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Pediatric Respirology and Critical Care Medicine

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Outcomes and Prediction

Understanding the short-term and long-term outcomes of diseases is of importance for clinicians. Moreover, recognizing factors that predict the outcomes may assist the clinicians to make a clinical decision in choosing investigations, providing treatment, and considering ethical issues and economic strategies. In this issue, three articles discussing outcomes of diseases and conditions related to respiratory problems and intensive care for children with different point of views are presented.

One of the significant adverse outcomes of obstructive sleep-disordered breathing (SDB) in children is neurocognitive dysfunction and behavioral problems.[1,2] This is thought as a result of recurrent nocturnal hypoxia and sleep fragmentation that occur during SDB. In the first article of this issue, Walter and Horne present a comprehensive review, compiling recent studies evaluating the effect of SDB in the child brain, which used near-infrared spectroscopy or functional magnetic resonance imaging of the brain.[3] From a limited number of studies, it was shown that children with SDB are better in maintaining cerebral oxygenation than adults, but SDB leads to adverse outcomes on the autonomic control, respiration, behavior, and neurocognition.

Lung is one of the major organs affected in sickle cell anemia (SCA).[4] Children with SCA are prone to have recurrent and chronic pulmonary diseases, which cause lung damage and may result in long-term outcomes of abnormalities of the lung function. In this issue, Kuti and Adegoke reported that restrictive lung function abnormalities were more common among Nigerian children with SCA compared to healthy children.[5] They also documented that children who were at adolescent age and had previous acute chest syndrome are more likely to have the lung function abnormalities. For clinicians, information of at which age is the lung function impairments is started is also important; hence, we can start aggressive treatment at that age to prevent chronic lung damage.

The short-term outcomes of children admitted to pediatric intensive care unit (PICU) are varied, but they are at high risk for mortality. A simple and objective tool to characterize the disease severity at admission and to predict mortality among these children is needed. The ideal tool should be simple, easy to use, low cost, easy to reproduce, minimally invasive, and accurate and does not require sophisticated tool. The Pediatric Risk of Mortality (PRISM) III is one of the scoring systems that has been used widely and had a good prediction for mortality.[6] Nevertheless, this scoring system needs arterial blood gas analysis as one of the variables, which is invasive and sometimes is not feasible to be performed in critically ill patients. Ruangnapa *et al*. developed and validated a modified PRISM III score, by removing blood gas analysis and added a number of clinical features.[7] This modified scoring system showed as good as the PRISM III performance in predicting mortality in PICU, not only in the first 2 days of hospitalization but also in 7-day mortality and overall mortality. The more simple and less invasive of the modified PRISM III will be more feasible for resource-limited settings such as in many countries in Asia.

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Review Article

Obstructive Sleep-Disordered Breathing in Children: Impact on the Developing Brain

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Abstract

Obstructive sleep-disordered breathing (SDB) affects up to 11% of children and forms a continuum of severity ranging from primary snoring to obstructive sleep apnea. Children with SDB exhibit significant neurocognitive and cardiovascular dysfunction, which is associated with repetitive hypoxia and sleep fragmentation that characterize the condition. We reviewed the recent literature pertaining to the effect of SDB on the brain in children. These include studies that utilized near-infrared spectroscopy to determine cerebral oxygenation and structural and functional magnetic resonance imaging (MRI) of the brain. Studies have identified that the effect of SDB on cerebral oxygenation in children is minimal and not clinically significant. There are conflicting reports on the association between the measures of cerebral oxygenation and peripheral arterial oxygen saturation (SpO_2), and further research needs to be conducted to elucidate the relationship between peripheral SpO_2, cerebral oxygenation, and SDB in children. MRI studies have reported significant structural and functional changes to the brains of children with SDB, in brain regions associated with neurocognition, behavior, and autonomic function. These include reduced white and gray matter and structural changes to a multitude of brain areas including, but not limited to, the hippocampus, cortex, amygdala, insula, thalamus, cerebellum, and basal ganglia. These studies utilize a variety of MRI techniques to address different research questions, but contribute to the gradually developing picture of the adverse effects of SDB on the brain in children.

Keywords: Cerebral oxygenation, MRI, obstructive sleep apnea, pediatric

Introduction

Sleep-disordered breathing (SDB) is an umbrella term encompassing a number of respiratory disorders including primary snoring (PS), upper airway resistance syndrome, obstructive sleep apnea (OSA), and central sleep apnea. This review will focus on obstructive SDB, which affects up to 11% of children born at term;[1] however, population cohort studies show that SDB is three–six times more common in children born preterm.[1,2] SDB involves either partial or complete cessation of breathing during sleep and has adverse cardiovascular and neurocognitive sequelae. The brain is believed to be the conduit between the respiratory pathophysiology of SDB and the cardiovascular and neurocognitive outcomes. To understand the mechanisms that underpin this association, noninvasive tools have been utilized, with the most common being magnetic resonance imaging (MRI) and near-infrared spectroscopy (NIRS). MRI provides information on the structure, function, neuronal circuitry, connectivity, blood flow, and metabolic composition of the brain, and NIRS provides the measures of cerebral oxygenation and cerebral tissue extraction. This review will focus on the findings of studies which have examined NIRS and MRI in children with SDB.

Sleep-Disordered Breathing

SDB is characterized by habitual snoring. At the mild end of the SDB spectrum, PS is not associated with gas exchange abnormalities or sleep fragmentation. OSA is characterized by repeated hypoxia, hypercarbia, and sleep fragmentation. The most common cause of OSA is upper airway obstruction caused by abnormal anatomy (e.g., adenotonsillar hypertrophy in children) and/or inadequate control of the muscles that maintain patency of the upper airway. In OSA, respiratory effort is maintained, but airflow is either partially or completely obstructed.

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Adverse outcomes of sleep-disordered breathing

In both adults and children, the adverse cardiovascular outcomes of SDB are mediated by increased sympathetic activity and impaired cardiac autonomic control.[3] The cardiovascular effects of the repetitive hypoxia, reoxygenation, hypercarbia, apnea, and arousals in children with obstructive SDB include elevated blood pressure[4-6] and blood pressure variability,[7,8] together with reduced baroreflex sensitivity[7-9] and heart rate variability.[10,11] Physiological changes as a result of this autonomic dysfunction are apparent not only in the cardiovascular system, but also in the brain.[3] SDB has significant adverse neurocognitive and behavioral sequelae in children,[12-18] which are also believed to be due to the intermittent nocturnal hypoxia and sleep fragmentation that occur during SDB.

Near-Infrared Spectroscopy

Biological tissues are transparent to the near-infrared range (700–1300 nm), making it possible to measure cerebral tissue oxygen saturation.[19] Both tissue oxygen saturation and tissue hemoglobin content can be evaluated by measuring the difference in intensity between the transmitted and the received light wavelength. Hemoglobin and cytochrome are the main chromophores (light-absorbing molecules) within biological tissues. NIRS measures tissue-derived chromophores from a number of different compartments including the arteries, veins, and capillaries, with the cerebral cortex made up of approximately 70% venous blood and 30% arterial blood.[19] NIRS devices are manufactured to be specifically sensitive to wavelengths between 700 and 850 nm as these wavelengths encompass the absorption spectra of deoxyhemoglobin (DOxHb), which peaks at 650–1000 nm; oxyhemoglobin (OxHb), which peaks from 700 to 1150 nm; and cytochrome oxidase which has a peak at 820–840 nm, while also having minimal overlap with water, which peaks between 950 and 1050 nm and above 1300 nm.

Determining cerebral oxygenation noninvasively using NIRS is advantageous over measuring peripheral hypoxia as NIRS has a faster response time[20,21] and superior detection of desaturation[22] compared with oximetry. Studies using NIRS have found reduced cerebral oxygenation in adults with SDB (or OSA) compared with nonsnoring controls[23,24] and in adults with severe OSA compared with those of mild and moderate OSA.[25] A slightly different technology which is based on the similar principles (near-infrared diffuse correlation spectroscopy) reported larger variations in cerebral oxygenation during periods of apnea compared with periods without apnea, which were significantly correlated with OSA severity.[26]

The three studies that have investigated the effect of SDB on cerebral oxygenation in children have reported conflicting results.[27-29] Khadra *et al*. studied 14 nonsnoring controls, 32 with PS, and 46 with OSA (7–12 years of age), during overnight polysomnography (PSG) with continuous monitoring of cerebral oxygenation and blood pressure. An index of cerebral oxygenation was obtained during sleep by referencing the sleep values to the wake values for each child.[28] Increasing cerebral oxygenation was predicted by increasing mean arterial blood pressure, age, and rapid eye movement (REM) sleep. Decreasing cerebral oxygenation was predicted by SDB, male sex, arousal index, and non-REM (NREM) sleep. This study identified that there was a complex relationship between SDB and cerebral oxygenation, as SDB had effects that both augment and diminish cerebral oxygenation. The authors identified increased cerebral oxygenation in children with PS compared to controls; however, the differences were very small averaging 2%. A small study of five children (1.5–15.8 years) with severe OSA used NIRS to assess the change from baseline in the tissue oxygenation index (TOI), OxHb, and DOxHb that occurred in association with arterial oxygen desaturations (SpO_2) measured by peripheral oximetry.[29] A fall in SpO_2 was correlated with the change in TOI, O_2Hb, and HHb, indicating a strong relationship between arterial and cerebral oxygenation in the children with severe OSA. In the most recent study, Tamanyan *et al*. categorized children with SDB and nonsnoring controls into groups of 3–6 years (n = 87) and 7–12 years (n = 72) of age and then further divided them into control, PS, mild OSA, and moderate/severe OSA.[27] All of the children underwent overnight PSG with continuous NIRS recording of cerebral oxygenation. Cognitive performance was also assessed within 2 weeks of the PSG study in a subset of the cohort (n = 102). This study also assessed TOI, which is a measure of the mixed oxygen saturation in all cerebral vascular compartments, and the fractional tissue oxygen extraction (FTOE), which accounts for arterial SpO_2, and therefore provides a ratio of cerebral oxygen consumption to delivery.[30] The authors reported that there were no differences between the SDB severity groups for either cerebral oxygenation (TOI) or oxygen extraction (FTOE) in the 3 to 6-year-old children. In the 7 to 12-year-old children, the control children had significantly lower cerebral oxygenation during wake, N1, and REM sleep and higher oxygen extraction during N1 sleep compared with the children with PS. There were no differences between the children with PS and those with OSA for either measurement. Furthermore, cerebral oxygenation was not associated with cognitive performance at either age. These data suggest that children can compensate for falls in peripheral oxygen saturation, thereby protecting cerebral oxygenation.

