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TITLE PAGE

Title:ROLE OF LUNG ULTRASOUND IN DIAGNOSIS OF RESPIRATORY DISTRESS SYNDROME IN PRE-TERM BABIES (≤ 32 WEEKS)

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ABSTRACT

The aim of the study was to evaluate the ability of lung ultrasound against chest X-ray in the diagnosis of RDS in pre-term infants born before 32 weeks and to follow up on the response to treatment. The study was conducted on sixty neonates with gestational age (GA) ≤32 weeks (mean GA 30.3±1.64 weeks) and birth weight appropriate for gestational age (mean birth weight 1,350±310 g) who were admitted to neonatal ICU within six hours after birth with respiratory distress. The LUS and chest X-ray findings were compared with the reference standard (i.e., clinical diagnosis) and the patients followed till clinical recovery, normal LUS scans or eventual fatal outcome, whichever was earlier. LUS diagnosed RDS with a sensitivity of 88.1% and specificity of 83.33%, while chest X-ray showed a sensitivity of 90.48% and specificity of 72.22%. Furthermore, an LUS score of 10 predicted RDS well in our study. The disease was mostly limited to the first few days following birth, with normal LUS scan, clinical recovery, or death mostly occurring

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within the first few days of life with a mean of 5.48±4.2 days. We concluded that lung ultrasound is comparable to a chest X-ray in diagnosing neonatal RDS with a high degree of accuracy while detecting other complications as well. With proper training and expertise, it is likely to replace chest X-ray as the primary modality of choice in diagnosing respiratory diseases, especially in neonates.

Keywords: neonate; lung; respiratory distress syndrome; x-ray; ultrasonography

MAIN TEXT

Background

Respiratory distress syndrome (RDS) is a problem primarily affecting preterm neonates. It is related to structurally immature and surfactant-deficient lungs progressing through hypoventilation, hypoxemia, and respiratory acidosis.[1][2][3] It is a common reason for admission to the neonatal intensive care unit (NICU).[4][5]

In a study, the incidence rate was 80% in infants <28 weeks gestation, 60% at 29 weeks, 15–30% at 32–34 weeks, and 5% at 35–36 weeks. Accordingly, the rate is estimated to be 80% for infants weighing less than 750g at birth and 55% for infants weighing 750-1000g.[6] The total incidence is estimated at 6 per 1000 births.[2] In another study, 98% of babies born at 24 weeks had RDS, while at 34 weeks, the incidence was 5%, and at 37 weeks, it was less than 1%.[7]

Insufficient levels of surfactant compromise alveolar integrity, impeding normal gas exchange due to the deregulation of acinar surface tension.[1][2] The resulting atelectasis causes decreases lung compliance through an increase in collapsed alveoli in the terminal airways.[3]

Respiratory distress usually develop immediately or within six hours of life, worsening over the first 48–72 hours, followed by recovery, or may worsen over time progressing to respiratory failure, lethargy, apnoea, decreased urinary output, and death.

The diagnosis is made based on clinical features, blood gas analysis and radiological features. Antenatal glucocorticoids, continuous positive airway pressure (CPAP) and positive end-expiratory pressure (PEEP), and surfactant replacement therapy (SRT) have dramatically decreased morbidity and mortality from RDS.

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A plain chest radiograph is often the first investigation, with studies showing remarkable diagnostic value.[8] Chest X-ray (CXR) severity is assessed and graded as:

Stage I Fine homogenous ground glass shadowing

Stage II Bilateral widespread air bronchogram

Stage III Confluent alveolar shadowing

Stage IV Alveolar shadowing obscuring the cardiac border[4]

Lately, ultrasound has been used in the evaluation of many respiratory problems, with many studies addressing RDS.[9][10] It is being explored as an alternative modality to chest X-ray in the screening, diagnosis, and follow-up of infants with RDS, and a few studies have shown promising results.[11][9][12][13]

