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References: 1. Avamys Hong Kong Full Prescribing Information (Version GDS10/PI09201511109). **2.** Medical Design Excellence Awards 2008 available at: http://www.devicelink.com/expo/awards/awards/ index.php?cattId=-1&year=2008&view=View. Accessed 26 November 2019. **3.** Berger BE, Godfrey JW, Slater AL. Expert Opin. Drug Deliv 2007 4(6): 689-701. **4.** IQVIA Sales Data (GP Channel) in class R01A1 (NASAL CORTIC W/O ANTI-INF), 2015-2019. **5.** HKAPI Sales Data (Private) in class R1A (Topical Nasal Preparations), 2009-2014.

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From the Editorial Desk

The year of 2020 is momentous for humanity. With the raging COVID-19 across the world, we, the paediatric respirologist, are at the forefront of this war. Besides COVID-19, other aspects of health service go on. Yang YH, *et al*. presented a nice analysis of the risk factors for pre-term delivery in Taiwan. Pre-term delivery might result in bronchopulmonary dysplasia. Poulter C, *et al*. presented a comprehensive review of the management of BPD based on their experience in Nottingham, UK. Pre-term babies are at risk for sleep-disordered breathing. Unfortunately, a full sleep polysomnography in young children is often not readily available. An overnight oximetry or questionnaire is often used as a screening tool. Tansriratanawong S, *et al.* presented an elegant paper on improving the accuracy of McGill scoring of overnight oximetry by incorporating the OSA-18 score.

This Journal is established to promote the practice of paediatric respirology in Asia. As illustrated in the current issue, we have so much to share in terms of knowledge. I encourage readers to share your knowledge in this Journal, which is open access. The openness is important, especially in the current war against SARS-CoV-2. I take this opportunity to wish all readers to stay safe and well.

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Conflicts of interest

There are no conflicts of interest.

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Review Article

A Practical, Evidence-Based Approach to Postneonatal Management of Children with Bronchopulmonary Dysplasia

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Abstract

Despite increasing survival for babies born preterm, the incidence of bronchopulmonary dysplasia (BPD) remains similar and continues to be the most common chronic lung disease in the preterm population. Advances in neonatal management, including the use of antenatal steroids, exogenous surfactants and changes in ventilation, have resulted in a change in the pathophysiology of BPD to a condition characterized by an arrest in alveolar development and vascular remodeling. There are numerous diagnostic definitions used for this heterogeneous condition with those using the extent of respiratory support required at 36 weeks postmenstrual age shown to be the most effective in predicting long-term pulmonary outcomes. In this article, we will discuss definitions, etiology, and pathophysiology of BPD. Management of infants with established BPD requires a multi-disciplinary team, including neonatologists and respiratory pediatricians with support for families being crucial to long term care. In this article, we will review current guidelines on oxygen saturation targets for established BPD and discuss how the use of a structured weaning pathway, as used at our center, has been shown to reduce the total duration of home oxygen. Other cornerstones of management, including optimizing growth and nutrition, reducing second-hand smoke exposure, and infection prevention, are discussed. For infants with the most severe BPD, we will review the evidence base for pharmacological therapies and indications for long-term ventilatory support. With a number of emerging therapies such as mesenchymal stem cells at the stage of phase one clinical trials, we will discuss future directions in BPD management.

Keywords: Bronchopulmonary dysplasia, home oxygen, prematurity

Introduction

Bronchopulmonary dysplasia (BPD) is the most commonly seen chronic lung disease in preterm infants. Despite advances in neonatal medicine, rates of BPD have not changed over the past few decades. While the characteristics of patients with BPD have changed with improved neonatal care, the consensus in the definition of BPD has not been reached. We will review the definition of BPD and management of established BPD in the postneonatal period; strategies for prevention of BPD and management of long-term complications are outside the scope of this article.

History and Definition of Bronchopulmonary Dysplasia

BPD was first reported in 1967 by Northway *et al*. who described persistent radiological and clinical lung problems in 32 neonates born with severe hyaline membrane disease who had received warm humidified 80%–100% oxygen through mechanical ventilation.[1,2] Since then, efforts have been made to prevent the injury caused by oxygen therapy and barotrauma from mechanical ventilation. The wide use of antenatal steroids[3,4] and surfactant therapy has improved the survival of the more premature babies but not rates of BPD. Furthermore, the incidence of BPD was shown to be higher

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in babies with lower birth weight and gestational age.[5,6] The characteristics of babies with BPD have changed over time, so has the definition of BPD.

The need of continued use of oxygen therapy for 28 days was initially used as the diagnostic criterion for BPD.[7] In 1988, Shennan *et al*. suggested using oxygen dependency at 36 weeks postmenstrual age (PMA) to define BPD because it was a better predictor of pulmonary morbidity.[8] However, gestational age and severity of the BPD had not been addressed; hence, in June 2000, a National Institute of Child Health and Human Development (NICHD) workshop established another set of diagnostic criteria.[9] It was later shown that both the adverse pulmonary outcomes and neurodevelopmental impairment corresponded to the severity of BPD defined.[7] With the use of new modes of noninvasive ventilation such as high flow, NICHD proposed further refinements to the definition of BPD in the 2016 workshop.[10]

In the most recent publication by NICHD in 2019, using 18 definitions of BPD with different severity to test their predictability of death or serious respiratory morbidity at 18–26 months corrected age, it was noted that the mode of respiratory support was the best predictor of both, irrespective of the supplemental oxygen use.[11] This will simplify the classification, as the duration of previous use of oxygen and current level of oxygen use will not add a further benefit in predicting mortality and morbidity. Furthermore, oxygen reduction testing was not used in this study, which further enhanced the ease of use.

Pathophysiology Over Time

With the advent of surfactant use three decades ago, the pathology of the BPD has changed.[12-14] There are five stages of lung growth and development: Embryonic (3–7 weeks), pseudo glandular (7–17 weeks), canalicular (17–27 weeks), saccular (27–36 weeks) and alveolar (37 weeks to 7–10 years). Recent evidence suggests that alveolar growth may continue into late teenage years not only in children born at term but also in those who were born preterm and had developed BPD.[15-17] The formation of conducting systems is mostly completed in the first two stages. Most preterm babies are delivered during the late canalicular and saccular stages, which means the alveolar formation, saccular formation, vascularization, and surfactant production would be affected.

Old bronchopulmonary dysplasia

The old BPD was characterized by alternating areas of atelectasis and hyperinflation and extensive fibroproliferation, which were featured in the pre-surfactant era as a result of lung injury caused by barotrauma and volutrauma from mechanical ventilation in premature babies with older gestational age. Advances in technology and knowledge have allowed better and lung-protective strategies such as lower peak inspiratory pressure, volume ventilation with lower tidal volume, and lower oxygen concentration. However, even brief exposure to supraphysiologic oxygen can result in morphological and functional damage in the immature lung.[18] It has been demonstrated in animal models that supraphysiologic oxygen results in impaired alveolar development and pulmonary vascular remodeling.[19]

New bronchopulmonary dysplasia

In contrast, the characteristics of the postsurfactant new BPD mainly include largely simplified alveoli and capillary hypoplasia, which is due to an arrest in lung development at the canalicular stage (24–26 weeks).

Pathogenesis and Risk Factors

Inflammation

A pulmonary inflammatory response secondary to either prenatal events such as chorioamnionitis or postnatal events such as mechanical ventilation, sepsis, and oxygen therapy is suggested to explain the pathogenesis of new BPD.[20-22]

Infection

While the causal relationship between chorioamnionitis and BPD has remained controversial,[23] a recent 25-year cohort study concluded that sepsis increased the risks of developing moderate or severe BPD.[24]

Mechanical ventilation

Lung injury associated with mechanical ventilation includes barotrauma and volutrauma. Aggressive ventilation strategies using large tidal volumes to achieve a normal carbon dioxide result in hypocarbia, which is associated with higher risks of BPD.[25] The trend now is to adopt a more conservative approach using smaller tidal volumes and a volume-targeted approach.[26]

Oxygen toxicity

The lung injury induced by high concentrations of oxygen is thought to be mediated through overproduction of cytotoxic reactive oxygen metabolites, including superoxide free radicals which pose a burden that exceeds the handling ability of the preterm infants' immature antioxidant enzyme system.[27-29]

Nutrition and fetal growth restriction

Being small for gestational age (SGA) is associated with the severity of BPD[21,30] with the abnormal development of vasculature being proposed to contribute to the development of BPD in SGA preterm babies.[31]

Impaired angiogenesis

Pulmonary vascular changes are seen in BPD infants.[32] It is proposed that disruption of angiogenesis is associated with impaired alveolarization causing the development of new BPD.[33,34]

Genetics

Although studies have shown some support for a genetic basis for the development and severity of BPD, data are limited.[35]

Management of Bronchopulmonary Dysplasia

The European Respiratory Society (ERS) recently published a guideline on the long term management of children with BPD.[36] There have also been previous statements and guidelines produced by the British Thoracic Society (BTS)[37] and American Thoracic Society (ATS) on the management of children with BPD.[38] The following subsections will look at some of the current recommendations and evidence behind them.

Oxygen

All babies with BPD will, by definition need oxygen for a period of time, with a subgroup needing home oxygen for sometimes several months or years. The importance of targeting appropriate oxygen levels to help facilitate growth and development and reduce the risk of pulmonary hypertension is known.[37,38]

There is a lack of consensus on target saturation levels and what different indices should be used on oximetry both for initiating oxygen as well as when weaning babies off oxygen.[39-41] The BTS guideline on home oxygen in children states that saturation levels <90% in infants with BPD are associated with an increased risk of apparent life-threatening events and impaired sleep quality while saturations ≥93% are not. This guideline also discussed how saturations <92% are associated with suboptimal growth[37] and therefore recommends that oxygen therapy should be given to maintain saturations ≥93%. The recent ATS guideline recommends targeting a mean of a least 93% and percentage of total study time with saturations <90% of <5%.[42] Some of the recommendations in these guidelines are based on studies done with oxygen saturation monitors with long averaging times. There is emerging data using modern pulse oximeters with motion artifact extraction technology and shorter averaging times, which suggests that the targets should be different to those suggested in the past.[43,44] The recent ERS guideline on BPD management suggests a target saturation range of 90%–95%, but it states that further studies in this area and evidence looking at the impact on both pulmonary and other outcomes (e.g., growth and neurological outcomes) is urgently needed[36] [Table 1].

