment.

Intervention

Patients were randomized to receive either vasopressin or norepinephrine as first-line vasopressor therapy. Aside from vasopressor therapy, all other treatments were based on the Surviving Sepsis Campaign Guidelines.[11] Vasopressin (30 international units [IU]; BioLab Sanus Farmaceutica, Brazil) and norepinephrine (30 mg; Hypofarma, Brazil) were prepared in identical bags of 250 mL by an unblinded pharmacist, with final concentrations of 0.12 IU/mL vasopressin and 120 µg/mL norepinephrine, labeled with the patient number only. The vasopressor infusion was titrated to maintain MAP≥65 mmHg. Study-drug infusion started at 5 ml/h and increased by 2.5 mL/h every 10 min to achieve a maximum target rate of 30 ml/h, so that vasopressin doses ranged from

0.01 to 0.06 IU/min and norepinephrine doses from 10 to 60 µg/min. If the target MAP was not reached and further vasopressor support was required, open-label norepinephrine was started in addition to the study drug.

When the targeted MAP was exceeded, open-label norepinephrine was tapered first; only if open-label norepinephrine was weaned completely, tapering of the study drug was commenced.

Severe adverse events were defined as acute ST-segment elevation confirmed by a 12-lead electrocardiogram, serious or life-threatening cardiac arrhythmias, stroke, acute mesenteric ischemia, limb or skin ischemia, or hyponatremia (Na^+ <130mmol/L).

Outcomes

The primary outcome was 28 days all-cause mortality rate. The pre-specified secondary outcomes were: 90 days all-cause mortality ; number of days alive and free of vasopressor therapy, invasive mechanical ventilation and RRT at day 28; Sequential Organ Failure Assessment (SOFA) score 24 and 96 hours after randomization.[30] Outcomes definitions and adverse effects are described in the electronic supplemental material (ESM).

Systematic review and meta-analysis

A systematic review and meta-analysis of RCTs comparing vasopressin vs any comparator in septic shock patients with cancer was conducted in keeping with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Details on meta-analysis methodology are provided in the Supplementary Appendix.

Statistical methods

The sample size was calculated for a superiority study and it was postulated that patients of the norepinephrine group would present an incidence of the primary outcome of 55% compared to 37% of patients of the vasopressin group. Considering a statistical power of 80% and a type 1 error (alpha) of 5%, approximately 250 patients would be required for participating in the study.[13] A two-sided test was used.

We compared baseline characteristics, follow-up measures and clinical outcomes on an intention-to-treat basis according to the randomized study-group assignment. Continuous variables were analyzed using t-test or Mann–Whitney U-test, and categorical variables were compared using Pearson's χ^2 test, Fisher's exact test or a likelihood ratio test. Continuous data are expressed as mean with standard deviation (SD) or median with interquartile range (IQR). The primary outcome is reported as relative risk with 95% confidence interval (CI). A two-sided P value < 0.05 was considered statistically significant. Details on statistical analysis for the meta-analysis are provided in the Supplementary Appendix.

The statistical analyses were performed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Between July 2014 and July 2016, a total of 250 patients were randomized (125 into the vasopressin group and 125 into the norepinephrine group). There were 4 protocol deviations in the vasopressin group and 2 in the norepinephrine group. All patients were analyzed for the primary outcome. There were no losses or exclusions after randomization (Figure 1).

Baseline characteristics

There were no significant differences regarding baseline characteristics (ESM - eTable 1) between patients assigned to receive vasopressin or norepinephrine. Patients enrolled in the study were characterized by a median SOFA score of 7 in both groups. Gastrointestinal tract was the most common site of malignancy and almost 25% of patients had received chemotherapy within the last 4 weeks before randomization. The main sites of infection were the lungs, abdomen and urinary tract. Approximately two thirds of patients of both groups had a positive culture. Gram negative microorganisms were the most common agents identified in our study. Aside from cardiovascular dysfunction, the most common organ failures at the time of randomization were respiratory failure, renal and neurological dysfunction (Table 1).

Study outcomes

All-cause mortality at 28 days was 56.8% in the vasopressin group and 52.8% in the norepinephrine group (P=0.52) (Table 2 and Figure 2).

All-cause mortality rate at 90 days was also similar between groups. There was no significant difference between groups in SOFA score within the first 24 and 96 hours after randomization (Table 3). We did not observe significant difference in the number of days alive and free of vasopressor therapy, invasive mechanical ventilation and RRT. ICU readmission rate, length of ICU stay, and length of hospital stay were also similar between groups. No difference was observed between groups regarding the incidence of AKI and requirement of RRT (Table 2).

Vasopressor therapy and hemodynamic variables.

The duration of the vasopressor therapy was similar between groups; nevertheless more patients in the vasopressin group had persistent hypotension requiring rescue open-label norepinephrine (Table 2). No significant difference was observed regarding MAP, heart rate and central venous oxygen saturation between groups (ESM– eTable2 and eFigures 1-3). A similar urinary output during the period of intervention was observed (ESM – eTable3). Also, there were no significant differences between groups in perfusion markers such as arterial lactate, pH and base excess (ESM – eTable4).

