

# Lactate, endothelin, and central venous oxygen saturation as predictors of mortality in patients with Tetralogy of Fallot

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## ABSTRACT

**Background:** Lactate and central venous oxygen saturation (ScVO<sub>2</sub>) are well known biomarkers for adequacy of tissue oxygenation. Endothelin, an inflammatory marker has been associated with patient's nutritional status and degree of cyanosis. The aim of this study was to explore the hypothesis that lactate, ScVO<sub>2</sub> and endothelin before induction may be predictive of mortality in pediatric cardiac surgery. **Methods:** We conducted a prospective observational study of 150 pediatric (6 months to 12 years) patients who were posted for intracardiac repair for tetralogy of fallot and measured lactate, ScVO<sub>2</sub> and endothelin before induction (T<sub>1</sub>), 20 minutes after protamine administration (T<sub>2</sub>) and 24 hours after admission to ICU (T<sub>3</sub>). **Results:** Preinduction lactate and endothelin levels were found to predict mortality in patients of tetralogy of fallot with an odds ratio of 6.020 (95% CI 2.111-17.168) and 1.292(95% CI 1.091-1.531) respectively. In the ROC curve analysis for lactate at T<sub>1</sub>, the AUC was 0.713 (95% CI 0.526–0.899 *P* = 0.019). At the cutoff value of 1.750mmol/lit, the sensitivity and specificity for the prediction of mortality was 63.6% and 65.5%, respectively. For endothelin at T<sub>1</sub>, the AUC was 0.699 (95% CI 0.516–0.883, *P* = 0.028) and the cutoff value was ≤2.50 (sensitivity, 63.6%; specificity, 58.3 %). ScVO<sub>2</sub> (odds ratio 0.85) at all three time intervals, suggested that improving ScVO<sub>2</sub> can lead to 15% reduction in mortality. **Conclusions:** Lactate, ScVO<sub>2</sub> and endothelin all showed association with mortality with lactate having the maximum prediction. Lactate was found to be an independent, reliable and cost-effective measure of prediction of mortality in patients with tetralogy of fallot.

**Key words:** Central venous oxygen saturation; Epinephrine; Liver disease; Thiamine deficiency

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## INTRODUCTION

Central venous oxygen saturation (ScVO<sub>2</sub>) is a projection of balance between oxygen demand and supply. Its value decreases in condition with low oxygen supply as in the presence of low cardiac output, decreased hemoglobin, decreased arterial oxygen saturation, or in cases of increased oxygen demand as in cases of shivering, fever, agitation, and hypermetabolic state.<sup>[1]</sup>

Lactate, another routinely performed parameter, is elevated not only secondary to systemic hypoperfusion but also in liver disease, thiamine deficiency, epinephrine, other drugs/toxins, and inborn errors of metabolism.<sup>[1]</sup> Markedly elevated lactate levels in the setting of a normal

ScVO<sub>2</sub> following on-pump cardiac surgery were found to be associated with significantly higher incidence of major complications and prolonged length of stay in a study by Laine *et al.* In

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addition, a lactate level  $\geq 4$  mmol/L was found to be an independent predictor of major complications.<sup>[1]</sup> Lactate and ScVO<sub>2</sub> have been proven to have predictive power for major adverse events after pediatric cardiac surgery.<sup>[2]</sup>

Cyanotic patients with Tetralogy of Fallot (TOF) undergoing repair of heart defects are thought to have greater susceptibility to ischemia and reoxygenation injury because of chronic hypoxia.<sup>[3]</sup> ScVO<sub>2</sub> and blood lactate are different indices of the adequacy of oxygen delivery to the oxygen needs.<sup>[4]</sup> In patients with congenital heart disease undergoing surgery on cardiopulmonary bypass (CPB), there is a tendency for ScVO<sub>2</sub> to decrease and blood lactate to rise.<sup>[5]</sup>

Endothelin is also a marker of tissue inflammation and hypoxia. Its increased release has been documented in the early post-CPB period. During CPB, ischemia-reperfusion injury to the heart is associated with release of endothelin. This leads to both systolic and diastolic myocardial dysfunction that is considered to be a major cause of postbypass low cardiac output syndrome.<sup>[6]</sup> In our previous work,<sup>[3]</sup> we found correlation between baseline endothelin level and patients' nutritional status and degree of cyanosis. We hypothesize that this increase in endothelin preoperatively can also act as a predictor of mortality in patients of tetralogy.