The use of a structured program for monitoring and weaning oxygen has the benefits of a shorter duration of home oxygen therapy; unsupervised weaning is more likely associated with pulmonary hypertension.[46]

A protocol for monitoring and weaning home oxygen used in our center has recently been published,[46] which describes how by using a clear protocol, the duration of home oxygen therapy significantly reduced from 15 to 5 months with no difference in hospital readmission rates. This protocol recommends overnight oximetry studies (of at least 6–8 h duration) in all babies requiring ≥0.1 L/min of oxygen at 36 weeks postconceptual age. The oxygen flow rate is deemed optimal if the following targets are met on the overnight oximetry:

- average arterial oxygen saturation measured by pulse oximetry (S_{pO2}) of ≥93% (≥95% if there is evidence of pulmonary hypertension);
- S_{pO2} >90% for >95% of artifact-free total study time.

Repeat studies are conducted within 48 h of discharge in the same flow rate as at discharge and then at intervals of 3–5 weeks (generally weaning by 0.1 L/min). The same targets, as described above, are used to wean the oxygen flow rate until the flow rate is weaned to 0.1 L/min. At this point, trials in the air under supervision of the community nursing team for short periods in the day with target saturations ≥93% are used, before a study overnight in the air when the baby is tolerating day time off oxygen. A study 3 months after coming out of oxygen is also performed[46] [Figure 1].

Parents need to be aware of the effects of air travel on the need for oxygen. The BTS home oxygen in children guideline provides guidance on which children should undergo a hypoxic challenge test or pre-flight assessment.[37]

Tobacco smoke exposure

Studies have shown that a significant proportion of children with BPD are exposed to smoke in the home environment and have linked this to a tendency to need home oxygen therapy for longer and a trend toward increased use of inhaled corticosteroids.[47] There has also been work showing children with BPD exposed to smoke (measured by hair nicotine levels) have increased hospitalization episodes.[48] Avoidance of smoke exposure is recommended for children with BPD, as stated in the recent ERS guideline on BPD management in children[36] and the BTS guideline on home oxygen in children.[37] The

Table 1: A summary of guidance on target saturations for oximetry

Parameter	BTS 2010,[37] Palm *et al*. 2011,[40] Fitzgerald *et al*. 2008,[45] ATS 2019,[42] ERS 2019[36]	Wellington *et al*. 2018[44] (Mean gestation age 32.5 weeks, studies performed at 37 weeks PMA)	Evans *et al*. 2018[43] (Studies performed in term babies at 1 months and 3-4 months)
Median/mean SpO2%	≥93;[42] >90[36]	97.9 (97.2-98.8)	97.05 (96.6-97.5)
If raised PAP and/or ALTE, target SpO_2%	≥ 95	-	-
% of TST < SpO_2 90%	<5[42]	1.25/1.3 (0.7-4.2)	0.39 (0.26-0.55)
Mean DI4 (Dips of >4% from baseline/h)	<4	51 (31-74)/53 (33-75)	16.16 (13.7-18.6)/8.12 (6.5-9.8)
Duration of recording	-	12 h	≥4 h

PAP=Pulmonary Artery Pressure, ALTE=Acute Life-Threatening Events, now called BRUE=Brief Resolved Unexplained Event, TST=Total study time, BTS=British Thoracic Society, ATS=American Thoracic Society, ERS=European Respiratory Society, PMA=Postmenstrual age

ATS Information on BPD for parents also advises avoidance of tobacco smoke and air pollution[49] and links to information on smoking cessation support.

There is some research to suggest that professionals may not always broach this important topic with families, however.[50] This is clearly an important area to address. There is some work on how best to approach families to gain the most accurate information about this by correlating parental reports using questions about smoke exposure with objective parameters such as hair nicotine levels.[51] Smoking outside rather than inside the house was reported in 93% of caregivers who smoked in families with BPD,[52] suggesting that families appreciate the importance of these children avoiding smoke exposure. However, in this study, 18.9% of families of children with BPD still reported a smoker in the home, suggesting this is an ongoing challenge.[52]

Nutrition

Growth monitoring is a key component of follow-up of babies with BPD, and they will frequently have contact with a pediatric dietician to offer advice on this area. They may require supplements with breast milk or specific higher-calorie formulas.

ATS information for parents discusses the importance of good nutrition for optimal growth and the particular importance of this to optimize lung growth in the first two to three years of life. The higher calorie requirements[49] needed to help preterm babies grow, and the importance of good nutrition for a healthy immune system are other considerations.[38] The ERS BPD management guideline discusses that problems with nutrition can be a potential reason why children with BPD may require hospital admission again after discharge.[36]

It has been recognized that growth appears to be linked to when babies with BPD are ready to discontinue long-term home oxygen therapy. Studies have found that pre-weaning flow rates of ≤20 ml/kg/min were associated with successful weaning of home oxygen.[53] In our model, we have implemented flow rate per weight-based weaning and the pathway described in Figure 1 was further modified as shown in Figure 2 after we showed that successful weaning from home oxygen in a large cohort of babies with BPD is associated with pre-weaning flow rates of ≤20 ml/kg/min.[53] Current unpublished data confirm that three times as many babies can be successfully weaned off using the new pathway [Figure 2].

Discharge

For several years statements about the care of babies with BPD have recognized the importance of optimizing the time of discharge home, both to avoid the adverse impacts of prolonged hospitalization of families and to reduce the economic impact of these long stays on the health-care system.[38] The impact of prolonged hospital stays on families in terms of psychological impact and quality of life for both the infant and family is being considered in recent guidelines on this area. In 2019, the ERS guideline focused on the longer-term management of these babies postdischarge.[36]

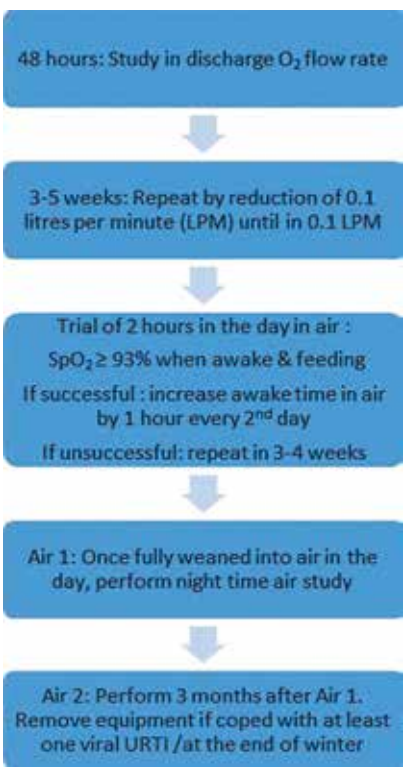

Figure 1: The pathway for weaning oxygen for babies with bronchopulmonary dysplasia in our service.

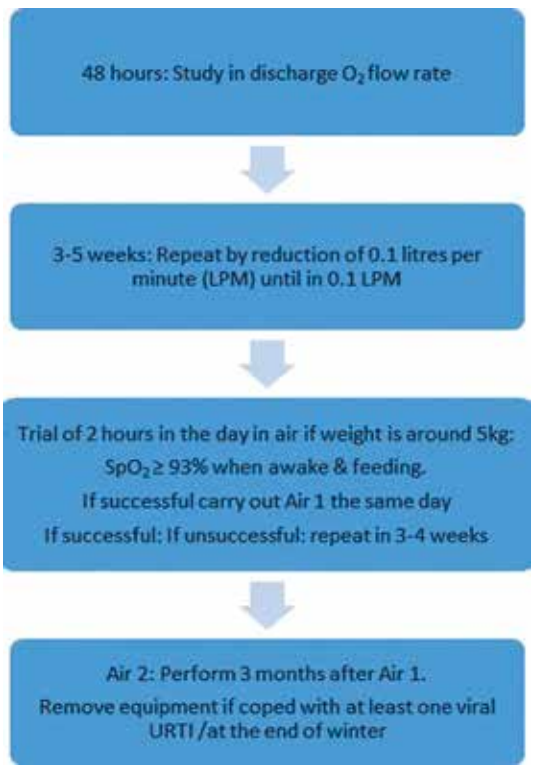

Figure 2: The modified oxygen weaning pathway for babies with bronchopulmonary dysplasia in our service.

These statements have also provided guidance on areas that it is suggested are important to consider when assessing whether a patient is ready for discharge. These include factors such as patient medical stability, family and home environment factors as well as the available community support.[38] Families need to have achieved appropriate training and feel supported at the point of discharge. Research in this area states the importance of considering the stress placed on families of taking home infants who are still medically fragile.[54]

Examples of published criteria that signify medical stability include a lack of apneas for at least 2 weeks, infrequent episodes of desaturation, and the ability to cope in the air for short periods (in case oxygen is accidentally displaced at home for a short period). In general, this occurs when babies are in oxygen flow rates of ≤0.5 L/min. Babies should be meeting targets on a set flow rate of oxygen. They should be otherwise medically stable and well, for example, gaining weight.[37,55]

It is important that we consider discharge criteria carefully to minimize the risk of babies with BPD needing readmission. As stated in the ERS guideline on BPD management, children with BPD may be readmitted due to a variety of reasons including increased susceptibility to respiratory viral illnesses requiring hospital care, nutritional problems, and other associated conditions secondary to preterm birth.[36]

Follow-up arrangements may differ between centers and may be provided by pediatric respiratory physicians or neonatologists. Babies with BPD may also benefit from the involvement of other specialists, for example, cardiologists for those with pulmonary hypertension.[36]

Infection prevention

As stated in the ERS guideline on BPD management, respiratory infection is a common reason for babies with BPD to require hospital readmission.[36] Guidance on ways to reduce the risk of babies with BPD acquiring infections is provided in family information provided by the ATS.[49] This provides basic information about good hand hygiene, avoiding unwell contacts, and the importance of routine childhood immunizations.

