UTILITY OF THE PEDIATRIC SHOCK INDEX AS A PREDICTOR OF OUTCOMES IN CASES OF DENGUE IN A PEDIATRIC TERTIARY CHILDREN'S HOSPITAL

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ABSTRACT

BACKGROUND: Despite extensive studies on dengue fever, there is still limited knowledge about factors associated with poor outcomes in cases of dengue fever. The shock index (SI) is a bedside tool previously used in the adult population, adopted as a marker for poor outcomes in many shock states. There are limited studies applying the SI in children. There are also no known local studies applying an age-adjusted version as a marker or predictor of poor outcomes in severe acute illness, such as dengue.

OBJECTIVES: To determine the diagnostic ability of the age-adjusted pediatric shock index in predicting outcomes in cases of dengue admitted at a tertiary children's hospital.

METHODS: This is a prospective cohort study performed in a pediatric tertiary hospital over a period of 30 days. Admitting heart rate (HR) and systolic blood pressure (SBP) were taken to determine their shock index. This was then grouped according to age groups based on known literature and corresponding acceptable age-adjusted shock indices (ASI), and compared with outcomes such as final dengue classification (non-severe vs severe), use of inotropes, and mortality.

RESULTS: A total of 90 patients were identified for the study. Three were excluded due to exclusion criteria. 87 cases were followed up after admission from the ER. Unadjusted Shock Index (USI) was found not to be associated with both final dengue classification (as severe dengue) and use of inotropic support. In contrast, ASI was associated with both final dengue classification ($p < 0.001$) and use of inotropes ($p < 0.039$). The ASI had a fairly accurate capability of predicting poor outcomes for both final dengue classifications, with an area under the ROC curve of 0.7122, and eventual use of inotropes, with an area under the ROC curve of 0.6435.

CONCLUSIONS AND RECOMMENDATIONS: SI was found to be a helpful tool in predicting poor outcomes, but only when the Age-adjusted Shock Index (ASI) was used. A longer data collection period is recommended to be able to include mortality as an outcome. The predictive value of the tool can be tested against various other markers of poor outcome to widen the application of this non-invasive measure of hemodynamic status.

KEYWORDS: shock, shock index, dengue shock, dengue, critical care

INTRODUCTION

Since the first reported case of dengue in the Philippines in 1953[1], the disease had been observed in the country's history throughout several epidemics, with the 1998 epidemic being the most notable one, with a case fatality rate of 2 percent[2]. Seventy percent of affected individuals were children below the age of 15 years old[2]. Since then, the disease has been widely studied in terms of its pathogenesis, its transmission, and ultimately its management and prevention. Yet, much remains to be known about the disease, including the factors affecting its clinical manifestations in different individuals, and its varying severity and outcomes. Several studies have explored the relationships between disease's outcomes and patient factors such as the presence of certain signs and symptoms on presentation at a health institution, and certain laboratory results in patients already admitted for the disease[3]. The most severe form of the disease is known as the Dengue Shock Syndrome (DSS), of which the hallmark is the presence of symptoms attributable to plasma leakage and its related effects. In recent years, many studies have revolved around finding sound basis for predicting outcomes in patients who have acquired severe dengue, with some exploring immunological markers and markers of vascular integrity or damage[4]. Although some techniques have shown promise in predicting outcomes of the disease, they are expensive and impractical especially in resource-limited countries. Due to the economic implications of dengue, early predictors of disease outcome should identify those in need of closer monitoring and more aggressive management in the early phases of the disease.

The shock index (SI) is a bedside tool used in several disease entities and is derived from the formula: heart rate/systolic BP. It was originally described by Allgower and Buri in 1967 where they identified the normal range of SI in healthy adults to be between 0.5 and 0.7. Consequently, an elevated SI ($\geq$ 0.9) has been associated with different poor outcomes in different disease entities. Since then, its application has been studied in various settings and clinical conditions, primarily in predicting outcomes in cases of septic and hypovolemic shock, blunt trauma, and traumatic brain injury[5, 6, 7, 8], among others. Most of these showed a direct relationship between a higher SI and a greater risk for more complicated disease or for poorer outcomes. Following these observations, many researchers attempted to correlate the same tool with poor outcomes in the pediatric population, where findings showed similar results.

