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

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Abstract

Background Lung ultrasound (LUS) is widely used to diagnose neonatal respiratory diseases. However, to our knowledge, few straightforward method was reported to predict respiratory support need precisely. Our aim is to determine the diagnostic accuracy of a semiquantitative LUS assessent method predicting the need for respiratory support. Methods We conducted a prospective diagnostic accuracy study following STARD (Standards for the Reporting of Diagnostic Accuracy Studies) guidelines at a tertiary level academic hospital between 2019 to 2020. 310 late preterm and term infants enrolled. They were delivered in the obstetric department and transferred to a monitoring room to determine whether they need NICU treatment. The LUS assessment was performed for each participant at one of following timings–0.5h, 1h, 2h, 4h, 6h after birth. Reliability was tested by ROC analysis. Surfactant administration and other respiratory support were based on 2019 European guidelines as well as their clinical condition. Results 74 were confirmed to need respiratory support and 236 were healthy according to a 3-day follow up. Six LUS image patterns can be seen in these infants right after birth. Two "high-risk" patterns well relate to respiratory support need(area under the curve(AUC) = 0.95; 95% CI, 0.92-0.98, $p<0.001$). This reliability can be supported by AUC of "low-risk" patterns(AUC = 0.89, 95%CI, 0.85-0.93, $p<0.001$). Predictive value of LUS is much greater than that of using respiratory symptoms(e.g.respiratory rate)(AUC of LUS vs AUC of respiratory rate, $p<0.01$). Conclusions LUS can predict respiratory support need and is more reliable than the assessment based on respiratory symptoms.

Title Page

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Short running title: Lung ultrasound can predict respiratory support need

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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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Background Lung ultrasound (LUS) is widely used to diagnose neonatal respiratory diseases. However, to our knowledge, few straightforward method was reported to predict respiratory support need precisely. Our aim is to determine the diagnostic accuracy of a semiquantitative LUS assessent method predicting the need for respiratory support.

Methods We conducted a prospective diagnostic accuracy study following STARD (Standards for the Reporting of Diagnostic Accuracy Studies) guidelines at a tertiary level academic hospital between 2019 to 2020. 310 late preterm and term infants enrolled. They were delivered in the obstetric department and transferred to a monitoring room to determine whether they need NICU treatment. The LUS assessment was performed for each participant at one of following timings–0.5h, 1h, 2h, 4h, 6h after birth. Reliability was tested by ROC analysis. Surfactant administration and other respiratory support were based on 2019 European guidelines as well as their clinical condition.

Results 74 were confirmed to need respiratory support and 236 were healthy according to a 3-day follow up. Six LUS image patterns can be seen in these infants right after birth. Two ”high-risk” patterns well relate to respiratory support need(area under the curve(AUC) = 0.95; 95% CI, 0.92-0.98, $p<0.001$). This reliability can be supported by AUC of ”low-risk” patterns(AUC = 0.89, 95%CI, 0.85-0.93, $p<0.001$). Predictive value of LUS is much greater than that of using respiratory symptoms(e.g.respiratory rate)(AUC of LUS vs AUC of respiratory rate, $p<0.01$).

Conclusions LUS can predict respiratory support need and is more reliable than the assessment based on respiratory symptoms.

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

Background

Lung ultrasound (LUS) has been becoming a widely used bedside examination technique in neonate intensive care unit(NICU), because it is radiationless and can be easily and immediately performed by the front-line neonatologists. A comprehensive and standardized LUS guideline has been built up[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], pneumothorax(PTX)[9].Some image patterns such as ”compact B-line”, ”white lung” and ”consolidation” are considered to relate to those diseases.

The most common neonatal respiratory conditions in late preterms and terms are TTN, and they usually have good outcomes with treatment continuous positive airway pressure (CPAP) or hood oxygen support[10].

However, some degree of surfactant damage, which can cause secondary RDS[11], may happen in severe or long-lasting TTN. Some late preterm and term infants with RDS also seem to have a more unfavorable prognosis even if PS applied[12-13]. Besides, other issues(e.g., MAS, PTX, pneumonia) that may lead to severe outcomes are common in these infants and may only manifest slightly right after birth. Thus, identifying those potential patients is important for neonatologists. And LUS, as it is radiationless and convenient, is a promising predictive tool to realize this goal.