The daily dose of norepinephrine and vasopressin administered from randomization to day 7 is presented in ESM (eTable 4 and eFigures 4-5).

Adverse Events

A total of 59 patients (47.2%) of the vasopressin group and 58 patients (46.4%) of the group norepinephrine presented ≥1 adverse event (P=0.420). Cardiac arrhythmia was the most common adverse event in both groups. There were no significant differences between groups regarding the incidence of limb or skin ischemia, stroke, myocardial infarction, ventricular and supraventricular arrhythmia, and mesenteric ischemia. No significant difference was observed in the incidence of hyponatremia between groups (Table 2).

Post hoc analyses

Post hoc subgroup analysis of rates for the main outcome of all-cause mortality at 28 days, no difference was observed between vasopressin group and norepinephrine group according to age, gender, metastatic disease, corticosteroid use, site of infection, AKI at the time of randomization and mechanical ventilation at the time of randomization (Figure 3). Since patients in the norepinephrine group had a higher baseline incidence of

multidrug resistant (MDR) infections we performed a post-hoc multiple logistic regression analysis adjusted for MDR which showed no difference in 28-days mortality (eTable 5). Association between lactate levels and outcomes is reported in the Supplementary Appendix (eTable 6 and eFigure 6).

Meta-analysis

Our search identified seven RCTs comparing vasopressin versus any comparator in septic shock patients[9,10,31-35] in addition to the present VANCS II trial. Data on cancer patients were available only for two RCTs. Trials characteristics are presented in the ESM (eTable 7 and eFigures 7-8).

Vasopressin was superior to control in reducing the need for RRT (14/150 [9.3%] versus 26/147 [17.7%] ; RR 0.46, 95% CI 0.23–0.93; p=0.03; p for heterogeneity = 0.39; I^2 = 0%; two included trials; eFigure 9).

There were no differences between vasopressin and comparator in any of the other outcomes (Details in ESM).

DISCUSSION

The main finding of this RCT is that among cancer patients with septic shock, vasopressin was not superior to norepinephrine in reducing 28-day mortality or improving other major outcomes. In addition, adverse effects rate, including mesenteric and digital ischemia, was not different between groups.

After including the results of this RCT in an meta-analysis, we confirmed that in septic shock patients with cancer, vasopressin decreases significantly the need for RRT, with no effect on other major outcomes.

Reducing the use of catecholamines is desirable in septic shock patients. High doses catecholamine may produce excessive chronotropic effect leading to tachyarrhythmias, impaired diastolic function, myocardial ischemia, immunosuppression, pulmonary edema, hypercoagulability and gut ischemia, and consequently might increase morbidity and mortality.[4,7,14]

Adding vasopressin to norepinephrine is an effective way of reducing catecholamines.[20] Few large RCTs were performed aiming to compare vasopressin with norepinephrine in patients with septic shock[17,18]Russell et al, in the Vasopressin and Septic Shock Trial (VASST), studied 778 patients with septic shock who received low-dose vasopressin (0.01-0.03 IU per minute) or norepinephrine (5-15 μg per minute) in addition to open-label vasopressors.[17] Although no difference was observed regarding 28-day mortality, patients with less severe septic shock presented a lower 28-day mortality rate in the vasopressin group. In a post-hoc analysis of the VASST trial, vasopressin reduced progression to AKI and mortality in patients with septic shock at risk of kidney injury.[36] In a more recent RCT, Gordon et al randomized 409 patients with septic shock to receive vasopressin or norepinephrine. Vasopressin was associated with a reduced use of RRT, without affecting mortality rates.[18] The Vasopressin vs Norepinephrine as Initial Therapy in Septic Shock (VANISH) trial was the first published RCT to compare head to head norepinephrine with vasopressin (titrated up to 0.06 IU/min) in septic shock.

Our findings support the data from VANISH study, showing that in a head to head comparison, the use of vasopressin (dose up to 0.06 IU/min) is not superior to norepinephrine alone in reducing septic shock mortality. In addition, in cancer patients with septic shock, vasopressin did not exert renal protective effect. Our data showed that more patients of the vasopressin group needed open-label norepinephrine. This

could be explained because there may be a subset of patients who have vasopressin resistance and also because some patients with septic shock may present more benefit from a multimodal therapy, with different action vasopressors.[37]

Previous meta-analyses showed benefits of vasopressin in comparison with norepinephrine in reducing AF and AKI in vasodilatory shock.[21-23,37] These published systematic reviews included both septic shock and vasoplegic shock after cardiac surgery.[21-23,38]

