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Association of Abnormal Central Venous Oxygen Saturation with Mortality in Sepsis and Polytrauma Patients: A Prospective Observational Study

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Abstract: *Abnormal central venous oxygen saturation (ScvO2) levels, including both low and supranormal values were found to be associated for cases with increased mortality across the patient populations in intensive care units in hospitals. Multivariate model analysis were performed for assessing ScvO2 levels and its association with patients' mortality. : The study found patients presented with hyperoxia condition had significantly higher likelihood of mortality risk (risk ratio 2.422) when on comparison with that of patients presenting normal ScvO2 levels. Hypoxia group showcased increased mortality risk (risk ratio 1.0256), though however not statistically significant. The study's findings suggests a J-shaped curve relationship between ScvO2 levels with that of patients' mortality, thereby indicating both hyperoxia and hypoxia are likely associated to higher degree of mortality cases when on comparison with normoxia patients.*

Key Words: *supranormal, polytrauma, normoxia hyperoxia condition.*

1. INTRODUCTION:

Clinical presentation of polytrauma and sepsis can be attributed as complex condition posing significant challenges in intensive care settings, often resulting in higher mortality rates despite the rapid advancements in management of critical care units (Dogjani et al., 2018; Perumal et al., 2021). Both polytrauma and sepsis can likely contribute in the development of systemic inflammatory response syndrome (SIRS), which further leads to organ failure and dysfunction in majority of clinical cases thereby ultimately resulting in patient's death when not managed effectively and promptly (Schefzik et al., 2023). Recent literature studies showcased that monitoring of central venous oxygen saturation (ScvO2) can serve as a potential biomarker in assessing tissue oxygenation followed by prognosis among critically ill patients, including patients with polytrauma and sepsis (Oberhofer & Tonković, 2012; Donati et al., 2011 & Pandey, 2024).

The underlying concept in the monitoring of ScvO2 originated from the very fact that the oxygen delivery (DO2) should be meeting with demands for oxygen consumption (VO2) for maintaining the tissue oxygenation, which in turn is crucial for preventing organ dysfunction (CB et al., 2020). In case of critically ill patients, alterations in VO2 or DO2 can ultimately result in hypoxia condition, which is a key determinant for mortality (Arlati, 2023). ScvO2 reflects a delicate balance between VO2 and DO2 and can be influenced by factors like hemoglobin concentration, cardiac output, and tissue's ability in oxygen extraction (Prakruthi, 2018). Therefore, from monitoring the levels of ScvO2 facilitate in seeking valuable insights pertaining to the actual adequacy required for tissue oxygenation and can in turn determine the severity of patients' illness from sepsis and polytrauma (Davies & Hutchings, 2016).

Several findings revolving around this study area presented that there lies a definitive association between ScvO2 levels and outcomes among the critically ill patients, however amidst the relationship there are certain conflicting results. Whilst some investigations presented a direct link between patients with low ScvO2 levels presented with increased mortality, others have failed to demonstrate a significant relationship. Moreover, ScvO2 and its role in the monitoring and guidance for resuscitation strategies followed with improving patients' outcomes who were presented with polytrauma and sepsis remained still a controversial and debatable topic.

Provided that the paucity of data on association between mortality and ScvO2 in sepsis and polytrauma patients, the following prospective observational investigation intended to characterize the underlying relationship. The study aimed at evaluating whether abnormal ScvO2 levels during the time of admission and during the time period of patient's stay in ICU are predictive on the patient's mortality status with regards to their condition on sepsis and polytrauma. Upon elucidating prognostic significance with respect to ScvO2 monitoring among the patient population, the study seeks to contribute by devising suitable study design, methods, and preliminary findings for the study, emphasizing on the key notion governing with abnormal ScvO2 levels and the actual prevalence of mortality among the patients with polytrauma and sepsis.

2. METHODS:

The research participants were selected from the Surgical Intensive Care Unit (SICU) of Christian Medical College Hospital, Vellore which is a 2000 bedded tertiary care hospital serving about 90,000 inpatients and 1.5 million outpatients annually. Christian Medical College Hospital is a university-affiliated tertiary care facility in Vellore, Tamil Nadu serving as the primary trauma center for the district of Vellore other than government hospitals. The Intensive Care Unit (ICU) is comprised of multidisciplinary medical/surgical/trauma unit that predominantly serves patients originating from the Emergency Department. Patients received treatment in accordance with both international standard care and the guidelines outlined in Advanced Trauma Life Support. Hemodynamic stability was achieved by monitoring vital signs including heart rate, blood pressure, and central venous pressure.

Patients aged 18 to 80 years who have been admitted to the Surgical Intensive Care Unit (SICU) and Surgical High Dependency Unit (SHDU) with a diagnosis of sepsis and polytrauma. The patients' demographic and clinical traits were obtained from the ICU-database established by the institution. The Vigileo system was utilized to consistently monitor $ScvO_2$ levels. A central catheter was promptly inserted into all enrolled patients within the initial two hours of admission. Throughout the first 24 hours following the traumatic event, the minimum $ScvO_2$ value, measured for a duration of at least 15 minutes, and the highest arterial lactate concentration were documented.

Statistical Analysis

The statistical analyses were conducted using the SPSS 10.0 software package (SPSS, Chicago, Illinois, USA). 1. The mortality rate was determined with a 95% confidence interval. The relationship between different factors (ScvO2, lactate, base excess) and mortality was evaluated through chi-square tests. Categorical data were analyzed using Fisher's exact test, with a two-sided P value less than 0.05 considered significant. The selection of cut-off values was based on the statistically significant mean values obtained from subgroup analysis. Demographic and clinical parameters were subjected to multiple logistic regression analysis. A significance level of less than 0.05 was deemed as statistically significant. The calculation of ORS with a 95% confidence interval was performed.0

The statistical significance of the mortality rates among the different groups was assessed by conducting a comparison using Fisher's exact test. To account for multiple comparisons, a Bonferonni correction was applied, with an alpha level set at 0.017 (0.05 divided by 3). To assess the association between ScvO2 and mortality, a comprehensive analysis of the collected covariates was conducted. Initially, a univariate analysis was performed using Fisher's exact test. Subsequently, both automated and manual stepwise logistic regression techniques were employed to identify significant covariates ($p < 0.05$). This approach allowed us to effectively control for potential confounders and evaluate the relationship between $ScvO_2$ and mortality.

