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Central venous oxygen saturation versus veno-arterial carbon dioxide gradient as a predictor of mortality in sepsis

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Abstract: Background: Sepsis refers to life threatening organ dysfunction caused by a dysregulated host response to infection. **Aim of the Work:** to test a hypothesis that mortality prediction in patients with sepsis can be done using veno-arterial CO_2 gradient as compared to central venous oxygen saturation. **Patients and Methods:** This prospective study was conducted on 30 adult critically ill patients admitted to ICU of AIN Shams University hospitals, either had sepsis or septic shock on admission during a 6 month period. An informed written consent was obtained from patients and/or their guardians before starting this study. **Results:** The most frequent comorbidities were DM (53.3%) followed by Hypertension (50%) and COPD (36.7%). Sources of infection were mostly Respiratory 80% then urinary 26.7%. The least Sources of infection were CNS infection and abdominal sepsis 20%. SCVO2 at admission and at hour 6 was a significant predictor of mortality in the studied patients. At cut off value of <or =72.5 at admission, the $SCVO_2$ yielded a sensitivity of 92% and specificity of 99%. At cut off value of < or = 58.5% at hour 6, the $ScvO_2$ yielded a sensitivity of 78% and specificity of 77%. Pv-aCO_2 at admission and at hour 6 was a significant predictor of mortality in the studied patients. At cut off value of > or = 6.95 at admission, the Pv-aCO_2 yielded a sensitivity of 92.9% and specificity of 86%. At cut off value of > or = 6.5 at hour 6, the Pv-aCO_2 yielded a sensitivity of 99% and specificity of 91%. Patients who died had significantly lower $ScvO_2$ values than patients who survived. Patients who died had significantly higher Pv-aCO_2 values than patients who survived. There was statistically significant positive correlation between $SCVO_2$ at admission and Pv-aCO_2 at admission (r= 0.55, p=0.002). there was a statistically insignificant difference between patients who survived and patients who died regarding Age and Sex (p>0.05). **Conclusion:** low $ScvO_2$ and high veno-arterial PCO_2 gradient are significant predictors of mortality in septic patients. Our study showed that $ScvO_2$ levels below 70% were significantly associated with mortality and yielded high diagnostic accuracy. Similarly, veno-arterial PCO_2 gradient levels above 6 mmHg within the first 24 h in septic patients were associated with poor outcomes. However, the usefulness of this parameter remains to be explored.

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Key words: Central venous oxygen saturation, veno-arterial carbon dioxide gradient, mortality sepsis

1. Introduction

Sepsis is defined as a syndrome of life threatening organ dysfunction caused by dysregulated host response to infection. If sepsis is unrecognized or left untreated, patients can quickly deteriorate, develop multisystem organ failure, and die. Resuscitation goals for the patient with sepsis and septic shock attempt to return the patient to physiologic state [1].

Central venous oxygen saturation ($ScvO_2$) monitoring can have diagnostic and therapeutic uses in understanding the efficacy of interventions in treating critically ill, haemodynamically unstable patients and has been shown to be a better indicator of tissue oxygenation and utilization of oxygen than routine observations[2].

Aim of the thesis

Aim of this study is to test a hypothesis that mortality prediction in patient with sepsis can be done using veno-arterial CO2 gradient as compared to central venous oxygen saturation.

2. Patients and method

Our study was done as a prospective observational study during a 6 month period that enrolled 30critically adult patients through their ICU admission, ICU stay after a written informed consent fromthier guardians.

All patients were diagnosed to sepsis or septic shock according to the Third International Consensus definitions for sepsis and septic shock [3].

The study included patients more than 18 years old that were critically ill either in sepsis or septic shock. While patients less than 18 years old, patient or relatives who refused to be included in this study, those with an absolute contraindication to chest or neck central venous catheter and pregnant patients were excluded from the study.