On the contrary, vasopressin seems to be superior to norepinephrine in vasodilatory shock after cardiac surgery,[19,23] mainly exerting benefits in reducing the occurrence of AKI, AF, requirement for RRT, decreasing length of hospital stay and facilitating the weaning of vasoactive drugs. In the largest trial performed in the setting of cardiac surgery, the Vasopressin versus Norepinephrine in Patients with Vasoplegic Shock after Cardiac Surgery (VANCS), 330 patients with post-operative vasodilatory shock were randomized to receive vasopressin (up to 0.06 IU/min) or norepinephrine (up to 60 µg/min) as first-line vasopressor therapy.[19] Patients randomized to vasopressin had a lower incidence of major complications, driven by a reduction in AKI incidence. Furthermore, length of ICU and hospital stay was significantly lower in the vasopressin group. The protocol for vasopressor administration was similar to that used in the present trial. However, the population enrolled in the VANCS trial was different, as also reflected by the lower 30-day mortality (23% versus 55%). In addition, we hypothesize that in the pathophysiology of cardiac-surgery associated vasoplegic shock, there might be a more significant reduction in vasopressin levels when compared to septic shock. However, it should be noted that data on vasopressin use in cardiac surgery derive from single-centers RCTs only, which carry a higher risk of bias when compared with multicenter RCTs.[39]

The renal protective effect of vasopressin is not clearly established. There is experimental evidence showing a preferential binding of norepinephrine to the α-1 receptors of renal afferent arterioles, while vasopressin binds preferentially to AVPR1a receptors on glomerular efferent arterioles, thus increasing glomerular perfusion pressure and filtration.[40] Renal protection related to reduced activation of the renin-aldosterone-angiotensin system is one of the hypothesized benefits of vasopressin in distributive shock; creatinine clearance has been shown to improve when vasopressin was started early after the onset of distributive shock.[32]

However, Post et al demonstrated in an ovine model of fecal peritonitis that norepinephrine and vasopressin may have different effects on renal autoregulation.[41] Our study is limited by its single-center design, but this may also increase the intrinsic value of the study reducing heterogeneity. Furthermore, we did not measure plasma vasopressin levels, as we did in the VANCS trial.[19] Maybe we have underestimated the sample size based in the hypothesis that vasopressin would reduce mortality when compared with norepinephrine. However, the overall 28-days mortality observed in the trial was 55%, as hypothesized during sample size calculation, with comparable mortality rates in the two groups. The absence of even a hint of survival benefit from vasopressin administration, supported by the results of the meta-analysis, suggest that it is unlikely that a larger sample size would have yielded different results. Interestingly, observed mortality was higher than predicted by SOFA score, suggesting that SOFA may be inaccurate in a subpopulation of patients with malignancy. Patients randomized to norepinephrine presented a high baseline incidence of MDR bacteria, that could have contributed to worse outcomes in these patients. However, in an adjusted model, the results were similar. The exclusion of patients with hyponatremia might limit the generalizability of the results. However, only 15 patients were excluded due to this

reason. Finally, patients in the vasopressin group required more open-label norepinephrine administration. This might be related to the study design, with use of vasopressin different from that recommended by current guidelines, and to the relatively long half-life of the drug, that may hinder adequate dose titration. However, previous trials showed that vasopressin can be used successfully as first line vasopressor therapy (also in double-blind trial) and the dose titrated to blood pressure targets.[18,42]

Results of our meta-analysis are limited by the low number of data on cancer patients available from published trials.

Considering that septic shock has a multifactorial pathophysiology and different clinical presentations, a single intervention such as therapy with only one vasopressor may not influence mortality. There is the possibility that the best therapy to improve results in septic shock would be the combination of multiple drugs with a different mechanism of action simultaneously in lower doses than usual, such as low doses of norepinephrine, low doses of vasopressin, angiotensin, steroids and, possibly, vitamin C and thiamine supplementation [43-45] Once the vasopressor sensitivities are assessed, the vasopressors are deescalated accordingly.[46] Further trials are needed with low doses of multiple vasopressors such as norepinephrine, vasopressin and angiotensin II in septic shock patients, addressing multiple defects in the pathophysiology of shock, and simultaneously avoiding adverse effects of high doses of the drugs. In a near future, the choice of vasopressors for septic shock treatment may be guided by predictive biomarkers, such as copeptin or vasopressinase, (leucyl/cystinyl aminopeptidase).

CONCLUSIONS

In conclusion, in cancer patients with septic shock, vasopressin did not reduce 28-day mortality.

ACKNOWLEDGEMENT

None

CONFLICT OF INTERESTS

Anthony C. Gordon is funded by a National Institute of Health Research (NIHR) Research Professorship award (RP-2015-06-018) and the NIHR Comprehensive Biomedical Research Centre based at Imperial College Healthcare NHS Trust and Imperial College London. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Anthony C. Gordon reports that outside of this work he has received speaker fees from Orion Corporation, Orion Pharma and Amomed Pharma. He has consulted for Ferring Pharmaceuticals, Tenax Therapeutics, Baxter Healthcare, Bristol-Myers Squibb and GSK, and received grant support from Orion Corporation Orion Pharma, Tenax Therapeutics and HCA International with funds paid to his institution.

FUNDING

The study was sponsored by University of São Paulo and supported by departmental funds only.