Magnetic Resonance Imaging

MRI scanning utilizes strong magnetic fields, magnetic field gradients, and radio waves to generate images of internal body structures, including brain structure and function. MRI provides superior images of parts of the body that are not easily seen with X-ray, computed tomography scans, or ultrasound. Furthermore, MRI does not involve the use of ionizing radiation. To its detriment are the high costs of MRI imaging, they typically take longer time, and are louder than the other imaging modalities; subjects are required to be inside a narrow

tube that can induce feelings of claustrophobia and subjects with certain medical implants or other nonremovable metal inside the body may be unable to undergo an MRI scan. There have been a substantial number of studies in adults with OSA using MRI scanning to detect anatomical and physiological alterations in the brain; however, much less research has been conducted in children using MRI.

Using structural MRI procedures that identified tissue loss or water content and diffusion changes indicative of injury, OSA in adults has been associated with injury to areas of the brain that have multiple functions and involve both gray and white matter.[31] Areas impacted include the insular, cingulate, ventral medial prefrontal cortices, cerebella deep nuclei and cortex, anterior hypothalamus, raphé, ventrolateral medulla, and basal ganglia. Furthermore, all SDB conditions are associated with significant axonal injury, notably in limbic structures related to affective processes; pontine projections to the cerebellum, which are essential motor and blood pressure regulatory fibers; and the cingulum bundle within the anterior cingulate cortex, which is important for respiratory patterning.[31] Injury to these areas has serious consequences on affective, autonomic, and cognitive functions and on mood regulation.[31]

Utilizing task or resting-state functional MRI (fMRI) and voxel-based morphometry, studies have reported that structural atrophy and functional disturbances in the right basolateral amygdala/hippocampus and the right central insula are associated with OSA.[32] Functional characterization of these regions is indicative of associations with dysfunctional emotional, sensory, and limbic processes. Resting-state fMRI studies have shown that dysfunctional connectivity of the posterior default-mode network underlies OSA's cognitive and depressive symptoms.[33]

A recent meta-analysis found that severe OSA is associated with more severe white-matter changes that are a risk factor for oxidative ischemic injury in adults.[34] Further cerebral changes in adults with OSA identified using MRI procedures included reduced cortical thickness (associated with autonomic dysfunction and impaired upper airway sensorimotor function);[35] gray-matter hypertrophy (hypoxemia, respiratory disturbances, and sleep fragmentation);[36] changes in brain metabolites (hypoxia, anxiety, and depression);[37,38] cerebral small-vessel disease (increased risk of cerebral infarction and hemorrhage);[39] reduced cerebral blood flow (increased OSA severity);[40,41] increased cerebrovascular reactivity[42] and decreased cerebrovascular reactivity[43] (increased stroke risk); and altered midbrain chemical concentrations (neuronal loss and inflammation).[44]

Although fewer than the studies in adults, pediatric research has ventured into using MRI processes to investigate whether the structural and functional changes found in adults with OSA are replicated in children. Nineteen children with moderate/severe OSA (Apnea–Hypopnea Index [AHI] >5 events/h) and 12 healthy controls, 6–16 years of age, underwent magnetic spectroscopic imaging, overnight PSG, and neuropsychological assessment to determine whether childhood OSA is associated with neuronal metabolite alterations in areas of the brain associated with neuropsychological function.[45] There was a decrease in the mean neuronal metabolite ratio of N-acetyl aspartate/choline in the left hippocampus and right frontal cortex in the children with OSA compared with the controls, indicating possible neuronal injury. This was in conjunction with significant deficits in intelligent quotient (IQ) and executive function. Neural support for executive functions involves a distributed neural network with cortical and subcortical components that include the frontal cortex,[46] and the authors speculated that untreated OSA during childhood could permanently alter cognitive potential in developing children.[45]

Executive functioning and empathy in ten children (7–11 years) with OSA and seven aged-matched controls were assessed in specific brain regions using fMRI.[47] The children underwent an overnight PSG, and OSA was defined as an AHI ≥2 events/h. During the fMRI, the children were given a color-word Stroop task, which consisted of three words, namely red, green, and blue, with matching color font. During the course of the test, the colors of the letters were changed randomly 96 times (e.g., the word red may have been presented with the letters in blue color), and the children were required to indicate the color of the letters. The children also performed an empathy task where they were shown sixty dynamic visual scenarios, which either depicted interpersonal harm or neutral actions (no harm) between two individuals. The regions of interest investigated by the fMRI during the Stroop test were the anterior cingulate cortex, inferior frontal junction, and the inferior parietal lobule. During the empathy test, the left and right regions of the amygdala, insula, anterior midcingulate cortex, ventromedial prefrontal cortex, and inferior frontal gyrus were scanned. Findings from this study suggested that, in order to perform at the same level as children without OSA, children with OSA needed greater neural recruitment of regions associated with cognitive control, conflict monitoring, and attentional allocation. Furthermore, OSA severity predicted less sensitivity to harm in the left amygdala. The authors concluded that OSA influences neural recruitment across a range of brain activities in children.

Children with moderate/severe OSA (n = 23; 8–13 years; obstructive AHI [OAHI] >5 events/h) and age-matched nonsnoring controls (n = 15) underwent overnight PSG, neurocognitive assessment, and MRI scanning with voxel-based morphometry, which is a technique for characterizing regional cerebral volume and tissue concentration differences.[48] Compared to controls, the children with OSA had gray-matter volume deficits in prefrontal and temporal regions, which was explained as being the result of the repeated apneas and hypoxic damage that characterize OSA. In addition, the ratio of gray-matter volume to total brain volume significantly correlated with visual fine motor coordination. The prefrontal cortex is involved in attention and executive functions,[49] which were reduced in the children in this study. Furthermore, the

lateral occipital gyrus is closely related to the visual cortex, and this could explain the correlation between reduced gray-matter and visual fine motor coordination.[48] The clinical relevance of this study relates to the need to identify and treat children with OSA early and mitigate the adverse effect that OSA has on the developing brain's neurocognitive potential in these children.

Similar findings were reported recently in a study of 16 children with OSA (8.1 ± 2.2 years [mean ± standard deviation (SD)], OAHI >2 events/h, plus a SpO_2 nadir <92%, and/or a Respiratory Arousal Index >2/h) and 9 control children who also underwent overnight PSG, neurocognitive assessment, and MRI with voxel-based morphometry.[50] In addition to the control children, MRI data were also compared against 191 scans from the NIH-Pediatric MRI database. Reductions in gray-matter volume were identified throughout the areas of the superior frontal and prefrontal and superior and lateral parietal cortices. This study also identified other affected sites such as the brain stem, ventral medial prefrontal cortex, and left superior temporal lobe. In contrast to Chan *et al*.,[48] there were no significant associations between regional gray-matter volumes and either OSA severity or cognition measured using the Differential Ability Scales. The authors acknowledged this difference between the two studies and attributed it to the lack of sensitivity of psychological tests and the high degree of variability in the cognitive outcomes associated with pediatric OSA.[50] The authors also acknowledged that, while inclusion of the scans from the NIH database greatly improved the estimation of true population levels of regional gray-matter volumes, sleep status was not assessed and a proportion of these children may have had OSA. Nonetheless, these findings add additional weight to the need for early identification and treatment of children with OSA.

T1-weighted brain MRI, whereby T1 refers to the use of a short repetition time (the amount of time between successive pulse sequences applied to the same slice) and a short time to echo (the time between the delivery of the radio frequency pulse and the receipt of the echo), identified significant atrophy in the ventral posterior nucleus and the medial dorsal nucleus of the left thalamus in 25 children with OSA (mean age 10.3 ± 1.5 SD years) compared with 30 controls (10.1 ± 1.8 SD years).[51] The children with OSA also exhibited significant regional dilation in both the internal and external segments of the left pallidum. These findings are consistent with the structural deficits found in the basal ganglia of adults with OSA.[52,53] The basal ganglia contribute to the regulation of autonomic motor, somatomotor, and neuropsychological functions, and alterations to these areas of the brain may be associated with deficits in these functions in patients with OSA.

In a study on 11 children with OSA (14 ± 1.5 years, Obstructive Apnea Index >1 event/h and/or the AHI >5 events/h) and 12 controls (mean age 15.1 ± 1.4 SD years), all children underwent overnight PSG, MRI scanning, and neuropsychological evaluation, with a battery of tests for IQ and cognitive assessment including both verbal and visual learning and memory.[54] In contrast to the above studies, this study found that, across the whole brain, there was no impact of OSA on white-matter integrity using tract-based spatial statistics, or gray-matter volumes using voxel-based morphometry.[54] Focusing on the dentate gyrus of the hippocampus, diffusion tensor imaging (DTI) was used to investigate the microstructure. DTI is a MRI imaging technique that enables estimation of the location, orientation, and anistrophy of the brain's white-matter tracts by measuring the restricted diffusion of water in the tissue. Decreased mean diffusivity of the dentate gyrus correlated with a higher AHI, a higher arousal index, and a lower verbal learning score. The authors concluded that the disrupted microstructure of the dentate gyrus may, in part, explain some of the neurocognitive deficits in children with OSA.

A recent study by our group collected T1- and T2-weighted images to examine for any visible brain pathology, and DTI imaging was conducted to determine mean diffusivity in children with SDB (n = 18; mean age 12.3 ± 0.7 SD years; OAHI >1 event/h) and controls (n = 20; 12.2 ± 0.6 years; OAHI ≤1 event/h; and no history of snoring), following overnight PSG and behavioral and neurocognitive testing.[55] Reduced mean diffusivity was identified in the hippocampus, insula, thalamus, and temporal, occipital, and cerebellar sites in children with SDB compared with controls. Reduced mean diffusivity indicates acute (recently incurred) alterations in these areas and may be more amenable to intervention. These areas of the brain are involved with the control of autonomic function, respiration, cognition, mood, and memory processes.[56-60] OAHI was negatively correlated with injury in widespread brain regions, including bilateral lingual gyrus, right anterior and left posterior cingulate, right cerebellar tonsil, inferior and middle occipital gyrus, left middle temporal gyrus, and right parahippocampal gyrus. The correlation with injury, being so widespread, indicates that the OAHI has a significant potential to exert functional deficits, including worsening of SDB. Increased mean diffusivity, indicative of chronic damage, was found in the frontal and prefrontal cortices. Positive correlations were found between OAHI and mean diffusivity in the left amygdala, left middle temporal gyrus, right putamen, right anterior insula, left hippocampus, and right superior temporal gyrus. The brain sites that had positive correlations with OAHI were limited, which was suggestive of the chronic brain damage that resulted from higher OAHI values with longer durations of SDB. The damage to the brain areas identified in this study was less severe than that seen in adults,[61,62] which was attributed to the young age of the children in the study and the shorter exposure to repetitive hypoxia. The conclusion to this study was that there are both short-term and long-lasting processes at play, which most likely result from a combination of the ischemic and hypoxic mechanisms that accompany SDB in children.

