ORIGINAL RESEARCH

Vital Sign alterations within 24 hours prior to death in children with retinopathy-positive Cerebral Malaria at Queen Elizabeth Central Hospital Malawi

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Abstract

Background

Malaria is a significant obstacle to child health and survival. *Plasmodium falciparum* infections, especially in children under five, lead to high morbidity and mortality. Cerebral malaria (CM) is a life-threatening complication characterized by coma, and its diagnosis can be improved by observing malarial retinopathy in children. Monitoring vital signs is essential for managing patients with CM.

Objectives

To determine if changes in vital signs predict death in children with retinopathy positive cerebral malaria (RPCM).

Methods

This was a retrospective case-control study using data collected from children admitted to the Paediatric Research Ward at Queen Elizabeth Central Hospital in Blantyre between 1997 and 2020. Patients who died 24 hours or more after admission were matched with control patients who survived. Linear regression analyses were used to assess the differential time trends of each vital sign in the survivor group and death group. Classification models were used to quantify various vital signs' predictive power of death.

Results

Among the population that died, the estimated change in average respiratory rate per hour approaching death was 0.02 breaths per minute compared to -0.25 breaths per minute among those who survive ($p < 0.001$), and the estimated change in average BCS per hour approaching death was -0.01 compared to 0.06 among the survivors ($p < 0.001$). Changes in temperature and heart rate were not associated with clinical deterioration. Three models were developed, and the best receiver operating characteristic curve was 100% sensitive, the corresponding false positive rate was 75%.

Conclusion

Changes in respiratory rate and BCS have prognostic significance in the final 24 hours before death in children with cerebral malaria. Extra attention should be paid to these two vital signs as they may help to identify children who are at increased risk of deteriorating.

Key Words: *Plasmodium falciparum*, cerebral malaria, retinopathy-positive

Introduction

Malaria is a major health problem in tropical and subtropical regions of the world. The disease is caused by protozoan parasites of the genus Plasmodium that are transmitted to humans through the bites of infected female Anopheles mosquitoes[1]. Malaria is responsible for high rates of morbidity and mortality particularly in children from the African region. Despite strategies to curb the spread of the disease, cases of malaria are still high with 241 million cases worldwide in 2021[2]. Malawi is a malaria endemic country in sub-Saharan Africa. In 2017 the Malawi demographic health survey revealed that almost four million people suffer from malaria every year. Children below the age of five are particularly vulnerable to malaria illness and may develop severe and complicated malaria due to their reduced immunity[3]. Approximately 15% to 20% of children hospitalized with severe malaria die despite receiving proper antimalarial therapy[4]. Cerebral malaria is a common form of severe malaria, defined as a reduced level of consciousness (BCS less than 3) in the presence of *P. falciparum* infection and the absence of other causes of coma[5]. The presence of malarial retinopathy, a constellation of findings in the optic fundus, helps improve the specificity of the clinical diagnosis of cerebral malaria by distinguishing likely malarial coma from coma unlikely to be of malarial cause[6] .

Useful information about the health status of an individual can be gained by measuring vital signs such as respiratory rate, oxygen saturation, temperature, heart rate and blood pressure. Changes in vital signs collected after admission have been shown to predict death within the first 24 hours after hospital admission in severely ill hospitalized children[7]. Studies predicting mortality in malaria have been performed in other countries.

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Table 1: Demographics of cases and controls

VARIABLE	COMBINED N (%)	DIED (cases) N (%)	SURVIVED (Controls) N%
GENDER			
Female	62 (43.7)	29 (40.8)	33 (46.5)
Male	80 (56.3)	42 (59.2)	38 (53.5)
AGE			
(<=60 months)	104 (73.2)	52 (73.2)	52 (73.2)
(>60months)	38 (26.8)	19 (26.8)	19 (26.8)
Mean (SD)	45.4 (27.6)	45.5 (27.4)	45.4 (27.9)
Blantyre Coma Score			
0	24 (16.9)	12 (16.9)	12 (16.9)
1	68 (47.9)	34 (47.9)	34 (47.9)
2	50 (35.2)	25 (35.2)	25 (35.2)

