Int. j. adv. multidisc. res. stud. 2026; 6(6):520-535

Received: 23-09-2026
Accepted: 03-11-2026

International Journal of Advanced Multidisciplinary Research and Studies

ISSN: 2583-049X

The Presenting Symptoms, Clinical Diagnosis and Shock Index Value of Children with Sepsis at the University College Hospital Ibadan: A Cross Sectional Study

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Abstract

Background: Sepsis is a global health concern accounting for a mortality rate of 25-30% with about 50-85% due to septic shock. The majority of sepsis cases (up to 85%) occur in Low and Middle- income countries. There were 48.9 million cases of sepsis worldwide, with children accounting for more than half of those cases. Nigeria is the second highest contributor to under-five mortality in the world, with majority of these deaths attributed to sepsis. The aim of this study is to determine the common presenting symptoms, clinical diagnosis and shock index value of children with sepsis at a tertiary Hospital.

Material and Method: This cross sectional study enrolled 102 children with sepsis. Their bio-demographic details were collected using a structured interviewer administered questionnaire. Their presenting symptoms and pathologic diagnosis weres gotten, also the shock index values were calculated using the properly measured blood pressure and heart rate. The data was analysed using spss version 23.0 for windows. P < or = 0.05 set as point of statistical significance.

Results: The study showed that, 68(66.7%) were males and 34(33.3%) were females. While 26(25.5%) were under one year, 39(38.2%) aged 1-5 years, 12(11.8) were 5-10 years and 25(24.5%) were 10-15 years. All the participants had symptom of fever. While breathlessness was the second commonest symptom. The commonest clinical diagnosis among the study participants was pneumonia. The shock index value of the study population ranged from 0.7 to 5.50 with median of 1.6(IQR 1.3- 1.9) the logistic regression showed that children with elevated shock index were 10.9 times more likely to develop septic shock when compared to those with normal shock index.(p=0.034, aOR = 10.899, CI = 1.20 – 98.79.

Conclusion: The higher the shock index, the more likely for the child to develop septic shock and its sequelae.

Keywords: Presenting Symptoms, Clinical Diagnosis, Shock Index, Children, Sepsis, Septic Shock

Introduction

Sepsis comprises a spectrum of physiologic, pathologic and biochemical disorders induced by infections by microorganisms (bacteria, viruses, fungi, parasites), as well as the toxins of these pathogens [1]. It is a life-threatening organ dysfunction from dysregulated host response to infection [2]. Septic shock exists in a subset of patients with sepsis who have circulatory dysfunction [2, 3]. Sepsis and septic shock are leading causes of morbidity, mortality, and healthcare utilisation worldwide [4-7]. Globally, sepsis affects 1.2 million children annually [8]. It constitutes a huge burden in the paediatric population, killing one in five children [9]. Majority of these deaths (about 80%) occur in developing countries, especially in Africa [10–14]. Early detection, prompt resuscitation and management are therefore critical in children with sepsis. Sepsis represents a global public health problem. There has been extensive research and provision of guidelines and strategies for improved sepsis management in well-resourced healthcare settings [30, 39]. There is however, paucity of published research on sepsis management especially for resource-limited health systems [30]. Lapses in care may occur, particularly if severity of sepsis is not assessed for [109]. Hence

the need to evaluate shock index values which are markers that enhance sepsis management.

The word "Sepsis" was derived from the Greek word 'sepo' which means 'I rot' and was first documented over 2700 years ago [46]. In the 1800s, the 'Germ theory' of disease was formulated and there was an acknowledgement that sepsis resulted from harmful microorganisms [47]. Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection [40]. So, sepsis is differentiated from uncomplicated infection by the presence of life-threatening organ dysfunction [52].

In 1992, the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) published the diagnostic criteria and definition of Systemic Inflammatory Response Syndrome (SIRS), sepsis, severe sepsis, septic shock and organ dysfunction. Following improvement in knowledge of clinical, epidemiological and therapeutic aspects of sepsis, limitations of the SIRS definitions were noted. The SIRS criteria appeared insufficiently precise in clinical practice [28]. Parameters such as tachypnoea and tachycardia were noted to be possible adaptive mechanisms in febrile children and not necessarily mean organ dysfunction [52]. Furthermore, using the criteria for the definition of sepsis leads to the excessive inclusion of patients with uncomplicated infection or inflammation and hence low specificity [30]. Despite these, the SIRS definition is currently still widely used for sepsis definition in Africa [30].

The sepsis definition was standardised in 2005 by the International Paediatric Sepsis Consensus Conference (IPSCC) to suit the paediatric age group [53]. According to IPSCC, sepsis is defined by the presence of two or more signs of SIRS, one of which should be abnormal temperature or leukocyte counts, with confirmed or suspected infection. Severe sepsis in children is the presence of sepsis and cardiovascular or respiratory dysfunction, or two or more organ dysfunctions (neurological, hepatic, hematologic, and renal). Septic shock is defined as sepsis and cardiovascular dysfunction. Cardiovascular dysfunction is defined by the presence of hypotension or the need for a vasoactive drug to maintain systolic arterial pressure in the normal range or at least two of the hypoperfusion criteria: Unexplained metabolic acidosis, hyperlactatemia i.e. lactate >2times the reference value, oliguria, prolonged capillary refill and core to peripheral temperature gap $>3^0$C despite administration of isotonic intravenous fluid bolus in 1hour [53].

Organ dysfunction is defined as a change of two points in the Sequential Organ Failure Assessment (SOFA) or quick Sequential Organ Failure Assessment score (qSOFA). To operationalise the definition at the bedside, ≥ 2 sepsis-related organ dysfunction assessment points identify sepsis [40]. Though the sepsis-3 task force excluded the paediatric population from the development of this definition, it is said to be applicable in all age groups [52, 32]. The sepsis-3 definition has been found to perform well in children [51, 53, 54]. For its use in children, SOFA has been adjusted and validated for the different paediatric age groups using various physiologically based scores such as quick Sequential Organ Failure Assessment (qSOFA), quick Paediatric Logistic Organ Dysfunction-2 (qPELOD-2), Paediatric Sequential Organ Failure Assessment score (pSOFA) and Liverpool quick Sequential Organ Failure Assessment (LqSOFA) [4, 52, 54-56] LqSOFA is based on heart rate and capillary refill time as haemodynamic parameters, whereas qSOFA and qPELOD-2 both require BP measurement [55]. Since heart rate and capillary refill time are easy to assess in children, LqSOFA is more easily implemented than scores that need blood pressure measurement [55]. To demonstrate the performance of LqSOFA score, it showed equal sensitivity (0.6) and specificity (0.988) for predicting sepsis-related mortality when compared with an age-adjusted qSOFA [56]. Furthermore, LqSOFA criteria had a low sensitivity of 0.392 but high specificity of 0.992 for the prediction of critical care admission within 48 hours in children with sepsis [56]. In addition, LqSOFA has undergone external validation for use in resource-constrained LMICs where its performance was found to be encouraging and comparable to that in its original derivation setting [57-65].