3. RESULTS:

Throughout the study timeframe, 86 patients satisfied the inclusion criteria. 171 individuals sought admission to the Emergency Room. The hospital's institutional review board for human research granted approval for this prospective, observational study, which was conducted in accordance with their guidelines. Written informed consent was obtained from every patient participating in the study. There was a nearly equal distribution of patients aged 18-45

years and those above 45 years, with a mean age of 43.85 (SD16.293). Among the patients, 32.56% were women and 67.44% were men. Many admissions (88%) were due to sepsis, while 12% were diagnosed with poly trauma. Common comorbidities included diabetes (17%), hypertension (4%), and chronic kidney disease (5.81%). The overall mortality rate for all patients was 11.63% (10 out of 86 patients). APACHE II has gained widespread acceptance in numerous clinical trials due to its ability to ensure uniformity across diverse groups. The APACHE II score's popularity stems from its user-friendly nature and the existence of software that streamlines analysis. Table 1 details the APACHE II score.

Table No. 1: APACHE II SCORE

	+4	+3	+2	+1	0	+1	+2	+3	+4
Rectal temp (C)	>41	39 - 40.9		38 - 38.9	36 - 38.4	34 - 35.9	32 - 33.9	30 - 31.9	<29.9
Mean arterial pressure (mmHg)	>160	130 - 159	110 - 129		70 - 109		50 - 69		<49
Heart rate (bpm)	>180	140 - 179	110 - 139		70 - 109		55 - 69	40 - 54	<39
Respiratory rate (bpm)	>50	35 - 49		25 - 34	12 - 24	10 - 11	6 - 9		<5
Oxygen delivery (ml/min)	>500	350 - 499	200 - 349		< 200				
PO2 (mmHg)					> 70	61 - 70		55 - 60	<55
arterial pH	>7.7	7.6 - 7.69		7.5 - 7.59	7.3 - 7.49		7.25 - 7.3	7.15 - 7.2	<7.15
Serum sodium (mmol/l)	>180	160 - 179	155 - 159	150 - 154	130 - 149		120 - 129	111 - 119	<110
Serum potassium (mmol/l)	>7	6 - 6.9		5.5 - 5.9	3.5 - 5.4	3 - 3.4	2.5 - 2.9		<2.5
Serum creatinine (mg/dl)	>3.5	2 - 3.4	1.5 - 1.9		0.6 - 1.4		< 0.6		
Haematocrit (%)	>60		50 - 59.9	46 - 49.9	30 - 45.9		20 - 29.9		<20
White cell count (103/ml)	>40		20 - 39.9	15 - 19.9	3 - 14.9		1 - 2.9		<1

The male gender was predominant in both cohorts, comprising 72% of the total population whereas female constituted 28%. The mean APACHE II score was 15.05, ranging from a minimum of 5 to a maximum of 32. In male patients, $SCVO_2$ was distributed with hypoxia (<60) in 9 patients followed by NORMOXIA (60-75) in 29 patients and HYPEROXIA (75.1-100) in 24 patients. Conversely, among female patients, the distribution of SCVO2 levels revealed that 4 patients experienced hypoxia (<60), followed by 11 patients with normoxia (60-75), and 9 patients with hyperoxia (75.1-100). The recorded mortality rate after 28 days was found to be 18.2%. Analysis of the differences between patients who survived and those who did not revealed that significant relative risks for mortality were present in individuals aged between 75.1 - 100 years. There was 3 patients in 60 – 75 years and 1 patient in <60 for mortality count. The mean age was highest for Hyperoxia category with 55 years. Table 2 gives a brief explanation of the details.

Table No. 2: $SCVO_2$ - Gender, Mortality, Age and APACHE II mean

		SCVO2		
		HYPOXIA (<60)	**NORMOXIA (60-75)**	**HYPEROXIA (75.1-100)**
GENDER	**MALE**	9	29	24
	FEMALE	4	11	9
MORTALITY	**YES**	1	3	6
	NO	12	37	27
AGE (years)	**MEAN**	43	42	**55**
APACHE II	**MEAN**	14	14.15	15.934

The gender distribution aligns with what is typically observed in our clinical setting. On average, deceased patients exhibited a notably higher age, specifically above 75 years. In line with these findings, there were significant differences in History of severe organ insufficiency between patients. There were equal points distributed among non-operative patients and Emergency postoperative patients with 5 points each whereas elective postoperative patients constituted 2 points. Table 3 discusses the points in detail.

Table No. 3: Age and History of severe organ insufficiency

Age	**Points**
<44	0
45-54	2
55-64	3
65-74	5
>75	6
History of severe organ insufficiency	**Points**
Non-operative patients	5
Emergency postoperative patients	5
Elective postoperative patients	2

BASELINE DATA

The ScvO2 serves as a metric for the oxygen content present in the bloodstream. An optimal ScvO2 typically falls within the range of 95% to 100%. Reduced levels of ScvO2 may suggest inadequate oxygen supply to the body. The horizontal axis of the chart is denoted as "scv02 at admission" and spans from 0 to 100. On the other hand, the vertical axis is labeled as "patients" and also ranges from 0 to 100. The graph exhibits a sole data set depicted as "Series1" and illustrated by a blue line. This line exhibits a slight upward trend, indicating a weak positive relationship between ScvO2 levels and the quantity of admitted patients. Essentially, the graph implies a potential rise in the number of admitted patients with an increase in ScvO2 levels upon admission. The mean SCVO2 at admission was 72.16 with a minimum of 44 and maximum value of 95. The plot below depicts the distribution of the SCVO2 values.