Table 2. Assessment of the time trend between vital signs in the death vs survivor groups. The variable death is an indicator variable that equals 1 if the patient was in the death group (case) and 0 if the person was a survivor (control)

		95% CI		
	Estimate	Lower	Upper	p-value
Heart Rate				
Time (hours)	0.47	-0.64	-0.31	<0.001
Death	2.64	-1.05	6.34	0.16
Time x Death	0.17	-0.43	0.09	0.19
Respiratory Rate				
Time (hours)	0.25	-0.33	-0.18	<0.001
Death	10.70	8.95	12.4	<0.001
Time x Death	-0.27	0.14	0.39	<0.001
Temperature				
Time (hours)	0.02	-0.03	-0.01	<0.001
Death	0.38	0.18	0.567	<0.001
Time x Death	-0.01	0.00	0.02	0.18
BCS				
Time to event (hours)	-0.06	0.05	0.07	<0.001
Death	-2.46	-2.68	-2.23	<0.001
Time x Death	0.07	-0.08	-0.05	<0.001

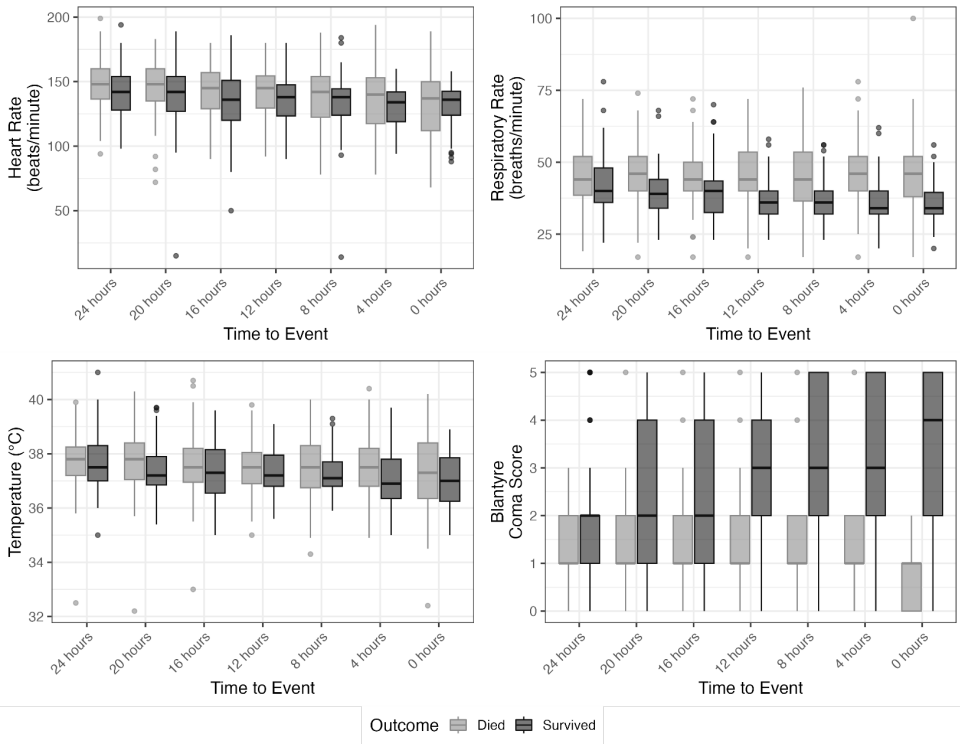

Figure 1. Boxplots of vital signs within 24 hours of endpoint at 4-hour intervals by survival outcome

One such study found that the risk of mortality in children with malaria was independently predicted by a low BCS, a high blood lactate level, and a high body mass index (BMI)[8]. Despite these observations in other populations, there may be significant variations in the clinical signs and symptoms of malaria at various ages and endemicity levels and this warrants evaluation of these signs in our population. Pediatric early warning systems are used in other disease states to detect signs in children who are clinically deteriorating so that more effective care can be provided[9]. Clinical deterioration in children with CM is often associated with hypoglycemia, worsening anemia and seizures, which can be subclinical and remain undetected[4,10]. All of these are treatable and identifying them rapidly would allow for intervention that could change the course of the disease[11]. The aim of this study was to investigate vital sign changes in the 24 hours prior to death in children with RPCM at Queen Elizabeth Central Hospital Paediatric Research Ward in Blantyre, Malawi. The time period of 24 hours was chosen as interventions detected and acted upon during this time frame could conceivably have an effect on patient survival.

