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Association between Fluid Balance and Outcome Variables in Mechanically Ventilated Children

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Abstract:

Background: Intravenous (IV) fluid therapy is often required in patients undergoing mechanical ventilation (MV) to restore hemodynamics and distal organ perfusion.. Prolonged mechanical ventilation (PMV) in critically ill children is associated with significant complications, including fluid balance disturbances. Understanding the relationship between fluid balance and PMV can improve patient outcomes. This study aimed to evaluate the association between fluid balance and PMV in critically ill children, as well as other outcomes like pediatric mortality index (PIM2),length of PICU stay & outcome of the patients . **Methods:** This cross sectional study was conducted on 40 mechanically ventilated children admitted to the pediatric intensive care unit (PICU) at Benha University Hospital from January to June 2023. Fluid balance was calculated during the first 48 hours of mechanical ventilation. PIM2 scores and other clinical parameters were recorded. **Results:** The mean age of patients was 4.1 ± 4.57 years. A significant positive correlation was found between fluid balance in the first 48 hours and PIM2 (r=0.568, P<0.001), as well as with the length of PICU stay (r=0.757, P<0.001). Fluid balance was significantly higher in non-survivors compared to survivors (P=0.003). Logistic regression identified high-risk diagnosis, diastolic blood pressure, fluid balance, PIM2, and duration of MV as significant predictors of mortality. **Conclusion:** Positive fluid balance in the first 48 hours is significantly associated with PMV and higher mortality in critically ill children. Early fluid management may improve outcomes in this population.

Keywords: Fluid Balance; Prolonged Mechanical Ventilation, PICU, PIM2, Mortality.

Introduction

Assisted mechanical ventilation (AMV) is a frequently used life-support system which, in spite of its benefit, might cause damage [1].

With the widespread application of mechanical ventilation technology, the survival rate of critically ill patients is constantly increasing. In recent years, numerous studies evaluating the duration of mechanical ventilation of patients with critical illnesses [2, 3].

Prolonging the duration of mechanical ventilation causes many challenging complications, such as ventilator-associated pneumonia (VAP), pulmonary hemorrhage, tracheal injury, diaphragm atrophy, neuromuscular disorders, an increased length of ICU stay and an unfavorable discharge destination. Moreover, there are no specialized weaning units for patients requiring PMV. Most children with PMV stay in the hospital indefinitely and are separated from their families, which adversely affects children's physical and emotional development [4].

Different strategies such as sedation and ventilator weaning protocols including spontaneous breathing trials and decreasing duration of AMV are under trial to decrease Ventilator-associated lung injury (VALI) [5, 6].Fluid balance is one of the cardinal outcome measures related to exposure time of AMV [7]. Fluid balance is a term used to describe the balance of the input and output of fluids in the body to allow metabolic processes to function correctly [8].It was shown that fluid balance accumulation in the first 3-7 days was associated with more days on AMV among adult patients with acute pulmonary injury and also to a higher mortality rate in patients with sepsis [9, 10], and with acute respiratory distress [11].

In children, it was shown that the balance accumulated in the first 72 hours was associated with more days on AMV in patients with acute lung injury [7, 12], and in those in the cardiovascular postoperative period [13]. A cumulative balance higher than 15% of the body weight was demonstrated to be associated with impaired oxygenation and prolonged AMV [14].Patients requiring AMV for more than 7 days were considered to have PMV [15].The purpose of this study is to exhibit the association between fluid balance and PMV as well as other associated outcome variables as pediatric mortality index (PIM2), VAP, lung injuries and other system dysfunction.

Patients and methods:

Patients:

This cross sectional study was conducted over all mechanically ventilated children in the pediatric intensive care unit (PICU) of Benha University hospital in the period from 1 January to 30 June 2023.

An informed written consent was obtained from the patients. Every patient received an explanation of the purpose of the study and had a secret code number.

Inclusion criteria were patients of both sexes aged between 29 days to 15 years and mechanically ventilated patients who admitted in the PICU.

Exclusion criteria were children previously admitted in the PICU of any other hospital and referred from those hospitals, patients whose medical records had incomplete information, patients with congenital lung anomalies and malformations, patients who had received renal function replacement therapy and burn patients, and patients who had evidence of left atrial hypertension either clinically or by echocardiogram or had any echocardiographic evidence of intracardiac shunt.

An informed written consent was obtained from patients’ caregivers.

