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Research Article

Physiological, Biochemical, and Pathological Determinants of Oxidative Stress in Pediatric Sepsis Requiring Intensive Care

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ABSTRACT

Background: Oxidative stress contributes to endothelial dysfunction, mitochondrial injury, and multiple-organ failure in pediatric sepsis, but its major clinical determinants remain insufficiently defined. This study evaluated physiological, biochemical, and pathological factors associated with oxidative stress among children with sepsis requiring intensive care.

Methods: This multicentre prospective observational cohort study included 120 children aged 1 month to 15 years admitted with sepsis between January and August 2025. Clinical and laboratory variables were recorded within six hours of admission. Malondialdehyde, 8-hydroxy-2′-deoxyguanosine, total antioxidant capacity, superoxide dismutase, and reduced glutathione were measured, and a composite oxidative stress index was calculated. Multivariable regression identified independent determinants of oxidative stress and its relationship with outcomes.

Results: The cohort included 68 males and 52 females. Septic shock occurred in 54 children, acute kidney injury in 34, pediatric acute respiratory distress syndrome in 29, and mortality in 25. Children with high oxidative stress had higher lactate concentrations, vasoactive-inotropic scores, rates of septic shock, mechanical ventilation, organ dysfunction, and mortality, but lower serum albumin and antioxidant levels. Independent determinants were serum lactate, vasoactive-inotropic score, hypoalbuminemia, septic shock, acute kidney injury, and pediatric acute respiratory distress syndrome. High oxidative stress independently predicted intensive care mortality.

Conclusion: Oxidative stress in pediatric sepsis reflects the combined effects of circulatory failure, reduced antioxidant reserve, and organ injury. Early recognition of these determinants may improve biological risk stratification in critically ill children and support timely escalation of organ-supportive management in intensive care settings.

Keywords: Pediatric Sepsis, Oxidative Stress, Malondialdehyde, Antioxidant Capacity, Septic Shock, Acute Kidney Injury, Intensive Care.

INTRODUCTION

Pediatric sepsis is a life-threatening syndrome in which an infection produces dysregulated host responses and acute organ dysfunction [1]. It remains a major cause of admission, prolonged hospitalization, multiple-organ dysfunction, and death in pediatric intensive care units, particularly in resource-limited settings where delayed presentation, malnutrition, restricted diagnostic facilities, and limited access to advanced organ support may increase disease severity. The 2024 international consensus criteria define pediatric sepsis as suspected or confirmed infection accompanied by a Phoenix Sepsis Score of at least 2, representing potentially life-threatening dysfunction of the respiratory,

cardiovascular, coagulation, or neurological systems. Septic shock is identified when sepsis is accompanied by cardiovascular dysfunction[2,3].

The progression of pediatric sepsis is determined not only by the infecting organism but also by complex interactions among immune activation, endothelial injury, microcirculatory dysfunction, coagulation abnormalities, mitochondrial impairment, and altered cellular metabolism[4]. Excessive inflammatory signaling promotes the activation of neutrophils, monocytes, platelets, and vascular endothelial cells, leading to the release of reactive oxygen and nitrogen species. Although these molecules participate in normal antimicrobial defense and intracellular signaling, their uncontrolled production may exceed the capacity of endogenous antioxidant systems. The resulting imbalance between oxidant generation and antioxidant protection is referred to as oxidative stress[5,6].

Oxidative stress contributes to sepsis-related cellular injury through lipid peroxidation, protein oxidation, mitochondrial dysfunction, nucleic-acid damage, endothelial barrier disruption, and activation of pro-apoptotic pathways[7]. Mitochondrial injury may further reduce adenosine triphosphate production and increase electron leakage, creating a self-perpetuating cycle of reactive oxygen species formation and cellular energy failure. At the vascular level, oxidative injury impairs vasomotor regulation, increases capillary permeability, promotes leukocyte adhesion, and contributes to tissue edema and heterogeneous organ perfusion. These abnormalities may explain why apparently adequate systemic blood pressure and oxygen delivery do not always prevent progressive organ dysfunction in severe sepsis[8,9].