Methods

Study type and setting

The study involved a secondary analysis of data collected during a prospective study of malaria pathogenesis.

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Table 3. Area under the receiver operating characteristic curve (AUC) for Models 1, 2, and 3 at 24, 16, and 8 hours to death

			95% CI	
	Time to death	AUC	Lower	Upper
Model 1	8 hours	0.71	0.62	0.80
	16 hours	0.66	0.57	0.76
	24 hours	0.61	0.51	0.70
Model 2	8 hours	0.87	0.81	0.93
	16 hours	0.78	0.70	0.86
	24 hours	0.66	0.57	0.75
Model 3	8 hours	0.85	0.78	0.92
	16 hours	0.77	0.68	0.85
	24 hours	0.65	0.56	0.73

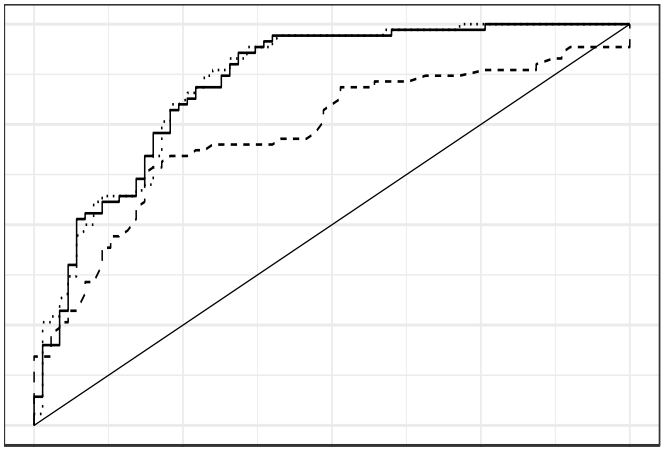

Figure 2. Receiver operating characteristic (ROC) curves for each Model at 8 hours prior to death

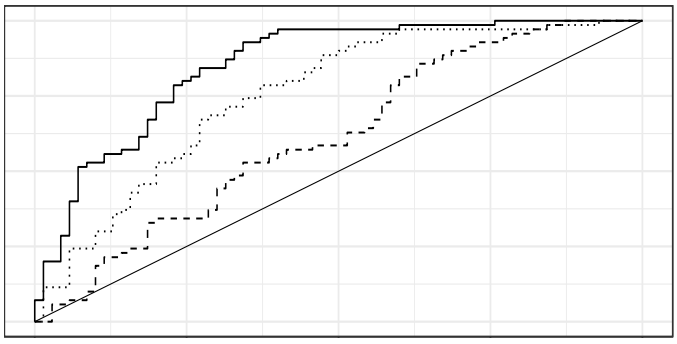

Figure 3. Receiver operating characteristic (ROC) curves for predicting death 24, 16, and 8 hours prior to event using classifier Model 2 (respiratory rate and BCS)

This analysis examines vital signs and their changes in the 24 hours prior to death in children with RPCM and concomitant controls at Queen Elizabeth Central Hospital Paediatric Research Ward (PRW) in Blantyre, Malawi.

Study population

This was a secondary analysis of data collected during an observational study of malaria pathogenesis[12]. Children admitted to an ongoing study of paediatric cerebral malaria on the PRW at Queen Elizabeth Central Hospital were eligible to be included if the admission BCS was less than or equal to 2, *P. falciparum* parasitemia was detected on peripheral blood smear, if there was no improvement after correcting hypoglycemia, no evidence of meningitis on lumbar puncture and the child was not in a post-ictal state. All patients were determined to be retinopathy-positive based on a dilated ophthalmologic exam. To allow for a meaningful time period for vital signs to fluctuate, only children that died more than 24 hours after admission were included. Patients meeting these criteria were matched to control patients, also with cerebral malaria, who survived. Controls who survived were selected by identifying patients of the same sex who were admitted during the same calendar year as the index case, who were within 6 months of age of the case, and who were admitted with the same BCS. A ratio of 1:1 was used. The time period of interest was the last 24 hours of life in those who died and the same time period (hours after admission) in the matched controls.

