

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Respiratory rate and pulse oximetry derived information as predictors of hospital admission in young children in Bangladesh: a prospective observational study
AUTHORS	Garde, Ainara; Zhou, Guohai; Raihana, Shahreen; Dunsmuir, Dustin; Karlen, Walter; Dehkordi, Parastoo; Huda, Tanvir; Arifeen, Shams E.; Larson, Charles P; Kissoon, Niranjana; Dumont, Guy; Ansermino, Mark

VERSION 1 - REVIEW

REVIEWER	Peter P. Moschovis Massachusetts General Hospital/Harvard Medical School, USA
REVIEW RETURNED	11-Mar-2016

GENERAL COMMENTS	<p>This is a well-written paper on a novel prediction tool for risk stratifying children seeking care in an emergency department of a tertiary hospital in a low-income country.</p> <p>The investigators used a mobile-phone based pulse oximeter to collect standard oximetry data in addition to detailed data on variability from the heart rate and oximetry signals. They then evaluated whether these features were associated with a higher risk of hospital admission in children being evaluated in an emergency department in a tertiary hospital in Bangladesh. They found that a multivariate logistic regression model using oximeter-based data alone had good performance in predicting odds of hospital admission.</p> <p>Strengths: large sample size, good analytic strategy, and novel approach to risk classification</p> <p>Weaknesses: large proportion excluded due to poor quality signal, no external validation cohort (which might indicate that the estimates of predictive ability are optimistic)</p> <p>Suggestions for improvement:</p> <ul style="list-style-type: none"> - I didn't see how many children were actually admitted (i.e., proportion admitted vs. not admitted). This could easily be added to Table 1. - It would be helpful to include some clinical data on the study subjects, if available (both diagnoses and outcomes would be nice to see). <p>Overall a good paper, and an important contribution to the field.</p>
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REVIEWER	Dr Nitya Wadhwa Translational Health Science and Technology Institute, India
REVIEW RETURNED	19-May-2016

GENERAL COMMENTS	<p>Aim was to develop predictive tool based on objective data to identify children at increased risk of hospital admission. Concept to come up with an objective criteria to identify U-5 children requiring hospital admission and replace the IMCI based clinical criteria which requires expertise or extensive training is good</p> <p>1. Authors should give more details on methodology/ how data was collected.</p> <p>The children who presented at the facility were obviously sick enough for the parent (s) to feel the need to get the child to the facility for management.</p> <p>The paper says the primary outcome was need for hospital admission based on expert physician review and follow-up. Did the physicians deciding on need for hospital admission of the children have a well-defined clinical criteria/ protocol or was this at the discretion of the physician?</p> <p>2. "This model is intended to support community healthcare workers with limited formal training, to recognize critical illness in children earlier in the course of their disease."</p> <p>How do the authors define critical illness?</p> <p>3. Is there any data on outcome of children who were not admitted in the hospital?</p> <p>4. How were the physicians blinded from the pulse oximetry information?</p> <p>5. Can the same tool be used for children in the community? In the community there will be (i) children who are unwell but not sick enough for the parent (s) to get the child to the hospital (ii) children who are sick, brought to the hospital but not admitted by physician (iii) children who are sick, brought to the hospital and admitted in the hospital by physician</p> <p>The authors themselves state that the predictive tool needs to be tested in the setting of a community-based study.</p> <p>6. In the community, the healthcare providers are using a clinical criteria based on IMCI to assess sick children and refer them to a higher centres for management. How much better is this assessment using objective criteria than the already in-use IMCI criteria?</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Peter P. Moschovis

Institution and Country: Massachusetts General Hospital/Harvard Medical School, USA

Competing Interests: None declared

1) Reviewer #1: This is a well-written paper on a novel prediction tool for risk stratifying children seeking care in an emergency department of a tertiary hospital in a low-income country. The investigators used a mobile-phone based pulse oximeter to collect standard oximetry data in addition to detailed data on variability from the heart rate and oximetry signals. They then evaluated whether these features were associated with a higher risk of hospital admission in children being evaluated in an emergency department in a tertiary hospital in Bangladesh. They found that a multivariate logistic regression model using oximeter-based data alone had good performance in predicting odds of

hospital admission.

Strengths: large sample size, good analytic strategy, and novel approach to risk classification

Weaknesses: large proportion excluded due to poor quality signal, no external validation cohort (which might indicate that the estimates of predictive ability are optimistic)

Suggestions for improvement:

- I didn't see how many children were actually admitted (i.e., proportion admitted vs. not admitted). This could easily be added to Table 1.
 - It would be helpful to include some clinical data on the study subjects, if available (both diagnoses and outcomes would be nice to see).
- Overall a good paper, and an important contribution to the field.

Author reply and action: We agree with the reviewer that the number and proportion of admitted and non-admitted children should be included in Table 1, and we have accordingly done that.

Feature Admission required

N=616 (30.0%) Admission not required

N=1435 (70.0%) p-value Odds ratio (95% CI)

Pulse rate variability analysis

Regarding clinical information about the diagnoses and outcomes, the following paragraph has been introduced in the Data Collection Section at the end of the 2nd paragraph.

The most common diagnoses included acute lower or upper respiratory infection, and eye or ear infection in admitted children; and acute upper respiratory infection, eye or ear infection, diarrhea, fever of unknown cause and gastrointestinal complains in non-admitted children; see [17] for more details of the distribution of diagnoses and outcomes.