The technique is based on the principle that ultrasound is reflected by an interface between media with different acoustic impedance.[14] The pleural line is a smooth and regular hyperechoic line that moves to and fro during respiration (lung sliding).[15] The A-lines are parallel lines at regular intervals below the pleural line representing the large change in acoustic impedance at the pleura-lung interface.[16] B-lines are hyperechoic, laser-like images originating from the pleural line and reaching the edge of the screen.[16] These are correlated with lung interstitial fluid content. Multiple B-lines indicate alveolar-interstitial syndrome.[17][18] When the air content further decreases, lung parenchyma is directly visualized by opening an acoustic window on the lung, i.e., lung consolidation, which is a region of hypoechoic, poorly defined, or wedge-shaped borders. [19]

The ultrasound features of RDS include compact B-lines with a white lung appearance, disappearance of A-lines, presence of a thickened and irregular pleural line, and multiple sub-pleural consolidations.

Lung ultrasound (LUS) is emerging as a semi-quantitative assessment tool for the evaluation of lung diseases. Many scoring systems have been established, with the first of its kind introduced by Brat et al.[20] Presently, most researchers and clinicians refer to this scoring system. Studies have also shown LUS to be useful in predicting the need for SRT in preterm neonates.[21] Hence, LUS is being evaluated as a dynamic modality with applications in the diagnosis, follow-up, and management of diseases with the potential to replace chest radiographs in the future.

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Aims and objectives

The aim was to evaluate the ability of LUS against CXR in the diagnosis of RDS in pre-term infants (≤32 weeks) and to follow up on the response to treatment.

Methods

The study was a prospective longitudinal study carried out over a period of two years from 2020-22 in the Department of Radiodiagnosis and Imaging and the Department of Paediatrics and Neonatology, Sher-i-Kashmir Institute of Medical Sciences, a tertiary care hospital in North-India.

The study was conducted on 60 neonates with gestational age (GA) ≤32 weeks admitted to NICU immediately or within six hours after birth with respiratory distress. Data was obtained about signs and symptoms like tachypnea, nasal flaring, grunting respirations, intercostal/subcostal retractions, and cyanosis. APGAR score was calculated, and the need for oxygen supplementation determined by the treating department at birth. Information was obtained about GA, birth order, time since delivery, and weight of the baby at birth.

Inclusion/exclusion criteria

Neonates with GA ≤32 weeks and birth weight appropriate for GA admitted with respiratory distress within 6 hours after birth were included in the study. Those with congenital malformations/chromosomal anomalies, GA >32 weeks, and 'small for GA' babies (as per the standard Fenton growth chart), were excluded.

Clinical assessment

All neonates were assessed by a certified pediatrician at birth. Signs of respiratory distress were recognized and graded using 'Downe's score'. The final diagnosis of RDS was made by the pediatrician on duty and was primarily based on 'clinical features' (including the need for O_2 supplementation), which was taken as standard for our study.

Radiological assessment

A plain CXR was obtained in all subjects by the treating department as a part of the diagnostic protocol which was read and graded by a certified radiologist to avoid bias. Additional laboratory tests were done wherever necessary.

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In all subjects, LUS was performed at the bedside within the first 24 hours of admission to NICU and before surfactant was given. Examinations were performed using Sonosite (FUJIFILM Sonosite, Inc. Bothell, WA 98021, USA) equipped with a linear high-frequency probe (6-13 MHz). Transthoracic scans were performed in all cases. Transabdominal scans were performed wherever necessary to scan lung bases and look for any pleural effusion. Examinations were carried out in supine and both lateral decubitus positions. In all cases, the LUS scoring system by Brat et al. was employed. [20]

The presence of A-lines or <3 B-lines, pleural line abnormalities (including indistinct, absent, interrupted, or thicker pleural lines of more than 5mm), the density of B-lines (including ≥3 well-spaced lines and confluent B-lines (white-out pattern)), pleural effusion, double lung point (referring to the differences in lung echogenicity between upper and lower lung areas, with lower zones showing more compact B-lines than upper zones), and consolidations, were recorded **(Fig. 1-5)**. The LUS and CXR findings were correlated, and the results were compared with the reference standard.