Several biomarkers have been used to characterize oxidative stress in critically ill children. Malondialdehyde is a product of polyunsaturated fatty-acid peroxidation and reflects oxidative injury to cell membranes[10]. Eight-hydroxy-2′-deoxyguanosine indicates oxidative DNA damage, while total antioxidant capacity represents the combined activity of circulating enzymatic and non-enzymatic antioxidants. Superoxide dismutase converts superoxide radicals into hydrogen peroxide, whereas reduced glutathione is an important intracellular antioxidant involved in peroxide detoxification and maintenance of cellular redox balance. Pediatric studies have demonstrated increased oxidant activity, altered thiol–disulfide homeostasis, and reduced antioxidant defence in children with sepsis, supporting a biologically important role for redox imbalance in disease progression[11,12].

The magnitude of oxidative stress may be influenced by several physiological disturbances commonly observed in pediatric sepsis[13]. Hypotension, prolonged capillary refill, hyperlactatemia, hypoxemia, fever, tachycardia, reduced urine output, and increasing vasoactive requirements may indicate impaired tissue perfusion and cellular oxygen utilization[14]. Tissue ischemia followed by reperfusion can markedly increase reactive oxygen species generation, while persistent adrenergic stimulation and severe cardiovascular dysfunction may intensify metabolic and mitochondrial stress. Elevated lactate, although not exclusively caused by tissue hypoxia, may therefore identify children with severe circulatory and metabolic derangement who are likely to experience a greater oxidative burden[15,16].

Biochemical abnormalities may additionally modify oxidant production and antioxidant reserve. Hypoalbuminemia may reduce extracellular antioxidant capacity because albumin contains reactive thiol groups and binds potentially pro-oxidant substances[17]. Hyperglycemia can promote mitochondrial reactive oxygen species generation, whereas acidosis, electrolyte disturbances, hepatic dysfunction, and impaired renal clearance may alter antioxidant enzyme activity or permit the accumulation of oxidative products. Inflammatory markers such as C-reactive protein and procalcitonin may also reflect the intensity of the systemic response associated with increased oxidant generation. However, conventional biochemical markers do not directly measure cellular oxidative injury, and their relationship with specific redox biomarkers in pediatric sepsis remains incompletely defined[18].

Pathological manifestations of severe sepsis, including septic shock, acute kidney injury, pediatric acute respiratory distress syndrome, hepatic dysfunction, disseminated intravascular coagulation, and multiple-organ dysfunction, may both result from and amplify oxidative stress. In the kidneys, mitochondrial and endothelial injury can promote tubular damage, while reduced clearance may increase circulating oxidative metabolites[19]. In the lungs, activated neutrophils, infection, supplemental oxygen exposure, and mechanical ventilation may contribute to oxidative epithelial and endothelial injury. Similarly, coagulation activation and microvascular thrombosis may worsen tissue ischemia and subsequent reperfusion-related oxidant production. These bidirectional relationships make it difficult to determine whether oxidative stress is primarily a marker of disease severity, an independent contributor to organ injury, or both[20].

Previous studies have frequently compared oxidative biomarkers between septic and non-septic children or evaluated individual markers in relatively small populations[5-7]. Consequently, limited evidence is

available regarding the simultaneous physiological, biochemical, and pathological determinants of oxidative stress among children already requiring intensive care. Recent investigations have also emphasized that larger clinical studies are needed before oxidative-stress measurements can be incorporated into routine pediatric sepsis assessment. Moreover, current pediatric sepsis guidance does not support routine antioxidant supplementation in the absence of a confirmed deficiency, highlighting the need for improved biological characterization before redox-directed treatments are considered[10-14]. Therefore, the present study aimed to identify the physiological, biochemical, and pathological factors associated with oxidative stress among children with sepsis requiring pediatric intensive care. It also evaluated the relationship of oxidative-stress biomarkers with septic shock, multiple-organ dysfunction, mechanical ventilation, duration of intensive care admission, and mortality. We hypothesized that circulatory hypoperfusion, greater vasoactive requirements, impaired antioxidant reserve, and sepsis-associated organ injury would independently predict a higher oxidative-stress burden.

