Ultrasound performed right after birth can predict the respiratory support needs of neonates—-A diagnostic accuracy study

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Abstract

Abstract Background Lung ultrasound (LUS) has been used to diagnose neonatal respiratory diseases. However, few simple method has been reported to predict respiratory support needs(RSN). Our aim was to determine the diagnostic accuracy of a semiquantitative LUS assessment method predicting respiratory support need. Methods We conducted a prospective diagnostic accuracy study following the STARD (Standards for the Reporting of Diagnostic Accuracy Studies) guidelines at a tertiary level academic hospital between 2019 and 2020. After birth, infants were transferred to a monitoring room to determine NICU treatment need. 310 late preterm and term infants with respiratory symptoms enrolled. The LUS assessment was performed for each participant at one of the following times: 0.5 h, 1 h, 2 h, 4 h, and 6 h after birth. Reliability was tested by ROC analysis. Surfactant administration and other RSNs were based on the 2019 European guidelines as well as the infant's clinical condition. Results 74 have RSN, and 236 were healthy according to a 3-day follow-up confirmation. Six LUS imaging patterns were found. Two "high-risk" patterns were highly correlated with RSN(area under the curve (AUC) = 0.95; 95% CI, 0.92-0.98, $p<0.001$). This accuracy is supported by the AUC of "low-risk" patterns (0.89, 95% CI, 0.85-0.93, $p<0.001$). The predictive value of LUS is greater than that of only using respiratory symptoms (e.g., respiratory rate) (AUC of LUS vs AUC of respiratory rate, $p<0.01$). Conclusions LUS is a useful tool to predict RSN and is more reliable than assessments based on respiratory symptoms alone.

Title Page

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Highlights

There are six LUS image patterns can be found in infants who just birth, including four "low-risk" patterns and two "high-risk" patterns.

The number of scanning regions with "high-risk" patterns has a great predictive value for respiratory support.(AUC = 0.95, optimal cut-off value is 2 with a sensitivity of 87.10% and specificity of 88.02%)

The predictive value of LUS is greater than that of assessment method based on respiratory symptoms.(e.g. respiratory rate)

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Methods We conducted a prospective diagnostic accuracy study following the STARD (Standards for the Reporting of Diagnostic Accuracy Studies) guidelines at a tertiary level academic hospital between 2019 and 2020. After birth, infants were transferred to a monitoring room to determine NICU treatment need. 310 late preterm and term infants with respiratory symptoms enrolled. The LUS assessment was performed for each participant at one of the following times: 0.5 h, 1 h, 2 h, 4 h, and 6 h after birth. Reliability was tested by ROC analysis. Surfactant administration and other RSNs were based on the 2019 European guidelines as well as the infant's clinical condition.

Results 74 have RSN, and 236 were healthy according to a 3-day follow-up confirmation. Six LUS imaging patterns were found. Two "high-risk" patterns were highly correlated with RSN(area under the curve (AUC) = 0.95; 95% CI, 0.92-0.98, p<0.001). This accuracy is supported by the AUC of "low-risk" patterns (0.89, 95% CI, 0.85-0.93, p<0.001). The predictive value of LUS is greater than that of only using respiratory symptoms (e.g., respiratory rate) (AUC of LUS vs AUC of respiratory rate, p<0.01).

Conclusions LUS is a useful tool to predict RSN and is more reliable than assessments based on respiratory symptoms alone.

Key words Lung ultrasound; respiratory support; predictive value; ROC

Background

Lung ultrasound (LUS) has become a widely used bedside examination technique in neonatal intensive care units (NICUs) because it is radiationless and can be easily and immediately performed by frontline neonatologists. A comprehensive and standardized LUS guideline has been developed[1-2] and validated by other studies[3-5]. Most neonatal lung diseases can be diagnosed using LUS, including respiratory distress syndrome (RDS)[6], transient tachypnea of the neonate (TTN)[7], meconium aspiration syndrome (MAS)[8], and pneumothorax (PTX)[9]. Some imaging patterns, such as "compact B-line", "white lung" and "consolidation", are considered to relate to those diseases.

