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### **Multiorgan Dysfunction Syndrome in Abusive and Accidental Pediatric Traumatic Brain Injury**

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#### **Abstract**

**Background:** Abusive head trauma (AHT) is a mechanism of pediatric traumatic brain injury (TBI) with high morbidity and mortality. Multiorgan dysfunction syndrome (MODS), defined as organ dysfunction in two or more organ systems, is also associated with morbidity and mortality in critically ill children. Our objective was to compare the frequency of MODS and evaluate its association with outcome between AHT and accidental TBI (aTBI).

**Methods:** This was a single center, retrospective cohort study including children under 3 years old admitted to the pediatric intensive care unit with nonpenetrating TBI between 2014 and 2021. Presence or absence of MODS on days 1, 3, and 7 using the Pediatric Logistic Organ Dysfunction-2 score and new impairment status (Functional Status Scale score change > 1 compared with preinjury) at hospital discharge (HD), short-term timepoint, and long-term timepoint were abstracted from the electronic health record. Multiple logistic regression was

Ethical Approval/Informed Consent

This article complied with ethical approval and received approval from the University of Pittsburgh Institutional Review Board. Supplementary Information

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Author Contributions

CRM—Conceived and designed the analysis, Collected data, Performed analysis, Wrote the paper. KME—Conceived and designed the analysis, Reviewed data and analysis, Reviewed manuscript draft and provided critical feedback. AK—Collected data, Reviewed manuscript draft and provided critical feedback. CMH—Conceived and designed the analysis, Reviewed data and analysis, Reviewed manuscript draft and provided critical feedback. BAG—Contributed data, Reviewed manuscript draft and provided critical feedback. WMR—Contributed data, Reviewed manuscript draft and provided critical feedback. DWS—Conceived and designed the analysis, Reviewed data and analysis, Reviewed manuscript draft and provided critical feedback. PMK—Reviewed data and analysis, Reviewed manuscript draft and provided critical feedback. RPB—Conceived and designed the analysis, Reviewed data and analysis, Reviewed manuscript draft and provided critical feedback. ELF—Conceived and designed the analysis, Supervised project, Reviewed data and analysis, Reviewed manuscript draft and provided critical feedback, The final manuscript was approved by all authors.

Conflicts of interest

No authors have any personal or financial affiliations that could present a conflict of interest.

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performed to examine the association between MODS and TBI mechanism with new impairment status.

**Results:** Among 576 children, 215 (37%) had AHT and 361 (63%) had aTBI. More children with AHT had MODS on days 1 (34% vs. 23%,  $p = 0.003$ ), 3 (28% vs. 6%,  $p < 0.001$ ), and 7 (17% vs. 3%,  $p < 0.001$ ) compared with those with aTBI. The most common organ failures were cardiovascular ([AHT] 66% vs. [aTBI] 66%,  $p = 0.997$ ), neurologic (33% vs. 16%,  $p <$ 0.001), and respiratory (34% vs. 15%,  $p < 0.001$ ). MODS was associated with new impairment in multivariable logistic regression at HD (odds ratio 19.1 [95% confidence interval 9.8–38.6,  $p \lt$ 0.001]), short-term discharge (7.4 [3.7–15.2, p < 0.001]), and long-term discharge (4.3 [2.0–9.4,  $p < 0.001$ ]). AHT was also associated with new impairment at HD (3.4 [1.6–7.3,  $p = 0.001$ ]), short-term discharge  $(2.5 [1.3–4.7, p = 0.005])$ , and long-term discharge  $(2.1 [1.1–4.1, p = 0.036])$ .

**Conclusions:** Abusive head trauma as a mechanism was associated with MODS following TBI. Both AHT mechanism and MODS were associated with new impairment at all time points.

#### **Keywords**

Child abuse; Traumatic brain injury; Multiorgan dysfunction syndrome; Pediatric intensive care units; Long-term effects

#### **Introduction**

Abusive head trauma (AHT) is a common mechanism of traumatic brain injury (TBI) in infants and young children [1, 2]. AHT is associated with acquisition of new cognitive and physical impairments and epilepsy [1, 3–9]. Impairment may be exacerbated by secondary hypoxia and hypotension and injury to nonneurologic organs that may lead to multiple organ dysfunction syndrome (MODS) [10, 11].