The patients were followed till clinical recovery (i.e., maintaining saturation at room air) or normal ultrasound scans were obtained, or until the eventual fatal outcome, whichever was earlier.

Statistical analysis

The categorical variables were presented in the form of numbers and percentages (%). The quantitative data were presented as the means±SD and median with 25th and 75th percentiles (interquartile range). Sensitivity, specificity, and positive and negative predictive values were calculated from CXR and LUS findings for predicting RDS. Univariate and multivariate logistic regression were used to determine significant risk factors for RDS.

The data entry was done in the Microsoft Excel spreadsheet, and the final analysis was done using Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA, version 25.0.

For statistical significance, a p-value of less than 0.05 was considered statistically significant.

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Results

Patient characteristics

We studied 60 preterm neonates with a GA of ≤32 weeks, of which 37 were males and 23 were females. The mean GA was 30.3±1.64 weeks, with a median of 30.6 weeks (IQR 29.6-31.6 weeks). The birth weight, mode of delivery, birth order, antenatal steroid doses were also recorded **(Table 1).**

Clinical assessment at birth and hospital course

The mean Downe's score recoded was 5.48±1.27 (range 3-8) with a median score of 6(IQR 5-6). Subsequently, 34 (65.67%) subjects were put on CPAP, 18 (30.00%) needed mechanical ventilation, and 8 (13.33%) with mild distress were put on O_2 hood. The final diagnosis of RDS was made in 42 patients (70%) by the certified treating neonatologist. Other diagnoses included transient tachypnea of newborn (16%), apneic episode (1.66%), perinatal asphyxia (1.66%), early onset sepsis (5%), meconium aspiration syndrome (3.33%), and congenital pneumonia (1.66%). The need for surfactant was assessed by the treating department. 9 RDS patients received 2 doses of the same, 24 RDS patients received a single dose, and 27 subjects, of which 9 were RDS patients, didn't receive any dose.

Radiological assessment

On CXR, 43 patients (71.67%) had findings of RDS. Twelve patients (20%) had X-ray severity grade of 4, 18 patients (30%) showed grade 3 severity, 10 patients (16.67%) showed grade 2 severity, and 3 patients (5%) showed grade 1 severity. Seventeen patients (28.33%) had normal/non-RDS X-ray findings.

The LUS examination revealed the findings of RDS in 40(66.67%) subjects while 20 subjects had either normal LUS scans or findings that didn't qualify for RDS. **(Table 2)**

The mean LUS score recorded was 8.27±3.56 with a median of 8.5(IQR 5.75-11).

Follow-up/outcome

All the subjects were followed until normal scans, clinical improvement, or death (whichever was earlier). Eventually, 13.33%(8/60) of patients had a fatal outcome before any significant improvement in clinical or LUS parameters. It was observed that the disease was mostly limited to the first few days of life, i.e., the normal scan or clinical

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recovery or death occurred within a few days of birth with a median time interval of 4 days (IQR 3-7) and a mean of 5.48±4.2 days.

Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV)

Sensitivity, specificity, PPV, and NPV for CXR and LUS findings for diagnosing RDS were calculated within a 95% confidence interval. **(Table 3)**

Association of LUS score with X-ray findings and final diagnosis

A median LUS score of 10(IQR 8-12) was found to correlate well with X-ray diagnosis of RDS (n=43) with a significant p-value (<0.001) using the Mann Whitney test, while a median score of 5(IQR 3-6) was mostly associated with 'negative' X-ray findings for RDS(n=17).

Furthermore, on the Mann Whitney test, a median LUS score of 10(IQR 8-12) correlated well in subjects in whom a final diagnosis of RDS was made (n=42) with a p-value <0.001. In non-RDS patients(n=18), a median score of 4(IQR 3-5.75) was statistically significant.

Agreement between LUS diagnosis and X-ray findings/final diagnosis

A statistically significant association (p-value=0.001) was found between LUS diagnosis(n=40) and X-ray diagnosis(n=43) of RDS, with moderate inter-rater kappa values (0.416) for agreement between the two.

