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Balanço Hídrico Positivo no Trauma Pediátrico Grave / Fluid Overload in Pediatric Severe Trauma

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Marta João Silva

E sob a Coorientação de:
Dra. Maria João Baptista

Trabalho organizado de acordo com as normas da revista:
Brain Injury

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UC Dissertação/Projeto (6º Ano) - Declaração de Integridade

Eu, Ana Patrícia de Matos Coelho, abaixo assinado, nº mecanográfico 201606355, estudante do 6º ano do Ciclo de Estudos Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro ter atuado com absoluta integridade na elaboração deste projeto de opção.

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TÍTULO DISSERTAÇÃO/~~MONOGRAFIA~~ (riscar o que não interessa)

Fluid Overload in Pediatric Severe Trauma

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É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTE TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
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Dedicatória

À minha família, por ser o maior exemplo de resiliência.

À Rita, à Inês e ao Miguel, por serem uma inspiração brilhante.

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Fluid Overload in Pediatric Severe Trauma

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Fluid Overload in Pediatric Severe Trauma

Background and objective: Trauma is a leading cause of pediatric mortality and potential years of life lost in the developed world. Critically ill children frequently achieve a net positive fluid balance and fluid overload is associated with substantial morbidity and mortality in pediatrics. This study investigated the association between fluid balance status and clinical outcomes in pediatric severe trauma patients.

Methods: This is a unicentric, observational retrospective study. Sixty-six children with severe trauma admitted to a tertiary hospital PICU over a 3-year period were included. Electronic medical records were reviewed. Fluid balance in the first 24 hours of PICU admission was calculated.

Results: Males comprised 56% of the sample and median age was 12.2 years. Forty-one (62,1%) suffered polytrauma, 32 of these with traumatic brain injury (TBI), and 25 had isolated TBI. Seventeen (25,7%) patients had early fluid overload (FO). Early FO was not significantly associated with mortality, acute kidney injury, PICU length-of-stay, duration of mechanical ventilation and vasoactive support. TBI and polytrauma patients did not have increased risk of neither of these outcomes.

Conclusions: Unlike other ICU cohorts, fluid overload does not appear to be associated with worse clinical outcomes in severe trauma patients.

Keywords: pediatric intensive care; trauma; fluid balance

Introduction

Trauma has been reported as the leading cause of pediatric mortality, potential years of life lost, and medical costs in the developed world (1-3).

Children are particularly prone to water and electrolyte imbalances (4). This predisposition is explained by several reasons, including (i) a very high total body water content (75-80%, vs 60-70% of the body weight of an adult) (5), (ii) a higher metabolic rate (6), (iii) relatively higher insensible losses due to both a higher surface area to body mass ratio and a relatively higher production of CO2 and therefore a higher minute ventilation (7), and (iv) the possible presence of immature regulatory mechanisms (8, 9). Fluid therapy is therefore a

cornerstone of pediatric critical care medicine and should be considered as a pharmacological treatment with clear indications, contraindications, and possible side effects (5).

Critically ill children frequently receive a cumulative fluid delivery (as part of their management, i.e., nutrition, medications, and maintenance fluid) that exceeds fluid balance, leading to a net positive fluid balance. While timely administration of fluids is lifesaving, positive fluid balance after hemodynamic stabilization may impact organ function and negatively influence important outcomes in critically ill patients (10, 11). However, prior studies found no such association in pediatric severe traumatic brain injury (12). On the other hand, negative fluid balance may also be associated with reduced long-term survival in critically ill (13).

We hypothesized that there may be a correlation between fluid balance status and outcomes in pediatric severe trauma patients. Our main objective was to determine the frequency of early fluid overload in this population. Our secondary aim was to investigate the association between fluid balance status and clinically important outcome measures, such as mortality, acute kidney injury (AKI), length-of-stay (LOS) in the pediatric ICU (PICU), duration of mechanical ventilation, duration of vasoactive support.

Methods

Study design, Settings and Patients

We conducted a unicentric, observational study with retrospective enrollment. Through a sequential systematic sampling, all the trauma patients admitted to a tertiary European PICU over a 3-year consecutive period (between 1 January 2017 and 31 December 2019) were selected. Inclusion criteria were trauma admission, age between 1 month and 17 years and 364 days, LOS equal to or longer than 24 hours, and fluid balance information in the first 24 hours after admission. Exclusion criteria were LOS less than 24 hours and missing data for fluid balance in the first 24 hours after admission. This study was approved by the Ethics Committee

of Centro Hospitalar e Universitário São João.

