Multiple Organ Dysfunction and The pSOFA Score in Critically Ill Children: A Narrative Review

Saskia Putri Fadillah[1], Arina Setyaningtyas[2,5]*, Pradana Zaky Romadhon[3,6], Bambang Pujo Semedi[4,5]

[1]Medical Programme, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

[2]Department of Pediatrics, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

[3]Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

[4]Department of Anesthesiology and Reanimation, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

[5]Dr. Soetomo General Academic Hospital, Surabaya, Indonesia
[6]Universitas Airlangga Hospital, Surabaya, Indonesia

E-mail: saskia.putri.fadillah-2022@fk.unair.ac.id; arina-s@fk.unair.ac.id; zaky.romadhon@fk.unair.ac.id; bambang-p-s@fk.unair.ac.id

*Corresponding author details: Arina Setyaningtyas; arina-s@fk.unair.ac.id

ABSTRACT

Multiple organ dysfunction syndrome (MODS) is one of the medical conditions associated with morbidity and mortality in critically ill children. Organ damage develops through a series of complex mechanisms that affect the cardiovascular, respiratory, neurological, hepatobiliary, renal, and hematological systems. Early identification is important due to the wide range of manifestations of MODS. Pediatric sequential organ failure assessment (pSOFA), a modification of sequential organ failure assessment (SOFA) score for the adult population, provides an objective assessment of the severity of organ dysfunction and has been shown to have good predictive capability for mortality. This narrative review summarises the current evidence on MODS and the use of pSOFA as an important evaluation tool in the management of critically ill children. This comprehensive understanding is expected to strengthen clinical assessment and help optimise the management of children at risk of MODS in intensive care facilities.

Keywords: critically ill children; MODS; pSOFA score

INTRODUCTION

Critically ill children remain a major challenge in global health because they are associated with significant morbidity and mortality in pediatric patients [1]. The mortality rate of critically ill children treated in pediatric intensive care units (PICU) is quite high, especially in developing countries, ranging from 6.5% in China, 12.9% in Pakistan, 21.8% in Indonesia, to 37.4% in Saudi Arabia [2,3]. In critically ill children, multiple vital organ dysfunction is a major complication in intensive care units and determines the higher mortality outcome of hospitalised patients [4,5]. Organ dysfunction can arise from various underlying conditions, including sepsis, hypoxia of any source, trauma, congenital diseases, and certain medical interventions [6,7]. Regardless of the many etiologies and pathophysiological processes, dysfunction can occur in more than one organ, becoming multiple organ dysfunction syndrome (MODS). It is recognised as the final common pathway in critically ill children [8].

Approximately 20% of critically ill pediatric patients have two or more organ dysfunctions upon admission to the pediatric intensive care unit (PICU), while another 23% have multiple organ dysfunction during care in the PICU [8]. The pathological mechanism itself is not yet fully understood and is quite complex as it involves many factors from molecular pathways and genetic predisposition. However, there are two main factors causing MODS, including systemic inflammatory response syndrome (SIRS) and cellular hypoperfusion.

This process occurs and often affects organ systems such as the cardiovascular, respiratory, renal, hepatic, neurological, and hematological systems [5]. If left uncontrolled, multiple organ dysfunction can lead to death in critically ill pediatric patients [9].

Based on problems in critically ill pediatric patients with organ dysfunction, organ system evaluation is an important aspect of managing critically ill children in the PICU. Various scoring systems have been developed to quantify organ dysfunction in pediatric patients. Among these, the pediatric sequential organ failure assessment (pSOFA) has garnered significant attention as it is a modification of the adult sequential organ failure assessment (SOFA) score [10]. The pSOFA score evaluates six organ systems and has demonstrated excellent discrimination for PICU patient mortality [10,11]. Therefore, this review was conducted to gain further insight into organ dysfunction in pediatric patients in PICU so that early identification and appropriate care can be facilitated, thereby improving treatment outcomes for critically ill children.

METHODS

This narrative literature review was conducted to summarise the evidences related to the definition, mechanism, and clinical manifestations of organs in MODS. In addition, this review discusses the components, interpretation, development, and validity of the pSOFA score. The search was conducted by selecting articles that had been peer-reviewed, both original research and reviews that were considered relevant to the topic. Each source was thoroughly examined, and the main findings were combined into a structured review.