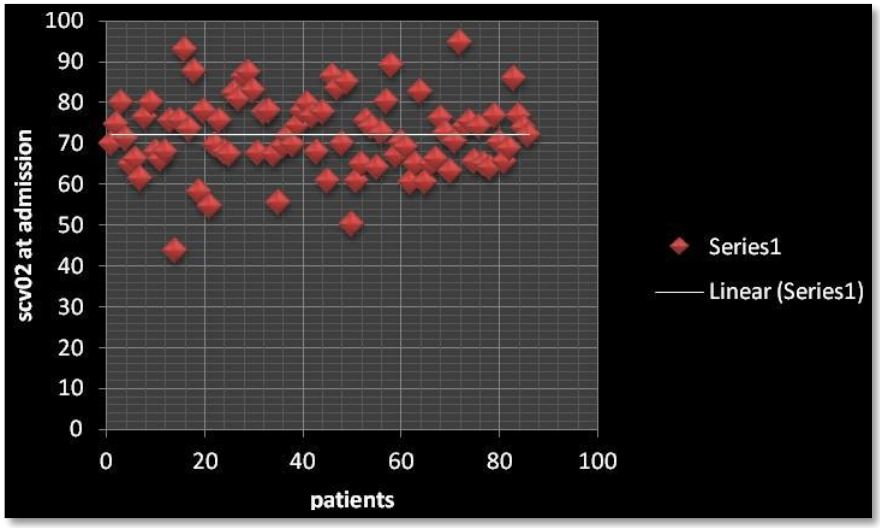

Fig. No. 1: Distribution of SCVO2 at admission.

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The graph displays the x-axis with $SCVO_2$ hour labels ranging from 0 to 100, while the y-axis is labeled as "patients" and spans from 0 to 100. In general, the graph illustrates that the highest number of values between 60 and 80 on the x-axis. A similar pattern with mean of 72.2 and minimum value of 45 and maximum of 85 was seen 6 hours after ICU admission as in fig.2

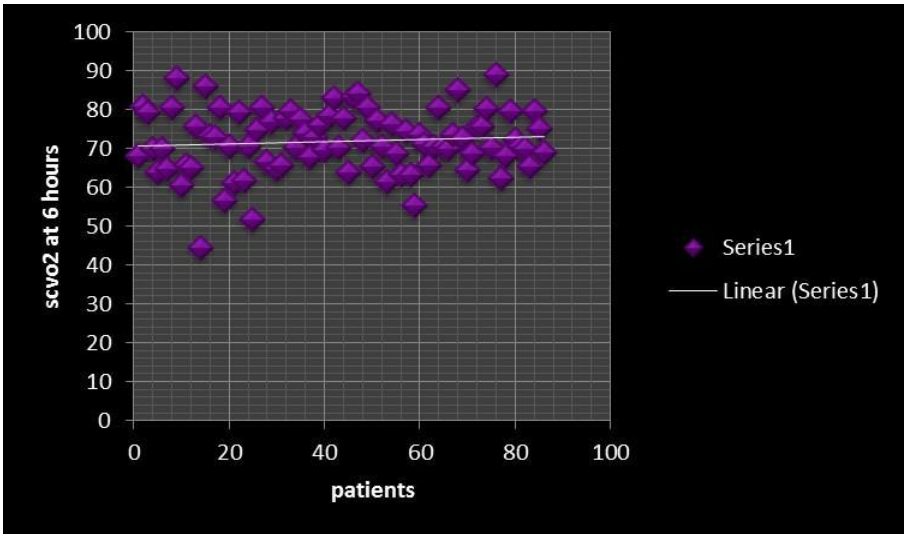

Fig. No. 2: Distribution of SCVO2 6 hours after ICU admission.

The study evaluated mortality related to SCVO2 values at admission to the ICU and to 6 hours after admission. At admission 15% had hypoxia (low SCVO2) with a mortality of 7.69% (1/13) and 46% had normoxia with a mortality of 7.65% (3/40) and 38% had hyperoxia (high SCVO2) with a mortality of 18.8% (6/33). After 6 hours of ICU admission, the mortality was nil in the hypoxia group, 7.76% in the normoxia group and 22.58% in the hyperoxia group. The mean SCVO2 at admission in the alive group was 71.65 (CI of 69.53- 73.76) and in the mortality group was 76.44 (CI of 70.07-82.81). These values were almost same after 6 hours of ICU admission. Similarly mean APACHE II score in the patients who survived was 14.08 and was 22.30 in the patients who did not survive.

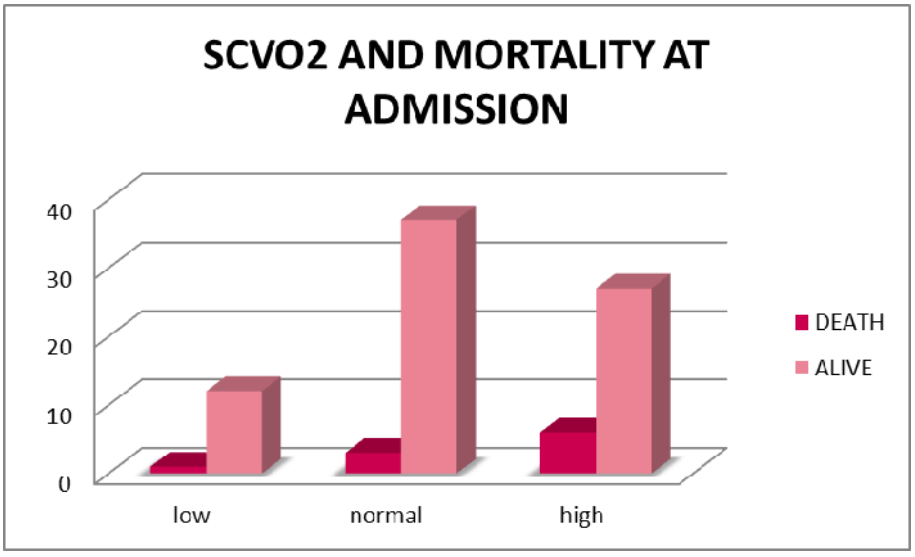

Fig. No. 3: Correlation of ScvO2 to mortality at admission

The graph provided illustrates an unexpected relationship between ScvO2 levels and mortality upon admission. Typically, a lower ScvO2 value suggests inadequate oxygen supply to the body, indicating a potential serious medical condition that could result in death. Surprisingly, the data reveals that individuals with higher ScvO2 levels upon admission had a higher likelihood of mortality. It is possible that patients who receive oxygen supplementation prior to ScvO2 measurement may exhibit artificially elevated ScvO2 levels. Conversely, an elevated ScvO2 reading could also signify excessive blood pumping by the heart, potentially indicating heart failure.

