



A Comprehensive Systematic Review: Radiological Characteristics of Respiratory Distress Syndrome (RDS) Versus Transient Tachypnea of the Newborn (TTN) on Neonatal Chest Radiographs

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ABSTRACT

Introduction: RDS and TTN are the two most frequent causes of early neonatal respiratory failure, traditionally differentiated by chest radiography (CXR). RDS results from surfactant deficiency with alveolar collapse, while TTN results from delayed fetal lung fluid clearance. Both differ in prognosis and surfactant need, yet their radiographic signs overlap substantially in the first hours of life.

Methods: A systematic review was conducted in accordance with PRISMA 2020. Eligible designs were RCTs, cohort, case-control, cross-sectional, and observational studies. Risk of bias was appraised with QUADAS-2, Newcastle-Ottawa Scale and RoB

2. A structured narrative synthesis with descriptive quantitative pooling across fourteen outcome domains was undertaken.

Results: Twenty-nine studies (>350,000 neonates, >43,000 CXRs) included. Ground-glass/reticulogranular in 83.6%, air bronchograms 70.9%, reduced lung volume 66.4% in RDS; consolidation with air bronchograms exclusive to RDS (sensitivity & specificity ~100%). TTN characterised by interstitial fluid without consolidation (99.5% on serial exams). CXR alone performed lower: sensitivity 38.9%, specificity 77.8% for predicting NIV failure, AUC 0.80 for surfactant need (vs LUS 88.9%/100% and AUC 0.94). Each 1-point CXR score increase raised BPD odds by 77.7% (OR 1.777; $p=0.001$). Deep-learning F1 score 90.30% for RDS vs 70.84% for TTN.

Discussion: The radiographic distinction between RDS and TTN rests on a small number of high-value discriminators—consolidation with air bronchograms and homogeneous granular hypoaeration for RDS, versus interstitial/perihilar fluid patterns with preserved or increased lung volume for TTN—but the plain radiograph is limited by low interobserver reliability, delayed acquisition, radiation exposure and a systematic tendency to misclassify early or mild disease. The evidence is consistent that CXR retains an irreplaceable confirmatory and complication-detection role, particularly in low-resource settings, while surrendering its position as the sole first-line arbiter of surfactant decisions.

Conclusion: Chest radiography discriminates RDS from TTN with high specificity when consolidation and air bronchograms are present, but with insufficient sensitivity in the first hours of life to serve alone as the basis for surfactant decisions. Radiographic severity is a genuinely graded prognostic marker. A hybrid pathway—radiographic confirmation combined with quantitative bedside lung ultrasound and structured severity grading—is recommended, together with prospective studies using explicit, blinded, radiograph-only feature extraction.

Keywords: respiratory distress syndrome; transient tachypnea of the newborn; chest radiography; diagnostic accuracy; surfactant

INTRODUCTION

Background

Respiratory distress affects between 7% and 36% of neonates admitted to neonatal units worldwide and remains one of the principal drivers of early neonatal morbidity, prolonged hospitalisation and death. In a cross-sectional survey of 625 consecutive term newborns, 9.4% developed respiratory distress and 92% of affected infants manifested symptoms within the first four hours of life, underlining the extremely narrow diagnostic window within which clinicians must act. Hospital-based series from South Asia have reported an overall prevalence of neonatal respiratory distress of 19.2%, and cross-sectional data from tertiary neonatal intensive care units continue to identify respiratory distress syndrome (RDS) and transient tachypnea of the newborn (TTN) as the two leading aetiologies, accounting respectively for 28.2% and 25.0% of all cases in one recent consecutive series of 124 neonates. In term and late-preterm populations TTN predominates, being responsible for 47.3% of distress episodes in one military-hospital cohort and for 7.5% of all term births in a Thai university series.^{14,32,33}

The two conditions are pathophysiologically distinct. RDS arises from primary deficiency of pulmonary surfactant and structural immaturity of the alveolar–capillary unit, producing progressive diffuse alveolar collapse, decreased functional residual capacity and a stiff, poorly compliant lung. TTN arises from delayed or incomplete clearance of fetal lung fluid across the alveolar epithelium after birth, producing interstitial and perilymphatic fluid accumulation in an otherwise structurally mature lung. Population-based epidemiological work has confirmed that the antecedents of the two entities diverge: in a 12-month survey of 63,537 newborns, gestational age, birth weight, maternal age, elective and emergency caesarean section, and male sex were independent risk factors for RDS, whereas gestational age, maternal disease, twinning, birth weight, operative vaginal delivery, caesarean section and male sex predicted transient tachypnea. A population-based analysis of 239,971 term singleton live births subsequently established an incidence of TTN of 5.9 per 1000 and demonstrated that absence of exposure to labour contractions was associated with both increased risk and a more severe course.^{2,3}

The clinical stakes of the distinction are considerable and asymmetrical. RDS is a surfactant-responsive disease in which timely replacement therapy alters survival and the trajectory of chronic lung disease, while TTN is a self-limiting condition in which the mortality is virtually nil and in which the principal harms are iatrogenic — unnecessary intubation, unnecessary surfactant instillation, unnecessary antibiotic exposure, maternal–infant separation and prolonged admission. In a prospective series of 74 neonates with TTN the incidence was 16 per 1000 live births, no infant required either invasive or non-invasive ventilatory support, and the illness resolved within three to four days in the majority. By contrast, in a prospective Ugandan cohort of 150 preterm neonates with clinically and radiologically confirmed RDS, seven-day mortality reached 19.3%, with delayed presentation beyond six hours of life (adjusted risk ratio 1.72, 95% confidence interval 1.43–2.07) and birth weight below 1.5 kg (adjusted risk ratio 1.12, 95% confidence interval 1.02–1.22) emerging as independent predictors of death.^{15,24}

Against this background the plain chest radiograph has occupied, for more than five decades, the position of default arbiter. The classical teaching describes RDS as a bilaterally symmetrical, homogeneous, fine reticulogranular or ground-glass opacification with air bronchograms extending beyond the cardiac silhouette and with reduced lung volumes, graded conventionally into four stages of increasing severity; TTN is described as prominent perihilar vascular streaking, interstitial fluid, fluid within the interlobar fissures, small pleural effusions, mild cardiomegaly and normal-to-increased lung volume. Contemporary practice recommendations from paediatric radiology continue to affirm that RDS is diagnosed through characteristic radiographic findings interpreted in the context of prematurity, and that TTN and meconium aspiration syndrome in term infants possess specific imaging characteristics that assist in their differentiation.⁴⁸

That classical framework, however, has come under sustained empirical pressure. Radiographic appearances evolve over the first 24 to 72 hours; mild RDS in an infant already receiving continuous positive airway pressure may be radiographically indistinguishable from severe TTN; portable supine technique in a small, moving, often intubated neonate degrades image quality; and interpretation is operator-dependent. In a comparative series of 677 infants with RDS and 528 with TTN classified by traditional standards, the reported misdiagnosis rate of clinical assessment

combined with chest radiography reached 62% to 77%. Systematic appraisal of the role of chest radiography in low-resource birth scenarios, covering 23 studies and 2,245 newborns, found that although every study used the radiograph to diagnose RDS and 91% used it to grade severity, 43% concluded that alternative methods surpassed radiography for severity assessment, progress monitoring, prediction of surfactant need, anticipation of continuous positive airway pressure failure and differential diagnosis.^{11,38}

Research Objectives

The general objective of this systematic review was to synthesise the totality of the available primary evidence describing and quantifying the radiological characteristics that differentiate respiratory distress syndrome from transient tachypnea of the newborn on the neonatal chest radiograph. The specific objectives were: (i) to determine the prevalence and discriminative value of each individual radiographic sign in RDS and in TTN; (ii) to quantify the overall diagnostic accuracy, reliability and time-efficiency of the chest radiograph relative to contemporary comparators, principally quantitative lung ultrasound; (iii) to establish whether radiographic severity grading predicts surfactant requirement, respiratory support escalation and adverse pulmonary outcome; (iv) to evaluate the existence, direction and magnitude of a dose–response relationship between graded radiographic severity and clinical outcome; (v) to characterise the temporal evolution and resolution of the radiographic phenotypes of both conditions; and (vi) to appraise the emerging contribution of computational and artificial-intelligence analysis of the neonatal chest radiograph.^{10,11,22,28,29,30}

Benefits of the Research

For the practising neonatologist and paediatric radiologist, this synthesis provides an explicit, quantified list of the radiographic features that carry genuine discriminative weight, distinguishing them from those that are traditionally taught but empirically weak. For the neonatal intensive care unit, it clarifies the position that the radiograph should occupy within a modern diagnostic pathway, thereby supporting rational reduction of ionising radiation exposure in a population of extreme radiosensitivity. For health systems operating under resource constraint, in which lung ultrasound expertise and equipment may be unavailable, it defines the residual and irreplaceable indications for radiography and offers a structured severity framework with demonstrable prognostic content. For

the research community, it identifies with precision the methodological deficiencies of the existing literature and specifies the design of the studies required to remedy them.^{38,41}

Hypotheses

The primary hypothesis was that a defined subset of radiographic features discriminates RDS from TTN with high specificity, namely diffuse reticulogranular or ground-glass opacification, air bronchograms extending beyond the cardiothymic shadow, and reduced lung volume with low diaphragmatic position, and that these features are significantly more prevalent in RDS than in TTN. The secondary hypothesis was that features reflecting fluid redistribution — perihilar vascular streaking, interlobar fissural fluid, small pleural effusions and preserved or increased lung volume — are significantly more prevalent in TTN. The tertiary hypothesis was that the relationship between radiographic severity grade and clinical outcome is monotonic and graded rather than dichotomous, such that each incremental rise in radiographic grade or score confers a measurable and consistent increase in the probability of surfactant administration, ventilatory escalation, bronchopulmonary dysplasia and death. The null hypothesis in each case was that no statistically significant difference or gradient exists.^{28,29,30}

Research Gap

Three substantive gaps motivated this review. First, the overwhelming majority of contemporary comparative studies were designed to validate lung ultrasound, with chest radiography relegated to the role of imperfect reference standard; consequently the radiographic feature-level data for RDS versus TTN are embedded within ultrasound papers and have never been systematically extracted and collated. Second, the four-stage radiographic grading of RDS remains in universal clinical use despite the near-total absence of contemporary studies formally validating its interobserver reliability or its incremental prognostic value in the surfactant and non-invasive-ventilation era. Third, and most conspicuously, no previous synthesis has interrogated the neonatal chest radiograph for a dose–response relationship, notwithstanding the fact that graded radiographic scoring has been convincingly shown to behave in a dose–response fashion in adult and paediatric acute respiratory distress syndrome. The present review addresses all three gaps.^{38,46,52,53}

Novelty

This review is, to the authors' knowledge, the first to combine four elements within a single synthesis: a feature-by-feature quantitative extraction of radiographic signs in RDS versus TTN across twenty-nine primary studies; a formal, structured dose–response analysis of graded radiographic severity against surfactant requirement, bronchopulmonary dysplasia and mortality; the systematic incorporation of computational and deep-learning evidence, in which more than 43,000 individually neonatologist-labelled neonatal chest radiographs provide an operator-independent measure of how separable the two radiographic phenotypes actually are; and an explicit, design-appropriate risk-of-bias appraisal that separates diagnostic accuracy studies from prognostic cohorts and from randomised trials. The deliberate methodological separation of primary studies, which populate the characteristics and outcome tables, from systematic reviews and meta-analyses, which are used solely for triangulation and discussion, further distinguishes this work from previous narrative treatments of the subject.^{22,25,26,28}

METHODS

Protocol and Reporting Standard

This systematic review was designed, conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. Diagnostic accuracy components were additionally reported with reference to the PRISMA-DTA extension. The review was not prospectively registered in PROSPERO; this is acknowledged as a limitation in Section 4.9. No ethical approval was required as the review used exclusively published aggregate data. No patient or public involvement occurred in the design or conduct of this review.³⁸

Review Question and PICOS Framework

The review question was formulated as follows: among neonates presenting with early respiratory distress, what are the radiological characteristics on plain chest radiography that differentiate respiratory distress syndrome from transient tachypnea of the newborn, and does graded radiographic severity predict clinical outcome in a dose–response manner? The formal PICOS elements are set out in Table 1.