The most common neonatal respiratory condition in late preterm infants is TTN, and these infants usually have good outcomes with continuous positive airway pressure (CPAP) treatment or hood oxygen support[10]. However, some degree of surfactant damage, which can cause secondary RDS[11], may occur in severe or long-lasting TTN. Some late preterm and term infants with RDS also seem to have a more unfavorable prognosis

even if pulmonary surfactant(PS) is applied[12-13]. In addition, other issues (e.g., MAS, PTX, pneumonia) that may lead to severe outcomes are common in these infants and may only manifest immediately after birth. Thus, identifying these potential patients is important for neonatologists. As it is radiationless and convenient, LUS a promising predictive tool to realize this goal.

Roselyne Brat et al[14]. described the usefulness of LUS in predicting PS in preterm infants. They used a relatively precise scoring system and tested its relation to oxygenation. Others performed similar research and confirmed Brat's findings[15-16]. However, they did not provide information to predict other respiratory support needs, and calculating scores according to different images may be complicated or challenging in some cases. By contrast, Raimondi et al[17-18] used only three straightforward LUS patterns to predict NICU admission or the need for intubation. Nevertheless, we believe that using a semiquantitative method would be more precise to predict respiratory support needs.

Our goal was to test whether a simplified semiquantitative evaluation method based on high-risk LUS imaging patterns could predict respiratory support needs. We hypothesized that the number of scanning regions with "high-risk" patterns has high predictive value for respiratory support needs in preterm and term infants and is more reliable than assessments based on respiratory symptoms.

Methods

Participants

This was a prospective diagnostic accuracy study that followed the STARD (Standards for the Reporting of Diagnostic Accuracy Studies) guidelines[19]. The study was conducted at a top-ranking obstetrics and gynecology hospital in China between 2019 and 2020. All included infants were delivered at our hospital and were transferred to a monitoring room for 6-hour monitoring before going back to their mothers (healthy infants) or admission to the NICU (infants with respiratory issues or other diseases). (Figure 1A) Infants who had respiratory symptoms, including anhelation, retractions, or transcutaneous oxygen saturation (TcSO2) constantly below 95%, were considered eligible for the study. Then, the infants were confirmed to be healthy or in need of respiratory support over a 3-day follow-up. The exclusion criteria were as follows: (1) chromosomal abnormalities or complex congenital malformations; (2) congenital lung diseases; (3) transfer to other hospitals so that they could not be followed up; and (4) no qualified LUS images or complete data.

LUS assessment

LUS was performed using CX50; (Philips Healthcare, Eindhoven, Netherlands) The frequency of the linear array probe was 10 to 13 MHz.

Lung ultrasound was performed at one of the following timings after birth: 0.5 h, 1 h, 2 h, 4 h, and 6 h. The LUS was performed by a physician who received two months of formal training. This training includes a 2-day course and practice on no less than 100 cases under senior supervision[14].

The scanning protocol was based on an adult adaptive method[20] and adjusted for infants. LUS was performed in a total of ten regions, as shown in Figure S1. Scanning was performed continuously and quickly in each region to avoid missing images or images disturbed by the motion of the infants. A similar protocol has been used in other studies[21,] but we reduced the total number of regions from twelve (in the previous studies) to ten because the area of two lateral (left and right) regions was nearly as large as that of the other eight regions. The infants were positioned in a supine, lateral, or prone position, as needed. In every region, if any "high-risk" patterns were detected, then the region was marked as "high-risk". By contrast, regions were only defined as "low-risk" when the whole region had no "high-risk" patterns. The number of "high-risk" regions and "low-risk" regions were used to assess the accuracy of the prediction. The definitions of "high-risk" patterns and "low-risk" patterns were determined by a pilot experiment and confirmed in this study and are shown in Figure 2.

Results were recorded on a dedicated study form that was not included in patients' files and was masked to other clinicians; this was the best way to mask the clinical conditions from the colleagues performing the

LUS and the LUS results from other clinicians[14]. The images and their interpretations for each participant were recorded by the LUS examiner and were linked to a serial number (SN) from 1 to 310 (after excluding those without qualified data). The SNs then linked to the infant outcomes by the physician who offered NICU treatment or followed these infants. Finally, an independent data analyst who had no knowledge of the lung ultrasound results analyzed the data.