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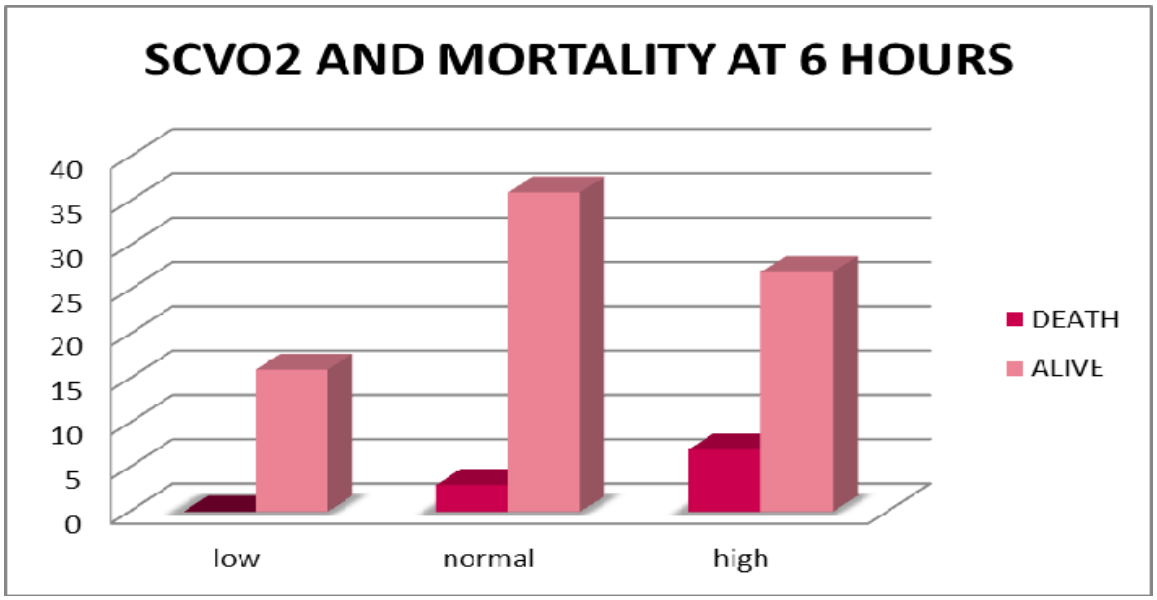

Fig. No. 4: Correlation of ScvO2 to mortality after 6 hours

In figure 3 and figure 4, it is visually evident that the hyperoxia group exhibits a higher mortality rate; however, this difference is not statistically significant. When compared to the normoxia group, the hyperoxia group had a mortality rate that was 2.422 times higher, although this difference did not reach statistical significance. On the other hand, the hypoxia group had a 1.0256 times higher likelihood of mortality compared to the normoxia group. When comparing the hypoxia group to the hyperoxia group, the risk ratio for mortality was 2.36 times higher in the hyperoxia group, but the p-value did not reach statistical significance. It is important to note that these findings may be influenced by the fact that only 86 patients were recruited instead of the planned 170, due to time constraints. Additionally, the study is still ongoing, and it is possible that the results may become statistically significant once all the patients are recruited.

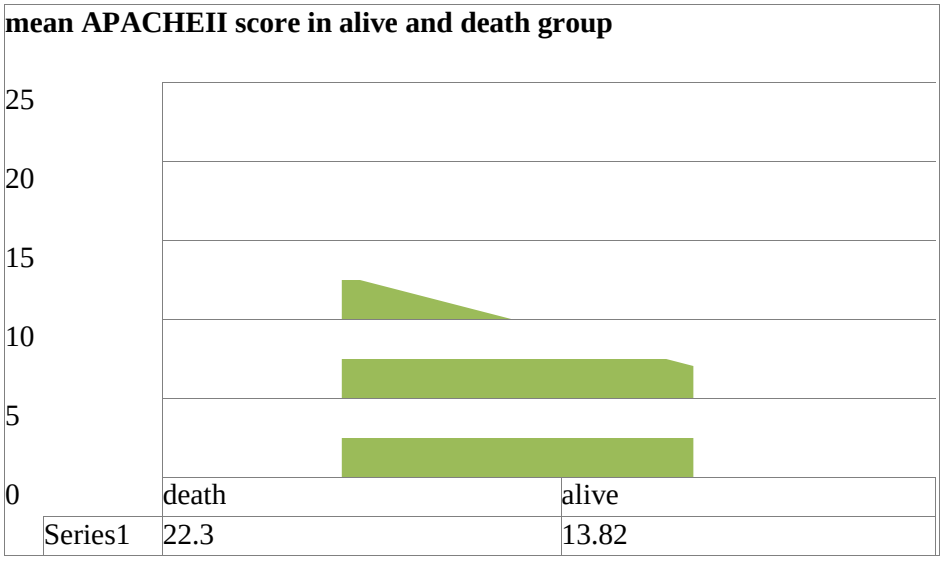

Fig. No. 5: Correlation of APACHE II score and mortality

The Apache II score, as demonstrated in previous research, serves as a reliable predictor of mortality, particularly when the scores are elevated, as illustrated in figure 5. In contrast, when examining the oxygen extraction ratio, the hyperoxia group exhibited a notably lower ratio, as depicted in figure 6. However, when comparing both groups in terms of mortality, no significant differences were observed.

