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Vasopressin in Conjunction With Norepinephrine in Septic Shock: A Retrospective Cohort Study From a Low Middle-Income Country

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Objectives: Guidelines recommend use of norepinephrine as the first-line treatment for fluid-refractory septic shock and if septic shock persists vasopressin may be initiated. Since there are limited data from low middle-income countries with high disease burden of sepsis, we aimed to compare the outcomes of using vasopressin adjunct to norepinephrine in comparison with norepinephrine alone.

Design: Retrospective cohort study.

Setting: Aga Khan University Hospital, Karachi, Pakistan.

Patients: Six-hundred fifty-three patients diagnosed with septic shock from January 2019 to December 2019, with 498 given norepinephrine only and 155 given norepinephrine-vasopressin combination.

Interventions: None.

Measurements and Main Results: Primary outcome was in-hospital mortality. Secondary outcomes were duration of vasopressor used, length of hospital stay, length of ICU stay, and days on ventilatory support. After adjustment by multivariable logistic regression, it was found that mortality was not significantly associated with the norepinephrine-vasopressin combination (adjusted odds ratio, 0.633 [95% CI, 0.370–1.081]). However, Sequential Organ Failure Assessment score at admission (1.100 [1.014–1.193]), lactate at admission (1.167 [1.109–1.227]), duration of vasopressor used (1.481 [1.316–1.666]), and level of care (3.025 [1.682–5.441]) were found to be independently associated with the adjunct usage of norepinephrine and vasopressin.

Conclusions: The use of norepinephrine-vasopressin combination has remained debatable in literature. Our study showed that although there was no difference in mortality between the two groups, admission Sequential Organ Failure Assessment scores and admission lactate levels were found to be significantly higher in the norepinephrine-vasopressin group. Hence, physicians from Pakistan used the norepinephrine-vasopressin combination in resistant septic shock patients who were sicker to begin with. Furthermore, duration of vasopressor therapy and ICU admission were also significantly higher in the combination group. Considering the recent hyperinflation of vasopressors costs and that most healthcare expenditure for patients in Pakistan is out-of-pocket, this can consequently lead to unwarranted financial burden for patients and their families.

Key Words: mortality; norepinephrine; sepsis; septic shock; shock; vasopressin

Sepsis, as per the Third International Consensus Definitions for Sepsis and Septic Shock, is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection (1). Septic shock, a subcategory of sepsis, is when there are fundamental metabolic, cellular, and circulatory irregularities present which are significant enough to considerably increase mortality. Millions of people are affected by sepsis and septic shock every year, causing the death of at least one in four individuals (2, 3). Severe septic shock and sepsis are still critical causes of mortality and morbidity in present ICUs (4), and despite significant improvement in critical care approach, they are still identified as the cause of death in 30–50% of hospitalizations (5). Although data from low middle-income countries (LMICs) have historically been sparse, outcomes of sepsis have found to be disproportionately affected by location, with Rudd et al recently estimating that 84.8% of sepsis related deaths in 2017 occurred in LMICs (6).

In the event of progression of sepsis to septic shock, where the patient is unable to maintain a mean arterial pressure (MAP) of 65 mm Hg or greater, despite fluid resuscitation, the use of vasopressors is recommended as per the International Guidelines for Management of Sepsis and Septic Shock (7). In case norepinephrine fails to raise the MAP adequately, vasopressin may be added to

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the regimen due to "relative vasopressin deficiency" experienced within the first 36 hours of onset of septic shock (8, 9). Concomitant vasopressin administration has been seen to improve vascular tone, MAP, urine output, and creatinine clearance. Additionally, vasopressin acts as a catecholamine sparing agent, by effectively reducing the dosage of norepinephrine required. This may prevent the occurrence of some of the unwanted effects associated with high-dosage of norepinephrine, including but not limited to oxidative stress, myocyte injury, and detrimental exacerbation of sepsis-associated immunoparalysis (10).