MATERIALS AND METHODS

Study Design and Setting

This multicentre prospective observational cohort study was conducted from January to August 2025. Children with sepsis were recruited primarily from the Department of Pediatric Medicine, Shahida Islam Teaching Hospital, Lodhran, Punjab, Pakistan. Additional clinical data were obtained from pediatric patients receiving intensive care support in the Department of Anesthesia, Jinnah Hospital, Lahore, Pakistan. Oxidative-stress biomarker analysis was performed in the Department of Biochemistry, Quaid-e-Azam Medical College, Bahawalpur, Punjab, Pakistan.

Study Population

A total of 120 children aged 1 month to 15 years with suspected or confirmed infection and sepsis requiring intensive care were enrolled through consecutive sampling. Pediatric sepsis was defined as infection accompanied by a Phoenix Sepsis Score of at least 2, while septic shock was defined by the presence of cardiovascular dysfunction.

Children with chronic kidney or liver disease, malignancy, congenital metabolic disorders, primary immunodeficiency, autoimmune disease, or long-term immunosuppressive therapy were excluded. Patients receiving antioxidant supplements during the preceding four weeks, those treated in another intensive care unit for more than 24 hours before sampling, and those with inadequate or hemolyzed samples were also excluded.

Sample-Size Calculation

The sample size was calculated for multivariable regression using a moderate effect size of 0.15, 80% statistical power, a 5% significance level, and approximately 10 potential predictors. The required sample was rounded to 120 participants.

Data Collection

Demographic and clinical data included age, sex, nutritional status, comorbidities, duration of illness, source of infection, previous antimicrobial use, microbiological findings, and treatment received. Physiological variables recorded over the first 6 hours included temperature, heart rate, respiratory rate, blood pressure, oxygen saturation, capillary refill time, urine output, level of consciousness, need for mechanical ventilation and for vasoactive support. The highest vasoactive-inotropic score during the first 24 hours was calculated. The Phoenix Sepsis Score was determined using the most abnormal respiratory, cardiovascular, coagulation, and neurological findings recorded during the first 24 hours.

Laboratory Assessment

Routine investigations included complete blood count, serum lactate, blood glucose, albumin, bilirubin, liver enzymes, urea, creatinine, electrolytes, C-reactive protein, procalcitonin, blood gases, and coagulation profile. Blood cultures and other clinically indicated specimens were collected before antimicrobial treatment whenever possible.

Hyperlactatemia was defined as serum lactate of at least 4 mmol/L, while hypoalbuminemia was defined as serum albumin below 3.0 g/dL.

Oxidative-Stress Biomarkers

Approximately 4 mL of venous blood was collected within six hours of intensive care admission or recognition of sepsis. Serum and plasma were separated by centrifugation and stored at −80°C until analysis.

Malondialdehyde was measured as a marker of lipid peroxidation using the thiobarbituric acid-reactive substances method. Eight-hydroxy-2′-deoxyguanosine was measured by enzyme-linked immunosorbent assay as a marker of oxidative DNA damage. Total antioxidant capacity, superoxide dismutase activity, and reduced glutathione were measured using standard spectrophotometric

methods. All samples were analyzed in duplicate, and laboratory personnel were blinded to clinical outcomes.

Oxidative Stress Index

A composite oxidative stress index was calculated using standardized values of malondialdehyde, 8-hydroxy-2′-deoxyguanosine, total antioxidant capacity, superoxide dismutase, and reduced glutathione. Higher values represented greater oxidative injury and reduced antioxidant defense. High oxidative stress was defined as an index within the upper tertile of the study population.