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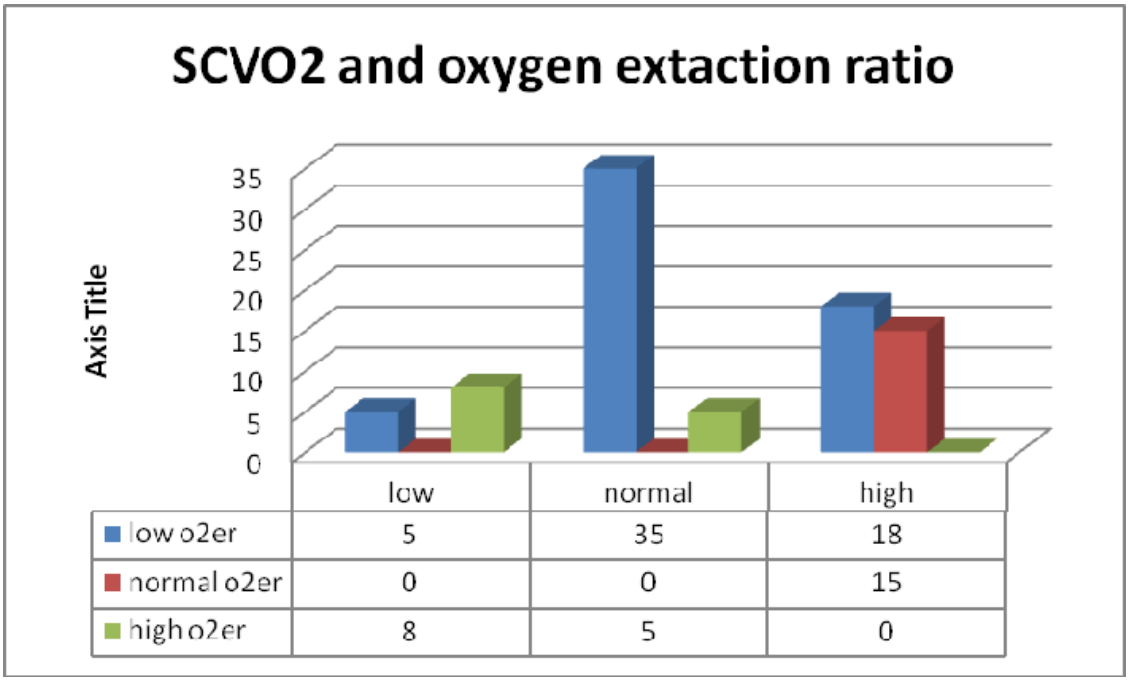

Fig. No. 6: Correlation of oxygen extraction ratio to ScvO2

Subsequently, we observed the correlation between SCVO2 and various factors such as the length of stay in the intensive care unit (ICU), the necessity for dialysis, the duration of inotropic support, and the presence of coagulopathy. The findings indicated that both the hypoxia and hyperoxia groups required a slightly lengthier duration of inotropic support, had a higher need for dialysis, and exhibited the presence of coagulopathy. However, these results did not demonstrate statistical significance. Conversely, when comparing the duration of ICU stay, the normoxia group had a longer stay, potentially due to their improved survival rate, while the other groups experienced early mortality.

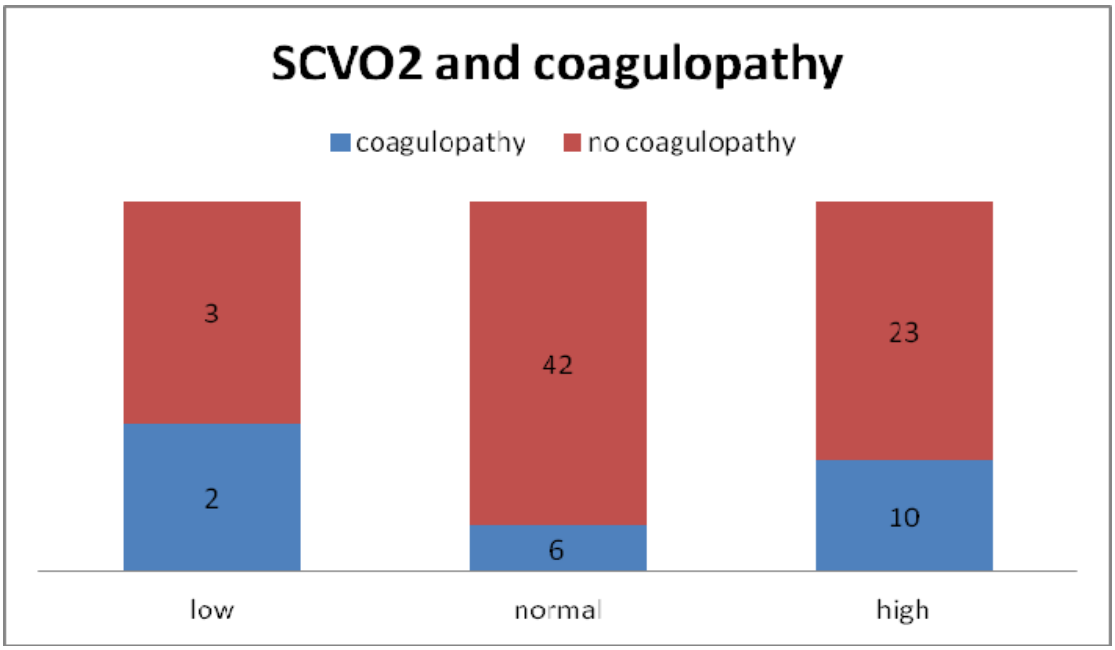

Fig. No. 7: incidence of coagulopathy with ScvO2

The chart you sent shows the association between ScvO2 (central venous oxygen saturation) and coagulopathy (a blood clotting disorder). The x-axis of the chart labeled "SCVO2" goes from low to high. The y-axis labeled "coagulopathy" is divided into three categories: no coagulopathy, low ScvO2, and high ScvO2. The number of patients in each category is listed.

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Low ScvO2: There are 2 people with coagulopathy and 3people without coagulopathy.

Normal ScvO2: There are 6 people with coagulopathy and 42 people without coagulopathy.

High ScvO2: There are 10 people with coagulopathy and 23 people without coagulopathy.

The data presented in the chart indicates that individuals with coagulopathy tend to have a higher ScvO2 compared to those with a low ScvO2. Nevertheless, it is crucial to consider several factors before making any definitive conclusions. Firstly, it is important to note that the sample size is relatively small, consisting of only 86 data points. This limited sample size makes it challenging to establish a definite correlation between ScvO2 and coagulopathy. Additionally, the chart does not provide information about other potential variables that could potentially influence the risk of coagulopathy, such as age, underlying medical conditions, and medications. Therefore, it is necessary to consider these factors and conduct further research to gain a comprehensive understanding of the relationship between ScvO2 and coagulopathy.