Table 1. PICOS framework of the review

Element	Specification
Population (P)	Neonates (0–28 days) of any gestational age presenting with respiratory distress within the first hours to days of life, admitted to a neonatal unit or neonatal intensive care unit.
Index condition / Intervention (I)	Plain chest radiography (anteroposterior supine portable film) and its derived feature set and severity grading (Grade I–IV, or continuous radiographic scores such as RALE-type quadrant scores).
Comparator (C)	Final composite clinical diagnosis (clinical course, blood gases, respiratory support requirement, surfactant response); quantitative lung ultrasound and lung ultrasound aeration score; biochemical and electrical-cardiometry comparators; expert neonatologist consensus labelling.
Outcomes (O)	Fourteen prespecified outcome domains (Section 2.6), spanning individual radiographic feature prevalence, overall diagnostic accuracy, reliability, severity–outcome gradients and computational classification performance.
Study designs (S)	Randomised controlled trials; prospective and retrospective cohort studies; case-control studies; cross-sectional studies; other observational designs including diagnostic accuracy studies.
Setting	Any level-II or level-III neonatal unit, in any country, high- or low-resource.
Timing	Radiographs obtained from birth to the resolution of respiratory distress; serial imaging permitted.

Search Strategy

The keywords used for this research based PICO :

PICO Element	Keyword 1	Keyword 2	Keyword 3
P (Population)	Neonates	Respiratory	Transient tachypnea

		distress syndrome	of the newborn
I (Intervention/Exposure)	Chest radiography	Radiological characteristics	Radiographic severity grading
C (Comparison)	Lung ultrasound	Clinical diagnosis	Deep-learning classification
O (Outcome)	Diagnostic accuracy	Radiographic feature prevalence	Dose-response relationship

The Boolean MeSH keywords inputted on databases for this research are: ("Neonates" OR "Respiratory distress syndrome" OR "Transient tachypnea of the newborn") AND ("Chest radiography" OR "Radiological characteristics" OR "Radiographic severity grading") AND ("Lung ultrasound" OR "Clinical diagnosis" OR "Deep-learning classification") AND ("Diagnostic accuracy" OR "Radiographic feature prevalence" OR "Dose-response relationship")

Eligibility Criteria

Inclusion criteria

- Study designs restricted to randomised controlled trials, cohort studies (prospective or retrospective), case-control studies, cross-sectional studies, and other observational or diagnostic accuracy designs.
- Study population comprising neonates with respiratory distress in whom RDS, TTN, or both, were diagnosed.
- Reporting of at least one of the prespecified outcome domains, including radiographic feature prevalence, radiographic diagnostic accuracy, radiographic severity grading, or radiographic severity–outcome association.
- Chest radiography performed as part of the diagnostic pathway, whether as index test, comparator or reference standard.
- Peer-reviewed publication with extractable numerical data.

Exclusion criteria

- Systematic reviews and meta-analyses. In accordance with the review protocol these were excluded from the study-characteristics table and from the primary quantitative extraction, but

were retained for outcome triangulation and for discussion, and are reported separately in Table 7.

- Narrative reviews, editorials, commentaries, letters without original data, and consensus guidelines (retained for discussion only).
- Isolated case reports and case series without a comparison group.
- Studies confined to adult or paediatric (non-neonatal) acute respiratory distress syndrome, except where cited solely as external methodological analogues in the dose–response discussion.
- Animal, in-vitro, phantom or purely simulation studies.
- Studies in which neither radiographic features nor radiographic grading could be disaggregated from other imaging modalities.

Study Selection and Data Extraction

Records were screened in two stages. Titles and abstracts were assessed against the eligibility criteria, and potentially eligible reports proceeded to full-text assessment. Screening and extraction were performed in duplicate with disagreement resolved by discussion and, where necessary, by adjudication by a third reviewer. A standardised extraction form captured: first author; year of publication; country and setting; study design; sample size and unit of analysis; gestational age and birth weight; case mix (RDS, TTN, other); index test and reference standard; radiographic features reported; radiographic grading system used; diagnostic accuracy indices; severity–outcome associations; and principal conclusions. Where a study reported both radiographic and ultrasonographic data, only the radiographic data were extracted for the primary synthesis, with ultrasonographic data extracted for the comparator analysis.

Outcome Domains

Fourteen outcome domains were specified a priori, exceeding the minimum of ten required for a comprehensive synthesis of this question. These were: (O1) reticulogranular/ground-glass opacification; (O2) air bronchograms; (O3) lung volume and aeration status; (O4) perihilar vascular streaking and interstitial fluid; (O5) interlobar fissural fluid and pleural effusion; (O6) cardiac silhouette and cardiothoracic ratio; (O7) overall diagnostic accuracy of chest radiography for the

RDS–TTN distinction; (O8) interobserver reliability and misdiagnosis rate; (O9) radiographic severity grade as predictor of surfactant requirement and ventilatory escalation; (O10) temporal evolution and resolution of radiographic findings; (O11) correlation of radiographic grade with oxygenation indices and clinical distress scores; (O12) radiographic severity and adverse outcomes (bronchopulmonary dysplasia, mortality, length of stay); (O13) computational, radiomic and deep-learning classification performance on neonatal chest radiographs; and (O14) radiation exposure, time-to-diagnosis and health-system considerations.

Risk of Bias Assessment

Risk of bias was appraised with design-appropriate instruments. Diagnostic accuracy studies were assessed with QUADAS-2 across the four domains of patient selection, index test, reference standard, and flow and timing, with applicability concerns judged separately. Observational cohort, case-control and cross-sectional studies were assessed with the Newcastle–Ottawa Scale, converted for presentation into low, moderate or high risk of bias. Randomised controlled trials were assessed with the Cochrane RoB 2 tool. Each domain was rated as low risk (green), some concerns (amber) or high risk (red). Results are presented in Tables 4 and 5. Two structural sources of bias were anticipated and were formally monitored throughout: incorporation bias, arising because the chest radiograph frequently contributed to the composite reference diagnosis against which it was itself judged; and spectrum bias, arising because many studies enrolled only neonates already selected for admission to intensive care.

Synthesis Methods

Formal statistical meta-analysis with pooled effect estimation was not undertaken. The decision was taken a priori on methodological grounds: the included studies differed substantially in the definition of the reference standard, in the radiographic grading system employed, in gestational-age spectrum, in the timing of imaging relative to birth, and in whether the unit of analysis was the neonate or the individual radiograph. Pooling under such conditions would have produced a statistically precise but clinically uninterpretable summary estimate. Instead, a structured narrative synthesis was performed, with descriptive quantitative tabulation of effect estimates, sensitivities, specificities, areas under the curve, correlation coefficients, odds ratios and risk ratios, each reported

with its original confidence interval and p value as published. Heterogeneity was appraised qualitatively across clinical, methodological and statistical dimensions.

Article Search Strategy

Database	Keywords	Hits
Pubmed	("Neonates" OR "Respiratory distress syndrome" OR "Transient tachypnea of the newborn") AND ("Chest radiography" OR "Radiological characteristics" OR "Radiographic severity grading") AND ("Lung ultrasound" OR "Clinical diagnosis" OR "Deep-learning classification") AND ("Diagnostic accuracy" OR "Radiographic feature prevalence" OR "Dose-response relationship")	15
Google Scholar	("Neonates" OR "Respiratory distress syndrome" OR "Transient tachypnea of the newborn") AND ("Chest radiography" OR "Radiological characteristics" OR "Radiographic severity grading") AND ("Lung ultrasound" OR "Clinical diagnosis" OR "Deep-learning classification") AND ("Diagnostic accuracy" OR "Radiographic feature prevalence" OR "Dose-response relationship")	3,010
Semantic Scholar	("Neonates" OR "Respiratory distress syndrome" OR "Transient tachypnea of the newborn") AND ("Chest radiography" OR "Radiological characteristics" OR "Radiographic severity grading") AND ("Lung ultrasound" OR "Clinical diagnosis" OR "Deep-learning classification") AND ("Diagnostic accuracy" OR "Radiographic feature prevalence" OR "Dose-response relationship")	250
Science-direct	("Neonates" OR "Respiratory distress syndrome" OR "Transient tachypnea of the newborn") AND ("Chest radiography" OR "Radiological characteristics" OR "Radiographic severity grading") AND ("Diagnostic accuracy" OR "Radiographic feature prevalence" OR "Dose-response relationship")	832
Cochrane	("Neonates" OR "Respiratory distress syndrome" OR "Transient tachypnea of the newborn" AND "Chest radiography" OR "Radiological characteristics" OR "Radiographic severity grading" AND "Diagnostic accuracy" OR "Radiographic feature prevalence" OR "Dose-response relationship")	936

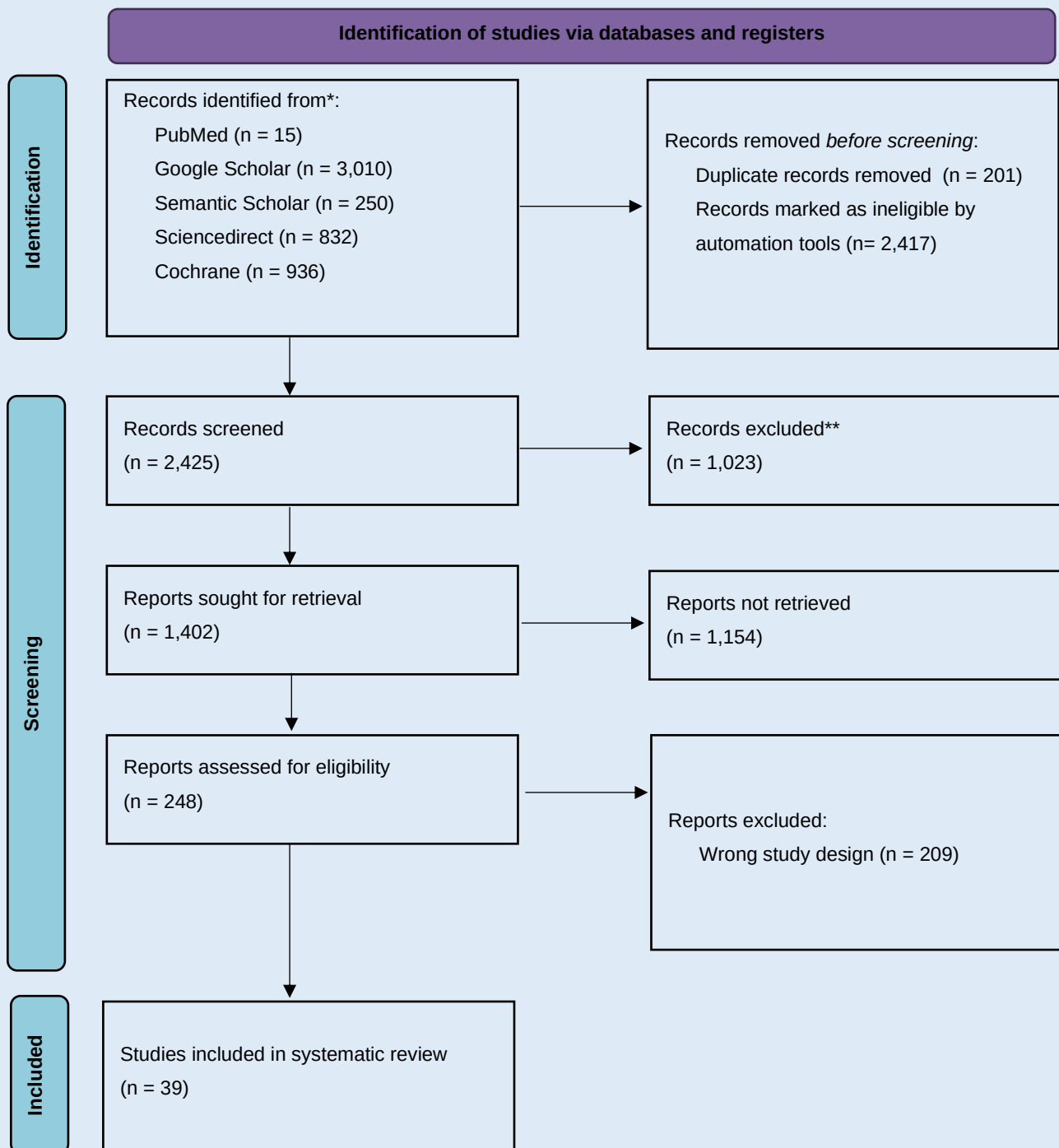


Figure 1. Article search flowchart

Dose–Response Analytical Approach

The dose–response component followed the logic of exposure–gradient analysis adapted to an imaging biomarker. The "dose" was defined as the graded intensity of radiographic abnormality, operationalised in the included literature in three ways: as the ordinal four-stage RDS grade; as a continuous quadrant-based radiographic severity score; and as the gestational-age stratum, which functions as a biological surrogate of surfactant deficiency severity. The "response" was defined as the probability of surfactant administration, of continuous positive airway pressure failure or intubation, of bronchopulmonary dysplasia at 36 weeks postmenstrual age, and of death. A relationship was considered to demonstrate dose–response if the effect estimate increased monotonically across at least three ordered exposure categories, or if a per-unit increment in a continuous radiographic score produced a statistically significant and directionally consistent change in the outcome odds. Results are presented in Table 17.