Pathological Determinants and Outcomes

Pathological determinants included septic shock, acute kidney injury, pediatric acute respiratory distress syndrome, hepatic dysfunction, coagulation dysfunction, bacteremia, and multiple-organ dysfunction syndrome. Acute kidney injury was classified using serum creatinine and urine-output criteria. Multiple-organ dysfunction was defined as dysfunction of at least two organ systems.

The primary outcome was the composite oxidative stress index. Secondary outcomes included mechanical ventilation, vasoactive support, acute kidney injury, pediatric acute respiratory distress syndrome, multiple-organ dysfunction, length of intensive care stay, and mortality.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics version 29. Continuous variables were presented as mean ± standard deviation or median with interquartile range, while categorical variables were reported as frequencies and percentages. Between-group comparisons were performed using the independent-samples t test, Mann–Whitney U test, chi-square test, or Fisher exact test, as appropriate.

Pearson or Spearman correlation was used to assess relationships between oxidative biomarkers and clinical variables. Univariable and multivariable linear regression were performed to identify determinants of the oxidative stress index. Logistic regression was used to determine independent predictors of high oxidative stress and mortality. Adjusted odds ratios with 95% confidence intervals were reported, and a p value below 0.05 was considered statistically significant.

Ethical Considerations

Ethical approval was obtained from the relevant institutional review boards before recruitment. Written informed consent was obtained from the parents or legal guardians of all participants. The confirmed ethics approval numbers should be inserted before manuscript submission.

RESULTS

A total of 132 children with suspected or confirmed sepsis were assessed for eligibility. Twelve were excluded because of chronic renal or hepatic disease, previous prolonged intensive care treatment, antioxidant supplementation, or inadequate blood specimens. The final analysis included 120 children. Both sexes were represented, including 68 males (56.7%) and 52 females (43.3%), giving a male-to-female ratio of 1.3:1. The median age was 4.1 years (interquartile range, 1.4–8.0 years). The median age was 4.2 years among males and 4.0 years among females, with no significant difference between the groups (p=0.714). Malnutrition was present in 35 children (29.2%).

Respiratory tract infection was the most frequent source of sepsis, occurring in 51 children (42.5%), followed by bloodstream infection in 24 (20.0%), central nervous system infection in 18 (15.0%), intra-abdominal infection in 15 (12.5%), and other infections in 12 (10.0%). Microbiological cultures were positive in 48 children (40.0%).

The median Phoenix Sepsis Score was 5 (interquartile range, 3–7). Septic shock was diagnosed in 54 children (45.0%), while 64 (53.3%) required mechanical ventilation. Acute kidney injury occurred in 34 children (28.3%), pediatric acute respiratory distress syndrome in 29 (24.2%), disseminated intravascular coagulation in 17 (14.2%), and multiple-organ dysfunction in 44 (36.7%). Twenty-five children died during intensive care admission, giving an overall mortality rate of 20.8%.

High oxidative stress, defined as a composite oxidative stress index within the upper tertile of the study population, was present in 40 children (33.3%). The remaining 80 children (66.7%) had lower or moderate oxidative stress. High oxidative stress was observed in 24 of 68 males (35.3%) and 16 of 52 females (30.8%). The difference was not statistically significant (p=0.602), indicating that sex was not associated with oxidative-stress category.

Children with high oxidative stress had significantly higher frequencies of malnutrition, septic shock, prolonged capillary refill, mechanical ventilation, acute kidney injury, pediatric acute respiratory distress syndrome, disseminated intravascular coagulation, and multiple-organ dysfunction. They also had higher serum lactate concentrations and vasoactive-inotropic scores, lower serum albumin concentrations, longer intensive care stays, and higher mortality, as shown in Table 1.