Procedures

All patients were subjected to the following:

History taking including age-sex-DM- HTN-smoking-stress on symptoms of presence or absence of infection and its site e.g. fever-shortness of breath – purulent sputum-previous hospital or ICU admission, Hemodynamic monitoring: heart rate monitoring-blood pressure monitoring- respiratory rate monitoring – CVP monitoring –temperature assessment –pulse oximetry –urine output every 6 hours. Central venous catheterization was done to all patients, through which CVP and $ScvO_2$ measured Scoring system: SOFA score Routine laboratory investigations: CBC/ Coagulation profile; INR-PT-PTT/ Renal function tests: serumcreatinine and urea/ Liver function tests: SGPT-SGOT-albumin –total and direct bilirubin /Serum electrolytes: Na- K-Ca-Mg /ABG-CRP-RBG. All patients were managed according to EGDT protocol: once a patient met the criteria for sepsis or septic shock, fluid resuscitation and hemodynamic monitoring were initiated with placement of central venous catheter, through which CVP and $ScvO_2$ monitoring can be done. First: isotonic crystalloid was administered to target CVP more than or equal 8 mmHg. Second: If SBP more than or equal 90 mmHg or MAP more than or equal 60 mmHg were not achieved with fluid administration, vasopressors (preferably norepinephrine as first agent) were initiated to achieve this goal. Finally: $ScvO_2$ more than or equal 70% was targeted after CVP and BP goals were met. If $ScvO_2$ less than 70% and HCT less than 30, packed RBCs transfusion was done to achieve the target HCT.

Microbiological studies:

At least 2 blood cultures from different sites were collected from each patient on admission using 10 ml of blood withdrawn aseptically after disinfection of the venipuncture site on the skin of the patient for at least 5 minutes and allowing drying. Cultures from any suspected site of infection, e.g. sputum-urine – wound, were collected on admission.

All patients were exposed to close observation, and central venous oxygen saturation and veno-arterial carbon dioxide gradient were measured on admission and at 6,12,18,24,30,36,42,48 hours after admission Also mortality outcome was observed.

Data management & Statistical Analysis:

The collected data were revised, coded, tabulated and introduced to a PC using statistical package for social sciences (IBM SPSS 20.0). Data was presented and suitable analysis was done according to the type of data obtained for each parameter.

I- Descriptive Statistics:

Mean, Standard deviation (+ SD) and range for parametric numerical data, while Median and Interquartile range (IQR) for non parametric data.

II- Analytical Statistics:

1- Mann whitney U test was used to assess the statistical significance of the difference of non parametric variable between two independent medians of two study groups.

2- Sign Rank test was used to assess the statistical significance of the median differences between serial of measurements $SCVO_2$ & Pv-aCO2 and their base line measurement at admission in the same group of patients (Died/Survived).

3- Spearman Correlation Coefficient (r): Correlation was used as a measure of the strength of a linear association between two quantitative variables. The Spearman correlation coefficient, *rho*, can take a range of values from +1 to -1. A value of 0 indicates that there is no association between the two variables. A value greater than 0 indicates a positive association; that is, as the value of one variable increases, so does the value of the other variable. A value less than 0 indicates a negative association; that is, as the value of one variable increases, the value of the other variable decreases.

ROC Curve:

The diagnostic performance of a test or the accuracy of a test to discriminate diseased cases from normal cases is evaluated using Receiver Operating Characteristic (ROC) curve analysis. ROC curves can also be used to compare the diagnostic performance of two or more laboratory or diagnostic tests. In a ROC curve the true positive rate (Sensitivity) is plotted in function of the false positive rate (100-Specificity) for different cut-off points of a parameter. Each point on the ROC curve represents a sensitivity/specificity pair corresponding to a particular decision threshold. The area under the ROC curve (AUC) is a measure of how well a parameter can distinguish between two diagnostic groups (diseased/normal).

Interpretation of ROC Curve,.90-1 = excellent (A),.80-.90 = good (B),.70-.80 = fair (C),.60-.70 = poor (D),.50-.60 = fail (F)

5- Regression Analysis of independent predictors of septic patients' mortality; if $P<0.05$ for any of the risk factors; therefore this risk factor is an independent predictor of septic patients' mortality.