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

Our goal is to test whether a simplified semiquantitative evaluating method, based on the high-risk LUS image patterns, can predict respiratory support need. We hypothesized that the number of scanning regions with "high-risk" patterns has high predictive value for respiratory supoort need in the preterms and terms, and is more reliable compared to the assessment based on respiratory symptoms.

Method

Participants

This is a prospective diagnostic accuracy study following STARD (Standards for the Reporting of Diagnostic Accuracy Studies) guidelines[19].The study was conducted at a top-ranking obstetrics and gynaecology hospital in China between 2019 to 2020. All inborn infants were given birth in our hospital and were transferred to a monitoring room for 6-hour monitoring before going back to their mothers(healthy infants) or admission to NICU(infants with respiratory issues or other diseases). (Fig1.A) Infants who have respiratory symptoms, including anhelation, retractions, or transcutaneous oxygen saturation(TcSO2) constantly below 95% were considered eligible for the study. Then they were confirmed to be healthy or in need of respiratory support through a 3-day follow up. Exclusion criteria are following: (1) chromosomal abnormalities or complex congenital malformations; (2) congenital lung diseases; (3) were transferred to other hospitals so that can not be followed up; (4) without qualified LUS images or complete data;

LUS assessment

LUS is performed using GE Voluson S10 or Philip EP5 ultrasound equipment . The frequency of the linear array probe was 10 to 13 MHz.

Lung ultrasound was performed at one of the following timings after birth: 0.5h, 1h, 2h, 4, 6h. And the performer was 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. The LUS was performed in totally ten regions, as shown in Figure S1. Scanning was performed continuously in each region in case of missing and finished quacky in case of being disturbed by the motion of infants. A similar protocol can be seen in other studies[21] but we reduced total twelve regions in theirs to ten regions due to the area of two lateral(left and right) regions is nearly as large as other eight regions. The infants may be posed in a supine position, later position, or prone position if needed. In every region, if any of "high-risk" patterns were detected, then the region was marked as "high-risk". By contrast, only when the whole region has no "high-risk" patterns, this region can be defined as "low-risk". The number of "high-risk" regions and "low-risk" regions were used to assess the reliability of prediction. The definitions of "high-risk" patterns and "low-risk" patterns were determined by a pre-experiment and were shown in Figure 2.

Results were recorded on a dedicated sheet, not included in patients' files and masked to other clinicians:

this was the best way to mask the clinical conditions to the colleagues performing LUS and the LUS results to other clinicians[14]. The images and its interpretations for each participant were recorded by the LUS examiner and were linked to a serial number(SN) from1 to 310(after excluded those without qualified data). The SNs were then corresponded to infants outcomes by the physician who offer NICU treatment or follow up these infants. Finally, an independent data analyst who has no idea of lung ultrasound analyzed the data.

Definition of respiratory support need

Respiratory need in our study includes hood oxygen support, CPAP, mechanical ventilation(MV) and pulmonary surfactant(PS). In this study, we defined "hood oxygen support need" as over 6-hour support after birth that still can not relief infants' respiratory difficulty. Different from temperary usage, this prolonged hood oxygen support is high likely a harbinger of severe TTN, RDS or other lung diseases according to our experience. As our policy, pure oxygen with pressure of 6 cm H2O was lead into a hood covered the head of infants completely, so it mixed with air and provide him/her oxygen of approxmate 30% oxygen with atmospheric pressure. The CPAP applied when hood oxygen support can not stabilize infants' oxygen saturation, or severe lung diseases were confirmed by chest X-ray. The CPAP using a mask with a starting pressure of about 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 have failed. Pulmonary surfactant 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 a threshold[22]. All infants received respiratory support were confirmed with certain lung diseases later, and the diagnosis was made according to integrating evidence of prenatal and postnatal clinical data (such as GA, inflammatory markers, microbiological test results, and physical examination findings) and X-ray inspection(RDS[22-23],TTN[24], pneumonia[23], MAS[25]).

