PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Pediatric dengue shock syndrome and acute respiratory failure: a single centre retrospective study
AUTHORS	Preeprem, Nutnicha Phumeetham, Suwannee

VERSION 1 – REVIEW

REVIEWER	Reviewer name: Natalie Napolitano Institution and Country: United Kingdom of Great Britain and Northern Ireland Competing interests: Research/consulting relationships with Drager, Timpel, Philips/.Respironics, Actuated Medical, VERO-Biotech
REVIEW RETURNED	28-Jun-2022

GENERAL COMMENTS	This is a well written and important article. The authors mention in the discussion that comparison with other reports/studies of pediatric patients with DSS is not easily comparable and case counts differ as there are differing definitions of ARF/pARDS. I would suggest the transition of the definition to the PALICC guidelines definition and utilize OI/OSI for the definition. if all trend to using this as the gold standard they will be more easily compared. do you have SpO2 for all subjects? if so please include and use as the definition for pARDS/ARF. As interesting as the conclusion of controlling fluid accumulation is - I believe that the variation in management of mechanical ventilation may also be a related. The use of adequate PEEP/CPAP or mean airway pressure can assist with pushing our or limiting the invasion of fluid into the lungs. Can you report the median PEEP/CPAP and mean airway pressure from those on invasive and non-invasive ventilation?

REVIEWER	Reviewer name: Daniel H. Paris Institution and Country: United Kingdom of Great Britain and Northern Ireland Competing interests: None
REVIEW RETURNED	02-Jul-2022

GENERAL COMMENTS	General This well-written, concise report on a study in pediatric DSS with primary outcome being ARF – a sign of excessive fluid administration during management contributing to mortality in DSS – showed that assessing fluid balance at 72h correlated well with development of ARF and as such an accumulation of >15% serves as a predictor/RF for this severe condition. The data serves towards more careful fluid management and assessment to prevent ARF in children with DSS. A strength of the study is that disease severity was assessed for all participants using a validated scoring system, unlike similar previous reports. Patients with ARF had higher disease severity at 24h post

	admission. Ethics are addressed; the IRB from Siriraj Hospital approved the study, with exemption of written informed consent due to retrospective nature of study. Limitations are well described: retrospective study design, fluid accumulation was calculated as the net balance between fluid intake and output from notes (substantial bias introduction possible), primary outcome is ARF due to sample size not mortality (the latter would be much stronger). Major The VIS calculation applied requires a citation, normally vasopressin is included in this score, but not in the formula applied for this study? Is the validity of the score granted in this case? Was the same scoring system applied to all patients? Additional info / citation needs to be provided. Minor L7 – typo: rate(s)

REVIEWER	Reviewer name: Dr. Peter Flom Institution and Country: Peter Flom Consulting, United States Competing interests: None
REVIEW RETURNED	22-Jun-2022

GENERAL COMMENTS	I confine my remarks to statistical aspects of this paper. Abstract The large CI for the AOR for fluid accumulation is worrisome. One issue is that FA was dichotomized. (see below)./ p. 3 line 27-44 Please put a reference to table 1 here, so people can get details of the variables. p. 4 line 8. First, in the abstract, it says 15%, here it says 10%. More seriously, do not dichotomize continuous variables. This increases type I and type II error (and, therefore, increases the CI) and invokes a kind of "magical thinking" -- that something special happens at the cutpoint. Instead, leave fluid accumulation as a number and use splines to investigate nonlinearity For more, see my blog post https://medium.com/@peterflom/what-happens-when-we-categorize-an-independent-variable-in-regression-77d4c5862b6c Line 22-23 The data do not need to be normal and the KS test is not really useful. Line 29-30 Why was no imputation done? Line 32 This is known as bivariate screening and is not recommended. All the output of the multivariable regression will be wrong. Standard errors will be too small, p values too low, and parameter estimates biased away from 0. It is best to use subtantive knowledge to build a model, but if the authors insist on an automated method, LOESS isn't bad. For details, examples, and proofs, see *Regression Modeling Strategies* by Frank Harrell.