Data collection

Data collection included patient demographics, admission diagnosis and clinical outcomes including overall mortality, PICU LOS, severity of illness, duration of mechanical ventilation, duration of vasoactive support, AKI and the total daily fluid input and output (in L) in the first 24 hours after admission.

Assessment of Fluid Balance

Fluid input included all enterally and parenterally administered fluids, including blood products and intravenous medications. Fluid output included urine, stool, nasogastric output, blood loss, insensible losses, or any other output from surgical drains.

The fluid balance in the first 24 hours of PICU admission for each patient was recorded based on the previously reported formula: fluid balance % = (total amount of fluid intake [L] – total amount of fluid output [L])/ admission weight (kg) x 100% (11). Early fluid overload (FO) was defined as cumulative fluid accumulation ≥5% of admission body weight, occurring in the first 24 hours of PICU admission. Fluid restriction was defined as negative fluid balance (<0%) in the first 24 hours of PICU admission. Even fluid balance was defined as a fluid balance between 0 and 5%.

Severity of Illness Assessment

Severity of Illness was assessed using Pediatric Risk of Mortality (PRISM III) scoring system. PRISM III is used in PICUs to control for severity of illness or injury when comparing within and between PICUs. It is the only validated predictor of critical care outcome in pediatrics and incorporates information regarding cardiovascular and neurologic parameters, as well as acid-base, electrolyte and hematologic values (14). The neurologic assessment includes calculation

of Glasgow Coma Scores (GCS). For the sedated patients, the Glasgow Coma Scores calculated before administration of sedation was used.

AKI Assessment

AKI in the first 24 h after admission was defined according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria, as any of the following: (i) increase in serum creatinine (sCr) by ≥ 0.3 mg/dl (≥ 26.5 μmol/l) within 48 hours, or (ii) an increase in sCr to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days, or (iii) urine volume < 0.5 ml/kg/h for 6 hours (15). The baseline serum creatinine (sCr) was retrieved from the electronic medical record as the lowest registered in the previous 3 months. If the baseline sCr was unobtainable, it was calculated using the patient's height and an estimated glomerular filtration rate of 120 mL/min per 1.73 m^2 as previously described in the literature (16).

Statistical analysis

The primary outcome studied was frequency of early fluid overload. The secondary outcome was the effect of fluid balance status on clinical outcomes.

First, normality of continuous variables was examined based on skewness and kurtosis values, results of the Kolmogorov-Smirnov and Shapiro-Wilk tests and plots. Descriptive statistics were calculated for all variables of interest and included means ± SDs or median (interquartile range), for normally distributed and not normally distributed continuous variables, respectively, or counts and percentages, for categorical variables. While initially we aimed to compare three groups (fluid restriction, even fluid balance, fluid overload), considering our sample size and the fact that some groups were more residual, we opted to dichotomize the variable Fluid Balance in two groups (fluid overloaded and not fluid overloaded), in order to simplify data analysis. Clinical characteristics, demographics, and outcomes were compared among patients with or without early fluid overload. We used the

Chi-square test or Fisher's exact test, in case the percentage of cells with expected count lower than 5 was over 20%, for categorical variables and t-test for independent samples or Mann-Whitney test for continuous variables, when the assumption of normality was and was not met, respectively.

For the categorical outcomes of death and AKI, as there were very few cases where these outcomes were present in this sample, and only in one of the groups being compared, it was not possible to carry out regression analyses, and thus only descriptive analyses are presented. As to the continuous outcomes, as these did not present a normal distribution, we opted to dichotomize them based on their median value and carried out the adjusted analysis using logistic regression; the effect of fluid overload on these outcomes is presented as odds ratios with 95% CIs. The assumptions of logistic regression were verified, and were met, namely the absence of outliers influencing the model and the absence of multicollinearity.

Statistical analyses were performed using IBM® Statistical Package for the Social Sciences (SPSS Statistics®) Version 27. A p value < 0.05 was considered significant.

Results

Patients Characteristics

A total of 931 patients were admitted during the study period, of whom 67 (7.2%) were trauma patients. 66 met inclusion criteria, 1 was excluded due to PICU LOS less than 24 hours.