Septic shock is a subset of sepsis in which underlying circulatory, cellular and metabolic abnormalities are associated with a greater risk of mortality than sepsis alone. It is sepsis in addition to shock that requires the use of a vasopressor to maintain arterial pressure at 65mmHg or greater, and serum lactate greater than 2mmol/L, despite adequate fluid volume resuscitation [40]. The sepsis-3 task force recognised that in settings in which lactate measurement is not available, the use of a working diagnosis of septic shock using hypotension and other criteria consistent with tissue hypoperfusion may be necessary [40].

Shock index (SI) is defined as the ratio of heart rate and systolic blood pressure (SBP) [1, 22]. It is a marker of vascular or myocardial dysfunction and hence an indicator of tissue perfusion [23]. It is an inexpensive tool that helps clinicians remain vigilant in the emergency room or paediatric intensive care unit, acting as a 'red flag' for sepsis [1, 24]. Being an indicator of tissue hypoperfusion, SI has been found to correlate positively with other indices of end-organ perfusion such as central venous oxygen saturation [23, 25]. A normal SI has been proposed to be a strong predictor of the absence of increased lactate levels [26]. The utility of SI in clinical care has not been well explored in children in low-middle-income country (LMIC) settings. The cut-off values of SI that predict septic shock in paediatric patients with sepsis are unclear and has remained a grey area [16, 27].

Furthermore, male preponderance in the occurrence of sepsis in children has been noticed [8, 13, 54, 64]. Some clinical and experimental studies have demonstrated gender differences concerning sepsis [65, 66]. Male gender has been found as a risk factor for the development and progression of infection [65]. The reasons have been attributed to genetic, hormonal, and immune responses [65, 66]. According to Angele *et al* [65], females have natural advantages for sepsis compared to males because male sex hormones are suppressive on cell-mediated immune responses. These gender-specific effects on different immune cell functions are influenced by an X-chromosome mosaicism that exists naturally in females. Based on genetics, heterozygous cellular mosaicism presents a unique biological circumstance in females because either the maternal or the paternal X-chromosomes are inactivated in each cell whereas males carry exclusively the maternal X-chromosome [66]. Experimental studies revealed that the X-chromosome bears some rare genes of immunity and the female chromosome mosaicism diversifies leukocyte responses during endotoxemia and may contribute to the dimorphic character of the inflammatory response [65, 66].

The common symptoms associated more with sepsis in children includes, fever, cough, fast breathing, weakness, passage of loose stool and vomiting [8]. With regards to the primary sites of infection in children with sepsis, the respiratory system was the commonest followed by the bloodstream in many studies [8, 54, 79]. This may be due to a high rate of colonisation of respiratory pathogens in children which can invade and cause sepsis in the face of depressed cell-mediated immunity in these patients [80].

Clinical components of shock index

Heart Rate: Heart rate is the number of contractions of the heart per minute. It is usually a close approximation of the pulse rate. It varies with the body's physiology. Activities that would cause an increased need for oxygen such as exercise, illness, stress, and anxiety tend to increase the heart rate. The normal heart rate for different ages in Paediatrics is shown in Table 1.

Table 1: Normal Heart Rates per Minute for Age in beats per minute [1, 125]

Age	Awake rate	Sleeping Rate
Neonate(<28days)	100-205	90-160
Infant(1month-1year)	100-190	90-160
Toddler (1-2yrs)	98-140	80-120
Preschool (3-5yrs)	80-120	65-100
School-age(6-11yrs)	75-118	58-90
Adolescent (12-15yrs)	60-100	50-90

Blood pressure: Blood pressure is defined as the lateral pressure applied by the column of blood on arterial walls [1, 126]. It varies with the systole and diastole of the heart. Systolic pressure is the peak pressure produced during cardiac output. Diastolic blood pressure is the peak pressure recorded during diastole. Blood pressure can be measured either by direct or indirect methods [1]. Direct method involves connecting an intravascular access to a pressure transducer or a mercury manometer. Indirect blood pressure measurement is by use of the sphygmomanometer by any of the following methods: Auscultatory, palpatory, flush, oscillometry, or Doppler method [1]. The normal blood pressure values for children of different age ranges are shown in Table 2.

Table 2: Normal Blood pressure in Children by Age (measured in mmhg) [1, 125]

Age	Systolic Pressure	Diastolic pressure	Systolic hypotension
Birth (12h, <1000g)	39-59	16-36	<40-50
Birth (12h, 3kg)	60-76	31-45	<50
Neonate (96h)	67-84	35-53	<60
Infant (1-12mo)	72-104	37-56	<70
Toddler (1-2yrs)	86-106	42-63	<70+(age in years x2)
Pre-schooler (3-5yrs)	89-112	46-72	<70+(age in years x2)
School-age (6-9yrs)	97-115	57-76	<70+(age in years x2)
Preadolescent (10-11yrs)	102-120	61-80	<90
Adolescent (12-15yrs)	110-131	64-83	<90

Shock index was first introduced in the1960s by Allgower and Buri who found that the normal value in a healthy adult ranged from 0.5 to 0.7 [24]. The SI is a quick and useful indicator that can alert clinicians of potential underlying problems related to sepsis that might be overlooked if vital signs such as HR and SBP were reviewed in isolation. The calculation of this index does not involve additional measurements beyond routine vital signs and it provides a unified measurement that potentially gives a more complete and integrated assessment of the patient's hemodynamic and clinical status.