In spite of this, the clinically utility of vasopressin in improving outcomes is somewhat unclear, with conflicting data from prior literature. Two randomized control trials have demonstrated no significant improvement in mortality following concomitant norepinephrine and vasopressin administration as compared to norepinephrine alone (11, 12). Yet, another study demonstrated increase in mortality when using vasopressin in addition with norepinephrine that norepinephrine alone (54.4% vs 20.3%; $p < 0.001$) (13). Interestingly, within the Vasopressin in Septic Shock Trial (VASST) trial, it was found that vasopressin administration was beneficial for patients categorized with less severe septic shock and significantly reduced mortality when compared with only norepinephrine (26.5% vs 35.7%; $p = 0.05$) (11). Further to this, studies have also shown that although concomitant usage of vasopressin and norepinephrine may not have a mortality benefit, this regimen enables a target MAP of greater than 65 mm Hg to be reached more quickly (14).

Pakistan has a high disease burden of sepsis, with limited data and research done in this field. Furthermore, a nationwide registry of sepsis does not exist. The need for locally sourced data regarding sepsis outcomes, especially from the context of a resource constrained setting of an LMIC, is paramount in allowing physicians in such areas to make sound evidence-based decisions. Especially since the clinical utility of adjunct vasopressin therapy continues to remain controversial and at the discretion of the attending physician. Further to this, the potential benefit of adding vasopressin to the regimen is especially important to elucidate within the context of an LMIC, since the majority of healthcare financing is through out-of-pocket expenditure, and as such, adding unnecessary drugs without a clear rationale may lead to undue financial burden to the patient and their family. Hence, the present study aims to assess the difference in outcomes between patients receiving norepinephrine and vasopressin, compared with norepinephrine alone, within the setting of an LMIC.

MATERIALS AND METHODS

Study Design and Data Source

This is a retrospective cohort study in which we assessed adult patients (>18 yr) diagnosed with septic shock from January 2019 till December 2019. This study was conducted at the Aga Khan University Hospital, which is a Quaternary Care Referral Center with 740 beds located in Karachi city. The Institutional Review Board at Aga Khan University, Karachi, permitted this study to be conducted.

For the retrospective chart review, two reviewers (authors F.G., M.K.) independently reviewed patient medical records to determine their eligibility. **Figure 1** shows a flow diagram representing the patient selection process. Records of 1,220 patients who received vasopressors from January to December 2019 were screened in order to identify those patients who had fluid-refractory septic shock and were administered vasopressin and norepinephrine. The cases were defined by the *International Classification of Disease*, 9th Edition, Clinical Modification codes for sepsis (995.91), severe sepsis (995.92), or septic shock (785.52). This method provides a very specific cohort of sepsis; hence, it is a careful estimate of sepsis patients, as stated by modern literature (15).

A total of 567 studies were excluded by the following exclusion criteria: patients in whom vasopressors/inotropes were used for reasons other than septic shock; patients who received vasopressors other than norepinephrine and vasopressin, vasopressors used in operation theaters, pregnant mothers, burn injuries; patients who had a goal MAP of greater than or equal to 70 mm Hg; postcardiac surgery patients, transferred patients from other hospitals; and those patients who were discharged from the hospital on request or left against medical advice.

Outcomes

The main outcome we aimed to measure was in-hospital mortality. Secondary outcomes were duration of vasopressor used, length of hospital stay, length of ICU or special care unit (SCU) stay, duration of mechanical ventilation, and duration of ventilator free survival (**Table 1**). Medical ICUs are closed units, whereas SCUs are open units, both of which follow standardized care for sepsis management including for fluid therapy and antibiotic usage, as per sepsis guideline protocols. We also recorded baseline patient characteristics and hospitalization factors including Sequential Organ Failure Assessment (SOFA) scores and quick SOFA (qSOFA) scores (**Table 2**), as well as source of infection and etiology (**Table 3**).

Statistical Analysis

Data analysis was done using IBM SPSS Statistics for Windows, version 23 (IBM Corp., Armonk, NY) and Microsoft Excel 2016 (v16.0). We compared the patient characteristics and clinical outcomes of the group given norepinephrine only with norepinephrine and vasopressin. We performed this comparison using the chi-square test and Fisher exact test for categorical variables and Wilcoxon rank-sum test or Student *t* test for the continuous variables. Univariate and multivariable logistic regression were then performed. Variables with *p* value less than 0.25 on univariate analysis were included in the multivariable model. Any result with a *p* value of less than or equal to 0.05 was considered to be significant.

