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REVIEW

Global, Regional and National Trends in the Burden of Neonatal Respiratory Failure and essentials of its diagnosis and management from 1992 to 2022: a scoping review

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Abstract

Neonatal respiratory failure (NRF) is an emergency which has not been examined extensively. We critically synthesized the contemporary in-hospital prevalence, mortality rate, predictors, aetiologies, diagnosis and management of NRF to better formulate measures to curb its burden. We searched MEDLINE and Google Scholar from 01/01/1992 to 31/12/2022 for relevant publications. We identified 237 papers from 58 high-income and low-and middle-income countries (LMICs). NRF prevalence ranged from 0.64 to 88.4% with some heterogeneity. The prevalence was highest in Africa, the Middle East and Asia. Globally as well as in Asia and the Americas, respiratory distress syndrome (RDS) was the leading aetiology of NRF. Neonatal sepsis was first aetiology in Africa, whereas in both Europe and the Middle East it was transient tachypnoea of the newborn. Independent predictors of NRF were prematurity, male gender, ethnicity, low/high birth weight, young/advanced maternal age, primiparity/multiparity, maternal smoking, pregestational/gestational diabetes mellitus, infectious anamneses, antepartum haemorrhage, gestational hypertensive disorders, multiple pregnancy, caesarean delivery, antenatal drugs, foetal distress, APGAR score, meconium-stained amniotic fluid and poor pregnancy follow-up. The NRF-related in-hospital mortality rate was 0.21–57.3%, highest in Africa, Asia and the Middle East. This death toll was primarily due to RDS globally and in all regions. Clinical evaluation using the Silverman-Anderson score was widely used and reliable. Initial resuscitation followed by specific management was the common clinical practice.

Conclusion: NRF has a high burden globally, driven by RDS, especially in LIMCs where more aggressive treatment and innovations, preferably subsidized, are warranted to curb its alarming burden.

What is Known:

- *Neonatal respiratory failure is a frequent emergency associated with a significant morbidity and mortality, yet there is no comprehensive research paper summarizing its global burden.*
- *Neonatal respiratory failure needs prompt diagnosis and treatment geared at improving neonatal survival.*

What is New:

- *Neonatal respiratory failure has an alarmingly high global burden largely attributed to Respiratory distress syndrome. Low resource settings are disproportionately affected by the burden of neonatal respiratory failure.*
- *Independent preditors of neonatal respiratory failure are several but can be classified into foetal, maternal and obstetrical factors. An illustrative pedagogical algorithm is provided to facilitate diagnosis and management of neonatal respiratory failure by healthcare providers.*

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Keywords Neonate · Respiratory failure · Epidemiology · Mortality · Diagnosis · Management

Abbreviations

95% CI	95% Confidence interval
ACOG	American College of Obstetricians and Gynaecologists
AAP	American Academy of Paediatrics
aOR	Adjusted odds ratio
aRR	Adjusted risk ratio
AUC	Area under the curve
BPD	Bronchopulmonary dysplasia
CS	Caesarean section
CBC	Complete blood count
CDH	Congenital diaphragmatic hernia
CHD	Congenital heart diseases
CPAP	Continuous positive airway pressure
CRP	C-reactive proteins
CT-scan	Computerized tomography scan
ECMO	Extracorporeal membrane oxygenation
FiO_2	Fraction of inspired oxygen
GA	Gestational age
GDM	Gestational diabetes mellitus
IMV	Invasive mechanical ventilation
iNO	Inhaled nitric oxide
IV	Intravenous
IUGR	Intra-uterine growth retardation
HAS	Haute Autorité de Santé
HMD	Hyaline membrane disease
HIE	Hypoxic ischaemic encephalopathy
LBW	Low birth weight
LMICs	Low- and middle-income countries
MAS	Meconium aspiration syndrome
MSAF	Meconium stained amniotic fluid
NA	Not available
NARDS	Neonatal acute respiratory distress syndrome
NI	Neonatal infection
NICU	Neonatal intensive care unit
NIHFV	Non-invasive high-frequency ventilation
NIV	Non-invasive ventilation
NRD	Neonatal respiratory distress
NRP	Neonatal Resuscitation Program
NRF	Neonatal respiratory failure
NRFS	Non-reassuring foetal status
PaO2	Partial pressure of oxygen
PaCO2	Partial pressure of carbon dioxide
PGDM	Pregestational diabetes mellitus
PPHN	Persistent pulmonary hypertension
PROM	Prolonged rupture of membranes
OI	Oxygenation index
OR	Odds ratio
OAWOWTE	Oesophageal atresia with or without tracheoesophageal fistula
RCT	Randomized controlled trial
RDS	Respiratory distress syndrome
ROB	Risk of bias assessment
RR	Risk ratio
TTN	Transient tachypnoea of the newborn
TEF	Tracheoesophageal fistula
SSA	Sub-Saharan Africa
SCBU	Special baby care unit

Background

Rationale

The term neonatal respiratory failure (NRF), formerly termed neonatal respiratory distress, applies to an inability of the newborn infant to maintain breathing homeostasis with resultant dysfunction in ventilation-perfusion mismatch and gaseous exchange. Its urgency translates into a quick diagnosis and prompt management of its aetiology [1, 2]. NRF is one of the most common clinical manifestations of disease in the early neonatal period and a common neonatal emergency worldwide [1–4].

A tremendous decrease in the NRF case fatality rate has occurred over the last seven decades in high-income countries (HICs) [5]. In 1997, the mortality rate due to NRF in India was between 40 and 60%, which was equivalent to the rate in the USA during the 1950s and 1960s [5]. This improvement in neonatal outcomes due to NRF in HICs is related to several improvements in neonatal units and neonatal intensive care units (NICUs), still scarce or non-existent in low- and middle-income countries (LMICs) [5, 6]. Hence, to reduce the high NRF case fatality rate in resource-constraint settings, it is recommended to prevent NRF through early screening of its predictors geared towards anticipation of preventive and curative management of its aetiologies [3, 7–9]. There are several aetiologies of NRF and can either be categorized as medical and surgical causes, with the medical causes being predominant [2, 10]. NRF may be due to self-limiting illnesses like transient tachypnoea of the newborn or could be the first clinical manifestation of life-threatening sepsis, perinatal asphyxia, congenital malformations or neonatal acute respiratory distress syndrome [7, 11], which put the vital prognosis of the neonate at risk.

After an extensive literature search, we did not find a comprehensive summary addressing this potentially lethal neonatal emergency, which continues to plague LMICs in particular where it is a major contributor to the neonatal mortality ratio [3, 11, 12]. This contributes in hindering LMICs to achieve the target of "fewer than 10 deaths per 1000 live births by 2035" stipulated in Sustainable Development Goal 3 [13]. Furthermore, NRF has been inconsistently described in

LMICs where healthcare providers like neonatologists, paediatricians, obstetricians, foetal medicine experts, intensivists, paediatric anaesthesiologists, general practitioners and midwives should be fully aware of the diagnostic and therapeutic approach to NRF. Consequently, the emerging scope of future research in this field has recently been tailored to the description of the epidemiology, precipitating factors, diagnosis, management and outcomes of NRF [11]. Here, big data studies like scoping reviews constitute a source of good scientific evidence which may serve as a reliable asset to shape recommendations, guidelines and daily clinical practice.

Objectives

Hence, we undertook this scoping review to critically summarize at a global scene: (i) the prevalence/incidence and aetiologies of NRF, (ii) the in-hospital NRF-related mortality rate and leading aetiologies of mortality, (iii) the risk factors associated with NRF, (iv) diagnostic approaches to NRF and (v) the management of NRF. The research goal of this scoping review was not to assess these identified relevant studies for methodological rigour, but rather make a broad comprehensive global overview of NRF, highlight gaps in the contemporary literature and generate directions for future research. Its findings are expected to help formulate public health interventions to curb the morbidity and mortality associated with NRF worldwide.

Materials and methods

This scoping review was carried out and reported in conformity with the Preferred Reporting Items for Systematic Reviews and Meta-analysis Extension for Scoping Reviews (PRISMA-ScR) [14] and is available as Supplementary File 1. We adopted the methodological framework for scoping reviews developed by Arksey and O'Malley which entails identifying the research question, searching for relevant studies, selecting studies, charting the data and collating, summarizing and reporting the results [15].

Data source, study eligibility criteria and search strategy

We conducted a digital search in MEDLINE and Google Scholar, between January 01, 1992 and December 31, 2022. We included observational studies, experimental studies and reviews that reported sufficient data on the prevalence/incidence, mortality, predictors, aetiologies, diagnosis and management of NRF in the general neonatal population (age 0–28 days old). The search strategy used the following keywords: "neonate", "respiratory failure", "prevalence", "mortality", "risk factor", "aetiologies", "diagnosis" and "management", cross-referenced with the names of all countries to yield the maximum possible number of research articles (Table 1). No language and geographical restrictions were applied to the search. Retrieved records were independently screened by abstract and title by two independent investigators. Subsequently, they screened relevant full texts for articles that reported the prevalence/incidence, mortality, risk factor, aetiologies, diagnosis and management of NRF. The references of the included articles were scrutinized as potential sources for additional studies. We excluded commentaries, experts' opinions, editorial letters, case reports and case series with less than 30 participants. For more homogeneity on prevalence, aetiological and mortality NRF data, exclusion was also applied to research work carried out in neonates selected based on the presence of NRF-specific diseases or conditions like respiratory distress syndrome (RDS), transient tachypnoea

Table 1 Search strategy for MEDLINE and adaptability to all databases

Search term	Search terms
#1	Neonatal [tiab] OR Neonat* OR Newborn[MESH] OR Baby
#2	Respiratory failure [MESH] OR Respiratory distress [MESH] OR Respiratory disease[tiab] OR Respiratory disorder[tiab] OR Respiratory morbidity[tiab] OR Respiratory condition[tiab] OR Respiratory difficulty[tiab] OR Respiratory problem[tiab] OR Respiratory complication[tiab] OR Respiratory compromise[tiab] OR Breathing difficulty[tiab] OR Breathing problem [tiab] OR Breathlessness[tiab] OR Abnormal breathing [tiab]
#3	Prevalence [MESH] OR Incidence [MESH] OR Mortality [MESH] OR Profile[tiab] OR Spectrum[tiab] OR Fatality[tiab] OR Neonatal Death[tiab] OR Risk factors[tiab] OR Predictors[tiab] OR Determinants[tiab] OR Etiologies[tiab] OR Aetiologies[tiab] OR Causes[tiab] OR Management[tiab] OR Treatment[tiab]
#4	#1 AND #2 AND #3 AND #4
#5	Limits: 01/01/1992 to 31/12/2022 with no language restriction

of the newborn (TTN), COVID-19 and neonates delivered to NRF high-risk pregnancies (e.g. gestational diabetes mellitus, COVID-19-infected mothers).

Data extraction and analysis

A standardized and pre-tested data extraction form was used by two reviewers to independently chart the following data from each included study: bibliometric information (the name of the first author, the country where the study was conducted and the year of publication), study setting, diagnostic criteria used for NRF, the sample size of the study, the proportion of male, the mean gestational age (GA), the GA range, prevalence or incidence, in-hospital mortality rate, risk factors, aetiologies, diagnostic criteria (clinical, laboratory and imaging diagnoses) and management of NRF. For more quality assurance, all extracted and charted data were reviewed for accuracy and completeness. Any discrepancies in a citation were solved through consensus. Two reviewers scrutinized eligible studies for the quality of their methods using the Hoy et al. tool [16], the SPIRIT 2013 tool [17] and the AMSTAR 2 tool [18] for epidemiological studies, clinical trials and systematic reviews, respectively. This risk of bias assessment was for a rough appraisal of the scientific evidence of the final results of the scoping review and not for strict methodological rigour. Sub-analyses of the most frequent global aetiologies of NRF and the deadliest global aetiologies were performed independently by two authors via the summation of the number of affected neonates of each NRF aetiology per study. Finally, using data retrieved from a myriad of epidemiological studies, interventional studies, narrative or scoping reviews and systematic reviews, the ensuing results present a narrative synthesis of the most up-to-date and key literature regarding neonatal respiratory failure.

Table 2 Characteristics of the 237 papers included in the review

Characteristic of the study	Number of papers (percentage)
Year of publication	
1992–2001	22 (9.3%)
2002–2011	49 (20.7%)
2012–2022	166 (70%)
Region	
Asia (9 countries)	91 (38.4%)
The Americas (8 countries)	44 (18.6%)
Europe (13 countries)	42 (17.7%)
Africa (19 countries)	40 (16.8%)
Middle East (7 countries)	17 (7.2%)
Oceania (2 countries)	03 (1.3%)
Study design	
Cross-sectional	102 (47.6%)
Case–control	07 (3.3%)
Cohort	84 (30.2%)
Clinical trial	04 (1.9%)
Narrative or scoping review	15 (6.6%)
Systematic review and meta-analysis	15 (6.1%)
Guidelines	10 (4.3%)
Study content[a]	
Prevalence studies	99 (41.8%)
Aetiological studies	110 (46.4%)
NRF predictors or risk factors	68 (28.7%)
Diagnosis and management	138 (58.3%)
Risk of bias assessment	
Low	152 (64.1%)
Moderate	63 (26.6%)
High	22 (9.3%)

NRF, neonatal respiratory failure

[a]78 papers had more than one study content

Results

Flow of studies through the scoping review

Characteristics of the included studies

We included 237 research articles from over 1000 centres across 58 countries around the globe (Supplementary file 2). The vast majority of papers emanated from Asia (38.4%), the Americas (18.6%), Europe (17.7%) and Africa (16.8%), see Table 2. More precisely, India, USA, China and France accounted for 50, 33, 20 and 12 citations, respectively, see Fig. 1. The majority of the papers were published within the last decade (70%) (Fig. 2). There were 15 systematic reviews, 15 narrative reviews and 10 guidelines (Table 2). Overall, the risk of bias was rated low in 152 (64.1%), moderate in 63 (26.6%) and high in 22 (9.3%) (Table 2).

