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Risk Factors for Mortality and Functional Status Among Survivors of Pediatric Acute Respiratory Distress Syndrome

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Abstract

Objectives: Although the mortality rate of pediatric acute respiratory distress syndrome (PARDS) continues to decrease, the increased incidence of clinical sequelae in survivors has become a focus of clinical practice. This study aimed to determine the functional status of PARDS survivors at hospital discharge using the Functional Status Scale and to identify risk factors associated with mortality. **Methods:** We retrospectively analyzed the clinical data of patients with PARDS assessed upon admission and discharge from our hospital's pediatric intensive care unit between January 2013 and January 2020. Patients were categorized into survival and non-survival groups for intergroup clinical characteristics and therapeutic intervention comparisons. **Results:** Of the 149 study participants, 96 (64.4%) died during hospitalization, and 53 (35.6%) survived until discharge. Severe PARDS, defined as an oxygenation index score of [?]16, was an independent risk factor for mortality. Although surviving participants showed improvements in their clinical status, the new morbidity rate at discharge was 24.5%, with respiratory, feeding, and motor functions being the domains most affected. **Conclusion:** Severe PARDS was an independent risk factor for mortality. Despite the PARDS survival rate for the participants being 33.33%, approximately a quarter of survivors experienced new morbidities after discharge. The most affected functions included those related to respiration, feeding, and motor activity; therefore, special attention should be given to maintaining these functions in survivors.

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Competing Interests: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Ethics Approval: This study was approved by the Institute of Research Medical Ethics Committee of Shengjing Hospital (approval number: 2022PS489K).

Consent to Participate: As this was a retrospective study, the requirement for informed consent from patients was waived.

Consent to Publish: Not applicable.

Keywords: risk factor, mortality, pediatric, new morbidity, acute respiratory distress syndrome

Running head: Mortality and Function in PARDS Survivors

Abstract

Objectives: Although the mortality rate of pediatric acute respiratory distress syndrome (PARDS) continues to decrease, the increased incidence of clinical sequelae in survivors has become a focus of clinical practice. This study aimed to determine the functional status of PARDS survivors at hospital discharge using the Functional Status Scale and to identify risk factors associated with mortality.

Methods: We retrospectively analyzed the clinical data of patients with PARDS assessed upon admission and discharge from our hospital's pediatric intensive care unit between January 2013 and January 2020. Patients were categorized into survival and non-survival groups for intergroup clinical characteristics and therapeutic intervention comparisons.

Results: Of the 149 study participants, 96 (64.4%) died during hospitalization, and 53 (35.6%) survived until discharge. Severe PARDS, defined as an oxygenation index score of [?]16, was an independent risk factor for mortality. Although surviving participants showed improvements in their clinical status, the new morbidity rate at discharge was 24.5%, with respiratory, feeding, and motor functions being the domains most affected.

Conclusion: Severe PARDS was an independent risk factor for mortality. Despite the PARDS survival rate for the participants being 33.33%, approximately a quarter of survivors experienced new morbidities after discharge. The most affected functions included those related to respiration, feeding, and motor activity; therefore, special attention should be given to maintaining these functions in survivors.

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Introduction

Pediatric acute respiratory distress syndrome (PARDS) is a highly heterogeneous and complex clinical syndrome that exhibits certain clinical hallmarks, including hypoxemia accompanied by bilateral and diffuse pulmonary infiltrates. The prevalence of PARDS is relatively low, accounting for approximately 1%–10% of all pediatric intensive care unit (PICU) admissions, and its overall mortality rate has decreased from 40% to 18% over the past three decades [1, 2]. However, the increasing number of survivors has led to the realization that many experience long-term sequelae after PICU discharge, including respiratory and motor dysfunction. New morbidity in survivors refers to dysfunction caused by either the disease itself or the treatment modality, and such morbidity has been the subject of growing interest and concern in the field in recent years [3].