Sample size

Based on the existing database of cases that occurred over the course of 24 years (1997–2020), a total of 71 fatal cases met inclusion criteria, an additional 71 survivors were matched to these, as described above. This available sample size would allow the detection of a 10% difference in vital signs between those who died and those who survived with a power of 92.3% and a confidence level of 0.05.

Data collection

A case report template that is currently in use on the PRW was used. Data on baseline demographics (age and sex) and vital signs (blood pressure, heart rate, respiratory rate, oxygen saturation and BCS) were abstracted for 71 cases and the appropriately matched controls. The baseline demographic data and vital signs were transferred to a study specific data collection tool along with the values of vital signs collected for every 2-hour interval over the 24-hour time period.

Data Analysis

All data analysis and visualization were performed in RStudio 2022.12. Due to significant amount of missing data on blood pressure and oxygen saturation, logistic regression was performed only on heart rate, temperature, respiratory rate, and BCS

Missing Data

Last observation carried forward was used to impute missing vital signs. If a vital sign was missing at 24 hours prior to death, the first recorded observation was carried back.

Linear Regression

Linear regression analyses were used to assess the time trend in each vital sign of interest among study participants who survived and died. An interaction term between a binary variable indicating if a person died or survived and time (in hours) was used to determine if the time trend in each vital sign was different between two groups.

Prediction modeling

To assess and quantify which vital signs best help predict death, we constructed classifiers at three different time points (24 hours, 16 hours, and 8 hours prior to death) based on logistic regression models. Model 1 included respiratory rate as a single predictor. Model 2 included respiratory rate and BCS. A comparison of Model 2 to Model 1 helps assess the additional contribution of BCS to the predictive power in addition to respiratory rate. Model 3 included all four vital signs (respiratory rate, BCS, temperature, and heart rate).

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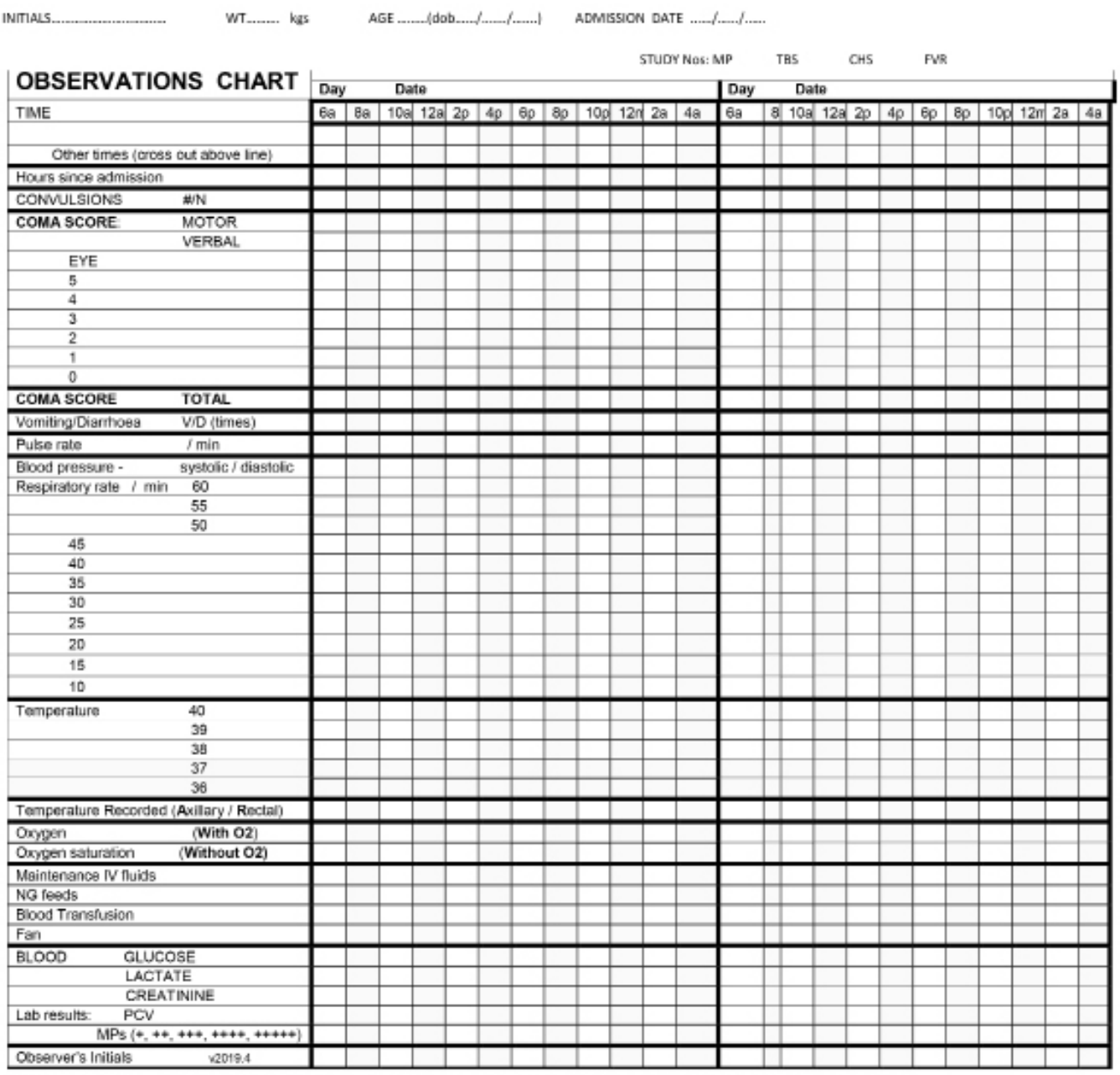