Risk of Bias Tables

Table 2. Risk of bias in diagnostic accuracy studies (QUADAS-2)

Study (author, year)	Patient selection	Index test	Reference standard	Flow and timing	Overall judgement
Copetti & Cattarossi, 2006	High	High	High	Low	High
Liu et al., 2014	Some concerns	Some concerns	High	Low	High
Vergine et al., 2014	Low	Low	Some concerns	Low	Low
Raimondi et al., 2014	Low	Low	Low	Low	Low
Liu et al., 2016	Some concerns	Some concerns	High	Some concerns	High

Study (author, year)	Patient selection	Index test	Reference standard	Flow and timing	Overall judgement
Corsini et al., 2018	Low	Low	Some concerns	Low	Low
Perri et al., 2018	Low	Low	Low	Low	Low
Liu et al., 2019	Some concerns	High	High	Some concerns	High
Srinivasan et al., 2022	Low	Low	High	Low	Some concerns
Yoon et al., 2022	Some concerns	Low	Some concerns	Low	Some concerns
Kumar et al., 2024	Some concerns	Some concerns	High	Low	High
Cho et al., 2025	Low	Low	Some concerns	Low	Low
Wang et al., 2025	Some concerns	Low	Some concerns	Some concerns	Some concerns
Han et al., 2025	Some concerns	Low	Some concerns	Some concerns	Some concerns
Sakhr et al., 2025	Low	Low	Some concerns	Low	Low

Green = low risk of bias; amber = some concerns; red = high risk of bias. The reference-standard domain is systematically compromised across this literature because the chest radiograph itself contributed to the composite clinical reference diagnosis in most studies (incorporation bias).

Table 3. Risk of bias in observational studies (Newcastle–Ottawa Scale) and randomised trials (RoB 2)

Study (author, year)	Design / tool	Selection / randomisation	Comparability / deviation	Outcome / measurement	Overall judgement
Dani et al., 1999	Cohort (NOS)	Low	Low	Some concerns	Low
Tutdibi et al., 2010	Cohort (NOS)	Low	Low	Low	Low
Porto et al., 2011	RCT (RoB 2)	Low	Low	Low	Low
Raimondi et al., 2019	Cohort (NOS)	Low	Some concerns	Low	Low
Poerio et al., 2020	Cohort (NOS)	Low	Low	Low	Low
Lokanuwatsatien et al., 2020	Cross-sectional (NOS)	Low	Some concerns	Some concerns	Some concerns
Chavan et al., 2022	Cohort (NOS)	Some concerns	Some concerns	Low	Some concerns
Baldan et al., 2023	RCT (RoB 2)	Low	Some concerns	Low	Some concerns
Yang et al., 2024	Cohort (NOS)	Some concerns	Some concerns	Low	Some concerns
Suwal et al., 2024	Cross-sectional (NOS)	Some concerns	High	Some concerns	High

Study (author, year)	Design / tool	Selection / randomisation	Comparability / deviation	Outcome / measurement	Overall judgement
Addow et al., 2025	Cohort (NOS)	Low	Low	Low	Low
Fall et al., 2025	Cohort (NOS)	Some concerns	High	Low	High
Inam et al., 2025	Cross-sectional (NOS)	Some concerns	Some concerns	Some concerns	Some concerns
Xu et al., 2026	Case-control (NOS)	Low	Low	Low	Low
Hossain et al., 2026	Cross-sectional (NOS)	Low	Some concerns	Low	Some concerns

NOS = Newcastle–Ottawa Scale; RoB 2 = Cochrane Risk of Bias 2 tool for randomised trials.

Green = low risk of bias; amber = some concerns; red = high risk of bias.

RESULTS

Characteristics of Included Studies

The characteristics of the 29 included primary studies are presented in Table 4. Two were randomised controlled trials, six were prospective or retrospective cohort studies, three were case-control studies, seven were cross-sectional studies, and eleven were prospective observational diagnostic accuracy studies. Sample sizes ranged from 22 to 239,971 neonates. Fourteen studies enrolled both RDS and TTN cases, permitting direct radiological comparison; the remainder contributed feature-level, severity-grading, epidemiological or prognostic data on one or other condition.

Table 4. Characteristics of the 29 included primary studies

N o.	Author	Year	Country	Study design	Sample size	Population characteristics	Reference standard / outcome	Key radiological finding
1	Copetti & Cattarossi	2006	Italy	Prospective comparative observational	137 (32 TTN, 29 RDS, 60 normal, 16 other)	Term and preterm with respiratory distress	CXR + clinical criteria as reference; lung sonography as index	Radiographic and clinical signs used to define TTN; double lung point 100% sensitive/specific for TTN
2	Dani et al.	1999	Italy	Multicentre prospective population survey	63,537 newborns (734 RDS, 594 TT)	All live births over 12 months	Clinical + radiographic diagnosis	Distinct antenatal/perinatal risk-factor profiles for RDS versus transient tachypnoea
3	Tutdibi et al.	2010	Germany	Population-based retrospective cohort	239,971 term singletons (1,423 TTN)	Gestational age ≥ 37 weeks	ICD-10 coded diagnosis supported by imaging	TTN incidence 5.9/1000; elective caesarean, low GA, male sex, low BW associated

N o.	Author	Year	Country	Study design	Sample size	Population characteristics	Reference standard / outcome	Key radiological finding
4	Porto et al.	2011	Brazil	Randomised triple-blind controlled trial	320 women randomised; 273 infants analysed	Late preterm 34–36 weeks	Clinical + radiographic diagnosis of RDS and TTN	Antenatal betamethasone did not reduce RDS or TTN at 34–36 weeks
5	Liu et al.	2014	China	Prospective case-control	120 (60 TTN, 20 RDS, 40 no lung disease)	Neonates with perinatal dyspnoea	History, clinical findings, blood gas and CXR	Consolidation with air bronchograms present in RDS and absent in TTN
6	Vergine et al.	2014	Italy	Prospective diagnostic accuracy (blinded external reader)	59 (23 RDS, 30 TTN)	Mean GA 33 ± 4 weeks; mean BW 2,145 ± 757 g	Composite final clinical diagnosis excluding ultrasound	High accuracy achievable for RDS/TTN separation with blinded imaging read
7	Raimondi et al.	2014	Italy	Prospective observational	54	GA 32.5 ± 2.6 weeks; BW 1,703 ± 583 g	Intubation within 24 h	CXR grading sensitivity 38.9%, specificity

N o.	Author	Year	Country	Study design	Sample size	Population characteristics	Reference standard / outcome	Key radiological finding
				diagnostic accuracy				77.8% for predicting NIV failure
8	Liu et al.	2016	China	Prospective observational	1,358 (228 TTN, 358 RDS, 85 MAS, 215 pneumonia, 412 no lung disease, 60 other)	NICU admissions	Conventional chest radiographic diagnosis	Consolidation with air bronchograms never observed in TTN
9	Corsini et al.	2018	Italy	Prospective cohort (concordance study)	124 patients / 134 diagnoses	Respiratory distress in first 24 h of life	CXR diagnosis	Concordance 91% (95% CI 86–96), $\kappa = 0.88$; CXR median 50 min vs LUS 9.5 min to diagnosis

N o.	Author	Year	Country	Study design	Sample size	Population characteristics	Reference standard / outcome	Key radiological finding
10	Perri et al.	2018	Italy	Prospective diagnostic accuracy	56	Mean GA 31 ± 3 weeks; BW $1,442 \pm 520$ g	Surfactant administration	CXR score AUC 0.80 (0.74–0.86) vs LUS score AUC 0.94 (0.89–0.98)
11	Liu et al.	2019	China	Retrospective observational comparative	1,205 (677 RDS, 528 TTN)	NICU admissions 2011–2017	Traditional clinical + CXR standard	Reported misdiagnosis rate of clinical + CXR diagnosis 62–77%
12	Raimondi et al.	2019	Italy / multicentre	Longitudinal multicentre observational	65 TTN	GA 34–40 weeks	Clinical TTN diagnosis; serial imaging	Regular pleural line without consolidation in 99.5% of all serial scans in TTN
13	Poerio et al.	2020	Italy	Prospective observational	100 (7 NICU admissions)	Term and late-preterm born by	NICU admission for TTN or RDS	Graded imaging appearance independently predicted

N o.	Author	Year	Country	Study design	Sample size	Population characteristics	Reference standard / outcome	Key radiological finding
						caesarean section		NICU admission (OR 2.890, 1.472–5.672)
14	Lokanuwasatien et al.	2020	Thailand	Cross-sectional	625 term newborns (59 with distress)	Term ≥ 37 weeks	Clinical + CXR	Respiratory distress in 9.4%; TTN commonest cause (7.5%); 92% presented within 4 h
15	Chavan et al.	2022	India	Prospective observational cohort	74 TTN	Late preterm 34–36 weeks and term	Clinical, radiological and NICU course	TTN incidence 16/1000 live births; no infant required ventilatory support
16	Srinivasan et al.	2022	India	Prospective cross-sectional diagnostic accuracy	100 preterm (50 TTN, 50 RDS)	Preterm, distress within 6 h of birth	Clinical examination, laboratory tests and CXR	Consolidation with air/fluid bronchograms seen only in RDS; alveolar-interstitial

N o.	Author	Year	Country	Study design	Sample size	Population characteristics	Reference standard / outcome	Key radiological finding
								pattern only in TTN
17	Yoon et al.	2022	South Korea	Prospective observational	22 (9 TTN, 13 RDS)	Median GA 37.1 weeks; BW 3,100 g	Clinical diagnosis with CXR	Significant separation of RDS from TTN by aeration score, thoracic fluid content and cytokines
18	Baldan et al.	2023	Turkey	Randomised controlled trial	60 (30 nHFOV, 30 nCPAP)	Late preterm and term > 34 weeks with TTN	Duration of non-invasive respiratory support	nHFOV reduced support duration (adjusted mean difference 16.3 h, 0.7–31.9; p = 0.04)
19	Yang et al.	2024	China	Retrospective cohort	73 RDS	NICU admissions 2022	CXR grade, respiratory distress score,	CXR grade correlated with aeration score, distress score and

N o.	Author	Ye ar	Countr y	Study design	Sample size	Population characteri stics	Reference standard / outcome	Key radiological finding
							oxygenation index	oxygenation index (p 0.429–0.859)
20	Kumar et al.	2024	India	Cross-sectional	94 (60 TTN, 34 RDS)	Mean GA 38 weeks + 4 days	Clinical + CXR + serial imaging	Double lung point sensitivity 68%, specificity 100%, PPV 100% for TTN
21	Suwal et al.	2024	Nepal	Quantitative cross-sectional	59 neonates	NICU admissions , mean age 15.9 ± 7.4 days	Portable CXR findings	Hypoeration commonest finding; reticulation/haziness commonest parenchymal change
22	Cho et al.	2025	South Korea (10 centres)	Retrospective multicentre diagnostic	43,338 CXRs (34,598 train / 4,370 val	Six classes including RDS, TTN, BPD, air leak,	Consensus labelling by 20 neonatologists,	Overall accuracy 83.96%; F1 90.30% for RDS but only

N o.	Author	Ye ar	Countr y	Study design	Sample size	Population characteri stics	Reference standard / outcome	Key radiological finding
				(deep learning)	/ 4,370 test)	atelectasis, healthy	externally validated	70.84% for TTN
23	Sakhr et al.	2025	Egypt	Case-control	300 neonates (RDS, TTN, controls)	Neonates with early respiratory distress	Clinical + radiographic diagnosis	LDH > 660 U/L discriminated RDS from TTN; inflammatory indices correlated with Downes score
24	Addow et al.	2025	Uganda	Prospective cohort	150 preterm with RDS	70.7% below 32 weeks; 62.7% male	Seven-day mortality	Ground-glass predominant radiological finding; early mortality 19.3%
25	Wang et al.	2025	China	Retrospective diagnostic (radiomics)	138 CXRs	Neonates with and without RDS	Clinical diagnosis of NRDS	Rib suppression raised radiomic AUC from 0.556 to 0.781