Seeing paucity in literature about ScVO<sub>2</sub>, lactate, and especially endothelin as predictor of mortality in TOF patients, we undertook this study.

The aim of this study was to determine lactate levels, endothelin along with ScVO<sub>2</sub> in patients undergoing open intracardiac repair in TOF patients at three different time intervals.

## MATERIALS AND METHODS

After approval from the Institute Ethics Committee and written informed consent from the patients or parents (in case of children), a prospective, observational study was conducted in 150 patients between 6 months and 12 years of age with TOF undergoing elective intracardiac repair. Patients with preexisting congestive cardiac failure, coagulopathy, renal failure (serum creatinine  $>2$  mg/dL, anuria, or oliguria requiring dialysis), hepatic dysfunction (aspartate aminotransferase  $>40$  U/L, alanine aminotransferase  $>40$  U/L), immune or central nervous system dysfunction, local or systemic infection or inflammation (fever, leukocytosis), and on immunosuppressive or

anti-inflammatory therapy were excluded from the study.

Ketamine (1–2 mg/kg) and fentanyl (3–5  $\mu$ g/kg) were administered for the induction of anesthesia and rocuronium (1 mg/kg) was used for endotracheal intubation. Maintenance of anesthesia was done with intermittent doses of fentanyl and midazolam, and muscle relaxation was supplemented with vecuronium.

After induction of anesthesia, patient received a percutaneously inserted right internal jugular vein catheter ScVO<sub>2</sub> (Edwards PediaSat oximetry catheter sized 4.5 Fr or 5.5 Fr) or a PreSep catheter (Edwards Lifesciences, CA, USA) in case of adults more than 14 years of age for measuring continuous ScVO<sub>2</sub> on Vigileo Monitor screen during CPB and up to 48 h post-CPB.

Corticosteroids or antifibrinolytics were not administered to any patient. Before initiation of CPB, heparin was administered into a central vein in the dosage of 400 U/kg to maintain the kaolin activated clotting time (ACT) above 480 s. A membrane oxygenator was used for all patients during the CPB. The CPB circuit was primed with lactated ringer solution 20 mL/kg; sodium bicarbonate (7.5%) 1 mL/kg; mannitol (20%) 0.5 g/kg; and heparin 100 U/kg. All patients were cooled to 28°C while on CPB. Myocardial protection was achieved by using blood cardioplegia solution with a cardioplegia delivery system. Systemic pump flows were maintained between 120 and 200 mL/kg/min. Packed red blood cells were added on CPB, and conventional ultrafiltration was performed during the rewarming phase of CPB to maintain a hematocrit of 25–35%. After separation from CPB, protamine sulfate was administered in a dose of 1.0 mg per 100 U of heparin to reverse the effects of heparin. An additional dose of protamine 0.5 mg/kg was administered if the ACT was more than 130 s.

Patients have weaned from CPB at 36°C nasopharyngeal temperature. Vasopressors (dopamine, dobutamine, adrenaline, noradrenaline) were used as required to maintain hemodynamics.

Baseline blood samples were collected before induction of anesthesia (T1), 20 min after protamine administration (T2), and 24 h after admission to Intensive Care Unit (ICU) (T3) in vacutainer tubes. Plasma was recovered immediately from these samples by centrifugation (3000 rpm for ten minutes) at 4°C, divided into aliquots, and frozen at  $-70^{\circ}\text{C}$  until use. The endothelin levels were measured using by Human Endothelin-1 ELISA

kit (Fitzgerald Industries International, USA). Arterial blood sample was collected in heparinized syringe and was sent for blood gas analysis that included lactate.

ScVO<sub>2</sub> was recorded corresponding to sampling times (T<sub>1</sub>, T<sub>2</sub>, and T<sub>3</sub>) from Vigileo monitor.