P-value: Level of significance:

- $P>0.05$: Non significant (NS) - $P<0.05$: Significant (S) - $P<0.01$: Highly significant (HS)

Results

Table (1) shows that median age in the studied patients is 57.00, IQR is 8.97 and ranged from (40.0-75.0); (60.0%) were males while (40.0%) were females.

Table (1): Age and Sex in all studied patients (n=30)

Variables	Median	IQR	Range
Age	57.00	8.97	(40.00 – 75.00)
Variables		**No.**	**%**
Sex	**Male**	12	40.0%
	Female	18	60.0%

Table (2) shows that more than half of the studied patients (53.3%) were diabetics, more than one third (36.7%) were smokers and half of them (50.0%) were hypertensive.

Table (2): Assosciated comorbidities in all studied patients (n=30)

Variables		No.	%
DM	**No**	14	46.7%
	Yes	16	53.3%
COPD	**No**	19	63.3%
	Yes	11	36.7%
HTN	**No**	15	50.0%
	Yes	15	50.0%

Table (3) shows that half of the studied patients (50.0%) had pneumonia, (30.0%) had wound infection and (26.7%) had UTI, (20.0%) had COPD exacerbation, (13.3%) had asthma exacerbation, (13.3%) had abdominal sepsis, (6.7%) had CNS infections, (66.7%) had septic shock. Regarding the fate of the studied patients; half of them (50.0%) died and (50.0%) survived.

Predictive Values of $ScvO_2$ and Pv-aCO_2

Table (4) shows that $ScvO_2$ at admission and at hour 6 was a significant predictor of mortality in the studied patients. At cut off value of ≤ 72.5% at admission, the $ScvO_2$ yielded a sensitivity of 92% and Specificity of 99%. At cut off value of ≤ 58.5% at hour 6, the $ScvO_2$ yielded a sensitivity of 78% and Specificity of 77%.

Table (3): Source of infection (sepsis) in all studied patients (n=30)

Variables		No.	%
Pneumonia	**No**	15	50.0%
	Yes	15	50.0%
Wound Infection	**No**	21	70.0%
	Yes	9	30.0%
UTI	**No**	22	73.3%
	Yes	8	26.7%
COPD Exacerbation	**No**	24	80.0%
	Yes	6	20.0%
Asthma Exacerbation	**No**	26	86.7%
	Yes	4	13.3%
Abdominal Sepsis	**No**	26	86.7%
	Yes	4	13.3%
CNS Infection	**No**	28	93.3%
	Yes	2	6.7%
Sepsis	**Sepsis**	10	33.3%
	Septic shock	20	66.7%
Mortality	**Survived**	15	50.0%
	Died	15	50.0%

Table 4: Area under the curve displaying diagnostic accuracy of $SCVO_2$ at predicting mortality in the studied patties

Test Result Variable (s)	Area, 95% CI	P-value	Cut-off value	Sensitivity	Specificity
$ScvO_2$ at admission	0.99 (0.97- 0.99)	<0.001**	≤ 72.5%	92%	99%
$ScvO_2$ Hour6	0.82 (0.68-0.97)	0.003**	≤ 58.5%	78%	77%