Similarly, LUS diagnosis (n=40) correlated well with the final diagnosis(n=42) with a p-value <0.001 and substantial inter-rater kappa agreement value (0.692) between the two.

Univariate and multivariate logistic regression

Using univariate logistic regression, GA, male gender, and second birth order were found to be independent risk factors for RDS (p-values<0.05), with significant p-values of association with LUS score, X-ray severity grade of 2/3/4, and white lung appearance on LUS. On multivariate analysis, LUS score and gender showed significant associations with the disease.

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Discussion

Our study included 60 neonates with a GA≤32 weeks, of which 37 were males and 23 were females. Gupta et al. evaluated the role of LUS in 77 neonates with respiratory distress.[22] AL-Kayat et al. evaluated the role of trans-abdominal LUS in detecting pulmonary manifestations of RDS in 65 neonates, of which 42 were males and 23 were females.[23]

The mean GA and mean birth weight of our study group were 30.3±1.64 weeks and 1,350±310g, respectively. Gupta et al. recorded a mean GA of 32.9±2.5 weeks and a mean birth weight of 1,813±625.9g.[22]

In our study, 76.67% (46/60) neonates were born by LSCS and 23.33% (14/60) by NVDs. Al-Kayat et al. recorded 66.1% (43/65) neonates born by LSCS and 33.8% (22/65) neonates born by NVD.[23]

The mean Downe's score in our study was 5.48±1.27 with a median of 6 (IQR 5-6). Manusha et al. recorded Downe's scores ranging from 4 to 8, with 15(25%) neonates scoring 4, 10(16.66%) scoring 5, 15(25%) scoring 6, 16(26.66%) scoring 7 and 4(6.66%) neonates scoring 8.[24]

In our study, 56.67% of neonates were given CPAP, 30.00% were put on mechanical ventilation, and 13.33% with mild distress maintained saturation using an O_2 hood. In the study by Manusha et al, 66.66% of neonates were put on a ventilator, and 33.33% received CPAP.[24]

RDS was the final diagnosis in 70% (42/60) of our study subjects. In the study by Gupta et al., 63.6% (49/77) of infants were diagnosed with RDS.[22]

Among our RDS patients, 78.5% (33/42) received surfactant replacement therapy, while Gupta et al. recorded the same in 20.4% (10/49) of RDS patients.[22] This difference was likely due to the lower mean GA of our study subjects (30.3±1.64 weeks vs. 32.9±2.5 weeks).

We found that CXR diagnosed RDS in 43 of the 60 subjects, with grade III RDS as the most common finding, followed by grade IV, grade II, and grade I RDS. Manusha et al. [24] and Liu et al. [5] reported grade IV RDS as the most common finding in their respective studies.

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In our study, LUS could diagnose RDS in 40 of the 60 subjects with mean LUS score of 8.27±3.56 and a median of 8.5(IQR 5.75-11). The most common finding was interstitial edema (≥3 B-lines), followed by absence of A-lines, white lung appearance, consolidations, pleural line abnormalities, and pleural effusion **(Table 2)**. Gupta et al. reported pleural line abnormalities as one of the most common LUS findings.[22] Zarei and Alizadeh also reported pleural line abnormalities as the most common observation, followed by ≥3 B-lines, echographic white lung, and consolidation.[25]

The sensitivity, specificity, PPV, and NPV of LUS in our study**(Table 3)** were comparable with those found by Gupta et al.[22] Pasic et al observed that LUS and chest X-ray have somewhat similar results.[26] Liang et al. found the specificity and diagnostic accuracy to be higher for LUS, whereas the sensitivity was higher for X-ray.[27] El-Malah et al. found an LUS sensitivity of 98% and a specificity of 92% in their study.[4] Liu et al. showed that the simultaneous demonstration of lung consolidation, pleural line abnormalities, and bilateral white lung, or lung consolidation, pleural line abnormalities, and A-line disappearance, co-existed with a sensitivity and specificity of 100% for diagnosing RDS.[5] Similar results were drawn by Copetti et al. in their study. [28]

Abdelsadek et al. found that ultrasound overestimated the diagnosis of RDS.[29] In our study, however, CXR seemed to overestimate the diagnosis.