Definition of respiratory support need

The respiratory needs in our study included hood oxygen support, CPAP, mechanical ventilation (MV) and PS. In this study, we defined "hood oxygen support need" as over 6 hours of support after birth that still did not relieve the infant's respiratory difficulty. Different from temporary usage, this prolonged hood oxygen support is highly likely a harbinger of severe TTN, RDS or other lung diseases according to our experience. According to our policy, pure oxygen with a pressure of 6 cm H2O was led into a hood that covered the infant's head completely, so it mixed with ambient air and provided the infant with approximately 30% oxygen and atmospheric pressure. CPAP was applied when hood oxygen support could not stabilize the infant's oxygen saturation, or when severe lung diseases were confirmed by chest X-ray. CPAP using a mask with a starting pressure of approximately 6-8 cm H2O and positive end-expiratory pressure (PEEP) was individualized depending on clinical condition, oxygenation and perfusion. MV was used in infants with RDS or when other methods of respiratory support failed. PS use depends on a combination of clinical evidence (e.g., FiO2 to maintain normal saturations, work of breathing) and appearance on chest X-ray. Usually, FiO2 >0.30 in infants on CPAP is regarded as the threshold[22]. All infants received respiratory support and were later confirmed to have certain lung diseases, and the diagnosis was made according to the integration of evidence from prenatal and postnatal clinical data (such as GA, inflammatory markers, microbiological test results, and physical examination findings) and X-ray images (RDS[22-23], TTN[24], pneumonia[23], MAS[25]).

Statistical Analysis

Data were tested for normality using the Kolmogorov-Smirnov test and expressed as the mean (standard deviation) or median (interquartile range), as appropriate. Receiver operating characteristic (ROC) analysis was used to evaluate the accuracy of the LUS to predict all kinds of respiratory support needs (comprehensively and separately). Areas under the curves (AUCs) and cutoff values showing the highest sensitivity were reported. The AUCs were compared using the method by Hanley and McNeil[26], and $p < .05$ was considered statistically significant. Analyses were performed using SPSS version 15.0 (SPSS Inc.) and MedCalc version 13.3 (MedCalc bvba) statistical software.

Results

Baseline characters of participants

The baseline characteristics of the participants are summarized in Table 1. Throughout the study (Figure 1B), 322 infants developed symptoms or signs of respiratory distress in the monitoring room. All of them underwent LUS, and clinical data were collected. Twelve of these infants were excluded according to the stated criteria (4 with complex malformation or congenital lung diseases, 3 were transferred to another hospital, and 5 did not have qualified LUS images). A total of 310 infants were enrolled, and their LUS images were obtained at one of following times—-(67, 85, 92, 37, 29 infants with LUS obtained at at 0.5 h, 1 h, 2 h, 4 h, 6 h after birth, respectively). After the three-day follow-up, 236 infants were confirmed to be healthy, and 74 were admitted to the NICU due to pulmonary issues, including RDS (28/74), TTN (31/74), pneumonia (6/74) and MAS (6/74). The GA range was 34w+0d to 41w+5d, and the birth weight range was 1990 g to 4520 g. Most NICU and healthy infants were scanned at second 2 hour after birth. Infants admitted to the NICU were more likely to have a higher respiratory rate (65 (87.8%) vs 57 (24.2%), $p<0.01$) and a higher incidence of lower TcSO2 (below 95% for more than 3 mins, 23 (31.1%) vs 18 (7.6%), $p<0.01$) than the healthy infants.

High-risk patterns and Low-risk patterns

Six LUS imaging patterns were found in these late preterm and term infants immediately after birth (Figure

2). These patterns were categorized as "high-risk" and "low-risk". The low-risk patterns, which indicate a lower likelihood of lung issues, include the "pure A-line" pattern, "scarce discrete B-line" pattern, "moderate discrete B-line" pattern, and "abundant discrete B-line" pattern. In fact, the three kinds of "discrete B-line" patterns can be easily discerned when performing LUS, and there was no need to identify each of them, as they were all significantly different from the "pure A-line" patterns and high-risk patterns, and they are less likely to be a sign of lung issues. High-risk patterns included the "coalesced B-line" and "consolidation" patterns.