(**) Highly statistically significant at P<0.01

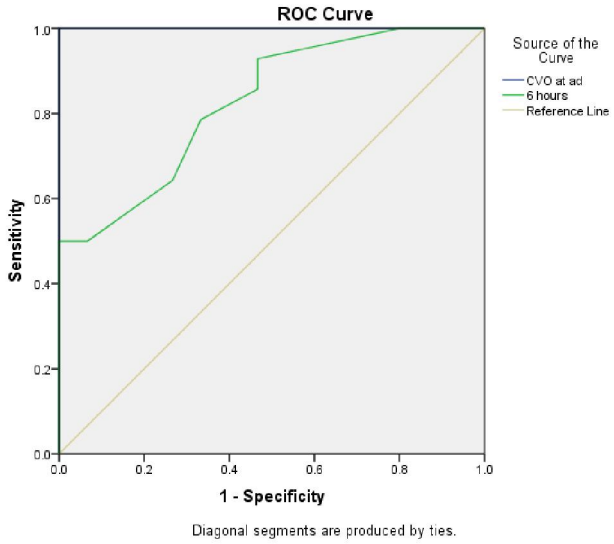

Figure 1: ROC analysis for $ScvO_2$ at admission and hour

Table (5) shows that Pv-aCO_2 at admission and at hour 6 was a significant predictor of mortality in the studied patients. At cut off value of ≥ 6.95 at admission, the Pv-aCO_2 yielded a sensitivity of 92.9% and Specificity of 86%. At cut off value of ≥ 6.5% at hour 6, the Pv-aCO_2 yielded a sensitivity of 99% and Specificity of 91%.

Table 5: Area under the curve displaying diagnostic accuracy of Pv-aCO_2 at predicting mortality in the studied patients

Test Result Variable (s)	Area, 95% CI	P-value	Cut-off value	Sensitivity	Specificity
Pv-aCO_2 at admission	0.86 (0.67- 0.99)	<0.001**	≥ 6.95	92.9%	86%
Pv-aCO_2 Hour 6	0.92 (0.79-0.99)	0.001**	≥ 6.5%	99%	91%

(**) Highly statistically significant at P<0.01

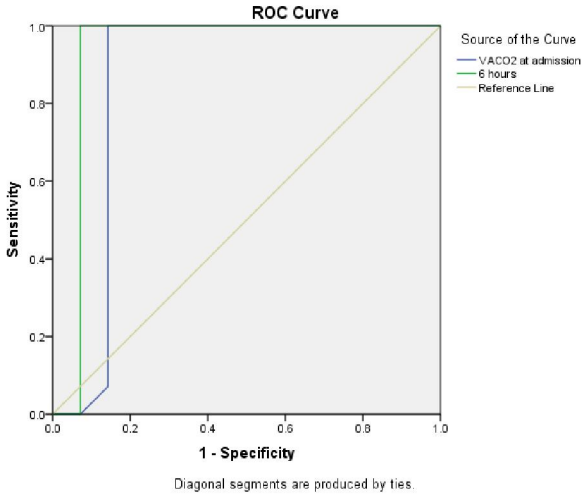

Figure 2: ROC analysis for $PvaCO_2$ at admission and hour 6

Correlation between $ScvO_2$, Pv-aCO_2, and mortality

Table 6 shows that there is a highly statistically significant difference between patients who survived and patients who died regarding $ScvO_2$ at admission, hour 6, 12, 18, 24, 30, 36, 42, and 48 (P<0.01). Patients who died had significantly lower $ScvO_2$ values.

Table 6: Comparison between patients who survived and patients who died regarding $ScvO_2$ Recordings

Variables	Mortality				Mann Whitney U test	P-value
	Survived		Mortality			
	Median	IQR	Median	IQR		
$ScvO_2$ (at admission)	87.2	2.1	57.26	7.25	86.000	0.001**
$ScvO_2$ (Hour6)	61.5	3.02	55.5	2.76	36.500	0.002**
$ScvO_2$(Hour12)	68.00	2.04	52.00	5.17	0.000	0.000**
$ScvO_2$ (Hour18)	74.00	3.52	50.00	4.69	0.000	0.000**
$ScvO_2$(Hour24)	75.00	3.34	48.00	4.31	0.000	0.000**
$ScvO_2$ (Hour30)	79.00	3.42	43.00	3.77	0.000	0.000**
$ScvO_2$ (Hour36)	80.00	3.29	44.00	3.72	0.000	0.000**
$ScvO_2$ (Hour42)	81.00	3.16	42.00	4.39	0.000	0.000**
$ScvO_2$ (Hour48)	83.00	3.31	39.00	4.68	0.000	0.000**

(**) Highly statistically significant at P<0.01

Table 7 shows that there is a statistically significant difference between patients who survived and patients who died regarding Pv-aCO_2 at admission, hour 6, 12, 18, 24, 30, 36, 42, and 48 (P<0.05). Patients who died had significantly higher Pv-aCO_2.