The most recent study to be conducted using MRI-assessed regional brain cortical thickness using T1-weighted images was conducted in 16 children with OSA (8.4 ± 1.2 years [mean ± SD];

OAHI >2 events/h, a SpO_2 nadir <92%, and/or a respiratory arousal index >2 events/h), 9 controls (8.3 ± 1.1 years), and 138 further controls from the NIH -Pediatric MRI database.[63] The children with OSA and the nine local controls underwent overnight PSG, neurocognitive assessment, and MRI scanning using T1-weighted images. Examining the whole brain, children with OSA exhibited cortical thinning in the superior and medial frontal, prefrontal, and parietal cortices and the occipital cortex compared with the whole control group (9 local controls plus 138 controls from NIH-Pediatric MRI database). Cortical thickness increased in children with OSA in the bilateral precentral gyrus, left central gyrus, regions in bilateral posterior mid and right anterior insular cortices, posterior cingulate, sub-genu of the anterior cingulate cortices extending into medial prefrontal areas, and temporal cortex and poles. No significant relationship was determined between cortical thickness and cognition measured using the Differential Ability Scales. The cortical thinning identified in this study is consistent with reduced gray matter reported in previous studies.[48,50,51,54] Thinning was suggestive of damage to the cortex in areas related to motor function, problem solving, memory, language, impulse control, social behavior, executive function, attention, and personality development.[64] The authors posited that the cortical thinning seen in children with OSA could be attributed to the effect of repeated hypoxia and sleep fragmentation, resulting in direct neuronal injury, in addition to the disruption of the normal neural developmental processes. Cortical thickening was found in areas involved in emotional control, self-awareness, cognitive function, motor control, reward, decision-making, autonomic regulation, human awareness, pain, episodic memory retrieval, and long-term memory.[65-70] The authors suggested that cortical thickening could be due to hypoxia-induced neuroinflammation and glial activation via an immune response. The small sample size in this study was a possible reason for not detecting an association between the structural findings in the cortex and cognitive performance. This was not considered particularly surprising given the large heterogeneity in the prevalence of a cognitive deficit phenotype. Subregions of some cortical structures have distinct functions; therefore, the neuropsychological consequences of OSA may differ between the subregions. Furthermore, there is a question of how long the children have had the condition; whether cortical thickening represents a late-stage effect due to atrophy. The authors concluded that further research is required to elucidate if the presence of injury to the brain is a consequence of cell loss, disruption to maturational processes, and/or hypoxia-induced inflammation.

A limitation common to most of the pediatric studies that involve MRIs is the small sample size, which can mostly be attributed to the high cost, the time commitment required by the parents and children, and the unwillingness of the children to participate in the procedure, or their parent to consent to it. Although not as comprehensively investigated in children as in adults, the studies that have assessed changes to the brain associated with SDB in children using MRI technologies have identified a plethora of brain areas affected. There is both commonality and disparity in the brain areas identified between studies, and this may reflect the different methodologies used with regard to classification of disease severity and to the MRI procedures. Furthermore, some studies performed whole-brain analyses, others focused on particular brain areas of interest, some studies used structural MRIs, and others used fMRIs.

Conclusions

The limited studies in children which have assessed cerebral oxygenation in children with SDB have identified that, in contrast to studies in adults, children appear to be able to maintain cerebral oxygenation. Nonetheless, it is clear that pediatric SDB has significant adverse effects on the brain in areas related to autonomic control, respiration, behavior, and neurocognition, all adverse sequelae identified in children with SDB. Of concern is that these changes to brain morphology and function are occurring during childhood when the brain is still undergoing significant development. It remains unknown whether they are permanent or can be reversed with treatment of the underlying SDB. Furthermore, it is unknown if this repair is dependent on the age of the child and for how long the child has had the disorder. Evidence would suggest that some areas of the brain are better at restoring their functional abilities following resolution of SDB in children than that in others, depending on the function that they are associated with. The resolution of obstructive SDB in preschool- or elementary school-aged children is not accompanied by significant improvements in neurocognition.[16,71-73] However, the effect of the resolution of SDB on cardiovascular function and control is less clear, as some studies report improvements concomitant with an improvement in SDB severity,[74-76] whereas others report no change.[77] Further longitudinal studies utilizing both cerebral oxygenation and imaging are needed to elucidate whether the brain recovers from injury following the resolution or improvement of SDB.

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Conflicts of interest

There are no conflicts of interest.

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HUMAN MILK COMPOSITION

Human milk is highly variable and provides both nutritional and bioactive components needed for infant's growth and development[1]

Nutritional Components

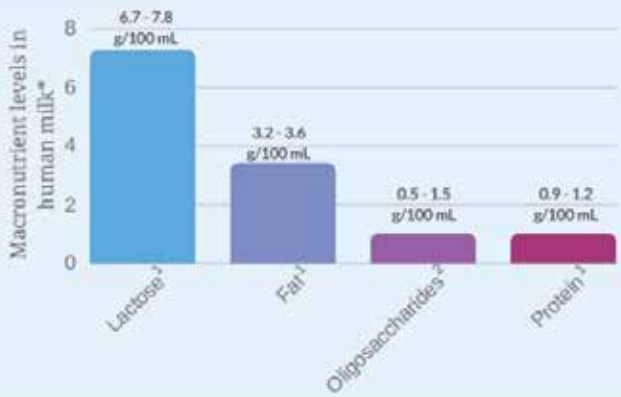
May derive from three possible sources[1]
1. Lactocytes
2. Maternal diet
3. Maternal stores

Fat

- High content of palmitic acid (at the *sn*-2 position of triglycerides) and oleic acid (at the *sn*-1 and *sn*-3 positions) [1]
- Fatty acid profile is associated with maternal diet, in particular long chain polyunsaturated fatty acids (LCPUFAs) such as DHA[1]

Lactose

- Least variable of the macronutrients, but higher levels are found in milk of mothers who produce more milk[1]



Protein

- Divided into whey and casein fractions[1]

- Human milk oligosaccharides (HMOs) serve as prebiotics that selectively stimulate the growth of beneficial bacteria in the gut, also has a role as pathogen-binding inhibitors on the intestinal surface[1]
- The most predominant species is 2'-Fucosyllactose (2'FL)[3]

Oligosaccharides

* Mean values of term mature milk, note there is high variability between individuals and composition will be different in preterm infants

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Validation of a Modified Pediatric Risk of Mortality III Model in a Pediatric Intensive Care Unit in Thailand

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Abstract

Objective: The objective of this study is to compare the performance of a modified Pediatric Risk of Mortality (PRISM) III model with the original PRISM III in prediction of mortality risk in a Thailand pediatric intensive care unit (PICU). **Subjects and Methods:** Children aged 1 month to 18 years who stayed in the PICU for more than 8 h during November 2013 to December 2016 were included in the study. **Results:** The medical records of 1175 PICU patients were included in the analysis. The patients were randomly split into two equal groups: a development (n = 588) and a validation (n = 587) sample. A modified PRISM III model was derived from the original PRISM III by omitting arterial blood gas parameters and adding selected clinical variables. The model was developed using a multiple logistic regression model on the development sample and assessed using the area under the curve (AUC) obtained from a receiver operating characteristic curve. The modified PRISM III scores were significantly higher in nonsurvivors (median = 9, interquartile range [IQR] = 4 − 13) compared to survivors (median = 2, IQR = 0 − 5). The modified PRISM III model had similar discriminative performances compared to the original PRISM III in predicting 2-day mortality (AUC: 0.874 vs. 0.873), 7-day mortality (AUC: 0.851 vs. 0.851) and overall mortality (AUC: 0.845 vs. 0.956). The modified PRISM III model was calibrated in the validation sample, and the standardized mortality ratios (SMRs) were similar. **Conclusions:** The performance of a modified PRISM III model in predicting mortality risk was comparable to the original PRISM III. Both had similar discriminative performance and SMR for overall mortality prediction in a PICU.

Keywords: Mortality prediction, pediatric intensive care unit, Pediatric Risk of Mortality III

Introduction

Critically ill children admitted in a pediatric intensive care unit (PICU) have a high risk of mortality. Various severity scoring systems have been developed to classify PICU patients on admission and determine their risk of mortality.[1] The Pediatric Risk of Mortality (PRISM) III[2] is a widely accepted scoring system[3,4] which uses the worst physiologic and laboratory values of patients on the day of admission to predict PICU mortality, similar to other scoring systems.[1,2]

PICU patients who die earlier are usually patients who had more severe illness on admission and often die within 48 h after admission.[5,6] Severity scoring systems such as PRISM III, which assesses patients on admission, may perform better for mortality prediction in these patients. However, advances in critical care have resulted in a lengthening of PICU admissions and an increase in the number of long-stay patients.[7] These patients utilize more hospital resources and require more intensive therapy such as mechanical ventilation.[7,8] In addition, the discriminative performance of various severity scoring systems has shown poorer performance in prediction of mortality among long-stay PICU patients.[7,9]

From a previous study, the discriminative performance of PRISM III for mortality prediction was improved by adding eight physiologic variables measured during admission to the PICU.[2] As mentioned above, the dynamic conditions of the patient and management in the PICU can alter the mortality risk, especially in long-stay patients. Critically ill patients who require intense or rescue therapy such as

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mechanical ventilation,[10,11] high-frequency oscillatory ventilation (HFOV),[12,13] or cardiopulmonary resuscitation[14] have an increased risk of mortality. To achieve a good prediction model, both discrimination and calibration assessment are essential.[15]

Another limitation of PRISM III is the requirement for arterial blood gas measurements, which is arguably unethical in children who have no prior clinical indications.[16,17] Due to the nonfeasibility of performing invasive arterial blood gas measurements in some children and the benefit of adding other clinical variables, we modified the original PRISM III by removed the blood gas parameters and added a number of clinical variables we felt would create a better prognostic picture. This study aimed to assess the performance of the modified PRISM III model compared to the original PRISM III in predicting mortality.