Given the wide range of normal values of both heart rate and blood pressure in the pediatric population, attempts have been made to adjust the pediatric shock index to different age groups to improve the sensitivity of the tool in identifying cases expected to have poorer outcomes. Most studies based their normal values for the basis for computation of SI on the normal vital signs per age group as suggested by Nelson's Textbook of Pediatrics[17]. Such tools are helpful in many ways, and have huge impacts both medically and economically, making them invaluable in practice. They may be especially helpful in

diseases encountered at health care facilities daily, and diseases with large impact on society such as dengue.

This study attempts to validate a low-cost tool that may improve the management of cases of dengue by identifying individuals who are more at risk for severe illness and poor outcomes, and to decrease mortality and complications by instituting more aggressive measures on patients expected to progress to more severe disease.

When left untreated or unrecognized, certain patients progress from the mild form of the disease to its more severe manifestations, of which one is profound shock. As recommended by the World Health Organization (WHO), the classification of dengue was revised to separate dengue without warning signs from dengue with warning signs, and severe dengue. Under the category of severe dengue are several mechanisms by which the nomenclature "severe" is considered: 1) severe plasma leakage leading to shock or fluid accumulation with respiratory distress, 2) severe bleeding, 3) severe organ involvement[13]. Furthermore, the WHO, in 2012, identified most deaths in dengue were due to shock. To date, no single identifying factor has been found to explain the occurrence of shock in one patient and the absence in another. Several studies have explored and have attempted to identify risk factors associated with poor outcomes in dengue such as demographic factors (i.e., population density, economic status), initial symptoms at presentation at the Emergency Department, age groups, etc. It is due to this that, despite many years of improving diagnostics and available management, the need to determine specific populations at risk for developing the severe manifestations of the disease is still relevant.

Shock is an acute process characterized by the body's inability to deliver adequate oxygen to meet the metabolic demands of vital organs and tissues[17]. Five categories of shock have been determined, depending on their underlying mechanisms and etiologies, of which the most associated with dengue is the hypovolemic type. In most types of shock, there is time for the body to activate compensatory mechanisms to preserve perfusion to the more vital parts of the body. Compensatory mechanisms include increase in heart rate, stroke volume, and vascular smooth muscle tone, all working to maintain perfusion and oxygen delivery to vital tissues. In the presence of these signs therefore, health practitioners can identify shock in its early stages delivering a window for intervention before profound shock sets in.

In 1967, Allgower and Buri first described the shock index as a simple and effective means of gauging the degree of hypovolemia in hemorrhagic and infectious shock states[16]. Since then, there have been numerous other studies exploring the utility of the shock index in predicting poor outcomes in different disease states, such as in septic shock, etc. Following these studies, which suggest that a higher SI relates to poorer outcomes, several researches were published, applying the same concept in the pediatric population. Disease states of interest in these published works included: sepsis and septic shock, traumatic brain

injury and blunt trauma. These reports had varying measurements and markers for poorer outcomes as hypothesized to be associated with an increased SI versus those with normal values for SI.

To our knowledge, no such studies have been published exploring the possible relationship and utility of the SI as a predictor of poor outcome in patients managed for dengue and its severe form – dengue shock.

OBJECTIVES OF THE STUDY

A. General Objective

To determine the diagnostic ability of the age-adjusted pediatric shock index in predicting outcomes in cases of dengue admitted at a tertiary children's hospital.

