PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Vascular Reactivity Index and PELOD-2 as a Mortality Predictor in Pediatric Septic Shock
AUTHORS	Yuniar, Irene Setianingsih, Utami Kurniawati Pardede, Sudung O Kadim, Muzal Iskandar, Adhi Teguh Perma Prawira, Yogi

VERSION 1 – REVIEW

REVIEWER	Reviewer name: Dr. Emmanouil Bagkeris Institution and Country: University College London, United Kingdom of Great Britain and Northern Ireland Competing interests: None
REVIEW RETURNED	13-Jul-2022V

GENERAL COMMENTS	1. The conclusion of the abstract would benefit from highlighting the how much faster, and easier the VRI method is compared to the PELOD-2. 2. Please be consistent with the decimal places used when reporting the CFR in the first paragraph of the introduction (31.7% vs. 31,7%). 3. Last sentence of the second paragraph of the introduction makes a strong statement "Therefore, a non-invasive method is needed…". Perhaps consider re-phrasing. 4. How were the cut-offs for the cardiac index classification determined? Please provide a reference if there is an established method or explain in more detail why you chose to use those cut-offs. 5. In figure 2 perhaps add a dotted line at the intersection of sensitivity and specificity to the suggested cut-off of 32.1. 6. Have you considered exploring the reliability of VRI and PELOD-2 using Bland-Altman Limits of Agreement? I am not convinced that the correlation coefficient provides a valuable or interpretable statistic in this occasion.

REVIEWER	Reviewer name: Prof. Kee Chong Ng Institution and Country: KK Women's and Children's Hospital, Singapore Competing interests: Nil
REVIEW RETURNED	08-Jul-2022

GENERAL COMMENTS	Interesting paper promoting the possible use of VRI on the ground from retrospective data - affirming preliminary studies particularly from Lee at al. In the "Discussion" section, other than having the last paragraph affirming its limitatons cos its a retrospective study, could the authors also : 1) Discuss conclusions from the paper by Kazune et al 9paper's Ref f#10), albeit this is ref paper is more than just for paeds? 2) Share with us readers how to move forward since this initial retrospective paper shows much promise - eg? they are planning to do a larger prospective study - with a different design and purpose to validate or are they proceeding to cautiously implement this for their ground practice? Or make preliminary recommrndations to the Indonesian Pediatric Society Guidelines committee?? Otherwise, I am fine to recommend - with minor revisions as stated above thx

VERSION 1 - AUTHOR'S RESPONSE

Response to

Editor in Chief comments

suggestions number 1-6 have been corrected in the paper

Associate Editor

Abstract

1. Because the authors want to emphasize the use of VRI as a new way to predict mortality in pediatric septic shock. Thanks for the suggestion, we will add the word PELOD-2 to the study objective in the abstract.

2. Thank you for your correction. This study compares VRI and PELOD-2 prognosis accuracy with a variety of diagnostic parameters (sensitivity, specificity, LR+ & LR-). Our study was conducted in a retrospective cohort, so we took the term "retrospective study" into consideration.

Introduction

1. In the discussion section, we have written the results of previous studies by Lee et al but data on sensitivity, specificity, LR+ & LR- have not been included in our paper. In the introduction it was explained that septic shock is defined as the development of sepsis with circulatory, metabolic, and cellular abnormalities that can substantially increase mortality. The clinical relevance found was circulatory disturbances in the form of hypotension due to vasodilation of blood vessels to cause vasoplegic which was reflected in the low systemic vascular resistance on the USCOM device. A low IVRI reflects a non-reactive vascular tone following the administration of vasoactive drugs.

2. Less invasive, easy, and fast methods are preferable to predict mortality in pediatric sepsis.

3. We will add primary and secondary objectives to the introduction.

Methods

1. The timing of the study will be further explained.

2. yes, we did a sample size estimation before the study started.

3.

- The authors expected a higher sensitivity of 90% because Lee et al. previous study entitled "vascular reactivity index as an effective predictor of mortality in children with refractory septic shock" found a VRI value of 31 with a sensitivity of 85%.

- When using a one-tailed test, we are testing for the possibility of the relationship in one direction and completely disregarding the possibility of a relationship in the other direction. We strongly believe that if the VRI is low, the mortality is high. according to the condition of vasoplegic blood vessels that do not respond to the administration of vasoactive drugs

- We calculate the sample size in 3 ways:

o The sample size calculation formula for the proportion of a population.

o sample size calculation for cut-off values

o sample size for comparing the area under curve (AUC)

4. Inclusion criteria were pediatric patients aged 1 month to 18 years with ICD 10 administrative coding of septic shock (R65.21). we will add the inclusion criteria.

5. Altered hemodynamic conditions are tightly linked to cardiac defects. Blood flow or vascular tone may change in relation to preload, contractility, and afterload in congenital heart disease. Therefore, in order to avoid measurement bias, the authors excluded patients with congenital heart disease.

6. Non-invasive hemodynamic monitoring using transthoracic ultrasonography (Doppler) has developed rapidly. In this study, ultrasonic cardiac output monitoring (USCOM) was used. SVRI is a parameter obtained from USCOM examination.

7. I will correct the sentence maximum dose of vasoactive and inotropic drugs used to calculate VIS to be the highest dose used in the first 6 hours since the septic shock diagnosis, so that it is not confusing. for example in the first hour using 10 mcg of dobutamine then at the 5th hour the dose increased to 15 mcg, then the number 15 will be entered for the calculation of VIS.

8. The authors have described the excluded patients in the results chapter. 70 subjects with congenital heart disease were excluded as well as 38 with incomplete data, and 14 were double screened.