### Outcomes

The outcomes were ScVO<sub>2</sub>, endothelin, and lactate levels at three different time intervals and their association with mortality.

Mortality was defined as death occurring during the hospital stay.

### Statistical analysis

The data were analyzed using SPSS version 17 software (SPSS, Chicago, IL, USA). Quantitative data were described as mean and standard deviation and qualitative data by frequency and percentage. The analysis of quantitative variables with normal distribution was analyzed using Student's *t*-test and for nonparametric test the Mann–Whitney test was used. For qualitative data, we used the Chi-square test.

Association of independent variables with the outcome measurements, i.e. mortality was explored by using a logistic regression analysis. Multivariate logistic regression analysis was used, producing odds ratios with a 95% confidence interval (CI).

The predictive accuracy of lactate, ScVO<sub>2</sub>, and endothelin for mortality was explored by using the receiver operating characteristic (ROC) curve and the relative area under the curve (AUC). For each parameter, different cutoff points were tested for sensitivity and specificity.

*AP* < 0.05 was considered to be statistically significant for all statistical tests.

### RESULTS

In this prospective observational study, 150 patients between 6 months 12 years of age with TOF underwent elective intracardiac repair. Out of the total 150 patients, 139 (92.7%) survived with a mortality of 11 (7.3%) patients.

Uni- and multi-variate logistic regression analyses were performed to determine significant predictors of mortality. Preinduction parameters of lactate, ScVO<sub>2</sub>, and endothelin levels among survivors and nonsurvivors are depicted in Table 1. Lactate and endothelin level showed significant difference between survivors and nonsurvivors (*P* = 0.000, *P* = 0.003) while ScVO<sub>2</sub> had no significant difference between survivors and non survivors (*P* = 0.092). Preinduction lactate and endothelin levels were also found to predict mortality in patients of TOF with an odds ratio of 6.020 (95% CI, 2.111–17.168) and 1.292 (95% CI, 1.091–1.531), respectively [Table 1].

**Table 1: Mortality prediction with parameters at baseline preinduction (T<sub>1</sub>)**

Parameter	Survivors (139)	Nonsurvivors (11)	<i>P</i>	OR (95% CI)
Lactate (T <sub>1</sub> )	1.62±0.038	2.29±0.278	0.000	6.020 (2.111-17.168)
ScVO <sub>2</sub> (T <sub>1</sub> )	57.94±0.42	55.27±1.67	0.092	0.881 (0.759-1.023)
Endothelin (T <sub>1</sub> )	2.68±0.196	5.45±1.337	0.003	1.292 (1.091-1.531)

OR: Odds ratio, CI: Confidence interval

**Table 2: Mortality prediction with parameters at 20 min postprotamine (T<sub>2</sub>)**

Parameter	Survivors (139)	Nonsurvivors (11)	<i>P</i>	OR (95% CI)
Lactate (T <sub>2</sub> )	3.202±0.637	3.263±0.708	0.761	1.161 (0.444-3.034)
ScVO <sub>2</sub> (T <sub>2</sub> )	74.90±5.177	60.55±16.591	0.000	0.851 (0.789-0.918)
Endothelin (T <sub>2</sub> )	8.74±6.284	13.36±10.856	0.044	1.066 (1.002-1.135)

OR: Odds ratio, CI: Confidence interval

**Table 3: Mortality prediction with parameters at 24 h after admission to Intensive Care Unit (T<sub>3</sub>)**

Parameter	Survivors (139)	Nonsurvivors (11)	<i>P</i>	OR (95% CI)
Lactate (T <sub>3</sub> )	2.056±0.542	3.009±1.217	0.000	4.946 (2.085-11.732)
ScVO <sub>2</sub> (T <sub>3</sub> )	68.17±4.530	53.09±16.152	0.000	0.838 (0.770-0.912)
Endothelin (T <sub>3</sub> )	5.55±4.371	10.09±5.147	0.005	1.143 (1.040-1.255)

OR: Odds ratio, CI: Confidence interval

At T<sub>2</sub> and T<sub>3</sub> also, lactate and endothelin were found to be predictors of mortality [Tables 2 and 3].