Table 1. Clinical and Biochemical Characteristics According to Oxidative-Stress Category

Characteristic	Lower or moderate oxidative stress (n=80)	High oxidative stress (n=40)	p value
Age, years, median (interquartile range)	4.3 (1.6–8.2)	3.7 (1.1–7.4)	0.318
Male, n (%)	44 (55.0)	24 (60.0)	0.602
Female, n (%)	36 (45.0)	16 (40.0)	0.602
Malnutrition, n (%)	18 (22.5)	17 (42.5)	0.022
Septic shock, n (%)	25 (31.3)	29 (72.5)	<0.001
Capillary refill greater than 3 seconds, n (%)	22 (27.5)	24 (60.0)	0.001
Vasoactive-inotropic score, median (interquartile range)	4 (0–9)	17 (8–29)	<0.001
Serum lactate, mmol/L, median (interquartile range)	2.8 (1.8–4.2)	5.5 (3.7–7.8)	<0.001
Serum albumin, g/dL, mean ± standard deviation	3.18 ± 0.59	2.67 ± 0.56	<0.001
Mechanical ventilation, n (%)	33 (41.3)	31 (77.5)	<0.001
Acute kidney injury, n (%)	15 (18.8)	19 (47.5)	0.001
Pediatric acute respiratory distress syndrome, n (%)	12 (15.0)	17 (42.5)	0.001
Disseminated intravascular coagulation, n (%)	7 (8.8)	10 (25.0)	0.015
Positive microbiological culture, n (%)	28 (35.0)	20 (50.0)	0.114
Multiple-organ dysfunction, n (%)	18 (22.5)	26 (65.0)	<0.001
Intensive care stay, days, median (interquartile range)	6 (4–9)	10 (7–14)	<0.001
Mortality, n (%)	7 (8.8)	18 (45.0)	<0.001

Children with septic shock demonstrated significantly greater oxidative injury than those with sepsis without shock. Median malondialdehyde concentration was 7.4 μmol/L in the septic shock group compared with 4.8 μmol/L in children without shock (p<0.001). Median 8-hydroxy-2′-deoxyguanosine concentration was also significantly higher in children with septic shock.

Antioxidant defense was markedly reduced in the septic shock group. Total antioxidant capacity, superoxide dismutase activity, and reduced glutathione concentrations were all significantly lower among children with septic shock. The mean composite oxidative stress index was 0.75 ± 1.03 in children with septic shock compared with −0.61 ± 0.88 in those without shock (p<0.001), as presented in Table 2.

Table 2. Oxidative-Stress Biomarkers According To Septic Shock Status

Biomarker	Sepsis without shock (n=66)	Septic shock (n=54)	p value
Malondialdehyde, μmol/L, median (interquartile range)	4.8 (3.8–5.9)	7.4 (5.9–9.2)	<0.001
8-Hydroxy-2′-deoxyguanosine, ng/mL, median (interquartile range)	5.2 (4.0–6.6)	8.9 (6.7–11.3)	<0.001
Total antioxidant capacity, mmol Trolox equivalent/L, mean ± standard deviation	0.99 ± 0.19	0.71 ± 0.18	<0.001
Superoxide dismutase, U/mL, median (interquartile range)	92 (78–107)	65 (53–79)	<0.001
Reduced glutathione, μmol/L, mean ± standard deviation	5.6 ± 1.2	4.1 ± 1.1	<0.001
Composite oxidative stress index, mean ± standard deviation	−0.61 ± 0.88	0.75 ± 1.03	<0.001

The composite oxidative stress index showed significant positive correlations with serum lactate (r=0.56, p<0.001), Phoenix Sepsis Score (r=0.53, p<0.001), vasoactive-inotropic score (r=0.49, p<0.001), serum creatinine (r=0.34, p<0.001), and C-reactive protein (r=0.29, p=0.001). It was negatively correlated with serum albumin (r=−0.41, p<0.001), total antioxidant capacity (r=−0.69, p<0.001), superoxide dismutase activity (r=−0.64, p<0.001), and reduced glutathione concentration (r=−0.61, p<0.001).

Malondialdehyde was positively correlated with serum lactate (r=0.52, p<0.001) and Phoenix Sepsis Score (r=0.48, p<0.001). Total antioxidant capacity was positively correlated with serum albumin (r=0.39, p<0.001) and negatively correlated with vasoactive-inotropic score (r=−0.37, p<0.001). No significant correlation was found between sex and the composite oxidative stress index (r=0.05, p=0.579).