Prevalence of neonatal respiratory failure

The prevalence of NRF was obtained from 99 studies involving 1,474,404 neonates from 36 countries (Table 3). Overall, the global prevalence of NRF ranged from 0.64 to 88.4%. Across regions, the prevalence varied as follows: Africa 0.64–88.4% [3, 12, 21, 34, 36, 43, 45, 48, 53, 56, 58, 66–68, 70, 72, 74, 77, 79, 81, 83, 85, 93, 95, 99, 100, 109, 114], Middle East 2.1–84.8% [7, 30, 31, 46, 49, 57, 88, 91, 92, 94, 101, 111], Asia 0.9–60% [20, 24, 25, 33, 41, 44, 52, 54, 55, 59–65, 69, 71, 73, 75, 78, 80, 82, 84, 86, 87, 89, 90, 97, 102–108, 110, 112–116], the Americas 2.1–21% [26–29,

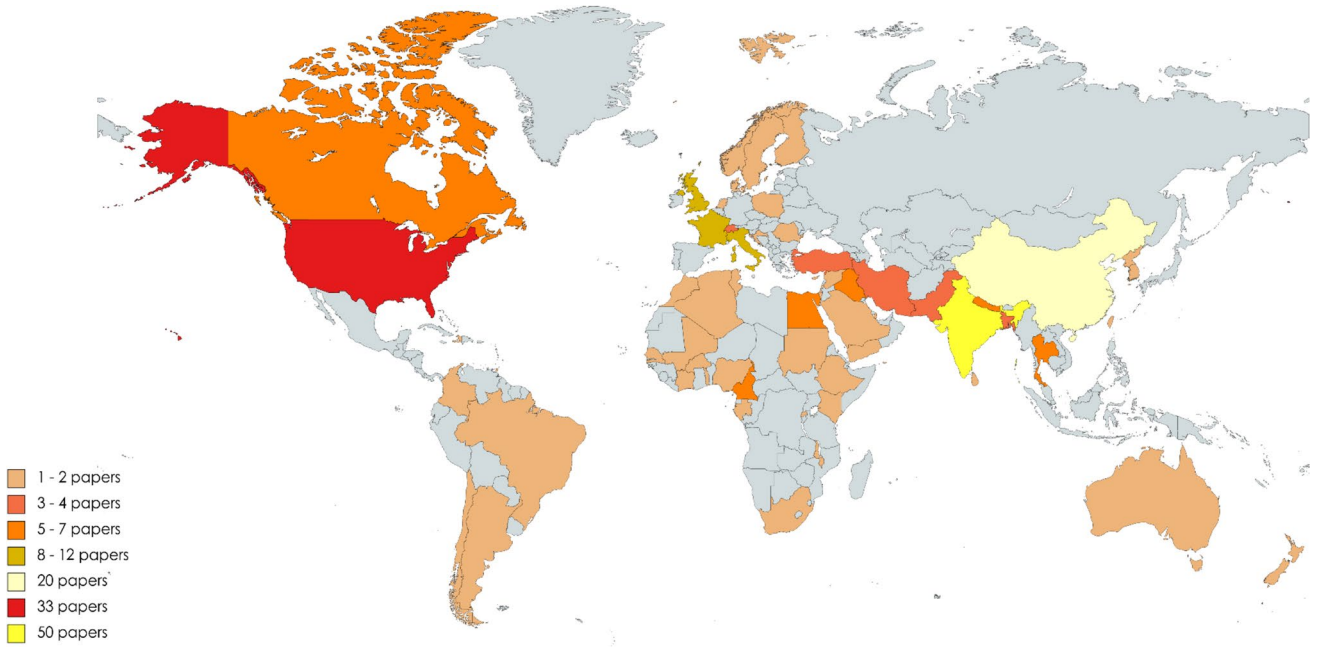

Fig. 1 Number of research articles on neonatal respiratory failure per country in the world between 1992 and 2022 (created with mapchart.net)

39, 42] and Europe 1.2–19.8% [6, 19, 22, 23, 32, 35, 37, 40, 47, 51, 76]. More national representative prevalence data indicate that the highest NRF prevalence rates were in Egypt 88.4% [45], Iraq 84.8% [94] and Saudi Arabia 78.5% [88], whereas the lowest rates were in South Africa 0.64% [21], China 0.9% [59] and Sweden 1.2% [51], see Table 3.

Fig. 2 Number of publications per year between 1992 and 2022

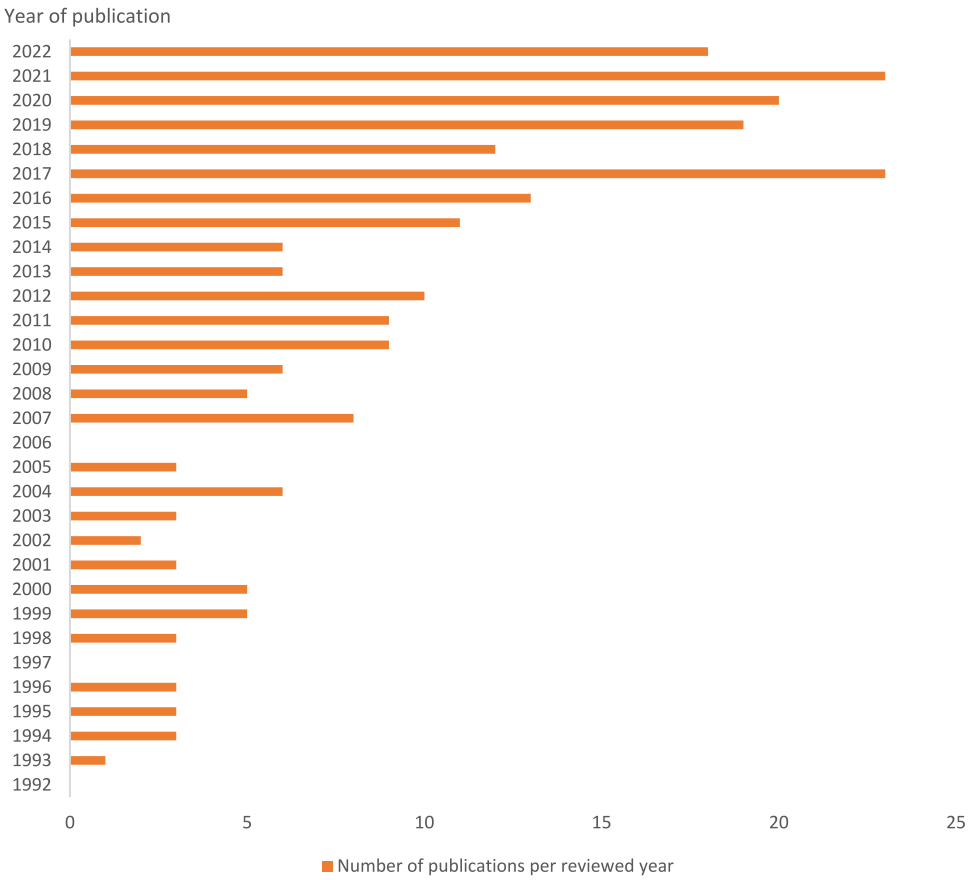

Table 3 Global trends in the prevalence of neonatal respiratory failure

First name of author, publication year	Country	Study design	Setting (number of sites if multicentre)	Diagnostic criteria of NRD	Sample size (*n*)	Male (%)	Mean GA (weeks)	Prematurity rate (%)	CS rate (%)	Prevalence (%)	Mortality rate (%)	ROB
Bonafe, 1996 [19]	Italy	Cohort	NICU, neonatal unit and maternity (16)	NR	7588	64.1	NR	5	69	3.3	8.4	Moderate
Kumar, 1996 [20]	India	Cohort	Maternity	One or more of these clinical signs for > 2 h: RR ≥ 60/min, grunting, intercostal or subcostal retraction	4505	NR	NR	20.7	NR	6.7	19	Low
Rinjswijk, 1996 [21]	South Africa	Cross-sectional	Maternity (21)	Tachypnoea plus any of central cyanosis, grunting, nasal flaring, subcostal or intercostal retractions	7539	NR	NR	NR	NR	0.64	0.21	Low
Rubaltelli, 1998 [22]	Italy	Cohort	Neonatal unit (65)	NR	17,192	NR	NR	7.3	26.7	2.8	15.8	Low
Rubaltelli, 1998 [23]	Italy	Cohort	Neonatal unit (65)	NR	63,537	51.6	NR	8	37	2.2	14.6	Low
Nagendra, 1999 [24]	India	Cross-sectional	Maternity	Two or more of RR > 60/min, recessions, nasal flaring, expiratory grunting and cyanosis	1986	52.1	NR	66	NR	2.42	NR	Moderate
Bhakoo, 2000 [25]	India	Cross-sectional	Neonatal unit	Two or more of RR ≥ 60/min, grunting, retractions	243	NR	NR	NR	NR	60	49.3	Low
Wiswell, 2000 [26]	USA	Clinical trial	Neonatal unit (12)	NR	2094	50.3	NR	NR	21.7	7.1	0.24	Low

Table 3 (continued)

First name of author, publication year	Country	Study design	Setting (number of sites if multicentre)	Diagnostic criteria of NRD	Sample size (*n*)	Male (%)	Mean GA (weeks)	Prematurity rate (%)	CS rate (%)	Prevalence (%)	Mortality rate (%)	ROB
Agrawal, 2003 [27]	USA	Cross-sectional	NICU and neonatal unit (2)	One or more of RR > 60 breaths/min, retractions, nasal flaring or grunting	2805	55	NR	NR	18	21	3.3	Low
Ali, 2003 [28]	Trinidad and Tobago	Cross-sectional	NR	NR	5062	59.8	NR	20.6	NR	3.4	33	High
Loebel, 2004 [29]	USA	Cohort	Maternity	NR	1408	NR	NR	NR	34.1	2.6	NR	Moderate
Ersch, 2007 [6]	Switzerland	Cohort	NICU and neonatal unit (43)	Two or more of RR > 60 breaths/min, expiratory grunting, nasal flaring, retractions or cyanosis	315,279	NR	NR	NR	NR	1.9 to 3.8	15.5 to 3.5	Low
Hameed, 2007 [30]	Iraq	Cross-sectional	NICU	NR	2312	68	NR	0	70	2.1	4	Moderate
Dehdashtian, 2008 [31]	Iran	Cross-sectional	Maternity (4)	NR	1000	04	NR	0	50	3.5	2.8	High
Hansen, 2008 [32]	Denmark	Cohort	Maternity	NR	34,458	NR	NR	0	8.5	1.8	NR	Low
Qian, 2008 [33]	China	Cohort	NICU (23)	Requirement of respiratory support for ≥ 24 h during the first 7 days of life	13,070	75.5	34.9 ± 4.1	63.3	43.8	13.2	32.1	Low
Chakrouni, 2009 [34]	Morocco	Cross-sectional	NICU and neonatal unit (2)	NR	765	63.8	NR	0	28	9.8	33.3	High
De Luca, 2009 [35]	Switzerland	Cohort	Maternity	NR	56,549	50	NR	NR	13.3	13.1	NR	Low
Diakite, 2009 [36]	Mali	Cross-sectional	Neonatal unit	NR	1072	57	NR	19.8	NR	12.9	57.3	Moderate
Champion, 2010 [37]	France	Cross-sectional	Maternity	NR	186	47.3	31.2 ± 5.8	100	43.2	17.2	NR	High

Table 3 (continued)

First name of author, publication year	Country	Study design	Setting (number of sites if multicentre)	Diagnostic criteria of NRD	Sample size (*n*)	Male (%)	Mean GA (weeks)	Prematurity rate (%)	CS rate (%)	Prevalence (%)	Mortality rate (%)	ROB
Qian, 2010 [38]	China	Cohort	NICU	Two or more of tachypnoea, chest retraction, nasal flaring, expiratory grunting and cyanosis	13,059	72.3	NR	NR	49.3	20.5	16.8	Low
Hibbard, 2010 [39]	USA	Cohort	NICU (19)	NR	185,327	51	37.3 ± 0.9	9.14	28.3	2.5	NR	Moderate
Tsapis, 2010 [40]	France	Cross-sectional	SMUR	NR	252	66.7	NR	0	50	1.6	NR	High
Dutta, 2011 [41]	India	Cross-sectional	Neonatal unit	Two or more of; tachypnoea, retractions or grunting	2382	54	NR	37	NR	6.4	NR	Moderate
Fedakar, 2011 [7]	Turkey	Cross-sectional	NICU	NR	240	64.6	NR	20.4	71.7	61.5	1.25	Moderate
Horowitz, 2011 [42]	USA	Cohort	NICU	NR	9782	NR	38.5	0	35.8	2.1	NR	Moderate
Lasme-Guillao, 2011 [43]	Ivory Coast	Cross-sectional	Neonatal unit	NR	530	59.4	37.28	38.4	11.6	44.2	37.5	Moderate
Ma, 2011 [44]	China	Cohort	NICU (14)	Hypoxemia requiring respiratory support for > 24 h	11,100	72.3	35.0 ± 4.0	NR	55.6	16.9	31.4	Low
Zaazou, 2011 [45]	Egypt	Cross-sectional	NICU	NR	233	58.3	35.1	NR	53.8	88.4	18.9	Moderate
Annagür, 2012 [46]	Turkey	Cross-sectional	NICU	NR	1463	NR	32.9 ± 5	NR	NR	34.7	NR	High
Chalacon, 2012 [47]	France	Cohort	Maternity (19)	NR	579	NR	NR	100	50	18.5	NR	Moderate
Guedehoussou, 2012 [48]	Togo	Cross-sectional	NICU	NR	219	61.2	NR	NR	23.7	26.7	45.2	High