As the mortality rates of PARDS have improved, an increasing number of studies have focused on the associated morbidities and measurement of functional status among survivors. The Functional Status Scale (FSS) is a measurement tool used to quantify the degree of dysfunction in patients and their ability to perform normal daily activities required to meet basic needs [4]. The FSS score upon admission reflects baseline functional status before hospitalization, whereas the discharge score reflects the dysfunction level after treatment. Thus, given the simplicity of this scale, it has gradually become the most widely used grading system for evaluating the degree of dysfunction. For example, it has been used to accurately assess functional impairment in critically ill patients, including those with traumatic brain injury or septic shock, or in patients undergoing blood purification therapy [5-7]. However, only a few studies to date have used the FSS to evaluate functional status in patients with PARDS. The current morbidity rate among PARDS survivors is reportedly approximately 23% [8]. Additionally, patients with PARDS appear to exhibit poor overall functional status. The median FSS score upon admission to the PICU is 6, with a score of 11 after discharge, where FSS scores correlate with disease prognosis [9]. Moreover, children with acute respiratory distress syndrome (ARDS) are at risk of experiencing a decline in health-related quality of life and FSS scores that persist for up to 9 months post-discharge [10]. Therefore, identifying factors that influence mortality and functional status at discharge is crucial to ensuring optimal outcomes in this population.

This study had the following two aims: 1) to determine the mortality rate and analyze the associated risk factors of PARDS, with severe illness hypothesized to be associated with higher mortality rates; and 2) to determine the functional status of PARDS survivors upon admission and at discharge.

Materials and Methods

Study Population

This retrospective study enrolled all patients aged between 1 month and 14 years of age who were diagnosed with PARDS in the PICU of Shengjing Hospital between January 2013 and January 2020. Data were collected by searching the Health Information System (HIS) database for the PARDS diagnostic and clinical codes “principal diagnosis” and “all listed diagnoses,” yielding the final list of patients included in the study. In addition, patients’ diagnoses were confirmed from their medical records. Patients meeting the following criteria were included: 1) age between 1 month and 14 years; and 2) ARDS diagnosis and treatment with invasive mechanical ventilation. ARDS was defined in accordance with the Pediatric Acute Lung Injury Consensus Conference (PALICC) criteria [11]. Patients meeting the following criteria were excluded: 1) noninvasive ventilation treatment was received during the first 24 h following ARDS diagnosis; 2) missing data for any included variables; and 3) PICU admission lasting <24 h.

Data Collection

The following demographic and clinical data were retrospectively collected from electronic medical records (HIS records): 1) age and sex; 2) mortality and FSS scores upon admission and at hospital discharge; 3) data

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pertaining to treatment regimens following ARDS diagnosis, including inhaled nitric oxide, neuromuscular blockers, continuous renal replacement therapy, and extracorporeal membrane oxygenation (ECMO); 4) measurement data for the worst peak inspiratory pressure (PIP), positive end-expiratory pressure (PEEP), and inhaled oxygen concentration within the first 24 h after ARDS diagnosis (collected from blood tests); and 5) mechanical ventilation parameters. FSS scores upon admission and at discharge were determined retrospectively based on data recorded in the medical charts to assess and compare clinical and functional outcomes at those time points. The initial FSS score reflected each child's functional status upon hospital/PICU admission with critical illness and chronic comorbid conditions, both of which contribute to impaired functional status. The FSS is based on symptomology scores, such as those of the Pediatric Overall Performance Category Scale, Pediatric Cerebral Performance Category Scale, and Glasgow Coma Scale [12]. It comprises six domains (mental, sensory, communication, motor, feeding, and respiratory), with domain scores ranging from 1 (normal) to 5 (very severe dysfunction), and total scores ranging from 6–30, with scores of 6-7, 8-9, 10-15, 16-21, and >21 indicating good, mildly abnormal, moderately abnormal, severely abnormal, and very severely abnormal functional status, respectively [3].