Numerous studies on SI has been done in different countries like: In America by Tseng *et al* [44], Rappaport *et al* [127] Baez *et al* [128] and Kever *et al* [129-131]; Also in Austrail studies on SI has been done by Mitra *et al* [133] and Olaussen *et al* [132]; in France by Rousseaux *et al* [23]; in London by Samiran *et al* [22]; in United Kingdom by Sankaran *et al* [135], in Japan by Sato *et al* [136]; in India by Vandewalle *et al* [138], Gupta *et al* [137] and Rajendran *et al* [1], in Iran by Jorabi *et al* [139]; in Taiwan by Chen *et al* [140]; in Germany by Reinstadlar *et al* [141]; in Turkey by Celikkan *et al* and Yildirim *et al*; in Malasia by Yussof *et al* [142]; in South Africa by Brumns *et al* [143] and in Nigeria by Onah *et al* [144], Nwafor *et al* [145] and Kahyaoglu *et al* [146]. All these research works on SI were conducted extensively on Adult Medicine patients and Obstetrics Patient and very few were done in Paediatrics age group [1, 22, 137, 138]. It is therefore crucial to carry out further investigations to establish the utility of SI in Paediatrics medicine.

Shock index is the ratio of HR and SBP. Shock index could be a marker to identify patients that would require more aggressive resuscitation and a higher level of care [27]. In adults, SI >0.9 is significantly associated with tissue hypoxia [123]. Shock index in children is in ranges due to the confounding effect of the wide range of normal vital signs in various age groups thus creating a wide range of shock index in children [1, 27]. A high SI in children with sepsis is associated with an increased risk for mortality, hence the need for more aggressive resuscitation in such children [27]. Shock index is a better parameter than HR or SBP alone for evaluating hemodynamic status in paediatrics [67, 124]. Although heart rate and blood pressure ranges differ amongst paediatric age groups, the SI offers a single upper limit normal value for children aged 1 to <12 years making it easy to apply. The normal ranges of shock index in children of different ages are shown in Table 3.

The Systemic Inflammatory Response Syndrome (SIRS) criteria has been criticised for their shortfall in identifying hyperlactatemia and this has been replaced by shock index (SI) [26].

Table 3: Normal Ranges of Shock Index in Children Stratified according to Age [27]

Age	SI
<1year	0.8-2.3
1-3years	0.7-1.2
4-11years	0.5-1.2
≥12years	0.4-0.8

Methodology

Study Design: The study was a hospital-based, cross-sectional study.

Study Area: The study was carried out at the Otunba Tunwase Children's Emergency Ward (OTCHEW) of the Department of Paediatrics, at a Tertiary Teaching Hospital. The tertiary institution located in the central part of the town and serves as a referral facility for many states in the region. The Paediatric wards of the hospital includes an 18-bed Children's Emergency Ward, a 4-bed Paediatric Intensive

Care Unit, a 16-bed infant ward, two 28-bed and one 32-bed wards that admit children between 1 month and 15 years as well as two neonatology wards, both with a total of 36 beds. The Children's Emergency Ward is the entry point for children with life threatening infections and therefore served as the study area. It has a reception area, a 3-bed resuscitation bay, a 4-bed high dependency unit, a 4-bed isolation cubicle, a 7-bed open ward, a diagnostic/treatment unit, and a side laboratory. On average, about three to five children are admitted to the Children's Emergency Ward each day, with a monthly total of approximately 100 to 150 patients. The Children's Emergency ward operates a 24-hour, seven-day-a-week service. It is staffed with healthcare workers which include two Consultants, a Senior registrar, four to six Junior registrars who run 3-daily shift duties, four to eight house officers (internship doctors), nurses and healthcare assistants. Patients are received at the reception area by a triage nurse who promptly notifies the resident doctors on shift duty after a quick assessment.

Study Duration: The study was carried out between May 2022 and December, 2022.

Study Population: Children aged 1 month to 15 years admitted into the children's emergency ward with sepsis, defined as per the Sepsis-3 consensus [40] definition i.e., children with suspected infection and life-threatening organ dysfunction (at least a score of 2 in Sepsis-3 derived quick SOFA criteria validated score for the paediatric population) [56]. Those with sepsis who had additional requirements for vasoactive medications were deemed to have septic shock.

Inclusion criteria

- Children aged 1 month to 15 years.
- All children who met the Sepsis-3 criteria [40] for sepsis.
- Caregiver's consent, and assent for children aged 7 years and above.

Exclusion criteria

- Children on medications affecting heart rate such as propranolol, salbutamol.
- Children with non-infectious causes of fever such as thyrotoxicosis, malignant hyperthermia, dehydration, illicit drug users.

Sample size determination

Computation of the sample size was determined using the formula for a cross-sectional correlational study.

$$n = ([Z_\alpha + Z_\beta]/C)^2 + 3$$

Where n = minimum sample size [149]

$$C = 0.5 \times \ln([1 + r]/[1 - r])$$

α (two-tailed test) = 0.05 (type 1 error rate; probability for rejecting the null hypothesis when it is true)
β = 0.2 (type II error rate: Probability of failing to reject the null hypothesis when it is false)
1- β= power = 80%
Z_α = Standard normal deviate corresponding to type 1 error (α) at 5%= 1.96
Z_β = Standard normal deviate corresponding to a probability of type II error (β) and power of 80%= 0.842
r = expected correlation coefficient = 0.29 [Assumption: Null hypothesis = 0 thus correlation coefficient of 0.29 is considerable]
C = confidence interval

$$N = [(1.96+0.842) / \{0.298\}]^2 + 3$$

N= 91.4 which is approximately 92
Adjusting for a non-response rate of 10%, the sample size:
Let X be the adjusted sample size:

$$X - (10X/100) = 92$$

$$X - X/10 = 92$$

$$10X - X = 920$$

$$9X = 920$$

$$X = 920/9$$

$$X = 102$$

Therefore, the minimum sample size was 102. This represents the minimum number of children with sepsis that was recruited for this study.