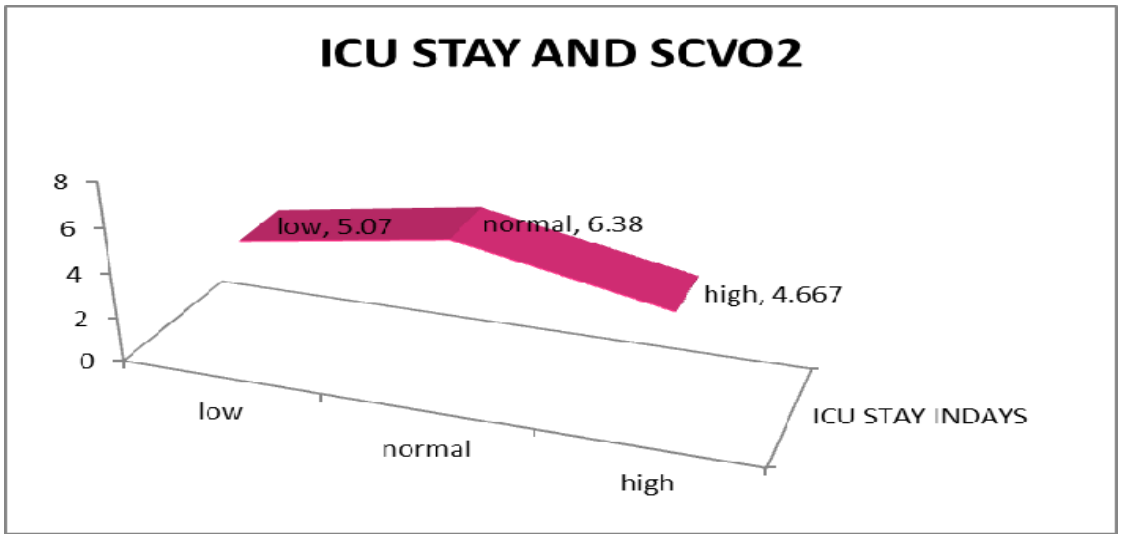

Fig. No. 8: Duration of ICU stay and ScvO2

There are three data series plotted on the graph, represented by different colored bars.

Patients with a lower ScvO2 level have an average ICU stay of 5.07 days, while those with a normal ScvO2 level stay for 6.38 days on average. On the other hand, patients with a higher ScvO2 level have a shorter average ICU stay of 4.667 days. The data indicates that patients with lower ScvO2 levels tend to have a longer ICU stay, possibly due to their increased illness severity and need for more intensive care.

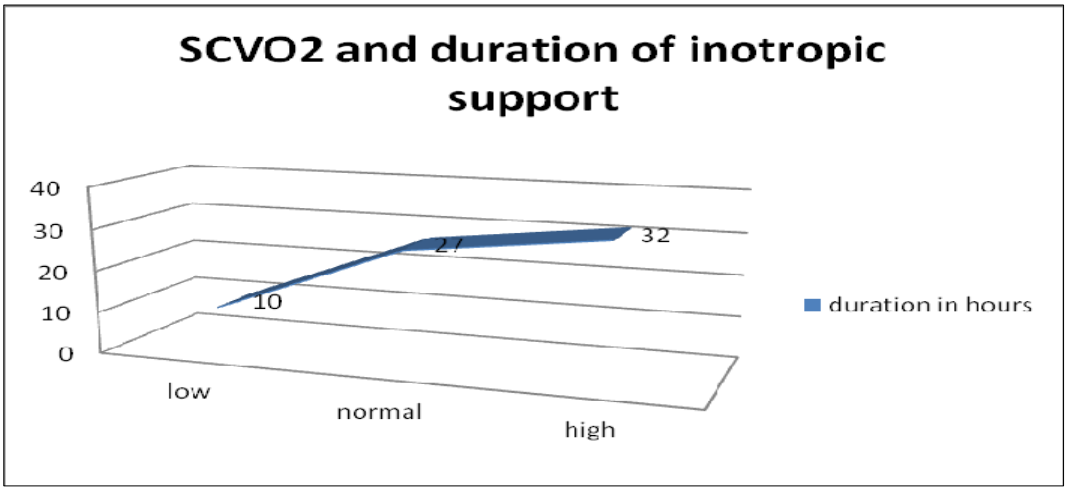

Fig. No. 9: Correlation of duration of inotropic support to ScvO2

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Patients with low central venous oxygen saturation (SCVO2) levels, indicating inadequate oxygen delivery to tissues, typically require an average duration of 10 hours of inotrope support. Inotropes are medications that increase the strength of the heart's contractions, improving cardiac output and oxygen delivery. Patients with low SCVO2 require an average duration of 10 hours of inotrope support, while patients with normal SCVO2 necessitate 30 hours, and those with high SCVO2 require 40 hours.

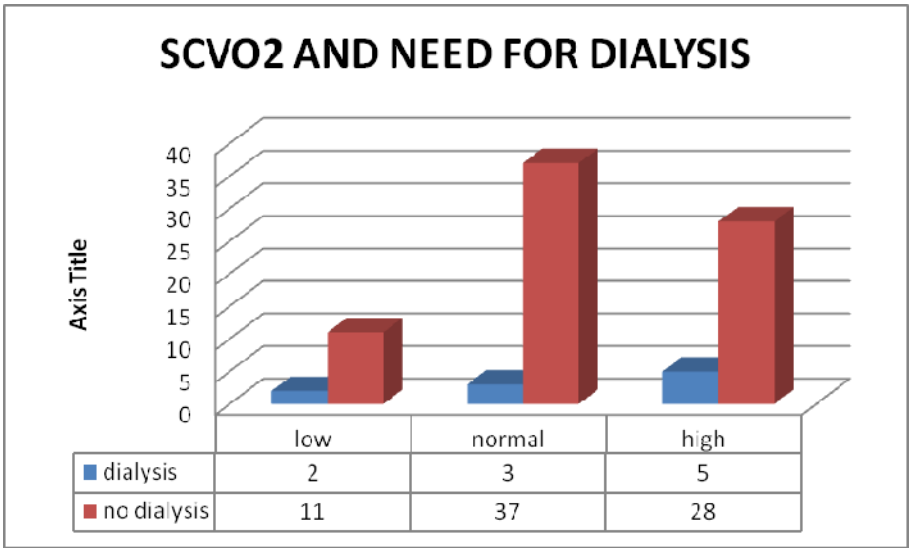

Fig. No. 10: ScvO2 and need for dialysis

The data for this graph is represented by bars. It is classified into 2 categories: Dialysis and no dialysis

No dialysis: There are 11 patients who did not require dialysis and 37 who did with a normal ScvO2 level. There are also 28 patients who did not require dialysis and who had high ScvO2 level.