	Also, colinearity should be investigated and it might be good to do a factor analysis of the variables and use the factor scores as variables. Table 1, 2, 3: The p value column should have a footnote that says what test was used. (E.g. t test). Figure 1 - I don't think the numbers for the values are needed, and they make the figure kind of cluttered. A figure is not a substitute for a table. Peter Flom

REVIEWER	Reviewer name: Prof. Aye Han Institution and Country: Royal College of Paediatrics and Child Health Global Health, United Kingdom of Great Britain and Northern Ireland Competing interests: Nil
REVIEW RETURNED	01-Jul-2022
GENERAL COMMENTS	This study is very beneficial for clinicians to be extra-careful with fluid resuscitation in DSS. It would be excellent if the authors could include in the discussion, how patients with ARF related to features of severe dengue and complications during PICU admission.

VERSION 1 – AUTHOR RESPONSE

August 1, 2022

Dear Editors-in-Chief:

Thank you for your consideration on our manuscript titled "Pediatric Dengue Shock Syndrome and Factors

Associated with Acute Respiratory Failure: An 11-Year Clinical Experience". We appreciated the reviewers' comments

and have addressed each comment as attached files. The revised manuscript also reflects our response to reviewers.

Thank you for your re-consideration.

Yours sincerely,

Suwannee Phumeetham, MD

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Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

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Reviewer 1 Comments

1. The large CI for the AOR for fluid accumulation is worrisome. One issue is that FA was dichotomized. (see

below)

Reply: To analyze fluid accumulation based on dichotomization provides the sensible results because the

documentation of degree of fluid accumulation will be applicable in a clinical practice. We realize that the small

sample size will contribute to wide range of CI.

2. Please put a reference to table 1 here, so people can get details of the variables.

Reply: A reference was added as suggested (Data collection, p. 3, line 36-38).

3. First, in the abstract, it says 15%, here it says 10%.

Reply: We would like to clarify the definitions related to fluid accumulation in this study, as shown below.

- Early fluid accumulation was defined as ≥10% in the first 24 hours after PICU admission. (This threshold

was recommended by Huang et al as a cutoff point for early fluid accumulation so the reference was added

in the Definition section in p 4, line 9.)

- Presence of ≥15% fluid accumulation at 72 hours after PICU admission was the other cutoff used.

In summary, both cutoffs were investigated in our study. As mentioned in the discussion, shock episodes in DSS

generally last 24-48 hours, and after this rescue phase, patients usually require some time for tissue perfusion

optimization. The probability of fluid accumulation is thought to be highest at approximately 72 hours.

4. More seriously, do not dichotomize continuous variables. This increases type I and type II error (and, therefore,

increases the CI) and invokes a kind of "magical thinking" -- that something special happens at the cutpoint.

Instead, leave fluid accumulation as a number and use splines to investigate nonlinearity

Reply: At present, clear consensus definitions for fluid accumulation do not exist. However, the cutoff point of

fluid accumulation ≥15% used in the present study was investigated by Arikan et al. The authors reported the

association between positive fluid balance ≥15% was independent associated with longer duration of

ventilation and PICU course in critically ill children.(1) However, fluid accumulation was analyzed as continuous

data and the results were consistent with those analyzed using dichotomization (Results, p. 5, line 7-8,).

5. The data do not need to be normal and the KS test is not really useful.

Reply: Histograms were used to assess normality and they showed non-normal distributions. We removed the

sentence “The normality of data was checked with the Kolmogrov-Smirnov test”. Texts were revised as

suggested (Statistical Analysis, p. 4, line 27-28).

6. Why was no imputation done?

Reply: The missing data in our study were lab data including lactate level and arterial pH value, as shown in

table 2. The proportions of the missing data of these 2 variables were large due to 10-year retrospective data

[35/60 missing for lactate (58%) and 21/60 (35%) missing for arterial pH]. According to recommendation by

Jakobsen et al., using observed data was suggested.(2)

7. This is known as bivariate screening and is not recommended. All the output of the multivariable regression will

be wrong. Standard errors will be too small, p values too low, and parameter estimates biased away from 0. It is

best to use subtantive knowledge to build a model, but if the authors insist on an automated method, LOESS

isn't bad. For details, examples, and proofs, see *Regression Modeling Strategies* by Frank Harrell.