Definitions

In-hospital mortality was defined as in-hospital death following PICU admission. FSS dysfunction was defined as a change in FSS score [?]3 between baseline and discharge. PARDS severity was determined according to the worst oxygenation index (OI) in the first 24 h following diagnosis, according to the PALICC categories [11]. Patients were stratified into two groups based on severity, with an OI <16 defined as mild/moderate PARDS and an OI [?]16 as severe PARDS. The partial pressure of arterial oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) (P/F) ratio was based on the Berlin definition issued by the European Society of Critical Care Medicine, where severity was graded as follows: mild/moderate, P/F >100, and severe, P/F [?]100 [13]. The Pediatric Logistic Organ Dysfunction-2 (PELOD-2) score was used to assess disease criticality in all patients upon admission [14]. The neuromuscular blocking agents used included rocuronium and vecuronium. Hemopurification refers to continuous renal replacement therapy. Direct and indirect PARDS were defined as ARDS caused by pneumonia, aspiration, or lung contusion and ARDS caused by non-pulmonary sepsis, leukemia, or pancreatitis, respectively.

Statistical Analysis

Categorical and continuous variables are presented as counts (percentages) and medians (interquartile ranges [IQRs]), respectively. Logistic regression analyses were conducted to evaluate the relationships between patient characteristics and PARDS outcomes. Any variables with a P <0.2 in the univariate logistic regression analysis were included in a subsequent multivariate logistic regression analysis. Survival curves were generated to analyze the survival outcomes of the direct and indirect PARDS groups. The log-rank test was utilized to compare the survival curves between the two groups. Statistical analyses were performed using Stata software (v13.0; StataCorp, College Station, TX, USA). Statistical significance was defined as P <0.05 (two-tailed test).

Ethical Approval Statement

All procedures were conducted in accordance with the ethical standards of the responsible committees on human experimentation, both institutional and national, and conformed with the 1975 principles of the Helsinki Declaration, as revised in 2008. This study was approved by the Institute of Research Medical Ethics Committee of Shengjing Hospital (approval number: 2022PS489K). As this was a retrospective study, the requirement for informed consent was waived.

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Results

A total of 186 patients met the inclusion criteria, 37 of whom were excluded for the following reasons: incomplete clinical data (n = 23); admission lasting <24 h (n = 13); and age >14 years (n = 1). The screening flowchart is shown in Figure 1. Among the remaining 149 patients, 88 (59.1%) were men, the median (IQR) age was 32 (10–60) months, and the median PELOD-2 score upon admission was 9 (7–11). The in-hospital mortality rate was 64.4% (96 patients), whereas 35.6% (53 patients) survived until discharge. Overall, 82 (55.0%) and 67 (45.0%) patients had direct and indirect PARDS, respectively, while 38 (71.7%) and 15 (28.3%) survivors had direct and indirect PARDS, respectively. The baseline characteristics of the study participants are presented in Table 1.

Changes in FSS Scores from Baseline

The median (IQR) FSS scores of survivors at the time of hospital admission and discharge were 6 (6–6) and 7 (6–7), respectively. A tendency toward improved functional status was seen by the time of discharge, with a median (IQR) change in FSS score of 1 (1–2). Upon discharge, 40 (75.5%) survivors exhibited good functional status, whereas nine (17.0%) and four (7.5%) exhibited mildly and moderately abnormal function, respectively. None of the survivors demonstrated severely or very severely abnormal functional status, and the new morbidity rate of survivors at discharge was 24.5%.

Assessment of FSS Domains at Discharge

Functional impairment was present upon discharge for most domains, although respiratory, feeding, and motor domains were the most commonly affected. The rates of dysfunction were the lowest in the communication domain at discharge. Among the survivors, 33 (62.3%) exhibited respiratory dysfunction, nine (17.0%) had feeding dysfunction, five (9.4%) were affected by motor dysfunction, four (7.5%) demonstrated sensory dysfunction, four (7.5%) had mental dysfunction, and two (3.8%) showed communication dysfunction (Figure 2). Additionally, 13 (24.5%) patients exhibited multi-domain dysfunction.