B. Specific Objectives

1. To determine the shock index of patients admitted from the emergency room with a diagnosis of dengue
2. To determine the association of an elevated pediatric shock index AND:
    a. age of patient
    b. sex of patient
    c. classification of dengue on admission (severe vs non-severe)
    d. use of inotropes
    e. mortality

METHODOLOGY

A prospective cohort was used in the study to determine the association and diagnostic ability of the shock index (both age-adjusted and non – age-adjusted) in predicting outcomes in patients admitted as dengue. Using Epi Info (CDC), and given a confidence interval of 95% and a power of 80% the sample size computed based on a similar study was 86 patients. This was the minimum number of samples required for this study.

All patients admitted from the Emergency Department, initially managed as dengue, whether by clinical diagnosis alone, or by laboratory confirmation were included in the study. Those who tested negative for either Dengue NS1 or dengue IgG/IgMwere excluded from the study upon follow-up. The patients were followed up on admission to the regular wards or to the PICU. Patients found to have other co-morbidities were excluded.

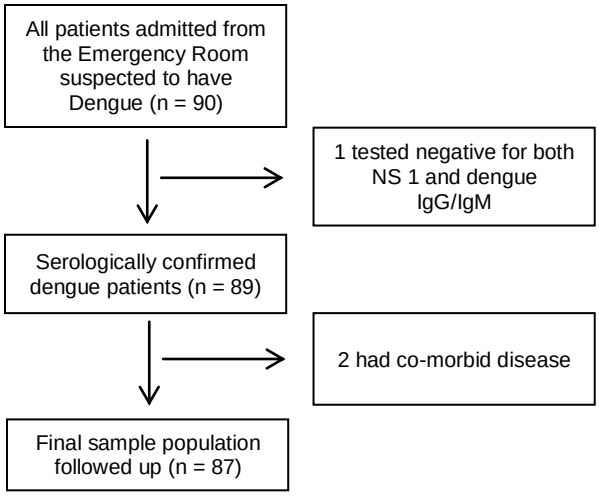

Figure 1. Flow diagram of the process of data collection

Upon approval from the Institutional Review Board, the study proceeded by case identification at the ER level. Patients admitted as dengue based on clinical signs, with or without serologic confirmation were included in the initial data gathering. Patients eventually serologically confirmed as not having dengue were dropped from the study. Data such as age and SI values were collected, and their course of management was followed until they were either discharged or had expired. Pertinent data pertaining to the outcome of management were collected, including dengue classification on admission, use of inotropes, final dengue classification and mortality.

For demographic data and general information of the samples, the admission sheet was used as the primary source. For uniformity, and to minimize bias, vital signs upon admission to the ER were taken solely from the ER form.

Data was analyzed using the STATA SE 14.2 software and processed from a table of collected data. Data were summarized as means and standard deviations for quantitative variables, and as frequencies and proportions for qualitative variable. Associations between variables were carried out first as a whole, without discrimination for age and corresponding normal SI values, then per age group. ROC analysis was conducted to determine the diagnostic ability and utility of the shock index in predicting poor outcomes among patients in the study. The sensitivity, specificity, PPV, NPV and accuracy to predict poor outcomes were determined and plotted in graph. Multiple regression analysis was used to determine the factors associated with poor outcomes.

Ethical considerations included issues regarding patient confidentiality as their patient records, specifically charts were the main source of data for the study. The study did not involve any additional intervention to the management of cases included in the study, nor did it involve withdrawal of any such intervention. Upon identification of cases included in the study, representatives of the patient (e.g., parent or legal guardian) were asked to give consent. A research assistant extracted information from patients' records from admission to discharge.

RESULTS

Two steps were employed to establish the association and diagnostic ability of the shock index as a tool in predicting outcomes in dengue. The statistical analyses were run involving first the unadjusted shock index (USI) used for the general population followed by analyses involving the age-adjusted shock index (ASI). The first involved determining the association of an elevated shock index and study outcomes, namely, final dengue classification and use of inotropes during admission. The second involved determining the diagnostic ability of the shock index as a tool for predicting the same outcomes. Mortality from dengue was originally a desired outcome for testing, however during the duration of the data collection for the study, only one patient expired, nullifying any statistical test involving this particular outcome.