RESULTS

In the period between January 2019 and December 2019, there were 870 patients at the Aga Khan University Hospital who were diagnosed with septic shock and received vasopressors. After careful assessment of each file, 653 patients met the inclusion criteria and were studied in detail. Out of these 653 patients, the number of patients given norepinephrine only was 498 (76.3%), whereas

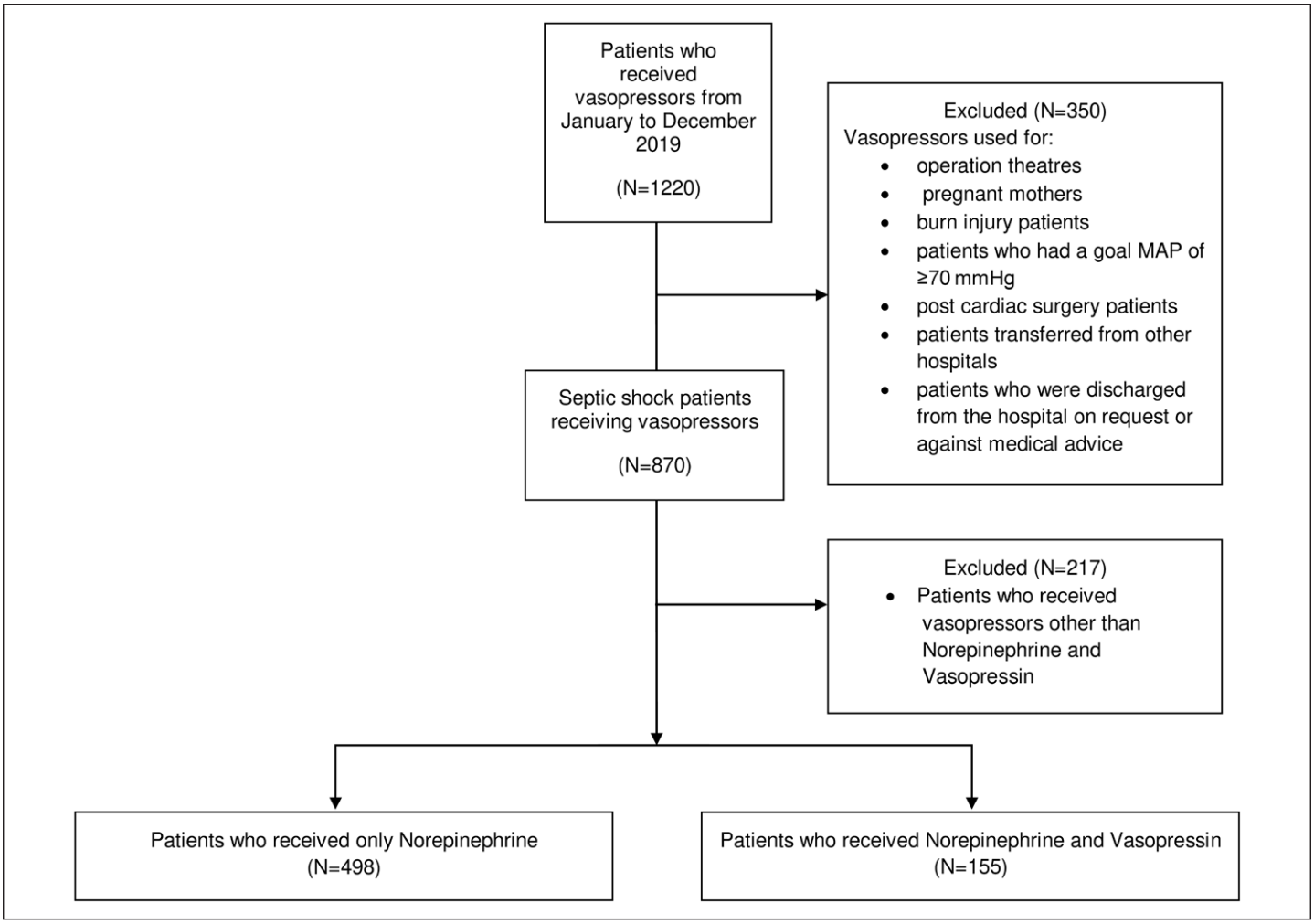

Figure 1. Patient selection flow diagram showing the screening process used to obtain records of only those patients diagnosed with septic shock who received norepinephrine or norepinephrine and vasopressin combination from January to December 2019. MAP = mean arterial pressure.

the number of patients given norepinephrine and vasopressin was 155 (23.7%).