Table 7: Comparison between patients who survived and patients who died regarding Pv-aCO_2 Recordings

Variables	Mortality				Mann Whitney U test	P-value
	Survived		Mortality			
	Median	IQR	Median	IQR		
Pv-aCO2 (at admission)	7.9	0.70	6.7	0.49	46.500	0.001**
PvaCO2 (Hour6)	8.14	0.69	5.4	0.37	58.500	0.001*
Pv-aCO2 (Hour12)	6.80	0.63	8.50	0.36	3.000	0.000**
Pv-aCO2 (Hour18)	6.00	0.62	8.90	0.18	0.000	0.000**
Pv-aCO2 (Hour24)	5.90	0.45	9.00	0.23	0.000	0.000**
Pv-aCO2 (Hour30)	5.40	0.44	9.60	0.27	0.000	0.000**
Pv-aCO2 (Hour36)	5.20	0.43	9.60	0.28	0.000	0.000**
Pv-aCO2 (Hour42)	5.20	0.39	9.60	0.30	0.000	0.000**
Pv-aCO2 (Hour48)	5.10	0.39	9.80	0.26	0.000	0.000**

(*) Statistically significant at P<0.05 (**), Highly statistically significant at P<0.01

Correlation between rate of change of $ScvO_2$ and mortality

Table 8 shows that there is a highly statistically significant difference between patients who survived and patients who died regarding the rate of change in $SCVO_2$ from admission value (P<0.01). Patients who died had significantly lower changes in $ScvO_2$ values from admission.

Table 8: Comparison between patients who survived and patients who died regarding $ScvO_2$ Recordings

Variables	Mortality				Mann Whitney U test	P-value
	Survived		Mortality			
	Mean CFB	SD	Mean CFB	SD		
$ScvO_2$ (Hour 6)	25.4	6.3	1.8	6.8	3.000	0.002**
$ScvO_2$ (Hour 12)	19.1	7.75	5.6	6.8	22.500	0.000**
$ScvO_2$ (Hour 18)	13.8	8.75	8.4	7	61.000	0.000**
$ScvO_2$ (Hour 24)	5.2	6.9	16	6.5	21.500	0.000**
$ScvO_2$ (Hour 30)	6.4	7.2	14.9	6.1	35.000	0.002**
$ScvO_2$ (Hour 36)	6	6.9	15.1	6.25	32.500	0.001**
$ScvO_2$ (Hour 42)	5.2	6.9	16.6	6.5	21.500	0.000**
$ScvO_2$ (Hour 48)	3.6	6.6	18.3	6.6	10.500	0.000**

(**) Highly statistically significant at P<0.01. CFB: Change from baseline

Predictors of Mortality

Table 9 shows that there only Pv-aCO_2 >6mmHg at admission was an independent predictor of mortality. Admission Pv-aCO_2 ≥6 mmHg was significantly associated (P = 0.018) with increased mortality (OR: 3.06, 95% CI: 1.23–7.94).

Table 9: Multivariate analysis of factors associated with mortality.

	Odds ratio	95% confidence interval	P- Value
Age in years	3.1	0.4- 4.98	0.99
Male patients	0.48	0.03 – 7.18	0.99
GCS	0.725	0.989 – 1.005	0.15
$ScvO_2$ at admission <70%	1.01	0.42–2.6	0.93
Pv-aCO_2 at admission > 6mmHg	3.06	1.23–7.94	0.018

*Data are presented as odds ratio and 95% confidence interval

(**) Highly statistically significant at P<0.01. CFB: Change from baseline

Correlation Analysis

Table 10 shows that there was statistically significant positive correlation between $ScvO_2$ at admission and Pv-aCO_2 at admission (r =0.55, p =0.002). Similarly, age correlated significantly with $ScvO_2$ (r =0.41, p =0.028) and Pv-aCO_2 at admission (r =0.38, p =0.042).

Table 10: Correlation analysis.