Every parent received an explanation of the purpose of the study and had a secret code number. The study was done after being approved by the Research Ethics Committee, Faculty of Medicine, Benha University. (MS 5-9-2022)

Methods:

All studied cases were subjected to the following:

Detailed history taking, including name, age, gender and body mass index (BMI), present history showing course of the disease and duration, date of admission, provisional clinical diagnosis, PIM2 score.

Full clinical examination: General examination including general comment on children conscious and mental state, vital signs as pulse, blood pressure, capillary filling time, respiratory rate and temperature. Systemic examination including: cardiovascular system for detection of any abnormal heart sounds or murmurs, respiratory system for detection of any abnormal breath sound, adventitious sounds and respiratory distress, gastrointestinal tract (GIT) and abdomen for presence of organomegaly or ascites, central nervous system (CNS) and musculoskeletal system.

The assessment included Glasgow Coma Score, pupillary reaction, and motor system examination (power, tone, reflexes). Blood investigation results, including arterial blood gases (PaO2, base excess, FiO2), were recorded. Fluid intake and output during the first 48 hours of mechanical ventilation were documented, covering blood products, nutrition, intravenous fluids, medications, urine output, blood loss, and other outputs. Insensible losses were excluded because in all ventilated patients active humidification and heating systems are used. Daily fluid balance was calculated per kilogram using actual body weight, as 24-hour intake minus output . Maintenance fluid intake was determined using the Holliday-Segar method [16]. Percent fluid overload was calculated using the formula , (Total Fluid Intake in Liters − Total Fluid Output in Liters) / Admission Weight in Kilograms] × 100 , described by **Goldstein et al.** [17].

Fluid balance definitions:

Fluid balance was assessed using daily weights, a reliable method consistent with guidelines. At admission, it was calculated as (fluid input − fluid output) /weight × 100 during the first 48 hours of AMV.

The Pediatric Index of Mortality 2 (PIM2) score was determined based on admission type and underlying conditions like cardiac arrest and immune deficiencies.

The PIM2 score, with a 99.8 cutoff and 95% confidence interval, was used to predict outcomes. A PaO2/FiO2 ratio <200 indicated hypoxic respiratory failure if no cyanotic heart disease or left ventricular dysfunction was present. Cardiovascular failure was defined by arterial hypotension (below the 5th percentile for age) or the need for vasoactive drugs (dopamine, epinephrine, norepinephrine).

Duration of mechanical ventilation , duration of PICU stay, and outcome were recorded subsequently and analyzed with precision. [18].

Approval code: MS 5-9-2022

Statistical analysis

Statistical analysis was done by SPSS v28 (IBM Inc., Chicago, IL, USA). Shapiro-Wilks test and histograms were used to evaluate the normality of the distribution of data. Quantitative parametric data were presented as mean and standard deviation (SD). Quantitative non-parametric data were presented as median and interquartile range (IQR). Qualitative variables were presented as frequency and percentage (%). Pearson and spearman correlation were done to estimate the degree of correlation between two quantitative variables. Logistic regression is also used to estimate the relationship between a dependent variable and one (univariate) or more (multivariate) independent variables.

Results:

In our study, regarding demographic data of the studied patients, age ranged from 0.12 to 15 years with a mean of 4.1 ± 4.57 years and a median of 2.75 (0.33-6) years. There were 18 (45%) males and 22 (55%) females.

The SBP of the studied patients ranged from 75 to 168 mmHg with a mean of 110.5 ± 21.62 mmHg and the DBP ranged from 70 to 110 mmHg with a mean of 92.4 ± 11.11 mmHg. **Table1**

The base excess ranged from -16.3 to 20.31 mEq/L with a mean of -5.2 ± 7.22 mEq/L. The PaO_2 ranged from 50 to 110 mmHg with a mean of 84.2 ± 18.2 mmHg. The FiO_2 ranged from 0.04 to 1 % with a mean of 0.4 ± 0.22 %. The FiO_2/ PaO_2 ranged from 0.04 to 1.72 with a mean of 0.5 ± 0.32. The fluid balance of the studied patients in the 1st 48 hours ranged from -2803 to 2418 with a mean of 582.4 ± 785.79. **Table2**

PIM2 of the studied patient ranged from 1.16 – 100 with a mean of 43.8 ± 35.29. **Table3** The duration of MV of the studied patient ranged from 2 to 30 days with a mean of 7.97 ± 6.12 days. The length of PICU stay ranged from 3 to 45 days with a mean of 14.4 ± 11.43 days. Regarding the outcome, 17 (42.5%) patients were discharged (survivors) and 23 (57.5%) patients were arrested (non-survivors).**Table 4**