REFERENCES

1. Singer M, Deutschman CS, Seymour CW, et al: The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016; 315:801-810.
2. Machado FR, Cavalcanti AB, Bozza FA, et al: The epidemiology of sepsis in Brazilian intensive care units (the Sepsis PREvalence Assessment Database, SPREAD): an observational study. *Lancet Infect Dis* 2017; 17:1180-1189.
3. Taccone FS, Artigas AA, Sprung CL, et al: Characteristics and outcomes of cancer patients in European ICUs. *Crit Care* 2009; 13:R15.
4. Soares M, Caruso P, Silva E, et al: Characteristics and outcomes of patients with cancer requiring admission to intensive care units: a prospective multicenter study. *Crit Care Med* 2010; 38:9-15.
5. Sakr Y, Jaschinski U, Wittebole X, et al: Sepsis in Intensive Care Unit Patients: Worldwide Data From the Intensive Care over Nations Audit. *Open Forum Infect Dis* 2018; 5:ofy313.
6. Jamme M, Daviaud F, Charpentier J, et al: Time Course of Septic Shock in Immunocompromised and Nonimmunocompromised Patients. *Crit Care Med* 2017; 45:2031-2039.
7. Azoulay E, Schellongowski P, Darmon M, et al: The Intensive Care Medicine research agenda on critically ill oncology and hematology patients. *Intensive Care Med* 2017; 43:1366-1382.
8. Bergamin FS, Almeida JP, Landoni G, et al: Liberal Versus Restrictive Transfusion Strategy in Critically Ill Oncologic Patients: The Transfusion Requirements in Critically Ill Oncologic Patients Randomized Controlled Trial. *Crit Care Med* 2017; 45:766-773.
9. Young A, Chapman O, Connor C, et al: Thrombosis and cancer. *Nat Rev Clin Oncol* 2012; 9:437-449.
10. Schnell D, Besset S, Lengline E, et al: Impact of a recent chemotherapy on the duration and intensity of the norepinephrine support during septic shock. *Shock* 2013; 39:138-143.
11. Dellinger RP, Levy MM, Rhodes A, et al: Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013; 41:580-637.
12. Dunser MW, Hasibeder WR: Sympathetic overstimulation during critical illness: adverse effects of adrenergic stress. *J Intensive Care Med* 2009; 24:293-316.
13. Andreis DT, Singer M: Catecholamines for inflammatory shock: a Jekyll-and-Hyde conundrum. *Intensive Care Med* 2016; 42:1387-1397.
14. Stolk RF, van der Poll T, Angus DC, et al: Potentially Inadvertent Immunomodulation: Norepinephrine Use in Sepsis. *Am J Respir Crit Care Med* 2016; 194:550-558.
15. De Backer D, Biston P, Devriendt J, et al: Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med* 2010; 362:779-789.
16. Jentzer JC, Vallabhajosyula S, Khanna AK, et al: Management of Refractory Vasodilatory Shock. *Chest* 2018; 154:416-426.
17. Russell JA, Walley KR, Singer J, et al: Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med* 2008; 358:877-887.
18. Gordon AC, Mason AJ, Thirunavukkarasu N, et al: Effect of Early Vasopressin vs Norepinephrine on Kidney Failure in Patients With Septic Shock: The VANISH Randomized Clinical Trial. *JAMA* 2016; 316:509-518.

19. Hajjar LA, Vincent JL, Barbosa Gomes Galas FR, et al: Vasopressin versus Norepinephrine in Patients with Vasoplegic Shock after Cardiac Surgery: The VANCS Randomized Controlled Trial. *Anesthesiology* 2017; 126:85-93.
20. Rhodes A, Evans LE, Alhazzani W, et al: Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Crit Care Med* 2017; 45:486-552.
21. Serpa Neto A, Nassar AP, Cardoso SO, et al: Vasopressin and terlipressin in adult vasodilatory shock: a systematic review and meta-analysis of nine randomized controlled trials. *Crit Care* 2012; 16:R154.
22. Belletti A, Musu M, Silvetti S, et al: Non-Adrenergic Vasopressors in Patients with or at Risk for Vasodilatory Shock. A Systematic Review and Meta-Analysis of Randomized Trials. *PLoS One* 2015; 10:e0142605.
23. McIntyre WF, Um KJ, Alhazzani W, et al: Association of Vasopressin Plus Catecholamine Vasopressors vs Catecholamines Alone With Atrial Fibrillation in Patients With Distributive Shock: A Systematic Review and Meta-analysis. *JAMA* 2018; 319:1889-1900.
24. Dunser MW, Bouvet O, Knotzer H, et al: Vasopressin in Cardiac Surgery: A Meta-analysis of Randomized Controlled Trials. *J Cardiothorac Vasc Anesth* 2018; 32:2225-2232
25. Russell JA: Bench-to-bedside review: Vasopressin in the management of septic shock. *Crit Care* 2011; 15:226.
26. Aguilera G, Rabadan-Diehl C: Vasopressinergic regulation of the hypothalamic-pituitary-adrenal axis: implications for stress adaptation. *Regul Pept* 2000; 96:23-29.
27. Tanoue A, Ito S, Honda K, et al: The vasopressin V1b receptor critically regulates hypothalamic-pituitary-adrenal axis activity under both stress and resting conditions. *J Clin Invest* 2004; 113:302-309.
28. Russell JA, Walley KR, Gordon AC, et al: Interaction of vasopressin infusion, corticosteroid treatment, and mortality of septic shock. *Crit Care Med* 2009; 37:811-818.
29. Russell JA, Fjell C, Hsu JL, et al: Vasopressin compared with norepinephrine augments the decline of plasma cytokine levels in septic shock. *Am J Respir Crit Care Med* 2013; 188:356-364.
30. Vincent JL, Moreno R, Takala J, et al: The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996; 22:707-710.
31. Malay MB, Ashton RC, Jr., Landry DW, et al: Low-dose vasopressin in the treatment of vasodilatory septic shock. *J Trauma* 1999; 47:699-703; discussion -5.
32. Lauzier F, Levy B, Lamarre P, et al. Vasopressin or norepinephrine in early hyperdynamic septic shock: a randomized clinical trial. *Intensive Care Med* 2006; 32:1782-1789.
33. Morelli A, Ertmer C, Rehberg S, et al: Continuous terlipressin versus vasopressin infusion in septic shock (TERLIVAP): a randomized, controlled pilot study. *Crit Care* 2009; 13:R130.
34. Barzegar E, Ahmadi A, Mousavi S, et al: The Therapeutic Role of Vasopressin on Improving Lactate Clearance During and After Vasogenic Shock: Microcirculation, Is It The Black Box? *Acta Med Iran* 2016; 54:15-23.