INITIALS..... WT..... kgs AGE .....(dob...../...../.....) ADMISSION DATE ...../...../.....

STUDY Nos: MP TBS CHS FVR

OBSERVATIONS CHART

	Day	Date											Day	Date										
TIME	6a	8a	10a	12a	2p	4p	6p	8p	10p	12n	2a	4a	6a	8	10a	12a	2p	4p	6p	8p	10p	12n	2a	4a
Other times (cross out above line)																								
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CONVULSIONS #/N																								
COMA SCORE: MOTOR																								
VERBAL																								
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MPs (+, ++, +++, ++++, +++++)																								
Observer's Initials v2019.4																								

ion Chart. The current CRF form used in the PRW has been modified to include the trends in respiratory rate and BCS.

Figure 4: Modified Observation Chart. The current CRF form used in the PRW has been modified to include the trends in respiratory rate and BCS

A comparison of Model 3 to Model 2 helps assess the additional contribution of temperature and heart rate to the predictive power in addition to respiratory rate and BCS. Predictive power of the classifier models was assessed using area under the receiver operating characteristic (AUROC). The larger the AUROC, the better the classifier model's performance is in predicting death versus survival. Prediction modeling and visualization of the ROC curves was performed in the R Super Learner package[13].

Ethical consideration

The main study was approved by the institutional review board at the Kamuzu University of Health Sciences (COMREC) in Malawi and at Michigan State University, and this particular sub-analysis was approved by the institutional review board at the Kamuzu University of Health Sciences (COMREC).

Results

Table 1 shows basic demographics of cases and controls compared to the combined population. When fatal CM cases were compared to matched CM survivors, significant differences were observed in the change over time in two parameters, BCS and respiratory rate. Figure 1 provides a visual summary of vital signs within 24 hours of endpoint among the died and survived groups at 4-hour increments.

During the 24-hour time period prior to death, the mean coma score dropped in those who died, and the mean respiratory rate increased. Among the population that died, the estimated change in average respiratory rate per hour approaching death is 0.02 breaths per minute compared to -0.25 breaths per minute among those who survive ($p < 0.001$). Among those who die, the estimated change in average BCS per hour approaching death is -0.01 compared to 0.06 among the survivors ($p < 0.001$). There were no statistically significant difference in change in heart rate or temperature per hour approaching death between those who died and those who survived (Table 2).