This guidance also recommends the seasonal influenza vaccine for babies with BPD over 6 months chronological age and advises parents and caregivers to have the influenza vaccine if possible if their baby is too young to receive this. In addition, these babies should be offered passive immunization against the respiratory syncytial virus (RSV). Palivizumab is a humanized monoclonal antibody that provides passive immunity against RSV.[56] It is administered as five injections at monthly intervals during the winter months to try to reduce hospitalizations and complications secondary to RSV infection in "high risk" patient groups such as those with BPD.[57] The summary of product characteristics (SPC) from the European Medicines Compendium 2015 states that Palivizumab is indicated in children under two years of age who have required treatment for BPD within the past 6 months. Palivizumab is a high-cost drug however and therefore cost-effectiveness criteria have been published to guide clinicians as to which children should be offered Palivizumab , which are more restrictive than in the SPC.[56,58] Several strategies, including maternal immunization against RSV and the use of a long-acting monoclonal antibody against RSV, are well described in a recent review.[59]

Daycare attendance

The ERS taskforce focusing on longterm BPD management recently looked at the evidence for whether daycare attendance affected important outcomes in babies with BPD such as hospital admissions, respiratory symptoms, neurodevelopment, and home oxygen duration.[36] They found no evidence to help support an answer to this question in the literature and thus suggested individual advice is given to families on this topic.

The task force members did not recommend or discourage parents from using daycare for their children but commented that the risk of this might be influenced by factors such as the age of the child, the time of year, and the severity of BPD. The decision about whether children with BPD should go to daycare centers is one to be made by the parents considering all factors (including pragmatic factors such as availability of alternative care arrangements) and the potential social and developmental benefits of attendance. In contrast, the ATS parent information suggests parents should avoid daycare for children with BPD if possible as well as crowded places like shopping malls.[49]

Severe Bronchopulmonary Dysplasia

Severe BPD (sBPD) represents around 16% of babies with BPD and is associated with the highest mortality and morbidity.[60] It is defined using the National Institute of Health criteria as the need for supplemental oxygen ≥30%, noninvasive or invasive respiratory support at 36 weeks PMA in babies born at <32 weeks gestation.[61] The BPD Collaborative recommends that sBPD be further sub-classified into those requiring nasal cannula oxygen, CPAP, or high flow nasal cannula oxygen (sBPD type 1) and those with a persisting need for mechanical ventilation (sBPD type 2).[60] Babies with sBPD constitute some of the sickest babies on the neonatal unit with longer length of stay, poorer cardiopulmonary long-term outcomes, and increased incidence of developmental problems.[60-62]

sBPD is a heterogeneous condition representing a broad spectrum of the underlying pathophysiology and clinical presentation. Physiological definitions based on pulmonary function testing and oxygen withdrawal tests have been proposed but are not routinely used.[63] The presence of pulmonary hypertension is not included in diagnostic criteria but likely contributes to the severity of the disease.[62]

Below we will discuss the current management strategies for sBPD and summarize evolving therapies.

Pharmacological management

Corticosteroids

Previously, courses of systemic steroids (largely dexamethasone) were frequently used at either early or late time points to prevent the development of BPD.[64,65] Steroids are potent anti-inflammatory agents and have been found to both shorten the duration of mechanical ventilation and facilitate extubation.[66,67] Although consistently effective in reducing the development of BPD at all time points used, concerns about the increased risk of cerebral palsy and neurodevelopmental problems have led to them being used more sparingly with a move toward lower doses of steroids being reserved for the most unwell, ventilator-dependent infants after the 1st week of life.[68-70]

A number of alternative steroid regimens have been trialed. The use of low dose hydrocortisone in the PREMILOC study resulted in a significant increase in survival without BPD in the treatment group; however, neurodevelopmental outcomes were not reported.[71] The NEUROSIS trial of inhaled budesonide in babies requiring respiratory support showed a reduction in the total duration of supplemental oxygen therapy but also did not assess neurodevelopmental outcomes.[72,73] With the aim of developing a more targeted therapy, Yeh *et al*. trialed the use of intra-tracheal delivery of budesonide with the surfactant, showing a significant reduction in BPD in the budesonide group with no significant adverse effects at follow-up two to four years later.[74,75]

Research into postnatal steroids has largely focused on the prevention of sBPD with little known about their efficacy in the long-term treatment of infants with established sBPD.[76] Consequently, the ERS Taskforce recommends that inhaled and systemic steroids should not be used routinely in established BPD however, if considered for use, for example, in those with severe symptoms or recurrent hospitalizations, the effects of treatment should be closely monitored for a trial period.[36]

Azithromycin

Macrolide antibiotics have anti-inflammatory effects with actions at multiple points in the inflammatory cascade and have been found to reduce hyperoxic lung injury in animal models.[77] A recent meta-analysis showed that prophylactic azithromycin is associated with a significant reduction in BPD development; however, larger clinical studies are needed before it is routinely used.[78,79]

Azithromycin has also been studied as a therapeutic agent in babies already colonized with ureaplasma. It has increased antimicrobial activity against ureaplasma and a better safety profile than erythromycin with better drug concentrations in the lung epithelium and alveolar macrophages.[80,81] However, studies have not shown a reduction in the development of BPD, and work is needed to determine the dose needed to achieve ureaplasma clearance.[82]

Hydroxychloroquine

Hydroxychloroquine is a quinolone and acts by inhibiting immune activation by reducing Toll-like receptor signaling and cytokine production.[83] Evidence for its use in BPD is extrapolated from use in interstitial lung disease in children where it has been observed to be effective in children with ABCA3 mutations.[84] In babies with sBPD, it has been used as part of a treatment protocol alongside methylprednisolone and azithromycin; however, further studies are needed.[85]

Diuretics

Diuretics are frequently used with the aim of reducing pulmonary edema and have been shown to result in a short-term benefit on pulmonary mechanics with improved lung compliance, reduced airway resistance, and improved oxygenation.[86] Patterns of use vary significantly across institutions, with the most frequently used being furosemide, a loop diuretic, and chlorothiazide which is often combined with spironolactone to minimize renal salt wasting.[87] There is a lack of evidence of benefit from long-term use with a recent Cochrane review showing no evidence of benefit on length of stay, need for ventilatory support, duration of home oxygen therapy[88] or long-term outcomes and a risk of adverse events including nephrocalcinosis, electrolyte disturbances, and osteopenia.[89]

For children with BPD who were commenced on diuretics in the neonatal period, the ERS Taskforce recommends a natural wean by a relative decrease in dose with weight gain, and if continued beyond this, careful monitoring of the effects of treatment during a trial period.[36]

Inhaled bronchodilators

Inhaled bronchodilators have a short-term effect on reducing airway resistance and improving lung compliance;[86,90] however, there is wide variability in response and a lack of evidence to suggest benefit in this cohort.[91] The recent ERS Taskforce Recommendations suggest that consideration of inhaled bronchodilators should be reserved for a subgroup of children, namely those with asthma-like symptoms, recurrent hospital admissions due to respiratory morbidity, exercise intolerance, and reversibility in lung function.[36]

Long term ventilation

The BPD Collaborative report tracheostomy insertion rates of around 12% in infants with sBPD across tertiary centers.[60] There is a lack of evidence to suggest which babies are most likely to benefit from long term ventilation and the optimal timing for this however Luo *et al*. propose that it could be considered in postterm babies with sBPD who are expected to need invasive respiratory support for a prolonged period of time if weaning their respiratory support negatively impacts on growth, development or the stability of pulmonary hypertension.[92]

The decision to initiate long term ventilation via tracheostomy is the complex and detailed discussion between the clinical team and family is crucial. Long-term ventilation for patients with sBPD has been shown to facilitate growth, improve developmental outcomes, and reduce sedative medication requirements.[92]

Management of co-morbidities

Babies with sBPD may have multiple prematurity related comorbidities, which both complicate and exacerbate their lung disease. Management of these should be optimized as part of the treatment of sBPD.

Pulmonary hypertension

Pulmonary hypertension affects around 25% of those with sBPD and is associated with increased morbidity and mortality.[60,62] It evolves due to abnormal vascular development and remodeling with increased pulmonary vascular resistance.[62] The gold standard diagnostic test is cardiac catheterization; however, echocardiogram is more widely used in practice.[93] The ATS has recently recommended screening for pulmonary hypertension using echocardiography in all babies with sBPD.[94]

Management should focus on the treatment of the underlying lung disease, avoiding periods of hypoxemia with oxygen saturation limits set between 92% and 95%.[60] While inhaled nitric oxide has been shown to cause transient improvement in pulmonary pressures, its longer-term use poses practical challenges.[86,95] Sildenafil, a selective type 5 phosphodiesterase inhibitor, has a longer half-life and causes vasodilatation and smooth muscle growth inhibition.[86,95,96] Studies have shown it to be effective in reducing pulmonary artery pressures and respiratory severity score, but it can have systemic side effects, including hypotension.[96,97] Further studies are needed to determine long term outcomes in this population.

Gastroesophageal reflux disease

Gastroesophageal reflux may exacerbate lung disease in sBPD.[60] Studies have shown increased pH events on esophageal pH impedance testing in babies with BPD compared to those without, with proposed mechanisms for this, including impaired esophageal motility and an altered autonomic nervous system response pattern.[98,99] Pharmacological measures should only be considered when other measures have been unsuccessful as there is limited evidence supporting their use in preterm babies and risk of adverse effects.[100] Surgical interventions for gastroesophageal reflux have shown a small but significant reduction in respiratory rate and oxygen requirement postintervention; however, data regarding longer-term outcomes is lacking.[101]

Large airway disease

Over five percent of babies with BPD have comorbid tracheobronchomalacia;[60] which may present with acute life-threatening episodes due to intermittent airway collapse and ventilatory requirements out of proportion to those expected.[102] They are likely to have a longer length of stay, spend longer requiring mechanical ventilatory support and are more likely to be mechanically ventilated on discharge.[103] Babies with suspected airway problems should be considered for bronchoscopy to assess airway anatomy.[104] A recent ERS statement describes the management of tracheobronchomalacia in children in detail.[105]

Feeding problems

Optimizing nutrition is key to achieving the "pro-growth" state required for lung growth and development. Babies with sBPD have increased metabolic demands alongside growth suppression induced by chronic stress, inflammation, and steroid use[60] with an estimated 15%–25% higher energy requirement than those without BPD.[106] A caloric intake of around 140 kcal/kg/day may be needed to achieve this, and concentrated formulas or fortified breast milk are likely to be needed to avoid very high fluid volumes.[106,107] Linear growth should be closely monitored, and nutritional intake titrated to maintain growth. Enteral feeding through naso-gastric tube or gastrostomy may be required postdischarge to supplement oral feeding.[60,108]

Aspiration is a risk factor for persistent lung injury in sBPD and may be due to dysfunctional swallowing, reflux, and pooling of oral secretions. It may present acutely with pneumonia necessitating increased respiratory support or more insidiously with chronic coughing, wheeze, tachypnea, desaturations and poor weight gain. Assessment by an experienced speech and language therapist is advised.[60]