We also observed that a median LUS score of 10 was significantly associated with both the CXR and clinical diagnosis of RDS. It was observed that RDS was mostly limited to the first few days of postnatal life, with a mean time interval of 5.48±4.2 days. Furthermore, using regression analysis, GA, male gender, and second birth order were found to be independent risk factors for RDS.

Conclusions

LUS is a non-invasive technique that is easily available, reliable, repeatable, and free of ionizing radiation. It is comparable to a CXR in diagnosing neonatal RDS with a high degree of accuracy while also detecting other complications. With proper training and expertise, it is highly likely to replace CXR as the primary modality of choice in diagnosing respiratory diseases, especially in neonates.

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Tables

Table 1: Patient characteristics

Gender		
Females	23	38.33%
Males	37	61.67%
Birth order		
1	35	58.33%
2	20	33.33%
3	4	6.67%
4	1	1.67%
Mode of delivery		
NVD	14	23.33%
LSCS	46	76.67%
Antenatal steroids (number of doses)		
0	10	16.67%
1	37	61.67%
2	13	21.67%
Gestational age of study subjects at birth (in weeks)		
Mean ± SD	30.3 ± 1.64	
Median (25th-75th percentile)	30.6 (29.6-31.6)	
Range	25.3-32.0	
Birth weight of study subjects (in grams)		
Mean ± SD	1,350 ± 310	
Median (25th-75th percentile)	1,350 (1,175-1,600)	
Range	700-1,900	
LSCS: Lower segment caesarean section; NVD: Normal vaginal delivery; SD: Standard deviation		

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Table 2: LUS findings

	Frequency	Percentage
LUS findings in diagnosed RDS patients (n=42)		
Pleural line abnormalities	12	28.5%
A-lines or <3 B lines	6	14.2%
Interstitial edema (≥ 3B lines in examined areas)	42	100%
Unilateral/ bilateral white lung	23	38.33%
Consolidations (with bronchograms)	13	31%
Double lung point	2	4.7%
Pleural effusion	3	7.1%
RDS on LUS		
Absent	20	33.33%
Present	40	66.67%
LUS: Lung ultrasound; RDS: Respiratory distress syndrome		

Table 3: Sensitivity, specificity, positive predictive value and negative predictive value

Variables	X-ray findings	LUS findings
Sensitivity (95% CI)	90.48% (77.38% to 97.34%)	88.1% (74.37% to 96.02%)
Specificity (95% CI)	72.22% (46.52% to 90.31%)	83.33% (58.58% to 96.42%)
AUC (95% CI)	0.81(0.69 to 0.90)	0.86(0.74 to 0.93)
Positive Predictive Value (95% CI)	88.37% (74.92% to 96.11%)	92.5% (79.61% to 98.43%)
Negative Predictive Value (95% CI)	76.47% (50.10% to 93.19%)	75% (50.90% to 91.34%)
Diagnostic accuracy	85.00%	86.67%
AUC: Area under curve; CI: Confidence interval; LUS: Lung ultrasound		

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Figures

Fig. 1 Normal lung ultrasound showing A-lines (yellow arrows)

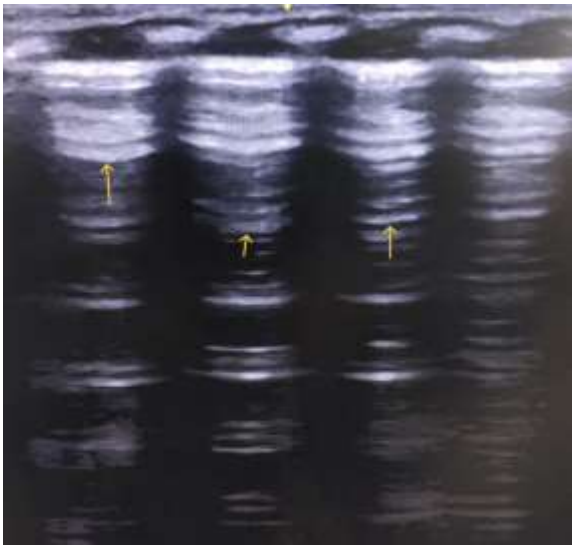

Fig. 2 Diffuse confluent B-lines (yellow arrows) – ‘white lung appearance’