MODS is associated with increased morbidity and mortality in general pediatric critical care populations and accidental TBI (aTBI); however, MODS is less characterized in the AHT population [12–15]. In pediatric TBI, MODS occurred in 20% of patients; AHT mechanism was identified as a risk factor, with 1,382/3,530 (39%) patients with abuse having MODS [16].

The most commonly used trauma scoring system, the Injury Severity Score (ISS), underestimates the risk of mortality and impaired functional outcome in patients who have experienced child abuse [17]. The Pediatric Logistic Organ Dysfunction-2 (PELOD-2) score is validated in pediatric critical illness for prediction of mortality, but it has not been evaluated in the AHT population [18]. In a previous study comparing various MODS scoring systems, PELOD-2 performed better than the pediatric multiple organ dysfunction score [19].

The objectives for this study were to compare the frequency of MODS between patients with AHT and patients with aTBI and analyze the association of TBI mechanism and MODS occurrence in the first week of admission with mortality and new functional impairment.

#### **Methods**

#### **Study Design and Setting**

The University of Pittsburgh Institutional Review Board approved this retrospective, observational cohort study.

#### **Inclusion and Exclusion Criteria**

Patients less than 3 years of age admitted to the pediatric intensive care unit with TBI between 2014 and 2021 were included. Patients admitted with penetrating trauma were excluded.

#### **Data Collection**

The Benedum Trauma Center database supplied the eligible patients, and the electronic health record was used to collect patient demographics, TBI details, brain computed tomography or magnetic resonance imaging results, laboratory results, and vital signs. AHT was defined by the conclusion of the multidisciplinary child protection team; patients designated as having injuries that were "highly concerning" or "diagnostic" for AHT were included [2, 20, 21]. ISS was obtained on admission. Glasgow Coma Score (GCS) scores between 13 and 15 were classified as mild TBI, between 9 and 12 as moderate TBI, and equal to or below 8 as severe TBI [22]. PELOD-2 was calculated at day 1, day 3, and day 7 of admission. PELOD-2 uses mean blood pressure and lactate to calculate cardiovascular dysfunction; GCS and pupillary reaction for neurologic dysfunction; PaO2 to FiO2 ratio, PCO2, and mechanical ventilation for respiratory dysfunction; white blood cell and platelet count for hematologic dysfunction; and creatinine for renal dysfunction [18]. After discharge, patients were assumed to be negative for MODS, and after patients died, they were removed from the day analysis after death. Organ failure is defined as a PELOD-2 score or greater than 1 for each specific organ system. MODS is defined as two or more organ failures.

#### **Outcomes**

The primary outcome was new impairment in children who survived, defined as an increase in validated Functional Status Scale of more than one between preinjury, hospital discharge (HD), short-term timepoint (closest to 1 year after discharge), and long-term timepoint (closest to 5 years after discharge) from clinical documentation of neurologic examination and developmental history in the electronic health record [23].

#### **Statistical Analyses**

Nonparametric tests (Wilcoxon rank-sum test, Pearson's  $\chi^2$  test, and Fisher's exact test) compared characteristics between AHT and aTBI groups. Multivariate logistic regressions were conducted to analyze the association between TBI mechanism, MODS status, and new impairment status at the three study time points. In a univariate regression, the following variables were assessed for association with impairment at each time point: TBI mechanism (AHT), age in months, ISS at admission, MODS on day 1, 3, or 7, race, seizure on electroencephalogram, and presence of subdural hemorrhage on initial head

computed tomography. These variables were chosen because they have been shown to impact outcomes; then, via backward stepwise regression for  $p$  values  $< 0.05$ , the variables included in the multivariate logistic regression were TBI mechanism (AHT vs. aTBI), age in months, ISS at admission, seizure, and presence of MODS on day 1, 3, or 7. In the logistic regression for patients with AHT, age in months was not significant in univariate analysis, so this was not included (Supplemental Table 2). In the logistic regression for patients with aTBI, race, and subdural hemorrhage were not significant in univariate analysis, so these were not included (Supplemental Table 3). There were no concerns for collinearity. All statistical analyses were performed by using RStudio version 2022.12.0 + 353 (Rstudio, Boston, MA) and R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria) with the following packages: broom, gtsummary, haven, knitr, lubridate, modelr, ggplot2,