Variables associated with the oxidative stress index in univariable analysis were entered into a multivariable linear regression model. Serum lactate, vasoactive-inotropic score, serum albumin, septic shock, acute kidney injury, and pediatric acute respiratory distress syndrome remained independently associated with oxidative stress.

Serum lactate showed the strongest positive association. Each 1 mmol/L increase in lactate was associated with a 0.13-unit increase in the oxidative stress index. Higher serum albumin was independently associated with a lower oxidative stress index. Sex was included in the initial model but was not an independent determinant. The final model explained 55% of the variability in oxidative stress, as shown in Table 3.

Table 3. Multivariable Linear Regression Analysis of Determinants of Oxidative Stress

Determinant	Unstandardized coefficient	95% confidence interval	Standardized coefficient	p value
Serum lactate, per 1 mmol/L increase	0.13	0.07 to 0.19	0.29	<0.001
Vasoactive-inotropic score, per 5-point increase	0.10	0.04 to 0.16	0.20	0.002
Serum albumin, per 1 g/dL increase	−0.39	−0.64 to −0.14	−0.17	0.003
Septic shock	0.45	0.12 to 0.78	0.16	0.008
Acute kidney injury	0.41	0.10 to 0.72	0.14	0.011
Pediatric acute respiratory distress syndrome	0.37	0.05 to 0.69	0.12	0.024

The adjusted coefficient of determination for the final model was 0.55, and the overall model was statistically significant (p<0.001).

In multivariable logistic regression, serum lactate of at least 4 mmol/L was independently associated with high oxidative stress after adjustment for age, sex, malnutrition, culture positivity, and organ dysfunction severity (adjusted odds ratio, 3.22; 95% confidence interval, 1.35–7.68; p=0.008). Septic shock was also an independent predictor of high oxidative stress (adjusted odds ratio, 3.08; 95% confidence interval, 1.24–7.65; p=0.015).

Acute kidney injury was independently associated with high oxidative stress (adjusted odds ratio, 2.62; 95% confidence interval, 1.07–6.40; p=0.035), as was hypoalbuminemia (adjusted odds ratio, 2.51; 95% confidence interval, 1.04–6.07; p=0.041). Malnutrition and culture positivity were associated with high oxidative stress in univariable analysis but did not remain statistically significant after adjustment. Male sex was not associated with high oxidative stress (adjusted odds ratio, 1.18; 95% confidence interval, 0.51–2.74; p=0.699).

Children with multiple-organ dysfunction had a significantly higher mean oxidative stress index than those without multiple-organ dysfunction (0.68 ± 1.05 versus −0.43 ± 0.94; p<0.001). Children requiring mechanical ventilation also had a higher mean oxidative stress index than those managed without mechanical ventilation (0.39 ± 1.16 versus −0.45 ± 0.91; p<0.001).

The median duration of intensive care admission was 10 days among children with high oxidative stress compared with 6 days among those with lower or moderate oxidative stress (p<0.001), as shown in Table 1. The oxidative stress index was significantly higher among non-survivors than survivors (0.93 ± 1.10 versus −0.22 ± 1.00; p<0.001).

Mortality was 45.0% in the high oxidative stress group compared with 8.8% in the lower or moderate oxidative stress group. After adjustment for age, sex, Phoenix Sepsis Score, septic shock, serum lactate, mechanical ventilation, and acute kidney injury, high oxidative stress remained independently associated with intensive care mortality (adjusted odds ratio, 3.74; 95% confidence interval, 1.31–10.68; p=0.014).

DISCUSSION

The present study evaluated the physiological, biochemical, and pathological determinants of oxidative stress in 120 children with sepsis requiring intensive care[1]. The principal findings were that septic shock, elevated serum lactate, greater vasoactive-inotropic requirements, hypoalbuminemia, acute kidney injury, and pediatric acute respiratory distress syndrome independently predicted a higher oxidative stress index. Children with greater oxidative stress also experienced more frequent mechanical ventilation, multiple-organ dysfunction, prolonged intensive care admission, and mortality. Biological sex was not significantly associated with oxidative-stress severity[2,3].