Statistical Analysis

Data were tested for normality with Kolmogorov-Smirnov test and expressed as mean (standard deviation) or median (interquartile range) as appropriate. Receiver operating characteristic (ROC) analysis was used to evaluate the reliability of the LUS to predict all kinds of respiratory support need(comprehensively and respectively). 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] .$p< .05$ 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 characters of participants are summarized in Tab 1. Thoroughtout the study(Fig 1.B), 322 infants developed symptoms or signs in the monitoring room. All of them were performed LUS, and clinic data were collected. Twelve of them were excluded according to criteria(4 with complex malformation or congenital lung diseases, 3 were transferred to another hospital; 5 without qualified LUS images). 310 infants enrolled in total, and their LUS images were obtained at one of following timing—-(67, 85, 92, 37, 29 infants; respectively at 0.5h, 1h, 2h, 4h, 6h after birth). After three-day follow, 236 infants were confirmed to be healthy, 74 were admitted to 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 1990g to 4520g. Most patients and healthy infants were scanned at the timing of 2 hours after birth. Patients were more likely to have a higher respiratory rate(65(87.8%) vs 57(24.2%), $p<0.01$) and higher incidence of lower TcSO2(bellow 95% for more than 3 mins, 23(31.1%) vs 18(7.6%), $p<0.01$).

High-risk patterns and Low-risk patterns

There are six LUS image patterns can be found in these late preterm and term infants right after their birth(Fig 2). These patterns can be categorized as "High-risk" and "Low-risk" ones. The low-risk patterns, which means less likelihood of lung issues, include "pure A-line" pattern, "Scarce discrete B-line" pattern, "Moderate discrete B-line" pattern, and "Abundant discrete B-line". In fact, the three kinds of "discrete B-line" can be easily discerned when performing LUS and there is no need to identify each of them, as they are significantly different from "pure A-line" and high-risk patterns, and they are less likely to be a sign of lung issues. High-risk patterns inlude "Coalesced B-line" and "Consolidation".

The reliability 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). By contrast, as for RR(respiratory rate) which we used conventionally to predict respiratory support need, its ROC only yield an AUC of 0.70(95%CI, 0.64-0.76, p<0.001). The ROC of LUS(high-patterns) and RR have a significant difference(p<0.01)(Fig 3). Table 2 shows reliability data for LUS and RR to predict any need for respiratory support. The ROC analysis for the subgroups also was conducted, and the result of hood oxygen support was shown(Tab 2), but due to an insufficient number of patients who only obtained CPAP, MV, and PS treatment(23/74, 18/74, 29/74, individually), the ROC for they may not reliable and results were not shown.

Discussion

We modified the LUS scanning method and developed a simplified assessing system(based on "high-risk" image patterns) to predict respiratory support need for the first time. As far as we know, this system is practical and useful in obstetrics and gynaecology hospital that need to identify infants with potential lung diseases in several hours right after birth. It can help physicians to pick up these potential patients before their respiratory symptoms deteriorated and chest X-ray applied so that physicians can implement NICU cares earlier.

Findings and interpretation: This study has two clinically relevant findings. (1) There are four "low-risk" patterns and two "high-risk" patterns can be found in late-preterm or term infants right after birth. Even if two of "low-risk" patterns, "moderate discrete B-line" pattern and "abundant discrete B-line", was reported to be pathological in previous studies[27-28], our study shows they can be seen as strong evidence of healthy infants right after birth. This ddiscrepancy may be because these two patterns are only the result of the delay of lung fluid clearance. This delay make a small amount of alveoli uninflated and full of fluid[29-31]but not enough to cause TTN. (2) Two "high-risk" patterns have high predictive reliability for respiratory support need. These two patterns are also regarded as evidence of other diseases, such RDS[15], MAS[8] and pneumonia[32]. This concordence indicated that our findings of "high-risk" patterns are high likely to be a early stage of RDS or MAS, especially when infants just have mild respiratory symptoms.

Because of the total ten scanning regions, the number of regions with "high-risk" reversely relate to those with "low-risk" patterns. Thus ROC of "low-risk" patterns can support the predictive reliability of "high-risk" patterns.