Males comprised 56% of the sample (Table 1), and median age was 12.2 years (IQR 4.5-15.9 yr). Median PRISM III score was 7.50 (IQR 4.5-11.0), with a median probability of death of 0.03 (IQR 0.01-0.08), and a median PICU LOS adjusted for severity of 3.73 days (IQR 2.82-4.40). The median weight of these patients was 41 kg. Forty-one (62.1%) of the 66 patients suffered polytrauma, 32 of these with TBI, and 25 (37.8%) had isolated TBI (without polytrauma). The mean (± SD) GCS of the TBI patients at presentation was 8 (± 0.71). Patients were ventilated for a median of 4 days (IQR 1-12 d). 28 (42.4%) of the 66 patients required

vasoactive support, for a median of 7.5 days (IQR 4-12 d). Median PICU LOS was 6 days (IQR 2-15 d). PICU overall mortality was 4.5% (3 of 66). AKI was present in 3.2% of patients (2 of 66). Data about intracranial pressure (ICP), creatine kinase (CK) and myoglobin were available only for 31, 35 and 20 of the 66 patients, respectively.

Patients were gathered into two groups (Table 2) according to the fluid balance status (with vs. without early fluid overload) in the first 24 hours of the PICU stay. In total, 26% had early fluid overload. Significant differences were found between the two groups regarding only weight at admission (p=0.042). Patients with more weight at admission presented less fluid overload.

Fluid Balance

Overall, 17/66 of patients had early fluid overload in this study (25,7%), with a median percentage of fluid balance (IQR) of 6.88 (5.87-18.35); 21/66 (31.8%) of patients had fluid restriction, with a median percentage of fluid balance (IQR) of 0.49 (-1.27-1.91) and 28/66 (42.2%) of them had even fluid balance.

Outcomes

In what concerns mortality, there were only three cases, all in the not fluid overloaded group. As to AKI, only 2 cases were observed, in the not fluid overloaded group. Given that very few cases were observed, and only in one group, no further analyses were carried out regarding these outcomes. There were no significant differences in the clinical outcomes of mortality and AKI for the fluid overloaded group when compared with the not fluid overloaded group.

Regarding PICU LOS, mechanical ventilation and vasoactive support, no significant associations were found to early fluid overload. After adjusting for differences in clinical and demographic variables, results remained the same, apart from the duration of vasoactive

support. Early fluid overload revealed to be associated with longer duration of vasoactive support, after accounting for gender, age, and severity of illness (p=0.029).

Isolated Traumatic Brain Injury (TBI) was not associated with PICU LOS, mechanical ventilation or vasoactive support (p>0.05). Polytrauma was not associated with neither of these outcomes. All the death and AKI cases in TBI or polytraumatized patients occurred in the not fluid overloaded group, and no significant association to those outcomes was found. Isolated TBI, without polytrauma, is not significantly associated with any of the outcomes under analysis.

The fluid restriction group registered 3 deaths (14.3%), while all the patients in the group without fluid restriction survived. This group of patients is more likely to survive (p=0.029). In what concerns AKI, PICU LOS, mechanical ventilation and vasoactive support, no significant associations were found to the fluid restriction (p>0.05).

Discussion

To our knowledge, this study is the first to explore the impact of fluid balance in clinical outcomes in pediatric severe trauma patients. Most previous studies have focused in general PICU populations (10, 11, 17, 18), or specifically in the pediatric severe traumatic brain injury population (12).

The proportion of children with positive fluid balance in this study was 26% (approximately 1 in 4 patients). The rate of fluid overload in critically ill pediatric population varied in previously reported data (12, 19-22); a meta-analysis reported a median rate of 33% (range 10%-83%) (11). The proportion of fluid restriction was 31.8%, within the range of reported negative fluid balance in critically ill patients (in up to 30-50%) (23, 24).

Positive fluid balance in PICU patients has been associated to worse clinical outcomes (10, 11, 17-19, 21, 22, 25). However, Stulce et al. found no such association in severe traumatic

brain injury patients (12). Sinitsky et al. (25) reported an association between fluid overload at 48 hours and respiratory morbidity but not mortality in a general PICU. In our study, the early fluid overload did not appear to have a negative impact in the clinical outcomes studied, even when we stratified the analysis to trauma subpopulations, such as TBI patients, polytrauma patients, and isolated TBI patients (i.e., without polytrauma). The controversy is not yet clearly explained, but it should be taken under consideration that this is a population with severe trauma. This group of patients often suffers blood loss and intravascular depletion from hemorrhage on presentation. Consequently, the initial weight used to determine fluid overload may be erroneously low.

As reported above, the adjusted analysis revealed early fluid overload to be independently associated with longer duration of vasoactive support, controlled for gender, age, and severity of illness (p=0.029). We do interpret our findings with caution since the unadjusted analysis did not report a significant association between early fluid overload and duration of vasoactive support.