Atypical presentation

In babies with an atypical presentation or progression of severe lung disease, thought should be given to excluding additional or alternative diagnoses such as cystic fibrosis, primary ciliary dyskinesia, and diffuse parenchymal lung disease. Pertinent investigations to perform in this population could include an echocardiogram, sweat test, immune function testing, and bronchoscopy.[60] The yield of positive results for surfactant protein gene mutations and the alveolar-capillary dysplasia spectrum is much less when pre-term babies with respiratory distress, which does not run the normal clinical course, are tested.[84]

Emerging therapies

Developing an understanding of the specific risk factors and mechanisms that lead to the development of this severe phenotype is crucial to tailoring therapeutic approaches.[60] There is a need to develop biomarkers and other early predictors for the development of sBPD. This has proven challenging due to the heterogeneous nature of sBPD and difficulty in determining the optimal specimen type, timing of collection, and an appropriate control cohort.[62,109] Potential biomarkers aim to target the causal pathways implicated in BPD pathogenesis including markers of inflammation e.g., serum cytokines, angiogenic growth factors e.g., vascular endothelial growth factor and platelet-derived growth factor and markers of pulmonary hypertension e.g., brain natriuretic peptide.[62,109,110]

A number of cell-based therapies are being investigated with the most promising results from the use of mesenchymal stem cells (MSCs), which have shown the potential to reduce inflammation via modulation of macrophages, prevent fibrosis, and promote alveolar growth in phase one trials.[111,112] However, a recent Cochrane review concluded that there is currently insufficient evidence for the safety and efficacy of

MSCs in the prevention and treatment of BPD.[113] Endothelial progenitor cells (EPCs) have been found to promote the repair of damaged blood vessels, and the finding that they become depleted in hyperoxic lung injury has led to exogenous EPC therapy being proposed.[114]

Exploration of anti-inflammatory modulators includes trials of prophylactic use of the anti-inflammatory agents interleukin-1 receptor antagonist (IL1-Ra) and Protein C (PC), which have been shown to be protective against the development of BPD in animal models with no adverse effects on brain development.[115-118]

In conclusion, BPD remains one of the most common morbidities of prematurity with implications for lung health and development into childhood and adolescence.[62] Although definitions vary, the extent of respiratory support required at 36 weeks PMA appears to be the most reliable indicator of longer-term outcomes.[10,11] BPD is now understood to be a complex disease resulting from an interaction of antenatal, perinatal, and postnatal factors affecting both alveolar and vascular development, with its incidence being inversely proportional to gestational age and birth weight.[5,6,61,62]

A number of babies with BPD will require supplemental oxygen on discharge, and we have summarized guidance on the target oximetry parameters, although there remains a lack of consensus on this.[36,37,39-41] A structured approach to oxygen weaning is important to facilitate growth and development, and at our center has been effective in reducing the total duration of home oxygen therapy with no increase in hospital readmission rates.[46] Support and education for families facilitated by a multi-professional team are essential and should include information on nutrition, reducing second-hand smoke exposure, and prevention of infections.[36-38]

A small cohort of infants will have a more severe form of BPD and may require a longer period of mechanical ventilation and hospital stay.[60] There are a number of pharmacological therapies used, although the evidence base underlying them is lacking in some cases. Alongside managing BPD, the management of any comorbidities should be optimized, and in atypical presentations, alternative or additional diagnoses should be considered.[60] There have been promising findings from early studies into new treatments for BPD, including the use of mesenchymal stem cells and anti-inflammatory therapies.[113,116,118]

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Preterm Birth-associated Factors Analysis: A Cross-sectional Study in 2015

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Abstract

Objective: The aim of this study is to investigate the current clinical factors associated with preterm birth in women delivering newborn infants in a tertiary medical center of a modern city. **Methods:** The medical records of women who delivered newborn infants in a tertiary medical center in Taipei city in 2015 were reviewed. To compare with the full-term group, the preterm group was defined by gestations of <37 weeks. Maternal characteristics, pregnant histories, underlying diseases, and peripartum conditions of enrolled mothers and the characteristics of their newborn infants were recorded and analyzed. Odds ratios (OR) were analyzed using logistic regression for factors associated with preterm deliveries. **Results:** A total of 1729 pregnant women (15–48 years) gave birth during the study period, including 1520 full-term and 209 (12.1%) preterm deliveries, accounting for 1778 newborns with 49 pairs of twins. After multivariate analysis, the following significant factors were found to be associated with preterm birth: multiple pregnancy (OR, 26.5; 95% confidence interval [CI], 12.7–55.4]), presence of maternal systemic lupus erythematosus (SLE) (OR, 10.4; 95% CI, 2.3–46.2), preeclampsia/eclampsia (OR, 7.6; 95% CI, 3.9–14.8), tocolysis requirement (OR, 6.6; 95% CI, 4.6–9.7), infection (OR, 2.4; 95% CI, 1.7–3.5), maternal diabetes (OR, 2.2; 95% CI, 1.0–4.4), and low maternal height (<155 cm) (OR, 2.2; 95% CI, 1.4–3.4). The preterm group also had more maternal blood loss (623 ± 543 vs. 399 ± 375 mL, $P < 0.05$) and a higher ratio of cesarean sections (59.3% vs. 26.8%, $P < 0.05$) than the full-term group. **Conclusion:** Multiple pregnancy, tocolysis requirement, lower maternal height (<155 cm), and the presence of maternal diseases during pregnancy, including SLE, preeclampsia/eclampsia, infection, and maternal diabetes, are significantly associated with preterm birth in Taipei city.

Keywords: Epidemiology, gestation, low birthweight, multiple pregnancy, preeclampsia, preterm birth

Introduction

Preterm birth of newborn infants is a major cause of neonatal mortality and morbidity. According to the World Health Organization, there are approximately 15 million babies born preterm every year, and the reported occurrence rate of preterm birth is 5%–18% worldwide.[1-3] In one recent review, the incidence rate of preterm birth was stated as approximately 11% of births.[3] Preterm birth is associated with a higher risk of developing adverse comorbidities and long-term outcomes, such as neurodevelopmental, cognitive, or physical problems.[2,4,5] Complications of preterm birth are the leading cause of death among children under 5 years of age.[1] Acute and chronic problems associated with preterm births not only cause infants to suffer but also burden their families.

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The common maternal problems related to preterm birth include placental abnormalities; multiple gestations; maternal diabetes; preeclampsia; and preexisting conditions, such as high blood pressure and respiratory, heart, and thyroid diseases.[6] Other maternal factors have also been associated with preterm birth, including maternal age, body weight, height, or body mass index (BMI).[7-11] However, there is presumably a significant

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variation in these factors depending on the racial, health, and social-industrial developmental conditions of a particular region. Investigating regional risk factors related to preterm birth is important for establishing effective preventive policy in a specific region.

In recent decades, delayed childbearing has become a trend in developed countries.[12] Investigators have reported that mothers of advanced age are more likely to deliver preterm infants than younger mothers.[13-18] In Taipei city, which is a representative modern city in northern Taiwan, many pregnant women are older than 30 years of age, and most complicated pregnancies are referred to as tertiary medical centers. Previously, the known premature birth rate in Taiwan was approximately 8%–10%,[16] and 75% of neonatal mortalities were related to very low-birthweight prematurity.[16] Further investigation of preterm births is important for future preventive medicine. This study was designed to investigate the current factors associated with preterm birth in women delivering newborn infants in a tertiary medical center of a modern city.

Methods

This study was approved by the Institutional Review Board of Taipei Veterans General Hospital (VGHIRB 2016-12-006CC).

All live births from a medical center in Taipei between January 1, 2015 and December 3, 2015, were reviewed, and the mothers and their newborn infants were enrolled in this study. If babies were delivered at a gestational age of <37 weeks, they were placed into the preterm group. Otherwise, they were placed into the full-term group.

The basic characteristics, medical histories, and peripartum conditions of enrolled mothers, along with the basic characteristics of their newborns, were recorded and compared between preterm and full-term groups.

The recorded maternal characteristics included maternal age, height, weight, 6-month weight gain, BMI, multiple pregnancy, gravidity, and parity. The recorded medical histories of enrolled mothers included previous abortions, smoking during pregnancy, drinking during pregnancy, preeclampsia/eclampsia, maternal diabetes, systemic lupus erythematosus (SLE), thyroid disease, and uterine myoma. The recorded peripartum conditions included tocolysis treatment, Group B streptococcus (GBS) screening, fetal distress, premature rupture of membrane (PROM), preterm PROM (PPROM), delivery mode, amount of maternal blood loss, presence of meconium in amniotic fluid, and maternal infection. The recorded infant characteristics included gender, birth height, birth weight, gestational age, Apgar scores, placental weight, and duration of skin-to-skin contact with mothers.

The data were presented as mean ± standard deviation or n (%) as appropriate. Microsoft Office Excel 2016 (Microsoft Corporation, Redmond, WA, USA) and SPSS version 19.0 (SPSS Inc., Chicago, IL, USA) were used to perform data analyses. Graphs were made using SigmaPlot 12.0 (Systat Software Inc. San Jose, CA, USA).

A Student's *t*-test was used to compare numerical data between the two groups. A Chi-square test was used for proportion comparison between the two groups. A Chi-square with linear-by-linear association test was used to compare groups for ordinal categorical grouping, including maternal age, body height, BMI, and previous abortion frequency. Logistic regression was used for univariate and multivariate analyses for potential associated factors of preterm birth. A value of $P < 0.05$ was considered statistically significant.

Results

In total, there were 1729 mothers enrolled in our study, including 49 with twin pregnancies. Among them, there were 209 mothers who experienced preterm birth, accounting for 12.1% of all enrolled cases, and they were categorized into the preterm group [Figure 1a].

The basic characteristics of the 1729 mothers enrolled are shown in Table 1. The ages of the mothers enrolled ranged from 15 to 48 years (mean, 33 ± 4 years), the body heights ranged from 138.5 to 177 cm (mean, 160 ± 5 cm), the body weights ranged from 37 to 121 kg (mean, 67 ± 10 kg), and BMIs ranged from 15.4 to 43.4 (mean, 26.1 ± 3.7). There was no significant difference in body weight, BMI, ethnicity, gravida, and the ratios of primiparas between the two groups.