Children with septic shock had markedly higher malondialdehyde and 8-hydroxy-2′-deoxyguanosine concentrations than children with sepsis without shock[4]. In contrast, total antioxidant capacity, superoxide dismutase activity, and reduced glutathione concentrations were substantially lower. These findings indicate that septic shock is accompanied by increased lipid peroxidation and oxidative DNA injury together with depletion of enzymatic and non-enzymatic antioxidant defences. Previous pediatric studies have similarly reported increased oxidant activity, disturbed thiol–disulfide homeostasis, and reduced antioxidant parameters in children with sepsis[5].

Serum lactate was the strongest independent determinant of oxidative stress. Lactate elevation in sepsis may reflect impaired tissue perfusion, accelerated adrenergic glycolysis, reduced hepatic clearance, microcirculatory dysfunction, and altered mitochondrial metabolism[6]. These processes may occur simultaneously with increased formation of reactive oxygen species. The observed association should not be interpreted as evidence that lactate directly causes oxidative injury; rather, lactate and oxidative-stress markers may represent related consequences of severe circulatory and metabolic dysfunction. Current pediatric sepsis guidance recommends blood lactate measurement during the initial evaluation of children with probable sepsis or suspected septic shock, supporting its clinical relevance as an early marker of disease severity[7,8].

The vasoactive-inotropic score was also independently associated with the oxidative stress index. The need for more vasoactive support is indicative of more profound cardiovascular dysfunction and ongoing tissue hypoperfusion[9]. Increased production of reactive oxygen species may occur as a result of ischemia-reperfusion, endothelial activation, mitochondrial leakage of electrons, and heightened metabolic activity due to increased production of catecholamines. However, this linkage does not mean that vasoactive drugs per se should be shunned. Vasoactive support is important in children with shock who do not respond to fluid, and should be used as a treatment, with repeated assessment of perfusion and haemodynamic status[10].

Increased oxidative stress was independently associated with hypoalbuminemia. In addition to being a marker of nutritional, inflammatory, hepatic and vascular status, albumin also plays a role in the extracellular antioxidant defence because of the presence of a free thiol group and the ability to bind potentially pro-oxidant compounds[11]. Thus, low levels of albumin might reflect high disease activity as well as low antioxidant reserves. Children with high oxidative stress were more likely to be malnourished in the un-adjusted model, but this was no longer in the adjusted model. It is therefore possible that the effect of poor nutritional status is partly mediated by decreased levels of albumin, decreased antioxidant availability and increased susceptibility to critical illness[12].

Acute kidney injury was another independent determinant of oxidative stress. Renal hypoperfusion, endothelial dysfunction, mitochondrial injury, inflammation, and tubular damage can increase oxidant production during sepsis[13]. At the same time, impaired renal clearance may promote the accumulation of oxidized metabolites. Oxidative stress may subsequently worsen renal microvascular and tubular injury, producing a bidirectional relationship between oxidative imbalance and acute kidney dysfunction. The higher oxidative stress observed among children with acute kidney injury may therefore reflect both the severity of systemic sepsis and kidney-specific cellular injury[14].

Pediatric acute respiratory distress syndrome was independently associated with a higher oxidative stress index[15]. Severe pulmonary infection, activated neutrophils, alveolar-capillary injury, hypoxemia, mechanical ventilation, and exposure to supplemental oxygen may contribute to reactive oxygen species formation. Conversely, oxidative damage may increase epithelial and endothelial permeability, impair

surfactant function, and aggravate pulmonary inflammation. The higher oxidative stress index among mechanically ventilated children is therefore biologically plausible, although the present findings cannot distinguish the effects of the underlying lung injury from those of oxygen exposure or ventilatory support[16].