Subjects and Methods

A retrospective study was conducted among children aged 1 month–18 years at the PICU of Prince of Songkla University, Songkhla, Thailand. The unit has eight beds with provisions for a mechanical ventilator and continuous hemodynamic monitoring. The study was approved by the Ethics Committee of the Faculty of Medicine, Prince of Songkla University.

Study population

The medical records of patients admitted to the PICU during November 2013–December 2016 were evaluated. Patients who were re-admitted during the study period were counted separately. Patients who had <8 h stay and were admitted for postprocedural care, including postcardiac catheterization or diagnostic bronchoscopy, were excluded. The required sample size was calculated based on a type I error of 5%, power of 90%, an overall mortality rate of 12.0%, and a sensitivity of 0.85. Using the formula for two-independent proportions,[18] at least 1030 participants were required for validating the mortality prediction model.

Eligible patients were identified from the registration database of the PICU. All required PRISM III variables were recorded using the most abnormal values of physiologic and laboratory data within 24 h of admission to the PICU. The scoring method of the original PRISM III was followed. A PRISM III score ranges from 0 to 74 and consists of five physiologic and 12 laboratory variables as described by Pollack *et al*.[2] which are categorized into four groups: cardiovascular/neurologic vital signs (range: 0–30), acid-based/blood gasses (range: 0–22), biochemical tests (range: 0–10), and hematological tests (range: 0–12). The modified PRISM III scores (range: 0–52) was derived from the PRISM III scores by excluding the scores of all acid-based/blood gas variables [Table 1].

Apart from the variables measured in PRISM III, selected patient demographic characteristics and clinical data were additionally collected and analyzed. These variables were selected based on scientific logic and previous studies investigating risk factors for mortality among patients admitted to an PICU.[2,6,10] There were two groups of variables. The first group, called "admission variables," included various factors from the day of PICU admission, notably postoperative care, postcardiac surgery, nonoperative cardiovascular diseases, chromosomal anomaly, malignancy, previous admission to a PICU, cardiopulmonary resuscitation (CPR) before admission, acute diabetic ketoacidosis, intubation on admission, and serum albumin level. Because the clinical condition of PICU patients is so dynamic, the second group of variables we called "therapeutic variables" that occurred during the course of the PICU stay was recorded for the overall mortality prediction model, namely mechanical ventilation use, HFOV use, inhaled nitric oxide use, and renal replacement therapy. All these variables except albumin level were coded as yes or no. All data were reviewed and verified by nurses who were not involved in the patient's care.

Statistical analysis

The data were analyzed with R software version 3.4.0.[19] The patients were randomly split into two equal groups, a development sample and a validation sample. The data were summarized using means with standard variations and medians with interquartile ranges (IQRs) as appropriate. The characteristics and clinical variables between the survivor and nonsurvivor groups were compared with the Chi-squared and Fisher's exact tests for categorical variables and Student's *t*-test or Mann–Whitney test for continuous variables. $P < 0.05$ was considered statistically significant.

All variables with $P < 0.2$ from the univariate analysis were included into the initial multivariate logistic regression model predicting death. For 2- and 7-day mortality, the original PRISM III scores were compared with the modified PRISM III scores with the additional admission variables. For overall mortality, the original PRISM III scores were compared with the modified PRISM III scores with the addition of the admission and therapeutic variables. The best model was selected based on the lowest Akaike's information criterion value. The discrimination capacity between nonsurvivors and survivors of the best model was assessed using receiver operating characteristic curves based on the area under the curve (AUC).[20] An AUC between 0.80 and 0.90 represents good discrimination whereas an AUC ≥0.90 represents excellent discrimination. Calibration of models was assessed in the validation sample using the standardized mortality ratio (SMR) calculated by dividing the observed number of deaths with the expected number within each decile of probability of mortality.

Results

There were 1202 PICU admissions during the study period, of which 27 were excluded because the length of PICU stay was less than 8 h ($n = 19$) or the reason for admission was diagnostic bronchoscopy ($n = 8$). A total of 1175 admissions were, therefore, included in the analysis, which were randomly

Table 1: Scores for the modified Pediatric Risk of Mortality III by omitting arterial blood gas measurements from original PRISM III

Variable	Neonates	Infants	Children	Adolescents	Score
Cardiovascular and neurologic vital signs (score range 0-30)					
Systemic blood pressure (mmHg)	>55	>65	>75	>85	0
	40-55	45-65	55-75	65-85	3
	<40	<45	<55	<65	7
Heart rate	<215	<215	<185	<145	0
	215-225	215-225	185-205	145-155	3
	>225	>225	>205	>155	4
Temperature	All ages		33-40 c		0
			<33 or >40 c		3
Mental status	All ages		Glasgow coma score ≥8		0
			Glasgow coma score <8		5
Pupillary reflex	All ages		Both reactive		0
			One pupil fixed, pupil >3 mm		7
			Both pupils fixed, pupil >3 mm		11
Biochemical tests (score range 0-10)					
Blood glucose (mg %)	All ages		≤200		0
			>200		2
Potassium (mmol/L)	All ages		≤6.9		0
			>6.9		3
Creatinine (mg %)	≤0.85	≤0.9	≤0.9	≤1.3	0
	>0.85	>0.9	>0.9	>1.3	2
BUN* (mg %)	≤11.9		≤14.9 (non-neonates)		0
	>11.9		>14.9 (non-neonates)		3
Hematological tests (score range 0-12)					
White blood cell count	All ages		≥3000 cells/mm^3		0
			<3000 cells/mm^3		4
Platelets (cells/mm^3)	All ages		>200,000		0
			100,000-200,000		2
			50,000-99,999		4
			<50,000		5
PT† (s) or PTT‡ (s)		Neonates		Non-neonates	
		PT ≤22 and PTT≤85		PT ≤22 and PTT ≤57	0
		PT >22 or PTT>85		PT >22 or PTT >57	3
Total score					0-52

*BUN: Blood urea nitrogen, †PT: Prothrombin time, ‡PTT: Partial thromboplastin time

split into the development (n = 588) and validation (n = 587) samples.

For the development sample, 53% were male and 58% were aged <5 years. The most common reasons for admission to PICU were cardiovascular (36.5%) and respiratory (30.1%) problems followed by neurological problems (19.1%). Fifty-two percent of the patients were admitted for treatment of medical illnesses and 48% for postoperative care. Among the postoperative care patients, 22% underwent emergency/unscheduled surgery and 47.7% had cardiac surgery, including both open and closed heart surgeries. The median length of PICU stay was 3.5 days (IQR: 2−7.2), and the PICU mortality rate was 13.9%. A comparison of the patients' demographic characteristics and clinical variables between survivors and nonsurvivors is shown in Table 2. Significantly higher modified PRISM III scores were found for nonsurvivors (median [IQR] = 9 [4−13]), compared to survivors (median [IQR] = 2 [0−5]) and PRISM III scores (median [IQRs] = 12 [8−18] vs. 4 [0−7]), respectively.

Table 3 shows the factors significantly associated with overall mortality from the multiple logistic regression model. Four admission variables, such as postoperative care, CPR before admission, intubation on admission, and serum albumin level, and three therapeutic variables, such as mechanical ventilation use, HFOV use, and CPR during PICU stay, were significantly associated with overall mortality. These seven variables were used in the overall mortality prediction model.

The discriminative performances of the modified PRISM III with admission variables and original PRISM III for 2-day and 7-day mortality are shown in Figure 1. The modified PRISM III was comparable to the original PRISM III in predicting

Table 2: Characteristics of survivors and nonsurvivors (*n*=588)

Variable	Survivors (*n*=506)	Nonsurvivors (*n*=82)	Total (*n*=588)	*P*
Male	267 (52.8)*	46 (56.1)	313 (53.2)	0.659
Age (months), median (IQR)	35.5 (9.2-97.6)	66 (12.6-125.8)	37.9 (9.8-105)	0.148
Admission type				
Elective	114 (22.5)	4 (4.9)	118 (20.1)	<0.001
Emergency/urgent	392 (77.5)	78 (95.1)	470 (79.9)	
PRISM III, median (IQR)	4 (0-7)	12 (8-18)	4 (0.8-9)	<0.001
Modified PRISM III, median (IQR)	2 (0-5)	9 (4-13)	2 (0-5)	<0.001
PICU length of stay (days), median (IQR)	3 (2-7)	6 (2-16)	3.5 (2-7.2)	0.006
Ventilator duration (days), median (IQR)	1 (1-5)	5 (1-15.5)	2 (1-6)	<0.001
Admission variables†				
Postoperative care	266 (52.6)	17 (20.7)	283 (48.1)	<0.001
Postcardiac surgery	125 (24.7)	10 (12.2)	135 (23.0)	0.018
Serum albumin level (g/dL), median (IQR)	3.5 (3.1-3.9)	3.0 (2.6-3.4)	3.4 (3-3.9)	<0.001
Nonoperative cardiovascular disease	79 (15.6)	12 (14.6)	91 (15.5)	0.950
Chromosomal anomaly	21 (4.2)	4 (4.9)	25 (4.3)	0.767
Malignancy	96 (19.0)	24 (29.3)	120 (20.4)	0.046
Previous PICU admission	75 (14.8)	18 (22.0)	93 (15.8)	0.139
CPR before admission	11 (2.2)	10 (12.2)	21 (3.6)	<0.001
Acute diabetic ketoacidosis	2 (0.4)	0 (0.0)	2 (0.3)	1.000
Intubation on admission	355 (70.2)	66 (80.5)	421 (71.6)	0.073
Therapeutic variables‡				
Mechanical ventilation use	385 (76.1)	79 (96.3)	464 (78.9)	<0.001
Ventilator duration (days), median (IQR)	1 (1-5)	5 (1-15.5)	2 (1-6)	<0.001
High frequency oscillatory ventilator use	19 (3.8)	25 (30.5)	44 (7.5)	<0.001
Renal replacement therapy	13 (2.6)	10 (12.2)	23 (3.9)	<0.001
CPR during PICU admission	9 (1.8)	36 (43.9)	45 (7.7)	<0.001

*Numbers in the table are frequency (%) unless stated otherwise, †Variables present on the day of PICU admission, ‡Variables recorded during PICU stay. IQR: Interquartile range, PRISM: Pediatric Risk of Mortality, PICU: Pediatric intensive care unit, CPR: Cardiopulmonary resuscitation

Table 3: Significant variables associated with mortality from multiple logistic regression

Variable	Crude OR (95% CI)	Adjusted OR (95% CI)	*P**
Modified PRISM III score	1.3 (1.2-1.3)	1.2 (1.1-1.3)	<0.001
Admission variables†			
Postoperative care	0.3 (0.2-0.5)	0.5 (0.3-1.0)	<0.001
CPR before admission	9.6 (3.8-24.2)	5.3 (1.5-18.6)	0.02
Intubation on admission	2.6 (1.2-6.0)	2.5 (1.0-6.4)	0.04
Serum albumin level	0.4 (0.3-0.6)	0.6 (0.4-0.9)	0.02
Therapeutic variables‡			
Mechanical ventilation use	8.3 (2.6-26.7)	12.1 (2.3-58.4)	<0.001
HFOV use	11.2 (5.8-21.7)	6.5 (2.6-16.0)	<0.001
CPR during PICU stay	43.2 (19.6-95.3)	30.6 (10.7-87.5)	<0.001

*Likelihood ratio test, †Variables present on the day of PICU admission, ‡Variables measured during PICU stay. PRISM: Pediatric Risk of Mortality, PICU: Pediatric intensive care unit, CPR: Cardiopulmonary resuscitation, HFOV: High-frequency oscillatory ventilation, OR: Odds ratio, CI: Confidence interval

both 2-day (AUC 0.874 vs. 0.873) and 7-day mortalities (AUC 0.851 vs. 0.853), of which the mortality prediction was better for 2-day than for 7-day mortality.