Dialysis: There are 2 patients who required dialysis and had a low ScvO2 level. There are 3 patients who required dialysis under normal ScvO2 and 5 under dialysis category having high ScvO2 level.

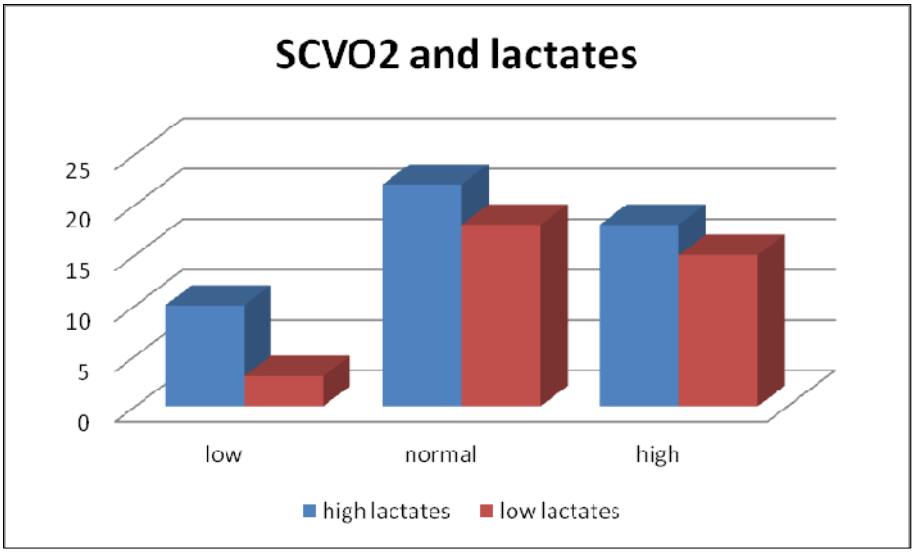

Fig. No. 11: ScvO2 and lactates

There was no statistically significant relation between the 3 groups of SCV02 when compared with APACHE II score, base excess, lactate levels. When lactates, base excess and Scv02 were compared to mortality though not significant gave a j shaped curve suggestive that mortality is higher both in the hypoxia and the hyperoxia group compared to the normoxia group.

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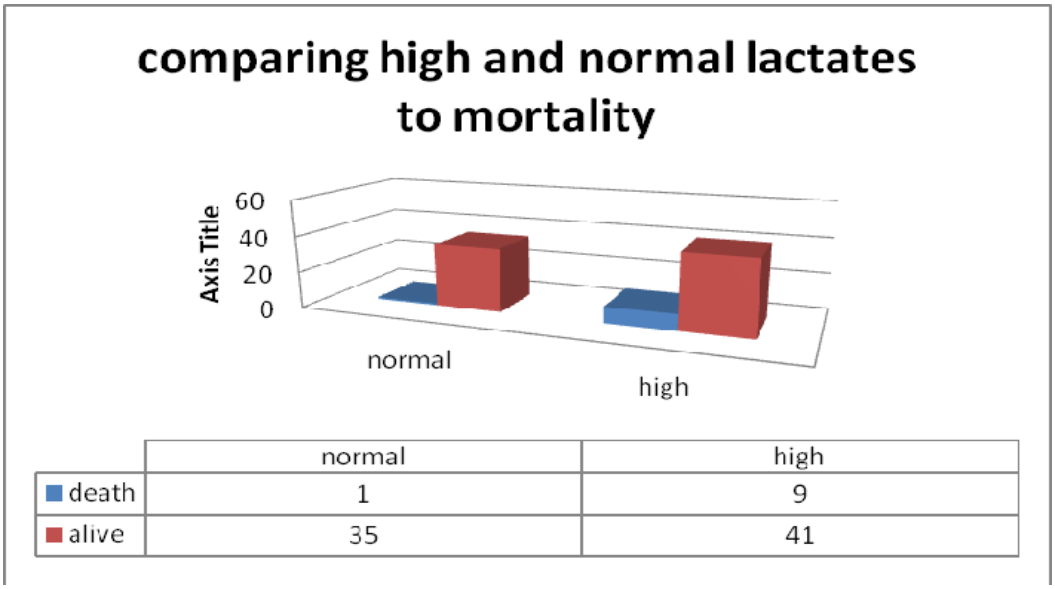

Fig. No. 12: Correlation of lactate levels to mortality

- Normal lactate: There is a single mortality rate for patients with normal lactate levels whereas 35 patients are alive.
- High lactate: There is a count of 9 mortality rate for patients with high lactate levels and 41 alive patients.

Patients with high lactate levels have a higher mortality rate than patients with normal lactate levels. Lactate levels can be an indicator of how well oxygen is being delivered to your body's tissues. High lactate levels can be a sign of shock, sepsis, or other serious medical conditions.