There were significant trends showing higher ratios of preterm birth associated with the mother's older age [Figure 1b, $P = 0.042$] and lower body height [Figure 1c, $P = 0.004$] in a linear-by-linear association Chi-square test but with no significant trend in BMI [Figure 1d, $P = 0.136$]. Comparisons based on mother's characteristics, proportions in the preterm group, were significantly higher than in the full-term group in the subgroup that included mother's age ≥40 years, height <155 cm, and BMI ≥30 ($P < 0.05$) [Table 1]. Furthermore, 6-month weight gain before delivery was significantly lower, and the proportion of multiple pregnancies was significantly higher in the preterm group ($P < 0.05$) [Table 1]. In the present cohort, all multiple pregnancies were twins.

Conditions of the enrolled mothers before and during this pregnancy are summarized in Table 2. Although the linear-by-linear association Chi-square test analysis of previous abortions was not statistically significant ($P = 0.063$), the proportion of previous abortions ≥3 times was significantly higher in the preterm group ($P = 0.017$). There were significantly higher proportions of mothers with pregnancy-related diseases (preeclampsia/eclampsia and maternal diabetes) and maternal diseases (maternal infection and SLE) ($P < 0.05$) in the preterm group when compared to the full-term group [Table 2]. The ratios of the tocolysis requirement and PROM ≥18 h were also significantly higher in the preterm group than in the full-term group [Table 2]. Conversely, the ratios of receiving

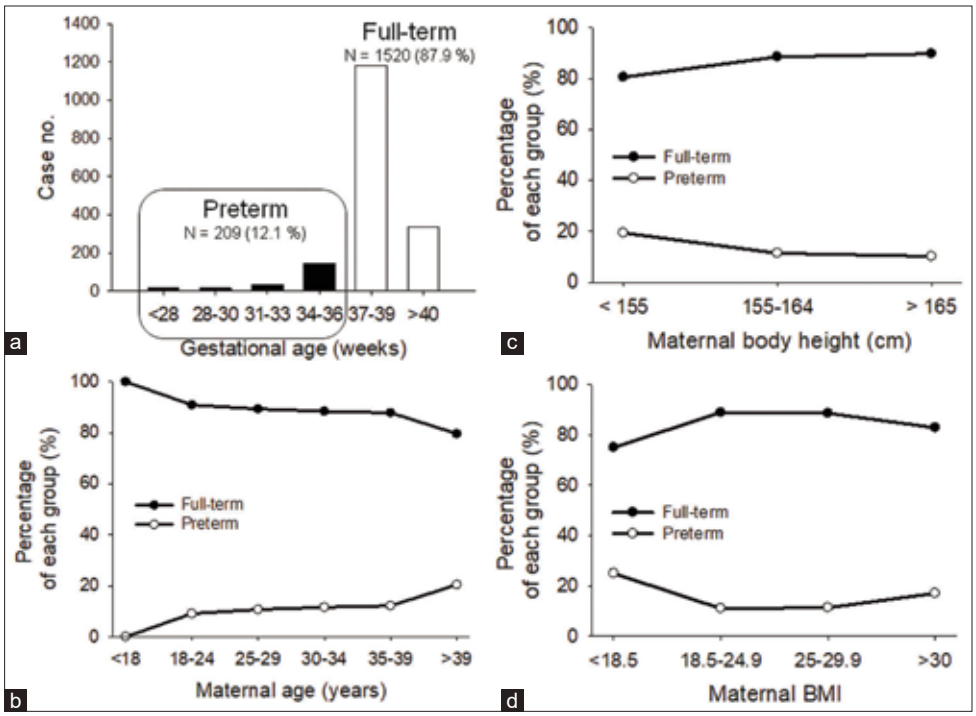

Figure 1: Distributions of categorical maternal characteristics in preterm and full-term groups. (a) Gestational age; (b) maternal age ($P = 0.042$); (c) maternal body height ($P = 0.004$); (d) maternal body mass index ($P = 0.136$). *P* values were obtained by using Chi-square with linear-by-linear association tests for Graphs B–D. BMI: Body mass index

Table 1: Characteristics of the 1729 mothers enrolled at delivery

Characteristics	Total (n=1729), n (%)	Full-term (n=1520)	Preterm (n=209)	*P*
Age (years)	33±4	33±4	34±4	0.066
≤17	1 (0.1)	1 (100)	0 (0)	0.711
18-24	55 (3.2)	50 (90.9)	5 (2.4)	0.488
25-29	262 (15.2)	234 (15.4)	28 (13.4)	0.450
30-34	733 (42.4)	648 (42.6)	85 (40.7)	0.591
35-39	580 (33.4)	509 (33.5)	71 (34.0)	0.889
≥40	98 (5.7)	78 (5.1)	20 (9.6)	0.009
Body height (cm)	160±5	160±5	159±6	0.001
<155	211 (12.3)	170 (11.3)	41 (19.7)	0.000
155-164	1147 (67.0)	1016 (67.6)	131 (63.0)	0.232
≥165	353 (20.6)	317 (21.1)	36 (17.3)	0.222
Body weight (kg)	67±10	67.0±10.0	66.8±11.8	0.756
6-month weight gain (kg)	12±5	12.3±4.4	9.5±5.3	0.000
BMI	26.1±3.7	26.0±3.8	26.3±4.3	0.193
<18.5	15 (0.9)	11 (0.7)	4 (1.9)	0.111
18.5-24.9	712 (41.9)	633 (42.4)	79 (38.3)	0.290
25-29.9	755 (44.4)	669 (44.8)	86 (41.7)	0.434
≥30	216 (12.7)	179 (12.0)	37 (18.0)	0.015
Multiple pregnancy*	49 (2.8)	13 (0.9)	36 (17.2)	0.000
Gravida	2.1±1.2	2.0±1.2	2.2±1.5	0.181
Primiparas	958 (55.4)	834 (54.9)	124 (59.3)	0.222

Data are presented as mean±SD or *n* (%) as appropriate. *All were twin pregnancies. BMI=Body mass index, SD=Standard deviation

GBS screening and having positive GBS screening tests were significantly lower in the preterm group ($P < 0.05$). There was no significant difference in maternal smoking, alcoholism during pregnancy, or the presence of fetal distress between the two groups ($P > 0.05$).

Univariate and multivariate analyses are shown in Table 3. The multivariate analysis results show that the top three associated factors were multiple pregnancy [odds ratio (OR), 26.5; $P < 0.05$], maternal SLE (OR, 10.4; $P < 0.05$), and maternal preeclampsia/eclampsia (OR, 7.6; $P < 0.05$) [Table 3].

Table 2: Conditions before and during this pregnancy in the 1729 mothers enrolled

History	Total (*n*=1729), *n* (%)	Full-term (*n*=1520), *n* (%)	Preterm (*n*=209), *n* (%)	*P*
Previous abortion				0.063*
None	1148 (66.4)	1017 (66.9)	131 (62.7)	0.225
1-2 times	510 (29.5)	447 (29.4)	63 (30.1)	0.827
≥3 times	71 (4.1)	56 (3.9)	15 (7.2)	0.017
Smoking during pregnancy	17 (1.0)	14 (0.9)	3 (1.4)	0.497
Alcoholism during pregnancy	3 (0.2)	3 (0.2)	0 (0)	0.513
Pregnant-related problem	112 (6.5)	68 (4.5)	44 (21.1)	0.000
Preeclampsia/eclampsia	60 (3.5)	28 (1.8)	32 (15.3)	0.000
Maternal diabetes	61 (3.5)	42 (2.8)	19 (6.6)	0.000
Maternal disease (any)	784 (45.3)	677 (44.5)	107 (51.2)	0.070
Maternal infection	462 (26.7)	377 (24.8)	85 (40.7)	0.000
SLE	9 (0.5)	4 (0.3)	5 (2.4)	0.000
Thyroid disease	64 (3.7)	52 (3.4)	12 (5.7)	0.096
Uterine myoma	106 (6.1)	91 (6.0)	15 (7.2)	0.501
Tocolysis requirement	222 (12.8)	128 (6.6)	94 (45.0)	0.000
Tocolysis duration (days)	24±33	23±32	26±36	0.446
Receiving GBS screening[#]	1260/1353 (93.1)	1157/1215 (95.2)	103/138 (74.6)	0.000
Positive GBS screening test[#]	293/1260 (23.3)	281/1157 (24.3)	12/103 (11.5)	0.004
Fetal distress before delivery	249 (14.4)	218 (14.3)	31 (14.8)	0.850
PROM ≥18 h	71 (4.1)	57 (3.8)	14 (6.7)	0.044
PPROM		-	88 (42.1)	

Data are presented as mean±SD or *n* (%) as appropriate. *By linear-by-linear association Chi-square test, [#]Cases of unknown status were excluded. SD=Standard deviation, PROM=Premature rupture of membrane, PPROM=Preterm premature rupture of membrane, SLE=Systemic lupus erythematous

Other significant associated factors included tocolysis requirement (OR, 6.6; $P < 0.05$), maternal infection (OR, 2.4; $P < 0.05$), maternal diabetes (OR, 2.2; $P < 0.05$), and body height < 155 cm (OR, 2.2; $P < 0.05$) [Table 3].

At delivery, mothers in the preterm group had significantly higher ratios of undergoing cesarean sections (49.3% vs. 22.9%, $P < 0.05$) and blood loss ≥500 ml during labor than in the full-term group (59.3% vs. 26.8%, $P < 0.05$) [Table 4]. Conversely, the ratios of spontaneous vaginal delivery, vacuum extraction, dysfunctional labor, and meconium stains in amniotic fluid were significantly lower in the preterm group [Table 4] ($P < 0.05$).

Characteristics of the 1778 delivered infants are shown in Table 5, including 49 pairs of twins. Comparing infants of the preterm and full-term groups, the infants of preterm birth had a significantly higher proportion of twins, shorter body length, lower birth weight, lower Apgar scores at 1 and 5 min after birth, higher ratios of infants having Apgar score <6 at 5 min, lighter placental weight, and lower ratios of skin-to-skin contact right after delivery than in the full-term group ($P < 0.05$) [Table 5]. Comparing the duration of those having skin-to-skin contact with their mothers, there was no significant difference between the two groups [Table 5].