Reply: There was a typo which was corrected (p 4, line 34). It should be noted that variables with univariable pvalue less than 0.1 were entered into multiple logistic regression analysis. Since there were only 26 out of 60

subjects with respiratory failure, the number of independent variables should be less than 3 according to rule of

thumb of 10 EPV (events per variable)(3, 4)

8. Also, collinearity should be investigated and it might be good to do a factor analysis of the variables and use the

factor scores as variables.

Reply: Three variables included in multiple logistic regression were not clinically correlated and this was

confirmed with variance inflation factor (VIF) of 1.06, 1.05 and 1.10.

9. The p value column should have a footnote that says what test was used. (E.g., t test).

Reply: Footnotes were added at the bottom of table 1, 2, 3, as suggested.

10. I don't think the numbers for the values are needed, and they make the figure kind of cluttered. A figure is not a

substitute for a table.

Reply: The figure was edited and the data was added into Table 3.

Reviewer 2 Comments

1. The authors mention in the discussion that comparison with other reports/studies of pediatric patients with DSS

is not easily comparable and case counts differ as there are differing definitions of ARF/pARDS. I would suggest

the transition of the definition to the PALICC guidelines definition and utilize OI/OSI for the definition. if all trend

to using this as the gold standard they will be more easily compared. do you have SpO2 for all subjects? if so

please include and use as the definition for pARDS/ARF.

Reply: The definition of ARF in this study was meant to be pragmatic, based on clinical diagnosis of requiring

respiratory support with non-invasive or invasive mechanical ventilation. In addition, our NIV equipment could

not measure FiO2

. The lack of FiO2

in patients with NIV precludes calculation of values required to make

diagnosis as per PALICC guidelines.

2. As interesting as the conclusion of controlling fluid accumulation is - I believe that the variation in management

of mechanical ventilation may also be a related. The use of adequate PEEP/CPAP or mean airway pressure can

assist with pushing our or limiting the invasion of fluid into the lungs. Can you report the median PEEP/CPAP and

mean airway pressure from those on invasive and non-invasive ventilation?

Reply: Median PEEP/CPAP and mean airway pressure from those on invasive and non-invasive ventilation were

added as suggested (Results, p 4, line 47-52).

Reviewer 3 Comments

1. It would be excellent if the authors could include in the discussion, how patients with ARF related to features of

severe dengue and complications during PICU admission.

Reply: Texts were added in the part of discussion (Discussion, p 9, line 20-31).

Reviewer 4 Comments

1. The VIS calculation applied requires a citation, normally vasopressin is included in this score, but not in the

formula applied for this study? Is the validity of the score granted in this case? Was the same scoring system

applied to all patients? Additional info / citation needs to be provided.

Reply: Vasopressin is not available in Thailand. According to suggestion, vasopressin dose was added in the

formula in the manuscript. For the validation of VIS score, there has been a study conducted by McIntosh et al

that assessed the validity of VIS as a scoring system for cardiovascular support and surrogate outcome in

pediatric sepsis. The author concluded that VIS in pediatric sepsis patients is independently associated with

important clinically relevant outcomes including ICU length of stay, ventilator days, and cardiac

arrest/ECMO/mortality.(5) So the citation was provided according to suggestion.

2. Typo: rate(s)

Reply: Typo was edited. In addition, texts were edited in table 4.

References

1. Arikan AA, Zappitelli M, Goldstein SL, Naipaul A, Jefferson LS, Loftis LL. Fluid overload is associated with

impaired oxygenation and morbidity in critically ill children. Pediatr Crit Care Med. 2012;13(3):253-8.

2. Jakobsen JC, Gluud C, Wetterslev J, Winkel P. When and how should multiple imputation be used for handling

missing data in randomised clinical trials – a practical guide with flowcharts. BMC Medical Research Methodology.

2017;17(1):162.