The mean age of the patients was 59.7 ± 16.10, the total number of males was 376 (57.6%), whereas the total number of females was 277 (42.4%). The most common comorbid conditions were diabetes (49.0%), hypertension (45.2%), and ischemic heart disease (24.7%). Upon admission, patients who eventually received both norepinephrine and vasopressin had a significantly greater SOFA score ($p = 0.000$), qSOFA score ($p = 0.005$), and serum lactate ($p = 0.000$). Furthermore, the level of care between the groups also significantly varied, with patient requiring adjunct vasopressin more likely to be admitted to the ICU in comparison with patients requiring just norepinephrine. The overall demographics, patient characteristics, and hospitalization factors are presented in Table 2.

TABLE 1. Patient Outcomes

Outcomes	Overall ($n = 653$) *n* (%)/Mean ± SD	Norepinephrine Only ($n = 498$) *n* (%)/Mean ± SD	Norepinephrine and Vasopressin ($n = 155$) *n* (%)/Mean ± SD	*p*
Mortality, *n* (%)	312 (47.8)	226 (45.4)	86 (55.5)	**0.028**
Length of hospital stay (d), mean ± SD	8.0 ± 6.20	8.2 ± 6.21	7.4 ± 6.15	0.205
ICU/special care unit length of stay (d), mean ± SD	6.1 ± 4.59	6.2 ± 4.54	5.8 ± 4.76	0.441
Duration on ventilator (d), mean ± SD	5.0 ± 4.08	5.0 ± 3.93	4.8 ± 4.53	0.688
Duration off ventilator (d), mean ± SD	3.0 ± 3.98	3.2 ± 4.18	2.5 ± 3.21	0.071
Duration of vasopressor use (d), mean ± SD	2.4 ± 1.61	2.2 ± 1.44	3.2 ± 1.90	**0.000**

Boldface values indicate statistically significant (p value ≤0.05) upon analysis.

TABLE 2. Patients Characteristics and Hospitalization Factors

Variables	Overall (*n* = 653)	Norepinephrine Only (*n* = 498)	Norepinephrine and Vasopressin (*n* = 155)	*p*
Mean age (yr), mean ± SD	59.7 ± 16.10	60.9 ± 15.86	55.9 ± 16.33	**0.001**
Gender, *n* (%)				
Male	376 (57.6)	284 (57.0)	92 (59.4)	0.609
Female	277 (42.4)	214 (43.0)	63 (40.6)	
Comorbid conditions, *n* (%)				
Diabetes	320 (49.0)	247 (49.6)	73 (47.1)	0.586
Hypertension	295 (45.2)	224 (45.0)	71 (45.8)	0.857
Ischemic heart disease	161 (24.7)	125 (25.1)	36 (23.2)	0.636
Chronic kidney disease	153 (23.4)	112 (22.5)	41 (26.5)	0.309
Malignancy	69 (10.6)	51 (10.2)	18 (11.6)	0.628
Charlson Comorbidity Index, mean ± SD	3.9 ± 2.56	4.0 ± 2.56	3.7 ± 2.56	0.246
Hospitalization factors, mean ± SD				
SOFA score at admission	5.3 ± 3.35	5.0 ± 3.21	6.3 ± 3.60	**0.000**
Quick SOFA score at admission	1.5 ± 1.03	1.5 ± 1.04	1.7 ± 0.97	**0.005**
Lactate at admission (mmol/L)	4.3 ± 3.80	3.7 ± 3.28	6.1 ± 4.69	**0.000**
Serum creatinine at admission (mg/dL)	3.0 ± 2.86	3.0 ± 3.07	3.0 ± 2.08	0.775
Hemoglobin at admission (g/dL)	10.7 ± 2.52	10.6 ± 2.41	10.9 ± 2.85	0.350
Level of care, *n* (%)				
Patients in ICU care	497 (76.1)	359 (72.1)	138 (89.0)	**0.000**
Patient in special care unit care	156 (23.9)	139 (27.9)	17 (11.0)	

SOFA = Sequential Organ Failure Assessment.
Boldface values indicate statistically significant (p value ≤0.05) upon analysis.