35. Barzegar E, Nouri M, Mousavi S, et al: Vasopressin in Septic Shock; Assessment of Sepsis Biomarkers: A Randomized, Controlled Trial. *Indian J Crit Care Med* 2017; 21:578-584.
36. Gordon AC, Russell JA, Walley KR, et al: The effects of vasopressin on acute kidney injury in septic shock. *Intensive Care Med* 2010; 36:83-91.
37. Sacha GL, Lam SW, Duggal A, et al: Predictors of response to fixed-dose vasopressin in adult patients with septic shock. *Ann. Intensive Care* 2018; 8:35.
38. Nedel WL, Rech TH, Ribeiro RA, et al: Renal Outcomes of Vasopressin and Its Analogs in Distributive Shock: A Systematic Review and Meta-Analysis of Randomized Trials. *Crit Care Med* 2019; 47:e44-e51.
39. Landoni G, Pieri M, Young PJ, et al: Why do multicenter randomized controlled trials not confirm the positive findings of single center randomized controlled trials in acute care? *Minerva Anestesiol* 2019; 85:194-200.
40. Edwards RM, Trizna W, Kinter LB: Renal microvascular effects of vasopressin and vasopressin antagonists. *Am J Physiol* 1989; 256:F274-F278.
41. Post EH, Su F, Righy Shinotsuka C, et al. Renal autoregulation in experimental septic shock and its response to vasopressin and norepinephrine administration. *J Appl Physiol* (1985). doi: 10.1152/japplphysiol.00783.2017.
42. Gordon AC, Mason AJ, Perkins GD, et al: The interaction of vasopressin and corticosteroids in septic shock: a pilot randomized controlled trial. *Crit Care Med* 2014; 42:1325-33.
43. Khanna A, English SW, Wang XS, et al: Angiotensin II for the Treatment of Vasodilatory Shock. *N Engl J Med* 2017; 377:419-430.
44. Annane D, Renault A, Brun-Buisson C, et al: Hydrocortisone plus Fludrocortisone for Adults with Septic Shock. *N Engl J Med* 2018; 378:809-818.
45. Marik PE, Khangoora V, Rivera R, et al: Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock: A Retrospective Before-After Study. *Chest* 2017; 151:1229-1238.
46. Chawla LS, Ostermann M, Forni L, et al: Broad spectrum vasopressors: a new approach to the initial management of septic shock? *Crit Care* 2019; 23:124.

FIGURE LEGENDS

Figure 1 – Study flow-chart

Figure 2 – Kaplan-Meier probability for 28 days mortality using the log-rank test

Figure 3 – Subgroup analyses.

AKI = acute kidney injury; CI = confidence interval; MV = mechanical ventilation; OR = odds ratio