The prediction models for overall mortality are illustrated in Figure 2. The modified PRISM III with combined variables was found to give the best prediction. Based on the AUC, the discriminative performance of this modified PRISM III model (AUC = 0.956) was better than the modified PRISM III with admission variables alone (AUC = 0.850) and the original PRISM III (AUC = 0.850).

In the validation sample, the PICU mortality rate was 13.6%, which was similar to the developmental sample. The observed and expected mortality rates for the validation samples using the modified PRISM III with admission and therapeutic variables and original PRISM III are shown in Table 4. For all deciles of mortality probability, the SMR was close to one except for probabilities in the range of 0–0.1 which gave an SMR of 0.23 indicating an overprediction of mortality. The average standardized mortality rates from the modified PRISM III and original PRISM III were 0.99 and 0.98, respectively.

Discussion

A modified PRISM III model which omitted arterial blood gas variables and added some clinical variables had a similar discriminative performance compared to the original PRISM III. The addition of admission variables was useful in the modified PRISM III model in predicting 2-day (AUC: 0.874 vs. 0.873) and 7-day mortality (AUC: 0.851 vs. 0.853), and the addition of therapeutic variables was useful for

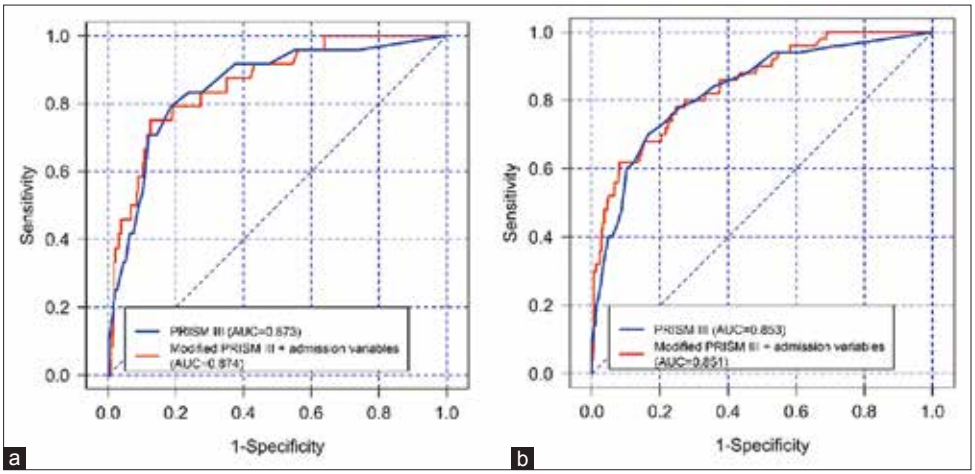

Figure 1: Receiver operating characteristic curves for (a) 2-day mortality and (b) 7-day mortality prediction using the modified Pediatric Risk of Mortality III score with admission variables versus the original Pediatric Risk of Mortality III. The additional admission variables were postoperative care, cardiopulmonary resuscitation before admission, intubation on admission, and serum albumin. PRISM III: Pediatric Risk of Mortality III, AUC: Area under the curve.

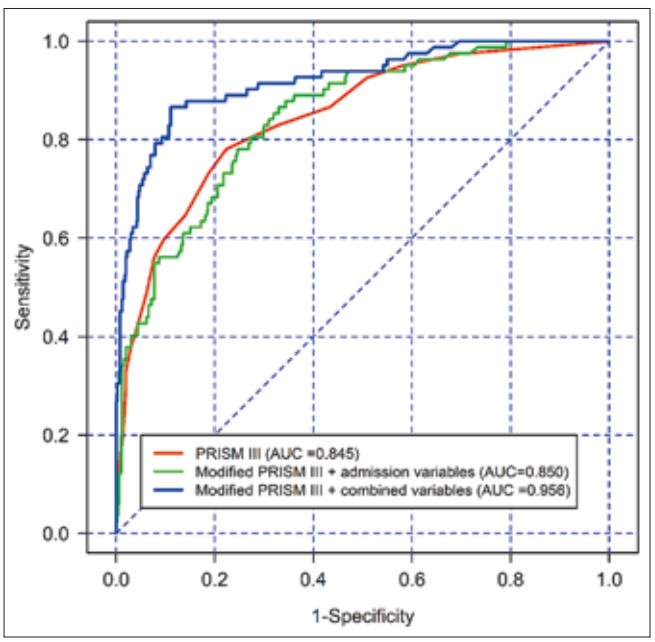

Figure 2: Receiver operating characteristic curves for overall mortality prediction using the different models. The combined variables consist of four admission variables (postoperative care, cardiopulmonary resuscitation before admission, intubation on admission, and serum albumin) and three therapeutic variables (mechanical ventilation use, high-frequency oscillatory ventilation use, and cardiopulmonary resuscitation during pediatric intensive care unit stay). PRISM III: Pediatric Risk of Mortality III, AUC: Area under the curve.

predicting overall mortality (AUC: 0.956 vs. 0.845). These modified PRISM III models can be applied when blood gas measurements are not feasible.

In modernized pediatric critical care, there is an increasing trend to use noninvasive techniques where feasible. For example, previous studies have suggested the use of oxygen saturation (SpO_2) obtained by pulse oximetry instead of arterial partial pressure of oxygen (PaO_2) in respiratory distress, even among mechanically ventilated children,[16] and encouraged the use of end-tidal CO_2 to estimate $PaCO_2$[17] to assess the severity of disease and follow treatment response. The use of noninvasive ventilation and high-flow nasal cannulae as initial respiratory support in various types of cardiorespiratory failure in children, including those with postoperative conditions, has been increasing;[21-23] thus, arterial blood gas monitoring is being performed less frequently and might even be considered unethical in this population. A recent study by Ray *et al*.[24] demonstrated the feasibility of using SpO_2/FiO_2 instead of PaO_2/FiO_2 values for calculating pediatric index of mortality (PIM) scores for use in predicting PICU mortality.

Our mortality prediction model demonstrated that the addition of important admission and therapeutic variables could improve the discriminative ability of the original PRISM III model. Due to dynamic changes in any critically ill patient's clinical status, the variables from the first few hours on the day of admission may not be sufficient to reflect the condition of long-stay patients with the PRISM III. Visser *et al*.[9] demonstrated that both the PRISM and PIM models have poorer discriminative performance for patients who stay in a PICU longer than 6 days compared to those who stay ≤6 days. The median length of stay for nonsurvivors in our study was 6 days, which was similar to two other studies.[7,8] This is the reason that our modified PRISM, with the addition of therapeutic variables during PICU stay, seems to be more useful in mortality prediction.

Additional variables used in the overall mortality prediction model of our study included postoperative care, serum albumin level, intubation on admission, CPR before admission, mechanical ventilator use, HFOV use, and CPR during the PICU stay. Some of these variables were associated with mortality in previous studies among critically ill patients.[10-14] In our study, postoperative care patients had a lower mortality risk compared to those with medical illnesses.

Table 4: Calibration of the modified Pediatric Risk of Mortality III model in a validation sample (*n*=587; 80 deaths) to predict overall mortality

Probability of mortality	Patients, *n* (%)	Survivors		Nonsurvivors		SMR*
		Observed	Expected	Observed	Expected	
Modified PRISM III						
0-0.1	441 (75.1)	436	414.2	5	22.0	0.23
0.1-0.2	41 (7.0)	33	28.0	8	6.1	1.30
0.2-0.3	15 (2.6)	12	9.0	3	3.7	0.80
0.3-0.4	19 (3.2)	11	7.1	8	6.6	1.20
0.4-0.5	12 (2.0)	4	2.2	8	5.4	1.48
0.5-0.6	9 (1.5)	3	1.3	6	5.0	1.21
0.6-0.7	9 (1.5)	2	0.7	7	5.8	1.20
0.7-0.8	6 (1.0)	1	0.2	5	4.5	1.11
0.8-0.9	14 (2.4)	5	0.7	9	12.0	0.76
0.9-1.0	21 (3.6)	0	0.0	21	20.0	1.05
Total	587	507	426.4	80	80.6	0.99
PRISM III						
0-0.1	440 (75.0)	435	413.2	5	22.0	0.23
0.1-0.2	39 (6.6)	31	26.3	8	5.8	1.37
0.2-0.3	22 (3.7)	15	11.2	7	5.5	1.27
0.3-0.4	16 (2.7)	10	6.5	6	5.6	1.07
0.4-0.5	9 (1.5)	4	2.2	5	4.0	1.23
0.5-0.6	6 (1.0)	3	1.3	3	3.3	0.91
0.6-0.7	7 (1.2)	2	0.7	5	4.5	1.10
0.7-0.8	9 (1.5)	2	0.5	7	6.7	1.04
0.8-0.9	13 (2.2)	3	0.4	10	11.0	0.90
0.9-1.0	26 (4.4)	2	0.1	24	24.7	0.97
Total	587	507	425.3	80	81.7	0.98

*SMR: Standardized mortality ratio=Observed mortality/expected mortality. SMR: Standardized mortality ratio, PRISM: Pediatric Risk of Mortality