#### **Results**

#### **Patients**

There were 576 patients eligible for inclusion. Two hundred fifteen (37%) children had AHT and 361 (63%) had aTBI (Fig. 1). There was no difference in age, sex, race, or history of medical comorbidities between mechanism groups (Table 1).

and tidyverse. Missing data were not imputed. Statistical significance was defined as  $p <$ 

#### **Hospitalization Details**

0.05.

At admission, more patients with AHT had a severe TBI classified by admission GCS  $(47/215 [22\%]$  vs. 37/361 [10%],  $p < 0.001$ ) and higher ISS scores (median 17 [interquartile range,  $10-26$ ] vs. 10,  $p < 0.001$ ) than patients with aTBI. Patients with AHT were more frequently mechanically ventilated  $(69/215 [32\%] \text{ vs. } 54/361 [15\%], p < 0.001)$  and diagnosed with seizures  $(66/215 \, [31\%] \, \text{vs. } 27/361 \, [8\%]$ ,  $p < 0.001$ ) during hospitalization. They also had more intracranial hemorrhage (195/215 [91%] vs. 295/361 [82%],  $p = 0.003$ ) and neurosurgical intervention  $(39/215 \mid 18\%)$  vs.  $27/361 \mid 8\%$ ,  $p < 0.001$ ) (Table 1).

#### **MODS**

Of the 576 patients, 288 remained hospitalized on day 3 and 110 on day 7. Seven patients died before day 3 and 13 patients died before days 4–7, leaving 569 patients for analysis on day 3 and 556 on day 7. MODS was more frequent in patients with AHT than patients with aTBI on days 1 (74/215 [34%] vs. 83/361 [23%],  $p = 0.003$ ), 3 (59/210 [28%] vs. 22/359 [6%],  $p < 0.001$ ], and 7 (33/199 [17%] vs. 12/357 [3%],  $p < 0.001$ ] (Fig. 2).

On day 1, more patients with AHT had three organs  $(3/215 \ (15\%)$  vs.  $34/361 \ (9\%)$ ,  $p =$ 0.032) and 4–5 organs involved (25/215 (12%) vs. 14/361 (4%),  $p = 0.003$ ). All 27 patients who died qualified for MODS on at least one day, highest on day 1 (26/27 [96%]), and all 84 patients with severe TBI by admission GCS also qualified for MODS on day 1. Forty out of 576 patients (7%) had MODS on day 1, day 3, and day 7 with 45/576 patients (8%) having MODS on day 7. (Table 2).

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The most frequent organ system failures overall were cardiovascular (381/576 [66%]), neurologic (128/576 [22%]), and respiratory (128/576 [22%]). In the AHT group, more children had neurologic, respiratory, hematologic, and renal failure compared to the aTBI group [Neurologic (70/215 [33%] vs. 58/361 [16%], p < 0.001), Respiratory (74/215 [34%] vs. 54/361 [15%],  $p < 0.001$ ), Hematologic (25/215 [12%] vs. 20/361 [6%],  $p = 0.008$ ), Renal (55/215 [26%] vs. 53/361 [15%],  $p = 0.001$ ] (Fig. 3).

Table 2 also details the organ systems by day. On day 1, AHT had more failure than aTBI in the neurologic (65/215 [30%] vs. 57/361 [16%],  $p < 0.001$ ), respiratory (65/215 [30%] vs. 53/361 [15%],  $p < 0.001$ ), and renal (50/215 [23%] vs. 51/361 [14%],  $p = 0.005$ ) organ systems. On day 3, AHT had more failure all organ systems than aTBI. On day 7, AHT had more failure than aTBI in cardiovascular  $(26/199 [13\%] \text{ vs. } 16/357 [5\%], p < 0.001)$ , neurologic (26/199 [13%] vs. 11/357 [3%],  $p < 0.001$ ), respiratory (31/199 [16%] vs. 10/357 [3%],  $p < 0.001$ ), and renal (5/199 [2%] vs. 1/357 [0%],  $p = 0.024$ ) organ systems.