The association between fluid restriction and increased mortality should be carefully interpreted, due to the small number of deaths registered (n=3). Bellomo et al. reported an association between fluid restriction and lower risk-adjusted short-term mortality (24), whereas other studies found no association (26). Balakumar et al. reported a variable association with mortality: early after ICU admission, fluid restriction was associated with decreased risk of death; later on, it was associated with higher mortality risk that persisted up to one year (13). Furthermore, exposure to fluid restriction may induce harm, such as neurocognitive dysfunction (27).

Our study has important limitations. First, being an observational study, it is not possible to state causal inferences between fluid balance status and outcomes observed. Second, this study covers 3 years of patient data, during which aspects of patient management may have

changed. Third, because it is a unicentric study, our conclusions may not be generalizable to other PICU populations. Fourth, the number of research subjects was small. Fifth, the trauma spectrum (traumatic brain injury, polytrauma, penetrating injury) was complex (28), and, due to the retrospective design, it was not possible to collect data to apply specific trauma scores, such as the Pediatric Trauma Score (29). Nevertheless, considering we are studying critically ill children, it seems appropriate to use a severity of illness score (e.g., PRISM III).

Conclusions

Unlike other ICU cohorts, fluid overload does not appear to be associated with worse clinical outcomes in severe trauma patients. More large prospective pediatric studies are still needed to further explore the association between fluid balance status and outcomes in trauma patients.

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Tables

Table 1. Patients Characteristics

Characteristic	
Sex (male), *n* (%)	37 (56)
Age (year), median (IQR)	12.2 (4.5-15.9)
Weight at admission (kg), median (IQR)	41 (17-60)
PRISM III score, median (IQR)	7.50 (4.5-11.0)
PRISM III probability of death, median (IQR)	0.03 (0.01-0.08)
PRISM III PICU LOS adjusted for severity, median (IQR)	3.73 (2.82-4.40)
Polytrauma, *n* (%)	41 (62.1)
TBI, *n* (%)	57 (86.4)
Isolated TBI, *n* (%)	25 (37.8)
TBI with associated polytrauma, *n* (%)	32 (47.3)
GCS at presentation, mean ± SD	8 (± 0.71)
Mechanical ventilation (days), median (IQR)	4 (1-12)
Vasoactive support, *n* (%)	30 (45)
Vasoactive support, median (IQR)	8 (4-12)
PICU LOS, median (IQR)	6 (2-15)
Mortality, *n* (%)	3 (4.5)
AKI, *n* (%)	2 (3.2)

PRISM III Pediatric Risk of Mortality, *PICU* Pediatric Intensive Care Unit, *LOS* length-of-stay, *TBI* traumatic brain injury, *GCS* Glasgow Coma Scale, *AKI* acute kidney injury

Table 2. Comparison of Patient Characteristics Stratified by Fluid Balance Status

Characteristic	Not Overloaded	Fluid Overloaded	*p* value
Sex, *n* (%)			0.572
Male	26 (53.1)	11 (64.7)	
Female	23 (46.9)	6 (35.3)	
Age (years), median (IQR)	13.9 (5.9-16.2)	7.1 (1.3-14.3)	0.066
Age (years), *n* (%)			0.362
Infant (<1 year old)	4 (8.2)	3 (17.6)	
≥ 1 year old	45 (91.8)	14 (82.4)	
Weight at admission (kg), median (IQR)	48.0 (18.8-64.0)	18.0 (11.0-55.0)	**0.042**
Baseline sCr (mg/dL), mean ± SD	0.49 ± 0.22	0.44 ± 0.25	0.433
PRISM III score, median (IQR)	7.0 (4.0-11.0)	8.0 (3.5-11.0)	0.900
Polytrauma, n (%)	26 (57.8)	15 (71.4)	0.415
TBI, *n* (%)	40 (88.9)	17 (81.0)	0.450
Isolated TBI, *n* (%)	19 (42.2)	6 (28.6)	0.415
TBI with associated polytrauma, *n* (%)	21 (46.7)	11 (52.4)	0.793
GCS at presentation, mean ± SD	8.59 ± 4.15	7.53 ± 4.24	0.369
ICP, median (IQR)	14.0 (9.0-19.3)	18.0 (10.5-19.0)	0.556
Pupils abnormality, *n* (%)	15 (30.6)	7 (41.2)	0.552
CK (U/L), median (IQR)	797 (311-2358)	565 (131-5991)	0.913
Myoglobin (µg/L), median (IQR)	661.7 (224.5-1428.1)	693.7 (70.4-2249.3)	0.777
Fluid balance at 24h (%), median (IQR)	0.49 (-1.27-1.91)	6.88 (5.87-18.35)	