The trend analysis of lactate, ScVO<sub>2</sub>, and endothelin with time (T<sub>1</sub>, T<sub>2</sub>, and T<sub>3</sub>) is shown in Figures 1-3, respectively. All parameter showed a similar trend with peak levels 20 min after protamine and a decline at 24 h after admission in ICU although these values were higher than the preinduction values, except in nonsurvivors; ScVO<sub>2</sub> levels 24 h after ICU admission were lower than preinduction values.

The ROC for mortality in relation with lactate levels, ScVO<sub>2</sub>, and endothelin levels at different time intervals is depicted in Figures 4-6, respectively. Different cutoff points explored for sensitivity and specificity are also depicted.

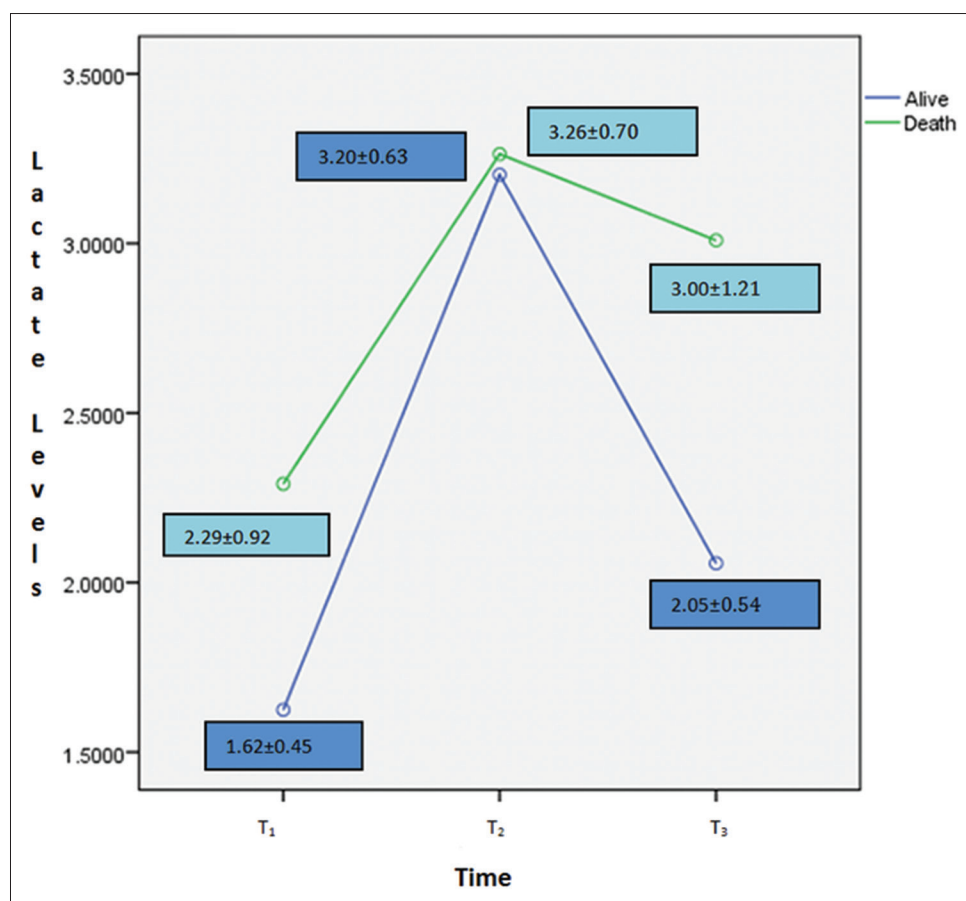
In the ROC curve analysis for lactate at T<sub>1</sub>, which was a significant biomarker, the AUC was 0.713 (95% CI, 0.526–0.899, *P* = 0.019) [Figure 4]. The cutoff value with both maximal sensitivity and specificity was 1.750 mmol/l. At this cutoff, the sensitivity and specificity of lactate for the prediction of mortality were

63.6% and 65.5%, respectively. For endothelin at T<sub>1</sub>, the AUC was 0.699 (95% CI, 0.516–0.883, *P* = 0.028) and the cut-off value was ≤2.50 (sensitivity, 63.6%; specificity, 58.3%) [Figure 6]. Similarly, values at T<sub>2</sub> and T<sub>3</sub> are depicted in the same figure.