Table 3 (continued)

First name of author, publication year	Country	Study design	Setting (number of sites if multicentre)	Diagnostic criteria of NRD	Sample size (*n*)	Male (%)	Mean GA (weeks)	Prematurity rate (%)	CS rate (%)	Prevalence (%)	Mortality rate (%)	ROB
Wadi, 2012 [49]	Iraq	Cross-sectional	Neonatal unit	One or more of tachypnoea, apnoea, retraction, grunting or cyanosis	2858	61.7	NR	0	50.3	47.2	9	Low
Wang, 2012 [50]	China	Cohort	NICU (55)	Hypoxemia requiring MV and/or nCPAP ≥ 24 h	34,842	70.9	34.9 ± 3.9	62.8	55.3	19.7	24.7	Low
Altman, 2013 [51]	Sweden	Cohort	Maternity	NR	471,194	49.2	36.1 ± 1	41.8	NR	1.2	NR	Low
Haque, 2013 [52]	Bangladesh	Cross-sectional	SCBU	One or more of RR > 60/min, chest retractions, nasal flaring, grunting	562	64.6	34.6 ± 3.1	65.6	84.4	34.1	16.7	Moderate
Nagalo, 2013 [53]	Burkina Faso	Cross-sectional	Neonatal unit	NR	697	55.3	37.4 ± 3.5	33.6	42.8	4.7	6.06	Moderate
Santosh, 2013 [54]	India	Cross-sectional	NICU	Two or more of RR ≥ 60/min, chest retractions, nasal flaring, expiratory grunting and cyanosis in room air	553	NR	NR	61	NR	13.7	7.8	Low
Zaman, 2013 [55]	Pakistan	Cross-sectional	Maternity	One or more of for > 2 h: RR > 60/min, chest retractions, grunt, stridor or wheeze	655	50	NR	53.6	20	4.24	NR	Low
Abdelrahman, 2014 [56]	Sudan	Cross-sectional	Maternity	NR	2071	54	NR	38	NR	4.83	36	Low
Chioukh, 2014 [57]	Tunisia	Cross-sectional	NICU	NR	273	60.1	NR	100	46.2	23.1	NR	High
Feroui, 2014 [58]	Algeria	Cross-sectional	Neonatal unit	NR	1623	54.5	37	NR	31.3	26.9	35	High
Pan, 2014 [59]	China	Cohort	NICU	NR	60,986	71.6	35.0 ± 4.0	64.1	NR	0.91	22.5	Moderate

Table 3 (continued)

First name of author, publication year	Country	Study design	Setting (number of sites if multicentre)	Diagnostic criteria of NRD	Sample size (*n*)	Male (%)	Mean GA (weeks)	Prematurity rate (%)	CS rate (%)	Prevalence (%)	Mortality rate (%)	ROB
Shakya, 2014 [60]	Nepal	Cross-sectional	NICU	NR	279	57.7	NR	10.8	NR	14.7	NR	Moderate
Ezhilvannan, 2015 [61]	India	Cross-sectional	Neonatal unit	NR	144	60.4	NR	100	35.4	35.4	NR	Moderate
Parkash, 2015 [62]	Pakistan	Cross-sectional	NICU	One or more of RR ≥ 60/min, chest retractions, nasal flaring, grunting and cyanosis	615	58.6	36.3 ± 2.7	NR	NR	33.3	32.7	Low
Swarnkar, 2015 [63]	India	Cross-sectional	NICU	Two or more of RR ≥ 60/min, chest retractions, nasal flaring, expiratory grunt and cyanosis	855	NR	NR	NR	60	16.37	22.86	Low
Bajad, 2016 [64]	India	Cross-sectional	NICU	Two or more of RR > 60/min, nasal flaring, chest retractions and grunting	3268	NR	NR	NR	NR	32	22.33	Low
Barkiya, 2016 [65]	India	Cohort	NICU	Two or more of RR ≥ 60/min, chest retractions, nasal flaring, expiratory grunt and cyanosis	300	65	NR	43	41	34	2	Low
Diouf, 2016 [66]	Senegal	Cross-sectional	Neonatal unit	NR	147	43.5	NR	100	18.3	49.6	27.4	High
Essomba, 2016 [67]	Cameroon	Cross-sectional	Neonatal unit	One or more of tachypnoea, apnoea, with or without central cyanosis	269	51.5	NR	33.4	20.4	31.2	39.3	Moderate
Faye, 2016 [68]	Senegal	Cross-sectional	Neonatal unit	NR	615	51.4	NR	0	18.2	34.8	31.8	Moderate

Table 3 (continued)

First name of author, publication year	Country	Study design	Setting (number of sites if multicentre)	Diagnostic criteria of NRD	Sample size (*n*)	Male (%)	Mean GA (weeks)	Prematurity rate (%)	CS rate (%)	Prevalence (%)	Mortality rate (%)	ROB
Islam, 2016 [69]	India	Cross-sectional	NICU	Two of the following: RR ≥ 60/min, chest retraction, nasal flaring, expiratory grunting and cyanosis in room air	5743	61.5	NR	NR	NR	5.3	23	Low
Okolo, 2016 [70]	Nigeria	Cohort	SCBU	NR	576	51	33.2 ± 3.7	77.6	55.1	8.5	36.7	Moderate
Tochie, 2016 [3]	Cameroon	Cross-sectional	Neonatal unit	One or more of an abnormal RR, signs of laboured breathing, with or without cyanosis	703	52.8	37.0 ± 3.9	32.4	30.7	47.5	24.5	Low
Sauparna, 2016 [71]	India	Cross-sectional	NICU	NR	675	NR	NR	17.5	NR	29.6	41	High
Adebami, 2017 [72]	Nigeria	Cross-sectional	SCBU	All of grunting, stridor, nasal flaring, poor feeding, RR > 60/min, retractions and cyanosis	625	61.4	NR	37.4	40.9	26.2	36.6	Low
Adhikari, 2017 [73]	Nepal	Case–control	NICU	NR	1306	58.5	NR	NR	NR	9.1	NR	Moderate
Amani, 2017 [74]	Rwanda	Cross-sectional	NICU	One or more of an abnormal RR, expiratory grunting, nasal flaring, chest wall recessions with or without cyanosis	247	56	NR	61.78	44.2	60	43.2	Low

Table 3 (continued)

First name of author, publication year	Country	Study design	Setting (number of sites if multicentre)	Diagnostic criteria of NRD	Sample size (*n*)	Male (%)	Mean GA (weeks)	Prematurity rate (%)	CS rate (%)	Prevalence (%)	Mortality rate (%)	ROB
Mehta, 2017 [75]	India	Cross-sectional	Neonatal unit	On two consecutive examinations at least 1 h apart, two or more of RR ≥ 60/min, chest retraction and expiratory grunt	1032	67.8	NR	69	NR	31.98	31.52	Low
Milas, 2017 [76]	Croatia	Cross-sectional	NICU	NR	348	61	NR	37.4	NR	19.8	NR	High
Ndombo, 2017 [77]	Cameroon	Cohort	Neonatal unit	NR	332	53	36 ± 3.9	33.4	NR	8.1	NR	Low
Nirosha, 2017 [78]	India	Cross-sectional	Neonatal unit	Two or more of RR ≥ 60/min, grunting, retractions	2152	64	NR	0	52.1	30.4	9.01	Low
Ouedraogo, 2017 [79]	Burkina Faso	Cross-sectional	Neonatal unit	NR	1776	56.8	NR	35.85	19.8	20.4	NR	Moderate
Rao, 2017 [80]	India	Cross-sectional	NICU	NR	1500	54.6	NR	32	NR	13.3	2.5	Moderate
Siham, 2017 [81]	Algeria	Cohort	Neonatal unit	NR	1020	63.1	NR	64.6	37.5	43.63	16.62	Moderate
Zhang, 2017 [82]	China	Cohort	NICU (12)	Hypoxemia requiring nasal CPAP or MV combined with surfactant for ≥ 24 h	9816	NR	NR	60.2	44.1	13.4	15.5	Low
Abou-Faddan, 2018 [83]	Egypt	Cross-sectional	NICU	One or more of tachypnoea, chest retractions, nasal flaring or grunting	919	54.1	NR	68.8	66.3	52.9	56.7	Low
Anureka, 2018 [84]	India	Cross-sectional	NICU	NR	7108	55.5	NR	54.62	NR	7.86	28.6	Moderate

Table 3 (continued)

First name of author, publication year	Country	Study design	Setting (number of sites if multicentre)	Diagnostic criteria of NRD	Sample size (*n*)	Male (%)	Mean GA (weeks)	Prematurity rate (%)	CS rate (%)	Prevalence (%)	Mortality rate (%)	ROB
Kuti, 2018 [85]	Nigeria	Cohort	SCBU	One or more of RR ≥ 60/min, chest in-drawing, nasal flaring, grunting and cyanosis	428	57.9	NR	32.5	37.6	58.4	17.2	Low
Manerkar, 2018 [86]	India	Cohort	Neonatal unit	RR > 60 breaths/min with or without retractions	110	40.9	NR	100	NR	24.54	NR	Low
Mannan, 2018 [87]	Bangladesh	Cross-sectional	NICU	One or more of noisy or difficult breathing, RR > 60/min, chest retraction, cyanosis or grunting	1108	NR	NR	NR	NR	24	NR	Low
Qari, 2018 [88]	Saudi Arabia	Cross-sectional	NR	NR	503	57.1	33.2 ± 3.1	95.3	63.3	78.5	NR	High
Rijal, 2018 [89]	Nepal	Cross-sectional	NICU	Two or more of RR ≥ 60 breaths/min, chest retractions, nasal flaring, expiratory grunting and cyanosis in room air	317	61.4	NR	23.8	39.4	34.3	12.8	Low
Verma, 2018 [90]	India	Cross-sectional	NICU	One or more of tachypnoea, retractions, nasal flaring, grunting or cyanosis	1424	53.9	NR	37	30.4	39	NR	Moderate
Ahmed, 2019 [91]	Iraq	Case–control	NICU	NR	2173	61.9	NR	0	69.6	2.76	5	Moderate

Table 3 (continued)

First name of author, publication year	Country	Study design	Setting (number of sites if multicentre)	Diagnostic criteria of NRD	Sample size (*n*)	Male (%)	Mean GA (weeks)	Prematurity rate (%)	CS rate (%)	Prevalence (%)	Mortality rate (%)	ROB
Al Ajeli, 2019 [92]	Iraq	Cross-sectional	Maternity	One or more for > 2 h: tachypnoea, increase chest in-drawing on respiration and grunting	5828	57.8	NR	42.2	36.3	2.5	NR	Low
Ali, 2019 [93]	Egypt	Cohort	NICU	One or more of RR > 60/min, nasal flaring, grunting, retractions, cyanosis	657	55.5	NR	42.9	67.8	71.53	22.9	Moderate
Aljawadi, 2019 [94]	Iraq	Cross-sectional	Neonatal unit	WHO criteria: RR > 60 or < 30 breaths/min, apnoea, expiratory grunting, chest in-drawing or central cyanosis	870	63.8	NR	44.6	55.2	84.8	21	Low
Bouattara, 2019 [95]	Mali	Cross-sectional	Neonatal unit	NR	5165	49	NR	60	19	3.87	28	Moderate
Kedy, 2019 [96]	Cameroon	Cross-sectional	Neonatal unit	Two or more of abnormal respiratory rate, signs of increased work of breathing, expiratory grunting, central cyanosis and apnoea	499	60.5	NR	0	41.3	34.5	22.1	Moderate
Lamichhane, 2019 [97]	Nepal	Cross-sectional	NICU	Two or more of; tachypnoea, nasal flaring, grunting intercostal and subcostal recessions	1694	60.3	NR	59.46	51.3	6.55	4.5	Low

Table 3 (continued)

First name of author, publication year	Country	Study design	Setting (number of sites if multicentre)	Diagnostic criteria of NRD	Sample size (*n*)	Male (%)	Mean GA (weeks)	Prematurity rate (%)	CS rate (%)	Prevalence (%)	Mortality rate (%)	ROB
Wang, 2019 [98]	China	Cross-sectional	NICU (55)	Hypoxemia requiring MV or nCPAP ≥ 24 h	39,127	NR	35.0 ± 3.9	NR	NR	17.5	24.7	Low
Aynalem, 2020 [99]	Ethiopia	Cohort	NICU	Two or more of an abnormal respiratory rate, signs of laboured breathing with or without cyanosis	571	52.3	NR	41.8	41.1	42.9	NR	Low
Baseer, 2020 [100]	Egypt	Cross-sectional	NICU	NR	312	55.9	34.5 ± 3.3	56	76.6	46.5	26.2	Moderate
Bahwal, 2020 [101]	Yemen	Cross-sectional	NICU	One or more of RR > 60 breaths/min, signs of laboured breathing, with or without cyanosis	430	72	NR	56.8	70.8	58.1	49.2	Low
Baloch, 2020 [102]	Pakistan	Cross-sectional	NICU	NR	1188	NR	35.28	NR	53	25.1	26.84	Moderate
Chandini, 2020 [103]	India	Cross-sectional	NICU	NR	720	NR	NR	61	42	28	NR	Moderate
Gamhewage, 2020 [104]	Sri Lanka	Cross-sectional	Maternity	One or more of RR ≥ 60/min, chest retractions, nasal flaring, expiratory grunting and cyanosis	2439	51.5	NR	0	NR	8.2	3.5	Low
Harshini, 2020 [105]	India	Cross-sectional	NICU	NR	810	53.3	NR	17.8	41	18.5	4.66	Moderate
Lokanuwatsatien, 2020 [106]	Thailand	Cross-sectional	NICU	NR	625	51	38.7 ± 0.9	0	45	9.4	1.6	Moderate