IQR interquartile range, *sCR* serum creatinine, *TBI* traumatic brain injury, GSC Glasgow Coma Scale, ICP intracranial pressure, *CK* creatine kinase, $p < 0.05$ was considered significant (bold)

Table 3. Comparison of outcomes stratified by fluid balance status

Outcome	Not Overloaded	Fluid Overloaded	*p*
Mortality, *n* (%)	3 (6.1)	0 (0.0)	0.563
AKI, *n* (%)	2 (4.3)	0 (0)	1.000
PICU LOS (days), median (IQR)	6.0 (2.5-13.5)	6.0 (2.0-17.0)	0.976
Mechanical ventilation (days), median (IQR)	4.0 (1.0-11.5)	6.0 (0.5-13.5)	0.906
Vasoactive support (days), median (IQR)	0.0 (0.0-6.5)	3.0 (0.0-8.0)	0.176

AKI acute kidney injury, *LOS* length of stay, *IQR* interquartile range, $p < 0.05$ was considered significant

Table 4. Adjusted outcomes analysis

Outcome	Unadjusted	*p*	Adjusted	*p*
PICU LOS, OR (95% CI)	1.01 (0.33-3.04)	0.993	1.30 (0.37-4.61)	0.682
Not Overloaded				
Fluid Overloaded				
Mechanical ventilation (days), OR (95% CI)	1.38 (0.46-4.17)	0.568	1.90 (0.54-6.69)	0.315
Not Overloaded				
Fluid Overloaded				
Vasoactive support (days), OR (95% CI)	2.90 (0.92-9.13)	0.070	4.48 (1.16-17.29)	**0.029**
Not Overloaded				
Fluid Overloaded				

PICU Pediatric Intensive Care Unit, *LOS* length-of-stay, *OR* odds ratio, $p < 0.05$ was considered significant (bold)

Apêndice I - *Reporting guidelines*

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	**(*a*) Indicate the study's design with a commonly used term in the title or the abstract** (Parágrafo 3) "We conducted a unicentric, observational study with retrospective enrollment."	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found (Parágrafo 1) "This study investigated the association between fluid balance status and clinical outcomes in pediatric severe trauma patients." (Parágrafo 3) "Early FO was not significantly associated with mortality, acute kidney injury, PICU length-of-stay, duration of mechanical ventilation and vasoactive support. TBI and polytrauma patients did not have increased risk of neither of these outcomes."	1
Introduction			
Background/rationale	2	**Explain the scientific background and rationale for the investigation being reported** (Parágrafo 6-8) "Trauma has been reported as the leading cause of pediatric mortality, potential years of life lost, and medical costs in the developed world. (…) Critically ill children frequently receive a cumulative fluid delivery, (…) leading to a net positive fluid balance. (…) may impact organ function and negatively influence important outcomes in critically ill patients"	1, 2
Objectives	3	**State specific objectives, including any prespecified hypotheses** (Parágrafo 2) "We hypothesized that there may be a correlation between fluid balance status and outcomes in pediatric severe trauma patients. Our main objective was to determine the frequency of early fluid overload in this population. Our secondary aim was to investigate the association between fluid balance status and clinically important outcome measures (…)"	2
Methods			
Study design	4	**Present key elements of study design early in the paper** (Parágrafo 3) "We conducted a unicentric, observational study with retrospective enrollment."	2
Setting	5	**Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection** (Parágrafo 3) "Through a sequential systematic sampling, all the trauma patients admitted to a tertiary European PICU over a 3-year consecutive period (between 1 January 2017 and 31 December 2019) were selected." (Parágrafo 4) "Data collection included patient demographics, admission diagnosis and clinical outcomes (…)"	2
Participants	6	(***a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up** (Parágrafo 3) "Inclusion criteria were trauma admission, age between 1 month and 17 years and 364 days, LOS equal to or longer than 24 hours, and fluid balance information in the first 24 hours after admission.	2