There was a significant positive correlation between the PIM2 and fluid balance at 1st 48 hours (r= 0.568, P<0.001). There was insignificant correlation between the PIM2 and different parameters (age, SBP, DBP, base excess, PaO_2, FiO_2, FiO_2/ PaO_2). **Figure 1**

There was a significant positive correlation between the PIM2 and length of PICU stay (r= 0.757, P<0.001). **Figure 2**

There were significant relations between PMV and fluid balance at 1st 48 hours and PIM2 (P=0.011, <0.001 respectively). **Table 5** Also, there were a significant relation between fluid balance at 1st 48 hours and outcome, being better in survivors group compared to non-survivors (P=0.003).

The univariate logistic regression analysis revealed that sex, high risk diagnosis, DBP, fluid balance at 1st 48 hours, PIM2 and duration of MV were significant predictors of mortality of the studied patients.

The multivariate logistic regression analysis revealed that high risk diagnosis, DBP, fluid balance at 1st 48 hours, PIM2 and duration of MV were the only significant predictors of mortality of the studied patients. **Table 6**

Table 1: Demographic data and BP of the studied patients.

		N=40
Age (years)	**Mean ± SD**	4.1 ± 4.57
	Range	0.12 - 15
	Median (IQR)	2.75 (0.33-6)
Sex	**Male**	18 (45%)
	Female	22 (55%)
SBP (mmHg)	**Mean ± SD**	110.5 ± 21.62
	Range	75 - 168
DBP (mmHg)	**Mean ± SD**	92.4 ± 11.11
	Range	70 - 110

SBP; Systolic Blood Pressure, DBP; Diastolic Blood Pressure.

Table 2: Base excess and ventilation parameters, and fluid balance at 1st 48 hours of the studied patients.

		N=40
Base excess (me/L)	**Mean ± SD**	-5.2 ± 7.22
	Range	-16.3 - 20.31
	Median (IQR)	-4.3 (-9.7- -2.55)
PaO_2 (mmHg)	**Mean ± SD**	84.2 ± 18.2
	Range	50 - 110
FiO_2 (%)	**Mean ± SD**	0.4 ± 0.22
	Range	0.04 - 1
	Median (IQR)	0.3 (0.29 - 0.4)
FiO_2/ PaO_2	**Mean ± SD**	0.5 ± 0.32
	Range	0.04 - 1.72
	Median (IQR)	0.47 (0.27 - 0.63)
Fluid balance at 1st 48 hours (ml)	**Mean ± SD**	582.4 ± 785.79
	Range	-2803 to 2418
	Median (IQR)	500.45 (204.65 - 868.5)

SBP: systolic blood pressure, DBP: diastolic blood pressure, IQR: interquartile range. PaO_2: partial pressure of oxygen, FiO_2: fraction of inspired oxygen, IQR: interquartile range.

Table 3: Items of PIm2 score.

		N=40
Post cardiac surgery		1 (2.5%)
Pneumonia		17 (42.5%)
CNS infection		3 (7.5%)
Asthmatic		1 (2.5%)
Convulsions (CP)		1 (2.5%)
Elective		1 (2.5%)
FB aspiration		1 (2.5%)
Guillain-Barré syndrome		3 (7.5%)
Hypernatremic dehydration		1 (2.5%)
Polytrauma		5 (12.5%)
Pulmonary hemorrhage		2 (5%)
Sepsis		2 (5%)
TAPVR		1 (2.5%)
TB &Acute kidney injury		1 (2.5%)
Elective admission		3 (7.5%)
Cardiac bypass		1 (2.5%)
High risk diagnosis		21 (52.5%)
Low risk diagnosis		0 (0%)
Mechanical ventilation (1st hour)		24 (60%)
Response of pupils to light (<3m)		7 (17.5%)
PIM2	**Mean ± SD**	43.8 ± 35.29
	Range	1.16 - 100
	Median (IQR)	42.04 (6.54 - 83.75)

Table 4: Duration of mechanical ventilation, length of PICU stay and outcome of the studied patients.