Table 3 (continued)

First name of author, publication year	Country	Study design	Setting (number of sites if multicentre)	Diagnostic criteria of NRD	Sample size (*n*)	Male (%)	Mean GA (weeks)	Prematurity rate (%)	CS rate (%)	Prevalence (%)	Mortality rate (%)	ROB
Mishra, 2020 [107]	India	Cross-sectional	NICU	Two or more of RR ≥ 60/min, chest recessions, expiratory grunt/groaning, nasal flaring, decrease air entry on auscultation of the chest	6120	50	NR	53.5	30	4.4	NR	Low
Ahmed, 2021 [108]	India	Cross-sectional	NICU	NR	502	38.3	NR	51.7	13	58.16	1.03	Moderate
Kue, 2021 [109]	Cameroon	Cross-sectional	Neonatal unit	All of abnormalities of frequency of breathing, work, ventilation and oxygenation	2312	68.8	38	0	NR	8	10.4	Moderate
Raha, 2021 [110]	Bangladesh	Cross-sectional	NICU	One or more of for > 2 h: RR > 60/min, chest retractions, grunt, stridor or wheeze	287	54.5	35.6 ± 3.1	50	71.1	19.2	1.8	Low
Bijow, 2022 [111]	Syria	Cross-sectional	NICU	NR	460	67.5	38	NR	90.3	36.1	NR	Moderate
Chavan, 2022 [112]	India	Cross-sectional	Maternity	NR	4562	63.5	NR	24.3	70.3	4.1	NR	Moderate
Ding, 2022 [113]	China	Cohort	NICU	Clinically and blood gas confirmed hypoxemia requiring CPAP and/or intra-tracheal MV for at least 24 h	7960	56.6	39	24.4	52.3	9.6	18.4	Low

Table 3 (continued)

First name of author, publication year	Country	Study design	Setting (number of sites if multicentre)	Diagnostic criteria of NRD	Sample size (*n*)	Male (%)	Mean GA (weeks)	Prematurity rate (%)	CS rate (%)	Prevalence (%)	Mortality rate (%)	ROB
Enyew, 2022 [114]	Ethiopia	Cohort	NICU	Two or more of an abnormal respiratory rate, signs of laboured breathing with or without cyanosis	2703	55.5	NR	43.58	28.7	11.5	16.37	Low

CPAP continuous positive airway pressure, *nCPAP* nasal continuous positive airway pressure, *CS* caesarean section, *GA* gestational age, *MV* mechanical ventilation, *NR* not reported, *NRF* neonatal respiratory failure, *NICU* neonatal intensive care unit, *ROB* risk of bias assessment, *RR* respiratory rate, *SCBU* special care baby unit, *SMUR* structure mobile d'urgence et de reanimation

Aetiologies of neonatal respiratory failure

In the subgroup analysis of the aetiologies of NRF, we computed data from 110 studies entailing 1,075,380 neonates from 37 countries (Table 4). At the global scale, the leading aetiologies of NRF were RDS ($n=21,117$), TTN ($n=13,272$), neonatal infections ($n=12,995$), meconium aspiration syndrome (MAS) ($n=5746$) and hypoxic-ischaemic encephalopathy (HIE) ($n=2566$), see Table 4. The leading aetiologies of NRF changed at regional levels. Neonatal sepsis was the leading NRF aetiology in Africa. In Europe and the Middle East, TTN was the primary aetiology, whilst RDS still remained predominant in Asia and the Americas as summarized at the end of Table 4.

NRF-related death predictors, mortality rate and aetiologies of death

Cited predictors of NRF mortality include APGAR at 1 min = 0–3 (OR = 177.99), APGAR at 1 min = 4–6 (OR = 38.10), APGAR at 5 min ≤ 6 (OR = 12.7), GA ≤ 31 weeks (OR = 14.59), Downes score > 4 (OR = 12.15), birth weight ≤ 1620 g (OR = 9.09), baseline SpO2 ≤ 86% (OR = 6.29), use of mechanical ventilation (OR = 4.58–29.4), Silverman score > 5 on first assessment (OR = 3.07), very low birth weight (OR = 2.66), small for gestational age (OR = 2.1), male gender (OR = 1.7), congenital anomalies (OR = 1.79), antepartum haemorrhage (OR = 1.6), higher SNAPPE-II (OR = 1.43), large for gestational age (OR = 1.3), pneumonia/sepsis (OR = 1.35), presence of risk factors for sepsis (OR = 2.19) and resuscitation in delivery room (OR = 1.18) [100, 104, 115, 123]. On the other hand, caesarean delivery (OR = 0.60) and surfactant therapy (OR = 0.43) have been reported to reduce the risk of NRF-related mortality [115].

Globally, NRF-related in-hospital mortality varied between 0.21 and 57.3% and varied across regions as follows: Africa 0.21–57.3% [3, 21, 34, 36, 43, 45, 48, 53, 56, 58, 66–68, 70, 72, 74, 81, 83, 85, 93, 95, 96, 100, 109, 114, 118], Asia 1.03–49.3% [20, 25, 33, 44, 52, 54, 59, 62–65, 69, 71, 75, 78, 80, 82, 84, 89, 97, 98, 102, 104–106, 108, 110, 113, 115, 126, 128, 130, 131, 134, 135, 140, 143], the Middle East 1.25–49.2% [7, 30, 31, 49, 91, 94, 101, 132], the Americas 0.24–33% [26–28] and Europe 3.5–15.8% [6, 19, 22, 23]. At national levels, this mortality rate was highest in Mali 57.3% [36] and Egypt 56.7% [83] and lowest in South Africa 0.21% [21] and the USA 0.24% [26], see Table 3.

In another subgroup analysis of NRF-related mortality, we computed data from 48 studies representing 166,000 neonates from 19 countries (Table 5). At a global level, the first four leading aetiologies of NRF-related deaths were RDS ($n=1614$), neonatal infections ($n=650$), HIE ($n=372$) and MAS ($n=316$). The trend did not vary much per regions with RDS still being the lead cause of NRF-related in-hospital

Table 4 Aetiologies of neonatal respiratory failure by countries and regions

First name of author, publication year	Country	Sample size (*n*)	NRD cases (*n*)	Number of cases of the different aetiologies of NRF (*n*)										ROB
				TTN	RDS or HMD	MAS	NI	HIE	CA	CHD	CDH	OA/TEF	Others	
Malhotra, 1995 [117]	India	50	50	07	09	06	06	06	00	02	00	00	14	Low
Bonafe, 1996 [19]	Italy	7588	251	85	128	09	12	60	00	00	00	00	17	Moderate
Kumar, 1996 [20]	India	4505	300	128	28	32	51	20	00	06	06	00	39	Low
Rinjswijk, 1996 [21]	South Africa	7539	48	06	07	05	20	01	00	01	00	00	08	Low
Rubaltelli, 1998 [22]	Italy	17,192	491	202	213	19	22	00	00	00	00	00	85	Low
Rubaltelli, 1998 [23]	Italy	63,537	1427	594	735	38	45	00	00	00	00	00	15	Low
Nagendra, 1999 [24]	India	1986	48	07	09	06	06	06	00	02	00	00	12	Moderate
Bhakoo, 2000 [25]	India	243	146	40	52	03	41	00	00	00	00	00	10	Low
Wiswell, 2000 [26]	USA	2094	149	52	00	62	10	00	00	00	00	00	25	Low
Sévère, 2001 [4]	Haiti	372	372	12	00	60	89	00	00	00	00	03	208	Moderate
Agrawal, 2003 [27]	USA	2805	584	53	117	41	18	00	00	00	00	00	355	Low
Ali Z., 2003 [28]	Trinidad and Tobago	5062	174	00	51	00	68	17	00	00	00	00	00	High
Ganga-Zandzou, 2004 [118]	Gabon	174	174	86	06	00	10	68	00	00	00	00	04	High
Clark, 2005 [119]	USA	1011	1011	40	437	98	84	31	00	12	31	13	282	Low
Hameed, 2007 [30]	Iraq	2312	50	39	06	02	01	00	00	02	00	00	00	Moderate
Dehdashtian, 2008 [31]	Iran	1000	35	32	01	00	00	01	00	00	00	00	01	High
Gouyon, 2008 [120]	France	65,000	1112	468	247	397	00	00	00	00	00	00	00	Low
Qian, 2008 [33]	China	13,070	1722	129	602	163	316	107	00	27	13	00	365	Low
Chakrouni, 2009 [34]	Morocco	765	75	07	00	18	48	00	00	02	00	00	00	High
Diakite, 2009 [36]	Mali	1072	138	00	24	33	64	00	00	00	00	00	17	Moderate
Champion, 2010 [37]	France	186	32	18	14	00	00	00	00	00	00	00	02	High
Hibbard, 2010 [39]	USA	185,327	4701	1466	1649	188	475	00	00	00	00	00	1106	Moderate
Ma, 2010 [121]	China	503	503	123	164	22	93	60	00	00	00	00	41	Low
Qian, 2010 [38]	China	13,058	2677	239	711	409	589	00	00	00	10	00	719	Low
Dutta, 2011 [41]	India	2382	152	49	12	20	37	19	00	05	02	02	06	Moderate
Fedakar, 2011 [7]	Turkey	390	240	184	15	20	09	09	00	00	00	00	03	Moderate
Horowitz, 2011 [42]	USA	9802	202	87	26	49	16	00	00	00	00	00	24	Moderate
Ma, 2011 [44]	China	11,100	1875	219	878	146	469	04	00	00	00	00	159	Low
Zaazou, 2011 [45]	Egypt	233	206	74	43	16	14	15	00	17	03	04	20	Moderate
Guedehoussou, 2012 [48]	Togo	219	58	00	00	00	28	15	00	00	00	00	15	High
Annagür, 2012 [46]	Turkey	1463	507	22	185	23	408	00	00	76	00	00	129	High
Wadi, 2012 [49]	Iraq	2858	167	75	02	16	27	22	00	13	00	00	12	Low
Wang, 2012 [115]	China	34,842	6864	556	3013	480	1490	00	00	527	00	00	798	Low
Altman, 2013 [51]	Sweden	471,194	5502	2833	969	00	674	00	00	00	00	00	1026	Low
Haque, 2013 [52]	Bangladesh	562	192	83	58	03	54	48	00	20	00	00	04	Moderate

Table 4 (continued)

First name of author, publication year	Country	Sample size (*n*)	NRD cases (*n*)	Number of cases of the different aetiologies of NRF (*n*)										ROB
				TTN	RDS or HMD	MAS	NI	HIE	CA	CHD	CDH	OA/TEF	Others	
Kattan, 2013 [122]	Chile	259	259	00	100	47	00	00	00	00	75	00	37	Low
Santosh, 2013 [54]	India	553	76	35	24	06	19	19	00	01	00	00	03	Low
Zaman, 2013 [55]	Pakistan	655	28	10	07	05	02	00	00	00	00	00	02	Low
Abdelrahman, 2014 [56]	Sudan	2071	100	28	15	06	24	00	03	09	02	00	13	Low
Chioukh, 2014 [57]	Tunisia	273	63	21	10	00	26	00	00	00	00	00	06	High
Feroui, 2014 [58]	Algeria	1623	437	02	08	03	00	00	03	00	01	00	00	High
Shakya, 2014 [60]	Nepal	279	41	20	01	13	07	00	00	00	00	00	00	Moderate
John, 2015 [123]	India	165	165	62	67	19	09	05	00	00	00	00	03	Moderate
Hundalani, 2015 [124]	Malawi	325	325	78	48	19	26	40	00	00	00	00	114	Moderate
Kim, 2015 [125]	Korea	260	260	98	16	76	19	00	00	00	00	00	51	Moderate
Parkash, 2015 [62]	Pakistan	615	205	29	47	34	73	22	00	00	00	00	00	Low
Sahoo, 2015 [126]	India	100	100	32	29	18	11	00	00	06	00	00	04	High
Swarnkar, 2015 [63]	India	855	140	57	24	13	11	16	00	05	00	00	14	Low
Bajad, 2016 [64]	India	3268	1030	43	262	73	242	254	00	44	00	54	58	Low
Barkiya, 2016 [65]	India	300	102	45	25	05	15	10	00	01	00	00	01	Low
Chandrasekhar, 2016 [127]	India	100	100	60	06	31	00	00	01	01	00	00	00	Moderate
Faye, 2016 [68]	Senegal	615	214	00	00	30	118	53	09	29	00	00	20	Moderate
Islam, 2016 [69]	India	5743	304	130	18	25	117	16	00	09	02	01	00	Low
Kisku, 2016 [128]	India	100	100	22	15	08	32	07	00	00	00	00	16	High
Lee, 2016 [129]	Korea	242	242	132	21	18	05	00	00	00	00	00	66	Low
Okolo, 2016 [70]	Nigeria	576	49	01	27	00	06	10	00	00	00	00	05	Moderate
Sauparna, 2016 [71]	India	675	200	20	46	41	77	00	00	12	02	00	02	High
Tochie, 2016 [3]	Cameroon	703	334	84	45	35	105	28	02	09	04	02	20	Low
Adebami, 2017 [72]	Nigeria	625	164	17	32	10	59	36	00	10	00	00	54	Low
Adhikari, 2017 [73]	Nepal	1308	118	15	21	07	61	06	00	04	00	02	02	Moderate
Amani, 2017 [74]	Rwanda	247	148	39	25	06	59	00	00	00	00	00	19	Low
Kommawar, 2017 [130]	India	400	400	160	107	31	26	49	00	19	00	00	08	Moderate
Mehta, 2017 [75]	India	1032	330	24	44	38	153	63	00	08	00	00	00	Low
Milas, 2017 [76]	Croatia	348	69	00	00	01	12	12	00	03	00	00	41	High
Nirosha, 2017 [78]	India	2152	655	242	01	93	73	144	02	78	01	01	24	Low
Palod, 2017 [131]	India	281	281	47	88	31	79	42	00	12	00	00	33	Moderate
Rao, 2017 [80]	India	1500	200	18	64	70	02	37	00	07	02	00	00	Moderate
Sabzehei, 2017 [132]	Iran	93	93	13	34	07	28	01	00	08	01	00	01	High
Siham, 2017 [81]	Algeria	1020	445	82	97	33	91	00	02	00	03	06	101	Moderate
Thirupathireddy, 2017 [133]	India	200	200	24	60	54	16	12	00	15	04	08	07	Moderate
Wang, 2017 [116]	China	5650	5650	520	2164	463	1317	00	00	00	00	00	1186	Low
Zhang, 2017 [82]	China	9816	1324	64	515	29	503	00	00	00	00	00	213	Low