Figure 1

Click here to access/download;Figure;2. VANCS II_Figure 1.tif

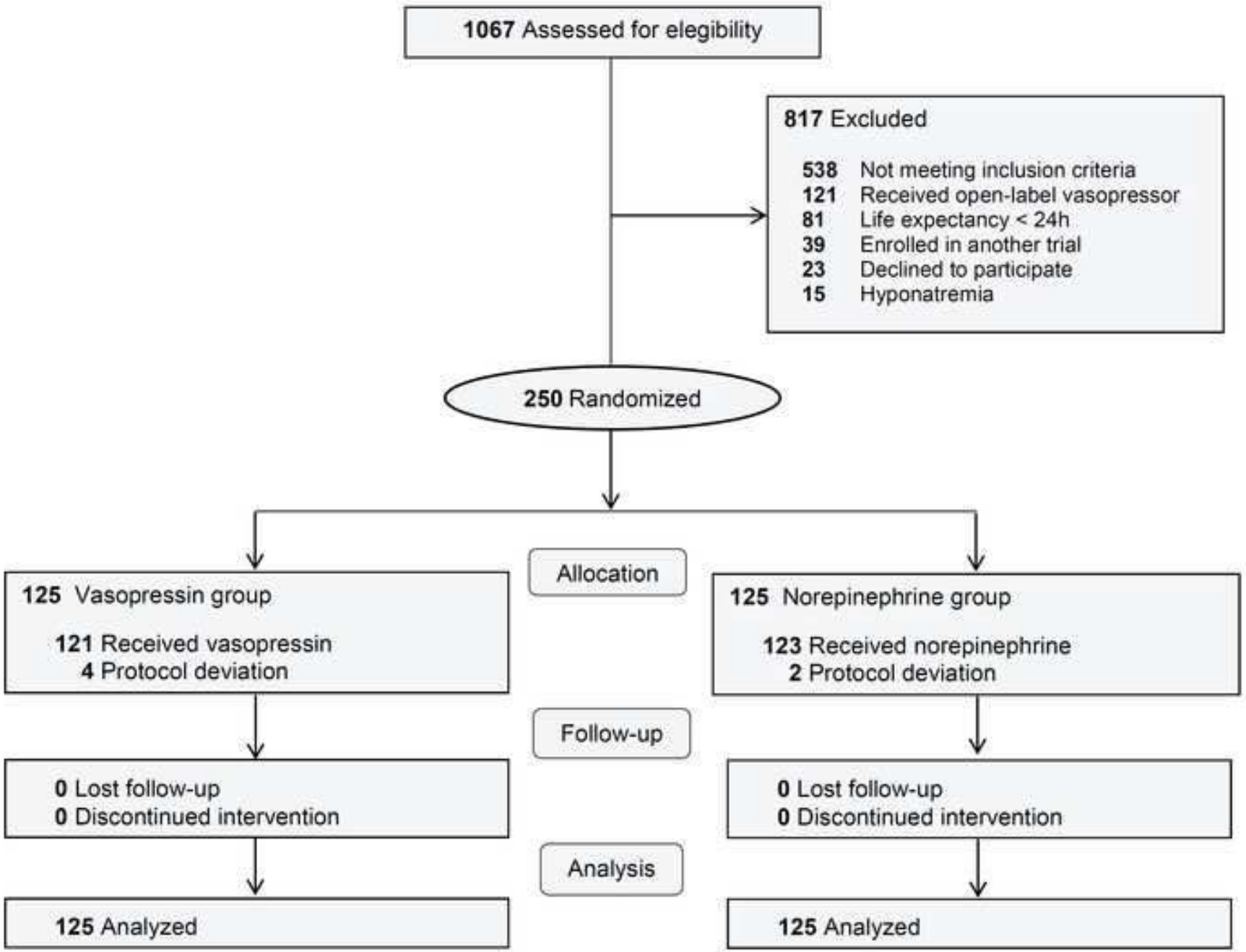

Figure 2

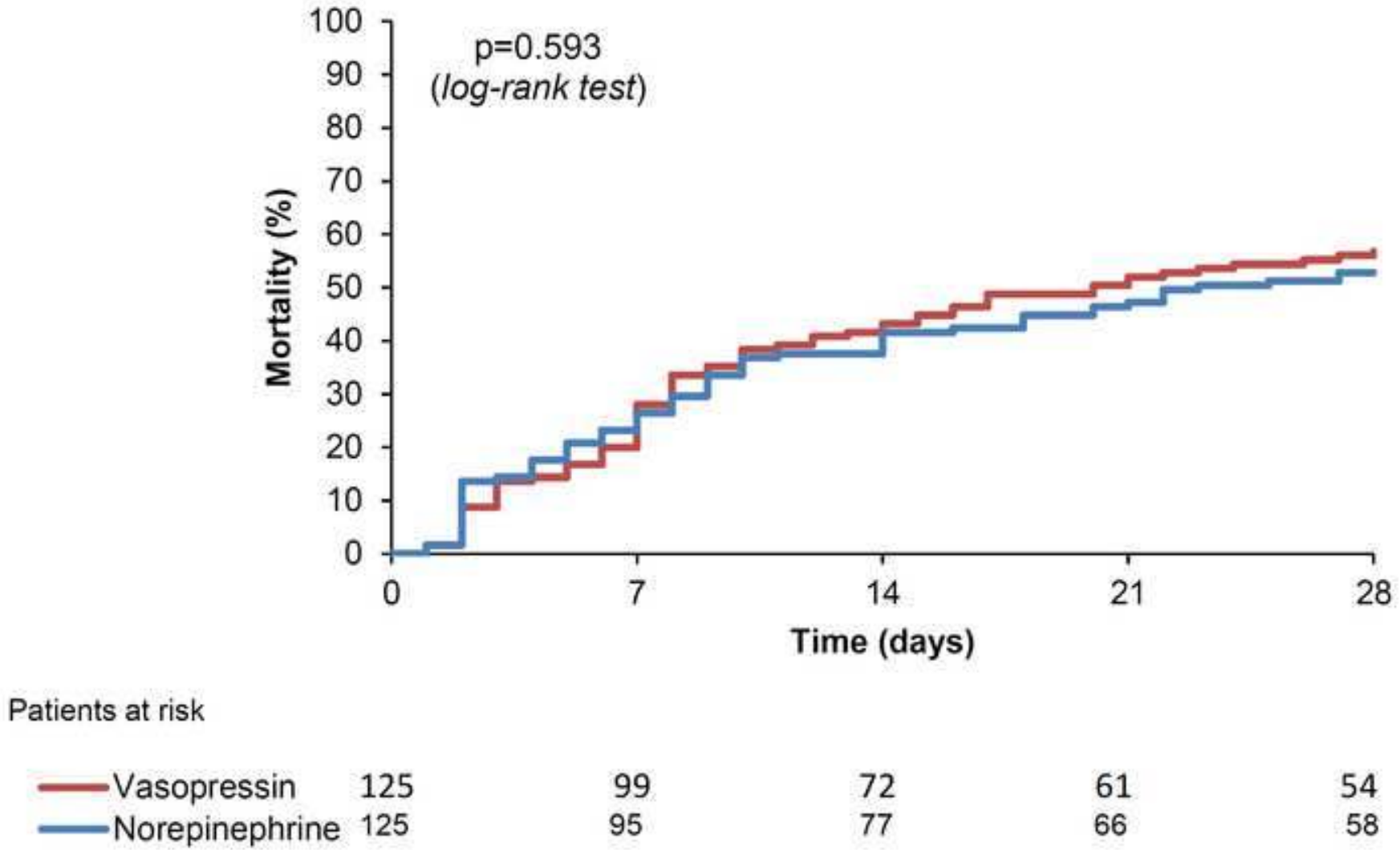

Figure 3

28-day mortality	Vasopressin	Norepinephrine	OR (95%CI)	P[a]
Age, *n* (%)				
≤60 years	22/45 (48.9%)	29/53 (54.7%)	1.26 (0.57 - 2.80)	0.565
>60 years	49/80 (61.3%)	37/72 (51.4%)	0.67 (0.35 - 1.27)	0.221
Gender, *n* (%)				
Male	31/57 (54.4%)	30/56 (53.6%)	0.97 (0.46 - 2.03)	0.931
Female	40/68 (58.8%)	36/69 (52.2%)	0.76 (0.39 - 1.5)	0.434
Metastasis, *n* (%)				
No	17/32 (53.1%)	15/34 (44.1%)	0.69 (0.26 - 1.84)	0.465
Yes	52/89 (58.4%)	48/86 (55.8%)	0.89 (0.49 – 1.63)	0.765
Infection site, *n* (%)				
Pulmonary	46/71 (64.8%)	35/67 (52.2%)	0.59 (0.30 - 1.18)	0.136
Abdominal	12/24 (50.0%)	13/22 (59.1%)	1.44 (0.45 - 4.64)	0.537
Others	13/30 (43.3%)	18/36 (50.0%)	1.31 (0.49 - 3.46)	0.589
AKI at admission, *n* (%)				
No	36/70 (51.4%)	39/76 (51.3%)	1.00 (0.52 - 1.91)	0.989
Yes	31/51 (60.8%)	27/49 (55.1%)	0.79 (0.36 - 1.75)	0.565
MV at admission, *n* (%)				
No	51/96 (53.1%)	49/97 (50.5%)	0.90 (0.51 - 1.58)	0.717
Yes	20/29 (69.0%)	17/28 (60.7%)	0.70 (0.23 - 2.07)	0.515
Corticostheroids, *n* (%)				
No	19/40 (47.5%)	18/41 (43.9%)	0.86 (0.36 - 2.07)	0.745
Yes	52/85 (61.2%)	48/84 (57.1%)	0.85 (0.46 - 1.56)	0.594