RESULTS

Multiple Organ Dysfunction Syndrome

- *Definition of MODS*

Multiple organ dysfunction syndrome (MODS) is a syndrome, defined as a critical illness characterised by reversible physiological abnormalities in two or more organs occurring simultaneously, resulting in the patient being admitted to the the intensive care unit (ICU), prolonged duration of care in the ICU, and in severe cases, higher mortality rates [5,12]. In children, MODS is most often associated with sepsis and the inflammation it causes. However, this condition can also arise in a number of other conditions, such as massive bleeding and/or multiple trauma. Conceptually, MODS is seen as the final stage of a spectrum of organ dysfunction that generally occurs as a result of a systemic inflammatory process or simply systemic inflammatory response syndrome (SIRS) without infection, resulting in widespread endothelial dysfunction and organ injury [13]. In the literature, MODS is divided into two types, namely early/primary and late/secondary. Primary MODS is a direct result of a well-defined insult, where organ dysfunction occurs earlier in the first week after injury and can be directly linked to the injury itself. Secondary MODS mostly develops as a consequence of the host response and is identified in the context of SIRS, emerging after the initial phase has passed [12,14].

A condition must meet three main criteria to be considered a syndrome. First, the condition must have a consistent set of symptoms that appear together in affected individuals. Second, there must be a common mechanism that causes these symptoms to appear. Third, the syndrome must have predictable outcomes or consequences. In MODS, the first criterion for a syndrome is the presence of dysfunction in more than one organ system occurring simultaneously. Although organ system dysfunction may vary in number, type, and severity among patients and over time, this variation does not preclude MODS from being a syndrome. In fact, many other syndromes also have variations in the symptoms that appear. The second criterion for qualifying MODS as a syndrome is the presence of a common underlying mechanism for all organ system dysfunctions. For most cases of MODS in children, this criterion includes a severe systemic inflammatory response and/or a common cellular energy crisis, although other mechanisms may also be involved. For the third criterion, multiple organ dysfunction syndrome appears to have worse outcomes compared to patients with other scenarios involving additive organ dysfunction [15].

- *Mechanism of MODS*

The development of MODS generally begins with an excessive proinflammatory response following conditions such as sepsis, injury, burns, and hypoperfusion. In addition, secondary events such as bacterial infection and surgical intervention can trigger a second reaction [5]. In this condition, the immune system, which has previously been primed, experiences an imbalance between pro-inflammatory and anti-inflammatory cytokines. This imbalance triggers excessive and repeated activation of neutrophils and macrophages, forming a chain of inflammation that perpetuates damage. The impact of this process damages the vascular endothelium, causing it to become more permeable, altering vascular tone, and triggering microthrombus formation. This endothelial damage causes decreased organ perfusion [16].

Perfusion impairment is not the only mechanism involved in MODS. Changes occur at the cellular level, particularly in the mitochondria. Cells can experience metabolic failure and mitochondrial damage secondary to impaired oxidative phosphorylation or increased reactive oxygen species (ROS) production, causing organ dysfunction [16]. On the other hand, cytokines such as IL-6, IL-1β, and TNF-α can affect mitochondrial membrane permeability and promote the production of reactive species. Additionally, immune cells including macrophages, neutrophils, and lymphocytes, add to the oxidative burden by producing reactive oxygen species (ROS) and reactive nitrogen species (RNS).

The accumulation of oxidative stress leads to mitochondrial dysfunction, causing cytopathic hypoxia, cellular energy failure, and cell apoptosis, ultimately resulting in organ damage [17]. These findings suggest that organ failure is enhanced by mitochondrial dysfunction.

The gastrointestinal system also plays a role in the development of MODS. Damage to the intestinal mucosa, changes in tight junction structure, and bacterial translocation trigger or exacerbate systemic inflammation, thereby worsening MODS [16]. When intestinal permeability increases in critical illness, systemic inflammation intensifies and promotes the development of MODS. This condition is often accompanied by a decrease in mucosal IgA, frequently due to nutritional deficiencies, which increases susceptibility to additional infections. Additionally, changes may occur in gut commensal bacteria due to antibiotic use, as well as the activation of bacterial virulence factors to help bacteria survive during critical Illness [12]. The combination of these processes makes the gastrointestinal system one of the sources that enhance systemic inflammation and support the development of MODS.