	SCVO2		Pv-aCO_2	
	r	P-value	r	P-value
$ScvO_2$	---	----	0.55	0.002
Pv-aCO_2	0.55	0.002	----	----
Age	0.41	0.028	0.38	0.042
GCS	-0.08	0.67	-0.015	0.94

Comparison between Survivors and non-survivors

Table 11 shows that there is a statistically insignificant difference between patients who survived and patients who died regarding Age & Sex (P>0.05).

Table 11: Comparison between patients who survived and patients who died regarding Age & Sex

		Mortality				Mann Whitney U test	P-value
Age		**Survived**		**Mortality**			
		Median	**IQR**	**Median**	**IQR**		
		56.00	9.63	57.00	8.52	105.000	0.755
Variables		**Mortality**				**Chi square**	**P-value**
		Survived		**Mortality**			
		No.	**%**	**No.**	**%**		
Sex	**Male**	6	50.0%	6	50.0%	0.000	1.000
	Female	9	50.0%	9	50.0%		

4. Discussion

Sepsis is the leading cause of death from infection and major public health concern in most countries. In addition, it is one of the most common causes of death among hospitalized patients in the intensive care unit (ICU). Septic shock is a subset of sepsis which includes circulatory and metabolic dysfunction associated with higher mortality risk. It is particularly difficult to diagnose in this setting because of the multiple comorbidities and underlying diseases that these patients present[4].

Recently, a growing body of evidence has linked the changes in central venous oxygen saturation ($ScvO_2$) and veno-arterial carbon dioxide (PCO_2) gradient to the higher risks of mortality in septic patients. Levels of $ScvO_2$ above 80% were found to correlate with increased mortality and that this correlation is likely due to impaired ability to extract oxygen. Nevertheless, there is no consensus in the published literature regarding the potential role of both $ScvO_2$ and veno-arterial PCO^2 gradient as mortality markers[5].

Therefore, we conducted the present study in order totest whether the mortality prediction in patients with sepsis can be done using veno-arterial PCO_2 gradient as compared to $ScvO_2$. The present study was a prospective study that included 30 patients with sepsis or septic shock who were recruited from General ICU of Ain Shams University Hospitals. The median age of the included patients was 57 (40 – 75) and the majority of patients were females (60%).

Sepsis and septic shock occur at all ages. However, a strong correlation exists between advanced age and the incidence of septic shock, with a sharp increase in the number of cases in patients older than 50 years. Similar to our results, **Melhammar and Colleagues**[6] performed a retrospective chart review of septic patients ≥18 years, who were recruited from 2 hospitals in Sweden. The results showed that the majority of the patients were older than 55 years old.

Chronic comorbid conditions that alter immune function (chronic renal failure, diabetes mellitus, HIV, alcohol abuse) were reported to be prevalent in sepsis patients. Moreover, patients with cardiovascular risk factors exhibited high risk of sepsis as well[7]). In the present study, almost half of the patients were diabetic and hypertensive, while 36% of them were smokers.

Similarly **Wang and Colleagues**[8] conducted alongitudinal cohort study using the 30,239 community-dwelling participants of the REGARDS cohort to determine the associations between baseline chronic medical conditions and incident sepsis episodes. Over the mean observation time of 4.6 years (February 5, 2003 through October 14, 2011), there were 975 incident cases of sepsis. Incident sepsis episodes were associated with tobacco use, diabetes, and hypertension.

In terms of sepsis outcomes in our cohort, 66.7% of the patients developed septic shock; while the mortality rate was 50%.

In agreement with our findings, **Sakr et al.**[9] performed a secondary analysis on Intensive Care over Nations (ICON) audit which included all adult (>16 years) patients admitted to the ICU between May 8 and May 18, 2012. Data were collected daily for a maximum of 28 days in the ICU**.** The audit included 10069 patients from Europe (54.1%), Asia (19.2%), America (17.1%), and Africa (9.6%). The authors reported that the mortality rates in septic patients from Africa was 47%.

Additionally, **Sobhy et al.**[10] performed an observational case-control one on 60 patients admitted to the ICU of Kasr Al-ainy hospital with sepsis. Mortality increased from 35% in the sepsis group to 60% in the group of septic shock patients.