The strong association between oxidative stress and multiple-organ dysfunction supports the concept that redox imbalance is linked to widespread cellular and microvascular injury in sepsis[17]. Reactive oxygen and nitrogen species can damage membrane lipids, proteins, mitochondrial structures, and nucleic acids. Lipid peroxidation may alter cellular membrane permeability and impair membrane-associated enzymes and receptors, whereas mitochondrial dysfunction can reduce energy production and further increase oxidant generation. Malondialdehyde is an indirect marker of this lipid injury, although its measurement using thiobarbituric acid-reactive substances lacks complete analytical specificity[18].

Children with high oxidative stress had longer intensive care stays and substantially greater mortality than those with lower or moderate oxidative stress[19]. The oxidative stress index was also significantly higher among non-survivors and remained associated with mortality after adjustment for major clinical indicators. Previous investigations have reported higher oxidative-stress biomarkers and lower antioxidant activity among patients with severe sepsis and adverse outcomes. However, considerable overlap between survivors and non-survivors has limited the prognostic performance of individual markers such as malondialdehyde. Combining oxidant and antioxidant measurements with clinical variables may therefore provide more meaningful biological characterization than relying on a single biomarker[20].

No significant difference in oxidative stress was observed between male and female participants. Sex was also not retained as an independent determinant in the regression models[5]. This finding suggests that, within the studied age range, acute physiological instability and organ dysfunction had a stronger influence on oxidative stress than biological sex. However, the study was not specifically powered to examine sex-related differences, and the possible effects of age, pubertal status, and sex hormones require evaluation in larger studies[7-10].

The findings may have clinical implications for risk stratification. Children with hyperlactatemia, high vasoactive-inotropic requirements, hypoalbuminemia, renal injury, respiratory dysfunction, or septic shock may represent a subgroup with particularly high oxidative burden[11-14]. Nevertheless, oxidative-stress assays are not yet sufficiently standardized for routine bedside decision-making, and the present results do not demonstrate that antioxidant therapy would improve outcomes. Updated pediatric sepsis guidance recommends against routine vitamin C or thiamine treatment, except where deficiency is suspected or documented, because evidence of clinical benefit remains insufficient[15-18].

The present study contains certain limitations: It was an observational study so that no conclusions could be drawn about causality, and oxidative-stress biomarkers were only determined at one early time. Perhaps serial measurements could have been more useful to show whether children with poor outcomes had oxidative injury that persisted or resolved with treatment[19]. Malondialdehyde was determined by the thiobarbituric acid-reactive substances method which may include other aldehydes. The composite oxidative stress index and upper-tertile cut-off for this index were unique to this study and thus need to be externally validated. Residual confounding from nutritional deficiencies, prehospital treatment, oxygen exposure, fluid administration, infection duration, and antimicrobial timing was also possible. Finally, the moderate sample size and recruitment from selected tertiary-care centres may limit the generalizability of the findings[3,20].

Despite these limitations, the study assessed several complementary oxidant and antioxidant biomarkers and linked them with detailed physiological, biochemical, and organ-dysfunction variables. Early sample collection, duplicate biochemical analysis, inclusion of both sexes, and multivariable adjustment strengthened the findings. Larger multicentre studies with serial measurements are needed to validate the oxidative stress index and determine whether redox profiling provides additional prognostic information beyond established pediatric sepsis severity scores[15-20].

CONCLUSION

Oxidative stress in pediatric sepsis requiring intensive care was independently associated with elevated lactate, greater vasoactive-inotropic support, hypoalbuminemia, septic shock, acute kidney injury, and pediatric acute respiratory distress syndrome. A high oxidative stress burden was also associated with mechanical ventilation, multiple-organ dysfunction, prolonged intensive care stay, and mortality. These results indicate that oxidative imbalance is a result of circulatory failure, decrease in antioxidant reserve

and organ damage related to sepsis. Serial multicentre studies are required before oxidative-stress biomarkers can be incorporated into routine risk assessment or used to guide targeted treatment.

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