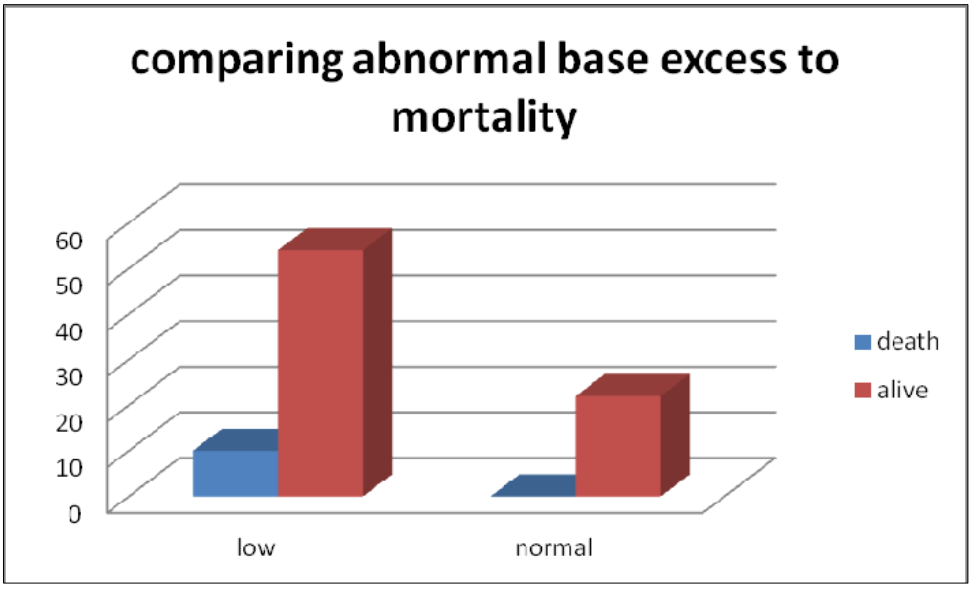

Fig. No. 13: Base excess to mortality

The data presented in the graph indicates a potential association between abnormal base excess and mortality. In simpler terms, individuals with abnormal base excess levels may have a higher likelihood of experiencing death compared to those with normal base excess levels. Nevertheless, it is important to note that the graph does not establish a direct cause-and-effect relationship. It is plausible that abnormal base excess serves as an indicator of an underlying condition that is responsible for the elevated risk of mortality.

4. DISCUSSION:

From the achieved findings from the study adds further insights to the growing body of evidences suggesting the complex relationships between the ScvO2 levels monitored among patients and its impact on patient's mortality who are presenting with polytrauma and sepsis. The study has revealed hyperoxia, which could be determined with the ScvO2 levels >75%, during the time of admission and 6 hours post-admission were associated increased likelihood of mortality risk when on comparison to that of patients presenting with normoxia and hypoxia. Findings appeared to be consistent with the previous investigation by Pope et al., (2010) in a multicentre study which presented that both hyperoxia and hypoxia were associated to higher mortality rates among patients presented with sepsis.

Furthermore, the association between hyperoxia and mortality can be attributed from multiple factors. One pertinent explanation concerning with high ScvO2 levels can be reflected from the mitochondrial or microcirculatory failure, despite adequate macrocirculatory parameters. In cases wherein, patients with sepsis and polytrauma, tissue hypoperfusion tend to take place even when the patients showcasing normal blood pressure with findings presenting with adequate cardiac output, leading to a condition known to as cryptic shock (Kumar, 2020). The maldistribution in the blood flow in microvascular level or from the mitochondrial dysfunction may lead cellular hypoxia, thus contributing in mortality or organ dysfunction (Roy & Secomb, 2021).

Furthermore, hyperoxia patients were in need of slightly longer duration for inotropes and had a higher likelihood for undergoing dialysis (Smit et al., 2018), however such differences were found to be not statistically significant in our study findings. This furthermore suggests hyperoxia cases may present with more severe illness or may led to a greater degree of organ dysfunction thereby can contribute for increased mortality risk (Singer et al., 2021). In addition, the data exhibited lower oxygen extraction ratio among hyperoxia group which in turn supported the very notion revolving around cellular hypoxia irrespective of adequate macrocirculatory parameters shown in the study.

The concept revolving around the mitochondrial dysfunction as well as with regards to the impaired oxygen utilization for patients with polytrauma and sepsis is witnessed and also supported from previous researches (Jang et al., 2017; Hof et al., 2022). Studies showed patients showcasing septic shock exhibited lower skeletal muscle ATP concentration ranges, thus attributing in the dysfunction in the mitochondrial oxidative phosphorylation (Zhang et al., 2018; Wasyluk & Zwolak, 2021). The condition of cellular hypoxia resultant from mitochondrial and microcirculatory failure may actually provide the explanation and provide valid argument revolving higher mortality rates among patients with hyperoxia (Burtscher et al., 2022).

Furthermore, the study highlighted certain key limitations on current resuscitation protocols, namely Early Goal-Directed Therapy (EGDT) algorithm, as it focused with increasing the systemic oxygen delivery or in the overall improvement of microcirculation (Zhang et al., 2017). Whilst the protocols aimed at correcting the macrocirculatory failure, they however failed in addressing microcirculatory and mitochondrial failure, that pose as the actual reason and key factor responsible for patients condition on tissue hypoxia and organ dysfunction for patients with polytrauma and sepsis.

5. CONCLUSION:

The study highlighted the significance behind monitoring ScvO2 in patients who are admitted to surgical ICU with polytrauma or sepsis. Findings suggested that both hypoxia and hyperoxia are associated with increased mortality compared to normoxia, as evidenced by the J-shaped curve relationship observed. This underscores the need for careful management of ScvO2 levels in these patients to optimize outcomes. As our study provided valuable insights, there lies several limitations that needs to be addressed. Smaller sample size might led to limited statistical power for detection of significant differences in case for some variables. Additionally, observational nature of study precludes with the causal inferences. Furthermore, upon conducting research on a larger sample sizes with devising prospective, interventional design could warrant or confirm findings credibility and can explore on devising potential interventions for improved outcomes among patient population to prevent from uncertain deaths of patients. In conclusion, our study contributes for the growing literature evidence governing this study and stressed primarily on the ScvO2 monitoring and its significance in the management of critically ill patients. Upon identifying ScvO2 levels and its association with the patient's mortality who are initially presented with sepsis or polytrauma, as the study findings provided necessary implications for the clinical practice. Future studies should strive towards further validation and confirmation on such findings and explore strategies for optimization of ScvO2 levels and achieve enhanced outcomes among such vulnerable population.

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