A total of 90 patients were originally included in the study. Three patients were excluded from the final list of patients as they were sero-negative for dengue infection or were diagnosed to have co-morbids (Table 1). The remaining patients were followed up over 30days. The average age of subjects was 8 years old, with majority from the 4-11 y/o age group. There was an almost equal distribution between males and females. The average admitting heart rate (HR) was recorded at 112 bpm with a mean systolic BP (SBP) of 90mmHg. The average shock index was computed at 1.2. A total of 73 patients (83.91%) had an elevated shock index upon admission, based on the USI. However, when compared against the different shock indices acceptable for every age group, 53 patients (60.92%) had normal values while only 34 (39.08%) had elevated values. Fifty-nine patients (67.82%) were classified as non-severe upon discharge. Sixteen patients (18.39%) among those classified as severe utilized inotropes at some point during their admission. Only one patient (1.15%) died for the duration of the data collection.

Table 1. Demographic and clinical characteristics

Variables	**Value**
Age, years (mean, SD)	8.56 (4.02)
Age group (n, %)	
Less than 1 year	2 (2.30)
1 to 3 years	9 (10.34)
4 to 11 years	57 (65.52)
More than 12 years	19 (21.84)
Sex (n, %)	
Female	43 (49.43)
Male	44 (50.57)
Admitting heart rate, bpm (mean, SD)	111.68 (19.31)
Admittingsystolic blood pressure, mmHg (mean, SD)	92.18 (13.76)
Shock index (mean, SD)	1.20 (0.29)
Shock index classification (n, %)	53 (60.92)
Within normal range	34 (39.08)
Elevated	
Final classification (n, %)	
Non-severe	59 (67.82)
Severe	28 (32.18)
Use of inotropes (n, %)	
No	71 (81.61)
Yes	16 (18.39)
Mortality (n, %)	
No	86 (98.85)
Yes	1 (1.15)

One patient was excluded due to a negative dengue NS1 and dengue.

IgG/IgM; another 2 were excluded due to co-morbidities.

The mean shock index by age group and by sex are shown in table 2.

Table 2. Mean shock index by age group and sex

Variables	Mean shock index (mean, SD)
Age group	
Less than 1 year	1.54 (0.06)
1 to 3 years	1.39 (0.20)
4 to 11 years	1.16 (0.29)
More than 12 years	1.19 (0.30)
Sex	
Female	1.23 (0.29)
Male	1.170.30)

Both final dengue classification and use of inotropes were found not to be significantly associated with an elevated shock index when USI was used for reference (Table 3).

Table 3. Association of elevated Unadjusted Shock Index (USI) with outcomes

Outcomes of interest	Odds ratio (95% CI)	p-value
Outcome 1: Final dengue classification	7.63 (0.94 to 61.61)	0.057
Outcome 2: Use of inotropes	3.36 (0.41 to 27.78)	0.260

However, when the ASI was used, shock index was associated with both final classification of severe dengue ($p < 0.001$) and use of inotropes (p 0.039) (Table 4).

Table 4. Association of elevated Age-Adjusted Shock Index (ASI) with outcomes

Outcomes of interest	Odds ratio (95% CI)	p-value
Outcome 1: Final dengue classification	6.19 (2.31 to 16.60)	<0.001
Outcome 2: Use of inotropes	3.26 (1.06 to 10.06)	0.039

The odds of having severe dengue is 6.19 times higher (95% CI 2.31 to 16.60) among those with elevated ASI compared to those with normal ASI, while the odds of using inotropes during treatment is 3.26 times higher (95% CI 1.06 to 10.06) among those with elevated ASI compared to those with normal ASI.