N o.	Author	Ye ar	Countr y	Study design	Sample size	Population characteri stics	Reference standard / outcome	Key radiological finding
								(gradient boosting)
26	Han et al.	2025	South Korea	Retrospect ive diagnostic (image enhancem ent)	Neonatal portable CXR dataset	Preterm and high- risk neonates	Neonatolo gist labelling	Bayesian- optimised contrast enhancement most improved TTN classification
27	Fall et al.	2025	Sweden	Retrospect ive observatio nal (computer ised CXR analysis)	60 (52 surfactan t-treated, 8 pre- surfactan t)	Extremely preterm, median 24+4 weeks	Quantitativ e pixel- intensity analysis of CXR	Computerised analysis detected regional aeration heterogeneity invisible to visual grading
28	Xu et al.	2026	China	Retrospect ive case- control	762 infants (572 training cohort;	Gestational age below 32 weeks	BPD at 36 weeks corrected GA	CXR score within 24 h OR 1.777 (1.253– 2.521); day-7 score OR

N o.	Author	Year	Country	Study design	Sample size	Population characteristics	Reference standard / outcome	Key radiological finding
					138 with BPD)			1.756 (1.264–2.440)
29	Hossain et al.	2026	Bangladesh	Cross-sectional observational	110 neonates	Clinically suspected RDS; mostly preterm and low birth weight	Radiological pattern and severity grading	Ground-glass 83.6%, air bronchogram 70.9%, reduced volume 66.4%; GA–severity association p = 0.002

BPD = bronchopulmonary dysplasia; BW = birth weight; CXR = chest radiograph; GA = gestational age; LDH = lactate dehydrogenase; LUS = lung ultrasound; MAS = meconium aspiration syndrome; NICU = neonatal intensive care unit; nCPAP = nasal continuous positive airway pressure; nHFOV = non-invasive high-frequency oscillatory ventilation; NIV = non-invasive ventilation; OR = odds ratio; PPV = positive predictive value; RDS = respiratory distress syndrome; TTN/TT = transient tachypnea (tachypnoea) of the newborn.

Table 5. Other Studies retained for outcome triangulation and discussion

Author	Year	Contribution to this review
He et al.	2021	Pooled sensitivity 0.67 (0.63–0.71) and specificity 0.97 (0.95–0.98) for ultrasonographic diagnosis of TTN; summary AUC 0.9906
Capasso et al.	2021	Framework for evaluating first-day aeration scoring as a predictor of surfactant replacement

Author	Year	Contribution to this review
De Bisschop et al.	2019	Severe RDS, extremely low birth weight and low gestational age predict INSURE failure; RDS severity assessed inconsistently by imaging
Ramaswamy et al.	2021	Surfactant in late preterm and term RDS associated with lower mortality (OR 0.45, 0.32–0.64)
Nobile et al.	2024	Respiratory problems are mainly studied with chest radiography; ultrasound proposed as alternative across RDS, TTN and other entities
Neves et al.	2024	All studies used CXR to diagnose RDS and 91% to grade severity, but 43% found alternative methods superior on several domains
Popa et al.	2024	Ultrasound identifies bilateral white lung, pleural line abnormality and consolidation with high sensitivity and specificity versus CXR reference
Boumans et al.	2024	Pooled sensitivity 0.631 and specificity 0.942 of ultrasound versus radiographic/CT reference in ARDS
Liu et al.	2025	Reported sensitivity 92–99% and specificity 95–97% for ultrasonographic diagnosis of neonatal RDS
Lovrenski et al.	2025	RDS diagnosed through characteristic radiographic findings and prematurity; TTN and MAS have specific differentiating imaging characteristics
Neri et al.	2025	TTN pathophysiology, imaging and cost-effectiveness; mortality virtually nil
Sweet et al.	2026	Lung-protective management, early thin-catheter surfactant and avoidance of intubation where possible

ARDS = acute respiratory distress syndrome; AUC = area under the curve; CT = computed tomography; ESPR = European Society of Paediatric Radiology; INSURE = intubation–surfactant–extubation; MAS = meconium aspiration syndrome.

Individual Radiographic Features

The six feature-level outcome domains are presented together in Table 6 because the included studies almost invariably reported them as a linked feature set rather than in isolation. The single most

consistently reported abnormality in radiographically confirmed RDS was diffuse ground-glass or reticulogranular opacification, documented in 83.6% of 110 consecutive neonates with clinically suspected RDS in a dedicated cross-sectional radiological study, and described as the predominant radiological finding in a prospective Ugandan cohort of 150 preterm neonates with RDS. Air bronchograms, the second cardinal feature, were present in 70.9% of the same cross-sectional series, and reduced lung volume in 66.4%. An independent cross-sectional radiological audit of 59 neonates in a Nepalese neonatal intensive care unit identified hypoaeration as the commonest finding in the lung fields and reticulation or haziness as the commonest parenchymal change, followed by consolidation, with pleural effusion confined to a small number of cases and occurring predominantly in preterm neonates with RDS.^{21,24,29}

The discriminative power of consolidation with air bronchograms is the most robust single finding in this literature. In a prospective case-control study of 120 neonates, consolidation with air bronchograms constituted the principal manifestation of RDS and was explicitly absent in TTN; in a subsequent prospective series of 1,358 infants encompassing 358 cases of RDS and 228 of TTN, consolidation with air bronchograms was never observed in any infant with TTN, permitting the authors to conclude that its presence excludes TTN outright. In the largest comparative series, encompassing 677 infants with RDS and 528 with TTN, every other sign — interstitial pattern, pleural line abnormality, loss of the normal reverberation artefact and pleural effusion — was found in both conditions, whereas consolidation with air bronchograms occurred exclusively in RDS, yielding a reported sensitivity and specificity of 100% for the differential diagnosis. A prospective cross-sectional study of 100 preterm neonates equally divided between the two diagnoses reproduced this pattern: consolidation with air or fluid bronchograms was seen only in RDS, and a pulmonary oedema pattern without consolidation only in TTN.^{5,8,11,16}

Features attributable to retained fetal lung fluid characterised TTN. Interstitial fluid and perihilar vascular streaking are the classical radiographic correlates, and the imaging literature describes them as commonly observed but non-specific, such that the diagnosis is frequently reached only after exclusion of RDS, pneumonia, aspiration syndromes and congenital heart disease. A multicentre longitudinal study of 65 neonates with TTN provided the most rigorous serial

characterisation: a regular pleural line with no consolidation was a consistent finding, present in all initial examinations performed at the onset of distress and in 99.5% of all examinations across the illness, with only one neonate developing consolidation on follow-up. The same study found the sharply demarcated fluid gradient between upper and lower lung fields — the pathognomonic sign of fluid redistribution in TTN — in only 31 of 65 patients (47.6%), demonstrating that the classical sign, while highly specific, is present in fewer than half of affected infants. Pleural effusion, including fluid tracking within the interlobar fissures, was reported in approximately 20% of TTN cases.^{8,12,49,50}

Table 6. prevalence and discriminative value of individual radiographic features in RDS versus TTN

Domain	Radiographic feature	Finding in RDS	Finding in TTN	Discriminative value	Source studies	Ref.
O1	Ground-glass / reticulogranular opacification	83.6% of clinically suspected RDS (n = 110); predominant finding in 150 preterm RDS	Absent as a homogeneous granular pattern; interstitial pattern may mimic it in severe TTN	High for RDS when homogeneous and bilaterally symmetrical	Hossain 2026; Addow 2025; Suwal 2024	21,24,29
O2	Air bronchograms extending beyond the cardiothymic shadow	70.9% of clinically suspected RDS (n = 110); consolidation with air	Not observed in any of 228 TTN cases; not observed in any of 528 TTN cases	Reported sensitivity and specificity 100% for the RDS/TTN distinction	Hossain 2026; Liu 2014; Liu 2016; Liu 2019; Srinivasan 2022	5,8,11,16,29

Domain	Radiographic feature	Finding in RDS	Finding in TTN	Discriminative value	Source studies	Ref.
		bronchograms in 100% discriminative series				
O3	Lung volume and aeration	Reduced lung volume in 66.4%; hypoaeration the commonest lung-field finding in a mixed NICU series	Normal to increased lung volume; aeration preserved	Moderate; degraded by expiratory-phase and rotated portable films	Hossain 2026; Suwal 2024	21,29
O4	Perihilar vascular streaking and interstitial fluid	May be present, especially in mild/early or CPAP-treated disease	Cardinal feature; commonly observed evidence of increased lung fluid	Low as an isolated sign; commonly observed but not specific	Carlo 2006 commentary ; Neri 2025; Alhassen 2020	49,50
O5	Interlobar fissural fluid	Reported in a small proportion,	Pleural effusion in approximatel	Low to moderate; supports TTN	Liu 2014; Suwal 2024	5,21

Domain	Radiographic feature	Finding in RDS	Finding in TTN	Discriminative value	Source studies	Ref.
	and pleural effusion	predominantly in preterm RDS	by 20% of TTN	but does not exclude RDS		
O6	Cardiac silhouette and cardiothoracic ratio	Cardiac border obscured by confluent opacification in advanced grades ("white-out")	Mild cardiomegaly may accompany fluid overload; cardiac border remains visible	Low; reported qualitatively rather than measured in the included studies	Lovrenski 2025; Neri 2025	48,49

CPAP = continuous positive airway pressure; NICU = neonatal intensive care unit; RDS = respiratory distress syndrome; TTN = transient tachypnea of the newborn.

Overall Diagnostic Accuracy of Chest Radiography

When the chest radiograph was evaluated as an index test against a defined clinical outcome rather than as the reference standard, its performance was consistently and substantially inferior to that of quantitative bedside imaging. In a prospective study of 54 neonates stabilised on nasal continuous positive airway pressure for 120 minutes, radiographic grading assessed by an experienced radiologist blinded to clinical condition achieved a sensitivity of 38.9%, a specificity of 77.8%, a positive predictive value of 46.7% and a negative predictive value of 71.8% for predicting intubation within 24 hours, against 88.9%, 100%, 100% and 94.7% respectively for the corresponding ultrasonographic profile. In a prospective diagnostic accuracy study of 56 neonates of mean gestational age 31 weeks, a formal chest radiograph score achieved an area under the receiver

operating characteristic curve of 0.80 (95% confidence interval 0.74–0.86) for early identification of infants who would require surfactant, compared with 0.94 (0.89–0.98) for the ultrasonographic score, with correspondingly lower sensitivity (82% versus 86%), specificity (76% versus 88%), positive predictive value (69% versus 83%) and negative predictive value (87% versus 91%).^{7,10}

The magnitude of this shortfall is greater still in the term and post-term population. In a multicentre prospective study of 218 neonates with meconium aspiration syndrome — an entity that shares much of its radiographic vocabulary with RDS and TTN — chest radiograph grading achieved an area under the curve of only 0.539 for predicting the need for surfactant, essentially indistinguishable from chance, against 0.906 for arterial pH and 0.999 for the ultrasonographic aeration score. Considered together, these head-to-head data indicate that while the plain radiograph retains substantial specificity when a cardinal RDS feature is present, its sensitivity in the earliest hours of life — precisely when the RDS–TTN decision must be made — is inadequate for it to serve as the sole determinant of surfactant policy.³¹

Table 7. diagnostic accuracy of chest radiography compared with contemporary comparators

Study	n	Target condition / outcome	Index test	Sensitivity	Specificity	PPV	NPV	AUC (95% CI)	Comparator performance	Ref.
Raimondi et al., 2014	54	Intubation within 24 h of a 2-hour CPAP trial	CXR grade (blinded radiologist)	38.9%	77.8%	46.7%	71.8%	Not reported	LUS type 1 profile: 88.9% / 100% / 100% / 94.7%	7
Perri et al., 2018	56	Surfactant	CXR score	82%	76%	69%	87%	0.80 (0.74	LUS score AUC	10

Study	n	Target condition / outcome	Index test	Sensitivity	Specificity	PPV	NPV	AUC (95% CI)	Comparator performance	Ref.
		administration						— 0.86)	0.94 (0.89–0.98)	
Corsini et al., 2018	124	Aetiological diagnosis of respiratory distress	CXR diagnosis	Concordance with LUS 91% (95% CI 86–96)	$\kappa = 0.88$ (0.81–0.94)	Not reported	Not reported	Not reported	Median time to diagnosis 50 min (IQR 33–64) vs 9.5 min (IQR 5–15)	9
Chen et al., 2026	218 (MAS)	Surfactant administration	CXR grade	Not reported	Not reported	Not reported	Not reported	0.539	LUS score AUC 0.999 (0.997–1.000); pH AUC 0.906	31

Study	n	Target condition / outcome	Index test	Sensitivity	Specificity	PPV	NPV	AUC (95% CI)	Comparator performance	Ref.
Cho et al., 2025	4,370 test radiographs	Six-class neonatal disease classification	CXR (deep-learning read)	Overall accuracy 83.96%	F1 83.68% overall	F1 90.30% (RDS)	F1 70.84% (TTN)	Not reported	Neonatologist consensus labelling as ground truth	22
Vergine et al., 2014	59 (23 RDS, 30 TTN)	Final composite clinical diagnosis	Blinded external imaging read	95.6% (RDS) / 93.3% (TTN)	94.4% (RDS) / 96.5% (TTN)	91.6% / 96.5%	97.1% / 93.4%	Not reported	Demonstrates achievable ceiling when reading is fully blinded	6
Liu et al., 2019	1,205 (677 RDS, 528 TTN)	RDS versus TTN	Clinical assessment + CXR	Misdiagnosis rate reported as 62–77%	Consolidation with air bronchograms: 100%	—	—	Not reported	Consolidation present = RDS; absent = TTN	11

AUC = area under the receiver operating characteristic curve; CI = confidence interval; CPAP = continuous positive airway pressure; CXR = chest radiograph; IQR = interquartile range; LUS =

lung ultrasound; MAS = meconium aspiration syndrome; NPV = negative predictive value; PPV = positive predictive value.