The accuracy of LUS to predict respiratory support in late preterm and term infants

The ROC analysis for any respiratory support needs using high-risk patterns yielded an AUC of 0.95 (95% CI, 0.92-0.98, $p<0.001$). Correspondingly, the ROC analysis for any respiratory support needs using low-risk patterns yielded an AUC of 0.89 (95% CI, 0.85-0.93, $p<0.001$). In contrast, the ROC for RR (respiratory rate), which we conventionally use to predict respiratory support needs, yielded an AUC of 0.70 (95% CI, 0.64-0.76, $p<0.001$). The ROC curves for LUS (high-risk patterns) and RR were significantly different ($p<0.01$) (Figure 3). Table 2 shows the accuracy data for LUS and RR prediction of any need for respiratory support. A ROC analysis within respiratory support subgroups was also conducted, and the result for hood oxygen support is shown (Table 2). However, due to an insufficient number of patients who only obtained CPAP, MV, and PS treatment (23/74, 18/74, and 29/74, individually), the ROC curves for these analyses may not reliable and results are not shown.

Discussion

We modified the LUS scanning method and developed a simplified assessment system (based on "high-risk" imaging patterns) to predict respiratory support needs for the first time. To the best of our knowledge, this system is practical and useful in obstetrics and gynecology hospitals that need to identify infants with potential lung diseases in the several hours immediately after birth. This approach can help physicians identify these patients before their respiratory symptoms deteriorate, and chest X-ray can be applied so that physicians can implement NICU care earlier.

Findings and interpretation: This study has two clinically relevant findings. (1) Four "low-risk" patterns, and two "high-risk" patterns can be found in late preterm or term infants immediately after birth. While two "low-risk" patterns, the "moderate discrete B-line" and "abundant discrete B-line" patterns, were reported to be pathological in previous studies[27-28], our study shows that they can be seen as strong evidence of healthy infants immediately after birth. This discrepancy may be because of different extent of delay in lung fluid clearance. This delay results in a small number of alveoli that are uninflated and full of fluid[29-31] but not enough to cause TTN. (2) Two "high-risk" patterns have high predictive accuracy for respiratory support needs. These two patterns are also regarded as evidence of other diseases, such RDS[15], MAS[8] and pneumonia[32]. This concordance indicates that our findings of "high-risk" patterns are highly likely to be an early stage of RDS or MAS, especially when infants have only mild respiratory symptoms.

Because a total of ten scanning regions were evaluated, the number of regions with "high-risk" patterns was inversely related to those with "low-risk" patterns. Thus, the ROC curve of "low-risk" patterns can support the predictive accuracy of "high-risk" patterns.

Strengths and Limitations of our study: To our knowledge, this is the most straightforward semiquantitative method to predict lung diseases in late preterm and term infants. The assessment requires only a count of the number of scanning regions on the chest wall with "high-risk" patterns, and these patterns are easy to discern. More importantly, finding more than two regions with "high-risk" patterns provides 87.10% sensitivity and 88.02% specificity. Coupled with LUS's radiationless and convenience, this method can be used as an effective lung disease screening tool between the delivery room and NICU.

Nevertheless, there are some limitations to our study. Most significantly, there was an insufficient number of patients who received CPAP (23/74), MV (18/74), and PS (29/74). This insufficiency made it difficult to draw a convincing conclusion to predict these individual modes of advanced respiratory support. But

considering our goal is to discern potential lung diseases patients, and nearly all of their treatment starts with a hood oxygen support need, it's not necessary to predict every advanced respiratory support need at such an early stage of life. Besides, this limitation, if needed, can be improved in later research containing more patients with severe respiratory diseases. The second limitation is the possible inconsistency of image interpretation. Our study used only one LUS interpreter due to the limited budget, so we did not test consistency between interpreters. This may lead to a variance in predictive accuracy. This drawback may be corrected in later research by us or others. The last limitation is the concern about the overuse of LUS. Our participants were all late preterm and term infants, which means that they had a lower incidence of lung diseases than smaller preterm infants. Of all infants who undergo LUS, only a small part may develop lung diseases and need respiratory support. However, because LUS is radiationless, easy to perform, and economical, we think it is reasonable to perform LUS on every late preterm and term infant with respiratory symptoms. Also, as smaller preterm infants will receive more attention from physicians from birth, their respiratory issues are less likely to be ignored than those in late preterm and term infants.