When divided into presenting GCS severity, patients with AHT had more MODS on days 3 (19/161 [12%] vs. 3/307 [1%],  $p < 0.001$ ) and 7 (12/161 [8%] vs. 1/307 [0%],  $p < 0.001$ ) in the mild GCS category than aTBI (Supplemental Table 1). In the severe GCS category, there was more MODS in patients with AHT on days 3 (36/47 [86%] vs.  $14/37$  [40%],  $p$  < 0.001) and 7 (18/47 [58%] vs. 10/37 [29%],  $p = 0.016$ ). In both TBI mechanisms, there were similar rates of MODS in mild, moderate, and severe GCS categories on day 1.

#### **Outcomes**

There were more deaths in the AHT versus aTBI group  $(22/215 \text{ [10%]} \text{ vs. } 5/361 \text{ [1%]}, p <$ 0.001). Patients with AHT also had longer hospital length of stay  $(4 \, 3, 12]$  vs.  $2 \, 1, 3]$ , p  $< 0.001$ ). The short-term time point was performed at a median of 11 months (5, 12) post hospitalization for patients with AHT and 10 months (2, 12) for patients with aTBI ( $p =$ 0.015). The long-term time point was performed at a median of 43 months (25, 62) post hospitalization for patients with AHT and 44 months (30, 61) for patients with aTBI ( $p =$ 0.3). Patients with AHT had a higher frequency of new impairment compared with patients with aTBI at all time points: HD (53/193 [27%] vs. 35/356 [10%],  $p < 0.001$ ), short-term discharge (56/189 [30%] vs. 28/323 [9%],  $p < 0.001$ ), and long-term discharge (42/133 [32%] vs. 22/214 [10%],  $p < 0.001$ ) (Table 1).

#### **Multivariable Logistic Regression for the Association with New Impairment at Each Study Time Points**

Table 3 displays the results of univariate and multivariate logistic regressions for the association with new impairment by study time point. MODS was associated with new impairment after adjustment for age, subdural hemorrhage, and admission ISS in multivariable logistic regression at HD (odds ratio 19.1 [95% confidence interval 9.8, 38.6,  $p < 0.001$ ]), short-term (7.4 [3.7, 15.2,  $p < 0.001$ ]), and long-term (4.3 [2.0, 9.4,  $p < 0.001$ ]). AHT was associated with new impairment in multivariable logistic regression at HD (3.4  $[1.6, 7.3, p = 0.001]$ ), short-term  $(2.5 [1.3, 4.7, p = 0.005])$ , and long-term  $(2.1 [1.1, 4.1, p = 1.000]$ 0.036]). Seizures on electroencephalogram during admission were also associated with new

impairment at HD  $(4.8 \, [2.4, 10.1, p < 0.001])$ , short-term  $(6.1 \, [3.2, 11.7, p < 0.001])$ , and long-term  $(4.1 [2.0, 9.2, p < 0.001])$ .

To examine the impact of MODS specifically on each TBI mechanism, multivariable logistic regressions were conducted on the patients with AHT and patients with aTBI separately. AHT survivors had higher odds ratios for MODS at each time point: HD (14.5 [5.7, 9.7,  $p$ )  $< 0.001$ ]), short-term (5.4 [2.3, 13.3,  $p < 0.001$ ]), and long-term (4.7 [1.7, 13.7,  $p = 0.004$ ]) (Supplemental Table 2). MODS was only significantly associated with impairment in aTBI survivors at the first two time points: HD (19.2 [7.5, 57.4,  $p < 0.001$ ]), short-term (6.8 [2.9, 17.1,  $p < 0.001$ ]), and long-term (1.4 [0.5, 4.1,  $p = 0.500$ ]) (Supplemental Table 3).