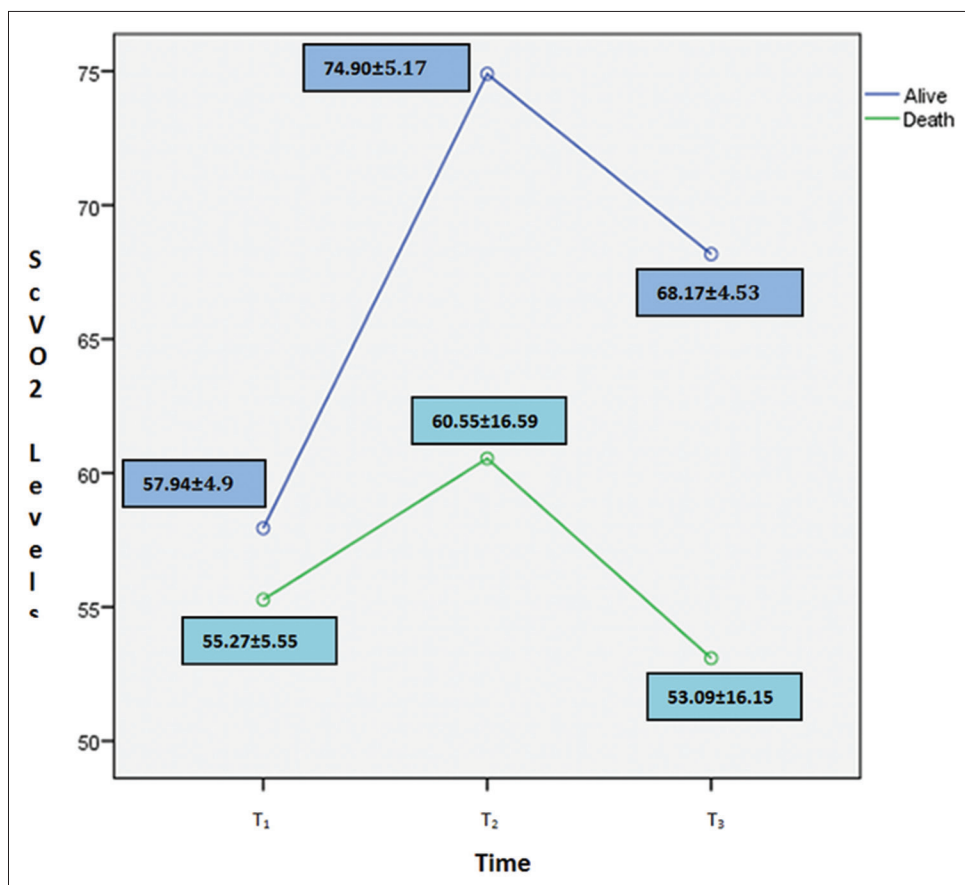
## DISCUSSION

Lactate and ScVO<sub>2</sub> are markers of hypoperfusion and hypoxia while endothelin is an inflammatory marker.

The clinical application of ScVO<sub>2</sub> as a surrogate for tissue oxygenation has generated interest in recent years. Continuous monitoring and maintenance of ScVO<sub>2</sub> above 70% has been successfully used as an early goal-directed therapy in the management of early sepsis, resulting in a 15% reduction of mortality and leading to an adoption in the guidelines of the Surviving Sepsis Campaign.<sup>[6,7]</sup> The lowest ScVO<sub>2</sub> was independently associated with postoperative complications after major surgery in adults.<sup>[8]</sup> Thus, continuous measurement of ScVO<sub>2</sub>, in combination with other surrogates of organ perfusion (vital signs, lactate concentrations,