The diagnostic ability of the shock index to predict outcomes was computed via the roctab command in STATA SE v 14. via Receiver Operating Characteristic (ROC) analysis. The USI was found to be a sensitive (96.43%) tool in determining patients who proceeded to be classified as having non-severe dengue after having been admitted as the same. The tool was however found to be poorly specific (22.03%), with only 45.98% of patients correctly classified as having severe dengue as a final diagnosis. Furthermore, with an area under the ROC

curve of 0.5923 (95% CI 0.5285 to 0.6561), the non-adjusted SI (USI) was an imprecise predictor of outcomes for final dengue classification (Figure 1).

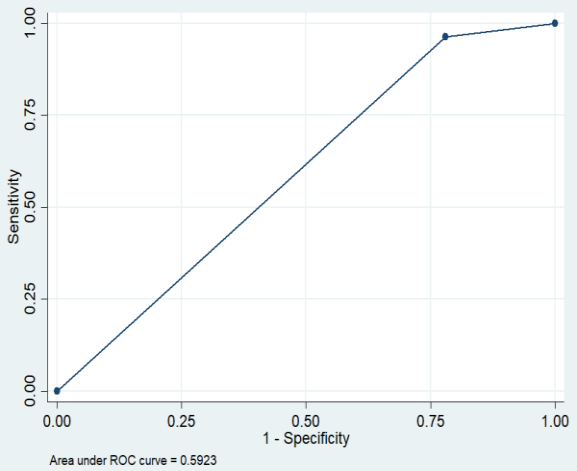

Figure 1. ROC Curve Graph for USI and final dengue classification

Similarly, in testing the tool as a predictor for the use of inotropes, the USI was found to be sensitive (93.75%). However, the tool was found to be poorly specific (18.31%), with only 32.18% of patients correctly predicted to have used inotropes during admission. With an area under the ROC curve of 0.5603 (95% CI 0.4841 to 0.6365), the non-adjusted SI (USI) was determined to be an imprecise predictor of outcomes for the use of inotropic support at any point within the duration of admission (Figure 2).

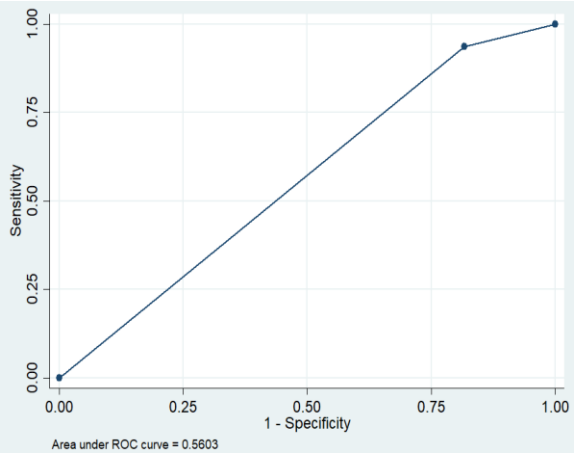

Figure 2. ROC Curve Graph for USI and use of inotropes

Pediatric Age-Adjusted Shock Index and Outcomes

On the other hand, ASI was found to be a more specific (74.58%) rather than a sensitive (67.86%) tool in predicting the final classification of patients, regardless of classification upon admission. The tool was also found to have a higher Negative Predictive Value (83.02%) than a Positive Predictive value (55.88%). Overall, the area under the ROC curve was 0.7122 (95% CI 0.6078 to 0.8166), demonstrating a much higher capability of accurately predicting those who will progress to severe dengue (Figure 3).