Respiratory dysfunction was associated with pleural effusion (9 patients, 17.0%), lobar pneumonia (14 patients, 26.4%), pneumothorax (5 patients, 9.4%), and pulmonary fibrosis (2 patients, 3.8%), for which oxygen therapy or suction was required post-discharge. None of the patients required a tracheostomy or ventilation management. Feeding dysfunction was predominantly associated with digestive problems; for example, two patients (3.8%) remained on liquid meals due to pancreatitis, four (7.5%) required preterm milk and special formula, and three (5.7%) needed nasogastric feeding. Motor dysfunction was associated with primary disease and treatment; for example, three cases (5.7%) were caused by a primary disease (one case each of cerebral development anomalies, leg edema, and fingertip necrosis). Moreover, two patients (3.8%) underwent ECMO treatment and experienced lower extremity thrombosis.

Comparison Between Survival and Non-Survival Groups

The survival and non-survival groups differed significantly in terms of PARDS severity, P/F ratio on day 1 after diagnosis, PELOD-2 score upon admission, PARDS etiology, rate of inhaled nitric oxide use, PIP, PEEP, and FiO_2 measurements, duration of hospitalization, hemopurification, immunosuppression, and comorbidity. The characteristics of survivors and non-survivors are presented in Table 2.

When assessing risk factors, severe PARDS was related to survival rate (odds ratio [OR] = 0.24; 95% confidence interval [CI]: 0.07–0.80; P = 0.02), after correcting for other factors. The results of statistical analyses are presented in Table 3. OR values for the other variables in the regression analysis (Model 2) are shown in Table 4.

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Survival Curves of the Direct and Indirect PARDS Groups

A comparison of the survival curves of the direct and indirect PARDS groups using the log-rank test revealed significant separation, with the indirect group having a lower survival rate than the direct group. Additionally, the indirect PARDS group had a poorer survival rate and a worse prognosis ($P < 0.05$) (Figure 3).

Discussion

The findings of this study demonstrated high mortality rates in patients with PARDS; only a third of patients survived, and nearly a quarter of survivors exhibited new morbidities, with respiratory, feeding, and motor functions being predominantly affected. Additionally, severe PARDS was an independent risk factor for mortality.

The 64.4% mortality rate observed among patients in this study was more than double the previously reported rate of 24% [15]. A multicenter study from China found a similar mortality rate of 61% in patients with PARDS; however, the large variability in mortality rates could be due to various factors, such as differences in referral infrastructure, PICU admission and discharge policies, illness severity, patient composition, level of patient care, and accessibility of resources [16]. The present study also excluded patients who were admitted for <24 h, most of whom were in a near-death state upon admission. As a result, mortality rates may have been underestimated. Several factors could explain the high mortality rate in our center. The mean PELOD-2 score of 9 upon admission was higher than that reported for the mortality groups in other centers (mean PELOD-2 score of 7.9) [2]. Additionally, every patient in this study was treated with invasive ventilation. Patients undergoing mechanical ventilation have greater disease severity than those undergoing noninvasive ventilation. In addition, more than half of the patients were diagnosed with severe PARDS, which would be expected to contribute to the high mortality rate. A previous study reported a mortality rate of 10–15% in patients with mild/moderate PARDS and 33% in patients with severe PARDS [17]. Moreover, patients who withdrew from treatment midway would be expected to have a higher mortality rate.

Consistent with the findings of other studies, multi-organ dysfunction was the leading cause of death in patients with PARDS [18]. In this study, severe PARDS was found to be an independent risk factor for mortality, which is also consistent with previous studies [19]. However, the present results demonstrated associations between both the OI and P/F and survival rates. At the onset of PARDS, both the prevalence and severity of non-pulmonary organ failure were shown to increase with severity of hypoxemia [20]. When assessing severe PARDS, the OI was consistent with the P/F ratio. Consequently, our study's results further support the utility of the P/F ratio as a reliable and practical metric for assessing the prognosis of patients with severe PARDS.