**Figure 1:** Trend analysis of total lactate levels at various time intervals among survivors and nonsurvivors



**Figure 2:** Trend analysis of total central venous oxygen saturation levels at various time intervals among survivors and nonsurvivors

urine output), can be used as a reliable monitor of cardiocirculatory function.<sup>[9]</sup>

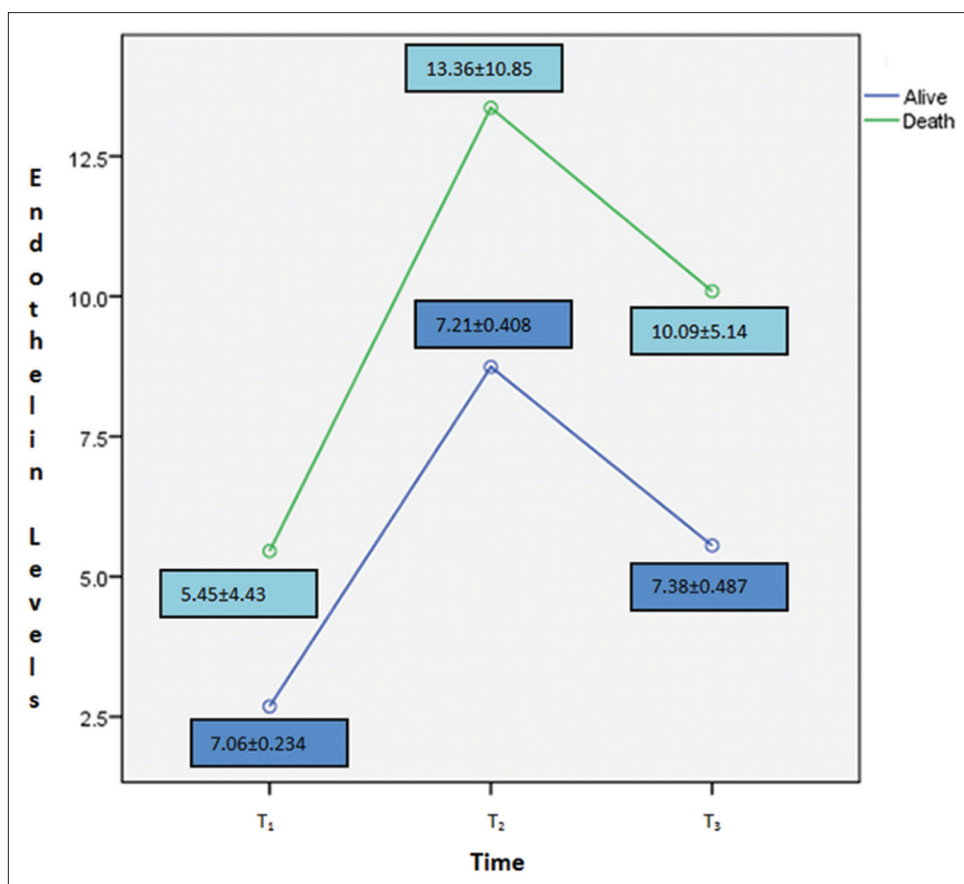
The results of our study showed significant association of lactate and ScVO<sub>2</sub> with mortality at all 3 time intervals. This is similar to the results by Ranucci *et al.*<sup>[4]</sup> although they studied nadir ScVO<sub>2</sub> and peak lactate levels only during CPB. We did not take values during CPB because ScVO<sub>2</sub> levels vary and are usually not reliable during CPB and its values can easily be corrected by increasing the pump flow rates. ScVO<sub>2</sub> and lactate in our study at T<sub>2</sub> had an odds ratio of 0.851 (95% CI, 0.789–0.918) and 1.161 (95% CI, 0.444–3.034), respectively which was comparable to 0.89 (0.84–0.95) for ScVO<sub>2</sub>; however, for lactate, the odds ratio was 2 (1.46–2.76), double the value of our study. The difference can be explained since they took the peak lactate values during CPB while ours was time-bound value taken at 20 min after protamine administration. At T<sub>2</sub>, we found even endothelin to be a predictor of mortality with an odds ratio of 1.066.

