COMMENTARY

The ROX index: "Propelled" by high-flow nasal cannula therapy during the COVID-19 pandemic into greater applicability in respiratory support

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INTRODUCTION

COVID-19 has rapidly spread worldwide, with thousands of new cases diagnosed daily, particularly during waves of contamination [1]. The severity of the disease has decreased considerably due to the effectiveness of the currently available vaccine, and half of the world's population has been fully vaccinated [2]. However, the initial pandemic scenario caused a considerable societal, economic and health burden resulting in millions of deaths and billions of dollars spent on treating and managing COVID-19 [3].

SARS-CoV-2 is primarily a respiratory virus with clinical manifestations similar to pneumonia, such as coughing, dyspnoea and fever [4]. While a considerable proportion of the infected population remains asymptomatic or develops mild symptoms [5], a large portion of people with COVID-19 did suffer from moderate to severe respiratory failure due to the development of hypoxia, as well as additional systemic complications that required hospital admission, especially in intensive care units (ICUs) [6]. Other forms of oxygen support that offered higher fractions of inspired oxygen, such as the high-flow nasal cannula (HFNC), were rapidly considered as treatment options due to the possibility of patient management outside the ICUs [7], therefore minimizing more severe outcomes, such as intubation [8].

The "usual" challenge during the COVID-19 pandemic

The peak stage of the pandemic was marked by hospitals operating at maximal capacity and shortages in qualified health care staff and medical equipment, specifically mechanical ventilators [9]. As a result, many ad hoc ICUs [10] and medical wards [11] were created worldwide. The overall purpose of these units was to manage respiratory distress in situ, therefore reducing the need for ICU transfer [10]. In addition, a number of wards were rapidly equipped with mechanical ventilators and other types of equipment to provide oxygen support, such as the HFNC [11].

HFNC therapy: the basis for the respiratory rate-oxygenation (ROX) index

HFNC therapy is a noninvasive oxygen therapy that provides a heated and humidified high flow of blended oxygen using a single circuit and a nasal prong. The flow can be adjusted between 10 and 60 litres per minute (L/min), with a fraction of inspired oxygen (FiO_2) ranging from 0.21 to 1.0. Some physiological benefits of this therapy include oxygenation improvement, reduction of anatomical dead space and the potential provision of positive end-expiratory pressure (PEEP), helping to reduce the work of breathing [12].

The HFNC has been used mainly to avoid more invasive forms of oxygen therapy, such as mechanical ventilation [13]. This therapy has been used to treat a variety of subjects of different age ranges, from neonates to adults, with various respiratory conditions, including acute hypoxemic respiratory failure to hypercapnic lung failure, given the PEEP-like effect [14]. Although reduction in the work of breathing has been reported, limited evidence is available regarding clinical outcomes among patients with hypercapnic failure [15], and caution has been advised to avoid the deterioration of respiratory drive at higher oxygen concentrations, particularly among individuals with chronic obstructive pulmonary disease [14]. The HFNC has also been able to treat respiratory failure in trauma and immunosuppressed patients, provide comfort in palliative care and provide oxygen support during specific procedures, such as bronchoscopy [14].

The respiratory rate-oxygenation (ROX) index is defined as the ratio of peripheral oxygen saturation/FiO_2 to respiratory rate [16]:

$$\frac{Ratio\ of\ peripheral\ oxygen\ saturation\ /FiO_2}{respiratory\ rate}$$

Roca et al. [16, 17] created it to predict the need for mechanical ventilation among patients with pneumonia and acute respiratory failure treated with HFNC. The authors showed that a ROX index consistently equal to or greater than 4.88 measured 2 h, 6 h and 12 h after HFNC therapy indicated a lower risk for needing mechanical ventilation [16, 17].

The ROX index has been closely used in conjunction with the HFNC, serving as a guiding parameter to help monitor this therapy's success or failure. Since the start of the COVID-19 pandemic, there has been a number of studies corroborating the ROX index as a valuable predictor of the success or failure of the HFNC therapy among COVID-19 patients [18], as well as non–COVID-19 patients [19]. Its predictive validity in detecting respiratory-related adverse events has surpassed

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other instruments, such as the National Early Warning Score, in COVID-19 patients [20], partly due to the use of FiO_2 as a continuous variable. This index has had similar accuracy compared to other oxygenation monitoring parameters, such as the SpO_2/FiO_2 and the PaO_2/FiO_2 [21]. The pandemic scenario has facilitated the applicability of the ROX index, departing from monitoring the effectiveness of the HFNC. The following sections highlight the contributions of this index for respiratory monitoring during the COVID-19 pandemic and its potential future applicability.

During the COVID-19 pandemic

Reducing the risk of intubation with the HFNC therapy
Delaying time for intubation, particularly among COVID-19 patients, has been associated with several negative physiological and clinical outcomes, such as higher mortality and higher dead space ratio [22]. Therefore, it is paramount to identify when it is necessary to discontinue noninvasive oxygen therapy and initiate mechanical ventilation. It has been shown that the ROX index ≤ 3.85 12 h after HFNC initiation strongly predicts invasive mechanical ventilation among COVID-19 patients. The index was, in fact, included in the routine monitoring in the northern California health delivery system to optimize inpatient surge [23]. Suliman et al. [24] also validated the ROX index, particularly on day 1 (at admission), as a reliable tool for predicting the risk of intubation in COVID-19 patients using the HFNC. Although a higher cut-off value was reported as ≤ 25.26 on day 1, the authors acknowledged that milder cases of COVID-19 were considered, increasing the index's value [24].