Table 4 (continued)

First name of author, publication year	Country	Sample size (*n*)	NRD cases (*n*)	Number of cases of the different aetiologies of NRF (*n*)										ROB
				TTN	RDS or HMD	MAS	NI	HIE	CA	CHD	CDH	OA/TEF	Others	
Abou-Faddan, 2018 [83]	Egypt	919	487	83	223	09	86	00	00	00	00	00	86	Low
Anureka, 2018 [84]	India	7108	559	399	559	311	00	00	00	00	00	00	109	Moderate
Kuti, 2018 [85]	Nigeria	428	250	25	41	10	75	134	00	04	00	00	187	Low
Manerkar, 2018 [86]	India	110	27	03	10	00	03	03	00	00	00	00	08	Low
Rijal, 2018 [89]	Nepal	317	109	17	13	23	34	13	00	07	00	00	02	Low
Sodawat, 2018 [134]	India	600	600	196	145	56	116	45	00	24	00	00	18	Moderate
Sonawane, 2018 [135]	India	78	78	47	05	23	01	00	00	01	01	00	00	Moderate
Verma, 2018 [90]	India	1424	555	122	167	100	83	00	00	00	00	00	139	Moderate
Ahmed, 2019 [91]	Iraq	2173	60	42	05	06	03	00	01	02	01	00	00	Moderate
Al Ajeli, 2019 [92]	Iraq	5828	147	60	51	21	03	00	00	08	02	02	00	Low
Ali, 2019 [93]	Egypt	657	470	60	150	08	130	40	00	00	00	00	82	Moderate
Aljawadi, 2019 [94]	Iraq	870	738	244	302	19	12	131	00	00	00	00	30	Low
Bouattara, 2019 [95]	Mali	5165	200	00	66	00	41	77	00	00	00	00	16	Moderate
Kedy, 2019 [96]	Cameroon	499	172	61	00	21	160	67	00	08	00	00	68	Moderate
Kshirsagar, 2019 [136]	India	100	100	32	29	18	11	00	00	00	00	00	00	High
Manandhar, 2019 [137]	Nepal	63	63	06	07	12	22	08	00	06	00	00	02	Low
Meena, 2019 [138]	India	500	500	63	154	56	151	52	00	11	00	00	13	Moderate
Pandya, 2019 [139]	USA	918	918	00	493	00	371	00	00	380	00	00	322	Low
Sastry, 2019 [140]	India	200	200	18	64	20	02	37	00	07	02	00	00	Moderate
Wang, 2019 [98]	China	39,127	6864	558	3010	478	1487	00	00	00	00	00	1767	Low
Aynalem, 2020 [99]	Ethiopia	571	245	37	106	85	00	00	00	00	00	00	17	Low
Bahwal, 2020 [101]	Yemen	430	250	47	110	30	14	35	00	10	00	00	04	Low
Baloch, 2020 [102]	Pakistan	1188	298	89	66	47	25	51	00	00	00	00	20	Moderate
Baseer, 2020 [100]	Egypt	312	145	32	72	09	25	00	00	00	03	02	02	Moderate
Gamhewage, 2020 [104]	Sri Lanka	2439	200	60	00	29	63	00	00	02	02	00	44	Low
Harshini, 2020 [105]	India	810	150	45	50	34	03	06	00	00	00	00	12	Moderate
Lokanuwatsatien, 2020 [106]	Thailand	625	59	47	00	01	04	03	00	00	00	00	04	Moderate
Mishra, 2020 [107]	India	6120	269	95	73	49	09	00	00	00	00	00	43	Low
Panigrahi, 2020 [141]	India	202	202	51	80	31	71	21	00	10	00	00	90	Low
Todkar, 2020 [142]	India	190	190	37	52	14	35	33	00	04	02	04	09	Moderate
Wanare, 2020 [143]	India	100	100	58	12	20	05	00	00	05	00	00	00	Low
Ahmed, 2021 [108]	India	502	292	132	19	06	97	06	00	00	00	00	32	Moderate
Kue, 2021 [109]	Cameroon	2312	186	66	02	31	82	00	01	00	01	01	02	Moderate
Raha, 2021 [110]	Bangladesh	287	55	26	16	01	04	06	00	02	00	00	00	Low
Bijow, 2022 [111]	Syria	460	166	51	15	04	114	10	00	30	00	00	32	Moderate
Chavan, 2022 [112]	India	4562	189	74	30	70	00	00	00	00	00	00	15	Moderate
Ding, 2022 [113]	China	7960	788	00	287	13	849	397	00	100	05	00	114	Low

Table 4 (continued)

First name of author, publication year	Country	Sample size (*n*)	NRD cases (*n*)	Number of cases of the different aetiologies of NRF (*n*)										ROB
				TTN	RDS or HMD	MAS	NI	HIE	CA	CHD	CDH	OA/TEF	Others	
Enyew, 2022 [114]	Ethiopia	2703	452	00	109	299	87	00	00	00	00	00	168	Low
Total (*n*)		1,075,380	64,519	13,272	21,117	5,746	12,995	2,566	24	1,623	181	105	11,102	
Regions	**Number of studies**	**Sample of the studies (*n*)**	**Total NRD cases (*n*)**	**TTN**	**RDS or HMD**	**MAS**	**NI**	**HIE**	**CA**	**CHD**	**CDH**	**OA/TEF**	**Others**	
Europe [19, 22, 23, 37, 51, 76, 120]	07	62,5045	8,884	4,200	2,306	464	765	72	0	3	0	0	1186	
Americas [4, 26–28, 39, 42, 119, 122, 139]	09	20,7650	8,370	1,710	2,873	545	1,131	48	0	392	106	16	2359	
Middle East [7, 30, 31, 46, 49, 91, 92, 94, 132]	11	17,877	2,453	809	726	148	619	209	01	149	04	02	212	
Africa [3, 21, 34, 36, 45, 48, 56–58, 68, 70, 72, 74, 81, 83, 85, 93, 95, 96, 99, 100, 109, 114, 118, 124]	25	31,646	5,585	889	1,156	686	1,384	584	20	89	17	15	1044	
Asia [20, 24, 25, 33, 38, 41, 44, 52, 54, 55, 60, 62–65, 69, 71, 73, 75, 78, 80, 82, 84, 86, 89, 90, 98, 102, 104–108, 110, 112, 113, 115–117, 121, 123, 125–131, 133–138, 140–143]	58	19,3162	39,227	5,664	14,056	3,903	9,096	1,653	3	990	54	72	6301	

Others (n): aspiration of amniotic fluid or milk = 2908; pneumothorax = 1307; unprecised congenital anomalies and surgical causes = 971; persistent pulmonary hypertension = 712; anaemia = 471; metabolic causes (acidosis, hypoglycaemia and hyperglycaemia) = 291; intraventricular haemorrhage = 127; apnoea of prematurity = 77; pulmonary hypoplasia = 47; pulmonary haemorrhage = 44; bronchopulmonary dysplasia = 21

CA choanal atresia, *CHD* congenital heart diseases, *CDH* congenital diaphragmatic hernia, *HMD* hyaline membrane disease, *HIE* hypoxic ischaemic encephalopathy, *MAS* meconium aspiration syndrome, *NI* neonatal infection (neonatal sepsis, septicaemia, neonatal pneumonia and/or congenital pneumonia), *NRF* neonatal respiratory failure, *OA/TEF* oesophageal atresia with or without tracheoesophageal fistula, *RDS* respiratory distress syndrome, *ROB* risk of bias, *TTN* transient tachypnoea of the newborn

Table 5 Mortality related to neonates with respiratory failure per its aetiologies at national and regional levels

First name of author, publication year	Country	Sample size (*n*)	NRD (*n*)	NRD—deaths (*n*)	Number of dead neonates per aetiologies of NRF (*n*)										ROB
					TTN	RDS or HMD	MAS	NI	HIE	CA	CHD	CDH	OA/TEF	Others	
Malhotra, 1995 [117]	India	50	50	19	00	08	00	02	02	00	02	00	00	05	Low
Kumar, 1996 [20]	India	4505	300	57	00	16	07	08	00	00	00	00	00	26	Low
Bonafe, 1996 [19]	Italy	7588	251	21	00	19	00	00	00	00	00	00	00	02	Moderate
Rubaltelli, 1998 [22]	Italy	17,192	491	78	04	56	03	06	00	00	00	00	00	22	Low
Rubaltelli, 1998 [23]	Italy	63,537	1427	208	08	176	04	10	00	00	00	00	00	10	Low
Rinjswijk, 1996 [21]	South Africa	7539	48	16	00	07	00	08	00	00	01	00	00	00	Low
Agrawal, 2003 [27]	USA	2805	584	19	00	12	00	00	00	00	00	00	00	07	Low
Ganga-Zandzou, 2004 [118]	Gabon	174	174	13	00	00	00	00	09	00	00	00	00	04	High
Hameed, 2007 [30]	Iraq	2312	50	02	00	01	00	00	00	00	01	00	00	00	Moderate
Dehdashtian, 2008 [31]	Iran	1000	35	01	00	00	00	00	01	00	00	00	00	00	High
Qian, 2008 [33]	China	13,070	1722	553	14	203	64	82	67	00	00	00	00	22	Low
Qian, 2010 [38]	China	13,059	2677	450	12	223	73	80	00	00	00	00	00	62	Low
Fedakar, 2011 [7]	Turkey	390	240	03	00	00	00	00	01	00	01	00	00	01	Moderate
Zaazou, 2011 [45]	Egypt	233	206	39	00	25	04	00	06	00	00	00	00	08	Moderate
Guedehoussou, 2012 [48]	Togo	219	59	26	00	00	00	12	05	00	00	00	00	09	High
Wadi, 2012 [49]	Iraq	2858	167	15	00	00	00	05	05	00	02	00	00	03	Low
Santosh, 2013 [54]	India	553	76	06	00	04	00	01	01	00	00	00	00	00	Low
Abdelrahman, 2014 [56]	Sudan	2071	100	36	00	13	02	08	00	02	05	02	00	04	Low
Parkash, 2015 [62]	Pakistan	615	205	67	00	36	07	18	06	00	00	00	00	00	Low
Sahoo, 2015 [126]	India	100	100	10	00	07	02	01	00	00	00	00	00	00	High
Swarnkar, 2015 [63]	India	855	140	32	00	15	04	04	05	00	03	00	00	01	Low
Bajad, 2016 [64]	India	3268	1030	230	00	93	10	44	57	00	07	00	10	09	Low
Kisku, 2016 [128]	India	100	100	28	00	06	02	13	02	00	00	00	00	05	High
Islam, 2016 [69]	India	5743	304	70	00	14	11	33	09	00	06	02	01	00	Low
Tochie, 2016 [3]	Cameroon	703	334	82	00	20	03	35	13	00	00	00	00	11	Low
Adebami, 2017 [72]	Nigeria	625	164	60	00	15	04	21	14	00	03	00	00	09	Low
Amani, 2017 [74]	Rwanda	247	148	64	08	11	03	32	00	00	00	00	00	08	Low
Kommawar, 2017 [130]	India	400	400	86	01	53	07	02	15	00	02	00	00	06	Moderate
Mehta, 2017 [75]	India	1032	330	104	00	26	08	44	23	00	03	00	00	00	Low
Nirosha, 2017 [78]	India	2152	655	59	00	00	17	03	30	00	04	00	00	05	Low
Palod, 2017 [131]	India	281	281	35	01	12	04	14	09	00	03	00	00	08	Moderate
Rao, 2017 [80]	India	1500	200	05	00	03	00	00	00	00	00	02	00	00	Moderate
Sabzehei, 2017 [132]	Iran	93	93	18	00	06	01	06	00	00	03	00	00	02	High
Abou-Faddan, 2018 [83]	Egypt	919	487	276	00	155	06	48	00	00	00	00	00	67	Low

Table 5 (continued)