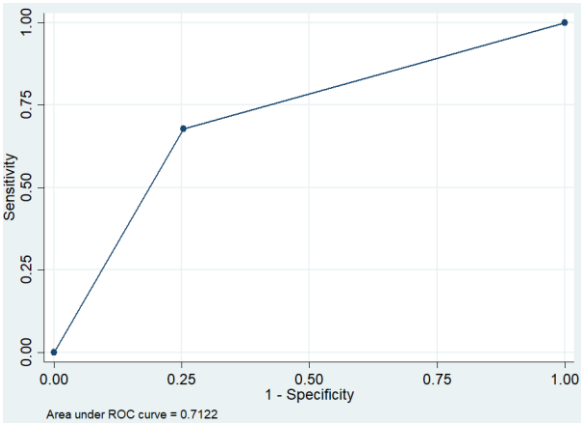

Figure 3. ROC Curve Graph for ASI and final dengue classification

In terms of the tool's ability to predict use of inotropes in patients, the ASI was found to be as equally specific (66.20%) as sensitive (62.5%). Its Negative Predictive Value (88.68%) is much higher than its Positive Predictive Value (29.41%). Overall, the area under the ROC curve showed was 0.6435 (95% CI 0.5090 to 0.7779), demonstrating a modest degree of accuracy in predicting who among those admitted will proceed to use inotropic support during their admission (Figure 4).

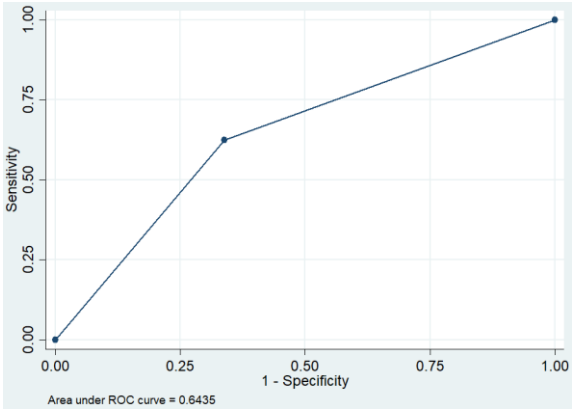

Figure 4. ROC Curve Graph for ASI and use of inotropes

DISCUSSION

The body's natural compensatory mechanism in states of shock includes an elevation in either stroke volume or cardiac rate to maintain a desired cardiac output (CO = SV x HR). Thus, a shock index that represents a widening of the difference between the heart rate and the systolic BP reflects a patient who is deteriorating in terms of a falling blood pressure, or one who is heavily compensating in terms of a rising heart rate. However, when applied to the pediatric population, defining a single SI value is challenging given the changes in vital signs as the child advances in age. This difference can be illustrated by comparing an adult with a baseline HR of 75 bpm and baseline systolic BP of 110, with a resulting SI of 0.68. If in trying to compensate during a shock state, the HR increases to 110, the resulting SI increases to 1, a value above the acceptable range of 0.5 – 0.7, and above the value identified in previous studies to be associated with worse outcomes. In contrast, if an infant whose baseline HR is at 130 bpm, assuming a heart rate increase like that of the adult example to 165 bpm (35 beats increase), with a systolic BP of 80, the SI changes from 1.6 to 2.0, which is a much higher value than that acceptable for the general population. This change of SI justifies the need for a pediatric age-adjusted SI.

Our results show a significant difference between the USI and ASI in the degree of association and accuracy of the tool in determining those who were classified as severe dengue as a final diagnosis, regardless of admitting classification. Using

the USI, neither the final dengue classification nor the use of inotropes was found to have been associated with the admitting SI. However, when adjusted for specific age-adjusted vital signs and SI (ASI), both the final dengue classification and the use of inotropes were found to be associated. This demonstrates the importance of taking into consideration the age group of the patient in drawing associations with the predetermined outcomes. Using the ASI, patients who ended up being assigned a final classification of "severe dengue" were 6.19 times more likely to have had an elevated SI upon admission versus those who had a normal SI. Similarly, those who ended up with inotropic support were around 3.26 times more likely to have had an elevated ASI upon admission.

To explore the predictive capability of the SI in terms of outcomes, anROC analysis was done, which revealed results similar to the above findings. USI was found to be poorly predictive of the patients' final dengue classification as well as eventual use of inotropes within the admission. However, when age-adjusted vital signs were considered, the tool had a fairly accurate prognostic capability in identifying both those who would progress to severe dengue, and those who would need inotropes.