		N=40
Duration of MV (days)	**Mean ± SD**	7.97 ± 6.12
	Range	2 - 30
	Median (IQR)	6.5 (4 – 9)
Length of PICU stay (days)	**Mean ± SD**	14.4 ± 11.43
	Range	3 - 45
	Median (IQR)	10 (7 – 17)
Outcome	**Survivors**	17 (42.5%)
	Non-survivors	23 (57.5%)

IQR: interquartile range, IQR: interquartile range. MV: mechanical ventilation, PICU: Pediatric intensive care unit.

Table5: Relation between prolonged mechanical ventilation and different parameters

	Prolonged mechanical ventilation	**P value**
Age (years)	4.1 ± 4.57	0.296
SBP (mmHg)	110.5 ± 21.62	0.070
DBP (mmHg)	92.76 ± 11.216	0.451
Base excess (mEq/L)	-5.40 ± 7.53	0.152
PaO_2 (mmHg)	84.40 ± 18.91	0.445
FiO_2 (%)	0.04 - 1	0.093
FiO_2/ PaO_2	0.5 ± 0.32	0.159
Fluid balance at 1st 48 hours	582.4 ± 785.79	**0.011***
Predicted death rate	43.8 ± 35.29	**<0.001***

SBP: systolic blood pressure, DBP: diastolic blood pressure, PaO2: partial pressure of oxygen, FiO2: fraction of inspired oxygen, *: statistically significant as P value <0.05

Table 6: Multivariate logistic regression analysis for prediction of mortality.

	OR	**95% CI**	**P value**
Age (years)	0.9164	0.7204 to 1.1658	0.477
Sex	0.4088	0.0446 to 3.7436	0.428
Elective admission	1.3766	0.0696 to 27.240	0.833
Cardiac bypass	1.0501	0.9062 to 1.2168	0.515
High risk diagnosis	51.8816	6.605 to 407.468	**<0.001***
Response of pupils to light (<3m)	7.0783	0.6569 to 76.273	0.106
SBP (mmHg)	1.0146	0.9814 to 1.0490	0.391
DBP (mmHg)	1.0732	1.0045 to 1.1467	**0.036***
Base excess (mEq/L)	0.9368	0.8424 to 1.0419	0.229
PaO_2 (mmHg)	1.0040	0.9225 to 1.0926	0.926
FiO_2 (%)	1.0672	0.9140 to 1.2460	0.411
FiO_2/ PaO_2	3.2702	0.3536 to 30.241	0.296
Fluid balance at 1st 48 hours (ml)	0.9990	0.9981 to 0.9999	**0.032***
PIM2	1.1333	1.0355 to 1.2404	**0.006***
Duration of MV (days)	1.5361	1.0907 to 2.1635	**0.014***
Length of PICU stay (days)	0.9245	0.8199 to 1.0425	0.200

OR: odds ratio, CI: confidence interval, SBP: systolic blood pressure, DBP: diastolic blood pressure, PaO2: partial pressure of oxygen, FiO2: fraction of inspired oxygen, MV: mechanical ventilation, PICU: Pediatric intensive care unit, *: statistically significant as p value <0.05.

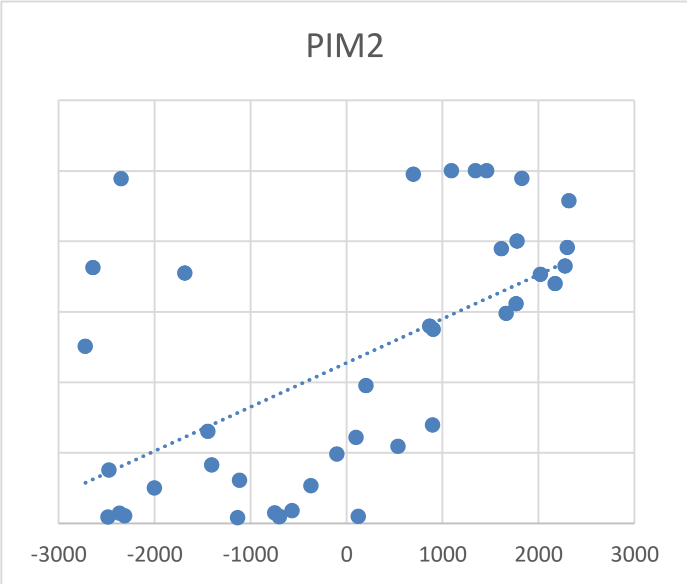

Figure 1: Correlation between the PIM2 and Fluid balance at 1st 48 hours of the studied patients.