Multi-organ failure, including sepsis-associated delirium, septic encephalopathy, capillary leakage-induced edema of the extremities, and intestinal failure leading to feeding intolerance, affects mortality rates and functional status at discharge. In addition to dysfunction caused by the disease itself, treatment factors can also cause new morbidity. For example, in the current study, lower extremity deep vein thrombosis, jugular vein thrombosis, intracranial hemorrhage, and cerebral infarction, which are adverse events that are being increasingly investigated, could have developed during ECMO treatment. Two patients developed lower extremity deep vein thromboses after this treatment, leading to a motor domain FSS score of 2 at discharge. All the included patients were in critical condition at the time of admission. Although survivors showed greatly improved functional status after discharge, 24.5% experienced residual dysfunction. A recent study reported similar residual dysfunction among survivors of PARDS, with 24.5% of patients being discharged to a rehabilitation facility [12]. Similarly, consistent with the present findings, another study revealed new morbidities in 15.6% of patients with PARDS upon discharge with an FSS score of 7 [5].

The results demonstrated that respiratory, feeding, and motor functions were the domains most affected at the time of PICU discharge. More than half the survivors exhibited respiratory dysfunction, most likely due to 71.7% (38/53) of them having direct PARDS. Most cases of mild respiratory dysfunction (respiratory FSS score = 2) were due to localized lung injuries, including pleural effusion, lobar pneumonia, pneumothorax,

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and pulmonary fibrosis; patients with these injuries required oxygen therapy or suction after discharge. Further, respiratory function may affect the quality of life after discharge. One study reported respiratory dysfunction in 36.8% of patients with PARDS, 33% of whom continued to experience mild-to-moderate impairment of lung function 3 months after discharge [21].

Furthermore, feeding dysfunction is a common factor affecting the long-term outcomes of PARDS and is likely to be altered in the PICU. One study revealed a significant increase in FSS feeding domain scores compared with scores measured upon admission [12]. Another study found that 37.8% of patients with PARDS still required enteral assistance [5] which was higher than the 17% rate of feeding dysfunction in the present study. Most of those patients required preterm milk, special formulas, liquid meals, feeding assistance, and nasogastric tube feeding after discharge, although there was minimal need for total parenteral nutrition at discharge.

Motor dysfunction was one of the main complications experienced by survivors, with the most common causes being mental disorders, edema or venous thrombosis of the extremities, and finger ischemia or necrosis. Thus, special attention should be paid to the respiratory, feeding, and motor domains of PARDS survivors.

Strengths

This is one of a few studies that provide data from an Asian population on the use of the FSS to assess illness severity upon PICU admission and discharge, with a focus on factors affecting mortality rate and functional status at discharge. Additionally, this study describes the functional status of a subgroup of patients with PARDS who underwent invasive ventilation. Finally, respiratory, feeding, and motor dysfunctions were identified as the most common areas requiring rehabilitation.

Limitations

This study had a small sample size; thus, the true incidence of the disease could not be accurately estimated. Additionally, the study was based on data from a single pediatric center. Therefore, there is a risk of missing data and information bias. Moreover, because this was a retrospective study, patients who had nearly drowned or had severe pneumonia, aspiration pneumonia, lung contusions, or severe sepsis but had not obtained a PARDS diagnosis may have been missed. Further, the FSS has not been validated for retrospective assessment of PARDS, and its ability to predict outcomes in patients in the PICU has not been investigated. Thus, it is unclear whether FSS dysfunction upon hospital discharge reflects baseline functional disability or new morbidities associated with PARDS. Additional limitations include the fact that the study did not list modifiable risk factors for functional status dysfunction (FSS > 8) at hospital discharge in patients with PARDS.

Further research should focus on investigating the functional status of patients from multiple centers, and follow-up clinical trials involving patients with PARDS are warranted. In addition, future studies should establish an objective outcome measure of mortality or significant functional morbidity upon hospital discharge.

Conclusions

PARDS was associated with high mortality rates, and severe PARDS was an independent risk factor affecting mortality. One out of three patients survived, and about a quarter of them exhibited new morbidity, with respiratory, feeding, and motor functions being the domains most commonly affected. Hence, special attention should be given to maintaining these functions in survivors.

Acknowledgments

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Data Availability Statement

Data is available from the corresponding author upon reasonable request. All data relevant to the study is included in the article or uploaded as supplementary information.