Pretesting of clinical measurements for inter-rater reliability

Prior to the commencement of the study, a pretest was carried out on 10 patients with sepsis at the Otunba Tunwase Children's Emergency Ward of the study centers. This was done to assess the reliability of the clinical measurements and face validation from the supervising Consultant. This pretest was done by the researcher and the supervising Consultant for shock index measurement. The heart rate was counted manually for a full minute while the patient was calm by auscultating with a 3M™ Littmann® Classic II Paediatric Stethoscope on the apical area of the precordium. The average of two separate readings done 2 minutes apart was used for intra-observer reliability. Blood pressure was measured using the non-invasive method. This was with the OMRON M2® basic automatic upper arm blood pressure monitor (HEM-7120-E) using appropriate cuffs for age with the right arm at the same level as the heart. A cuff covering at least 80% of the length of the arm and the inflatable bladder width covering about 40% of the circumference of the upper arm midway between the olecranon and the acromion was considered appropriate. The machine was checked and calibrated by a hospital Biomedical Engineer prior to the commencement of the study and monthly during the study. This was to ensure that the readings were accurate and reliable. The average of two systolic and diastolic blood pressure values done 2 minutes apart was used to limit inter-reading variability. The supervising Consultant also performed the same measurements on the same patients with the same stethoscope and OMRON M2® blood pressure monitor to ascertain the level of concordance. SI was the ratio of HR and SBP. The study proceeded after an excellent Intraclass Correlation Coefficient between the researcher's values and those obtained by the supervising consultant (r = 0.998, p=0.0001). Table 4 illustrates this.

Table 4: Intraclass Correlation Coefficient for Interrater reliability

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single measures	0.997[a]	0.987	0.999	679.133	9	9	0.000
Average measures	0.998[c]	0.993	1.000	679.133	9	9	0.000

df1: Numerator degrees of freedom, df2: Denominator degrees of freedom, sig: Level of significance

Sampling technique: Consecutive patients presenting to the Children's Emergency Ward who met the inclusion criteria were enrolled until the calculated sample size was reached. Unique identification numbers were given to each subject recruited for easy identification and to avoid double enrolment.

Data Collection Methods and Measurements

The researcher was posted to the Children's Emergency Ward during the period of data collection for the research. A notice of the inclusion criteria was put up in the Children's Emergency Ward and the researcher was contacted by fellow resident doctors in the Children's Emergency Ward when eligible patients presented while the researcher was off-duty. In those cases, the researcher promptly got to the ward and enrolled the patients. The researcher was resident on University College Hospital Campus and so could arrive the Children's Emergency Ward at short notice. Resident doctors in the emergency room were equally trained on the study protocol and assisted the researcher in obtaining consents/assents and filling in details in the proforma. They also assisted in the measurements of anthropometry, temperature and oxygen saturations. The clinical examination measurements for shock index was however solely done by the researcher. Once eligibility was confirmed, consent was obtained then a rest period of 5 minutes before the shock index measurements were promptly obtained to minimise the impact of resuscitation and other therapeutic strategies on these values and to avoid delaying the start of medical treatment. The other examination measurements were completed within one hour of patients' arrival to the Emergency room and the time of enrolment was recorded. This time frame was chosen because it is within the 3-hour time frame recommended in the Surviving Sepsis Campaign (SSC) care bundle for sepsis management [4]. Further details about the particular methods used for enrolment, clinical assessments, and data gathering are provided below.

Consent taking and recruitment of subjects

Caregivers with children identified as study subjects were informed of the study and the test procedures. The purpose, procedure and benefits of the study were explained. It was explained that both the clinical measurements, clinical history taking of the presenting symproms and diagnosis of the system affected would assess for the severity of sepsis in their children/wards and the results would be disclosed to them as soon as possible. The possible length of time required for the clinical assessment was also disclosed as well as the fact that it would be performed at no cost to them. They were also informed that the measurements were safe. A written informed consent was obtained from the parent/caregiver and an assent obtained from children aged 7 to 15 years.

Demographics and Medical History: Personal data was obtained and recorded for each subject including age, gender, tribe and relationship of the informant to the patient. The caregivers of the subjects provided data on their occupation and educational level, which was used to place them on their socioeconomic class. Medical history was obtained to identify patients with features of sepsis such as fever, cough, fast breathing, loss of consciousness, vomiting, diarrhoea, skin rashes, convulsion, headache, irrational behaviour. Past medical history was reviewed to exclude known patients with medical conditions on medications that could affect heart rate or blood pressure. These include known retroviral disease patients on medications, asthma patients on salbutamol and cardiac patients with tetralogy of Fallot on propranolol as well as known patients with thyrotoxicosis and hypertensive patients on anti- hypertensive medications and patients noted to be on illicit drugs, were all excluded from the study. A predesigned structured proforma was used to record the history and examination measurements.

Physical examination and LqSOFA calculation

A quick general examination was performed on all the study participants for the following: Thermometry, jaundice, pallor, hydration status, digital clubbing, pedal oedema as well as anthropometry for nutritional status. Focused systemic examinations were carried out to determine LqSOFA scores for organ dysfunction using the novel-adapted quick SOFA Liverpool score (Appendix II) [56]. Capillary refill time was determined by applying light pressure on the nail bed to blanch for five seconds and the time until the colour refilled calculated. Level of consciousness was determined using the AVPU scale by assessing if the subject was alert, responsive to voice, pain or if the subject was unconscious. The respiratory rate was counted manually by visually counting the number of chest rise following inspiration in one full minute. The respiratory rates were plotted on the percentile charts. Temperature was measured using the same digital thermometer, model KT-DT4B® placed in the axilla. Value was read off at the beep of the thermometer. Fever was based on the WHO definition of axillary temperature of $\geq 37.5\ ^0C$ [169]. Thermometer was wiped with 70% alcohol swab for disinfection after each use. Oxygen saturation was measured using the same fingertip pulse oximeter, model JZK-303, version No. 04®. Operation was according to the manufacturer's manual of operation. Patients rested for at least 5 minutes with the hands made warm and nails devoid of polish or glitter. The index finger of the patient was cleaned with wet cotton wool swab (soaked in methylated spirit) and allowed to dry completely. The finger was put into the rubber hole of the oximeter with the nail upward. The power button was then switched on. The finger was kept steady for at least a minute or longer if the reading was not steady. The highest steady value was recorded once the oximeter showed a trace with a regular wave. Examination of other systems were also done. These include respiratory system (respiratory rate, any sign of respiratory distress, palpation, percussion notes and auscultation of breath sounds), cardiovascular system examination (pulse rate and characteristics, blood pressure, apex beat and auscultation of heart sounds), digestive system (oral cavity examination, signs of abdominal

distension, abdominal tenderness, palpation for abdominal organs), central nervous system examination (level of consciousness, signs of meningeal irritation, cranial nerves examinations as well as motor system examination).