Comparison with other studies: Many studies have verified the diagnostic value of LUS for neonatal lung diseases[2, 28, 33-34]. The difference between prior studies and ours is that we focused on predictive value. As we found that these abnormal LUS patterns identified immediately after birth do not have significant specificity for certain diseases, we can use LUS to predict respiratory needs for all kinds of severe lung diseases. Recently, some studies have also paid attention to the predictive value of LUS in neonatology[14-16, 35]. They evaluated the predictive value of LUS for PS need in preterm infants, whereas we studied the need for all kinds of respiratory support, including CPAP and MV, which are closely related to severe lung disease. Therefore, we believe our study is a good complement to current studies. Moreover, it is very useful since it provides evidence to support early interventions in high-risk infants.

Conclusion: Our assessment method allows a straightforward semiquantitative use of LUS to discern infants with potential lung diseases right after their birth. The LUS "high-risk" patterns show good accuracy to predict respiratory support needs in late preterm and term infants who manifest mild respiratory difficulty.

List of abbreviations

LUS: Lung ultrasound

STARD: Standards for the Reporting of Diagnostic Accuracy Studies

AUC: Area under the curve

ROC: Receiver operating characteristic curve

NICU: Neonate intensive care unit

RDS: Respiratory distress syndrome

TTN: Transient tachypnea of the neonate

MAS: Meconium aspiration syndrome

PTX: Pneumothorax

CPAP: Continuous positive airway pressure

SN: Serial number

MV: Mechanical ventilation

PS: Pulmonary surfactant

PEEP: Positive end-expiratory pressure

TcSO2: Transcutaneous oxygen saturation

GA: Gestational age

BW: Birth weight;

SGA: Small for gestational age;

SD: Standard deviation;

CI: Confidence interval;

DB: Discrete B-line

RR: Respiratory rate

HR: Heart rate;

Declarations

Ethics approval and consent to participate This study was approved by the ethics committee of Obstetrics and Gynecology Hospital of Fudan University (No. Kyy-2020-162). Oral informed consent was obtained from the parents of the infants for using the images and data for analysis.

Consent for publication Not applicable.

Availability of data and materials: All data generated or analysed during this study are included in this published article [and its supplementary information files].

Competing interests There is no conflict of interest associated with this manuscript.

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Author Contributions JM.W and GN.X proposed the idea of this research and designed the protocol. GN.X performed the LUS. JL.D and XF.W collected clinical data. Y.Y performed the statistics analysis. GN.X and JM.W drafted the article and revising it critically for important intellectual content. F.L, Y.Y, CQ.L, XF.W have been involved in revising the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

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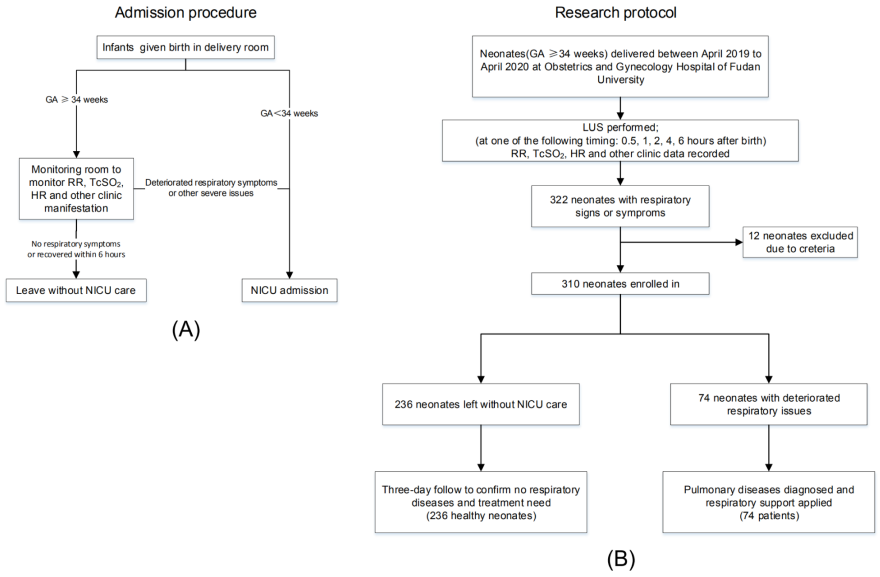