First name of author, publication year	Country	Sample size (*n*)	NRD (*n*)	NRD—deaths (*n*)	Number of dead neonates per aetiologies of NRF (*n*)										ROB
					TTN	RDS or HMD	MAS	NI	HIE	CA	CHD	CDH	OA/TEF	Others	
Sodawat, 2018 [134]	India	600	600	168	00	69	20	49	16	00	08	00	00	06	Moderate
Sonawane, 2018 [135]	India	78	78	04	00	02	02	00	00	00	00	00	00	00	Moderate
Ahmed, 2019 [91]	Iraq	2173	60	03	00	00	01	01	00	00	01	00	00	00	Moderate
Ali, 2019 [93]	Egypt	657	470	108	00	27	03	33	15	00	00	00	00	30	Moderate
Aljawadi, 2019 [94]	Iraq	870	738	152	00	102	05	07	28	00	00	00	00	10	Low
Sastry, 2019 [140]	India	200	200	05	00	03	00	00	00	00	00	02	00	00	Moderate
Baloch, 2020 [102]	Pakistan	1188	298	80	00	39	14	11	15	00	00	00	00	01	Moderate
Bahwal, 2020 [101]	Yemen	430	250	123	00	90	17	01	12	00	02	00	00	01	Low
Baseer, 2020 [100]	Egypt	312	145	38	00	28	03	04	00	00	00	01	01	00	Moderate
Lokanuwatsatien, 2020 [106]	Thailand	625	59	01	00	00	00	00	00	00	00	00	00	01	Moderate
Todkar, 2020 [142]	India	190	190	37	00	13	02	04	06	00	02	02	04	04	Moderate
Wanare, 2020 [143]	India	100	100	05	00	02	03	00	00	00	00	00	00	00	Low
Ahmed, 2021 [108]	India	502	292	03	00	03	00	00	00	00	00	00	00	00	Moderate
Raha, 2021 [110]	Bangladesh	287	55	01	00	01	00	00	00	00	00	00	00	00	Low
Total (*n*)		166,000	17,163	3,516	48	1,614	316	650	372	2	59	11	16	166,000	
Regions	**Number of studies**	**Sample of the studies (*n*)**	**Total NRD cases (*n*)**	**Total NRD—deaths (*n*)**	**TTN**	**RDS or HMD**	**MAS**	**NI**	**HIE**	**CA**	**CHD**	**CDH**	**OA/TEF**	**Others**	
Asia [20, 33, 38, 54, 62, 64, 69, 75, 78, 80, 102, 106, 108, 110, 117, 126, 128, 130, 131, 134, 135, 140, 142, 143]	25	46,548	10,142	2,058	28	835	250	405	263	0	40	8	15	46,548	
Africa [3, 21, 45, 48, 56, 72, 74, 83, 93, 100, 118]	11	13,699	2,335	758	8	301	28	201	62	2	9	3	1	150	
Middle East [7, 30, 31, 49, 94, 101, 108, 132]	08	10,126	1,633	317	0	199	24	20	47	0	10	0	0	17	
Europe [19, 22, 23]	03	88,317	2,169	307	12	251	7	16	0	0	0	0	0	34	
Americas [27]	01	2,805	584	19	00	12	00	00	00	00	00	00	00	07	

Others (n): unprecise congenital anomalies = 80; aspiration of amniotic fluid = 22; persistent pulmonary hypertension = 38; metabolic causes = 08; pneumothorax = 04; anaemia = 02

CA choanal atresia, *CHD* congenital heart diseases, *CDH* congenital diaphragmatic hernia, *HMD* hyaline membrane disease, *HIE* hypoxic ischaemic encephalopathy, *MAS* meconium aspiration syndrome, *NI* neonatal infection (neonatal sepsis, septicaemia, neonatal pneumonia and/or congenital pneumonia), *NR* not reported, *NRF* neonatal respiratory failure, *OA/TEF* oesophageal atresia with or without tracheoesophageal fistula, *RDS* respiratory distress syndrome, *ROB* risk of bias, *RR* respiratory rate, *TTN* transient tachypnoea of the newborn

mortality in Europe, the Americas, Africa, Asia and the Middle East as illustrated at the end of Table 5.

Risk factors associated with neonatal respiratory failure

Foetal factor

Gestational age (GA) Several studies without controversy have demonstrated that of all aetiologies of NRF are more common in premature newborns compared to their term and post-term counterparts [3, 49, 94, 99, 100, 127]. Prematurity (GA < 37 weeks) has specifically been reported to increase the odds of NRF by 1.74–4.91 [3, 47, 99]. Likewise, post-term GA (≥ 42 weeks) is increasingly recognized as a known risk factor for NRF [144].

Gender The male gender has repeatedly been reported to be an independent predictor of NRF [3, 30, 47, 49, 91, 94, 99]. Male neonates are 1.4–2.4-fold more likely to have NRF compared to females [3, 47, 99, 145].

Ethnicity Seven well-powered studies, mainly of cohort design and conducted in the UK and USA, demonstrate that irrespective of GA, black newborns have statistically significant lower incidences of NRF when compared with non-black newborns [146–152]. Also, unlike caucasian neonates, blacks are more responsive to antenatal steroid administration [147].

Birth weight There are mixed findings on the association between birth weight and NRF. One study found a statistically significant association between low birth weight (LBW) < 2500 g and NRF [153]. Other studies reported high birth weight ≥ 4000 g (aOR: 2.27, 95% CI: 1.06–4.87, *p*: 0.034) [3] and large for gestational age (aOR: 2.54, 95% CI: 1.1–6, *p*: 0.03) as independent risk factors for NRF [106]. By contrast, one Iraqi study [30] did not find LBW as a risk factor for NRF.

Maternal risk factor

Maternal age There are mixed results on the association of maternal age and NRF. Whilst an observational study from India [127] showed advanced maternal age as a risk factor for severe NRF, another primary study from Iraq [30] and France [47] observed no statistically significant difference between NRF and maternal age. Meanwhile, a recent systematic review and meta-analysis demonstrated that adolescent deliveries at a maternal age between 10 and 19 years are more likely than deliveries at maternal age > 19 years to have complications associated with NRF such as LBW (OR = 1.8; 95% CI: 1.6–2.1), neonatal asphyxia (OR = 1.7; 95% CI: 1.3–2.1) and preterm newborns (OR = 1.5; 95% CI: 1.1–1.9) [154].

Maternal smoking Two studies found a significant risk of NRF when a mother had been a chronic smoker than not [30, 91].

Parity Multiparity generally increases the odds of NRF by 2.2 [145] and this odds specifically increases to 4.216 for RDS [155]. Likewise, babies delivered by primiparous women are more likely to develop NRF (OR = 1.617; 95% CI = 1.433–4.967; $p = 0.034$) [85].

Obstetrical risk factors

Infectious anamneses Evidence abounds that a neonate with any infectious anamneses such as past and current maternal group B streptococcal genital tract infection, maternal temperature ≥ 38 °C during labour or following the next 2 h after delivery, unexplained spontaneous prematurity < 37 weeks of gestation, prolonged membrane rupture (PROM) > 12 h, premature rupture of membranes before 37 weeks and past history of neonatal sepsis by group B streptococcus (GBS) are predictors of NRF due to neonatal infection [3, 47, 156]. However, amongst these infectious predictors of NRF, there are mixed results on the effect of maternal fever and PROM. Reports from Ethiopia illustrate that neonates delivered from women with PROM have 1.1 times higher risk of NRF [99]. By contrast, citations from France and Cameroon reported PROM and maternal fever > 38 °C to convey protection against NRF via respective risk reductions of 36–62% (aOR: 0.38–0.64) [3, 47] and 43% (aOR: 0.57) [3].

Gestational diabetes mellitus Neonates delivered from mothers with chronic diabetes mellitus, diabetes mellitus (GDM) and pregestational diabetes mellitus (PGDM) have a 1.47–3.2-increment in risk of NRF [99, 157, 158].

Antepartum haemorrhage Many studies have proven placenta praevia or abruptio to increase the risk of NRF by 4.21–5-fold [47, 120].

Hypertensive disorders Several studies showed that hypertensive disorders of pregnancy are associated with respiratory morbidities at odds ratios of 1.12–17 [106, 159, 160, 160–166]. By contrast, three studies observed that infants born to mothers with hypertensive disorders and/or pre-eclamptic complications of HEELP syndrome were not more exposed to NRF than those whose mothers did not have hypertension during gestation [47, 167–169]. However, a more detailed narrative review of studies published between 2000 and 2008 on HELLP syndrome reported that HELLP syndrome is associated with a NRF incidence of 5.7–40% in neonates [170].

Multiple pregnancies Studies that have evaluated the association between NRF and multiple gestations have shown mixed results. On the one hand, twin pregnancies were

identified as an independent predictor of NRF in an Italian cohort study (OR 1.64, 95% CI 1.25–2.15, $p = 0.0004$) [171]. On the other hand, a French cross-sectional study instead demonstrated multiple pregnancies to convey a protective effect for NRF (OR = 0.60, 95% CI: 0.37–0.99) [47].

Mode of delivery Findings from a systematic review and meta-analysis of 26 primary studies ($n = 809{,}562$) published up to August 10, 2018, clearly show a pooled odds ratio of 1.76 (95% CI 1.48–2.09) for the association between caesarean section (CS) and the risk of NRF [172]. In the same study, emergency CS had 1.85 (95% CI 1.34–2.56) times higher risk for NRF whereas elective CS had a 2.38 (95% CI 1.89–2.99) times higher risk [172]. These observations concur with that of an earlier systematic review published in 2007 [173]. Isolated observational published after August 10, 2018, show that CS increases the risk of NRF by 1.9–15.03-fold [99, 155, 174, 175]. This risk of NRF following CS increases with a decrease in GA: at 37 weeks (OR 3.9; 95% CI: 2.4–6.5), 38 weeks (OR 3.0; 95% CI: 2.1–4.3) and 39 weeks (OR 1.9; 95% CI: 1.2–3.0) [32]. In the same vein, several other studies equally highlight that the risk of NRF following CS statistically significantly decreases with advancing weeks of gestation [176–178] and the best timing of term elective CS to avert the risk of NRF (a reduction of the odds of NRF by 2.4–2.7) has been reported to be between 39^{+0} and 39^{+6} weeks [178, 179]. Likewise, a minimum of a two-fold increment in risk of NRF has also been reported for early-term vaginal delivery (37–38 weeks) compared to late-term vaginal deliveries (≥ 39 weeks' gestation) [180, 181].

Antenatal drugs Anaesthetic drugs such as opioids, hypnotics and neuromuscular blocking agents administered before the clamping of the umbilical cord during CS under intravenous or general anaesthesia are associated with an inreased incidence of NRF [182–184]. There have been controversial evidence on the use of antenatal corticosteroids in preterm deliveries before 34 weeks of gestation: antenatal corticosteroids reduce the risk of NRF by about 32–54% (aOR: 0.46–0.68) [51, 160, 185, 186] or antenatal corticosteroids do not affect the risk of NRF [47]. However, good-quality evidence from a meta-analysis of 30 studies ($n = 7774$ women and 8158 neonates from HICs) published up to February 17, 2017 (findings; antenatal corticosteroids reduce the risk for RDS by 34%: RR 0.66, 95% CI 0.56–0.77) [187], updated with another meta-analysis of 27 studies ($n = 11{,}272$ women and 11,925 neonates from 20 LMICs) published up to September 3, 2020 [188], clearly demonstrate that the administration of a single dose of antenatal corticosteroids to pregnant women at risk for preterm delivery before 34 weeks of gestation reduces significantly the risk of NRF especially due to RDS by 29% (RR 0.71, 95% CI 0.65–0.78). The above evidence is reinforced by the 2019 European Consensus Guidelines on the Management of Respiratory Distress Syndrome which strongly recommends antenatal corticosteroids prophylaxis in all pregnancies with threatened preterm birth before 34 weeks of gestation (regardless of the level of income of the country) where active care of the newborn is anticipated [189].

Foetal distress or non-reassuring foetal status (NRFS) Foetal distress increases the odds of NRF by 3.2–5.59 [3, 120].

Meconium stained amniotic fluid (MSAF) MSAF is an independent risk factor for NRF which increases its odds by 2.85–7.8 [106, 120].

APGAR score A score ≤ 3 and < 7 at 1 min increases the likelihood of NRF by 2.7–72.9 [47, 120] and 3.1–5.19-fold [3, 99], respectively, whereas a score < 7 at 5 min increases the likelihood of NRF by 1.81–3.02 [47, 99].

Antenatal care visits One Thailand study reported that no antenatal care increases the likelihood of NRF by 5.23-fold (aOR: 5.23, 95% CI: 1.2–22.5, p: 0.02) [106]. Another study from Cameroon demonstrated that attending four or more antenatal care visits reduced the risk of NRF by 61% (aOR: 0.39, 95% CI: 0.16–0.98, p: 0.045) [3].

Diagnosis of neonatal respiratory distress

History

A detailed history guides in identifying the aforementioned maternal, foetal and/or obstetrical risk factors associated with the common aetiologies of NRF [190, 191].

Clinical diagnosis

All included studies diagnosed NRF mainly by physical examination of the newborn to assess the presence of either one or more criteria from a constellation of clinical signs. Overall, our search retrieved 41 different NRF definitions with 68 citations (Table 6). The most frequent NRF definition cited by 10 authors [6, 24, 38, 54, 63, 65, 69, 89, 138, 142] was the presence of at least two of the following signs: respiratory rate ≥ 60/min (tachypnoea), chest in-drawing/recessions/retractions (subcostal, xiphoid, suprasternal, intercostal or jugular), nasal flaring, expiratory grunting and cyanosis.