Discussion

The study demonstrated a preterm birth rate of 12.1% among live births from a tertiary medical center in a modern city, Taipei city, in 2015. Among the mothers enrolled, multiple pregnancies, maternal diseases during pregnancy, tocolysis requirement, and lower maternal height were significantly associated with preterm birth. Significant preterm birth-related maternal problems were SLE, preeclampsia/eclampsia, infection, and maternal diabetes. Higher ratios of receiving cesarean sections and the amount of blood loss at delivery were also observed in the preterm group when compared to the full-term group.

A worldwide preterm birth rate of approximately 11% was reported by Vogel *et al*. in 2018 and Blencowe *et al*. in 2013.[2,3] Artificially conceived, multiple pregnancies in developed countries accounted for many preterm births in the past decades.[11] Our analyzed incidence rate is slightly higher than that of the published reports because our data was collected in a tertiary medical center of a capital city, rather than on a nationwide scale. High-risk pregnant women are usually referred to as tertiary medical centers, which may contribute to the higher ratio of preterm deliveries observed in the present study.

Most of the preterm births cannot be directly attributed to any risk factors. Some of them are due to spontaneous onset of labor or PPROM, and others are due to provider-initiated induction of labor or elective cesarean section for maternal or fetal problems.[2] Investigators have previously reported that complications of placenta and cord, uterine over-distension, increased intrauterine volume, the prevalence of PPROM, and twin-to-twin transfusion syndrome may be risk factors for preterm birth in twin or multiple pregnancies.[11,19] Similar to other reports, we demonstrated that multiple pregnancies, underlying

diseases (including SLE and infections), pregnancy-induced preeclampsia/eclampsia or maternal diabetes, and tocolysis requirement were the main risk factors. Poor uterine situations not suitable for fetal growth in the diseased pregnant women could partially explain the mechanism of preterm births. Proper care for women with pregnancy-related diseases is important to reduce the risk of preterm birth.

Lower body height (<155 cm) of pregnant women was demonstrated as an independent risk factor for preterm birth in our study. This finding is compatible with the studies of Swedish women.[9,10] In a study conducted on 192,432 Swedish women, Derraik *et al*. found a positive association between decreasing height and the likelihood of preterm birth.[10] In a meta-analysis study, Han *et al*. demonstrated that women of lower stature had a higher unadjusted risk of preterm birth. Although there may be other maternal conditions of interest, body height appears to be an easier measurement to obtain.[20] Because different races/ethnicities may have different height distributions, Shachar *et al*. investigated the influence of maternal height on preterm birth within various racial groups. An inverse association between maternal height and the risk of spontaneous preterm birth was found in Non-Hispanic whites and Asians, but not among blacks and Hispanics.[21] A study investigating pregnant women from low- to middle-income countries indicated that lower maternal stature is associated with poor infant conditions.[22] From a mechanical perspective, the lower maternal height may be caused by malnutrition, which influences maternal health and diverts resources for neonatal development away from the fetus.[23] However, in this study, this conclusion may not be applicable due to socioeconomic differences in the areas. Further investigations are required to understand this factor.

Table 3: Univariate and multivariate analysis for underlying maternal factors associated with preterm delivery

Maternal factors	Univariate		Multivariate	
	OR	95% CI	OR	95% CI
Multiple pregnancy	24.1	12.6-46.4*	26.5	12.7-55.4*
SLE	9.3	2.5-34.9*	10.4	2.3-46.2*
Preeclampsia/eclampsia	8.3	4.9-14.1*	7.6	3.9-14.8*
Tocolysis requirement	8.9	6.4-12.3	6.6	4.6-9.7*
Maternal infection	1.6	1.2-2.2*	2.4	1.7-3.5*
Maternal diabetes	3.3	1.1-5.8*	2.2	1.0-4.4*
Body height (cm)				
155-164	1			
<155	1.9	1.3-2.7*	2.2	1.4-3.4*
≥165	0.9	0.6-1.3		
Age (years)				
18-34	1			
35-39	1.1	0.8-1.5		
≥40	2.0	1.2-3.4*	1.3	0.6-2.4
BMI				
18.5-24.9	1			
25-29.9		0.8-1.4		
≥30	1.7	1.1-2.5*	0.8	0.5-1.3
<18.5	2.7	0.8-8.5		
Previous abortion (frequency)				
0	1			
1-2	1.1	0. 8-1.6		
≥3	2.1	1.1-3.8*	1.6	0.8-3.2
PROM ≥18 h	1.8	1.0-3.4*	1.4	0.7-2.9

*P<0.05. BMI=Body mass index, OR=Odds ratio, CI=Confidence interval, PROM=Premature rupture of membrane, PPROM=Preterm premature rupture of membrane, SLE=Systemic lupus erythematosus

The mean age of pregnant women was 33 ± 4 years in the study in Taipei city, which is higher than in other areas.[12] In the past decades, delayed childbearing has become more common globally. Investigators have reported that pregnant women of both advanced age and young age should be regarded as risk groups for preterm deliveries.[13,18] In this study, we did not find a significant relationship between young age and preterm birth, which may be due to the limited number of patients. We noted that the proportion of pregnant women of age ≥ 40 years was significantly higher in the preterm than in the full-term group, but the multivariate analysis did not identify age as an independent risk factor for preterm birth. The result of a cohort study has demonstrated that advanced maternal age is associated with increased miscarriage, preeclampsia, small infant size for gestational age, maternal diabetes, and cesarean sections.[17] Jacobsson *et al*. demonstrated that the risk of developing pregnancy-induced hypertension, severe preeclampsia, or placenta previa also increased with maternal

Table 4: Comparisons of conditions at delivery of mothers enrolled in the full-term and preterm groups

Maternal condition	Total (n=1729)	Full-term (n=1520)	Preterm (n=209)	P
Gestational age (weeks)	38±2	39±1	34±3	0.000
Delivery mode				
Spontaneous vaginal delivery	896 (51.8)	823 (54.1)	73 (34.9)	0.000
Cesarean section	531 (30.7)	407 (26.8)	124 (59.3)	0.000
Vacuum extraction	207 (12.0)	202 (13.3)	5 (2.4)	0.000
Low forceps	95 (5.5)	88 (5.8)	7 (3.3)	0.147
Dysfunctional labor	402 (23.5)	385 (25.3)	17 (8.1)	0.000
Maternal blood loss	426±406	399±375	623±543	0.000
≥500 mL	451 (26.1)	348 (22.9)	103 (49.3)	0.000
Meconium stain in amniotic fluid	202 (11.7)	189 (12.4)	13 (6.2)	0.009

Data are presented as mean±SD or *n* (%) as appropriate. SD=Standard deviation

Table 5: Characteristics of 1778 newborn infants born by 1729 enrolled mothers*

Conditions	Total (*n*=1778), *n* (%)	Full-term (*n*=1553), *n* (%)	Preterm (*n*=245), *n* (%)	*P*
Gender				
Male	924 (52.0)	790 (51.5)	134 (54.7)	0.358
Female	854 (48.0)	743 (48.5)	111 (45.3)	
Twin	98 (5.5)	26 (1.7)	72 (29.4)	0.000
Birth length (cm)	48±3	48±2	43±5	0.000
Birth weight (g)	2999±555	3134±398	2152±642	0.000
Apgar score				
At 1 min	7±1	8±1	6±2	0.000
At 5 min	9±1	9±1	8±2	0.000
<6 within 5 min	95 (5.3)	37 (2.4)	58 (23.7)	0.000
Placenta weight	684±171	689±152	656±257	0.000
Skin-to-skin contact	1277 (71.8)	1211 (79.7)	66 (26.9)	0.000
Contact duration (min)#	40±21	40±21	41±24	0.945

Data are presented as mean±SD or *n* (%) as appropriate. *Including 48 pairs of twins, #Only includes the babies with skin-to-skin contact with their mothers. SD=Standard deviation

age.[14] Our study results are compatible with their findings. Aged women usually have a higher possibility of developing pregnancy-related diseases and presumably a higher need for artificial fertilization that causes multiple pregnancies, both of which may increase the risk of preterm birth. Therefore, maternal problems in older women, rather than age itself, are the main reasons for preterm birth.

In addition to maternal diseases, poor nutrition is also a potential risk factor in undeveloped countries. Furthermore, maternal obesity has been related to preterm birth in developed countries.[24,25] In Taipei city, poor nutrition is not a common problem for citizens. In the present study, we did not find a significant difference in women with BMI <18.5 between the preterm and full-term groups. One possible reason is that the sample population of BMI <18.5 was very small ($n = 15$) among the 1729 mothers enrolled. Conversely, we demonstrated that the proportion of maternal BMI ≥30 was significantly higher in the preterm than in the full-term group, but it was not identified as an independent risk factor after multivariate analysis.

Currently, obesity is recognized as an important health problem worldwide, including in pregnant women. The complex relationship between obesity and preterm birth has long been discussed.[26-28] In 2010, McDonald *et al*. conducted a meta-analysis to discuss the relationship between overweight mothers and preterm births.[27] They reported that there was an increase of induced preterm birth in overweight mothers.[27] Systemic inflammation, dyslipidemia, and multiple factors caused by obesity may contribute to the observed increase of preterm births.[24] Corresponding to our results, the comorbidity of obesity, as well as obesity *per se*, were the main causes for preterm birth reported by some investigators.[8,28] Preeclampsia or eclampsia due to obesity, was suggested to play an important role.[25,29,30] Conversely, a negative correlation between overweight mothers and preterm births was reported by Ehrenberg *et al*., and they found that the decrease of uterine activity in obese women may be partially responsible.[7] Therefore, the role of obesity in preterm birth is most likely related to obesity-associated maternal problems and requires further exploration.

The enrolled women in the preterm group revealed a significantly lower rate of performance in GBS screening than those in the full-term group in our study. The main reason was the current policy in Taiwan advising pregnant women to undergo examination for GBS status during gestations of 35–37 weeks,[31] leading to a limited number of pregnant women with preterm birth available for the test. In a systematic review, an increase of positive GBS in preterm cases was reported.[32] Surve *et al*. also demonstrated that membrane vesicles secreted by GBS are the cause of chorioamnionitis, PPROM, and preterm births.[33] Therefore, the role of GBS infection in pregnant women requires continued attention.