Strengths and Limitations of our study

To our knowledge, this is the straightforwardst semiquantitative method to predict lung diseases in late preterm and term infants. The assessment only needs to count on the number of scanning regions on the chest wall with "high-risk" patterns, and these patterns are easy to discern. What's more important is its reliability, that finding more than two regions with "high-risk" patterns provides an 87.10% sensitivity and 88.02% specificity. LUS is radiationless and easy to perform, coupled with predictive reliability found in our study so that it can be used as an effective lung diseases screening tool between the delivery room and NICU. Nevertheless, there are some limitations to our study. Most significant is insufficient patients who were served with CPAP(23/74), MV(18/74), PS(29/74). This insufficiency made it difficult to draw a convincing conclusion to predict this advanced respiratory support. But this limitation can be improved in later research containing more patients with severe respiratory diseases. The second limitation is the possible inconsistency of images interpretation. Our research only has one LUS interpreter due to limited budget; this made it impossible for a consistency test between interpreters. This may lead to a variance in predictive reliability. This drawback may be corrected in later research by us or others. The last limitation we realized is its generalisability. Our participants are all late preterm and term infants, which means they have a lower incidence of lung diseases than the smaller preterms. However, because LUS is radiationless, easy to perform, and economical, we think it's reasonable to perform LUS on every late preterm and term infants with respiratory symptoms. Besides, as the smaller preterms infants will receive more attention from physicians since their birth, their respiratory issues are less likely to be ignored than the late preterms and the terms.

Comparison with other studies

A lot of research has varified the diagnostic value of LUS on neonatal lung diseases[2, 28, 33-34]. The difference between theirs and ours is we focused on predictive value. As we found these abnormal LUS sign at early stage right after birth do not have significant specificity for certain diseases, we only use LUS to predict respiratory need that concerns all kinds of severe lung diseases. Recently, some study also paied attention to predictive value of LUS in neonatology[14-16, 35]. They evaluated mostly predictive value of PS need in preterm infants whereas we study need of all kinds of respiratory support, including CPAP and MV that closely relate to severe lung disease. So we believe our study is a good complement to current studies and very useful since it can provide evidence to offer early interventions to those high risk infants.