Assessment of the severity of NRF

Several clinical scores have been put forth to categorize the severity of NRF into mild, moderate and severe. The

Table 6 Existing case definitions of neonatal respiratory failure

Number of definition/number of citing authors	Authors	Definition
At least one criterion required in the definition of NRF		
01/06	Parkash [62] Sabzehei [132] Kuti [85] Verma [90] Ali [93] Gamhewage [104]	Tachypnoea or respiratory rate (RR) ≥ 60/min, chest retractions or in-drawings, grunting, nasal flaring and cyanosis
02/03	Tochie [3] Amani [74] Bahwal [101]	An abnormal RR (tachypnoea > 60 breaths/min, bradypnea < 30 breaths/min, respiratory pauses or apnoea); signs of laboured breathing (expiratory grunting, nasal flaring, intercostal recessions, xyphoid recessions or thoraco-abdominal asynchrony); with or without cyanosis
03/01	Hermansen [2]	Apnoea, cyanosis, grunting, inspiratory stridor, nasal flaring, poor feeding and tachypnoea (RR > 60 breaths per minute) and chest retractions (intercostal, subcostal or supracostal).
04/01	Mannan [87]	RR > 60/min, chest retraction, cyanosis, noisy or difficult breathing or grunting
05/03	Agrawal [27] Haque [52] Abou-Faddan [83]	Tachypnoea or RR > 60/min, chest retractions, nasal flaring, grunting
06/01	Wadi [49]	Tachypnoea or apnoea, chest retraction, grunting, cyanosis
07/01	Essomba [67]	Tachypnoea, apnoea with or without cyanosis
08/02	Zaman [55] Raha [110]	The presence of any of these clinical signs for > 2 h: RR > 60/min, chest retractions (subcostal, intercostal, sternal and suprasternal), noisy respiration in the form of grunt, stridor or wheeze
09/01	Al Ajeli [92]	The presence of any of these clinical signs for > 2 h: tachypnoea, increase chest in-drawing on respiration (subcostal, intercostal recessions) and grunting
10/01	Kumar [20]	The presence of any of these clinical signs for > 2 h: RR ≥ 60/min, grunting, intercostal or subcostal retraction
11/01	John [123]	One or more of the following within 6 h of birth: RR ≥ 60/min, grunting, intercostal or subcostal retraction, cyanosis
At least two criteria required in the definition of NRF		
12/10	Nagendra [24] Ersch [6] Qian [33] Santosh [54] Swarnkar [63] Barkiya [65] Islam [69] Rijal [89] Meena [138] Todkar [142]	Tachypnoea or RR ≥ 60/min, chest in-drawing/recessions/retractions (subcostal, xiphoid, suprasternal, intercostal or jugular), nasal flaring, expiratory grunting and cyanosis
13/01	Kisku [128]	RR > 60/min, subcostal retractions, intercostal retractions, xiphoid retractions, suprasternal retractions, expiratory grunt, flaring of alae nasi
14/02	Bajad [64] Lamichhane [97]	RR > 60/min, nasal flaring, grunting, intercostal or subcostal retractions
15/02	Aynalem [99] Enyew EF [114]	An abnormal respiratory rate (tachypnoea > 60 breaths/min, bradypnea < 30 breaths/min, respiratory pauses or apnoea); signs of laboured breathing (expiratory grunting, nasal flaring, intercostal recessions, xyphoid recessions); with or without cyanosis

Table 6 (continued)

Number of definition/number of citing authors	Authors	Definition
16/01	Mishra [107]	Respiratory rate ≥ 60/min, subcostal/intercostal recessions, expiratory grunt/groaning, in addition to these features that is presence of nasal flaring, suprasternal retractions, decrease air entry on auscultation of the chest
17/01	Kedy [96]	Abnormal respiratory rates (> 60 or < 30 breaths/min), signs of increased work of breathing (inspiratory sternal, intercostal and subcostal recession/in-drawing), expiratory grunting, central cyanosis and apnoea
18/01	Rinjswijk [21]	Tachypnoea with one of the following: central cyanosis, grunting, nasal flaring or subcostal or intercostal retractions
19/01	Manandhar [137]	RR > 60/min and at least one of the following low oxygen saturation (SpO_2 < 87%), chest retraction, grunting, nasal flaring and severe chest in-drawing
20/04	Malhotra [117] Bhakoo [25] Dutta [41] Nirosha [78]	Tachypnoea (RR ≥ 60/min), retractions and grunting
21/01	Sodawat [134]	At least 2 of the following on two consecutive examinations at least 1 h apart: RR ≥ 60/min, chest retraction (subcostal, xiphoid, suprasternal), flaring of alae nasi, expiratory grunt, cyanosis at room temperature
22/01	Panigrahi [141]	At least 2 of the following on two consecutive examinations at least 1 h apart: tachypnoea, chest wall retraction (subcostal, intercostal, suprasternal), apnoea, grunting, cyanosis at room air and gasping
23/01	Mehta [75]	At least 2 of the following on two consecutive examinations at least 1 h apart: tachypnoea, chest retraction (subcostal, xiphoid, suprasternal retraction) and expiratory grunt
All criteria listed in the definition are required for the diagnosis of NRF		
24/02	WHO [192] Aljawadi [94]	RR > 60 or < 30 breaths/min, grunting on expiration, chest in-drawing or central cyanosis (blue tongue and lips), apnoea (spontaneous cessation of breathing for > 20 s)
25/01	Kue [109]	Abnormalities of F (frequency of breathing), W (work), V (ventilation), O (oxygenation) assessed clinically based on rate of breathing, cyanosis and Silverman score and pulse oximetry
26/01	Pramanik [193]	Tachypnoea (RR > 60 breaths per min), cyanosis, expiratory grunting with chest retractions and nasal flaring
27/01	Adebami [72]	Grunting, inspiratory stridor, nasal flaring, poor feeding, RR > 60 breaths/min, retractions in the intercostal, subcostal or supra-costal spaces and cyanosis
28/01	Sévère [4]	Signs of laboured breathing (intercostal recessions, xiphoidal tugging, nasal flaring, expiratory grunting), lung crackles and organomegaly
29/01	Murki [194]	Increased work of breathing (WOB) in the form of tachypnoea, grunting, chest retractions and often associated with reduced air entry and cyanosis
30/01	Sathenahalli [84]	RR > 60/min, chest retraction, grunting, central cyanosis
31/01	Hundalani [124]	Tachypnoea (RR > 60/min), retractions and grunting
32/01	Manerkar [86]	Tachypnoea with RR > 60 breaths/min with or without retractions
33/01	Ding [96]	Clinically and blood gas confirmed hypoxemia requiring CPAP and/or intra-tracheal MV for at least 24 h or withdrawal of treatment/deaths within 24 h

Table 6 (continued)

Number of definition/number of citing authors	Authors	Definition
34/01	Qian [33]	Neonates who required endotracheal intubation and mechanical ventilation and/or nasal continuous positive airway pressure for at least 24 h during the first 7 days of life
35/01	Kattan [122]	Oxygenation index (OI) > 25 in two or more arterial blood gases
36/01	Lee [129]	Cyanosis, nasal flaring, moaning, tachypnoea and chest wall retraction
37/03	Wang [115] Wang [116] Wang [98]	Hypoxemia requiring endotracheal intubation and MV and/or nasal CPAP for at least 24 h during the first 7 days of life
38/01	Zhang [82]	Hypoxemia requiring nasal CPAP or intra-tracheal MV combined with surfactant for at least 24 h during the first 7 days of life
39/01	Ma [44]	Hypoxemia requiring respiratory support for more than 24 h
40/01	Oliver Rackham [196]	Persistent hypoxaemia or hypercapnia despite surfactant therapy and "maximal" conventional ventilation
41/01	Agnus [197]	MV (ICD-9-CM procedure codes 96.70, 96.71 and 96.72), excluding non-invasive CPAP in patients ≤ 28 days old on admission

RR respiratory rate, SpO_2 oxygen peripheral saturation, *CPAP* continuous positive airway, *MV* mechanical ventilation

most cited score is the Silverman-Anderson score with 26 citations [36, 43, 48, 54, 57, 64, 70, 75, 79, 81, 89, 95–97, 104, 107, 109, 126, 127, 135–137, 142, 143, 198, 199]; the Downes' score with 17 citations [24, 30, 54, 78, 85, 89, 105, 107, 117, 123, 126, 134, 136, 142, 143, 200, 201]; the Score for Neonatal Acute Physiology, Perinatal Extension II (SNAPPE-II) cited by nine studies [33, 44, 82, 98, 115, 116, 121, 195, 202]; the Neonatal Respiratory Distress Prognosis Score of Yopougon cited in two publications [8, 43] and the Acute Care at-Risk Newborns (ACoRN) respiratory score cited by one author [121]. Apart from being the most cited clinical score, increasing Silverman-Anderson score values correlate with worsening hypercapnia ($r = 0.35$, $p = 0.045$) and a score ≥ 5 predicts the need for respiratory support (AUC:0.85, sensitivity: 44%, specificity: 94%, positive likelihood ratio: 6.9, negative likelihood ratio: 0.9, $p < 0.001$) [203]. Meanwhile, a Downes' score of 5 points has a 94.12% sensitivity and 93.1% specificity in the clinical diagnosis of hypoxaemia in neonates with NRF [204]. However, compared to Silverman-Anderson score, Downes' score has been shown to have better accuracy and inter-rater reliability and it is easier to use by primary healthcare personnel (alpha = 0.69—acceptable, ICC—0.51 *vs.* alpha = 0.33—questionable, ICC—0.19) [205]. Other signs of NRF severity to note are cyanosis refractory to supplementary oxygen, haemodynamic instability, tachycardia > 160 beats per minute and capillary refill time > 3 s [206, 207].

Investigations

- Blood tests: complete blood count, C-reactive proteins (CRP), procalcitonin and blood glucose levels would help in the diagnosis of NRF aetiologies like neonatal infection, anaemia, polycythaemia, hypo/hyperglycaemia [191, 206–209].
- Microbiological tests: blood, urine or cerebrospinal fluid microbiology, culture and sensitivity would help identify the causative germ of a neonatal infection and would help to determine to which antibiotic the germ is sensitive [191, 206–209].
- Biochemical tests: serum malondialdehyde, superoxide dismutase, lactate dehydrogenase and blood pH are novel biomarkers that help predict and differentiate TTN from RDS [210].
- Imaging methods:
  - Chest X-ray: for the differential diagnosis of TTN, RDS, pneumonia and congenital malformations like oesophageal atresia and congenital diaphragmatic hernia [191, 208, 209].
  - Lung ultrasound: it is a relatively new, non-invasive, bedside, quick, reliable, highly informative, easy-to-use, reproducible and radiation-free imaging method that facilitates the diagnosis and differential diagnosis of RDS, TTN, pneumonia, pleural effu-

sions, pneumothorax and pulmonary malformations [211–213].
- Echocardiography: to exclude congenital heart diseases [2, 208].
- Transfontanel ultrasound: to exclude central aetiologies of NRD like perinatal asphyxia and its complications such as intracranial haemorrhage and periventricular leukomalacia [2, 208].

– Monitoring: transcutaneous pulse-oximetry, blood gases (PaO2 and PaCO2), electrocardiographic tracing, lung ultrasound features, ventricular ejection fraction, pulmonary arterial pressure. Here, shock, respiratory acidosis and pulmonary hypertension are signs of severity [193, 208].

Essentials of the diagnosis and management of some common aetiologies of NRF

Transient tachypnoea of the newborn

TTN, formerly called wet lung syndrome, is a benign condition due to delay in resorption of pulmonary fluid after birth [214]. A neonate with TTN typically presents with tachypnoea and diffuse fine crackles usually within 24 h of life [214]. There is mild oxygen dependence and no acidosis. Serum malondialdehyde cut-off value of 0.74 mmol/l (AUC = 0.983; sensitivity = 96%, specificity = 93%), serum superoxide dismutase cut-off value of 240 U/ml (AUC = 0.962; sensitivity = 93%, specificity = 90%), serum lactate dehydrogenase cut-off value of 483 IU/l (AUC = 0.920; sensitivity = 90%, specificity = 88%) and blood pH cut-off value of 7.39 (AUC = 0.897; sensitivity = 88%, specificity = 84%) are novel markers used to predict and differentiate TTN from RDS [210]. A chest X-ray may show interstitial opacities and occasionally thickened interlobular fissures suggestive of lung congestion [2]. Two systematic reviews with meta-analysis: one of six studies (n = 617 neonates) published until May 31, 2020 [215] and the second of seven studies (1514 neonates) published until January 31, 2021 [216], both clearly show that lung ultrasound scan has a high diagnostic performance for TTN respectively at AUC = 1.0 (0.98–1.0), sensitivity 0.98 (CI: 0.92–1.00), specificity 0.99 (CI: 0.91–1.00) [215] and AUC = 0.9906 (95% CI: 0.27–0.38), sensitivity 0.67 (95% CI: 0.63–0.71), specificity 0.97 (95% CI: 0.95–0.98) [216]. Lung ultrasound scores parallel respiratory severity scores and their use is currently advocated to monitor the clinical course of TTN [217] and to predict NICU admission for neonates delivered by CS [218]. TTN is a benign self-limiting disease and complete remission often occurs within 72 h of supplementary non-invasive oxygenation [207, 219, 220]. Because TTN is due to a delay in the resorption of pulmonary fluid after birth [214], there have been debates on whether fluid therapy in neonates with TTN should be restricted or not. Based on the findings of a recent systematic review of four clinical trials, it is impossible to determine whether fluid restriction has a benefit or harm in the management of TTN [221].