Heart rates and blood pressure measurements for Shock Index calculations

These measurements were conducted with the child calm and lying comfortably in supine position on the examination couch after a rest period of 5minutes. Just as was done during the pretest, the heart rate of each study participant was counted for a full minute while the patient was calm by auscultating with a 3M™ Littmann® Classic II Paediatric Stethoscope over the apical area of the precordium. The average of two separate readings done 2 minutes apart was used for intra-observer reliability. The heart rate was recorded on the proforma and also plotted on the percentile charts. The stethoscope was cleaned with methylated spirit swab and allowed to dry after each use.

Blood pressure was measured using the non-invasive method for all the study participants. This was with the same OMRON M2® basic automatic upper arm blood pressure monitor (HEM-7120-E) using appropriate cuffs for age according to the manufacturer's instructions. The design and operation of the machine were based upon the combined principles of compression of the brachial artery under an elastic, inflatable cuff and estimation of the systolic and diastolic blood pressure levels by oscillometric methods. The arm was made bare and unrestricted by clothing with the palm of the hand turned upward and the midpoint of the upper arm at the level of the heart. The right arm was used for all the participants as this is the recommendation for single arm repeated blood pressure measurements for consistency, ability to compare results to standard tables, and potential for aortic coarctation, which could result in false (low) readings in the left arm. The air plug of the arm cuff was inserted into the air jack on the left side of the main unit of the machine. A cuff covering at least 80% of the length of the arm and the inflatable bladder width covering at least 40% of the circumference of the upper arm midway between the olecranon and the acromion was considered appropriate. The mid-upper right arm circumference of the study subject was measured using a measuring tape at the mid-point between the acromion of the scapula and the olecranon of the ulna. The cuff was applied in a circular manner in a way that it was smooth and snug, 1-2cm above the right elbow according to the manufacturer's instructions. The fit of the cuff was checked to ensure it was secure but not tight. The start button of the OMRON M2® basic automatic upper arm blood pressure monitor was pressed to inflate the cuff. The cuff inflated automatically after which it took measurements while deflating automatically. The systolic and diastolic pressures in millimeters of mercury (mmHg) were displayed on the screen and read off. An average of two readings was taken at an interval of two minutes and the value was documented in the study proforma. The average of two systolic blood pressure and diastolic blood pressure values was used to limit intra-measurement variability. The interval time of 2 minutes in between measurements was within the recommended time for the artery to return to its pre-measurement condition before a repeat measurement. The arm cuff was removed after the measurement and the machine turned off. The blood pressure cuff was disinfected after each patient's use by spraying with 70% alcohol and it was allowed to dry. After the heart rate and blood pressure measurements, the SI was calculated by dividing the heart rate (HR) by the systolic blood pressure (SBP). Shock index was categorised as either normal or elevated based on expected values for age [27]. Measurements for shock index were obtained before all treatments (fluid or vasoactive drug administration) or invasive procedures (such as intubation).

Results

A total of 102 eligible children with sepsis were enrolled into the study. Of the 102 study participants, 27 (26.5%) had septic shock while 75 (73.5%) had severe sepsis without septic shock.

Socio-demographic characteristics of the study participants

Participants age ranged from 1 month to 15 years with a median age of 23.5 months (IQR=107.25 (10.5-117.75); CI=18.0 – 48.0). There were 68 (66.7%) males and 34 (33.3%) females. The male to female ratio was 2:1. Table 5 shows the socio-demographic characteristics of the study participants.

Table 5: Sociodemographic characteristics of the study participants

Variable	Frequency (N =102)	Percentage (%)
Age		
≥ 1 month - < 1year	26	25.5
1 - <5 years	39	38.2
5 - <10 years	12	11.8
10 - 15 years	25	24.5
Gender		
Male	68	66.7
Female	34	33.3
Ethnicity		
Yoruba	94	92.2
Igbo	7	6.9
Hausa	1	0.9
Social class		
I	5	4.9
II	9	8.8
III	25	24.5
IV	20	19.6
V	13	12.8
VI	30	29.4

N= Number of participants; %= Percentage; Social class was derived with Ibadin *et al* [166] Socio-economic Status classification; Classes I and II=Upper social class, Classes III and IV=Middle social class, Classes V and VI=Lower social class

Premorbid health status and presenting complaints of participants

All the study participants had fever. Fifty-five (53.9%) of the study participants presented with breathlessness while 50 (49%) had a presenting complaint of loss of consciousness. Nineteen participants (18.6%) had pre-existing conditions, with sickle cell disease 7/102 (6.8%) being the most common. Only two participants had available vaccination cards for verification and they had complete vaccinations for age, but 91 (89.2%) verbally reported complete vaccinations for age. Eight (7.8%) participants had incomplete vaccination, one participant (1.0%) had no history of vaccination, while the vaccination history of two (2.0%) of the study participants could not be ascertained. The

presenting complaints of the study participants are summarised in Fig 1.

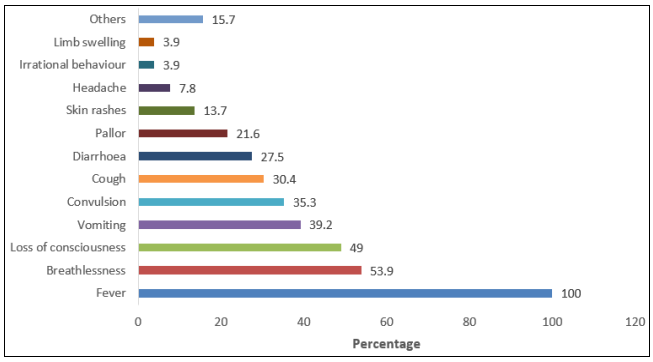


Fig 1: Showing the Presenting Symptoms of the Study Participants

Examination findings of the study participants

The median temperature of 38.1^{0}C (IQR 37.6^{0}C -39.0^{0}C) was recorded. Forty-five of the participants were unresponsive on admission (44.1%) and seventy-seven (75.5%) of the study participants had a Liverpool quick Sequential Organ Failure Assessment score of two. Anthropometric and clinical measurements of the participants are summarised in Table 6a to Table 6c.