Essentially, there are two main factors that cause multiple organ failure (MOF), including systemic inflammatory response syndrome (SIRS), which is characterised by an excessive immune response that leads to the formation of free radicals. Another factor is cellular hypoperfusion, which causes hypoxia, releasing reactive oxygen and nitrogen species. These species collectively produce profound intracellular oxidative stress, causing mitochondrial damage. The body's response to infection, particularly sepsis, involves both pro-inflammatory and anti-inflammatory immune responses. Pro-inflammatory cytokines are predominantly released during the early phase of MODS. They consist of TNF-α and IL-1β, along with increased VCAM-1 and ELAM-1, and increased lymphocyte adhesion to endothelial cells. Conversely, in the late phase of MODS, damage to the endothelium triggers an innate inflammatory response in the affected end organs and causes parenchymal injury. In addition, several other factors such as mitochondrial dysfunction, tissue fibrosis activation, and complement system activation are also involved in the pathogenesis of MODS [5].

In trauma patients, SIRS begin early after injury as a response to bleeding and tissue damage caused by the trauma. This condition is balanced by a compensatory anti-inflammatory response to help restore homeostasis. Initially, if the proinflammatory and anti-inflammatory cytokine responses are balanced, both can work together to return the immune system to normal function and act as a beneficial compensatory mechanism. However, if this inflammatory response persists or becomes excessive, it can lead to organ failure and ultimately cause MODS. The extent of tissue damage, persistence of shock, and severity of injury influence the extent of the inflammatory response to ongoing trauma, which is a determining factor in the development of MODS [5].

- *Manifestation in cardiovascular dysfunction*

Cardiovascular dysfunction is commonly found in critically ill patients and is associated with poor outcomes in various intensive care units. Cardiovascular involvement tends to be higher in patients with severe sepsis. In severe sepsis, this disorder often takes the form of systolic and diastolic dysfunction arising from a combination of myocardial depression by inflammatory mediators such as IL-6, increased metabolic demand, widespread endothelial damage, and reduced effective circulating volume [5,13]. Clinically, this may manifest as biventricular dilation, reversible reduction in ejection fraction, suboptimal response to fluid resuscitation, and inability to increase cardiac output despite high catecholamine levels. These manifestations may affect the left ventricle (both systolic and diastolic), the right ventricle, or both [18].

In conditions such as sepsis, the most common hemodynamic features are a significant decrease in systemic vascular resistance (SVR) and normal or increased cardiac output, while cardiac contractility is actually decreased. Patients can maintain stroke volume, but examination often reveals increased Left ventricular end systolic and end diastolic volumes, as well as decreased ejection fraction, which is then compensated by increased heart rate. Diastolic dysfunction is also evident through decreased left ventricular compliance and increased left ventricular end diastolic pressure. The same disorders also occur in the right ventricle. Circulating inflammatory mediators cause decreased contractility, increased right ventricular end diastolic and end systolic volume and decreased ejection fraction, which in some cases can progress to right heart failure. Because the right ventricle has a smaller muscle mass and is less efficient in coping with increased afterload, it is more susceptible to hemodynamic changes in sepsis [19].

Interestingly, several studies have shown that myocardial dysfunction occurs not only in the hypodynamic phase of shock, but also in the hyperdynamic phase, when cardiac output increases, SVR decreases, and the skin feels warm and well perfused. In this phase, left ventricular dilatation appears to be a compensatory mechanism through the Frank-Starling principle, and this finding is associated with a better prognosis if the compensatory response remains effective. Meanwhile, right ventricular involvement can affect left ventricular function through septal shift and decreased preload, although this phenomenon does not always occur in all patients [18].

In addition, supraventricular arrhythmias, particularly atrial fibrillation, are frequently observed, and septic shock is an independent predictor of these arrhythmias [19]. Arrhythmias

can occur due to ischemic injury or metabolic disturbances related to potassium and calcium. The balance between the sympathetic and parasympathetic systems may change in the regulation of several organ dysfunctions. This is mediated by several pathways, including stretch receptors in the lungs, brain regulatory centres, and decreased heart rate variability. This condition may predict a higher severity, further deterioration, and even death from MODS [13].