		Exclusion criteria were LOS less than 24 hours and missing data for fluid balance in the first 24 hours after admission." (***b***) **For matched studies, give matching criteria and number of exposed and unexposed** (Não aplicável)	
Variables	7	**Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable** (Parágrafo 4) "(…) clinical outcomes including overall mortality, PICU LOS, severity of illness, duration of mechanical ventilation, duration of vasoactive support, AKI and the total daily fluid intake and output (in L) in the first 24 hours after admission."	2
Data sources/ measurement	8*	**For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group** (Parágrafo 2) "The fluid balance in the first 24 hours of PICU admission for each patient was recorded based on the previously reported formula (…)" (Parágrafo 3) "Severity of Illness was assessed using Pediatric Risk of Mortality (PRISM III) scoring system." (Parágrafo 4) "AKI in the first 24 h after admission was defined according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria."	3
Bias	9	**Describe any efforts to address potential sources of bias** (Parágrafo 3) "As to the continuous outcomes, as these did not present a normal distribution, we opted to dichotomize them based on their median value and carried out the adjusted analysis using logistic regression"	4
Study size	10	**Explain how the study size was arrived at** (Parágrafo 2) "A total of 929 patients were admitted during the study period, of whom 67 (7.2%) were trauma patients. 66 met inclusion criteria, 1 was excluded due to PICU LOS less than 24 hours."	5
Quantitative variables	11	**Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why** (Parágrafo 2) "First, normality of continuous variables was examined based on skewness and kurtosis values, results of the Kolmogorov-Smirnov and Shapiro-Wilk tests and plots."	4
Statistical methods	12	(***a***) **Describe all statistical methods, including those used to control for confounding** **(**Pág. 9, Parágrafo 3) "(…) As to the continuous outcomes, as these did not present a normal distribution, we opted to dichotomize them based on their median value and carried out the adjusted analysis using logistic regression; the effect of fluid overload on these outcomes is presented as odds ratios with 95% CIs." (***b***) **Describe any methods used to examine subgroups and interactions** (Pág. 9, Parágrafo 2) "Clinical characteristics, demographics, and outcomes were compared among patients with or without early fluid overload." (***c***) **Explain how missing data were addressed** (Não aplicável) (***d***) **If applicable, explain how loss to follow-up was addressed**	4, 5

		(Não aplicável) **(e) Describe any sensitivity analyses** (Não aplicável)	
Results			
Participants	13*	**(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed** (Parágrafo 2) "A total of 929 patients were admitted during the study period, of whom 67 (7.2%) were trauma patients. 66 met inclusion criteria (…)" **(b) Give reasons for non-participation at each stage** (Parágrafo 2) "(…) 1 was excluded due to PICU LOS less than 24 hours." **(c) Consider use of a flow diagram** (Não aplicável)	5
Descriptive data	14*	(**a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders** (Parágrafo 3) "Males comprised 56% of the sample, and median age was 12.2 years (IQR 4.5-15.9 yr). (…)" **(b) Indicate number of participants with missing data for each variable of interest** (Parágrafo 3) "Data about intracranial pressure (ICP), creatine kinase (CK) and myoglobin was available only for 31, 35 and 20 of the 66 patients, respectively." **(c) Summarise follow-up time (eg, average and total amount)** (Parágrafo 3) "Median PICU LOS was 6 days (IQR 2-15 d)."	5
Outcome data	15*	**Report numbers of outcome events or summary measures over time** (Parágrafo 3) "Regarding PICU LOS, mechanical ventilation and vasoactive support, no significant associations were found to early fluid overload."	6

Main results	16	**(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included** (Pág. 6, Parágrafo 3) "Regarding PICU LOS, mechanical ventilation and vasoactive support, no significant associations were found to early fluid overload." (*b*) **Report category boundaries when continuous variables were categorized** (Página 4, Parágrafo 3) "As to the continuous outcomes, as these did not present a normal distribution, we opted to dichotomize them based on their median value and carried out the adjusted analysis using logistic regression." (*c*) **If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period** (Não aplicável)	4, 6
Other analyses	17	**Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses** (Parágrafo 2) "even when we stratified the analysis to trauma subpopulations, such as TBI patients, polytrauma patients, and isolated TBI patients (i.e., without polytrauma)."	7
Discussion			
Key results	18	**Summarise key results with reference to study objectives** (Parágrafo 1) "The proportion of children with positive fluid balance in this study was 26% (approximately 1 in 4 patients)." (Parágrafo 2) "In our study, the early fluid overload did not appear to have a negative impact in the clinical outcomes studied (…)"	7
Limitations	19	**Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias** (Parágrafo 1) "Our study has important limitations."	8
Interpretation	20	**Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence** (Parágrafo 4) "The association between fluid restriction and increased mortality should be carefully interpreted, due to the small number of deaths registered (n=3)."	7
Generalisability	21	**Discuss the generalisability (external validity) of the study results** (Parágrafo 1) "Third, because it is a unicentric study, our conclusions may not be generalizable to other PICU populations."	8
Other information			
Funding	22	**Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based** (Não aplicável)	

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Apêndice II - Regras de formatação

Font: Use Times New Roman font in size 12 with double-line spacing.