#### **Discussion**

This single center, observational study evaluated MODS prevalence and patient outcomes by etiology (AHT vs. aTBI). When compared with children with aTBI, patients with AHT more frequently had MODS on days 1, 3, and 7 with failure most often due to neurologic, respiratory, hematologic, and renal organ dysfunction. Furthermore, in a multivariate logistic regression, AHT and MODS were both independently associated with new functional impairment at all study time points.

In a large, retrospective cohort study examining MODS in pediatric patients with trauma by Killien et al. [16], published in 2022, 23.1% (8592/37177) of patients qualified for MODS with two or more organ systems. Mortality was higher in patients who developed MODS (20.1% vs. 0.5%); in survivors, there was a decline in function at discharge (58.9% vs. 31.8%) [16]. The analysis of our data over the first week post TBI shows that patients with AHT experience more MODS compared with patients with aTBI. All the patients who died, regardless of mechanism, qualified for MODS on at least one analyzed day. In both mechanisms, MODS still contributed to impairment in short-term outcomes and it seemed to impact AHT in the long term, as well.

A recent pediatric TBI outcome study published in 2023 by Keenan et al. [9] demonstrated prospectively that infants and toddlers with severe TBI have diffuse multidomain deficits that persist, whereas those with mild and moderate TBI have similar outcomes to an orthopedic injury group. As seen in other studies, AHT was a large contributor to the severe TBI group and the poor outcome trajectory [9]. There are many hypotheses on why patients with AHT have worse outcomes. One of those is that there is a delay in presentation, leading to secondary insults such as hypoxia, hypotension, and seizures [10, 24]. These secondary insults lead to MODS due to inflammation and hypoxic ischemic injury [25, 26]. Repeated injury is another hypothesis and with each additional injury, increased inflammation could trigger MODS and thus lead to more critical illness [27]. Seizures were also common in AHT and were associated with poor outcomes in this data set. It is unknown why seizures occur more frequently than in aTBI. Seizures, especially status epilepticus, could cause MODS, or perhaps the multiorgan inflammation from AHT could lead to seizures [28, 29].

Children with TBI, particularly AHT, frequently experience apnea due to impact, seizures, or polytrauma, causing hypoxia, and hypercarbia, which can potentially worsen neurologic

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outcomes [10]. Acute respiratory distress due to pneumonia, direct or indirect lung injury, and/or neurogenic pulmonary edema may affect later outcomes as well [30, 31]. Cardiovascular dysfunction was also common in both aTBI and AHT in our cohort, which may be related to hemorrhagic shock, multiple injury, sepsis, secondary effect of analgesic and sedating medications, and critical illness associated decreased systolic function after trauma [32]. Hematologic dysfunction is prevalent after TBI with international normalized ratio being an indicator of trauma related coagulopathy [33]. Last, in the setting of severe TBI, acute kidney injury is associated with increased mortality and is related to abdominal trauma, shock, or toxic medications [34, 35]. In our study, there was more significant involvement of neurologic, respiratory, hematologic, and renal organ systems in patients with AHT, implying organ failure needs to be monitored and treated promptly to potentially improve outcomes.

There are currently no specific treatments for MODS, although there are studies evaluating the use of immune modulating medications to decrease TBI-associated inflammation [36– 38]. To improve outcomes, patients with AHT need close monitoring in a pediatric intensive care unit setting immediately after presentation so that MODS can be prevented and organ failure can be addressed specifically. More research is needed to explore the organ dysfunction in this population and other aspects to their care because public health measures at prevention have not proven to be effective [39].