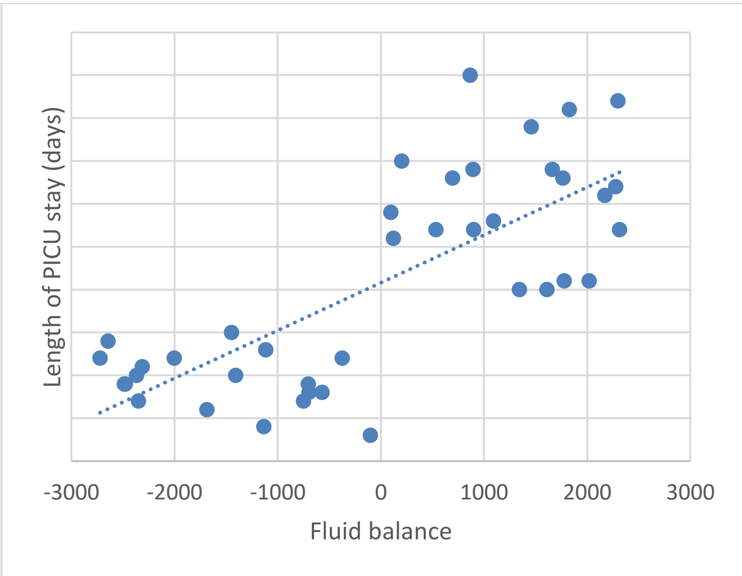

Figure 2: Correlation between the Fluid balance at 1st 48 hours and length of PICU stay of the studied patients.

Discussion:

In our study, regarding demographic data of the studied patients, age ranged from 0.12 to 15 years with a mean of 4.1 ± 4.57 years and a median of 2.75 (0.33-6) years. There were 18 (45%) males and 22 (55%) females.Flori, et al. who analyzed a database of 320 pediatric patients with acute lung injury (ALI), to test the hypothesis that positive fluid balance is associated with worse clinical outcomes in children with ALI. It was observed that median age was 3.4 yrs (1d–18 yrs) and male represented (56%) [19]. Furthermore, Vidal et al. evaluated whether fluid balance in the first 48 hours of assisted mechanical ventilation initiation was associated with a prolonged duration of this process among children in the PICU. Their results found that median age of this population was 1.2 years old (0.4-3.3) and Male sex represented (52.7%) [20]Regarding the provisional diagnosis of the studied patients, the most common was pneumonia in 17(42.5%) patient , followed by polytrauma in 5(12.5%) patient then CNS infection in 3(7.5%) patient and less commonly FB aspiration in 1(2.5%) patient, sepsis in2(5%) patient and Guillian-Barre`syndrome in 3(7.5%) patient.In the same line with our study , Vidal et al. reported that the decision to initiate AMV was respiratory in 47 (28.83%) of cases, cardiovascular in 45 (27.61%) of cases, neurological in 19 (11.66%) of cases, liver in 19 (11.66%) of cases, septic shock in 16 (9.82%) and others in 17 (10.43%) [20].Valentine et al. identified 168 patients with ALI meeting eligibility criteria. Five PICUs. Mechanically ventilated children (age ≥1 month to <18 years) with ALI admitted 2007–2010. ALI was triggered by direct pulmonary injury in 71% of the patients. Fifty-eight percent (58%) of the patients had at least one chronic condition on admission and 71% were admitted for a pulmonary reason [7].So there are different studies reporting respiratory system involvement as the main cause for initiation of mechanical ventilation in PICU and this is in the same line with our study.In the present study, regarding the clinical data of the studied patients, 3 (7.5%) patients had an elective admission, 1 (2.5%) patient had previous cardiac bypass, 21 (52.5%) patients had a high-risk diagnosis (post cardiac arrest & neurodegenerative disorders), no patient had a low-risk diagnosis. Among the studied patients, 24 (60%) patients required mechanical ventilation (at the 1st hour) and 7 (17.5%) showed a response of pupils to light (<3m).In the same line with our study, Costa et al. utilized PRISM and determination of mortality risk factors in a tertiary PICU. They noted that the patients who required the use of mechanical ventilation were (63%). The majority of patients was clinical (78%) and had underlying disease (86%), the most frequent were hepatological (23%) and oncological (19%), required the use of mechanical ventilation (63%) and vasoactive drugs (35%) [22].The SBP of the studied patients ranged from 75 to 168 mmHg with a mean of 110.5 ± 21.62 mmHg and the DBP ranged from 70 to 110 mmHg with a mean of 92.4 ± 11.11 mmHg. The base excess ranged from -16.3 to 20.31 mEq/L with a mean of -5.2 ± 7.22 mEq/L. The PaO2 ranged from 50 to 110 mmHg with a mean of 84.2 ± 18.2 mmHg. The FiO2 ranged from 0.04 to 1 % with a mean of 0.4 ± 0.22 %. The FiO2/ PaO2 ranged from 0.04 to 1.72 with a mean of 0.5 ± 0.32.In the current study, the fluid balance of the studied patients in the 1st 48 hours ranged from -2803 to 2418 with a mean of 582.4 ± 785.79. PIM2 of the studied patient ranged from 1.16 – 100 with a mean of 43.8 ± 35.29.Andriamuri et al. showed the association of fluid balance and duration of mechanical ventilation in the PICU. PIM was ranged from 0.82-96.8 with median of 23.4 [23].