9. yes. because our research was retrospective study which analyzed data based on medical records, so informed consent was not required

Discussion

1. Thanks for the advice.

Prof. Kee Chong Ng, KK Women's and Children's Hospital

1) we will add to the discussion regarding the research by Kazune et al.

2) Further studies should be carried out using a prospective multicenter design. In addition, we need to cooperate with the government regarding the availability and training of using USCOM tools so that this research can be carried out in many places and provide benefits to patients.

Dr. Emmanouil Bagkeris, Imperial College London

1. Thanks for the advice, we will add to the conclusion regarding other benefit of VRI.

2. Thanks for the advice, we will correct the typo

3. we will re-phrase to "Less invasive, easy, and fast methods are preferable to predict mortality in

pediatric sepsis."

4. Classification of cardiac index according to previous study by Ceneviva et al. we will add citation to the reference.

5. Thank for the advice. We will add a dotted line at the intersection of sensitivity and specificity in figure 2.

6. We have not considered exploring the reliability of VRI and PELOD-2 using the Bland-Altman Limits of agreement, but only assessed the correlation test.

VERSION 2 – REVIEW

REVIEWER	Reviewer name: Dr. Emmanouil Bagkeris Institution and Country: University College London, United Kingdom of Great Britain and Northern Ireland Competing interests: None
REVIEW RETURNED	23-Aug-2022
GENERAL COMMENTS	The authors have adequately adressed all points raised in the first round of reviews. I have no additional points to raise.

REVIEWER	Reviewer name: Prof. Kee Chong Ng Institution and Country: KK Women's and Children's Hospital, Singapore Competing interests: NIL
REVIEW RETURNED	21-Aug-2022
GENERAL COMMENTS	Minor Revisions : 1) Page 2 of 18 : ABSTRACT : Background "The mortality rate for children with septic shock is high in low and middle income countries, with approximately 31.7%." Sentence does NOT make sense -- ending in "with approximately 31.7%." Please rephrase sentence. 2) Page 4 of 18: First line -- "Lee et al. developed the calculation of VRI as a non-invasive method to predict mortality in children with refractory septic shock." Please reference the "Lee et al" attribution and number the reference accordingly. 3) Page 4 of 18: In the first paragraph of this page, can the authors clearly state the 'Primary Objective' of this study? They state the 'secondary objective' in the last line of the first paragraph but the primary objective is not stated. 4) Page 6 of 18 : Under "RESULTS" -- 2nd line : "Meanwhile, 70 subjects with congenital heart disease were excluded as well as 38 with incomplete data, and 14 were screened doubly." Please remove 'Meanwhile' from this sentence... 5) Page 6 of 18 : Last line of this page . "The highest number of subjects who died was found in the high cardiac index and low SVRI group with 17.6%.14." Not sure why there is a reference "14" at the end of this sentence. ? remove this reference?? 6) Page 12 of 16 : "DISCUSSION" -- Please remove sentences 2 and 3 from the first paragraph : "Furthermore, children <5 years old are more susceptible to severe infection due to their immature

	immune systems.15 The mortality rate which reached 47% is presumably because the study location was a tertiary hospital." 7) Page 12 of 18 ; 4th line from the bottom of page --> Again Lee et al has NO reference like above. Please reference and attribute as before "Moreover, Lee et al. analyzed hemodynamic parameters to identify predictors of mortality in children with septic shock and cardiogenic shock." 8) Page 13 of 18 : Last paragraph - 2nd & 3rd sentences --> Lee et al again has NO references and attribution. Please do as above. "

VERSION 2 – AUTHOR'S RESPONSE

Prof.Kee Chong Ng, KK Women's and Children's Hospital

1. Thanks for the advice, we will rephrase to "The mortality rate for children with septic shock is still quiet high in low and middle income countries (31.7%)."

corrections for suggestions numbers 2,7, and 8 regarding attribution and references have been corrected in the manuscript.

3. Thanks for the advice, To make the manuscript easier to understand, we added a "primary objective."

4. We removed the word "meanwhile" from the second line of the results section of the manuscript.

5. Thank you for pointing out that reference 14 should have been placed before "The highest number of subjects who died was found in the high cardiac index and low SVRI group with 17.6%." The reference position has been corrected.

6. We removed the sentences on the second and third lines of the discussion section.

VERSION 3 – REVIEW

REVIEWER	Reviewer name: Prof. Kee Chong Ng Institution and Country: KK Women's and Children's Hospital, Singapore Competing interests: NIL
REVIEW RETURNED	30-Sep-2022
GENERAL COMMENTS	There are only 3 minor revisions I would further suggest : 1) Page 2/36 Line 42 to 43 : "Furthermore, the VRI value was deter,mined by dividing..." Please remove "Furthermore" and "value" and rephrase sentence to : "The VRI was determined by divising ..." 2) Page 5/36 : Lines 33 to 38. Change "The VRI was defined as SVRI/vasoactive inotropic score (VIS) calculated based on ..." to "VRI is defined as SVRI/vasoactive inotropic score (VIS). VIS is calculated based on ..." 3) Page 5/36 : Lines 38 to 43

	Change "The value of VIS equals to dopamine dosage ..." to " The value of VIs is calculated as folows - dopamine dosage (ug/kg/min) + dobutamine dosage ..."
	4) Page 6/36 : Lines 41 to 44 Shift this line "The baseline hemodymanic profile.." to the last line of methods on the same page, that is after line `17 Page 6/36.
	5) Page 6/36. Lines 44 to 46. Change this line "One of the targets for septic shock therapy is cardiac index value ..." to "One of the targets for septic shock is a cadiac index value of 3.3-6 L/min/m2."

VERSION 3 – AUTHOR'S RESPONSE

Suggestions number 1-5 have been corrected in the paper.