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Tables

Table 1. Baseline characteristics of patients with PARDS.

PARDS, pediatric acute respiratory distress

Table 2. Baseline characteristics of PARDS survivors and non-survivors.

PARDS, pediatric acute respiratory distress

Table 3. Association between the oxygenation index (OI) and partial pressure of arterial oxygen/fraction of inspired oxygen ratio (P/F) on day 1 of hospitalization and PARDS survival rate[a].

PARDS, pediatric acute respiratory distress

Table 4. The OR with 95% CIs of all variables included in Model 2.

OR, odds ratio; CI, confidence interval

Figure Legends

Figure 1 Study population chart

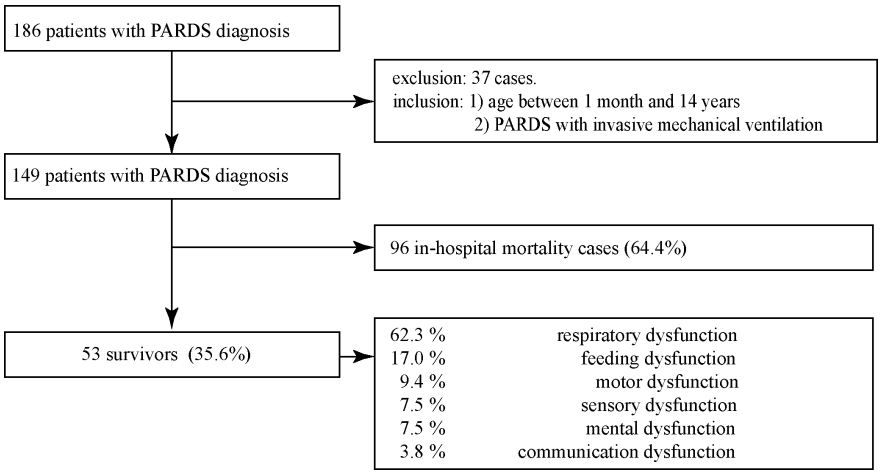
ARDS, acute respiratory distress syndrome; PARDS, pediatric acute respiratory distress syndrome