The most common source of infection was unspecified (43.6%) followed by respiratory tract (24.7%) and urinary (14.5%). The majority of patients (58.7%) in septic shock did not have any positive site-specific or blood cultures. Additionally, there was a significant difference in the culture reports between the two groups (p = 0.040). Patients who received norepinephrine alone had a significantly higher proportion of culture negative reports (60.6% vs 52.8%), whereas patients who received both vasopressors had a significantly greater proportion of polymicrobial culture reports (13.8% vs 8.6%). Detailed microbiological characteristics are presented in Table 3.

The overall mortality for the patients was 312 (47.8%), with significantly increased mortality in the group given both norepinephrine and vasopressin (55.5% vs 45.4%) (p = 0.028). Additionally, patients given both norepinephrine and vasopressin were on vasopressor therapy for a longer period of time (3.2 vs 2.2 d) (p = 0.000). Hospital outcomes of both groups are reported in Table 1. After performing univariate and multivariable logistic regression, while adjusting for potential confounders, including age, gender, Charlson Comorbidity Index, and other admission variables, it revealed that mortality was not significantly associated to the norepinephrine-vasopressin group (adjusted odds ratio [aOR], 0.633 [95% CI, 0.370–1.081]). However, SOFA score at admission (aOR, 1.100 [95% CI, 1.014–1.193]), lactate at admission (1.167 [1.109–1.227]), duration of vasopressor use (1.481 [1.316–1.666]), and level of care (3.025 [1.682–5.441]) were found to be independently associated with the adjunct usage of norepinephrine and vasopressin. These findings are presented in **Table 4**.

DISCUSSION

There is a lack of high-quality data on septic shock and vasopressors from LMICs, and to our knowledge, this is the first study in a resource-constrained setting of an LMIC that has compared the use of vasopressin in adjunct to norepinephrine versus the use of norepinephrine alone for the treatment of septic shock. Our study demonstrated that initially it appeared patients receiving both norepinephrine and vasopressin had statistically significant higher rates of mortality than those who received norepinephrine alone. However, once confounding factors were adjusted for, there was no longer a significant difference between mortality in the two groups, indicating that the mortality in the dual therapy group was likely due to the higher admission lactate and admission SOFA scores, rather than the vasopressor combination itself. This result is largely in line with results from the VASST,

TABLE 3. Source of Infection and Etiology

Characteristics	Overall (*n* = 653), *n* (%)	Norepinephrine Only (*n* = 498), *n* (%)	Norepinephrine and Vasopressin (*n* = 155), *n* (%)	*p*
Source of infection				
Respiratory	161 (24.7)	117 (23.5)	44 (28.4)	0.702
Urinary	95 (14.5)	78 (15.7)	17 (11.0)	
Central Line Associated Blood Stream Infection	14 (2.1)	11 (2.2)	3 (1.9)	
Cardiac	7 (1.1)	5 (1.0)	2 (1.3)	
CNS	9 (1.4)	7 (1.4)	2 (1.3)	
Skin/soft tissue	40 (6.1)	32 (6.4)	8 (5.2)	
Gastrointestinal	42 (6.4)	29 (5.8)	13 (8.4)	
Unspecified	285 (43.6)	219 (44.0)	66 (42.6)	
Culture Etiology	**Overall (*n* = 496)**	**Norepinephrine Only (*n* = 373)**	**Norepinephrine and Vasopressin (*n* = 123)**	***p***
Culture results				
Culture negative	291 (58.7)	226 (60.6)	65 (52.8)	**0.040**
Polymicrobial	49 (9.9)	32 (8.6)	17 (13.8)	
Gram positive	34 (6.9)	22 (5.9)	12 (9.8)	
Gram negative	97 (19.6)	78 (20.9)	19 (15.4)	
Fungi	25 (5.0)	15 (4.0)	10 (8.1)	

Boldface value indicates statistically significant (p value ≤0.05) upon analysis.