Quantifying the predictive power of vital signs

To assess which vital signs help to predict death, we performed logistic regression using three classifier models

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at three time points (24, 16 and 8 hours prior to endpoint). Model 1 included respiratory rate as the only predictor. Model 2 included respiratory rate and BCS. Model 3 included all four vital signs (respiratory rate, BCS, temperature, and heart rate).

Table 3 includes the AUROC corresponding to Models 1, 2 and 3 predicting death versus survival at each time point (24, 16 and 8 hours prior to endpoint).

As shown in Figure 2, the addition of BCS to respiratory rate alone (Model 2 vs Model 1) showed significant predictive improvement at 8 hours to endpoint. The addition of temperature and heart rate (Model 3) had minimal change in predictive ability.

We selected Model 2 as the model of interest due to its high predictive power. As seen in Figure 3, predictive power and being more parsimonious than Model 3. increased with proximity to death, with an AUROC of 0.87 (95% confidence interval: 0.81-0.93) at 8 hours prior to endpoint.

Discussion

This study evaluated the association between vital signs and the likelihood of death in a group of children with RPCM. Changes in these vital signs were evaluated over the 24 hours prior to death. We observed an association between outcome and both respiratory rate and coma score, with children who survived having decreasing respiratory rate and those dying having decreasing BCS. On the other hand, heart rate and temperature showed no correlation with death.

The findings of our study are similar to those of Clifton et al[14], who showed that in patients aged 2 months to 13 years, vital signs predicted death in all children who were admitted to the hospital.This was in all admitted children and malaria was uncommon in their setting . They found that the children who died were more likely to have high respiratory rates at 24-hours prior to death when compared to children who survived. The study also looked at BCS and they found that BCS of less than 5 was associated with inpatient death[14].

Our findings are also generally consistent with a study by Oduro et al that looked at severe P. falciparum malaria in Ghanaian children aged 6 to 59 months[15]. This study revealed that respiratory distress per se was one of the risk factors associated most deaths in children with malaria. The study did not look at respiratory rate but instead considered clinical signs related to respiratory distress[16]. The study showed that a higher proportion of children with cerebral malaria had respiratory distress (70.2%) than children without cerebral malaria (21.3%)[14, 15].

Our findings suggest that an increasing respiratory rate and decreasing BCS are risk factor for death in children with RPCM. This suggests that identifying these changes may be helpful for identifying patients as being at 'high risk' so that that care can be accelerated. We found that a model with both BCS and respiratory rate had better predictive power than a model with solely respiratory rate. The predictive power of the models improved as the endpoint approached with an AUROC of 0.66 if used 24 hours prior to death and a AUROC of 0.87 if used 8 hours prior to death. Other studies have shown that trends in vital signs over time, rather than a single value at a fixed time point, improved the accuracy of predicting the outcome[17].

Given that the trends in respiratory rate and BCS were shown to be the most important in predicting outcome in RPCM, we have modified the current case report form used in the PRW to better visualize the trends in these two variables (Figure 4). The 'danger trend' in respiratory rate is a lack of appropriate change, with children improving experiencing a decrease in respiratory rate. We realize that detecting a lack of change may be more difficult than detecting a change. Therefore, assiduous charting and specific attention to respiratory rate must be taken to notice this concern. By regularly charting these two vital signs, nurses may be able to detect trends and take preventative action more easily.

Strengths and limitations of the study

Our study has significant implications for clinical practice, suggesting frequent monitoring of vital signs by health care workers might lead to early prediction of death in children with RPCM. Because the study was limited to results from a single site and a single disease state other hospital settings and populations must be used to broaden these results. Further, the blood pressure data was not used because so many values were missing.

Conclusion

Trends in BCS and respiratory rate can predict death as early as 24 hours prior to death with predictive power increasing closer to the endpoint. Temperature, and heart rate in the 24 hours prior to death were not correlated with outcome in children with RPCM. This suggests that health care workers should prioritize assessments of respiratory rate and BCS to optimize the ability to predict those children likely to deteriorate clinically. This might aid in early intervention and thus reduce child mortality.

Acknowledgement

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