- *Manifestation in respiratory dysfunction*
Respiratory dysfunction in MODS generally reflects gas exchange failure due to a series of pathological mechanisms in the lungs. This disorder can take the form of a condition called acute lung injury (ALI). ALI causes interstitial and alveolar edema, which can lead to an imbalance in pulmonary perfusion and ventilation, as well as atelectasis resulting in hypoxemia. In its development, acute respiratory distress syndrome (ARDS) is an advanced stage of existing lung injury [13]. ARDS is characterised by widespread pulmonary infiltrates and increased alveolar-capillary membrane permeability, which causes edema and decreased oxygenation. In more severe phases, increased pulmonary vascular resistance can cause pulmonary hypertension and acute cor pulmonale, which worsens the hemodynamic condition. In addition, ventilator-induced lung injury can exacerbate existing lung damage and trigger a widespread systemic response, contributing to the progression of multiple organ failure in patients with ARDS [5].

- *Manifestation in liver dysfunction*
Liver dysfunction is an important component of MODS, especially in sepsis, because the liver plays a major role in clearing infectious agents and their products. In the early phase, the liver still attempts to maintain immune function through intercellular communication between hepatocytes. However, when regulation is disrupted, hepatic dysfunction occurs, leading to the loss of bacterial elimination capacity, increased procoagulant and inflammatory

responses, and ultimately contributing to the development of multiple organ failure [5]. This spectrum of abnormalities is often described as sepsis-associated liver injury (SALI), ranging from subclinical biochemical abnormalities to clinical manifestations such as hepatic encephalopathy and ascites. In the pediatric population, SALI is found in 31.3% of sepsis cases, especially in infants due to immature liver function, with cholestasis being the most common form [20].

Clinically, sepsis-associated liver dysfunction (SALD) can manifest as sepsis-associated cholestasis or hypoxic hepatitis due to a combination of systemic inflammation, hypoperfusion, and endothelial injury [21]. Since the liver is the site of synthesis for most coagulation factors, thrombopoietin (TPO), and several fibrinolytic proteins, SALD can result in hepatic synthetic dysfunction, which manifests as bleeding, particularly gastrointestinal bleeding and coagulopathy [21,22]. In the context of MODS, elevated serum bilirubin reflects cholestasis and impaired bile excretion, while episodes of hypotension can trigger transaminase spikes due to hepatocellular injury [13].

- *Manifestation in neurological dysfunction*
The first manifestation of neurological dysfunction in patients with MODS is a change in the level of consciousness. In the next stage, a phenomenon known as critical illness polyneuropathy occurs, which manifests clinically as muscle weakness and the patient's inability to wean off mechanical ventilation [13]. In the context of sepsis, the most common form in pediatric patients is sepsis-associated encephalopathy (SAE), which is diffuse brain dysfunction without evidence of direct CNS infection, with an incidence of 30-70% and recognised as one of the most common causes of organ dysfunction and associated with high mortality [23,24]. Its manifestations range from hypotonia, hypertonia, hyperreflexia, irritability, decreased consciousness, disorientation, and seizures [23].

TABLE 1: The pSOFA Score [27].

Variables	Score[a]				
	0	**1**	**2**	**3**	**4**
Respiratory					
PaO2:FiO2[b]	≥400	300-399	200-299	100-199 with respiratory support	<100 with respiratory support
or					
SpO2:FiO2[c]	≥292	264-291	221-264	148-220 with respiratory support	<148 with respiratory support
Coagulation					
Platelet count, x10³/μL	≥150	100-149	50-99	20-49	<20
Hepatic					
Total bilirubin, mg/dL	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12.0