Margins: Margins should be at least 2.5cm (1 inch).

Title: Use bold for your article title, with an initial capital letter for any proper nouns.

Abstract: Indicate the abstract paragraph with a heading or by reducing the font size. The instructions for authors for each journal will give specific guidelines on what's required here, including whether it should be a structured abstract or graphical abstract, and any word limits.

Keywords: Keywords help readers find your article, so are vital for discoverability. If the journal instructions for authors don't give a set number of keywords to provide, aim for five or six.

Headings: This will show you the different levels of the heading section in your article:

1. First-level headings (e.g. Introduction, Conclusion) should be in bold, with an initial capital letter for any proper nouns.
2. Second-level headings should be in bold italics, with an initial capital letter for any proper nouns.
3. Third-level headings should be in italics, with an initial capital letter for any proper nouns.
4. Fourth-level headings should be in bold italics, at the beginning of a paragraph. The text follows immediately after a full stop (full point) or other punctuation mark.
5. Fifth-level headings should be in italics, at the beginning of a paragraph. The text follows immediately after a full stop (full point) or other punctuation mark.

Tables and figures: Show clearly in your article text where the tables and figures should appear, for example, by writing [Table 1 near here].

Check the instructions for authors to see how you should supply tables and figures, whether at the end of the text or in separate files, and follow any guidance given on the submission system.

Data availability statement: If you're submitting a data availability statement for your article, include it within the text of your manuscript, before your 'References' section. Remember to give it the heading 'Data availability statement' so that readers can easily find it.

Spelling and punctuation: Each journal will have a preferred method for spelling and punctuation. You'll find this in the instructions for authors, available on the journal's homepage on Taylor and Francis Online. Make sure you apply the spelling and punctuation style consistently throughout your article.

Special characters: If you are preparing your manuscript in Microsoft Word and your article contains special characters, accents, or diacritics, we recommend you follow these steps:

- European accents (Greek, Hebrew, or Cyrillic letters, or phonetic symbols): choose Times New Roman font from the dropdown menu in the "Insert symbol" window and insert the character you require.
- Asian languages (such as Sanskrit, Korean, Chinese, or Japanese): choose Arial Unicode font from the dropdown menu in the "Insert symbol" window and insert the character you require.
- Transliterated Arabic: choose either Times New Roman or Arial Unicode (unless the instructions for authors specify a particular font). For ayns and hamzas, choose Arial Unicode font from the dropdown menu in the "Insert symbol" window. Type the Unicode hexes directly into the "Character code" box, using 02BF for ayn, and 02BE for hamza.

Running heads and received dates: These aren't required when submitting a manuscript for review. They will be added during the production process if your article is accepted for publication.

Preparing Your Paper: All authors submitting to medicine, biomedicine, health sciences, allied and public health journals should conform to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, prepared by the International Committee of Medical Journal Editors (ICMJE).

Structure: Your paper should be compiled in the following order: title page; abstract; keywords; main text introduction, materials and methods, results, discussion; acknowledgments; declaration of interest statement; references; appendices (as appropriate); table(s) with caption(s) (on individual pages); figures; figure captions (as a list).

Word Limits: Please include a word count for your paper. A typical paper for this journal should be no more than 5000 words.

Style Guidelines: Please refer to these quick style guidelines when preparing your paper, rather than any published articles or a sample copy. Please use American spelling style consistently throughout your manuscript. Please use single quotation marks, except where 'a quotation is "within" a quotation'. Please note that long quotations should be indented without quotation marks.

Brain Injury accepts the following types of submissions: Original Research and Letters to the Editor. Letters to the Editor will be considered for publication subject to editor approval and provided that they either relate to content previously published in the Journal or address any item that is felt to be of interest to the readership. Letters relating to articles previously published in the Journal should be received no more than three months after publication of the original

work. Pending editor approval, letters may be submitted to the author of the original paper in order that a reply be published simultaneously.

Letters to the Editor can be signed by a maximum of three authors, should be between 750 and 1,250 words, may contain one table/figure and may cite a maximum of five references. All Letters should be submitted via ScholarOne Manuscripts and should contain a Declaration of Interest statement. Some journals set a maximum length for submissions. Though *Brain Injury* does not have a specific limit, we prefer that manuscripts not exceed 5,000 words excluding abstract, references, tables, and figure legends. If articles are greater than 5,000 words, authors may be asked to shorten their manuscript.

Your paper should be compiled in the following order: title page; abstract; keywords; main text; acknowledgments; declaration of interest statement; references; appendices (as appropriate); table(s) with caption(s) (on individual pages); figures; figure captions (as a list).