Predicting hospitalization time and ICU mortality after intubation
Leszek et al. [25] investigated whether the median ROX index predicted mortality among COVID-19 patients who failed noninvasive ventilation (HFNC or continuous positive airway pressure, CPAP) and required mechanical ventilation. Results showed a median ROX of ≥ 7.0 predicted ICU survival [25]. The ROX index showed acceptable accuracy in predicting hospitalization and mortality rates among COVID-19 patients admitted to the emergency department. Gianstefani et al. [26] showed that a ROX index value of < 25.7 was associated with increased hospitalization time, while a value of < 22.3 was associated with a higher 30-day mortality rate.

Triage of COVID-19 patients with dyspnoea
The ROX index has been a valuable tool in assisting the emergency team in triaging COVID-19 patients with dyspnoea without confirmed respiratory distress but at risk for developing acute respiratory distress syndrome (ARDS) [27]. Zaboli et al. [27] assessed the ROX index during triage (at admission) and compared it to the incidence of ARDS and to the risk of intubation 72 h after triage. Patients who developed ARDS had a lower average median ROX index (value of 13.1) compared to those who did not develop ARDS (value of 25.2). Similarly, lower median ROX values were reported among those who underwent intubation procedure 72 h after triage (value of 15.3) compared to those who did not require intubation (value of 22.2). The study showed that this index could serve as a screening tool for predicting disease progression and risk of intubation.

Predicting CPAP failure
The ROX index was assessed as a prognostic indicator among COVID-19 patients receiving CPAP in a respiratory ward [28]. Results showed that ROX index values of > 6.32 pre-CPAP and > 7.77 after the first 24 h of CPAP therapy were indicative of successful therapy weaning in > 80% of cases [28].

ROX index applicability beyond the context of the COVID-19 pandemic

A helpful tool for patients with sepsis in the emergency department
The ROX index has been used to identify patients at risk for poor health outcomes, such as sepsis [29] and mechanical ventilation [30]. Lee et al.

[29] showed that a ROX index of ≤ 10 at admission in an emergency department was used as an independent prognostic factor for 28-day mortality among patients with sepsis or septic shock. The authors suggested that the ROX index can potentially be used as a prognostic marker [29].

Similarly, Ahn et al. [30] examined the predictive value of the ROX index in requiring mechanical ventilation among patients with sepsis admitted to the emergency department. Results showed that the ROX index was significantly lower (value of 4) among patients who required mechanical ventilation compared to those who did not require it (value of 10), with a sensitivity of 75% and a specificity of 81.6%. The index was independently associated with the use of mechanical ventilation within 24 h in the emergency department [30].

Predicting successful noninvasive ventilation among thoracic trauma patients
The index has also shown to be effective in predicting the successful use of noninvasive oxygen therapy (via standard oxygen therapy, HFNC or noninvasive ventilation) and, therefore, not requiring mechanical ventilation in thoracic trauma patients. A median ROX index of ≥ 12.85 in the first 24 h after the initiation of noninvasive oxygen therapy was a successful predictor of not requiring mechanical ventilation for the next seven days after thoracic trauma [31].

Is there an ideal cut-off value for the ROX index?
Although an ideal cut-off value for therapy success has not been reached, systematic reviews have provided a narrower range of values with adequate predictive capacity for successful HFNC weaning. Junhai et al. [19] have found acceptable specificity (0.72 (95% CI 0.65–0.78)) but low sensitivity (0.67 (95% CI 0.57–0.76)). In a subgroup analysis of COVID-19 patients only, the predictive value was moderate (pooled sensitivity and specificity of 0.71 (95% CI 0.56–0.82) and 0.73 (95% CI 0.63–0.81), respectively), and a cut-off value of > 5 in predicting HFNC failure was reported (sensitivity and specificity 0.59 (95% CI 0.54–0.65) and 0.83 (95% CI 0.79–0.86), respectively). Zhou et al. [32] showed that among patients with acute hypoxemic respiratory failure related to COVID-19, a ROX value between 4.2 and 5.4 measured either after 6 h or between 6 and 12 h after HFNC therapy initiation has shown to be a good predictor of therapy success (pooled sensitivity 0.71 (95% CI 0.64–0.78) and pooled specificity 0.78 (95% CI 0.70–0.84)).

Some limitations of the ROX index have been identified, which may influence consensus towards an ideal cut-off value. First, a variety of pathologies have been assessed using the ROX index, including sepsis [29], COVID-19, acute respiratory failure and pneumonia [19]. Second, different types of noninvasive oxygen therapy have been studied, including HFNC [32] and conventional oxygen therapy [31]. Third, a lack of regularity regarding measurement intervals has been reported, such as the first 6 h of therapy, the first 6 to 12 h [32], and the first day of admission [24]. Fourth, small sample sizes and a lack of high methodological quality studies have been reported [32]. Future studies should address these limitations to provide greater respiratory monitoring using this index.

CONCLUSION

The ROX index has shown to be a practical instrument. It has been used in a variety of health settings during the COVID-19 pandemic and has served to foster best practices related to the use of HFNC therapy. Its ability to predict health-related outcomes has been amplified beyond the COVID-19 pandemic, assisting the health care team in identifying patients at risk for potentially unfavourable respiratory outcomes and guiding the decision-making process. Its applicability has warranted further research.

DISCLOSURES

Contributors
All authors contributed to the conception or design of the work and the acquisition, analysis or interpretation of the data. All authors were involved in drafting and commenting on the paper and have approved the final version.

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