Limitations for this study include the retrospective nature and the dependence on electronic health record documentation, which led to a relatively low proportion traumatic brain injury, CI, confidence interval, EEG, electroencephalogram, GCS, Glasgow Coma Score, ISS, injury severity score, OR, odds ratio, PELOD-2, Pediatric Logistic Organ Dysfunction-2, Ref, reference of patients with long-term outcome data available. Limitations of the PELOD-2 score and other MODS score performance in patients with TBI also may have affected our results, especially in relation to more traditional assessments of neurologic function using GCS [40]. The PELOD-2 cutoff for neurologic failure is a GCS of 11, whereas more traditional GCS cutoffs are defined as 3–8 (severe), 9–13 (moderate), and 14– 15 (mild), and thus overlap exists. In addition, patients who meet the PELOD-2 neurologic failure threshold are frequently intubated, thus having coexisting respiratory failure. Further, there was a high frequency of patients with cardiovascular failure (66% on day 1) using PELOD-2 scoring that are based on a wide range of blood pressures, leading to a high frequency of MODS in this cohort. The recent Pediatric Organ Dysfunction Information Update Mandate, which is a summary of multiple MODS scores, details narrower age range limits for heart rate and systolic blood pressure; this measure was not available during the conduct of this study [41]. When using these scores, MODS was developed to assess risk for mortality and morbidity, which needs to be kept in mind when interpreting our impairment results.

#### **Conclusions**

Children with TBI due to AHT had more frequent MODS than children with aTBI; both AHT as a mechanism and MODS occurrence during the first week post TBI were associated with new impairment at HD, short-term discharge (11 months), and long-term discharge

(4 years). MODS scores such as PELOD-2 may serve as a useful tool to identify children at high risk for poor outcomes needing personalized organ support. Our study suggests that children with TBI, especially AHT, need close monitoring and treatment of organ dysfunction.

#### **Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

#### **Source of Support**

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#### **Fig. 1.**



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#### **Fig. 2.**

The frequency of multiorgan dysfunction syndrome (MODS) compared by TBI etiology is shown calculated by PELOD-2. More MODS was present in AHT on day 1 and day 3. The percentages per patient cohort at each time point are displayed in the appropriate areas, and stars indicate  $p$  values less than 0.05. AHT, abusive head trauma, aTBI, accidental traumatic brain injury, PELOD-2, Pediatric Logistic Organ Dysfunction-2, TBI, traumatic brain injury

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#### **Fig. 3.**

The frequency of dysfunction by organ system compared by TBI etiology is shown calculated by PELOD-2. The neurologic, respiratory, hematologic, and renal organ systems were more frequently dysfunctional in AHT than in aTBI. The percentages per patient cohort at each time point are displayed in the appropriate areas and stars indicate  $p$  values less than 0.05. AHT, abusive head trauma, aTBI, accidental traumatic brain injury, CV, cardiovascular, Heme, hematologic, Neuro, neurologic, PELOD-2, Pediatric Logistic Organ Dysfunction-2, Resp, respiratory, TBI, traumatic brain injury



Patient characteristics by TBI mechanism (

**Table 1**



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AHT, abusive head trauma, aTBI, accidental traumatic brain injury, GCS, Glasgow Coma Score, ISS, injury severity score, IQR, interquartile range, TBI, traumatic brain injury AHT, abusive head trauma, aTBI, accidental traumatic brain injury, GCS, Glasgow Coma Score, ISS, injury severity score, IQR, interquartile range, TBI, traumatic brain injury

a Median (IQR); n (%) b Wilcoxon rank-sum test; Pearson's  $\chi^2$  test Author Manuscript

# **Table 2**







b $\chi^2$  test

Wilcoxon rank-sum test; Pearson's

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**Table 3**

Associations with impairment at each time point Associations with impairment at each time point



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Univariate regression analysis was performed for variables that impact outcomes. A backward stepwise multivariable regression analysis was performed by removing variables with p values < 0.05  $p$  values  $< 0.05$ Univariate regression analysis was performed for variables that impact outcomes. A backward stepwise multivariable regression analysis was performed by removing variables with

AHT, abusive head trauma, aTBI, accidental traumatic brain injury, CI, confidence interval, EEG, electroencephalogram, GCS, Glasgow Coma Score, ISS, injury severity score, OR, odds ratio, PELOD-2, AHT, abusive head trauma, aTBI, accidental traumatic brain injury, CI, confidence interval, EEG, electroencephalogram, GCS, Glasgow Coma Score, ISS, injury severity score, OR, odds ratio, PELOD-2, Pediatric Logistic Organ Dysfunction-2, Ref, reference Pediatric Logistic Organ Dysfunction-2, Ref, reference