a multicenter, double-blind, randomized control trial published in 2008, which reported that the administration of vasopressin at 0.03 U/min 12 hours after the initiation of norepinephrine therapy did not significantly alter the 28-day and 90-day mortality rates, when compared with norepinephrine alone (11). The results of the vasopressin versus norepinephrine as Initial Therapy in Septic Shock (VANISH) trial conducted in 2016 also stated there was no difference in mortality between patients given norepinephrine versus vasopressin (12). In fact, in a recent meta-analysis which assessed mortality rates in 17 clinical trials which were comparing vasopressin in combination with catecholamine vasopressors with catecholamines alone, it was concluded that although mortality appeared to be lower in the dual therapy group, upon sensitivity analysis it was no longer significant (16). Yet interestingly, in the VASST trial, it was noted that vasopressin administration significantly improved 28-day and 90-day survival rates in the subset of patients with less severe septic shock (patients who were receiving norepinephrine at an infusion rate of < 15 μg/min) (11). This finding is somewhat contradictory to current guidelines and practices which suggest that adjunct use of vasopressin, in addition to norepinephrine, is only recommended when the patient is unable to maintain a MAP above 65 mm Hg with the use of norepinephrine alone, implying that vasopressin is essentially reserved as a second-line drug to be used in patients with severe septic shock (7). The results of our study reflect the practice of current guidelines, as patients receiving both drugs were clearly sicker from the onset, as they had significantly higher admission lactate levels and higher admission SOFA scores, which are well-established prognostic indicators in septic shock management.

To date, there have been few studies that have shown negative clinical outcomes associated with the use of vasopressin along with norepinephrine. In 2007, Micek et al (13) demonstrated increased 28-day mortality with the adjunct use of vasopressin with norepinephrine, in conditions of refractory septic shock (54.4% in vasopressin group vs. 20.3% in norepinephrine group, $p < 0.001$), concluding that the negative effects caused by the mechanism of action of vasopressin led to the increased mortality. In a propensity matched retrospective cohort study, Russell et al (17) found that in the same hospital where the VASST trial was conducted, a similar condition was found in the pre-VASST trial cohort study conducted at St. Paul's Hospital (SPH1) (28-d mortality: 60.8% in vasopressin group vs 46.2% in norepinephrine group; $p = 0.009$). However, in the post-VASST trial cohort study conducted at St. Paul's Hospital (SPH2), the in-hospital mortality between the two groups became statistically insignificant (28-d mortality: 31.2% in vasopressin group vs 26.9% in norepinephrine group; $p = 0.518$). A key factor to be noted is that the day 1 dose of vasopressin administered by physicians between the two periods was significantly different (0.036 U/min (SPH1) vs 0.032 U/min (SPH2); $p = 0.001$). The decrease in dosage associated with post-VASST period

TABLE 4. Univariate and Multivariable Logistic Regression

	Norepinephrine and Vasopressin			
Variables	**Crude OR (95% CI)**	***p***	**Adjusted OR (95% CI)[a]**	***p***
Age	0.981 (0.971–0.992)	**0.001**	0.985 (0.971–0.999)	0.043
Gender				
Male	1.100 (0.763–1.587)	0.609		
Female	Reference			
Diabetes	0.905 (0.631–1.298)	0.586		
Hypertension	1.034 (0.720–1.485)	0.857		
Ischemic heart disease	0.903 (0.591–1.380)	0.636		
Chronic kidney disease	1.240 (0.819–1.876)	0.310		
Malignancy	1.152 (0.651–2.037)	0.628		
Charlson Comorbidity Index	0.958 (0.892–1.030)	0.246	0.977 (0.890–1.072)	0.618
Hemoglobin at admission (g/dL)	1.038 (0.967–1.114)	0.307		
Serum creatinine at admission (mg/dL)	0.991 (0.929–1.056)	0.774		
SOFA score at admission	1.125 (1.066–1.188)	**< 0.001**	1.100 (1.014–1.193)	**0.022**
Quick SOFA score at admission	1.278 (1.070–1.525)	**0.007**	1.134 (0.868–1.483)	0.357
Lactate at admission (mmol/L)	1.159 (1.108–1.212)	**< 0.001**	1.167 (1.109–1.227)	**< 0.001**
Duration on ventilator (s)	0.991 (0.947–1.036)	0.688		
Duration of vasopressor use (s)	1.403 (1.259–1.564)	**< 0.001**	1.481 (1.316–1.666)	**< 0.001**
Level of care				
Patients in ICU care	3.143 (1.831–5.396)	**< 0.001**	3.025 (1.682–5.441)	**< 0.001**
Patients in Special Care Unit care	Reference			
Mortality	1.500 (1.044–2.156)	**0.028**	0.633 (0.370–1.081)	0.094

OR = odds ratio, SOFA = Sequential Organ Failure Assessment.

[a]Adjusted for variables with $p < 0.25$ on univariate analysis.