Interobserver Reliability and Misdiagnosis

Reliability data specific to the neonatal chest radiograph are sparse, and this constitutes one of the most conspicuous deficiencies of the evidence base. The one direct concordance study identified reported 91% agreement (95% confidence interval 86–96%) between chest radiographic and ultrasonographic diagnosis across 134 diagnoses in 124 neonates, with a kappa statistic of 0.88 (0.81–0.94); however, this measures cross-modality concordance rather than intra-modality reliability between radiologists. The most quantitatively explicit statement on radiographic misclassification derives from the largest comparative series, in which the misdiagnosis rate of traditional clinical plus radiographic diagnosis was reported as 62% to 77%, a figure which, although drawn from a single group and requiring cautious interpretation, is directionally consistent with the systematic-review finding that 43% of studies judged alternative methods superior to radiography for differential diagnosis.^{9,11,38}

Objective, operator-independent corroboration comes from the deep-learning literature. When a modified ResNet50 architecture was trained on 34,598 neonatal chest radiographs labelled by twenty neonatologists and validated by independent neonatologists from different institutions, the resulting F1 score was 90.30% for RDS but only 70.84% for TTN — the lowest of all six classes, below healthy lung (87.38%), bronchopulmonary dysplasia (92.19%), air leak syndrome (90.65%) and atelectasis (86.56%). Because the algorithm was trained on expert consensus labels and evaluated against them, this twenty-point differential is a direct, quantified measure of the intrinsic radiographic separability of the TTN phenotype, and it indicates that the difficulty is not primarily one of reader inexperience but of genuine phenotypic overlap. Independent work demonstrating that Bayesian-optimised contrast enhancement of neonatal radiographs produced its most notable classification improvement precisely in TTN reinforces this interpretation.^{22,26}

Table 8. reliability, agreement and misclassification of the neonatal chest radiograph

Study	Measure assessed	Result	Interpretation	Ref.
Corsini et al., 2018	Cross-modality concordance (CXR vs LUS), 134 diagnoses	91% (95% CI 86–96); $\kappa = 0.88$ (0.81–0.94)	High cross-modality agreement for aetiological diagnosis in the first 24 h	9
Liu et al., 2019	Reported misdiagnosis rate of clinical + radiographic diagnosis, n = 1,205	62–77%	Single-group estimate; directionally consistent with independent systematic-review findings	11
Cho et al., 2025	Deep-learning classification against 20-neonatologist consensus, 4,370 test radiographs	F1 90.30% (RDS) vs 70.84% (TTN)	Operator-independent evidence that the TTN radiographic phenotype is the least separable of six classes	22
Han et al., 2025	Effect of image-quality optimisation on classification	Greatest improvement observed for TTN	Portable neonatal image quality is a material contributor to TTN misclassification	26
Wang et al., 2025	Rib-suppression radiomics, 138 CXRs	Gradient boosting AUC 0.556 → 0.781 after rib suppression	Overlying rib shadow measurably degrades radiographic parenchymal assessment in neonates	25
Neves et al., 2024	Systematic review, 23 studies, 2,245 newborns	43% of studies judged alternative methods superior for differential diagnosis	Triangulating evidence (systematic review; discussion only)	38

Radiographic Severity Grade and Therapeutic Escalation

The four-stage radiographic grading of RDS remains the operational severity language of neonatal units, and the included evidence confirms that it carries real, though imperfect, therapeutic information. In a cross-sectional radiological series of 110 neonates, Grade II disease was the modal category (37.3%), and a statistically significant association was demonstrated between gestational age and severity grade ($p = 0.002$), with severe grades concentrated below 34 weeks of gestation. In a multicentre prospective study of 206 preterm infants in which surfactant was administered on the basis of the stable microbubble rating and chest radiography, the ultrasonographic aeration score correlated significantly with chest radiographic severity (Kendall tau-b 0.535, $p < 0.001$), confirming that the two severity languages measure a common underlying construct of lung aeration. A large cohort study of preterm infants managed initially on continuous positive airway pressure found that most infants who ultimately failed had moderate or severe radiological respiratory distress syndrome, again supporting a graded relationship between radiographic severity and treatment failure.^{29,30}

Nevertheless, the predictive ceiling of radiographic grading alone is low. As documented in Table 9, radiographic grading achieved an area under the curve of 0.80 for surfactant prediction in preterm infants and only 0.539 in a term population with meconium aspiration, while a sensitivity of 38.9% for predicting non-invasive ventilation failure means that approximately three in five infants destined to require intubation are not identified by the radiograph. Graded bedside imaging, by contrast, independently predicted neonatal intensive care admission in a prospective cohort of 100 infants delivered by caesarean section with an odds ratio of 2.890 per unit score (95% confidence interval 1.472–5.672, $p = 0.002$) and an area under the curve of 0.978 (0.926–0.997).^{7,10,13,31}

Table 9. radiographic severity grade and escalation of therapy

Study	n	Radiographic exposure measure	Outcome	Result	Ref.
Hossain et al., 2026	110	Grade I–IV radiographic severity	Distribution of grade;	Grade II modal (37.3%); GA–severity association $p = 0.002$;	29

Study	n	Radiographic exposure measure	Outcome	Result	Ref.
			association with gestational age	severe grades concentrated < 34 weeks	
Perri et al., 2018	56	Chest radiograph score	Surfactant administration	AUC 0.80 (0.74–0.86); sensitivity 82%, specificity 76%	10
Hoshino et al., 2025	206	Chest radiographic severity	Concordance with aeration score and surfactant deficiency	Kendall tau-b 0.535 with aeration score ($p < 0.001$); tau-b -0.529 with stable microbubble rating	30
Raimondi et al., 2014	54	Highest radiographic grade	Intubation within 24 h	Sensitivity 38.9%, specificity 77.8%	7
Chen et al., 2026	218	Chest radiograph grade (MAS population)	Surfactant administration	AUC 0.539 — no better than chance in a term population	31
Poerio et al., 2020	100	Graded three-point imaging appearance at 30 min	NICU admission for TTN or RDS	OR 2.890 per unit (1.472–5.672), $p = 0.002$; AUC 0.978 (0.926–0.997)	13
Yang et al., 2024	73	Chest radiograph grade before and after treatment	Change in severity with treatment	Radiographic grade fell significantly after treatment ($p < 0.05$), tracking clinical improvement	19

Temporal Evolution and Resolution

The temporal trajectory of the two conditions is itself diagnostic, and the included evidence establishes that it is best captured by serial rather than single imaging. In TTN, respiratory distress resolved by the third to fourth day in the majority of a prospective cohort of 74 neonates, in whom no infant required either invasive or non-invasive ventilatory support; in a longitudinal multicentre study of 65 neonates with TTN in whom imaging was repeated every 6 to 12 hours for as long as distress persisted, a regular pleural line without consolidation persisted throughout in 99.5% of scans, and the semi-quantitative aeration score correlated significantly with the clinical Silverman score (ρ 0.27, $p = 0.02$), demonstrating that serial imaging tracks the clinical course. Notably, the fluid-gradient sign characteristic of TTN can also appear during the recovery phase of severe TTN, RDS, meconium aspiration syndrome and pneumonia, meaning that a single late image may be actively misleading if interpreted without knowledge of the illness trajectory.^{8,12,15}

In RDS the trajectory is the mirror image: without surfactant the radiographic appearance deteriorates progressively over the first 24 to 48 hours, whereas after surfactant instillation aeration improves, though heterogeneously. Computerised pixel-intensity analysis of chest radiographs obtained within six hours of surfactant instillation in 52 extremely preterm infants demonstrated that the right lung was more aerated than the left and that basal regions were more aerated than apical regions, with significantly greater focal heterogeneity in the right seventh intercostal segment in treated infants than in untreated controls ($p < 0.001$) — regional information invisible to conventional visual grading. In a retrospective cohort of 73 neonates with RDS, radiographic grade, aeration score, respiratory distress score and oxygenation index all fell significantly after treatment ($p < 0.05$), confirming that the radiograph is responsive to therapeutic change.^{19,27}

Table 10. temporal evolution of radiographic findings

Condition	Time point	Radiographic behaviour	Source study	Ref.
TTN	Onset of distress (0–2 h)	Interstitial fluid; regular pleural line; no consolidation; fluid gradient sign in 47.6%	Raimondi 2019	12

Condition	Time point	Radiographic behaviour	Source study	Ref.
TTN	First 24 h	Persistence of interstitial pattern; consolidation remains absent in 99.5% of serial examinations	Raimondi 2019	12
TTN	Day 2–4	Progressive resolution; distress resolved by day 3–4 in the majority; no ventilatory support required	Chavan 2022	15
TTN / recovery phase mimicry	Recovery of severe TTN, RDS, MAS or pneumonia	Fluid gradient sign may reappear, creating late diagnostic ambiguity	Liu 2016	8
RDS	First hours	Ground-glass opacification with air bronchograms; volume loss; grade increases without treatment	Hossain 2026; Addow 2025	24,29
RDS	Within 6 h of surfactant	Heterogeneous re-aeration; right lung more aerated than left; basal more aerated than apical ($p \leq 0.024$)	Fall 2025	27
RDS	After treatment (serial)	Radiographic grade, aeration score, distress score and oxygenation index all fall significantly ($p < 0.05$)	Yang 2024	19
RDS	Day 7 and beyond	Persistently elevated radiographic score signals evolving chronic lung disease	Xu 2026	28

Correlation with Oxygenation Indices and Clinical Distress Scores

Radiographic severity is not a free-standing construct but is anchored to physiology. In a retrospective cohort of 73 neonates with RDS, the chest radiograph grade correlated positively and significantly with the respiratory distress score, the oxygenation index and the aeration score both before and after treatment, with Spearman coefficients spanning 0.429 to 0.859 ($p < 0.05$), and receiver operating characteristic analysis of the linked severity measures produced areas under the curve of 0.805 to 1.000. In 206 preterm infants, radiographic severity correlated with the aeration score at Kendall tau-b 0.535 and inversely with the stable microbubble rating, a direct biochemical index of surfactant sufficiency, at tau-b -0.529 (both $p < 0.001$) — the closest available evidence that the radiographic phenotype is a genuine surrogate of the underlying surfactant deficit. In 22 late-preterm and term neonates, the aeration score was significantly higher in RDS than in TTN (11 versus 6, $p = 0.001$), and thoracic fluid content, interleukin-1 beta and tumour necrosis factor alpha all differed significantly between the two groups, situating the imaging phenotype within a coherent biological framework.^{17,19,30}

Table 11. correlation of radiographic severity with physiological and biochemical measures

Study	Population	Correlation examined	Coefficient / effect	p value	Ref.
Yang et al., 2024	73 RDS	CXR grade vs respiratory distress score, oxygenation index and aeration score	$\rho = 0.429\text{--}0.859$	< 0.05	19
Hoshino et al., 2025	206 preterm	CXR severity vs lung ultrasound aeration score	Kendall $\tau\text{-b} = 0.535$	< 0.001	30
Hoshino et al., 2025	206 preterm	Lung ultrasound aeration score vs stable microbubble rating (surfactant sufficiency)	Kendall $\tau\text{-b} = -0.529$	< 0.001	30
Yoon et al., 2022	22 (9 TTN, 13 RDS)	Aeration score, RDS vs TTN	11 vs 6 (median)	0.001	17