Conlusion

Our assessment method allows a semiquantitative use of LUS findings and seems promising for further applications in neonatal critical care. The LUS high-risk patterns shows good reliability to predict resipratory support need in late-preterm and term infants who manifested 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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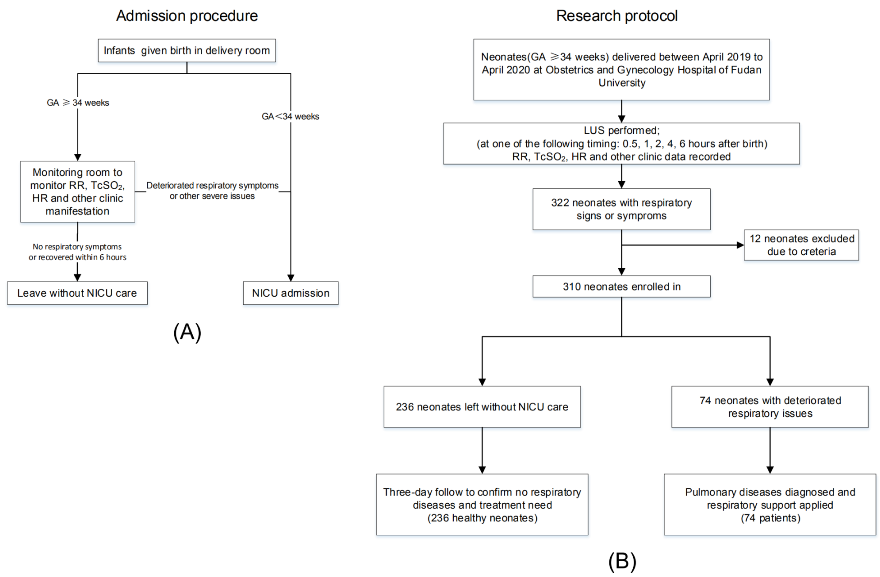
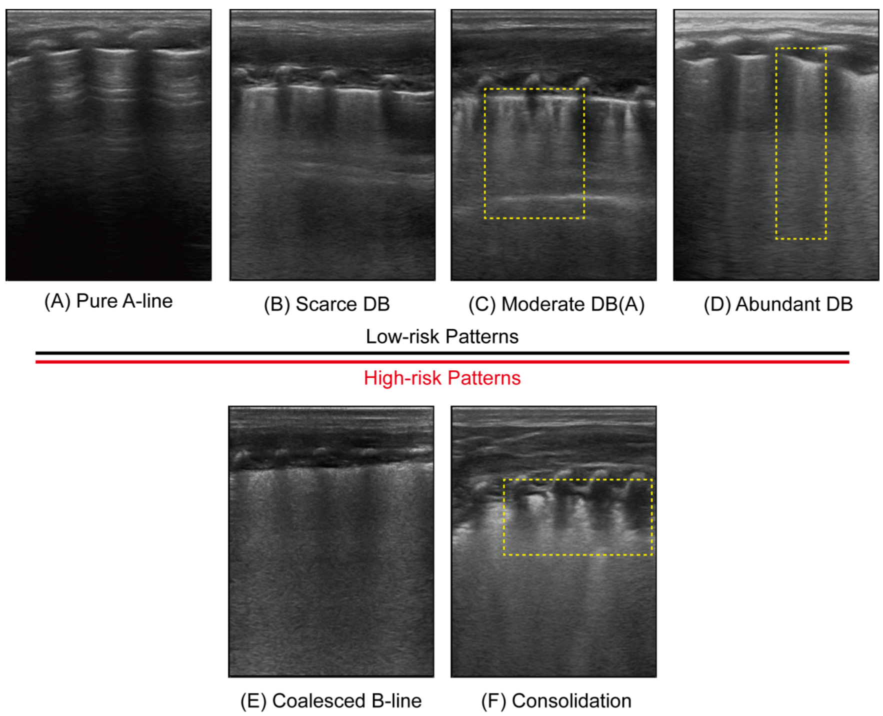
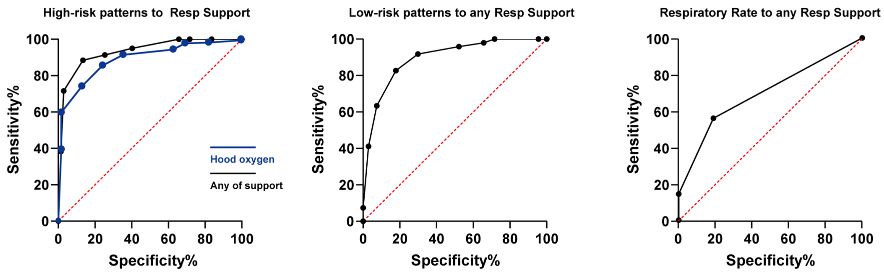
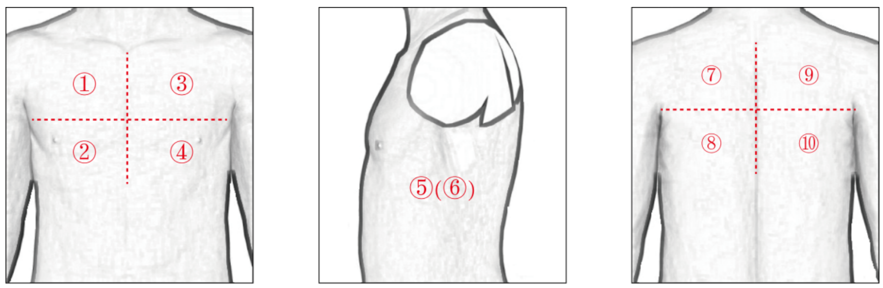

Admission procedure
Infants given birth in delivery room
GA ⩾ 34 weeks
GA＜34 weeks
Monitoring room to monitor RR, TcSO2, HR and other clinic manifestation
Deteriorated respiratory symptoms or other severe issues
No respiratory symptoms or recovered within 6 hours
Leave without NICU care
NICU admission
(A)
Research protocol
Neonates(GA ⩾34 weeks) delivered between April 2019 to April 2020 at Obstetrics and Gynecology Hospital of Fudan University
LUS performed; (at one of the following timing: 0.5, 1, 2, 4, 6 hours after birth) RR, TcSO2, HR and other clinic data recorded
322 neonates with respiratory signs or sympi roms
12 neonates excluded due to creteria
310 neonates enrolled in
236 neonates left without NICU care
74 neonates with deteriorated respiratory issues
Three-day follow to confirm no respiratory diseases and treatment need (236 healthy neonates)
Pulmonary diseases diagnosed and respiratory support applied (74 patients)
(B)


(A) Pure A-line
(B) Scarce DB
(C) Moderate DB(A)
(D) Abundant DB
Low-risk Patterns
High-risk Patterns
(E) Coalesced B-line
(F) Consolidation



(A) (B) (C)



(A) Anterior (A) Lateral (L and R) (A) Posterior

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tables.doc available at https://authorea.com/users/328608/articles/561941-ultrasound-performed-right-after-birth-can-predict-the-respiratory-support-need-of-neonates-a-diagnostic-accuracy-study