Notably, the mortality rates obtained from developed countries appear to be much lower than our study. For example, **Hall et al.**[11] reported on the results of their review of data from the National Hospital Discharge Survey, 2008. The average length of stay (LOS) for septic patients was 75% longer compared to those hospitalized for other conditions, and septic patients were eight times more likely to die during hospitalization. There were 17% in-hospital deaths among patients treated for septicemia compared to 2% of those treated for other conditions. This was similar to the 4-year epidemiological trends from the 2010 US census, which described a decrease in the overall mortality estimate from 22% to 17% over 4 years ([12]).

A retrospective analysis of 12-year data on severe septic patients in Australia and New Zealand demonstrated a significant decrease in absolute mortality, estimated at 18% ($p < 0.001$)[13]. While **Weiss et al.**[14] reported that the mortality rates of septic shock were 25% in developed countries.

The exact causes of such discrepancies regarding the mortality rate within the published literature are unclear. However, the study's setting potentially play an important role in this difference, the mortality rates appear to be higher in limited-resources countries than well-developed countries; this trend in mortality run in concordance with the previous WHO report which cited that the mortality rate of sepsis in children from pediatric ICU of developing countries is higher than 50%([15]). Additional factor that may contribute to this difference is the lack of a consensus definition of septic shock and lack of clear distinctions between sepsis and septic shock in the above-mentioned reports. Moreover, mortality was reported at different time points across the above-mentioned study which may be another contributing factor.

$ScvO_2$ is a useful tool reflecting the global transport and metabolism of oxygen. International guidelines suggest the need to optimize $ScvO_2$ in the early phase of management of severe sepsis and septic shock. Despite that low levels of $ScvO_2$ reflect an inadequate cardiac output or low level of arterial oxygen pressure. Therefore, it was proposed that low levels of $ScvO_2$ are correlated with an increased mortality rate[16].

In the present study, there is a highly statistically significant difference between patients who survived

and patients who died regarding $ScvO_2$ during the first 48 hours after admission. Patients who died had significantly lower $ScvO_2$ values. Notably, $ScvO_2$ at admission and at hour 6 was a significant predictor of mortality in the studied patients. At a cut off value of ≤ 72.5% at admission, the $ScvO_2$ yielded a sensitivity of 92% and Specificity of 99%. At a cut off value of ≤ 58.5% at hour 6, the $SCVO_2$ yielded a sensitivity of 78% and Specificity of 77%. However, the regression analysis showed that the $ScvO_2$ was not an independent predictor of mortality.

In concordance with our findings, **Boulain et al.**[17] performed a prospective, multicentre, observational study over a one-year period in ten French ICUs. A total of 363 septic patients were included. Initial $ScvO_2$ below 70% was present in 111 patients The day-28 mortality was higher in case of low initial $ScvO_2$, a low initial $ScvO_2$ and a low ScvO2 at hour 6 were associated with day-28 mortality by logistic regression.

Du et al. [18] performed a retrospective analysis of 172 patients treated for septic shock. All patients were treated using goal-directed therapy to achieve Scvo2 ≥ 70%. Overall, the 28-day mortality was significantly higher in patients with $ScvO_2$< 70% compared to those in whom $ScvO_2$exceeded 70%.

Lee et al.[19] performed a prospective study to evaluate the prognostic value of static and dynamic variables of $ScvO_2$ in patients with severe sepsis or septic shock. The area under the ROC curve showed that $ScvO_2$ was a significant discriminator for predicting 28-day mortality. In multivariable analysis, $ScvO_2$≥70% showed only a marginal association with 28-day mortality.

In contrary, **Chung et al.** [20] performed a prospective study that enrolled 124 noncirrhotic patients who were admitted to intensive care units for severe sepsis or septic shock. Compared with high $ScvO_2$ groups, low $ScvO_2$ groups showed no significant differences in 28-day mortality or hospital mortality.

The exact causes of such heterogeneity between our findings and the abovementioned study are unclear. However, this difference can be attributed to many methodological differences. Another explanation is the differences in sample size.