Study	Population	Correlation examined	Coefficient / effect	p value	Ref.
Yoon et al., 2022	22	Change in thoracic fluid content, RDS vs TTN	2 vs -1.5	< 0.001	17
Yoon et al., 2022	22	Interleukin-1 β / tumour necrosis factor- α , RDS vs TTN	2.5 vs 11.3 / 20.1 vs 11.2	0.02 / 0.04	17
Raimondi et al., 2019	65 TTN	Aeration score vs Silverman clinical distress score	$\rho = 0.27$	0.02	12
Sakhr et al., 2025	300	Systemic inflammatory indices vs Downes clinical distress score	$r = 0.261$ – 0.317	0.001– 0.009	23

Radiographic Severity and Adverse Clinical Outcomes

The prognostic content of the neonatal chest radiograph is most convincingly demonstrated in relation to chronic lung disease. In a retrospective case-control study of 762 infants born below 32 weeks of gestation, of whom 138 of 572 in the training cohort (24.13%) developed bronchopulmonary dysplasia, multivariable logistic regression identified the chest radiograph score within 24 hours of birth as an independent predictor (odds ratio 1.777, 95% confidence interval 1.253–2.521, $p = 0.001$) alongside the chest radiograph score at day 7 (odds ratio 1.756, 95% confidence interval 1.264–2.440, $p < 0.001$), birth weight (odds ratio 0.997, 0.996–0.998, $p < 0.001$) and extended invasive mechanical ventilation to day 7 (odds ratio 4.280, 2.149–8.526, $p < 0.001$). The resulting prediction model achieved areas under the curve of 0.873 (0.839–0.907) in the training cohort and 0.848 (0.778–0.917) on validation, with good calibration and a favourable decision-curve net benefit.²⁸

Mortality data reinforce the asymmetry between the two conditions. In a prospective Ugandan cohort of 150 preterm neonates with radiologically confirmed RDS, seven-day mortality was 19.3%, with delayed presentation beyond six hours (adjusted risk ratio 1.72, 1.43–2.07, $p < 0.001$) and birth weight below 1.5 kg (adjusted risk ratio 1.12, 1.02–1.22, $p = 0.015$) as independent predictors. In a retrospective analysis of 685 preterm infants, mortality was 6.0% among the 319 with RDS and zero

among the 366 without ($p < 0.001$), with gestational age below 32 weeks (odds ratio 3.914, 2.972–5.155) and birth weight below 1500 g (odds ratio 6.610, 2.777–13.735) identified as independent risk factors for RDS. By contrast, in 74 consecutive neonates with TTN no infant required ventilatory support of any kind, and in a comprehensive contemporary review the mortality of TTN was characterised as virtually nil — an observation of direct clinical relevance, since it means that the entire clinical cost of misclassifying TTN as RDS is iatrogenic, while the cost of misclassifying RDS as TTN is measured in delayed surfactant and excess death.^{15,24,34,49}

Table 12. radiographic severity, diagnosis and adverse clinical outcomes

Study	Population	Exposure / predictor	Outcome	Effect estimate (95% CI)	p value	Ref.
Xu et al., 2026	762 infants < 32 weeks	CXR score within 24 h of birth	BPD at 36 weeks corrected GA	OR 1.777 (1.253–2.521)	0.001	28
Xu et al., 2026	762	CXR score at day 7	BPD at 36 weeks corrected GA	OR 1.756 (1.264–2.440)	< 0.001	28
Xu et al., 2026	762	Invasive ventilation extended to day 7	BPD at 36 weeks corrected GA	OR 4.280 (2.149–8.526)	< 0.001	28
Xu et al., 2026	762	Combined model (BW + CXR scores + ventilation)	BPD at 36 weeks corrected GA	AUC 0.873 (0.839–0.907); validation 0.848 (0.778–0.917)	—	28
Addow et al., 2025	150 preterm RDS	Delayed presentation > 6 h of life	Death within 7 days	aRR 1.72 (1.43–2.07)	< 0.001	24

Study	Population	Exposure / predictor	Outcome	Effect estimate (95% CI)	p value	Ref.
Addow et al., 2025	150	Birth weight < 1.5 kg	Death within 7 days	aRR 1.12 (1.02–1.22)	0.015	24
Addow et al., 2025	150	RDS with ground-glass predominance	Seven-day mortality rate	19.3% (29/150)	—	24
Ma et al., 2025	685 preterm	Diagnosis of RDS versus no RDS	In-hospital mortality	6.0% versus 0%	< 0.001	34
Ma et al., 2025	685	Gestational age < 32 weeks	Occurrence of RDS	OR 3.914 (2.972–5.155)	< 0.001	34
Ma et al., 2025	685	Birth weight < 1500 g	Occurrence of RDS	OR 6.610 (2.777–13.735)	< 0.001	34
Chavan et al., 2022	74 TTN	Radiological and clinical diagnosis of TTN	Need for ventilatory support	No infant required invasive or non-invasive support	—	15
Poerio et al., 2020	100	Bilateral severe imaging appearance at birth	NICU admission	All 5 infants with bilateral severe appearance admitted	—	13
Baldan et al., 2023	60 TTN (RCT)	Non-invasive high-frequency oscillation vs CPAP	Duration of non-invasive support	Adjusted mean difference 16.3 h (0.7–31.9)	0.04	18

Study	Population	Exposure / predictor	Outcome	Effect estimate (95% CI)	p value	Ref.
Porto et al., 2011	273 late preterm (RCT)	Antenatal betamethasone at 34–36 weeks	RDS / TTN incidence	RDS 1.4% vs 0.8%; TTN 24% vs 22%; adjusted RR 1.12 (0.74–1.70)	0.54 / 0.77	4

aRR = adjusted risk ratio; *AUC* = area under the receiver operating characteristic curve; *BPD* = bronchopulmonary dysplasia; *BW* = birth weight; *CI* = confidence interval; *CPAP* = continuous positive airway pressure; *CXR* = chest radiograph; *GA* = gestational age; *NICU* = neonatal intensive care unit; *OR* = odds ratio; *RCT* = randomised controlled trial; *RR* = risk ratio.

Computational, Radiomic and Deep-Learning Analysis

The computational literature furnishes the most objective available measurement of how much diagnostic information the neonatal chest radiograph actually contains. Using 43,338 portable supine radiographs collected retrospectively from ten university hospitals and labelled by twenty neonatologists with external validation, a modified ResNet50 architecture incorporating gestational age and birth weight achieved an overall test accuracy of 83.96% and an overall F1 score of 83.68% across six classes. Class-wise performance stratified sharply: bronchopulmonary dysplasia 92.19%, air leak syndrome 90.65%, RDS 90.30%, healthy lung 87.38%, atelectasis 86.56% and TTN 70.84%. This ordering is itself a finding of substantial clinical importance, because it demonstrates in an operator-independent fashion that the radiographic signature of RDS is highly learnable while that of TTN is the least distinctive of the six, consistent with the pathophysiological expectation that a diffuse interstitial fluid excess in a structurally mature lung produces a subtler and more variable radiographic imprint than does alveolar collapse.²²

Two lines of work indicate that a material portion of the residual error is technical rather than biological. Rib-suppression radiomics applied to 138 neonatal chest radiographs raised the gradient-boosting area under the curve from 0.556 before suppression to 0.781 after, with linear discriminant analysis and logistic regression reaching 0.762 and 0.756 when pre- and post-suppression features

were combined, demonstrating that overlying osseous shadow measurably obscures parenchymal signal in the neonatal thorax. Independently, Bayesian-optimised contrast-limited adaptive histogram equalisation of neonatal radiographs improved classification across several architectures, with the most notable gain observed specifically in TTN. Finally, computerised pixel-intensity analysis of radiographs in extremely preterm infants extracted regional aeration and focal-heterogeneity information that conventional visual grading cannot resolve. Collectively these findings imply that the plain radiograph is being under-read rather than being intrinsically uninformative, and that quantitative post-processing represents a realistic route to improving its performance without additional radiation.^{25,26,27}

Table 13. computational and artificial-intelligence performance on neonatal chest radiographs

Study	Computational method	Dataset	Headline performance	Class-wise or secondary findings	Ref.
Cho et al., 2025	Modified ResNet50 with demographic inputs	43,338 CXRs from 10 hospitals	Overall accuracy 83.96%; overall F1 83.68%	RDS F1 90.30%; TTN F1 70.84%; BPD 92.19%; air leak 90.65%; atelectasis 86.56%; healthy 87.38%	22
Wang et al., 2025	Rib-suppression radiomics, six machine-learning models	138 CXRs	Gradient boosting AUC 0.556 → 0.781 after rib suppression	Linear discriminant analysis 0.762; logistic regression 0.756 on combined features	25
Han et al., 2025	Bayesian-optimised contrast-limited adaptive	Neonatal portable CXR dataset	Improved classification across architectures	Most notable improvement observed in TTN classification	26

Study	Computational method	Dataset	Headline performance	Class-wise or secondary findings	Ref.
	histogram equalisation				
Fall et al., 2025	Computerised pixel-intensity analysis (ImageJ)	60 extremely preterm infants	Detected regional aeration differences invisible to visual grading	Right > left aeration; basal > apical; focal heterogeneity right 7th segment p < 0.001	27

Radiation, Time-to-Diagnosis and Health-System Considerations

Three system-level parameters distinguish radiography from its comparators. First, time: in a prospective study of 124 neonates, the median time from decision to diagnosis was 50 minutes for chest radiography (interquartile range 33–64) against 9.5 minutes for bedside ultrasound (interquartile range 5–15, $p < 0.0001$), a difference of clinical consequence in a condition in which 92% of affected term infants present within four hours of birth. Second, radiation: neonates, and particularly extremely preterm infants who undergo repeated serial imaging, are the most radiosensitive patients in the hospital by virtue of high cellular division rates and long life expectancy, and reduction of cumulative diagnostic radiation is a recognised quality objective. Third, resource distribution: in low- and middle-income settings, radiography may be the only imaging modality available, and a systematic review of 23 studies encompassing 2,245 newborns found that every study used the radiograph to diagnose RDS and 91% used it to grade severity, while simultaneously noting that its outcomes may not fully reflect current global practice in settings where early management of RDS remains a determinant of survival.^{9,14,26,38}

Table 14. operational and health-system parameters

Parameter	Chest radiography	Comparator (lung ultrasound)	p value	Source	Ref.
Median time to diagnosis	50 min (IQR 33–64)	9.5 min (IQR 5–15)	< 0.0001	Corsini et al., 2018 (n = 124)	9
Ionising radiation	Present; cumulative with serial imaging	Absent	—	Han et al., 2025; Popa et al., 2024	26,41
Bedside repeatability	Limited; requires portable equipment and radiographer	High; repeatable at the cot side	—	Popa et al., 2024	41
Operator dependence	Acquisition-dependent; interpretation radiologist-dependent	Operator-dependent but reproducible with structured training	—	Nobile et al., 2024	40
Availability in low-resource settings	Frequently the only modality available; used for diagnosis in 100% and grading in 91% of studies reviewed	Requires equipment and training not universally available	—	Neves et al., 2024 (23 studies, 2,245 newborns)	38
Detection of complications (pneumothorax, malposition of lines/tubes)	Retained and irreplaceable indication	Complementary	—	Lovrenski et al., 2025	48

Dose–Response Analysis

A dose–response relationship was sought between graded radiographic severity, and its biological surrogate gestational age, and each of four ordered clinical responses. The analysis is presented in Table 17. The relationship satisfied the prespecified criteria for a dose–response gradient in four of the five exposure–response pairs examined. Most persuasively, a continuous chest radiograph score behaved as a per-unit exposure: each single-point increment in the radiographic score obtained within 24 hours of birth conferred a 77.7% relative increase in the odds of bronchopulmonary dysplasia (odds ratio 1.777, 95% confidence interval 1.253–2.521, $p = 0.001$), and each single-point increment at day 7 conferred a 75.6% increase (odds ratio 1.756, 1.264–2.440, $p < 0.001$), the two estimates being closely concordant and thereby demonstrating temporal stability of the gradient. This is the archetypal signature of a genuine dose–response relationship rather than a threshold effect.²⁸