In a prospective, observational study of 52 patients by Seear *et al.*,<sup>[2]</sup> measurements were made at 3,

6, 9, 12, and 24 h after surgery, including oxygen consumption, ScVO<sub>2</sub>, cardiac output (Fick), heart rate, arterial pressure, arterial lactate, urine output, core-toe temperature gradient, and derived hemodynamic variables. Lactate and ScVO<sub>2</sub> were the only postoperative measurements found to have predictive power for major adverse events. This correlates with our study where at T<sub>3</sub> lactate, ScVO<sub>2</sub>, and even endothelin were found to be associated with mortality although the odds were higher for outcome with lactate (4.946) and endothelin (1.143).

In a retrospective study<sup>[10]</sup> of 452 cardiac surgery patients, it was found that elevated ScVO<sub>2</sub> does not guarantee sufficient tissue oxygenation. Since ScVO<sub>2</sub> reflects only the oxygen metabolism in perfused microvascular beds with maintained cellular respiration additional lactate measurements were essential. ScVO<sub>2</sub> values improve with maintaining cardiac output despite the increase in lactate and endothelin levels.

High endothelin levels have been found in patients with severe cardiovascular stress, including cardiogenic shock, acute myocardial infarction, congestive heart



**Figure 3:** Trend analysis of total endothelin levels at various time intervals among survivors and nonsurvivors

failure, and essential hypertension.<sup>[11]</sup> Several studies have been done where postoperative lactate and ScVO<sub>2</sub> have been associated with mortality; however, to the best of our knowledge, no study provides endothelin as predictor of mortality.

The normal values of plasma ET-LI (plasma endothelin-like immunoreactivity) concentrations vary with age.<sup>[12]</sup> It is highest in infants younger than 3 months after which it is nearly constant and similar to that in adults.<sup>[13]</sup> Therefore, we included patients ranging from 6 months to 12 years of age.<sup>[12]</sup>

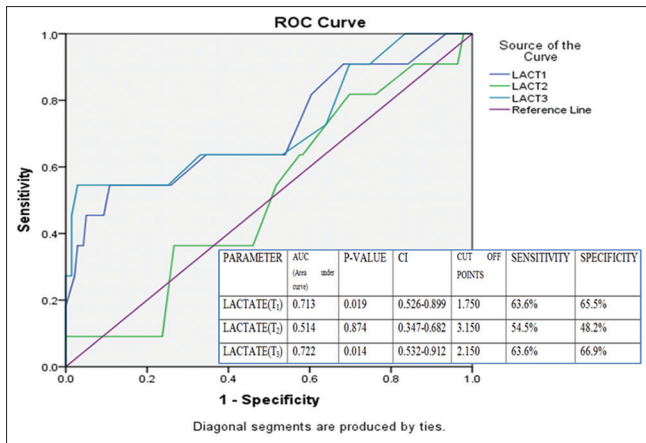
We found among 150 patients baseline lactate and endothelin as predictors of mortality. ScVO<sub>2</sub> at baseline was also associated with mortality. With an odds ratio of average 0.85 at all 3 time intervals, it can be said that improving ScVO<sub>2</sub> can lead to 15% reduction in mortality.

Lactate levels preinduction was found to be significant predictor of mortality with an odds ratio of 6.020 (95% CI, 2.111–17.168) in patients with TOF while endothelin