Variables	Score[a]				
	0	**1**	**2**	**3**	**4**
Cardiovascular					
MAP by age group or vasoactive infusion, mmHg or µg/kg/minute[d]					
<1 month	≥46	<46	Dopamine	Dopamine	Dopamine
1-11 month	≥55	<55		Hydrochloride >5 or Epinephrine ≤0.1 or Norepinephrine bitartrate ≤0.1	Hydrochloride >15 or Epinephrine ≤0.1 or Norepinephrine bitartrate ≤0.1
12-23 month	≥60	<60	Hydrochloride ≤5 or Dobutamine Hydrochloride (any)		
24-59 month	≥62	<62			
60-143 month	≥65	<65			
144-216 month	≥67	<67			
>216 month[e]	≥70	<70			
Neurologic					
Glasglow Coma Scale[f]	15	13-14	10-12	6-9	<6
Renal					
Creatinine by age group, mg/dL					
<1 month	<0.8	0.8-0.9	1.0-1.1	1.2-1.5	≥1.6
1-11 month	<0.3	0.3-0.4	0.5-0.7	0.8-1.1	≥1.2
12-23 month	<0.4	0.4-0.5	0.6-1.0	1.1-1.4	≥1.5
24-59 month	<0.6	0.6-0.8	0.9-1.5	1.6-2.2	≥2.3
60-143 month	<0.7	0.7-1.0	1.1-1.7	1.8-2.5	≥2.6
144-216 month	<1.0	1.0-1.6	1.7-2.8	2.9-4.1	≥4.2
>216 month	<1.2	1.2-1.9	2.0-3.4	3.5-4.9	≥5

Abbreviations: PaO2, partial pressure of arterial oxygen; FiO2, fraction of inspired oxygen; SpO2, peripheral oxygen saturation; MAP, mean arterial pressure; pSOFA, pediatric sequential organ failure assessment.
SI conversion factors: To convert bilirubin to micromoles per liter, multiply by 17.104; creatinine to micromoles per liter, multiply by 88.4; and platelet count to × 10^9/L, multiply by 1.

a. The pSOFA score was calculated for every 24-hour period. The worst value for every variable in each 24-hour period was used to calculate the subscore for each of the 6 organ systems. If a variable was not recorded in a given 24-hour period, it was assumed to be normal and a score of 0 was used. Daily pSOFA score was the sum of the 6 subscores (range, 0-24 points; higher scores indicate a worse outcome).
b. PaO2 was measured in millimeters of mercury.
c. Only SpO2 measurements of 97% or lower were used in the calculation.
d. MAP (measured in millimeters of mercury) was used for scores 0 and 1; vasoactive infusion (measured in micrograms per kilogram per minute), for scores 2 to 4. Maximum continuous vasoactive infusion was administered for at least 1 hour.
e. Cutoffs for patients older than 18 years (216 months) were identical to the original SOFA score.
f. Glasgow Coma Scale was calculated using the pediatric scale.

- *Manifestation in hematological dysfunction*

Hematological dysfunction is a finding that often occurs alongside MODS and can appear as a combination of cytopenias and abnormalities in plasma coagulation tests [25]. In severe infections, the bone marrow may fail, leading to significant changes in white blood cell counts, either increasing or decreasing, followed by the possibility of anemia and thrombocytopenia. Thrombocytopenia itself is often a characteristic feature of infection and may reflect a consumptive coagulopathy process, while coagulopathy is a common finding in MODS due to a combination of liver injury, hemodilution, or severe infection; most patients with MODS may even develop disseminated intravascular coagulation (DIC) [13]. In the pediatric population, cytopenia in the context of organ dysfunction is defined as a platelet count <100,000/µL in patients without hematological/oncological disease, <30,000/µL in patients with hematological/oncological disease, or a decrease of ≥50% from baseline if baseline <100,000/µL. Hematologic dysfunction is also characterised by a white blood cell count <3,000/µL, while a hemoglobin level <5 g/dL is defined as severe dysfunction and a range of 5-7 g/dL as mild dysfunction [25].

- *Manifestation in renal dysfunction*

Acute kidney injury (AKI) is a common problem that often occurs in patients with MODS [13]. The incidence ranges from 20% to 60% in children and infants treated in critical care units [26]. Kidney failure occurs when the kidneys are unable to excrete nitrogenous waste and maintain fluid and electrolyte balance properly. This results in oliguria and azotaemia, requiring continuous administration of diuretics or renal replacement therapy [13].