On the other hand, high levels of $ScvO_2$ could also reflect an impaired extraction of oxygen. Therefore, it was proposed that high levels of $ScvO_2$ are correlated with an increased mortality rate ([16]). Although we did not examine the predictive value of high $ScvO_2$ levels in the present study, **Textoris et al.**[21] aimed to evaluate the relation between $ScvO_2$ levels and survival among ICU patients with a septic shock through retrospective analysis of all admissions to ICU between January 2008 and December 2009. A total of 152 patients met the inclusion criteria. The level of $ScvO_2$ was significantly higher in the non-survivors compared with the survivors.

Nevertheless, it should be noted that the current literature is inconclusive regarding the predictive value of high $ScvO_2$ for mortality and that this is an area of future research.

Anerobic metabolism is crucial in the pathophysiology of septic shock; during anaerobic metabolism, CO_2 is produced from the bicarbonate that buffers acidic metabolites. Because CO_2 is about 20 times more soluble than oxygen, it is likely to be available outside ischemic tissues to the venous stream, and so it is a very sensitive marker of hypoperfusion. Therefore, the measurement of veno-arterial PCO2 gradient seems to be a good marker for correct microcirculation and a good prognostic indicator in septic shock, as it provides an index of tissue oxygenation[22].

In the present study, we found that there was a highly statistically significant difference between patients who survived and patients who died regarding veno-arterial PCO_2 gradient during the first 48 hours after admission. Patients who died had significantly higher veno-arterial PCO_2 gradient values. Notably, veno-arterial PCO_2 gradient at admission and at hour 6 was a significant predictor of mortality in the studied patients. At a cut off value of > or = 6.95 at admission, the veno-arterial PCO_2 gradient yielded a sensitivity of 92.9% and Specificity of 86%. At a cut off value of> or = 6.5 at hour 6, it yielded a sensitivity of 99% and Specificity of 91%. The regression analysis showed that the veno-arterial PCO_2 gradientwas an independent predictor of mortality.

In agreement with our findings, Ospina-**Tascon et al.**[23] conducted a prospective observational study in 85 patients with a new septic shock episode. Patients with persistently high and increasing veno-arterial PCO_2 gradient had significantly higher mortality rates at day-28 compared with patients who evolved with normal veno-arterial PCO_2 gradient.

Similarly, **Hemly et al.**[24] performed aprospective study to investigate the prognostic value of veno-arterial PCO_2 difference during the early resuscitation of patients with septic shock. Forty patients admitted to one Intensive Care Unit were enrolled. The results showed that high PCO_2 gap >7.8 mmHg after 6 hours from resuscitation of septic shock patients is associated with high mortality.

Troskot et al.[25] conducted a prospective study in General Hospital Holy Spirit from January 2004 to December 2007 and included 71 conveniently sampled adult patients (25 women and 46 men), who fulfilled the severe sepsis and septic shock criteria. Veno-arterial PCO_2 was a significant predictor of fatal outcome only in the non-ventilated group of patients.

Study's Limitations

We acknowledge that the present study has some limitations. The study was a single-center experience, with a small sample size, and therefore the results cannot be generalized to the general population. Furthermore, the interpretation of $ScvO_2$ remains a challenge. $ScvO_2$ depends on arterial oxygen saturation, cardiac output, oxygen consumption, haemoglobin levels and shunting. The ability of $ScvO_2$ to reflect systemic oxygen delivery/consumption is not constant in time as it depends on many conditions, including sedation, ventilator treatment, redistribution of blood as seen in shock and thus shock severity, the position of the catheter tip, which depends on the body position; and so on. Thus, the complex mechanisms influencing ScvO2 hamper the interpretation.

Conclusion

In conclusion, low$ScvO_2$ and high veno-arterial PCO_2 gradient are significant predictors of mortality in septic patients. Our study showed that $ScvO_2$ levels below 70% were significantly associated with mortality and yielded high diagnostic accuracy. Similarly, veno-arterial PCO_2 gradient levels above 6 mmHg within the first 24 h in septic patients were associated with poor outcomes. However, the usefulness of this parameter remains to be explored.

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