3. Bagley SC, White H, Golomb BA. Logistic regression in the medical literature: standards for use and reporting,

with particular attention to one medical domain. J Clin Epidemiol. 2001;54(10):979-85.

4. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per

variable in logistic regression analysis. J Clin Epidemiol. 1996;49(12):1373-9

VERSION 2 – REVIEW

REVIEWER	Reviewer name: Dr. Peter Flom Institution and Country: Peter Flom Consulting, United States Competing interests: None
REVIEW RETURNED	03-Aug-2022
GENERAL COMMENTS	I confine my remarks to statistical aspects of this paper. The general approach is fine, but I have some issues to resolve before I can recommend publication. p.4 line 26 While I applaud the authors for using graphical methods to assess normality, histograms are not a good method of doing this. Their appearacnce can vary greatly depending on the number of bins and the starting points. A better method is the quantile normal plot, but these can take some practice to interpret. Another alternative is the density plot.

	line 32 Why was no imputation done? line 32-34 First, I'd call these bivariate. Second, and more important, this method is known as bivariate screening and, while it is common, it is seriously flawed. The results of the final regression will be incorrect: P values will be too low, standard errors too small, and parameter estimates biased away from 0. For details, examples, and proofs, see *Regression Modeling Strategies* by Frank Harrell. It is better to use clinical knowledge (which the authors do, see line 34) but, for the automatic part (if the authors want to use one), a better method is LASSO (although other penaized methods are OK) Table 4 The usual terms for the columns would be "unadjusted" and "adjusted". This is really a style issue, so, I leave it to the editors. However, I'd like to see rows for ALL the variables that were considered for entry into the model. Figure 1 With such small N, it might be better to use a strip plot, or to add a strip plot to the box plot. Peter Flom

REVIEWER	Reviewer name: Prof. Aye Han Institution and Country: Royal College of Paediatrics and Child Health Global Health, United Kingdom of Great Britain and Northern Ireland Competing interests: Nil
REVIEW RETURNED	11-Aug-2022
GENERAL COMMENTS	Very useful insights into future management of DSS patients with ARF. It was mentioned that all patients who died were from the ARF group. Would be good to know whether this was the primary cause of mortality or any other contributory cause of death.

VERSION 2 – AUTHOR RESPONSE

Editor in Chief Comments

- Title amends to "Pediatric Dengue Shock Syndrome and Acute Respiratory Failure: A single centre retrospective

study"

- Add Key messages - see Instructions to authors

- Respond in full to the reviewers, especially the stats reviewer

- Discussion: delete the first two sentences

- Be cautious with your conclusions

- Abstract Results: 1st sentence avoid use of % (not needed for small numbers)

- Results: 1st paragraph avoid use of % (not needed for small numbers)

Author's reply: As suggested, the percentage results were changed to absolute values for small numbers in both the Abstract

Results (p. 2) and the Results (p. 4). The first two sentences in the Discussion were deleted (p. 8). Conclusion was reviewed and

edited (p. 9). Key messages were added after the Abstract (p. 3) as followed:

Key messages

o ARF is not an uncommon complication in pediatric DSS.

o This study demonstrated that fluid accumulation is a strong risk factor for developing ARF among

children with DSS.

o One shock stabilized, early recognition of fluid accumulation and prompt management of fluid removal

are needed to prevent unfavourable respiratory outcomes.

o However, further larger prospective cohort studies are required to establish evidence for the causal

relationship.

The number of decimal places of odds ratio were adjusted as appropriate in the section of Abstract Results, Results,

and Table 4. Please noted that typos were corrected (odds ratio).

Reviewer 1 comments

1. P.4 line 26: While I applaud the authors for using graphical methods to assess normality, histograms are not a good

method of doing this. Their appearance can vary greatly depending on the number of bins and the starting points. A

better method is the quantile normal plot, but these can take some practice to interpret. Another alternative is the

density plot.

Reply: We performed normality testing with quantile normal plots and density plots. The tests demonstrated that our

data were non-normally distributed. (Statistical Analysis section, p. 4)

2. Line 32: Why was no imputation done?

Reply: The missing data in our study were lab data including lactate level and arterial pH value, as shown in table 2.