Chen et al. enrolled 202 children in a PICU with severe sepsis. Their study noted that the median [interquartile range] of PIM2 was 4.2 [2.1–22.0] [24].Valentine et al. concluded that the mortality rate in their pediatric cohort was 11.3% [7].

Hannegård Hamrin et al. quantified excess mortality in children after admission to a PICU, compared to the age and sex matched general Swedish population. PICU death rate for the study cohort was 2.93% [25].The difference in PIM2 in our study and other studies may be due to small sample size ,increased incidence of sepsis and bad clinical condition of most of our patients at the time of our study as most of them (52%) had high risk in the form of post cardiac arrest needing inotropes and neurodegenerative disorders in the form of CP ,SMA and Werding-hoffman with very poor prognosis and under nutrition , requiring PMV and more

IVF and subsequently increased PIM2.There was a significant positive correlation between the PIM2 and fluid balance at 1st 48 hours (r= 0.568, P<0.001). There was insignificant correlation between the PIM2 and different parameters (age, SBP, DBP, base excess, PaO2, FiO2, FiO2/ PaO2).

On applying the Pearson chi-square test, it was found a significant association between positive fluid balance and PMV (P value = 2.25×10^{-7} (<0.05)). Likewise, a statistically significant association was found between PIM2 score and prolonged ventilation (P value = 1.19×10^{-5} (<0.05)) [(26)].The sex had no significant difference in survival in the ICU or the mortality at 28 days. Logistic regressions for outcome revealed that the following parameters were independently associated with ICU survival: wave, SOFA day1, remdesivir use, AKI, enteral insufficiency, sepsis, duration of ICU stay and WBC [(27)].Furthermore, Chen et al. concluded that there was a weak correlation between age and PIM2 (r = 0.197, P = 0.005) [(24)].In the current work, there were significant relations between PMV and fluid balance at 1st 48 hours and PIM2 (P=0.011, <0.001 respectively), whereas there were insignificant relations between PMV and other variables.Comparable to our findings, Loss et al. established the incidence of PMV in four intensive care units and reported different characteristics, hospital outcomes, and the impact of costs and services of PMV patients (mechanical ventilation dependency ≥ 21 days) compared with non-PMV patients (mechanical ventilation dependency < 21 days). PMV patients had a significant increase in intensive care unit mortality (absolute difference = 14.2%, p < 0.001) [(28)].Additionally, Andriamuri et al. showed significant association between fluid balance and duration of mechanical ventilation (p<0.001). Univariate logistic regression analysis showed that fluid balance had no significant association with mortality. Multivariate model also showed that PELOD-2 and PIM2 scores were associated with mortality (p<0.001) [(23)].

This study has some limitations including the relatively small sample size and it was a single center study which may limit the generalizability of the results.The study was limited to the first 48 hours of mechanical ventilation, and longer-term outcomes were not explored.other factors affecting fluid balance, such as nutritional status, underlying medical conditions, and specific treatment protocols, were not fully explored or controlled for, which could contribute to confounding effects.

Conclusion:

In conclusion, our study revealed a significant association between fluid balance and PMV in critically ill children. The findings showed the impact of fluid management on crucial outcome variables, including PIM2, VAP, lung injuries, and systemic dysfunction. While no significant correlation was observed with predicted mortality. Our study also highlights the significant role of thorough fluid evaluation in the initial 48 hours of mechanical ventilation.

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Author contribution

The authors contributed equally to the study.

Conflicts of interest

No conflicts of interest

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