Figure 2 Change in Functional Status Scale scores at discharge among survivors

FSS, Functional Status Scale

Figure 3 Survival curves in direct and indirect PARDS groups

PARDS, pediatric acute respiratory distress syndrome



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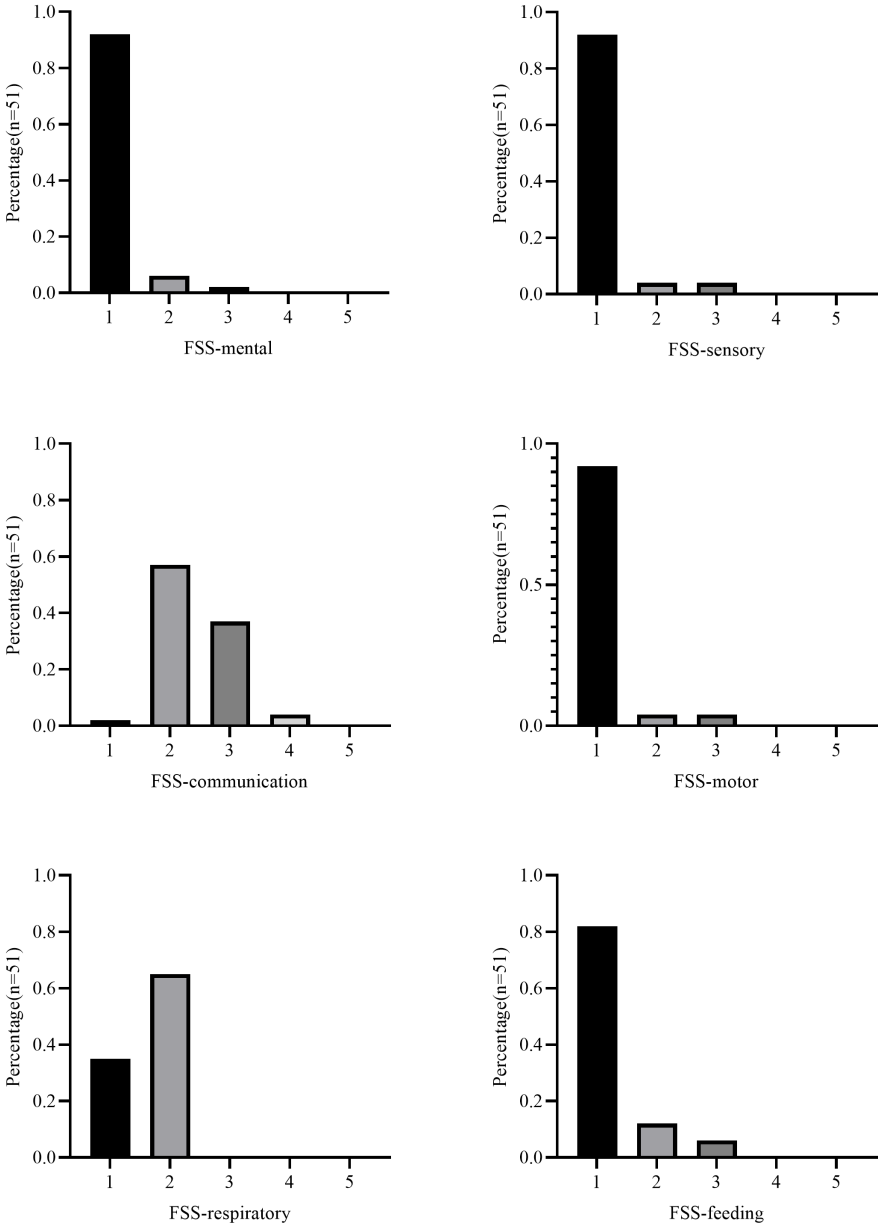
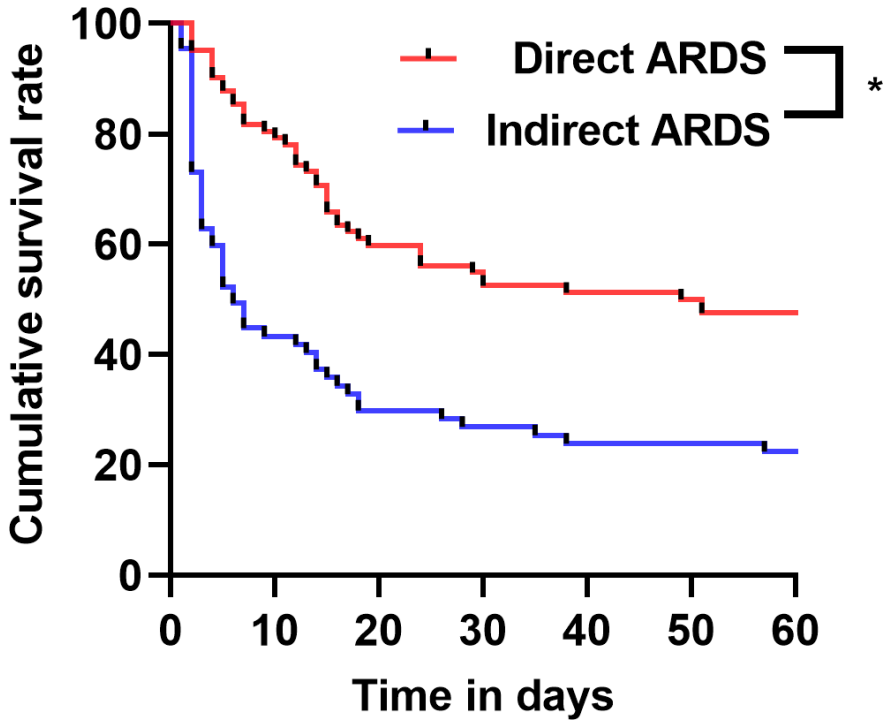
Discharge FSS





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