Table 6a: Examination findings of participants

Variable	Median	IQR (Q1 -Q3)	Range
Temperature (^{0}C)	38.1	1.4 (37.6 -39.0)	37.5 - 40.7
Weight (kg)	10.0	15.5 (6.5 -22.0)	2.5 - 48.0
Length/height (cm)	90.0	60.5 (68.0 -128.5)	46.0 - 170.0

IQR- Interquartile ranges, ^{0}C- Degree Celsius, Kg – Kilograms, cm – Centimetre, mmHg – millimetres of mercury

Table 6b: Examination findings of participants

Variable	Age groups	Mean ± SD	Range
Heart rate (beats/min)	≥ 1 month - < 1year	175.6 ± 23.0	112.0 - 224.0
	1 - < 5 years	159.3 ± 25.7	88.0 - 218.0
	5 - < 10 years	139.0 ± 24.0	108.0 - 172.0
	10 - 15 years	132.2 ± 20.3	89.0 - 163.0
Systolic BP (mmHg)	≥ 1 month - < 1year	84.3 ± 19.8	43.0 - 130.0
	1 - < 5 years	99.7 ± 18.7	50.0 - 138.0
	5 - < 10 years	104.2 ± 27.7	70.0 - 160.0
	10 - 15 years	106.1 ± 21.8	47.0 - 154.0
Diastolic BP (mmHg)	≥ 1 month - < 1year	54.0 ± 14.9	24.0 - 81.0
	1 - < 5 years	60.6 ± 16.6	30.0 - 95.0
	5 - < 10 years	68.9 ± 25.0	44.0 - 120.0
	10 - 15 years	62.4 ± 19.5	30.0 - 110.0
MAP (mmHg)	≥ 1 month - < 1year	63.5 ± 15.2	30.0 - 93.0
	1 - < 5 years	72.5 ± 15.7	38.3 - 102.0
	5 - < 10 years	79.7 ± 25.4	56.7 - 132.0
	10 - 15 years	77.2 ± 19.6	44.0 - 123.0

SD: Standard Deviation; BP: Blood pressure, MAP: Mean arterial pressure

Table 6c: Examination findings of participants

Variables	Frequency	Percentage (%)
AVPU Scale		
Alert	44	43.1
Verbal	5	4.9
Pain	8	7.9
Unresponsive	45	44.1
CRT in seconds		
< 3	66	64.7
≥ 3	36	35.3
LqSOFA		
2	77	75.5
3	19	18.6
4	6	5.9

AVPU: Alert, Voice, Pain, Unresponsive, GCS: Glasgow coma score, CRT: Capillary refill time, LqSOFA: Liverpool quick Sequential Organ Failure Assessment Score

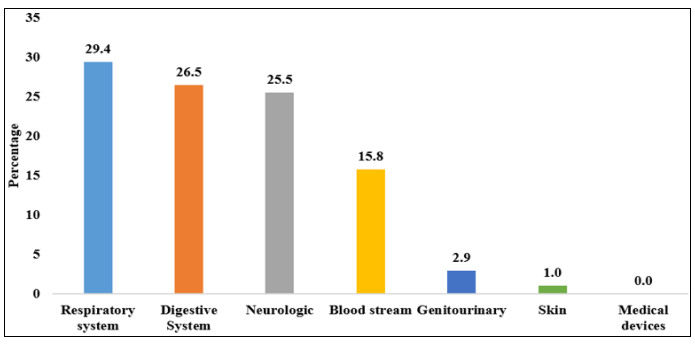


Fig 2: Showing the Systems most Affected from the Clinical Diagnosis of the Study Participants

Table 7: Distribution of primary and secondary diagnosis of participants

Primary diagnosis	Frequency	Percent (%) of 102	Secondary diagnosis	Frequency	Percent (%) of 20
Severe pneumonia	26	25.4	Ammoniacal dermatitis	4	20.0
Acute diarrhoeal disease	20	19.6	Underweight malnutrition	3	15.0
Severe malaria	17	16.7	Non-typhoidal salmonellosis	2	10.0
Meningitis	13	12.7	Impetigo	2	10.0
Sickle cell disease with Acute chest syndrome	7	6.8	Cutaneous candidiasis	2	10.0
Typhoid septicaemia	7	6.8	Tinea capitis	2	10.0
Acute laryngotracheobronchitis	2	2.0	Marasmus	1	5.0
Sepsis with Acute Kidney Injury	2	2.0	Adenoid hypertrophy	1	5.0
Pyomyositis with infective endocarditis	1	1.0	Cerebral palsy	1	5.0
Lipoid pneumonitis	1	1.0	Oral candidiasis	1	5.0
Measles encephalitis	1	1.0	Strabismus	1	5.0
Meningococcaemia	1	1.0			
Necrotising enterocolitis	1	1.0			
Necrotising fasciitis	1	1.0			
Orbital cellulitis	1	1.0			
Staphylococcal Scalded Skin Syndrome	1	1.0			

Table 8a: Shock index values of the study participants

Variable	Median	IQR (Q1 -Q3)	Range
Shock Index	1.6	0.6 (1.3 - 1.9)	0.7 -5.5

Table 8b: Shock index values of the study participants stratified by age groups

Age groups (years)	N (%)	Shock Index		
		Median	IQR (Q1 – Q3)	Range
≥ 1 month - < 1year	26 (25.5)	2.1	0.7 (1.8 – 2.5)	1.4 – 4.7
1 - <5 years	39 (38.2)	1.6	0.5 (1.3 – 1.8)	0.9- 5.5
5 - < 10 years	12 (11.8)	1.5	0.7 (1.0 – 1.7)	0.7- 2.0
10 – 15 years	25 (24.5)	1.2	0.5 (1.0 – 1.5)	0.8 – 2.9