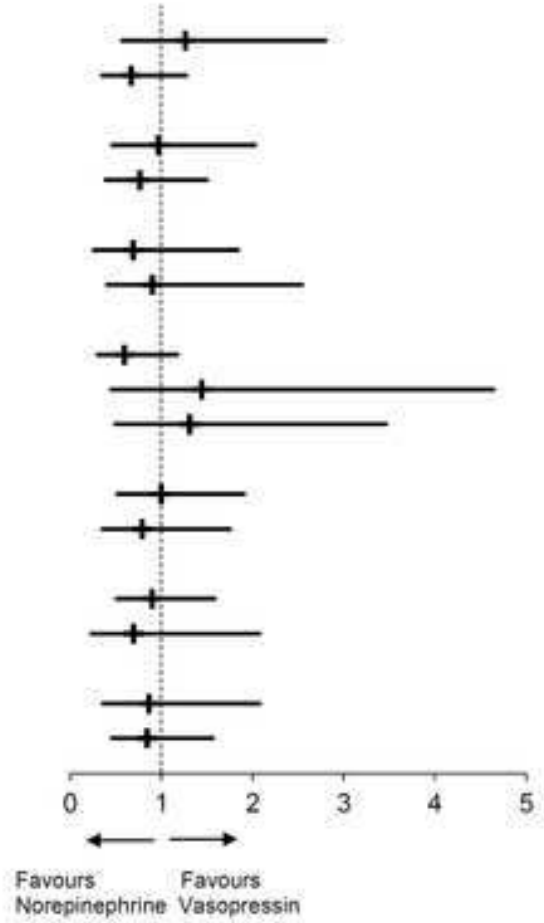

Table 1 – Characteristics of infection

Variable	Vasopressin n=125	Norepinephrine n=125	P
Infection site, n (%)			
Lung	71 (56.8%)	67 (53.6%)	
Abdomen	24 (19.2%)	22 (17.6%)	
Urinary tract	13 (10.4%)	12 (9.6%)	0.836*
Blood stream	4 (3.2%)	6 (4.8%)	
Others	13 (10.4%)	18 (14.4%)	
Cultures			
Positive cultures, n (%)	63 (51.2%)	77 (61.6%)	0.099*
Gram-positive	33 (26.4%)	37 (29.6%)	0.573*
Gram-negative	33 (26.4%)	50 (40%)	0.022*
Fungi	17 (13.6%)	17 (13.6%)	1.000*
Multi-drug resistant	10 (8%)	23 (18.4%)	0.015*
Organ dysfunction at ICU admission, n (%)			
Cardiovascular	125 (100%)	125 (100%)	-
Respiratory	64 (51.2%)	62 (49.6%)	0.800*
Renal	53 (42.4%)	52 (41.6%)	0.898*
Neurologic	27 (21.6%)	31 (24.8%)	0.549*
Hematologic	26 (20.8%)	32 (25.6%)	0.369*
Hepatic	10 (8%)	6 (4.8%)	0.301*

† Mann-Whitney test; * Pearson's chi square test; ** Likelihood Ratio Test..
Abbreviations: ICU = intensive care unit.

Table 2

Table 2 – Outcomes

Variable	Vasopressin n=125	Norepinephrine n=125	Absolut difference (95% CI)	P
Primary outcome				
28-day mortality. n (%)	71 (56.8%)	66 (52.8%)	4.0 (-8.2 to 16.1)	0.525*
Secondary outcomes				
90-day mortality. n (%)	90 (72.0%)	94 (75.2%)	-3.2 (-14.0 to 7.7)	0.566*
Days alive and free of mechanical ventilation	20 (6 - 28)	22 (7 - 28)		0.748†
Days alive and free of vasopressor agent	10 (1 - 23)	12 (1 - 24)		0.669†
Days alive and free of dialysis	20 (7 - 28)	21 (7 - 28)		0.819†
SOFA 24h	8 (5 - 11)	7 (5 - 10)		0.425†
SOFA 96h	7 (2 - 12)	7 (3 - 12)		0.825†
Other outcomes				
Norepinephrine use *open label*	67 (53.6%)	51 (40.8%)	12.8 (0.4 to 24.6)	0.043*
Days of norepinephrine *open label*	2 (2 – 5)	2 (1 – 3)		0.009†
Acute kidney injury	53 (42.4%)	52 (41.6%)	0.80 (-11.3 v 12.9)	0.898*
RRT	10 (8.0%)	17 (13.6%)	-5.60 (-13.6 to 2.25)	0.154*
Delirium	40 (32.0%)	40 (32.0%)	0 (-11.44 to 11.44)	1.000*
ICU readmission. n (%)	8 (6.4%)	11 (8.8%)	-2.40 (-9.41 to 4.48)	0.474*
ICU length of stay (days). median (IQR)	7 (4 - 12)	6 (4 - 12)		0.520†
Hospital length of stay (days). median (IQR)	11 (6 - 23)	12 (6 - 22)		0.835†
Adverse Events				
Arrhythmia. n (%)	34 (27.2%)	40 (32.0%)	-4.80 (-15.92 to 6.48)	0.406*
Hyponatremia. n (%)	31 (24.8%)	20 (16.0%)	8.80 (-1.23 to 18.66)	0.084*
Cerebral ischemia. n (%)	6 (4.8%)	1 (0.8%)	4.00 (-0.42 to 9.32)	0.120***
Acute myocardial infarction. n (%)	3 (2.4%)	7 (5.6%)	-3.2 (-8.93 to 2.06)	0.197*
Digital ischemia. n (%)	0 (0%)	2 (1.6%)	-1.60 (-5.65 to 1.60)	0.498***
Mesenteric ischemia. n (%)	0 (0%)	0 (0%)		-
No. of adverse events. n (%)				
0	66 (52.8%)	67 (53.6%)		0.420**
1	46 (36.8%)	46 (36.8%)		
2	11 (8.8%)	12 (9.6%)		
3	2 (1.6%)	0 (0%)		

† Mann-Whitney test; * Pearson's chi square test; ** Likelihood Ratio Test;*** Fisher's exact test.
Abbreviations: ICU = intensive care unit; RRT = renal replacement therapy; SOFA = sequential organ failure assessment.

Revised Supplementary Appendix (clean)

Revised Supplementary Appendix (tracked)