Pediatric Sequential Organ Failure Assessment (pSOFA) Score
The pediatric sequential organ failure assessment (pSOFA) is a descriptive assessment tool widely

used to describe the severity of illness in critically ill children, as seen in Table 1. The pSOFA score is based on modifications to the Sequential Organ Failure Assessment (SOFA) score used in adults. This score was developed as a modification of the adult SOFA, with threshold adjustments based on age adapted from PELOD-2, making it more appropriate for the physiological characteristics of children. The pSOFA evaluates six organ systems, such as respiratory, cardiovascular, neurological, hepatic, renal, and coagulation, through clinical parameters such as the PaO_2/FiO_2 or SpO_2/FiO_2 ratio, platelet count, total bilirubin, mean arterial pressure, GCS, and creatinine levels, thereby reflecting the degree of dysfunction in each organ [10,27].

- *Components and interpretation of pSOFA score*

In principle, pSOFA retains the adult SOFA scoring mechanism, in which the worst variable within 24 hours determines the subscore for each organ. The interpretation and score range remain similar, namely 0–4 for each subscale, with the final score reflecting the cumulative severity of organ dysfunction [28]. In the cardiovascular system, the subscore is based on Mean Arterial Pressure (MAP), with age-specific MAP limits from PELOD-2 as the cut-off for a score of 1, while scores of 2–4 follow the adult SOFA criteria. Renal function assessment uses age-adjusted serum creatinine levels, also adapted from PELOD-2 for a score of 1. Modifications were made for scores 2-4 by increasing the threshold values for each score by the same factor as the original SOFA criteria, with the exception of neonates due to differences in renal physiology, for whom the thresholds were adjusted to the infant group [27]. The respiratory component retained the PaO_2/FiO_2 threshold as in SOFA, but allowed the use of the SpO_2/FiO_2 ratio as an alternative, with the cut-off proposed by Khemani et al [29] to accommodate clinical conditions when blood gas analysis was not available [27–29]. The criteria for the coagulation and liver subscales, based on platelet count and bilirubin levels, remain consistent with the original SOFA score, while the neurological subscale (GCS) continues to follow the original SOFA criteria, although the GCS scale used is the pediatric version to enhance assessment accuracy [27].

- *Development and validity of pSOFA score*

To date, the pSOFA score has been developed and validated retrospectively and prospectively in critically ill children. Research was conducted by Matics et al in 2017, testing pSOFA retrospectively using the highest daily score from the first 24 hours to the 28th day of PICU care. The results showed that pSOFA has excellent discriminatory ability for hospital mortality and performs equally well, and in some aspects even better, than other pediatric organ dysfunction scores such as PELOD and PELOD-2. In addition, this score has also been shown to be more accurate than P-MODS in predicting the risk of death [27]. These findings are supported by a prospective study in Indonesia by Wulandari, Pudjiastuti and Martuti [30], which showed that pSOFA is a better predictor of mortality

than severe sepsis criteria or PELOD-2 in children with sepsis in the PICU and HCU. This study also identified a pSOFA cut-off value of ≥ 2 as an indicator of increased mortality risk, with the optimal value for predicting death being pSOFA > 8. Similar findings were reported by Lalitha et al [31], whose prospective study showed that pSOFA had good predictive performance compared to PRISM III and PELOD-2 criteria in predicting mortality in children with sepsis in the PICU.

CONCLUSIONS

Multiple organ dysfunction syndrome (MODS) in children poses a major challenge due to its complex interactions. This condition results in the involvement of various organs, including the heart, lungs, liver, nervous system, kidneys, and hematology, each of which exhibits a spectrum of manifestations ranging from subclinical to overt organ failure. Understanding the clinical picture and pathophysiological mechanisms is important for early detection and appropriate management. In this context, the pediatric sequential organ failure assessment (pSOFA) provides a standardised approach to assessing the severity of organ dysfunction using parameters adjusted for age. Various studies have shown that pSOFA is capable of accurately predicting mortality and has comparable, even superior, performance compared to other pediatric scores already in use. With this evidence, pSOFA can be considered an important tool in risk stratification and monitoring of critically ill children, and has the potential to become an integral part of clinical assessment in pediatric intensive care units.

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