IQR- Interquartile ranges

Table 9: Association of shock index with septic shock

Variables	Septic Shock		aOR	95% Confidence Interval		p-value
	No	Yes		Lower	Upper	
Shock Index						
Normal (Ref)	24 (96.0%)	1 (4.0%)	-	-	-	-
Elevated	51 (66.2%)	26 (33.8%)	10.899	1.203	98.785	0.034**
Age in year(s)						
< 1 (Ref)	19 (73.1%)	7 (26.9%)	-	-	-	-
1 - <5	29 (74.4%)	10 (25.6%)	0.475	0.122	1.846	0.282
5 - <10	10 (83.3%)	2 (16.7%)	0.278	0.040	1.945	0.197
10 – 15	17 (68.0%)	8 (32.0%)	0.584	0.136	2.499	0.468
Gender						
Male (Ref)	54 (79.4%)	14 (20.6%)	-	-	-	-
Female	21 (61.8%)	13 (38.2%)	1.703	0.623	4.658	0.299

** Statistical significance; aOR – Adjusted Odd Ratio; Ref – Reference group

Table 10: Receiver Operating Characteristics (ROC) of Shock Index

Age (years)	Area under Curve	Std. Error	p-value	95% Confidence Interval	
				Lower Bound	Upper Bound
Shock Index					
All age groups	0.668	0.066	0.011**	0.539	0.796
< 1	0.868	0.070	<0.001**	0.731	1.006
1 - <12	0.714	0.082	0.024**	0.554	0.874
12 and above	0.659	0.134	0.248	0.397	0.921

Primary and Secondary diagnosis of study participants

Out of the 102 participants in the study, severe pneumonia was the most common primary diagnosis found in 26/102 (25.4%), followed by acute diarrhoeal disease 20/102 (19.6%) and severe malaria 17/102 (16.7%). The respiratory system was the most commonly affected site of infection, 30/102 (29.4%), followed by the digestive system, 27/102 (26.5%) as seen in Fig 2. Among the participants, 27/102 (26.5%) had septic shock while the remaining 75/102 (73.5%) had sepsis without septic shock. These are shown in Table 7.

Shock index values of the study participants

Shock index of the study participants ranged from 0.70 to 5.50 with a median value of 1.6 (IQR1.3 - 1.9). Table 8a summarises the shock index values of the 102 study

participants with age group stratification summarised in Table 8b.

Association of shock index with septic shock

Logistic regression (See Table 9) was used to predict septic shock using shock index after adjusting for age and gender. The result revealed that those with elevated shock index were 10.9 times more likely to develop septic shock compared to those with normal shock index (p=0.034, aOR=10.899, CI = 1.203 - 98.785).

Discussion

This study set out to determine the shock index values in children with sepsis at a tertiary Teaching Hospital. It also determined the shock index values for predicting septic shock in children with sepsis. In this study, there was a high median shock index values. Majority of the patients had elevated shock index levels for age. Shock index could predict septic shock in children aged younger than 12 years.

The median shock index across all age groups observed in this study reflects a high shock index among children with sepsis. This was comparable to the median shock index of 1.7 (IQR 1.4-2.0) reported by Rousseaux *et al* [23] in France. The fact that both studies involved children and that shock index was determined by assessments completed prior to patients receiving fluid resuscitation may account for the similarities between the two studies. Three quarters of the study participants had elevated shock index values. This implies that a large proportion of the septic patients had significant levels of haemodynamic compromise at the time of arrival to the Emergency room. This was similar to the findings by Althunayyan *et al* [151] in Saudi Arabia and Prashanth *et al* [155] in India in which 80% and 84% of the septic patients had elevated shock index values respectively. This implies that considerable number of children presenting with features of sepsis in our emergency ward are at risk of impending circulatory collapse, requiring urgent review and intervention. These early haemodynamic changes may be initially subtle and reflect reduced left ventricular end diastolic pressure and circulatory volume. [23, 43] Shock index may therefore be useful in the quick triage of septic patients as it could alert clinicians of potential underlying complications related to sepsis.

The percentage of septic patients with elevated shock index in this present study was however higher than the proportion of 58% reported by Chen *et al* [140] and 40.6% by Reinstadler *et al* [141] in their studies. These disparities may be due to the differences in the populations studied. Whereas the present study was carried out on children, Chen *et al* [140] and Reinstadler *et al* [141] investigated Adult patients. Paediatric physiology and reserves differ from adults. It has also been established that patients with advancing age and chronic hypertension may not initially show signs of haemodynamic compromise, such as tachycardia and hypotension in sepsis. Consequently, whereas the present study excluded such patients, the use of antihypertensives by the adult patients in the study by Reinstadler *et al* [141] could have confounded their results. These may account for the discrepancies from the present study. These findings demonstrate how underlying physiologic framework and background comorbidities could impact on shock index elevation and utility.

A quarter of the participants in this study had septic shock, highlighting the potential of high mortality in children with sepsis and a call for early detection and intervention. The proportion of patients with septic shock in this present study was comparable to the findings by Rajendran *et al* [1] in India and Yussof *et al* [142] in Malaysia who recorded 30% and 38% of septic patients with septic shock respectively [1, 142]. These studies were all conducted in developing nations with emerging economies, where disease patterns are comparable, and therefore may account for their similarities to the current study. A higher proportion of 65.9% was recorded by Liu *et al* [114] while a markedly lower value (11.4%) was reported by Scott *et al* [154] both in the USA. These variances may be due to the differences in the populations studied. Unlike this present study, where sepsis was evaluated in children presenting to the emergency room, the study population in the Liu *et al* [114] study were solely patients admitted into the intensive care unit, suggesting a higher level of disease severity. The sample population of the present study therefore represents a less concentrated spectrum of severity compared to theirs done on ICU patients. Nevertheless, the risk of septic shock should always be evaluated for, in any septic child presenting to the hospital for prompt escalation of care.

With regards to the prediction of septic shock, this study showed that both shock index and serum lactate had good sensitivities but low specificities for the prediction of septic shock. The potential disadvantages of relying on such parameters, is related to overestimation of severity of sepsis and excessive treatment from high false positives. Given that these parameters are designed as tools to aid clinician decision-making, rather than simply predict outcome, they should be used only as screening tools in combination with other parameters, patient's individual characteristics as well as the clinician's professional judgement.