The proportions of the missing data of these 2 variables were large due to 10-year retrospective data [35/60 missing for

lactate (58%) and 21/60 (35%) missing for arterial pH].

According to the suggestions recommended by Jakobsen et al. The authors suggested that “If large

proportions of data are missing it ought to be considered just to report the results of the complete case analysis and

then clearly discuss the resulting interpretative limitations of the trial results.(1)

3. Line 32-34: First, I'd call these bivariate. Second, and more important, this method is known as bivariate screening and,

while it is common, it is seriously flawed. The results of the final regression will be incorrect: P values will be too low,

standard errors too small, and parameter estimates biased away from 0. For details, examples, and proofs, see

Regression Modelling Strategies by Frank Harrell. It is better to use clinical knowledge (which the authors do, see line

34) but, for the automatic part (if the authors want to use one), a better method is LASSO (although other penalized

methods are OK)

Reply: The term “bivariate analysis” was corrected in the part of “Statistical analysis” (p. 4) as suggested. In our

study, the selection of variables entered into multivariate analysis of ARF was primarily based on clinical knowledge and

secondarily on bivariate p-value of less than 0.1, not by an automatic procedure. In this study, there were 26 patients

with ARF and 34 without ARF. According to the suggestion of 10 EPV (Events Per Variable), only three independent

variables (i.e., presence of MODS, prothrombin time, and presence of □15% fluid accumulation at 72 hours) were put

into multiple logistic regression analysis of ARF to avoid the problem of overfitting. In addition, these three variables are

not related, so, there is no problem of collinearity. The variable PRISM III had a very small bivariate p-value of 0.013;

however, PRISM III was not entered into the logistic regression model due to its relationship with the presence of

MODS. The penalized linear regression model for the variable selection using LASSO may not be necessary in this

study.

4. Table 4: The usual terms for the columns would be "unadjusted" and "adjusted". This is really a style issue, so, I leave

it to the editors. However, I'd like to see rows for ALL the variables that were considered for entry into the model.

Reply: We changed the term used from “univariate” Odds Ratio to “unadjusted” Odds Ratio. Extra rows for variables

that were considered for entry into the model were added according to the suggestions (Table 4, p. 8).

5. Figure 1: With such small N, it might be better to use a strip plot, or to add a strip plot to the box plot.

Reply: The figure was changed to strip plot with box as attached (p. 8).

Reviewer 2 comments

1. It was mentioned that all patients who died were from the ARF group. Would be good to know whether this was the

primary cause of mortality or any other contributory cause of death.

Reply: In our opinion, although all non-survivors were from the ARF group, it is difficult to say that ARF was the

primary cause of mortality as all non-survivors had multiple organ dysfunctions(2) which could lead to death. The details of

multiorgan dysfunction are presented in the table below. However, we did not perform multivariate analysis on mortality outcome

in order to identify whether ARF is an independent factor associated with death as limited by a small number in non-survival group.

Organ dysfunction Patient no.	Cardiovascular	Respiratory	Neurological	Hematologic	Renal	Hepatic	Total number of ODs
1	*	*	*	*	*	*	6
2	*	*	*	*	*	*	6
3	*	*	*	*	*	*	6
4		*	*	*	*	*	5
5	*	*	*	*		*	5
6	*	*		*		*	4

*Developed organ dysfunction

References

1. Jakobsen JC, Gluud C, Wetterslev J, Winkel P. When and how should multiple imputation be used for handling missing

data in randomised clinical trials – a practical guide with flowcharts. BMC Medical Research Methodology. 2017;17(1):162.

2. Goldstein B, Giroir B, Randolph A, International Consensus Conference on Pediatric S. International pediatric sepsis

consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med. 2005;6(1):2-8.

VERSION 3 – REVIEW

REVIEWER	Reviewer name: Dr. Peter Flom Institution and Country: Peter Flom Consulting, United States Competing interests: None
REVIEW RETURNED	14-Sep-2022
GENERAL COMMENTS	The authors have addressed my concerns and I now recommend publication. Peter Flom