Formatting and Templates: Papers may be submitted in Word or LaTeX formats. Figures should be saved separately from the text. To assist you in preparing your paper, we provide formatting template(s). Word templates are available for this journal. Please save the template to your hard drive, ready for use. If you are not able to use the template via the links (or if you have any other template queries) please contact us here.

References: Please use this reference guide when preparing your paper. Taylor & Francis Editing Services. To help you improve your manuscript and prepare it for submission, Taylor & Francis provides a range of editing services. Choose from options such as English Language Editing, which will ensure that your article is free of spelling and grammar errors, Translation, and Artwork Preparation. For more information, including pricing, visit this website.

Checklist: What to Include

1. **Author details.** Please ensure everyone meeting the International Committee of Medical Journal Editors (ICMJE) requirements for authorship is included as an author of your paper. Please ensure all listed authors meet the Taylor & Francis authorship criteria. All authors of a manuscript should include their full name and affiliation on the cover page of the manuscript. Where available, please also include ORCiDs and social media handles (Facebook, Twitter or LinkedIn). One author will need to be identified as the corresponding author, with their email address normally displayed in the article PDF (depending on the journal) and the online article. Authors' affiliations are the affiliations where the research was conducted. If any of the named co-authors moves affiliation during the peer-review process, the new affiliation can be given as a footnote. Please note that no changes to affiliation can be made after your paper is accepted. Read more on authorship.
2. Should contain a structured abstract of 200 words.

   For papers reporting original research, state the primary objective and any hypothesis tested; describe the research design and your reasons for adopting that methodology; state the methods and procedures employed, including where appropriate tools, hardware, software, the selection and number of study areas/subjects, and the central experimental interventions; state the main outcomes and results, including relevant data; and state the conclusions that might be drawn from these data and results, including their implications for further research or application/practice.

   For review essays, state the primary objective of the review; the reasoning behind your literature selection; and the way you critically analyse the literature; state the main

outcomes and results of your review; and state the conclusions that might be drawn, including their implications for further research or application/practice.

Read tips on writing your abstract.

3. You can opt to include a **video abstract** with your article. Find out how these can help your work reach a wider audience, and what to think about when filming.
4. Between 3 and 5 **keywords**. Read making your article more discoverable, including information on choosing a title and search engine optimization.
5. **Funding details.** Please supply all details required by your funding and grant-awarding bodies as follows: *For single agency grant.* This work was supported by the [Funding Agency] under Grant [number xxxx]. *For multiple agency grants*. This work was supported by the [Funding Agency #1] under Grant [number xxxx]; [Funding Agency #2] under Grant [number xxxx]; and [Funding Agency #3] under Grant [number xxxx].
6. **Disclosure statement.** This is to acknowledge any financial or non-financial interest that has arisen from the direct applications of your research. If there are no relevant competing interests to declare please state this within the article, for example: *The authors report there are no competing interests to declare*. Further guidance on what is a conflict of interest and how to disclose it.
7. **Biographical note.** Please supply a short biographical note for each author. This could be adapted from your departmental website or academic networking profile and should be relatively brief (e.g. no more than 200 words).
8. **Data availability statement.** If there is a data set associated with the paper, please provide information about where the data supporting the results or analyses presented in the paper can be found. Where applicable, this should include the hyperlink, DOI or

other persistent identifier associated with the data set(s). Templates are also available to support authors.

9. **Data deposition.** If you choose to share or make the data underlying the study open, please deposit your data in a recognized data repository prior to or at the time of submission. You will be asked to provide the DOI, pre-reserved DOI, or other persistent identifier for the data set.
10. **Supplemental online material.** Supplemental material can be a video, dataset, fileset, sound file or anything which supports (and is pertinent to) your paper. We publish supplemental material online via Figshare. Find out more about supplemental material and how to submit it with your article.
11. **Figures.** Figures should be high quality (1200 dpi for line art, 600 dpi for grayscale and 300 dpi for color, at the correct size). Figures should be supplied in one of our preferred file formats: EPS, PS, JPEG, TIFF, or Microsoft Word (DOC or DOCX) files are acceptable for figures that have been drawn in Word. For information relating to other file types, please consult our Submission of electronic artwork document.
12. **Tables.** Tables should present new information rather than duplicating what is in the text. Readers should be able to interpret the table without reference to the text. Please supply editable files.
13. **Equations.** If you are submitting your manuscript as a Word document, please ensure that equations are editable. More information about mathematical symbols and equations.
14. **Units.** Please use SI units (non-italicized).