Boldface values indicate statistically significant (p value ≤0.05) upon analysis.

appears to have reduced the mortality in the vasopressin group. In conjunction with this, literature has reported that higher doses of vasopressin are associated with several adverse outcomes, including ischemic complications of the heart, gut, and renal systems (18).

The serum lactate level is a key biomarker to predict mortality and prognostic outcome in patients with septic shock. Current guidelines suggest initiating and monitoring resuscitation therapy in such a manner so as to normalize raised lactate levels, with elevated lactate levels being an indicator of tissue hypoperfusion (7). Lower lactate levels with greater lactate clearance have consistently been associated with improved outcomes and lower mortality (19–21). In fact, a recent study by Liu et al (22) found lactate to be an independent predictor for mortality in septic patients. This has been substantiated by our study's results, which demonstrated that higher mortality was not due to the vasopressor combination itself but rather due to the higher admission lactate level which was independently associated to the norepinephrine-vasopressin group. This once again demonstrates that physicians continue to reserve the use of dual therapy in patients who are significantly sicker. However, a post hoc analysis of the VASST trial found that vasopressin administration had a significant mortality benefit for lower serum lactate concentration (< 2 mmol/L) rather than higher lactate levels above 2 mmol/L (23). These findings were corroborated by Sacha et al (24) with a reduced lactate levels independently associated with a greater chance of an adequate hemodynamic response to vasopressin and norepinephrine therapy. To potentially explain this phenomenon, Severson et al (25) showed that administration of vasopressin was associated with rising serum lactate levels during therapy. As such adjunct vasopressin therapy may have the potential to elevate the serum lactate levels further despite our findings suggesting that vasopressin administration in conjunct to norepinephrine was not associated to increased mortality. These studies demonstrate findings that are largely in contradiction to the currently accepted practices, where vasopressin is reserved for substantially sicker patients. Although both groups in the present study had mean lactate levels at admission well above the cut off value of 2 mmol/L which was

used in these previous studies, our results support the notion that increased lactate levels are associated to vasopressin-norepinephrine usage. The question remains, however as to what lactate level is appropriate to begin adjunct vasopressin therapy, for which further large-scale studies are needed.

Additionally, in our study, a higher SOFA score at admission was independently associated to patients in the norepinephrine-vasopressin group compared with the norepinephrine group. The SOFA score, originally designed to predict ICU mortality, measures organ dysfunction in six organ systems and is a key predictor of mortality in patients with septic shock. Jones et al (26) showed that SOFA scores can be used to predict mortality with fairly good accuracy in patients with severe sepsis at the time of presentation in the emergency department. This was reflected in our study since the mortality in the combination group was not significant upon adjustment, indicating that the higher SOFA scores of the combination group patients caused the patients to be more critical to begin with. However, a study conducted by Hammond et al (14) did show a contrasting finding that there was no significant difference in median SOFA scores between norepinephrine alone versus vasopressin and norepinephrine. Nonetheless, SOFA score has been shown to have strong discriminative power, similar to lactate, for predicting 30-day mortality as shown by a recent study of sepsis patients (22). This once again reflects in physician attitudes practicing within an LMIC, suggesting that they are more likely to start dual therapy in case of higher SOFA scores and continue to use it along with lactate as an important prognostic indicator in predicting mortality in septic patients.