Approximately 80% of postoperative care patients admitted to a PICU have undergone elective surgery while medically ill patients who are admitted to a PICU usually have complicated problems leading to multiorgan dysfunction, which is known as a strong predictor of mortality.[10,11] Furthermore, serum albumin on admission, another independent predictor of mortality in our study, has been reported to be associated with higher mortality and poor PICU outcome including requiring prolonged mechanical ventilator use, longer duration of PICU stay, and risk of progression to multiorgan dysfunction.[25,26] Tiwari *et al*.[26] reported that hypoalbuminemia at admission was associated with a higher 60-day mortality and lower probability of discharge from intensive care, and an increase of 1.0 g/dL in serum albumin at admission resulted in a 73% reduction in mortality the hazard of death. Receiving CPR, either before PICU admission or during the course of their PICU stay, has also been reported as an independent factor associated with predicting mortality. Although the success rate (return to spontaneous circulation) of in-hospital pediatric CPR has been reported to be as high as 60%–75%,[14,27] both studies found that survival rate to discharge was only 20%. Another study reported that children who survived from CPR usually suffered from multiorgan dysfunction and metabolic disturbances and had high susceptibility to infection and metabolic disturbances and factors which are all associated with mortality.[28]

Cardiorespiratory failure and the need for respiratory support were the most common reasons for PICU admission in our study. As currently recommended,[23] our practice has been gradually changing to the use of noninvasive ventilation as first-line respiratory support in order to reduce PICU stay, ventilator-associated pneumonia, and postextubation complications.[29] Therefore, the requirement of intubation on admission as well as mechanical ventilation use would reflect failure of noninvasive ventilation or higher severity of illness and can be used as a predictor for mortality, similar to previous studies.[10,11] Yaman *et al*.[21] reported that the PICU patients who had failure of noninvasive ventilation use had higher PRISM III scores, more frequent underlying disease, longer PICU stay, and increased risk of mortality. Likewise, HFOV is often used as rescue therapy, particularly in patients with acute respiratory distress syndrome (ARDS) with refractory hypoxemia. Currently, there is insufficient evidence to support the benefit of HFOV use in terms of mortality reduction.[30,31] Furthermore, the use of HFOV increases the use of sedatives and vasoactive and neuromuscular blockage agents. HFOV has been reported to be associated with poor PICU outcomes and mortality.[32] In our practice, we do not use the early HFOV strategy, so patients receiving HFOV reflect the presence of moderate to severe ARDS and an unresponsiveness to conventional ventilation, a combination of factors which has been reported to be associated with a high risk of mortality.[33]

For the probability of mortality risk at all deciles, the SMR showed good concordance, except at the deciles of p 0–0.1. These findings are consistent with previous studies using the PRISM III model that also found good predictability of SMR for higher probabilities of mortality exceeding 0.5, although different scales of stratification were used.[2,4,34,35] The overprediction of SMR at deciles of *P* 0–0.1 in our study may have been due to a lower number of less severe patients in our study resulting in a large proportion of survivors in this decile. Slater *et al.*[34] observed a significant overprediction of deaths in the subgroups of respiratory (SMR = 0.65) and cardiac patients (SMR = 0.54), which constituted nearly two-thirds of our study population.

There were some limitations in our study. First, the study had a small sample size compared to the original PRISM III study.[2] However, our patient sample was adequate based on our sample size calculation. Second, all the datasets we used were from a single PICU. However, the parameters applied in our study are common practice for PICU patients in most countries in Asia.[33,36,37]

Conclusions

The modified PRISM III model, omitting arterial blood gas parameters with additional clinical and therapeutic variables, gave a similar discriminative performance for overall mortality prediction in PICU to the original PRISM III. The modified PRISM III model can be applied when blood gas measurements are not feasible. However, the risk scoring system using variables in our modified PRISM III model should be further validated in large-scale populations.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Pulmonary Function Abnormalities in Nigerian Children with Sickle Cell Anaemia: Prevalence, Pattern and Predictive Factors

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Abstract

Background: Advances in care of children with sickle cell anaemia (SCA) have increased their chances of survival to adolescence and adulthood though this is often associated with multi-organ system pathologies including lung dysfunctions. This study aimed to determine the prevalence, pattern and factors associated with pulmonary function abnormalities in Nigerian children with SCA. **Methods:** Pulmonary functions of 104 children with SCA in steady state and 104 age- and sex-matched haemoglobin AA controls aged 6 to 16 years at the Wesley Guild Hospital, Ilesa Nigeria, were assessed using Spirolab III (Medical International Research, Italy) spirometer following standard protocol. Socio-demographic characteristics, nutritional status and pulmonary function parameters of these children were compared, and the predictive factors of pulmonary function abnormalities in SCA children were determined using binary logistic regression. **Results:** SCA children had lower lung volumes and capacities and higher prevalence of pulmonary function abnormalities compared to controls, and a restrictive ventilatory pattern (22.1%) was the most predominant form. Adolescent age, previous acute chest syndrome (ACS), repeated painful crises and multiple hospitalisations in the previous year were significantly associated with pulmonary function abnormalities ($P < 0.05$). Only adolescent age group (odds ratio [OR] = 3.738; 95% confidence interval [CI] = 1.480–9.440; $P = 0.005$) and previous ACS (OR = 8.500; 95% CI = 2.044–12.959; $P = 0.044$) independently predicted pulmonary function impairments among the SCA children. **Conclusion:** SCA predisposes children to pulmonary dysfunction, particularly during adolescent years and in those with ACS, multiple crises and hospitalisations. Routine pulmonary function assessment in these children will facilitate early recognition and prompt management.

Keywords: Acute chest syndrome, painful crisis, pulmonary function, sickle cell anaemia

Introduction

Sickle cell anaemia (SCA) is an autosomal recessively inherited haemoglobinopathy characterised by both acute and chronic haemolytic anaemia, acute episodes of vaso-occlusive events and multi-organ dysfunctions due to repeated sickling phenomenon.[1] It results from a single-gene mutation in the deoxyribonucleic acid base sequence of the short arm of human chromosome 11, leading to the substitution of valine for glutamic acid in the sixth position of the β-globin chain of haemoglobin (Hb).[1]

SCA is a disease of public health significance, particularly in Sub-Saharan Africa where an estimated six million individuals with SCA live and the disease contributes to more than 5% of childhood mortality.[2] In Nigeria, more than 150, 000 homozygous infants were estimated to be born yearly, with about four million individuals affected by the disease.[3] Nigeria, therefore, bears the lion's share of the global burden of SCA.[3]

Advances in health-care delivery services even in developing countries had increased the chances of survival of children with SCA to adolescence and adulthood.[4] The better survival allows more morbidities to manifest in different systems, including the respiratory system.[5] The respiratory system like the other systems of the body is affected by infections and infarctions which characterise the disease.[5,6] Children with SCA are predisposed to recurrent chest infections, pulmonary infarctions,

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acute chest syndrome (ACS) and pulmonary thromboembolism including fat embolism and pulmonary hypertension.[5,6] Some of the pathogenetic mechanisms causing pulmonary disorders in this group of children include haemolysis, endothelial cell dysfunction and vasculopathy.[5,6] These respiratory disorders, particularly ACS, have been reported as a leading cause of hospitalisation, including admission to intensive care unit and premature death in individuals with sickle cell disease.[5,6] Consequently, pulmonary function assessments in children with SCA had been explored to facilitate early detection of pulmonary dysfunctions in these children with variable reports of predominantly restrictive, obstructive and even mixed ventilatory patterns.[7-12] Reported risk factors for lung function abnormalities among SCA children varied. For instance, Arteta *et al.*[9] reported increasing age, personal or family history of wheezing and evidence of haemolysis as risk factors of abnormal lung functions observed in 39% of American children with sickle cell disease. Previous hospital admission due to acute lung diseases was found as a predictor of lung function abnormalities in Brazilian children with SCA.[12] There is a paucity of reports, however, on the socio-demographic and clinical factors associated with pulmonary function abnormalities in these children, particularly in developing countries including Nigeria where the burden of the disease is large. This study sets out to determine the prevalence and pattern of pulmonary function abnormalities among children with SCA and their age- and sex-matched counterparts with Hb genotype AA and to determine the predictive factors associated with pulmonary function abnormalities in sickle cell anaemic children presenting to a tertiary health facility in Nigeria.

Methods

Study design

This was a hospital-based, comparative cross-sectional study.

Study location

This study was conducted at the paediatric haematology and children welfare clinics of the Wesley Guild Hospital (WGH), Ilesa, Nigeria. The haematology clinic runs once a week for children with haemato-oncologic disorders, while the welfare clinic runs daily for children with minor illness, pre-school entry medical examinations and minor surgical conditions. The WGH is a tertiary arm of the Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Southwest Nigeria. Ilesa is situated on latitude 7°35'N of the equator and longitude 4°51'E of the meridian and is the largest town in Ijesaland.[13]

Sample selection

Consecutively, children aged 6 to 16 years with Hb genotype SS in steady state (free of crises, infections or other illnesses for more than 4 weeks and not being transfused for more than 3 months)[14] who presented for routine clinic visits during the study were recruited. SCA children with stroke, congenital or acquired heart diseases and those who could not perform an acceptable or useable spirometry test were excluded.

The children in the comparative group were recruited from apparently healthy children with Hb genotype AA who presented to the child welfare clinic of the hospital for routine preschool entry medical examinations. These children were age, sex and ethnic matched with the SCA group.

Sample size determination

The minimum sample size for this study was estimated using OpenEpi sample size software®.[15] Using 5% significance (alpha) level, 80% study power and 95% confidence interval (CI), with the assumptions that: the mean difference of forced vital capacity (FVC) among children with Hb genotype SS and those with AA Hb genotype = 0.36 L and the standard deviation (SD) of 0.57 and 0.55 L for SS and AA children, respectively (Achigbu *et al.*)[7] and the ratio of SS to AA children was 1:1, the minimum sample size was estimated to be $n = 200$ (100 each for SCA and Hb AA children) but 208 (104 each for the groups) eligible children during the study period were studied.

Ethical consideration

Ethical approval of this study was granted by the Ethics and Research Committee of the OAUTHC, Ile-Ife, Nigeria (Approval no ERC/2015/08/05). Informed consent and assent as appropriate were obtained from the caregivers and study participants.

Study procedure

Using a data pro forma specifically designed for the study, a history obtained from the study participants and/or their caregivers included their age, sex and duration since the disease was diagnosed. The socio-economic classes of the children were obtained by rank assessment of parental occupation, highest level of educational qualification and income distribution as described by Ogunlesi *et al.*[16] Among the children with SS, the frequency of hospitalisation, blood transfusion and painful crises that required hospital visits were obtained from the clinical notes of the study participants. ACS was recorded as defined in the clinical notes as an acute illness characterised by fever and respiratory symptoms (dyspnoea and chest pain with or without cough) accompanied by new pulmonary infiltrates on chest radiograph.[14] Other complications such as chronic leg ulcer and avascular necrosis of femoral neck were also recorded.