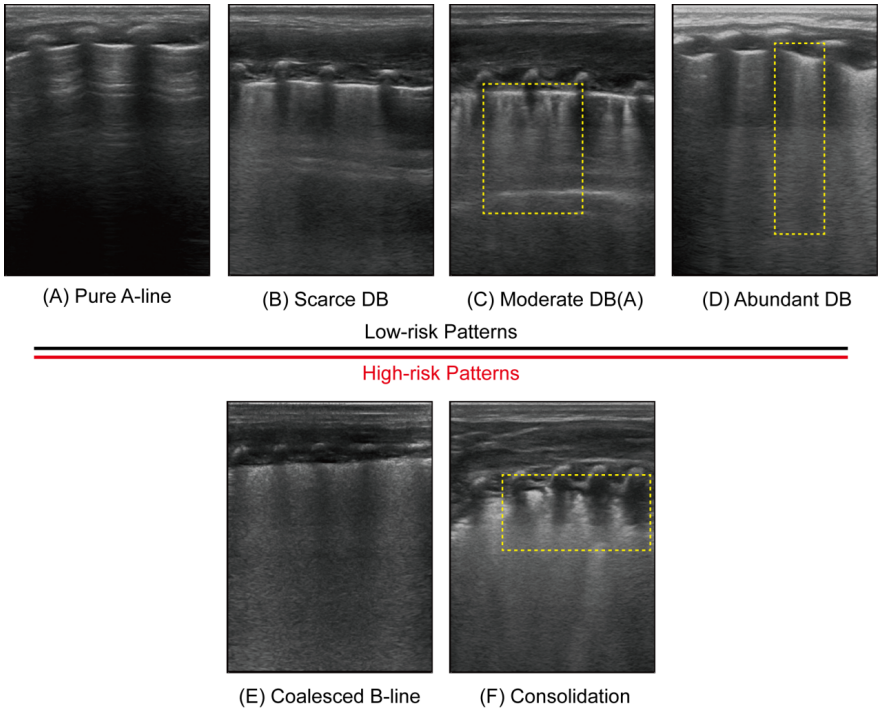

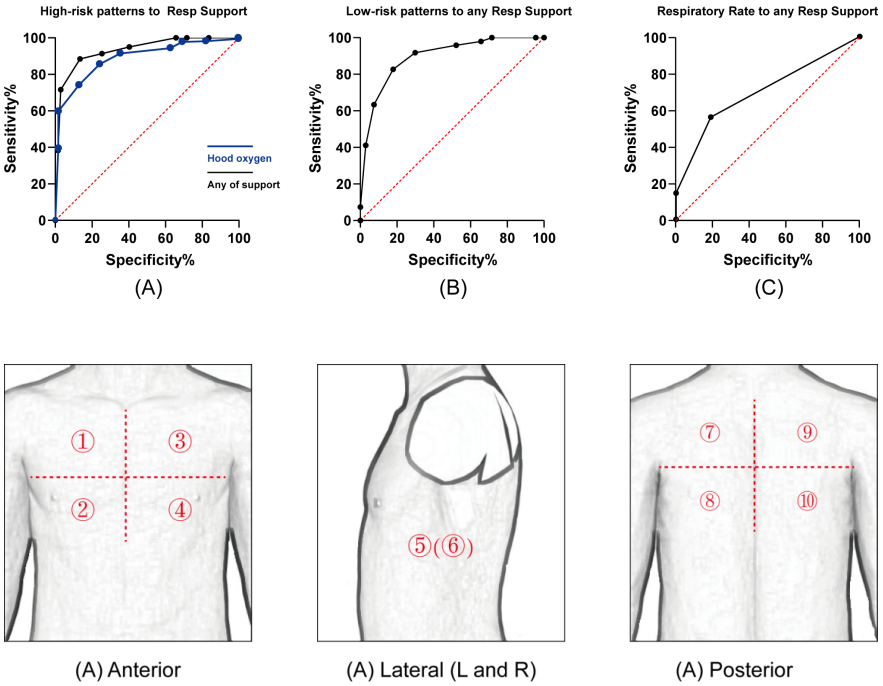

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