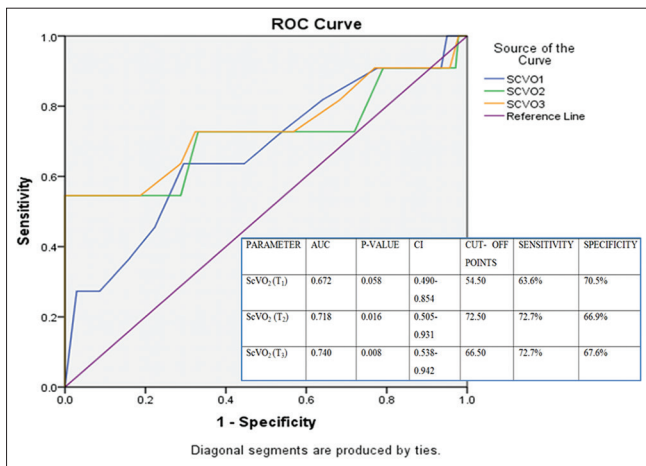
had an odd's ratio of 1.292 (95% CI, 1.091–1.531). Similar results were noted at T<sub>2</sub> and T<sub>3</sub>. The earlier the prediction, the better management of such high-risk population can be planned to avoid mortality.

Endothelin levels peaked 20 min after protamine and declined at 24 h after admission in ICU although these values were higher than the preinduction values. A similar trend was observed by Shirakami *et al.*<sup>[14]</sup> who studied effect of anesthesia and surgery on endothelin levels and found maximum increase following cardiac surgery ( $43.1 \pm 4.1$  pg/mL,  $n = 18$ ). They also found trends similar to our study where plasma ET-LI level did not increase during the initial 2 h, but increased gradually during surgery, reached a peak within a few hours after surgery, and declined slowly thereafter.

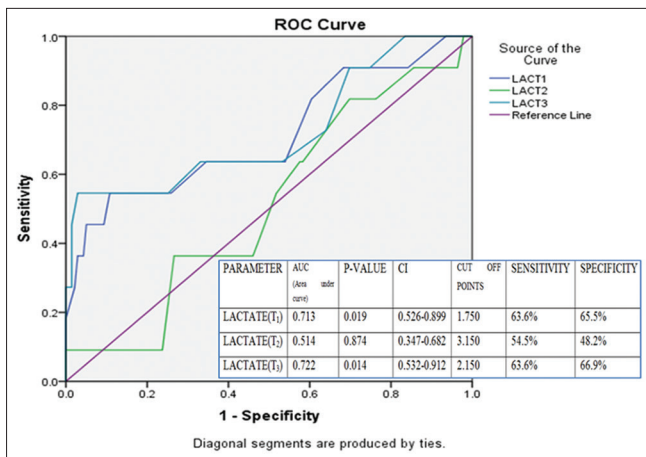
ScVO<sub>2</sub> catheter costs around 5000 rupees. Similarly, single endothelin test costs around 2000–2200 rupees. Although we compared all three parameters namely lactate, ScVO<sub>2</sub>, and endothelin, lactate seems to be the most cost-effective method for prediction of mortality



**Figure 4:** Receiver operating characteristic curve of lactate for prediction of mortality (LACT: Lactate1; AUC: Area under the ROC curve=0.713; CI: 95% Confidence intervals). Circle on receiver operating characteristic curve mean the cutoff value with maximal value of sum of sensitivity and specificity



**Figure 5:** Receiver operating characteristic curve of for prediction of mortality



**Figure 6:** Receiver operating characteristic curve of endothelin for prediction of mortality

since routinely done investigation of arterial blood gas analysis report provides us with lactate values. This

study done for research purpose emphasizes the role of ScVO<sub>2</sub> and endothelin as predictors of mortality but propagates its use based on cost-benefit ratio.

**Limitation**

ScVO<sub>2</sub>, lactate, and endothelin measurements were not performed at frequent intervals than 3 time intervals. This was mainly due to the cost associated with measuring endothelin. Lactate as a biomarker as influenced by other intraoperative factors such as postoperative hypoxia and the clearance of lactate post-CPB.

**CONCLUSION**

All the three parameters studied showed association with mortality with lactate having the maximum prediction. ScVO<sub>2</sub> monitoring although valuable is invasive, expensive, and cumbersome. Endothelin, a newer marker taken up by us for research purpose, is also not cost-effective. Finally, lactate alone is an independent, reliable, and cost-effective measure of prediction of mortality in patients with TOF and could potentially help clinicians in the initial risk assessment of TOF patients.

More prospective, randomized trials are needed to justify that baseline lactate and endothelin levels can be used as predictors of mortality.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

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