The weight and height of the study participants were measured using a weighing scale and an RGZ-160 stadiometer (Laerdal Medical Ltd., Orpington, Bromley, United Kingdom), respectively. Nutritional status of the children was then determined using the World Health Organization (WHO) growth reference chart.[17] Stunting, underweight and wasting were defined as height for age, Z score <−2SD from the mean; body mass index (BMI) (weight in Kg/height^2 in m^2) Z score <−2SD and weight for height Z score <−2SD from the mean, respectively, while overweight was defined as BMI > Z score + 2SD on the WHO growth reference chart.[17]

Lung function assessment of study participants

Lung function assessment was done using a spirometer (MIR Spirolab III, Medical International Research Srl,

Italy) following the American Thoracic Society/European Respiratory Society guidelines.[18] After demonstrating the procedure to the children, they were instructed to inspire to maximum capacity (total lung capacity) and blow through the mouthpiece as fast and as long as possible (to residual volume). The measurement was done in sitting position and with the study participants wearing a nose clip. Lung function assessments were done , for a minimum of three times and not more than eight times. The parameters of interest, i.e., forced expiratory volume in 1 s (FEV_1), FVC, Tiffeneau index (FEV_1/FVC ratio) and peaked expiratory flow rate (PEFR), were recorded from the best reading that met the acceptability criteria.[18] The reference value used for this study was based on the data of Knudson.[19]

Diagnosis of obstructive ventilatory pattern was made when FEV_1/FVC ratio was <80%, FEV_1% <80% predicted and FVC% >80% predicted or concavity in the flow-volume curve of spirogram. These were tested with short-acting bronchodilator to assess for significant reversibility (increased in actual $FEV_1 \geq 12\%$ from the baseline).[20] A restrictive ventilatory pattern was presumed when FVC% was <80% predicted, FEV_1/FVC >80% with the flow-volume spirogram curve showing convex shape. Those with FVC% <80% predicted for age, sex and height with FEV_1/FVC <80% were classified as having mixed impairment.[20]

Data analysis

Data analysis was performed using the Statistical Package for the Social Sciences software Version 17.0 (SPSS Inc., Chicago 2008, IL, USA). The age, weight and height as well as lung function parameters of the children were summarised using mean and SD. Proportions and percentages were determined for their sex, nutritional status and ventilatory pattern categories. Differences between the mean (SD) lung function parameters of the SCA and their Hb AA counterparts were analysed using Student's *t*-test, whereas categorical variables were analysed using Pearson's Chi-square test and Fisher's exact test as appropriate. Pearson's correlation tests were performed to determine the relationship between ages of the SCA and their lung function parameters. Binary logistic regression analysis was used to determine the predictive factors for lung function impairment in the children with SCA. The results were interpreted with odds ratios (ORs) and 95% CI. Statistical significance was established when the CI did not embrace unity and level of significance taken at $P < 0.05$.

Results

From October 2016 to September 2017, 208 children (104 each for SCA and age- and sex-matched Hb AA) were recruited for the study. Fifteen children with SCA were excluded including six with residual muscle weakness from a previous stroke, five with cardiac lesions and four children who could not perform acceptable spirometry tests.

The ages of the children ranged from 6 to 16 years with a mean (SD) age of 10.1 (3.0) years. There was no significant difference in the age distribution, gender and parental socio-economic status of the children with SCA and their Hb genotype AA counterparts [Table 1]. The mean age at diagnosis of SCA was 4.1 (2.7) years (range: 7 months to 12 years). The mean (SD) weight and height of the children with Hb AA was significantly higher than that of children with SCA [Table 2]. Likewise, there was a higher prevalence of undernutrition among the children with SCA compared to their Hb AA counterparts [Table 1].

The means (SD) of FEV_1, FVC and PEFR of the children with HB AA were significantly higher than that of the children with SCA [Table 2]. The age and sex distribution of the children with SCA and Hb AA as related to their pulmonary function parameters also showed significantly higher FEV_1 (FEV_1% predicted) and FVC among the children with Hb AA compared to those with SCA. [Table 3] The FVC% predicted was particularly lower in male adolescents. Furthermore, significantly more proportion of the SCA children had pulmonary function abnormalities compared to those with HB AA (29.8% vs. 3.6%; $\chi^2 = 27.875$; $P < 0.001$), and a restrictive ventilatory pattern was the most predominant pulmonary function impairment observed [Table 1 and Figure 1]. Of the 6 (5.8%) SCA children with obstructive ventilatory pattern, 4 (3.8%) had significant reversibility with a short-acting bronchodilator.

There was a significant but weakly negative correlation between the ages of the children with SCA and their lung function parameters (age and. FEV_1%; Pearson's correlation = −0.326; $P = 0.001$, age and FVC%; Pearson's correlation = −0.286; $P = 0.005$, age vs. PEFR%; Pearson's correlation = −0.322; $P = 0.019$, age and FEV_1/FVC Pearson's correlation = −0.297; $P = 0.004$).

More adolescents (study participants aged 11 to 16 years) had pulmonary function abnormalities, as 21 (43.8%) of the 48 adolescents compared to 10 (17.9%) of the 56 pre-adolescents had lung function impairments ($\chi^2 = 8.282$; $P = 0.004$). Likewise, children with multiple hospitalisations (>3 in the last year) (60.0% vs. 36.2%; $\chi^2 = 4.820$; $P = 0.028$), multiple painful crises (48.0% vs. 31.78%; $\chi^2 = 3.830$; $P = 0.023$) and

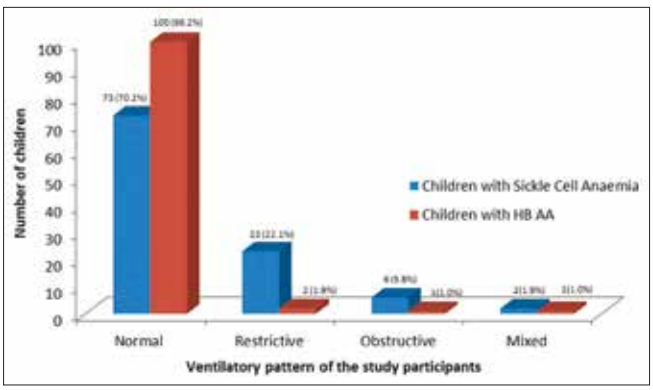

Figure 1: The distribution of the pattern of lung function abnormalities recorded in the study participants.

Table 1: Distribution of the study participants according to age, gender, social class, nutritional status and ventilatory pattern

Socio-demographic variables	Children with SCA (n=104), n (%)	Children with Hb AA (n=104), n (%)	P
Age range (years)			
6-9	46 (44.2)	45 (43.3)	0.889
10-13	32 (30.8)	33 (31.7)	0.881
14-16	26 (25.0)	26 (25.0)	1.000
Mean (SD) age	10.2 (3.3)	10.1 (3.1)	1.000
Gender			
Male	51 (49.0)	51 (49.0)	1.000
Female	53 (51.0)	53 (51.0)	
Socio-economic class			
Upper	20 (19.3)	25 (24.0)	0.400
Middle	59 (56.7)	69 (66.3)	0.869
Low	25 (24.0)	30 (28.7)	0.432
Nutritional status			
Underweight	15 (14.4)	6 (5.7)	0.038
Stunting	24 (23.0)	5 (4.7)	<0.001
Wasting	21 (20.1)	9 (8.4)	0.018
Overweight	0 (0.0)	2 (1.9)	0.477
Ventilatory pattern			
Normal	73 (70.2)	100 (96.2)	<0.001
Restrictive	23 (22.1)	2 (1.9)	<0.001
Obstructive	6 (5.8)	1 (0.9)	0.043
Mixed	2 (1.9)	1 (0.9)	1.000

SCA: Sickle cell anaemia, HB: Haemoglobin, SD: Standard deviation

Table 2: Anthropometric and pulmonary function parameters of the study participants

Parameters	Children with SCA		Children with Hb AA		t-test	P
	Mean (SD)	Range	Mean (SD)	Range		
Weight (kg)	26.2 (7.9)	14.0-51.0	32.6 (10.1)	17.5-63.0	5.090	<0.001
Height (m)	1.3 (0.2)	105-168	1.4 (0.1)	108-172	4.560	<0.001
FEV_1 (L)	1.4 (0.5)	0.55-3.01	1.7 (0.4)	0.68-2.81	4.780	<0.001
FEV_1 (%) predicted	85.9 (23.0)	47.0-119	92.2 (12.7)	48.0-140.0	2.450	0.015
FVC (L)	2.9 (1.4)	0.56-3.21	2.0 (0.5)	0.6-3.38	6.170	<0.001
FVC (%) predicted	87.7 (20.9)	57.0-138	93.6 (18.7)	40.0-140.0	2.150	0.033
FEV_1/FVC (%)	89.8 (14.0)	61.2-110.0	86.8 (9.4)	51.05-100.0	1.810	0.071
PEFR (L/s)	2.7 (1.3)	0.96-8.75	3.3 (1.0)	1.28-7.19	3.730	<0.001
PEFR (%) predicted	75.7 (18.3)	36.0-139.0	75.0 (20.5)	33.0-140.0	0.2600	0.795

SCA: Sickle cell anaemia, HB: Haemoglobin, SD: Standard deviation, FEV_1: Force expiratory volume in 1 s, FVC: Force vital capacity, PEFR: Peaked expiratory flow rate

previous ACS (75.0% vs. 26.0%; χ^2 = 7.611; P = 0.006) were significantly more likely to have pulmonary function abnormalities. Socio-demographic characteristics, frequency of blood transfusion, age at diagnosis of SCA and other SCA complications were not significantly related to the presence of pulmonary function abnormalities in the children [Table 4].

Using binary logistic regression analysis, adolescent age group (OR = 3.738; 95% CI = 1.480–9.440; P = 0.005) and previous ACS (OR = 8.500; 95% CI = 2.044–12.959; P = 0.044) were independent predictors of lung function impairment among the children with SCA [Table 5].