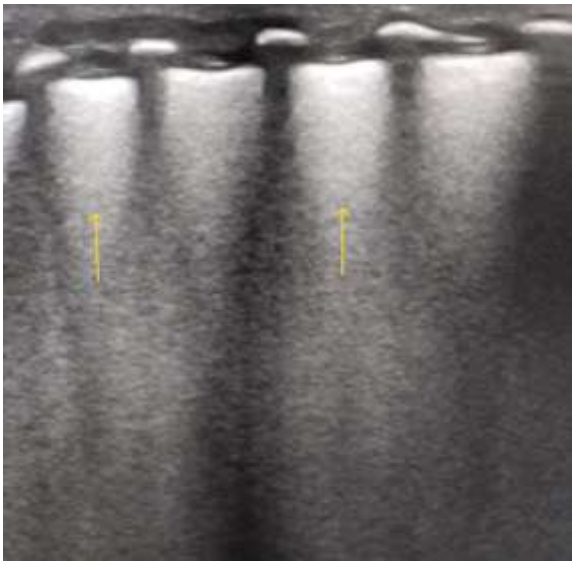

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Fig. 3 B-pattern with pleural thickening and sub-pleural consolidations (yellow arrows)

Fig. 4 Extensive consolidations involving sub-pleural locations (blue arrow) and deeper areas (yellow arrow)

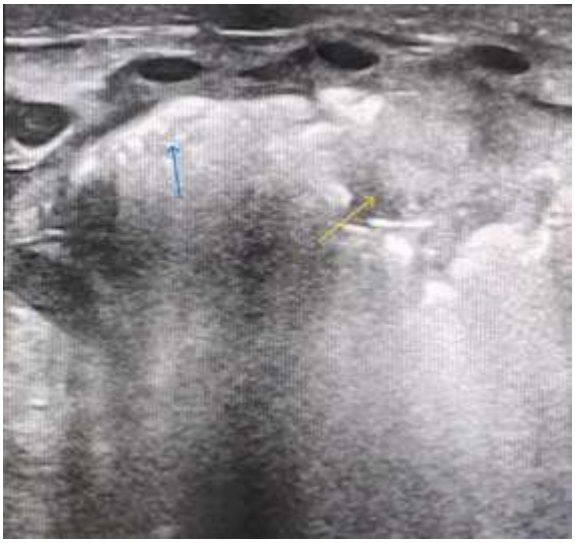

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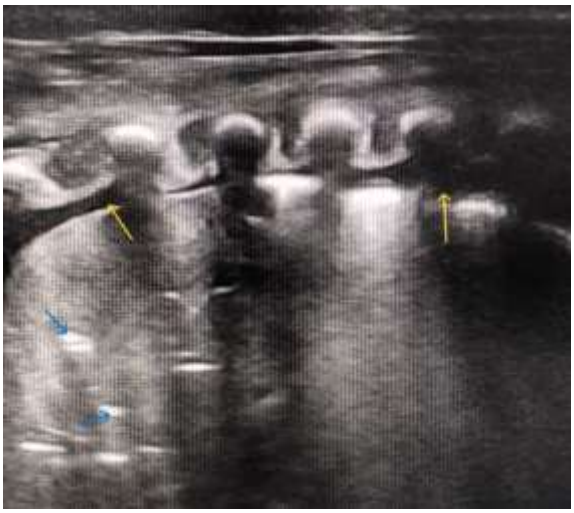
Fig. 5 Consolidated lung (hepatization) with bronchograms (blue arrows) and pleural effusion (yellow arrows)



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