The study revealed that shock index was a sensitive predictor of septic shock in children younger than 12 years. This was in tandem with the findings by Nadri *et al* [154] who found shock index as a very sensitive predictor in young children unlike lactate which was not statistically significant in their cohort of children studied. This could be explained by the complex dynamic pathophysiologic mechanisms and manifestations of sepsis and septic shock across different age groups. The immune response cascade in adolescents approximates those of adults because full immunologic maturity is attained in adolescence [5]. Older children, just like adults have more dysregulated inflammatory cascade with inflammatory activities in atheromatous plaques contributing to reduced tissue oxygenation and subsequent lactic acidosis [86]. Younger children, on the other hand, have less exaggerated inflammatory responses due to diminished cytotoxic lymphocyte activities compared to adolescents and adults [5]. Younger children have lower risk of atheromatous plaques, and better compensatory mechanisms in the face of shock [86]. The younger children can maintain cardiac output by employing extreme tachycardia for a prolonged period without inducing myocardial ischemia [5]. All these could explain why shock index which reflects heart rate compromise before stroke volume impairment would be more sensitive in predicting septic shock in younger children. Clearly, this may be an important area for further research as much remains to be learned about the impact of developmental age on host response to sepsis.

The inability of shock index to predict septic shock in the older children is consistent with the report by Cevik *et al,* [45] who found that unlike lactate, elevated initial shock index

could not predict the need for vasopressors in their patients. Wira *et al* [147] also alluded to this in their study as well. The fact that both studies involved older participants and utilised initial admission shock index and lactate measurements at the emergency departments may account for the similarities. The findings from this study therefore suggest that shock index is a better screening tool for septic shock in children younger than 12 years.

Concerning the cut-off values for the prediction of septic shock, the cut off shock index values of 2.3 and 1.3 were determined to have optimal sensitivities for predicting septic shock in infants and those aged 1-< 12years respectively in the present study. The cut-off value of 1.3 was similar to the value of >1.2 recorded by Prashanth *et al* [17] but higher than the cut-off values of ≥ 0.877 and ≥ 0.875 reported by Nadri *et al* [154] and Al-Aseri *et al* [149] respectively. These variations, however are related to the different age groups and sizes of populations investigated. Unlike the present study that involved 102 children aged 1month to 15 years, Nadri *et al* [154] investigated shock index in 50 children aged 1-5 years. This may not have been sufficient for significant Sconclusions to be drawn. Likewise, Al-Aseri *et al* [149] carried out their study on older patients aged ≥ 15years of age in whom lower values of shock indices are expected physiologically. These could explain the conflicting shock index cut-off values and therefore reinforce the fact that shock index ranges are related to age.

All the children in this study had fever in addition to other symptoms such as breathlessness, diarrhoea and loss of consciousness. Some of these symptoms are regarded as severe features in the World Health Organization's Integrated Management of Childhood Illnesses [155]. The fact that some of the children were particularly high-risk groups for serious infections such as those with sickle cell anaemia as well as those with incomplete vaccinations may have contributed to the disease severity. Similar findings were also reported by Igbokwe *et al* [19] in their study in South-East Nigeria. It may therefore be expected that any febrile child presenting with the aforementioned features should receive prompt attention at the Emergency room. There may be need for the optimisation of pragmatic solutions for targeted interventions for such high-risk groups.

The predominant clinical diagnosis resulting in sepsis found in this study was pneumonia which is in tandem with many other studies [18, 41]. This finding however differs from a previous study by Hassan-Hanga *et al* [15] in Kano, North-West, Nigeria where sepsis from severe malaria was more predominant than pneumonia. The reason for this difference may be due to the seasonality of these conditions as well as recent changes in environmental and meteorological factors of malaria transmission in the different regions. Recent geo-spatial analysis has confirmed that malaria incidence is lower in Southern Nigeria where the index study was conducted compared to Northern Nigeria [19]. This further strengthens the fact that there may be epidemiological regional variations in primary infections resulting to sepsis even within the same country.

Severe pneumonia was followed by acute diarrhoeal disease (19.6%) then severe malaria (16.7%) as predominant infections in this study. This is worrisome as pneumonia, acute diarrhoeal disease, and malaria have remained persistent burdens particularly among children in LMICs, despite control programmes [153]. The reasons for the persisting prevalence of these common preventable childhood infections may be due to the numerous challenges affecting children in Nigeria such as malnutrition, poor sanitation, overcrowding, insufficient immunisations, and environmental pollution. These are heightened by the current insecurity, population displacements, rapid urbanisation, and succession of disease outbreaks. The findings in this study therefore underscore the need for a scale-up of high-impact public health initiatives for the prevention of pneumonia, diarrhoea, and malaria in children in Nigeria.

Shock index which is a simple, inexpensive, non-invasive, bedside tool showed a significant positive correlation with serum lactate. Its predictive accuracy for septic shock was at least comparable with an established marker of sepsis; serum lactate. It also has a good sensitivity needed for clinical practice.

Conclusions

The main conclusions derived from this study are as follows:

1. A majority of children with sepsis have elevated shock index values for age.
2. Shock index cut-off values of 2.3 and 1.3 could potentially predict septic shock in infants and children younger than 12 years of age respectively.

Recommendations

From the findings of this study, the following recommendations are proposed:

1. Shock index may be used as a quick, inexpensive, non-invasive, risk-stratifying screening tool for children younger than 12 years presenting with sepsis at the Emergency room.
2. Shock index values of ≥2.3 and ≥ 1.3 may be included as 'alert values' in the management protocols of infants and children with sepsis at risk of septic shock respectively.
3. Shock index may be used as adjunctive screening tools, in conjunction with additional parameters for sepsis management and predicting the risk of septic shock in children.

Conflict of interest

The authors declare that there is no conflict of interest to disclose.

Authors declared no conflict of interest and jointly agreed to publish this manuscrit in turkish journal of paediatrics.

Ethical Clearance

This was obtained from the University of Ibadan/University College Hospital Research Ethics Committee before the commencement of the research with approval number UI/EC/21/0523. (Date: 24/10/2021) Written informed consent was obtained from the caregivers after explaining the study and its objectives.

Funding

The authors declare that the study received no funding.

Authors Contribution

All authors had equal contribution for the successful completion of this study, starting from conceptualization, data collection, data entry and analysis, writing –up and review. Study conception and Design: IU, BO, RO; data

collection: IU, BO, RO, KO, AC, NG; analysis and interpretation of result: IU, BO, RO, KO, AC, NG; draft manuscript preparation: NG, IU. All authors reviewed the results and approved the final version of the article.

Acknowledgement
The authors will like to acknowledge the Department of Paediatrics, UCH Ibadan for their support and assistance during the sample collection for the study.

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