Following logistic regression, our study also found that longer duration of vasopressor therapy and ICU admission were independently associated to the norepinephrine-vasopressin combination group. This is most likely a manifestation of severity of sepsis and use of combination therapy for sicker patients who were not responding to norepinephrine alone. Patients in the combination group were undoubtedly found to be more critical upon admission, with higher lactate and SOFA scores, leading to their protracted course of illness and hence needing longer duration of therapy and more ICU admission. Although appropriate recognition and management of septic shock is vital to prevent unwarranted mortality, economic restraints and costs for sepsis treatment cannot be ignored especially in LMICs such as Pakistan. Globally, sepsis is widely regarded as one of the most expensive conditions to treat. Although data for LMICs have historically been sparse, it would be unfair to underestimate that the impact of healthcare costs in LMICs. Within a high-income country like the United States, the treatment and subsequent management of sepsis is estimated to have an annual cost of approximately $20 billion (27). Sepsis treatment costs at a LMIC like Indonesia, varied between $1,011 and $1,406 per patient, with the national burden estimated to be $130 million per 100,000 sepsis patients (28). This is particularly troubling since Pakistan, which has a similar population to Indonesia, has an entire healthcare budget of approximately only $150 million for the fiscal year 2020–2021 (29). To add to this financial crisis, in the recent years, hyperinflation of vasopressor drugs has drastically occurred, with vasopressin cost in particular increasing by 60-fold in 2017 than it did in 2015 as shown by a study (30). Although healthcare costs in the United States are covered mostly by medical insurance, in majority of LMICs like Pakistan, very minimal percentage of the population has access to any form of health insurance that covers medicine costs. Thus, it is evident that most healthcare financing in Pakistan is out-of-pocket, with 70% of healthcare costs being covered by this method (31). High costs severely restrict access to ICU care in LMICs, especially for the majority of the population in Pakistan who are socioeconomically deprived and uninsured. In fact, many patients in Pakistan who cannot afford healthcare costs, especially in private hospitals, often leave the hospital against medical advice. The longer duration of vasopressor treatment and ICU admission, along with the mammoth out-of-pocket healthcare costs for treatment, will cause patients and their families in LMICs like Pakistan to experience significant unwarranted financial burden. This may further limit access to vital healthcare and treatment in Pakistan and consequently leads to unfortunate outcomes for septic shock patients, due to the lack of affordability. Therefore, further large-scale studies, particularly in LMICs, are required which advocates for the clinical benefit of using vasopressin and norepinephrine, so that both patients and physicians alike are assured that the high costs for vasopressor treatment are justified.

One of the limitations of this study is that being a retrospective study, the results may have been influenced by unmeasured residual confounding factors. Furthermore, the present study is a single-center study, inevitably leading to a smaller sample size as compared to multicenter studies. In the given study, the SOFA, qSOFA, and serum lactate levels were recorded upon admission and were not charted during the hospital admission. To gain a better understanding, further prospective studies are required where these variables are monitored in conjunction with administration of vasopressors. Further to this, due to the retrospective nature of the study, the initiation timings and dosage of vasopressors could not be accurately determined from our medical records, and hence these factors were not included in the study. Prior literature has shown that the timing of the dose of vasopressin may also be critical in eliciting a positive response. In fact, Lauzier et al (32) recently demonstrated that vasopressin administration was not able to raise and maintain the MAP above 70 mm Hg for most patients, in the early phases of hyperdynamic septic shock. The VANISH trial also found that higher doses of vasopressin (up to 0.06 U/min), administered within 6 hours of the patient entering septic shock had no effect on mortality (12). Therefore, further large-scale studies specifically deducing whether the timing of vasopressor administration significantly affects outcomes within an LMIC are warranted. Finally, another limitation lies in identifying septic shock by using MAP. Even though MAP is used routinely in clinical practice, other clinical variables are also used for the diagnosis of shock. Furthermore, a MAP of below 65 mm Hg does not always mean under perfusion of organs and cellular injury (33). Nevertheless, ICUs continue to use MAP as an indicator of septic shock, and since it is easily accessible, it remains as an ideal marker for future studies similar to ours. Despite these limitations, this study presents important results that are of clinical relevance, especially considering that this is the first study of its kind conducted in a LMIC, which has significantly different

socioeconomic demographic conditions. Furthermore, this article advocates that the vasopressin should be used with caution, especially considering the fact that there is reported potential overuse of vasopressin among physicians in the United States (34).

CONCLUSIONS

The benefit of the use of Vasopressin in adjunct to Norepinephrine has remained debatable in scientific literature, with a lack of data from LMICs. Our study showed that although there was no difference in mortality between the two groups, admission SOFA scores and admission lactate levels were found to be significantly higher in the norepinephrine-vasopressin combination group. Hence, physicians from Pakistan used the combination therapy in resistant septic shock patients who were sicker to begin with. Furthermore, duration of vasopressor therapy and ICU admission was also significantly higher in the norepinephrine-vasopressin group. Considering the recent hyperinflation of vasopressors costs and that most healthcare expenditure for patients in Pakistan is out-of-pocket, this can consequently lead to unwarranted financial burden for patients and their families. Therefore, future studies, especially from LMICs, are needed to justify the usage of vasopressin and norepinephrine for the treatment of septic shock.

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