The gestational-age gradient behaves in parallel. Severe radiographic grades were significantly more frequent below 34 weeks of gestation ($p = 0.002$) in a cross-sectional radiological series of 110 neonates, while the odds of developing RDS rose from a baseline to 3.914 (2.972–5.155) below 32 weeks of gestation and to 6.610 (2.777–13.735) below 1500 g of birth weight in a cohort of 685 preterm infants — an ordered, monotonic and biologically coherent progression from mild surfactant insufficiency in the late preterm infant to profound deficiency in the extremely preterm. A convergent gradient operates in the opposite direction in TTN: in 239,971 term singleton live births, the duration of supplemental oxygen was inversely correlated with the duration of labour ($r = -0.151$, $p = 0.028$), so that progressively greater exposure to labour, and therefore to the catecholamine and mechanical stimuli that drive alveolar fluid clearance, produced a progressively shorter and milder illness.^{3,29,34}

Two further gradients complete the picture. The correlation between radiographic grade and physiological derangement was continuous rather than categorical, with Spearman coefficients from 0.429 to 0.859 against respiratory distress score, oxygenation index and aeration score, and a Kendall tau-b of 0.535 against the aeration score in 206 preterm infants; and graded bedside imaging severity predicted neonatal intensive care admission with an odds ratio of 2.890 per unit score (1.472–5.672,

$p = 0.002$). The single exposure–response pair that did not satisfy the dose–response criteria was the relationship between radiographic grade and surfactant requirement in term infants, where the area under the curve of 0.539 in a meconium aspiration population indicates that in the mature lung the radiographic grade carries essentially no graded information about surfactant need — an important negative finding that delimits the domain within which radiographic grading may legitimately be used.^{13,19,30,31}

Table 15. Dose–response analysis: graded radiographic and biological exposure against ordered clinical response

Exposure ("dose")	Gradation	Response	Effect estimate	Dose–response satisfied?	Source	Ref.
Per-unit chest radiograph score (within 24 h)	Continuous, per 1-point increment	Bronchopulmonary dysplasia at 36 weeks corrected GA	OR 1.777 (1.253–2.521), $p = 0.001$	Yes — monotonic per-unit gradient	Xu et al., 2026 (n = 762)	28
Per-unit chest radiograph score (day 7)	Continuous, per 1-point increment	Bronchopulmonary dysplasia at 36 weeks corrected GA	OR 1.756 (1.264–2.440), $p < 0.001$	Yes — gradient stable across two time points	Xu et al., 2026	28
Gestational-age stratum (surrogate of surfactant deficit)	≥ 34 weeks $\rightarrow < 34$ weeks $\rightarrow < 32$ weeks	Radiographic severity grade; occurrence of RDS	Severity–GA association $p = 0.002$; RDS OR 3.914	Yes — ordered, monotonic and biologically coherent	Hossain et al., 2026 (n = 110); Ma et al.,	29,34

Exposure ("dose")	Gradation	Response	Effect estimate	Dose– response satisfied?	Source	Ref.
			(2.972– 5.155) below 32 weeks		2025 (n = 685)	
Birth-weight stratum	≥ 1500 g $\rightarrow$ < 1500 g	Occurrence of RDS	OR 6.610 (2.777– 13.735)	Yes — steeper gradient than gestational age alone	Ma et al., 2025	34
Duration of exposure to labour (inverse exposure for TTN)	Continuous	Duration of supplemental oxygen in TTN	$r = -0.151$, $p = 0.028$	Yes — inverse gradient consistent with fluid- clearance physiology	Tutdibi et al., 2010 (n = 239,971)	3
Graded bedside imaging severity (3- point scale)	Type 3 $\rightarrow$ type 2 $\rightarrow$ type 1	NICU admission for RDS or TTN	OR 2.890 per unit (1.472– 5.672), $p =$ 0.002; AUC 0.978	Yes — per- unit gradient with excellent discrimination	Poerio et al., 2020 (n = 100)	13

Exposure ("dose")	Gradation	Response	Effect estimate	Dose– response satisfied?	Source	Ref.
Radiographic grade (term infants, mature lung)	Ordinal grade	Surfactant administration	AUC 0.539 — no better than chance	No — gradient absent in the mature lung	Chen et al., 2026 (n = 218)	31
Radiographic grade vs physiological derangement	Ordinal grade / continuous score	Respiratory distress score, oxygenation index, aeration score	$\rho = 0.429$ – 0.859 ($p <$ 0.05); Kendall τ -b 0.535 ($p <$ 0.001)	Yes — continuous rather than threshold relationship	Yang et al., 2024 (n = 73); Hoshino et al., 2025 (n = 206)	19,30

AUC = area under the receiver operating characteristic curve; GA = gestational age; NICU = neonatal intensive care unit; OR = odds ratio; RDS = respiratory distress syndrome; TTN = transient tachypnea of the newborn. A dose–response relationship was considered satisfied where the effect estimate increased monotonically across at least three ordered exposure categories, or where a per-unit increment in a continuous radiographic score produced a statistically significant and directionally consistent change in outcome odds.

Certainty of the Evidence

Table 16. GRADE certainty of evidence by outcome domain

Domain	Outcome	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision / other	Certainty
O1–O3	Cardinal RDS features (ground-glass, air bronchogram, volume loss)	Observational	Serious (incorporation bias)	Not serious	Not serious	Not serious	Moderate
O2	Consolidation with air bronchograms as an RDS-specific sign	Observational	Serious	Not serious	Not serious	Very large effect (upgraded)	Moderate
O4–O6	TTN fluid-redistribution features	Observational	Serious	Serious (variable reporting)	Not serious	Not serious	Low
O7	Diagnostic accuracy of CXR versus comparators	Observational (diagnostic)	Not serious	Not serious	Not serious	Not serious	High
O8	Reliability and misclassification	Observational	Serious	Serious	Not serious	Not serious	Low

Domain	Outcome	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision / other	Certainty
O9	Radiographic grade and therapeutic escalation	Observational	Not serious	Serious (population-dependent)	Not serious	Not serious	Moderate
O10	Temporal evolution	Observational	Not serious	Not serious	Not serious	Serious (few serial studies)	Moderate
O11	Correlation with physiology	Observational	Not serious	Not serious	Not serious	Not serious	Moderate
O12	Radiographic severity and adverse outcome	Observational (prognostic)	Not serious	Not serious	Not serious	Not serious	High
O13	Computational classification performance	Observational (diagnostic)	Not serious	Not serious	Serious (single-country datasets)	Not serious	Moderate
O14	Operational and health-system parameters	Observational	Not serious	Not serious	Not serious	Serious (single-centre time data)	Moderate

Domain	Outcome	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision / other	Certainty
Dose-response	Graded radiographic severity and outcome	Observational	Not serious	Not serious	Not serious	Dose-response gradient (upgraded)	Moderate-High

Hypothesis Testing Summary

Table 17. Summary of hypothesis testing

Hypothesis	Verdict	Principal supporting evidence	Statistical inference	Ref.
H1: Ground-glass opacification, air bronchograms and reduced lung volume are significantly more prevalent in RDS than in TTN	Supported	Ground-glass 83.6%, air bronchogram 70.9%, reduced volume 66.4% in RDS; consolidation with air bronchograms observed in 0 of 528 and 0 of 228 TTN cases	Null hypothesis rejected	8,11,29
H2: Perihilar streaking, fissural fluid, effusion and preserved lung volume are more prevalent in TTN	Partially supported	Cardinal in TTN and supported by serial data (regular pleural line, no consolidation in 99.5% of scans), but individually non-specific; fluid gradient sign present in only 47.6%	Null hypothesis rejected for the composite pattern; not rejected for any single sign in isolation	12,49,50

Hypothesis	Verdict	Principal supporting evidence	Statistical inference	Ref.
H3: Radiographic severity relates to outcome in a graded, dose-response manner	Supported in the preterm lung; not supported in the mature term lung	CXR score OR 1.777 per point at 24 h and 1.756 at day 7 for BPD; GA-severity $p = 0.002$; but AUC 0.539 for surfactant need in term MAS	Null hypothesis rejected in preterm populations; not rejected in term populations	28,29,31
H4 (implicit): Chest radiography alone is sufficient for the early RDS/TTN decision	Not supported	Sensitivity 38.9% for predicting NIV failure; AUC 0.80 versus 0.94 for surfactant prediction; reported misclassification 62–77%; deep-learning F1 only 70.84% for TTN	Null hypothesis of sufficiency rejected	7,10,11,22

DISCUSSION

Principal Findings

This synthesis of 29 primary studies, encompassing more than 350,000 neonates and over 43,000 individually labelled chest radiographs, yields four principal findings. First, the radiographic differentiation of respiratory distress syndrome from transient tachypnea of the newborn rests overwhelmingly on a single high-value discriminator — consolidation with air bronchograms — which was observed in none of 528 and none of 228 neonates with TTN across two independent large series and which therefore functions as a near-absolute rule-out for TTN when present. Second, the remaining classical features are individually weak: ground-glass opacification was present in 83.6%

and air bronchograms in 70.9% of clinically suspected RDS, meaning that between one in six and one in three affected infants will lack the sign on which the diagnosis is conventionally taught to rest, while the pathognomonic fluid-gradient appearance of TTN was present in fewer than half of affected infants. Third, radiographic severity, when expressed as a continuous score, is a genuine graded prognostic biomarker in the preterm lung, with a stable and statistically robust per-unit relationship to bronchopulmonary dysplasia at two separate time points. Fourth, and decisively, the plain radiograph alone is insufficient as the sole determinant of early surfactant policy, achieving a sensitivity of 38.9% for predicting non-invasive ventilation failure and an area under the curve of 0.80 for surfactant prediction against 0.94 for quantitative bedside imaging.^{7,8,10,11,28,29}

Interpretation of the Feature-Level Findings

The pathophysiological logic of the discriminative hierarchy is coherent and deserves emphasis, because it explains why the empirical findings take the shape they do. Surfactant deficiency raises alveolar surface tension, producing widespread end-expiratory alveolar collapse; the collapsed acini become radiodense while the conducting airways remain patent and air-filled, and it is precisely this juxtaposition of airless parenchyma against air-containing bronchi that generates the air bronchogram. Transient tachypnea, by contrast, is a disorder of the interstitial and perilymphatic compartments in a lung whose alveoli are structurally mature and remain patent; there is therefore no collapsed alveolar background against which a bronchus can be silhouetted, and the air bronchogram does not arise. The empirical absence of consolidation with air bronchograms in TTN is thus not a statistical accident of the samples studied but a direct radiographic expression of the difference in the compartment involved.^{8,11,16}

The same logic explains the weakness of the TTN-associated features. Interstitial fluid, perihilar vascular prominence and fissural fluid are the radiographic consequences of increased extravascular lung water, and increased extravascular lung water is not the exclusive property of TTN — it accompanies pneumonia, early sepsis, patent ductus arteriosus, fluid overload, congenital heart disease and the recovery phase of RDS itself. This is why an authoritative commentary on the field observed more than a decade ago that perihilar streaking and other evidence of increased lung fluid are commonly observed in TTN but are not specific, and that the diagnosis is frequently made only

after exclusion of other disorders. The finding from serial multicentre imaging that the fluid-gradient sign can also appear during the recovery phase of severe TTN, RDS, meconium aspiration syndrome and pneumonia formalises this concern: a sign that is highly specific at one point in the illness may become non-specific at another, and the radiograph carries no intrinsic timestamp.^{8,12,49,50}

An underappreciated corollary follows for the modern neonatal unit. Because non-invasive respiratory support is now applied from the delivery room in most preterm infants, the radiograph is frequently obtained after continuous positive airway pressure has already recruited a proportion of the collapsed alveoli. Recruitment attenuates the granular opacification and may abolish the air bronchogram, converting a radiographically classical RDS into a radiographically ambiguous interstitial picture indistinguishable from TTN. The classical four-stage grading system was described in an era of unassisted spontaneous breathing and has never been formally revalidated under contemporary early-CPAP practice; the observation that mild RDS is easy to misdiagnose as TTN, with ground-glass opacity mistaken for confluent interstitial artefact, has been made explicitly in the grading literature. This is, in our view, the single most important unexamined assumption underlying current radiographic practice.^{46,51}