Dengue is a very dynamic disease with its severe form characterized by many clinical features such as severe plasma leakage, severe bleeding, and evidence of severe organ involvement [13]. Consequently, severe dengue is not always accompanied by the expected compensatory mechanism of tachycardia. For example, in cases of compensated shock, defined as a narrow pulse pressure, there may or may not be accompanying tachycardia, which may result in relatively low SI values. Similarly, other characteristics of severe dengue may or may not be accompanied by an expected rise in heart rate, such as those diagnosed as dengue myocarditis, and other forms of severe dengue characterized by end organ damage (elevated liver transaminases, encephalopathy, etc.). Despite the differences in the clinical presentation of dengue severe, the shock index, specifically the ASI, may prove to be useful in identifying those patients who may need closer attention upon admission, as they are at more risk of developing into severe dengue. Furthermore, of those who were originally admitted as severe dengue or those admitted as dengue with warning signs but eventually progressed into severe dengue, the age-adjusted SI was helpful in predicting those who might need inotropes at one point in their admission.

The management of shock, regardless of etiology, is generally guided by the improvement of physiologic, hemodynamic and laboratory variables observable in patients. For example, in septic shock, an improvement in the heart rate, meaning a normalization of the heart rate signifies an immediate improvement of the current shock state. Similarly, an improvement of the blood pressure after a fluid bolus in a patient initially presenting with hypotension is as well a sign of immediate stabilization of the patient's state of shock. However, from practice, and based on various studies, not all patients who are stabilized shortly

after admission proceed to recover despite the normalization of their hemodynamic variables. Likewise, not all those who are successfully resuscitated at the ER present with favourable outcomes during their course of admission. A tool, therefore, that identifies those at most risk of developing a complicated course, and at the same time is non-invasive and cost-efficient is valuable in the management of shock at the ER level. The shock index, specifically when age-adjusted, as demonstrated above, appears to be one such tool.

This non-invasive bedside tool can guide clinicians in identifying those in most need of closer monitoring. Especially in resource-limited healthcare institutions, this tool may correctly identify those at-risk patients and may be useful in properly allocating both physical resources and human resources available, by recognizing patients who need to be prioritized in terms of admission to the intensive care unit. This may be especially helpful in times of surge of dengue cases during peak months. This study suggests further that an age-adjusted shock index may pinpoint patients in more need of closer monitoring more accurately than when based solely on other parameters of shock such as an increased heart rate or decreased blood pressure alone.

Limitations of the Study

A limitation of the study includes the differences in the measurement of a patient's vital signs upon entry at the ER, where a variety of modalities and equipment were used in the monitoring of vital signs. Equipment and resources at the Emergency Room provide for only manual measurement of vital signs, taken by the triage officer upon admission. Vital signs manually measured were the heart rate and blood pressure, using age-appropriate cuffs, completely dependent on the operator.

Another limitation of the study is the number of patients included in the study. The collected data within the data collection period only covered one mortality from dengue, rendering statistical analyses involving this parameter void. To better test for this outcome, a longer data collection period may be helpful.

CONCLUSION AND RECOMMENDATIONS

The pediatric age-adjusted shock was demonstrated in this study to be a useful marker and predictive tool in identifying children at risk of developing severe dengue and further needing inotropic support during their admission. This measure is an easily obtainable bedside tool that may help physicians and healthcare facilities allot their limited resources better upon admission and point of care at the Emergency Rooms. It may be a helpful addition to the vital signs monitoring in terms of being a marker for the physiologic status of patients of both the severe and non-severe types.

Further recommendations to improve the study include a longer duration for data collection, to allow for a more varied range of outcomes, especially in terms of mortalities. Other markers for poor outcomes may also be explored, as used in

many different studies, such as use of blood transfusion, use of hemodialysis, and total length of stay in the hospital. The tool may also be compared to other objective laboratory markers of severe dengue such as degree of metabolic acidosis on admission, or degree of end-organ damage observable for both renal and hepatic functions, among many available laboratory markers.

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