Discussion

This study highlighted the prevalence and distribution of pulmonary function abnormalities in Nigerian children with SCA and determined the predictive factors for lung function abnormalities among children with SCA. Children with SCA were shorter, lighter and had a higher prevalence of undernutrition compared to their HB AA counterparts. These findings were similarly reported by other authors.[21-23] SCA was reported to affect growth and development of children.[5,24,25] This may arise from the chronic anaemic state, resulting in folate and other micronutrient wasting,[24] chronic hypoxaemia from the resultant anaemia[5] and growth hormone deficiency

Table 3: Age distribution of the male and female study participants as related to pulmonary function parameters

Age range (years)	Pulmonary function parameters					
	Male SCA	Male controls	*P*	Female SCA	Female controls	*P*
			FVC% predicted, mean (SD)			
6-9	99.9 (30.7)	90.2 (19.7)	0.242	105.8 (29.8)	96.5 (16.2)	0.168
10-13	83.9 (25.6)	92.7 (13.6)	0.084	87.7 (28.6)	94.3 (18.2)	0.432
14-16	70.2 (19.5)	85.8 (5.6)	0.014	80.6 (8.1)	86.4 (13.8)	0.187
			FEV_1% predicted			
6-9	87.6 (14.5)	97.7 (25.5)	0.022	91.5 (10.3)	108.0 (29.3)	0.001
10-13	83.5 (21.2)	93.7 (15.9)	0.033	82.0 (19.2)	91.2 (7.8)	0.015
14-16	82.8 (14.5)	89.6 (7.0)	0.036	80.8 (7.8)	88.8 (14.4)	0.016
			FEV_1/FVC ratio			
6-9	92.1 (8.6)	85.8 (12.5)	0.071	95.3 (7.8)	86.2 (10.1)	0.050
10-13	84.0 (19.9)	87.0 (7.7)	0.544	86.7 (12.7)	87.8 (9.5)	0.805
14-16	88.9 (21.8)	90.4 (6.3)	0.821	92.3 (9.7)	86.5 (6.7)	0.077
			PEFR% predicted			
6-9	80.3 (15.9)	82.8 (19.0)	0.305	83.9 (18.0)	81.1 (23.4)	0.335
10-13	68.7 (15.6)	71.1 (20.6)	0.345	72.1 (13.6)	69.8 (14.8)	0.245
14-16	72.8 (15.7)	83.3 (14.4)	<0.001	66.0 (16.2)	62.7 (20.1)	0.194

t-test applied. SCA: Sickle cell anaemia, SD: Standard deviation, FEV_1: Forced expiratory volume in 1 s, FVC: Forced vital capacity, PEFR: Peaked expiratory flow rate

which was reported in these children.[25] Hence, routine growth monitoring, folate and micronutrients supplementation are important parts of management of children with SCA.

Lower lung volumes and capacities were observed in children with SCA compared to their matched Hb AA controls. This difference in lung volumes was more pronounced during adolescence. Lung volume parameters were found to decline significantly with age. Similar findings had also been reported from developing and developed countries.[7-9] MacLean *et al.*[26] estimated that the average decline of FEV_1 and total lung capacity were 2.93% and 2.15% predicted per year for boys and 2.95% and 2.43% predicted per year for girls with sickle cell disease, respectively. Decline in lung function in children with SCA with age had been linked to poor somatic growth as lung growth and development continues through the first two decades of life.[27,28] Furthermore, with chronic haemolysis and release of intracellular red cell arginase and free Hb, there is a degradation of arginine which is an important substrate of nitric oxide synthase. This depletion of arginine and consequent nitric oxide deficiency results in endothelial dysfunction and pulmonary arterial hypertension.[5,29] The presence of pulmonary hypertension was reported in up to one-fifth of Nigerian school-age children with SCA[30] and was associated with exercise intolerance and progressive decline in pulmonary function.[31]

Pulmonary function impairment was observed in about one-third of the children with SCA in this study, with possible restrictive ventilatory pattern being the most predominant form. A restrictive ventilatory pattern observed in 22.1% of our cohort of children with SCA was also reported to be the predominant pulmonary function pattern by Vieira *et al.*[32] and MacLean *et al.*[26] among Brazilian and American children with SCA, respectively. However, predominantly obstructive ventilatory pattern was reported by other authors.[9,10] The difference in the predominance of the ventilatory abnormalities reported by various studies may be related to the difference in the age of the cohort of SCA children study. For instance, while Knight-Madden *et al.*[10] studied SCA with a much younger mean age of 7.7 years, the present study like that of Vieira *et al.*[32] studied much older age group with the mean age of over 10 years. It is speculated that pulmonary function evolves in children and adolescents with SCA from normal to obstructive and then to restrictive ventilatory pattern.[5] The exact age when abnormalities set in is still largely unknown. In the present study, adolescents were found to have more pulmonary abnormalities than their younger age group. This was also corroborated by MacLean *et al.*[26] who reported that 18.7% of adolescents as compared to 0.9% of 8-year-old children had a restrictive pattern. The importance of routine pulmonary function assessment in children and adolescents with SCA cannot, therefore, be overemphasised.

Apart from advancing age, ACS was observed as a predictive factor of pulmonary function abnormalities in this study. ACS has been reported as a leading cause of premature death in individuals with SCA and the second most common cause of hospitalisation, affecting up to 50% of individuals with SCA at least once in their lifetime.[5,6,33] It was related to lung function abnormalities in SCA by other authors.[33,34] ACS is related to infection and infarction which are the major reasons for hospitalisation in children with SCA. In our study, repeated painful crises and multiple hospitalisations in the previous year were associated with pulmonary function abnormalities in the cohort of children studied. This implies

Table 4: Factors associated with pulmonary functions abnormalities among children with sickle cell anaemia

Variables	Normal lung function ($n=73$), n (%)	Abnormal lung function ($n=31$), n (%)	χ^2	P
Age range (years)				
Preadolescent (610)	46 (63.0)	10 (32.3)	8.282	0.004
Adolescent (11-16)	27 (37.0)	21 (67.7)		
Sex				
Male	33 (45.2)	19 (61.3)	2.252	0.133
Female	40 (54.8)	12 (38.7)		
Socio-economic class				
Upper	15 (20.5)	5 (16.1)	0.271	0.601
Middle	40 (54.8)	18 (58.1)	0.094	0.759
Low	18 (24.7)	8 (25.8)	0.015	0.901
Age at diagnosis				
Infancy	12 (16.4)	10 (32.2)	3.234	0.072
Preschool	38 (52.1)	12 (38.7)	1.582	0.213
School age	23 (31.5)	9 (29.0)	0.020	0.889
Blood transfusion in the last year				
None	47 (64.4)	15 (48.4)	2.313	0.128
≤3	21 (28.8)	13 (41.9)	1.715	0.190
>3	5 (6.8)	3 (9.7)	0.236	0.627*
Hospitalisation in the last 1 year				
None	39 (54.4)	9 (29.0)	4.183	0.041
≤3	30 (41.1)	16 (51.6)	0.976	0.323
>3	4 (6.8)	6 (19.4)	4.820	0.028*
Painful crises in the last 1 year				
None	24 (32.9)	7 (22.6)	1.102	0.294
≤3	36 (49.3)	12 (38.7)	0.985	0.321
>3	13 (17.8)	12 (38.7)	3.830	0.023
Specific complications				
None	31 (42.5)	13 (37.1)	0.007	0.936
ACS	2 (2.7)	6 (19.4)	7.611	0.006*
Chronic leg ulcer	3 (4.1)	1 (3.3)	0.046	0.831*
Avascular necrosis of the femur	3 (4.1)	1 (3.3)	0.046	0.831*
Dactylitis	5 (6.8)	4 (12.1)	0.945	0.331*
Osteomyelitis/septic arthritis	1 (1.4)	2 (6.5)	1.789	0.181*
Gall stones	5 (6.8)	1 (3.3)	0.584	0.445*

*Fisher's exact test applied; The figures in parentheses are percentages along each column. ACS: Acute chest syndrome

Table 5: Predictors of pulmonary function impairment among the children with sickle cell anaemia using logistic regression analysis

Variable	β	SE	OR	95% CI of OR		P
				Lower	Upper	
Adolescents	1.318	0.473	3.738	1.480	9.440	0.005
ACS	1.582	0.786	8.500	2.044	12.959	0.044
Painful crises >3	0.913	0.503	2.915	0.929	6.677	0.070
Admission >3 times	−0.596	0.519	4.140	0.199	1.524	0.251

SE: Standard error, β: Coefficient of regression, CI: Confidence interval, OR: Odds ratio, ACS: Acute chest syndrome

that prevention of infarction and infections and by extension multiple hospitalisations by adequate hydration, appropriate immunisation, optimal hygiene practices and early diagnosis and prompt treatment as well as ensuring anti-sickling measures may also ensure lung health in children with SCA.[1-4]

Worthy of note from this study is that 5.8% of the SCA children had an obstructive ventilatory pattern and only 4 (3.8%) children had a significant reversal of the obstruction with a short-acting bronchodilator. Although the prevalence of spirometry diagnosed asthma (3.8%) among SCA children in this study may not be significantly different from the prevalence in general paediatric population,[35] asthma, however, carries a far more risk and burden in SCA children than non-SCA children.[10,11,34] Lower airway obstruction and asthma had been reported by other authors in SCA children and found to be associated with worse disease severity as asthma and other lower airway obstructions predispose them to ACS and poor prognosis.[10,11,34] Thus, routine pulmonary function assessment of children with SCA as part of standard care is of paramount importance.

The main limitations of the present study were the absence of total lung capacity, functional residual volume and diffusion capacity of carbon monoxide which could have further characterise the type of pulmonary function abnormalities observed in these children.

Conclusion

About one-third of Nigerian children with SCA had pulmonary function abnormalities with predominant restrictive ventilatory pattern. Advancing age, lifetime ACS and repeated painful crises and hospitalisation are factors associated with pulmonary function abnormalities in these children. Routine assessment of pulmonary functions and prevention of crises and hospitalisation will ensure better lung health and overall improved quality of life in these children.

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Conflicts of interest

There are no conflicts of interest.

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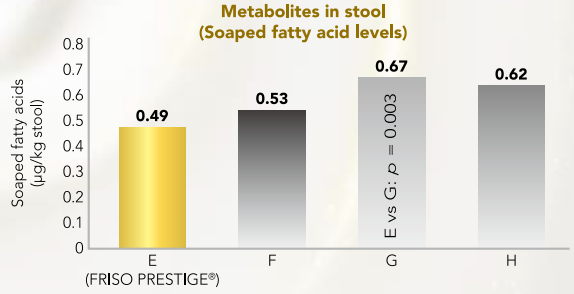

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