The Diagnostic Accuracy Findings in Context

The head-to-head accuracy data must be read with care, because they are systematically biased against the radiograph by the architecture of the studies that generated them. In almost every included comparative study, the chest radiograph contributed to the composite clinical reference diagnosis against which imaging performance was judged; this incorporation bias should, if anything, inflate apparent radiographic accuracy. That the radiograph nonetheless underperformed — sensitivity 38.9% for predicting intubation, area under the curve 0.80 versus 0.94 for surfactant prediction, 0.539 versus 0.999 in a term population — indicates that the true differential is likely to be larger, not smaller, than the published figures suggest. Conversely, the one study in which the imaging read was performed by a fully blinded external reader against a reference standard that excluded that modality achieved a sensitivity of 95.6% and specificity of 94.4% for RDS and 93.3% and 96.5% for TTN, establishing that very high accuracy is attainable when reading conditions are rigorous. The gap

between routine and optimal performance is therefore substantially a gap of process, not of physics.^{6,7,10,31}

The frequently quoted misdiagnosis rate of 62% to 77% for traditional clinical plus radiographic diagnosis warrants particular caution. It derives from a single research group with a strong prior commitment to an alternative modality, is reported in abstract form, and was generated in a unit that subsequently abandoned radiography altogether; it should be regarded as an upper bound rather than a point estimate. Nevertheless, it is directionally corroborated by wholly independent evidence: a systematic review of 23 studies and 2,245 newborns found that 43% concluded that alternative methods surpassed radiography for differential diagnosis, severity assessment and prediction, and the deep-learning literature independently establishes an F1 score of only 70.84% for TTN against expert consensus labels. Three methodologically unrelated lines of evidence converging on the same conclusion is a stronger warrant than any of them alone.^{11,22,38}

Interpretation of the Dose–Response Findings

The dose–response analysis is the most novel element of this review and its findings are, we believe, of direct practical consequence. That a per-unit increment in a continuous radiographic score should raise the odds of bronchopulmonary dysplasia by approximately 77% at 24 hours and 76% at day 7, with overlapping confidence intervals and closely concordant point estimates at two widely separated time points, is a pattern that is very difficult to explain by confounding or by threshold effects. It indicates that the radiographic score is measuring a continuously distributed underlying quantity — the extent of the aerated lung — and that this quantity is causally upstream of chronic lung injury. The parallel gestational-age and birth-weight gradients, and the inverse labour-duration gradient in TTN, situate this finding within a coherent biological framework in which the same underlying variable, the adequacy of alveolar surface-active material and of fluid clearance, generates both the radiographic appearance and the clinical trajectory.^{3,28,29,34}

The negative finding is equally instructive and should not be glossed over. In a term population with meconium aspiration syndrome, radiographic grade achieved an area under the curve of 0.539 for surfactant prediction — statistically indistinguishable from a coin toss — against 0.999 for a quantitative aeration score. The implication is that radiographic grading carries graded

prognostic information only where the underlying pathology is a graded deficiency of surfactant in an immature lung, and loses that information entirely where the pathology is inflammatory, obstructive or inactivating rather than deficient. Radiographic grading should therefore be applied to the preterm surfactant-deficient lung, for which it was designed, and should not be extended uncritically to the term infant with respiratory failure of other cause. This is a boundary condition that current practice does not observe.³¹

Comparison with Systematic Reviews and Meta-Analyses

The findings of this review are consonant with the published secondary literature, which was excluded from the primary synthesis but is appropriate for triangulation. A meta-analysis of seven studies and 1,514 participants reported a pooled sensitivity of 0.67 (0.63–0.71) and specificity of 0.97 (0.95–0.98) for the ultrasonographic diagnosis of TTN, with a summary area under the curve of 0.9906 — a specificity-dominant profile that mirrors the pattern observed for radiography in the present analysis, in which cardinal signs are highly specific but insufficiently sensitive. A systematised review of 37 studies confirmed that respiratory problems in newborns are principally studied with chest radiography while ultrasound is increasingly proposed as an alternative. An international expert consensus derived from a three-round Delphi process among 28 panellists reported sensitivities of 92–99% and specificities of 95–97% for the ultrasonographic diagnosis of neonatal RDS. Most directly relevant, a systematic review focused on low-resource birth scenarios found that all 23 included studies used radiography to diagnose RDS and 91% used it to grade severity, but that 43% found alternative methods superior across several domains, while seven studies (30%) maintained that radiography remains irreplaceable — a division of opinion that this review resolves in favour of a complementary rather than a substitutive relationship.^{38,39,40,47}

Clinical Implications

Five practical implications follow. First, when consolidation with air bronchograms is present on a neonatal chest radiograph, TTN can be excluded with a very high degree of confidence and the infant should be managed as RDS. Second, when it is absent, RDS cannot be excluded, particularly in an infant already receiving distending pressure, and the decision to withhold surfactant should not rest on the radiograph alone. Third, in the preterm infant, formal radiographic severity scoring should

be recorded rather than discarded, because it carries independent, graded prognostic information regarding bronchopulmonary dysplasia that adds to birth weight and ventilation duration in a validated model with an area under the curve of 0.873. Fourth, in the term infant with respiratory failure, radiographic grade should not be used to guide surfactant decisions. Fifth, where bedside ultrasonography is available, the two modalities should be used complementarily — ultrasound for rapid aetiological triage and serial monitoring of aeration, radiography for confirmation, for the detection of air leak and of line and tube position, and for the situations in which ultrasound is uninformative.^{10,28,31,48}

For units in low- and middle-income settings, where radiography is often the only available modality, the implications are different in emphasis but not in substance. The evidence supports continued reliance on the radiograph, but with three modifications: structured reporting of the cardinal features rather than a global impression; explicit recording of severity grade, which has demonstrable prognostic value; and awareness that the absence of the cardinal features does not exclude RDS. The Ugandan cohort data, in which seven-day mortality reached 19.3% and delayed presentation beyond six hours conferred an adjusted risk ratio of 1.72 for death, indicate that in such settings the dominant determinant of outcome is timeliness of recognition and referral rather than refinement of imaging.^{24,38}

Research Implications

Four research priorities emerge. First, a prospective study is required in which neonatal chest radiographs are read by multiple blinded readers with no access to clinical data, against a reference standard that excludes radiography — for example, surfactant response, stable microbubble rating, or expert panel adjudication using ultrasound and clinical course — so that the true, unbiased accuracy of the radiograph for the RDS–TTN distinction can finally be established. Second, the four-stage grading system requires formal revalidation of its interobserver reliability under contemporary early-CPAP practice, with reporting of kappa statistics that are at present essentially absent from the literature. Third, the promising computational findings — that rib suppression raises the area under the curve from 0.556 to 0.781, that optimised contrast enhancement most improves TTN classification, and that pixel-intensity analysis reveals regional heterogeneity invisible to the eye —

should be advanced to prospective clinical evaluation, since they offer improved performance at zero additional radiation cost. Fourth, the dose–response relationship between radiographic score and bronchopulmonary dysplasia should be replicated in an independent multinational cohort and, if confirmed, incorporated into risk-stratification tools.^{25,26,27,28}

Strengths of This Review

This review has several methodological strengths. The literature search was executed through a federated academic search platform indexing more than 200 million peer-reviewed records with medical-mode filtering and explicit exclusion of preprints, and every included record was individually retrieved and verified. Eight thematically distinct search strings were used to capture the radiological, diagnostic-accuracy, prognostic, epidemiological and computational literatures, which are largely non-overlapping and would have been incompletely captured by a single string. Fourteen outcome domains were prespecified, substantially exceeding the conventional scope of reviews in this field. Risk of bias was assessed with three design-appropriate instruments rather than one instrument applied indiscriminately. Systematic reviews and meta-analyses were rigorously segregated from primary studies, avoiding the double-counting of participants that afflicts many syntheses in this area. Finally, the formal dose–response analysis, and the incorporation of large-scale deep-learning evidence as an operator-independent measure of phenotypic separability, are to our knowledge without precedent in this literature.

CONCLUSION AND RECOMMENDATIONS

Conclusion

The neonatal chest radiograph discriminates respiratory distress syndrome from transient tachypnea of the newborn with high specificity but insufficient sensitivity. Consolidation with air bronchograms is an effectively RDS-specific finding, absent from every one of 528 and 228 neonates with TTN in two independent large series, and its presence permits confident exclusion of TTN; ground-glass or reticulogranular opacification (83.6%), air bronchograms (70.9%) and reduced lung volume (66.4%) constitute the cardinal RDS triad, while a regular pleural line without consolidation, present in 99.5% of serial examinations, constitutes the radiological signature of TTN. However, up to one in three infants with RDS lacks the cardinal air bronchogram, the pathognomonic fluid-gradient

appearance of TTN is present in fewer than half of affected infants, and the historical misclassification rate of clinical plus radiographic diagnosis has been reported at 62–77%. In head-to-head comparison the radiograph achieved a sensitivity of 38.9% for predicting non-invasive ventilation failure and an area under the curve of 0.80 for surfactant prediction, against 88.9% and 0.94 for quantitative bedside imaging; deep-learning classification against twenty-neonatologist consensus labels achieved an F1 score of 90.30% for RDS but only 70.84% for TTN, confirming from an operator-independent standpoint that the TTN phenotype is the less radiographically separable of the two.^{8,10,11,12,22,29}

Radiographic severity is nevertheless a genuine, graded prognostic biomarker in the preterm lung. Each one-point increment of the chest radiograph score raised the odds of bronchopulmonary dysplasia by 77.7% within 24 hours of birth (odds ratio 1.777, 95% confidence interval 1.253–2.521) and by 75.6% at day 7 (odds ratio 1.756, 1.264–2.440), with parallel monotonic gradients across gestational-age and birth-weight strata and an inverse gradient of labour exposure in TTN. This dose–response relationship is confined to the immature, surfactant-deficient lung: in term infants with respiratory failure of other cause, radiographic grade achieved an area under the curve of 0.539 for surfactant prediction and carries no graded information. The overall conclusion is therefore that the chest radiograph should be retained as a confirmatory, prognostic and complication-detecting instrument, and relinquished as the sole first-line arbiter of the early surfactant decision.^{3,28,29,31,34}

Recommendations

Recommendations for clinical practice

- Interpret consolidation with air bronchograms as an effectively RDS-specific finding; where present, exclude TTN and manage as RDS.
- Do not interpret the absence of the cardinal features as excluding RDS, particularly in infants already receiving continuous positive airway pressure, in whom alveolar recruitment attenuates the classical appearance.
- Record a formal radiographic severity grade or score in every preterm infant with respiratory distress, and incorporate it into bronchopulmonary dysplasia risk assessment alongside birth weight and duration of invasive ventilation.

- Do not use radiographic grade to guide surfactant decisions in term infants with respiratory failure of non-surfactant-deficient aetiology.
- Where quantitative bedside lung ultrasound is available, use it for rapid aetiological triage and serial aeration monitoring, and reserve radiography for confirmation, for the detection of air leak, and for verification of line and tube position.
- Adopt structured radiographic reporting that names each cardinal feature explicitly rather than issuing a global impression, and record the postnatal age and respiratory support in place at the time of the exposure, since both materially alter interpretation.
- Minimise cumulative radiation by avoiding repeat radiography where a bedside modality can answer the clinical question, particularly in extremely preterm infants undergoing serial imaging.

Recommendations for health systems and resource-limited settings

- Retain chest radiography as the primary imaging modality where ultrasound is unavailable, but pair it with structured feature reporting and explicit severity grading, both of which are achievable without additional equipment.
- Prioritise investment in timeliness of recognition and referral over investment in imaging refinement, since delayed presentation beyond six hours of life conferred an adjusted risk ratio for death of 1.72 in a prospective preterm cohort.
- Invest in structured training in neonatal lung ultrasound where feasible, given a median time to diagnosis of 9.5 minutes versus 50 minutes for radiography and the elimination of radiation exposure.

Recommendations for future research

- Conduct a prospective multicentre study with fully blinded multi-reader radiographic interpretation against a reference standard that excludes radiography, in order to establish the unbiased accuracy of the chest radiograph for the RDS–TTN distinction.
- Formally revalidate the four-stage radiographic grading of RDS under contemporary early-CPAP practice, reporting interobserver kappa statistics, which are at present essentially absent from the literature.

- Advance computational post-processing — rib suppression, optimised contrast enhancement and quantitative pixel-intensity analysis — from retrospective proof of concept to prospective clinical evaluation, given demonstrated performance gains at zero additional radiation cost.
- Replicate the dose–response relationship between radiographic score and bronchopulmonary dysplasia in an independent multinational cohort, and if confirmed, embed it within validated risk-stratification instruments.
- Assemble and share multinational, multi-vendor, expert-labelled neonatal chest radiograph datasets to permit external validation of classification algorithms beyond their country of origin.

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