Although we found some risk factors related to preterm birth in our cohort, we agree with Vogel's *et al*. opinion that the majority of preterm births occur in women without a clear risk factor.[3] Therefore, physicians still cannot neglect those pregnant women without risk factors for preterm birth and should provide proper care for newborn infants of preterm births to reduce their mortality and morbidity rates.[6]

There are several limitations to this study. First, this is a retrospective analysis; therefore, a few data are missing. Second, the GBS test was conducted less in the preterm group, and we could not adequately conclude the role of GBS in preterm births. Further investigation with a prospective, observational design may be helpful in future. Although we did not find distinct risk factors for preterm births compared to other studies, we have defined the current risk factors for preterm birth in a modern city, providing information for the health of women and infants.

Conclusion

The preterm birth rate was 12.1% in the medical center in Taipei during the year of 2015. Multiple pregnancies; presence

of maternal diseases during pregnancy, including preeclampsia/eclampsia, SLE, diabetes and infections; and lower maternal height (<155 cm) were significantly associated with a higher risk of preterm birth. Physicians should be alert when caring for pregnant women with these risk factors to prevent preterm deliveries and associated morbidities.

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Conflicts of interest

There are no conflicts of interest.

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Usefulness of Obstructive Sleep Apnea-18 as a Predictor of Moderate-to-Severe Obstructive Sleep Apnea in Children Who Have Normal/Inconclusive McGill Oximetry Score

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Abstract

Context: Overnight oximetry is a screening test for pediatric obstructive sleep apnea (OSA). However, those who demonstrate normal/inconclusive test still require diagnostic polysomnography (PSG). Since PSG has a long waiting list, an adjunct simple test for the prioritization would be helpful. **Aims:** The aim of this study is to determine whether the OSA-18 quality of life (QoL) questionnaire could predict moderate-to-severe OSA in children with normal/inconclusive overnight oximetry. **Settings and Design:** The study involves a cross-sectional study at a university hospital. **Subjects and Methods:** Overnight PSG and QoL assessed by the Thai-Version OSA-18 were performed in snoring children with normal/inconclusive overnight oximetry. **Statistical Analysis:** Unpaired Student's *t*-test, Chi-square, and receiver operating characteristic curve analysis were used. **Results:** A total of 218 children (age 6.4 ± 2.5 years, 62% male) were studied. Sixty percent had moderate-to-severe OSA, while 40% had primary snoring/mild OSA. The mean total OSA-18 score was not different between the two groups. Subgroup analysis among those who never had medical treatment for OSA ($n = 55$) showed a higher total OSA-18 score in moderate-to-severe compared to primary snoring/mild OSA groups (80.5 ± 10.7 vs. 72.2 ± 14.4; $P = 0.02$). Total OSA-18 score >78 was the best cutoff value for predicting moderate-to-severe OSA (61.5% sensitivity, 80% specificity, 72.7% positive predictive value, and 69.7% negative predictive value). Combining this cutoff value with overweight/obesity did not improve its predictivity. **Conclusions:** We found the association between high total OSA-18 score and moderate-to-severe OSA in snoring children who had normal/inconclusive overnight oximetry and never had medical treatment for OSA. However, the best cutoff value of the score and other potential add-on parameters are still needed to be investigated.

Keywords: Children, obstructive sleep apnea, obstructive sleep apnea-18, oximetry

Introduction

Overnight oximetry is a screening test for pediatric obstructive sleep apnea (OSA). However, those who demonstrate normal/inconclusive tests require polysomnography (PSG) for verifying the diagnosis.[1] Since PSG has a long waiting list, an adjunct simple test for prioritizing these children to get the urgent PSG would be helpful.

OSA-18 is a simple quality of life (QoL) questionnaires developed by Franco *et al*. in 2000 and has been widely used in the pediatric OSA population.[2-6] We, therefore, did the study to investigate the predictive value of Thai-Version OSA-18 in predicting moderate-to-severe OSA in children who had normal/inconclusive overnight oximetry.

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Subjects and Methods

Study design

This was a cross-sectional study performed in the Department of Pediatrics in a University Hospital of Thailand. The study

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protocol was reviewed and approved by the institutional review board for human research study. Informed consent and assent (where applicable) were obtained from the participants and their legal guardians before enroll in the study.

Population

Children aged 3–15 years who had habitual snoring, adenotonsillar hypertrophy, and normal/inconclusive overnight oximetry, according to the McGill Oximetry Scoring System, were enrolled.[7] The size of upper airway soft tissue was assessed by grading tonsillar size and X-ray of the lateral nasopharynx. All children had tonsillar size graded at least 3+ and adenoid hypertrophy demonstrated in the X-ray (adenoidal–nasopharyngeal ratio >0.6). Children whose caregivers did not understand the Thai language and those who were uncooperative with PSG or had the underlying conditions such as neuromuscular diseases, craniofacial anomalies, chronic lung diseases, asthma, and recent respiratory infection within 2 weeks before the study were excluded from the study.

Study protocol

All participants undertook attended overnight PSG to confirm the diagnosis of OSA and had Thai-Version OSA-18 QoL questionnaire completed by their caregivers on the following day after the PSG.

Polysomnography

The attended overnight PSG was performed at the Sleep Laboratory of the institute using the Sleep System Compumedics™ (Melbourne, Australia). The test was performed under the supervision of a well-trained sleep technician. The participants presented at the sleep laboratory at 8.30 P.M. and were discharged at 7.00 A.M. on the following day. All PSG used standard electroencephalographic monitoring, including frontal leads (F1, F2), central leads (C3, C4), occipital leads (O1, O2), and reference leads at the mastoids (M1, M2); electromyography; and electrooculography methodology. SpO_2 was measured with a finger probe, while airflow was measured by two methods, including nasal pressure transducer and oronasal thermocouple. The thoracic and abdominal respiratory movements were monitored by respiratory inductance plethysmography. The body position was measured by a position sensor attached to the anterior chest wall on the thoracic belt. Carbon dioxide was measured by end-tidal CO_2 monitoring or transcutaneous CO_2 monitoring. Sleep stages were scored in 30-s epochs, according to the American Academy of Sleep Medicine (AASM) Manual. Apnea was defined using oral–nasal thermocouple excursion, and hypopnea was defined using nasal pressure transducer excursion. Apnea, hypopnea, and respiratory effort-related arousals were scored using the standard criteria from the AASM updated manual (Versions 2.0, 2.1, 2.2, 2.3, and 2.4).[8-12] OSA was diagnosed if the participants demonstrated the events of obstructive apnea–hypopnea ≥1/h of total sleep time (TST) (obstructive apnea/hypopnea index [OAHI] ≥1 per TST). The severity of OSA was graded as mild, moderate, and severe in accordance with the OAHI (mild OSA: OAHI 1–4/TST; moderate OSA: OAHI 5–10/TST; and severe OSA: OAHI >10/TST).[13]

Quality of life assessment

Caregivers who regularly slept with the participants completed the QoL questionnaire on the following day after the PSG. The questionnaire used in this study was a Thai-Version OSA-18 developed and validated by Kuptanon *et al*.[14] It was translated from the original English version of Franco's Pediatric OSA instrument (OSA-18) under the permission of the original authors.[2] The questionnaire consisted of 18 items divided into five domains (sleep disturbance, physical symptoms, emotional symptoms, daytime functioning, and caregiver concerns). The 18 items were scored with a 7-point ordinal scale assessing the frequency of the specific symptoms. The scores on each of the 18 items were summed to produce a total score which ranged from 18 to 126. The higher score corresponded to the greater impact of OSA on QOL.

Sample size calculation

To investigate the best cutoff value of total OSA-18 score for predicting moderate-to-severe OSA, we used the following formula for calculating sample size:

$$n = \frac{(Z_{\alpha/2})^2 PQ}{d^2}$$

Where P represented the estimated sensitivity of the test and Q was derived from $1 - P$. The acceptable error (d) was set at 0.07, while α and β errors were set at 0.05 and 0.20, respectively. For the sensitivity of the test at 0.80, the calculated number of moderate-to-severe OSA children required for the study was 125. In accordance with the pilot survey, the proportion of moderate-to-severe OSA diagnosed by PSG among snoring children who had normal/inconclusive overnight oximetry in our institute was 56%. Therefore, the required number of enrolled participants was 224 cases.

Data acquisition and analysis

Collected data included demographic data, body weight, height, body mass index (BMI), total OSA-18 score, and OAHI. The participants were diagnosed with overweight and obese in accordance to the WHO criteria (https://www.who.int/growthref/who2007_bmi_for_age/en/). Mild and moderate-to-severe OSA were diagnosed basing upon the OAHI. Clinical data were compared between the two groups using the unpaired Student's *t*-test for continuous variables and the Chi-square or Fisher's exact test (where applicable) for categorical variables to identify the factors associated with moderate-to-severe OSA. Receiver operating characteristic (ROC) curve analysis was applied for identifying the best cutoff value of the total OSA-18 score for predicting moderate-to-severe OSA. Sensitivity, specificity, and positive and negative predictive values (PPV and NPV) of the best cutoff value were calculated. A two-tailed $P < 0.05$ was considered statistically significant. The analysis was performed using SPSS Version 16.0 (SPSS Inc., Chicago, IL, USA).

Results

Two hundred and eighteen children who had normal/inconclusive overnight oximetry were eligible and enrolled in the study. PSG revealed primary snoring, mild OSA, and moderate-to-severe OSA in 10 (5%), 76 (35%), and 132 cases (60%), respectively. Clinical data including demographic data and BMI as well as PSG findings and total OSA-18 score are shown in Table 1. Comparison between primary snoring/mild OSA and moderate-to-severe OSA groups found no difference in clinical data and mean total OSA-18 score between the two groups [Table 2]. However, subgroup analysis among children who never had medical treatment (such as montelukast and intranasal steroid) for their OSA ($n = 55$) found a higher total OSA-18 score in the moderate-to-severe compared to the primary snoring/mild OSA groups (80.5 ± 10.7 vs. 72.2 ± 14.4; $P = 0.02$) [Table 3]. The best cutoff value of the total OSA-18 score for predicting moderate-to-severe OSA in this subgroup analysis was 78 with the area under the curve of 0.70 (95% confidence interval [CI] 0.55–0.84; $P = 0.01$) [Figure 1]. The sensitivity, specificity, PPV, and NPV of this cutoff value were 61.5, 80, 72.7, and 69.7%, respectively. Children who had total OSA-18 score >78 had 2.1 times increased risk of moderate-to-severe OSA (95% CI 1.2–3.9; $P = 0.02$). There was a higher frequency of moderate-to-severe OSA among children who had total OSA-18 score >78 and overweight/obesity. However, this was not statistically significant [Table 3]. Combining total OSA-18 score >78 with overweight/obesity did not increase its predictivity for identifying moderate-to-severe OSA. The sensitivity, specificity, PPV, and NPV were 60%, 75%, 69.2%, and 66.7%, respectively, with the area under the curve of 0.77 (95% CI 0.60–0.94; $P = 0.01$) [Figure 2].