[17] Raihana S, Dunsmuir D, Huda T, et al. Development and internal validation of a predictive model including pulse oximetry for hospitalization of under-five children in Bangladesh. PLoS One 2015; 10(11). doi: 10.1371/journal.pone.0143213

Reviewer: 2

Reviewer Name: Dr Nitya Wadhwa

Institution and Country: Translational Health Science and Technology Institute, India

Competing Interests: None declared

2) Reviewer #2: Aim was to develop predictive tool based on objective data to identify children at increased risk of hospital admission. Concept to come up with an objective criterion to identify U-5 children requiring hospital admission and replace the IMCI based clinical criteria which requires expertise or extensive training is good. Authors should give more details on methodology/ how data was collected. The children who presented at the facility were obviously sick enough for the parent (s) to feel the need to get the child to the facility for management. The paper says the primary outcome was need for hospital admission based on expert physician review and follow-up. Did the physicians deciding on need for hospital admission of the children have a well-defined clinical criteria/ protocol or was this at the discretion of the physician?

Author reply: The children were evaluated by physicians not involved in the study, so these physicians were performing their regular decision making uninfluenced by the study. Pulse oximetry information

was not provided to the physicians; thus these physicians decided the need for hospital admission, at their discretion, without knowledge of the oxygen saturation. The physicians did not use a study specific protocol.

The purpose of this study was not to change the physician's routine with additional training but instead to provide a comparable level of decision making from the result of a predictive tool using only objective information, with the goal of putting this in the hands of community healthcare workers who do not have the physician's training.

Author action: We have added the information about severity (30% of cases were admitted) in table 1. In addition, the following sentence has been modified in the second paragraph of the Data Collection section.

Thus, the SpO2 recording did not influence clinical decisions, including the need for admission, which was decided at the physicians' discretion uninfluenced by the study.

3) Reviewer #2: "This model is intended to support community healthcare workers with limited formal training, to recognize critical illness in children earlier in the course of their disease." How do the authors define critical illness?

Author reply: We used the need for hospitalization, as made by an expert physician, for ongoing care, as an early indicator of critical illness. That is why our primary outcome was the need for hospitalization based on expert physician review and follow-up.

Author action: The last sentence has been edited in the last paragraph of the Introduction.

We consider the need for hospital admission as an early indicator of critical illness, and thus this model is intended to support community healthcare workers, with limited formal training, to recognize critical illness in children earlier in the course of their disease.

4) Reviewer #2: Is there any data on outcome of children who were not admitted in the hospital?

Author reply: We were able to contact 73.8% (1855 out of 2514) of children who were sent home. Our previously published paper [17] includes detailed information of the follow-up of the cohort of children.

Author action: We have included the following sentence in the Data Collection Section at the end of the 2nd paragraph:

From the children sent home, we were able to follow-up 1855/2514 (73.8%) and 14 were admitted on a subsequent visit.

5) Reviewer #2: How were the physicians blinded from the pulse oximetry information?

Author reply: A blinded version of the app was used in the study for the data acquisition. This version, illustrated in the figure 1.b, does not display oxygen saturation. The physicians did not have access to the oxygen saturation information of the children, thus the app could not influence their clinical decisions.

Author action: The following sentence has been modified in the second paragraph of the Data Collection section.

Pulse oximetry information was blinded (not displayed) within the app (Figure 1.b) and not provided to the physicians, as this was not routinely available in the facility.

6) Reviewer #2: Can the same tool be used for children in the community? In the community there will be (i) children who are unwell but not sick enough for the parent (s) to get the child to the hospital (ii) children who are sick, brought to the hospital but not admitted by physician (iii) children who are sick, brought to the hospital and admitted in the hospital by physician. The authors themselves state that the predictive tool needs to be tested in the setting of a community-based study.

Author reply: As with all clinical decisions there will be a tradeoff between unnecessary referrals and missed severe cases. We agree that the options i – iii do reflect the complexity of evaluating the performance of the model (iv- could be those who were admitted and did not need to be admitted). We recognize that different contexts will require different optimizations.

The same tool could be used in a community setting, but we have yet to validate the performance of the proposed predictive model in this setting. As mentioned in the limitations section, the proposed predictive model was internally validated with data acquired at a tertiary level facility rather than in the community. However in the setting we had chosen, the hospital did act as the first point of contact for any child. Thus, one of our future plans includes the validation of the proposed model, identifying children that should be referred to the hospital, in a community setting.

Author action: The last sentence of the third paragraph has been modified in the Limitations and future research section:

The model should be validated in a community setting, with data from a cohort of children assessed by community healthcare providers. The model and thresholds for referral will need to be optimized for the local context.

7) Reviewer #2: In the community, the healthcare providers are using a clinical criteria based on IMCI to assess sick children and refer them to a higher centres for management. How much better is this assessment using objective criteria than the already in-use IMCI criteria?

Author reply: The aim of the study is not to replace the IMCI criteria but to add more information that can improve the identification of critical illness. The proposed model provides a hospital admission risk score, which allows community healthcare workers with minimal training to identify a child that may require hospital admission. This information can be combined with additional clinical signs and symptoms to improve diagnostic performance. We did not specifically compare our predictions to the IMCI criteria as we lumped all children together (rather than the sign/symptom specific approach used for IMCI).

Author action: The following sentence has been added to end of the sixth paragraph of the Discussion:

The result of the app can than be considered together with treatment guidelines for a more informed decision on the level of care necessary for the child.

VERSION 2 – REVIEW

REVIEWER	Peter P. Moschovis Massachusetts General Hospital, USA
REVIEW RETURNED	18-Jun-2016

GENERAL COMMENTS	I have reviewed the changes and the manuscript looks fine to me.
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