Table 1: Clinical data, polysomnography findings, and total obstructive sleep apnea-18 score of the study patients (n=218)

Data	All (N=218)
Mean age (years)	6.4±2.5
Male	136 (62%)
Mean BMI	18.1±4.5 kg/m^2
Overweight/obesity	102 (46.7%)
Median AHI (IQR)	8 (4-13.4)/TST
Median OAHI (IQR)	6.7 (3.7-12.7)/TST
Mean nadir SpO_2	89.4%±6.8%
Mean peak $EtCO_2$	44.2±5.8 mmHg
Mean RERA	16.5±8/TST
Mean total OSA-18 score	65.9±17.9

AHI=Apnea/hypopnea index, BMI=Body mass index, $EtCO_2$=End-tidal carbon dioxide tension, IQR=Interquartile range, OAHI=Obstructive apnea/hypopnea index, RERA=Respiratory effort-related arousal index, SpO_2=Oxygen saturation measured by pulse oximetry, TST=Total sleep time, OSA=Obstructive sleep apnea

Discussion

In this study, we found that almost all of the children who had normal/inconclusive overnight oximetry had OSA demonstrated by PSG. Moreover, 60% of the cases had the moderate-to-severe disease. The high false-negative predictive value of the test is a known major limitation of overnight oximetry as a screening test for pediatric OSA. In the context where PSG is not widely available and costly, overnight oximetry still serves as the first test for screening OSA in children. However, the majority of the cases show normal or inconclusive results, which eventually require PSG to verify the diagnosis. A high proportion of moderate-to-severe OSA in children who had normal/inconclusive overnight oximetry in this study suggested that a measure to prioritize these children for the urgent diagnostic PSG would be helpful.

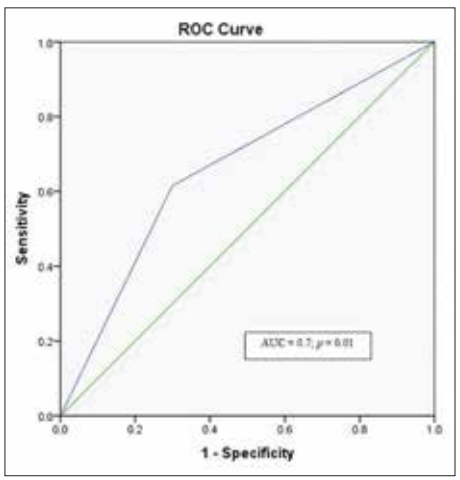

Figure 1: The receiver operating characteristic curve of total obstructive sleep apnea-18 score >78 in medical treatment for obstructive sleep apnea.

Table 2: Comparison of clinical data and total obstructive sleep apnea-18 score between primary snoring/mild obstructive sleep apnea and moderate-to-severe obstructive sleep apnea groups

	Primary snoring/ mild OSA (n=86)	Moderate-to-severe OSA (n=132)	95% CI		P
			Lower	Upper	
Mean age (years)	6.7±2.5	6.3±2.5	0.98	1.00	0.25
Male	52 (61.1%)	83 (62.9%)	0.74	2.32	0.41
BMI (kg/m^2)	17.6±4.0	18.5±4.8	1.00	1.17	0.15
Overweight/obesity	36 (41.8%)	66 (48.8%)	0.25	1.15	0.06
Total OSA-18 score	64.7±17.9	66.7±18	0.99	1.02	0.45

BMI=Body mass index, OSA=Obstructive sleep apnea, CI=Confidence interval

Table 3: Comparison of clinical data and total obstructive sleep apnea-18 score between primary snoring/mild obstructive sleep apnea and moderate-to-severe obstructive sleep apnea groups (subgroup analysis among children who never had medical treatment for obstructive sleep apnea)

	Primary snoring/ mild OSA ($n=29$)	Moderate-to-severe OSA ($n=26$)	95% CI		*P*
			Lower	Upper	
Mean age (years)	7.6±2.9	7.2±2.8	0.98	1.01	0.62
Male	12 (41.4%)	12 (46.2%)	0.28	2.83	0.72
BMI (kg/m^2)	19.3±3.8	19.3±5.1	0.91	1.20	0.99
Overweight/obesity	16 (55%)	15 (57%)	0.33	7.59	1.00
Total OSA-18 score	72.3±14.4	80.5±10.7	1.01	1.12	0.02
Total OSA-18 score >78	8 (27.5%)	16 (61.5%)	1.16	3.91	0.02
Total OSA-18 score >78 + overweight/obesity	4 (13.7%)	9 (34.6%)	0.96	4.83	0.11

BMI=Body mass index, OSA=Obstructive sleep apnea, CI=Confidence interval

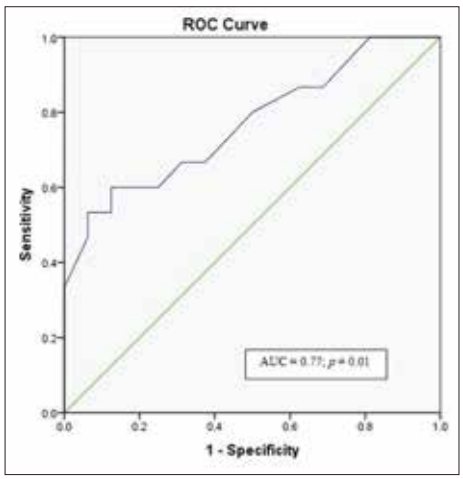

Figure 2: The receiver operating characteristic curve of total obstructive sleep apnea-18 score >78 in predicting moderate-to-severe obstructive sleep apnea in snoring children who were overweight/obese and never had medical treatment for obstructive sleep apnea.

There have been many simple tests developed for substituting overnight PSG in pediatric OSA. OSA-18 is a simple questionnaire for QoL assessment and has been widely studied in snoring children. However, the relationship between total OSA-18 score and OSA severity was various among the studies.[14-21] The discrepancies of the results could be due to the different diagnostic criteria for OSA, versions of PSG scoring system, and patient characteristics such as ethnicity, socioeconomic background, and current therapeutic interventions that could affect the QoL assessment. In this study, we evaluated the relationship between total OSA-18 score and OSA severity in habitually snoring children focusing on those who had adenotonsillar hypertrophy and normal/inconclusive overnight oximetry. We applied AASM updated manual 2012 for sleep staging and event scorings which is more sensitive in identifying obstructive hypopnea events when compared to the previous studies.[8-12]

In this study, we found no relationship between total OSA-18 score and OSA severity among the overall study population. However, subgroup analysis focusing on children who never had medical treatment (montelukast or intranasal steroid) for their OSA showed a positive relationship between total OSA-18 score and OSA severity. This implied that therapeutic intervention might have some impacts on this relationship. It has been reported that both medical and surgical interventions improved PSG findings and QoL in children who had OSA secondary to adenotonsillar hypertrophy.[22-27] However, the improvement of QoL might not be parallel with the improvement of PSG findings after therapeutic interventions. Kang *et al*. studied QoL and AHI before and after adenotonsillectomy in pediatric OSA and found total OSA-18 score was markedly improved in 93% of the cases while 45% still had residual OSA documented by PSG.[26] The authors addressed the possibility of "placebo effect" of the surgery for the discrepancy between QoL and AHI improvement after the treatment. In addition, they found a positive correlation between AHI and total OSA-18 score in the patients only before but not after the surgery.[26] Currently, there has been no study investigated whether medical treatment could have the same effect on the inconsistency between subjective and objective improvements in pediatric OSA. However, in this study, a relationship between total OSA-18 score and OAHI was found only among children who never had medical treatment for their OSA. These findings implied that therapeutic interventions, either medical or surgical treatment, could have an impact on the relationship between total OSA-18 score and OSA severity assessed by PSG. It could be possible that the various relationships between OSA-18 score and OSA severity reported in the previous studies were affected by the various therapeutic interventions in the study population.

In this study, the ROC curve analysis showed that total OSA-18 score >78 was the best cutoff value for predicting moderate-to-severe OSA (with the area under the curve of 0.70) in children who had normal/inconclusive overnight oximetry and never had medical treatment for their OSA. However, the sensitivity, specificity, PPV, and NPV of this cutoff value were not good. Further study in a larger population would provide us a precise validity of OSA-18 in predicting OSA severity in this population.

It has been known that obesity is another risk factor of OSA. In this study, moderate-to-severe OSA seemed to be more prevalent among children who had total OSA-18 score >78 and overweight/obesity [Table 3]. However, the predictivity of this combination for identifying moderate-to-severe OSA was not good either. Further study to identify other helpful add-on parameters such as Mallampati score, nasal turbinate assessment which represents the size of upper airway soft tissue, would be helpful to identify the best diagnostic tool for prioritizing children who need urgent diagnostic PSG.

Conclusions

We found an association between high total OSA-18 score and the occurrence of moderate-to-severe OSA in snoring children who had normal/inconclusive overnight oximetry, especially among those who never had medical treatment for their OSA. However, the best cutoff value of total OSA-18 score and other potential add-on parameters to increase its validity for prioritizing these children to get the urgent diagnostic PSG are still needed to be investigated.

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Conflicts of interest

There are no conflicts of interest.

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Executive Functions

3 Core Executive Functions (EFs)[1-2]

1. **Working Memory**: Ability to **update** information which is stored in memory

2. **Inhibition:** Ability to **control** attention, behavior, thoughts or emotions to override internal predisposition or external lure

3. **Cognitive Flexibility**: With the former two core EFs as a foundation, ability to **change** perspectives, think outside the box, and **adapt** to changed circumstances

Scientific evidence-based activities for improving EFs

age < 4[3-6]

1. Pre-kindergarten program
   - Early education programs, curricula and coaching

2. Pretend play/Spontaneous play
   - Children play who they'll be in a pretend scenario

3. Physical activity
   - E.g. Brisk walking, running

age 4+[7-9]

1. Computerized memory training
2. Combination of computer and non-computer games
3. Aerobic exercise and sports
4. Martial arts
5. Mindfulness training
6. Classroom curricula

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