Respiratory distress syndrome or hyaline membrane disease

RDS or HMD is predominantly a disease due to primary surfactant deficiency resulting from pulmonary physiology immaturity [222]. RDS has to be distinguished from secondary surfactant deficiency triggered by pulmonary and extra-pulmonary causes that may respectively lead to direct and indirect neonatal acute respiratory distress syndrome (NARDS) [220]. The surfactant deficit in RDS decreases alveolar compliance leading to atelectasis, pulmonary hypoperfusion, hypoxaemia and ischaemia. Hyaline membranes are the end products of sloughed epithelia, eosinophils, proteins and oedema which conjointly accumulate in the alveoli [2]. Clinically, RDS often presents as an acute NRF within 24 h of life with exacerbation and oxygen requirements within the first 24–48 h of life followed by a stable phase till 72 h, then rapid frank amelioration of NRF between the 3rd and 6th day of life [222]. Expiratory grunting is generally the first clinical sign whilst tachypnoea is predominant during the disease [222]. Radiology is not specific and may show a fine reticule-granular pattern or a "ground-glass appearance" representing diffuse atelectasis and air bronchogram. This evolves with time to a confluent opacity with loss of the cardiac, mediastinal and pulmonary contours resulting in complete bilateral opacity [222]. Antenatal tests like amniocentesis for lecithin-sphingomyelin ratio < 2 and prostaglandins levels also add more clues to its diagnosis [222]. Serum malondialdehyde cut-off value of 1.87 mmol/l (AUC = 0.991; sensitivity = 98%, specificity = 96%), serum superoxide dismutase cut-off value of 226 U/ml (AUC = 0.973; sensitivity = 96%, specificity = 94%), serum lactate dehydrogenase cut-off value of 935 IU/l (AUC = 0.943; sensitivity = 93%, specificity = 89%) and blood pH cut-off value of 7.29 (AUC = 0.917; sensitivity = 90%, specificity = 88%) are novel markers used to predict and differentiate RDS from TTN as earlier said [210]. As aforementioned, preventive measures using antenatal glucocorticoids is a strong current universal recommendation [189]. Supportive treatment includes caffeine therapy, enteral or parenteral nutrition, supplementary oxygen via non-invasive ventilation (such as continuous positive airway pressure [CPAP] and non-invasive high-frequency ventilation [NIHFV]) and invasive mechanical ventilation (IMV) if no respiratory autonomy by the neonate [207, 223–225]. Its curative treatment

entails administering exogenous surfactant [207, 223, 224]. Supportive treatment by supplementary oxygen targeting a fraction of inspired oxygen (FiO_2) best between 0.30 and 0.40 before surfactant treatment reduces the need for IMV [226]. Evidence from a retrospective cohort study recently demonstrated that compared to the use of non-invasive positive pressure ventilation, the use of NIHFV in the treatment of RDS statistically significantly increases the oxygenation indices (PO_2, a/APO_2, SaO_2) and reduces carbon dioxide retention ($PaCO_2$), the need of tracheal intubation and the duration of hospital stay [227]. Recent evidence from a systematic review and meta-analysis of 16 observational and one randomized controlled trial shows that exogenous surfactant administered to preterm and term neonates with RDS reduces the risk of air leak, persistent pulmonary hypertension (PPHN), the duration of IMV and the risk of death [228]. Likewise, a systematic review of 18 studies (amongst which 16 were RCTs) with meta-analysis published in 2021 is in favour of the administration of surfactant into the trachea through a thin catheter in spontaneously breathing preterm neonates (as opposed to through an endotracheal tube) because this significantly reduces the risk of mortality, respiratory support within the first 72 h of life, intra-cerebral haemorrhage and chronic complications such as BPD [229]. Endotracheal intubation with a thin catheter, followed by surfactant administration and then extubation within the first 2 h of life also significantly reduces the risk of CPAP failure, pneumothorax and PPHN in late preterm newborns ($33–36^{6/7}$ weeks) [230]. There is no evidence as to whether a second dose of surfactant improves outcomes in premature neonates with persistent RDS after the administration of the first dose of surfactant [231]. A recent well-powered meta-analysis of 17 RCTs ($n = 4780$) clearly showed that inhaled nitric oxide (iNO) does not improve clinical outcome [232]. Findings from a systematic review and meta-analysis of 4 RCTs affirm that the use of extracorporeal membrane oxygenation (ECMO) for severe RDS improves survival by 56% (reduction of mortality RR 0.44; 95% CI 0.31) with significant benefits on cost-effectiveness [233]. As seen in TTN, lung ultrasound score also accurately predicts NICU admission after CS birth [218]. The establishment of a national guideline for the management of RDS as seen in Wales is a positive step towards a significant improvement in the care of neonates with RDS [225]. Despite the above measures, the management of RDS remains complex and should be personalized according to the physiopathology and actual newborn's needs using especially, quantitative lung ultrasound assessment which has higher diagnostic accuracy (meta-analytic AUC: 0.952 [95% CI: 0.951–0.953]) and to a lesser extent, surfactant absorption assay (AUC: 0.840 [95% CI: 0.824–0.856]) and stable microtubule test (AUC: 0.800 [95% CI: 0.788–0.812]) [211].

Neonatal infection or neonatal sepsis

Neonatal sepsis has no pathognomonic sign or symptom. Per 2002 French guidelines, a characteristic neonate with NRF due to neonatal sepsis may have infection-related anamnestic criteria (aforementioned under the sub-heading "Infectious anamneses"), clinical signs of infection (jaundice, pallor, fever, hypothermia, refusal to feed, abdominal distension, vomiting, hypotonia, irritability, altered consciousness, convulsions, coma) and any of the following laboratory tests' findings: leucocytosis > 25,000/mm^3, leucopoenia < 5000/mm^3, myelemia (more than 10% of leucocyte counts is made of immature leucocytes), platelets count < 150,000/mm^3, CRP > 20 mg/l, elevated procalcitonin levels and positive bacterial culture from blood, urine or cerebrospinal fluid sample [234]. A multicentre cohort study published in 2022 identified the following as equally being significant risk factors of neonatal sepsis-related NRF: maternal hypertension, previous maternal hospitalization within 12 months, average or higher monthly household wages, ward size (> 11 beds) and type (neonatal unit or NICU), residing in a rural area, preterm birth, perinatal asphyxia and multiple births [235]. The mainstay of the treatment of neonatal infection is through the intravenous (IV) administration of at least two antibiotics, either ampicillin plus gentamycin or a third-generation cephalosporin plus gentamycin [156].

Meconium aspiration syndrome

MAS is defined as NRF due to inhalation of MSAF with resultant: (a) partial or complete obstruction of the airways by meconium plugs leading to some areas of atelectasis and hyper-inflated lungs; (b) damage of the epithelial lining of the bronchi, bronchioles and alveoli by foetal pancreatic enzymes contained in meconium; (c) surfactant inactivation by proteins and fatty acids contained in meconium and (d) chemical pneumonitis: meconium is a chemo-attractant for neutrophils and macrophages and also a source of pro-inflammatory mediators such as interleukins and tumour necrosis factors [144]. MAS presents clinically as early onset of NRF in a neonate born in MSAF with or without an antenatal history of NRFS. There is a hyper-inflated or a "barrel" chest, diffused crackles and sometimes a low APGAR score secondary to acute or chronic foetal distress [2, 144]. A chest X-ray shows a coarse nodular opacity, areas of hyperinflation and atelectasis [144]. Current guidelines on the management of MAS by the Neonatal Resuscitation Program (NRP) stipulate supplementary oxygen and assisted ventilation via endotracheal intubation followed by direct endotracheal suction soon after delivery for non-vigorous neonates born in MSAF who have NRF, poor muscle tone and/or heart rate less than 100/min [236, 237].

Previous treatment measures which are now contraindicated include routine intrapartum oropharyngeal and nasopharyngeal suctioning after delivery of the head for infants born with clear or MSAF [237, 238]. Also, ventilation before aspiration is contraindicated [144] and prophylactic use of antibiotics in MAS is only indicated in case of definite perinatal risk factors for neonatal sepsis [26].

Perinatal asphyxia or hypoxic-ischaemic encephalopathy

Prevention of the risk factors and causes of HIE is more important than treatment. The need for this risk assessment is primordial via reliable clinical diagnostic criteria for perinatal asphyxia. Amongst these diagnostic criteria, we distinguish the Sarnat and Sarnat score, the APGAR score [239], and the American Academy of Paediatrics (AAP) and the American College of Obstetricians and Gynaecologists (ACOG) criteria [240]. The Sarnat and Sarnat score helps in diagnosing and stratifying the severity of HIE into three stages based on the degree of neurological depression and alteration of the electroencephalogram of the neonate [241]. This score has been shown to have strong inter-rater reliability except for the motor tone and Moro reflex in preterm neonates [241]. The AAP and AGOG take into consideration four clinical criteria to characterize perinatal asphyxia [240]: a pH < 7 (from umbilical arterial blood samples); an APGAR score between 0 and 3 at the fifth minute; the presence of neurological signs in the immediate neonatal period (hypotonia, convulsion and coma) and clinical evidence of multi-organ dysfunction. Although the APGAR score has been criticized because it does not accurately identify or predict subsequent acute respiratory disorders and neurodevelopmental outcomes of the newborn, and many considered it obsolete, few would deny that its application at 1 and 5 min of life accomplishes a vital goal of focusing attention to the infant immediately after birth [239, 242]. The APGAR score is still the most feasible and practical neonatal clinical evaluation to perform in the delivery room [243] as well as it is still a valid and rapid index for assessing cardiorespiratory adaptation at birth and the effectiveness of resuscitative efforts [244]. The management of perinatal asphyxia includes admission into a neonatal unit or preferably in a NICU immediately after birth; respiratory support via non-invasive (nasal prongs or oxygen masks) or invasive measures via endotracheal intubation and mechanical ventilation as needed; assuring haemodynamic stability; avoiding metabolic imbalance like hypernatraemia, hyponatraemia, hypoglycaemia and hyperglycaemia as these are deleterious for the injured brain; treating any comorbidities such as sepsis; neuroprotection by the maintenance of a body temperature between 36 and 36.5 °C; and administering anticonvulsants in case of convulsions [207].

Neonatal acute respiratory distress syndrome

NARDS is one of the most dreadful NRF entity occurring at prevalence of 1.5% in NICUs and is associated with a high neonatal mortality rate of 23.8% [202]. It is due to an abnormality in surfactant function or surfactant amount and marked inflammation of lung parenchyma triggered by primary/direct/pulmonary causes (e.g. pneumonia, bronchiolitis, aspiration, lung haemorrhage, pertussis) or secondary/indirect/extra pulmonary causes (e.g. HIE, sepsis, chorioamnionitis, necrotising enterocolitis, peritonitis, surgery) [220]. This leads to an increased surface tension in alveoli causing atelectasis, intrapulmonary shunts, ventilation or perfusion mismatching which worsen hypoxaemia [220]. As a useful clinical clues: NARDS affects more male neonates; sepsis is the most frequent trigger of NARDS; direct NARDS is more common in term newborns and has a better survival rate than indirect NARDS; indirect NARDS is associated with infectious triggers and preterm neonates [202].

The "Montreux definition" published in 2017 by experts in a position paper is the universally accepted standard diagnosis of NARDS [220]. Per the latter definition, NADRS applies to a neonate with respiratory failure from birth to 4 weeks of age or 44 weeks' post-menstrual age regardless of GA, birth weight or means of respiratory support and fulfilling all the following five criteria: (i) timing of injury: acute onset (i.e. within 1 week) from a known or suspected clinical insult; (ii) exclusion criteria: absence of RDS, TTN or congenital malformation (e.g. CHD, CDH, pulmonary adenomatous or sequestration) as current acute primary respiratory disorder; (iii) lung imaging: presence of diffuse, bilateral, irregular opacities, infiltrates or complete pulmonary opacification, which are not fully explained by the conditions representing the exclusion criteria; (iv) exclusion of a cardiac origin oedema by using heart ultrasound to rule out a CHD and (v) oxygenation impairment evaluated as oxygenation index (OI): OI of 4.0–7.9 for mild NARDS, 8.0–15.9 for moderate NARDS and 16.0 or higher for severe NARDS [220]. The management of NARDS is complex and depends on the type of trigger and severity of NARDS [202]. Major therapeutic modalities currently use include exogenous surfactant (mainly indicated for direct and infectious NARDS), NIV (e.g. nasal intermittent positive pressure ventilation, nasal high-frequency oscillatory ventilation, nasal CPAP, bi-level positive airway pressure), invasive ventilation (e.g. high-frequency oscillatory ventilation and conventional mechanical ventilation) and ECMO as rescue therapy for intractable NRF [195, 202].

Congenital heart diseases

Congenital heart diseases (CHD) could be cyanotic or acyanotic heart diseases [245]. In both cases, the newborn can

present with NRF, a heart murmur, cardiomegaly and/or signs of heart failure depending on the severity of the CHD [3, 245]. However, cyanosis and hypoxaemia refractory to supplementary oxygen are solely features of cyanotic heart diseases [245]. A heart ultrasound or an echocardiography often confirms the diagnosis by identifying the type of CHD and its severity and helps to differentiate a cyanotic CHD from PPHN of the newborn [3, 245]. The treatment of CHD can be medical or surgical depending on its severity and the type of CHD [245].

Choanal atresia

It is a congenital malformation caused by partial or complete imperforation of the posterior nasal cavity into the rhinopharynx. This pathology is important because the newborn breathes exclusively through the nostrils [10]. The diagnosis is suspected clinically in case of the impossibility of passing a nasogastric tube through the nostrils into the nasopharynx and NRF which improves when the baby cries. The diagnosis can be confirmed by a CT-scan of the nasal cavity [3, 10]. The definitive treatment to date is surgery. Whilst waiting for surgery, securing the oropharyngeal airway with a Guedel cannula is recommended [10].

Congenital diaphragmatic hernia (CDH)

CDH is caused by herniation of abdominal viscera through the diaphragm (usually at the postero-lateral foramen of Bochdalek or the anterior foramen of Morgagni) which leads to pulmonary compression and pulmonary hypoplasia resulting in NRF [10]. The clinical diagnosis is evoked in the presence of NRF associated with a scaphoid abdomen, a displaced apex heartbeat, absence of breath sounds on the affected side and bowel sounds in the chest [2, 10, 193]. A chest radiograph shows air-filled bowel loops usually in the left hemithorax (usually the left hemithorax) with non-visualization of the diaphragmatic margin, mediastinal shift and a relative paucity of abdominal gas. A bedside cardiac ultrasound scan is mandatory to rule in or out any associated congenital heart defect which usually aggravates the prognosis [10]. It is worth mentioning that prenatal diagnosis of CDH is possible via an antenatal ultrasound for foetal morphological assessment. The emergency measures include inserting a nasogastric tube to drain intra-thoracic draped intraluminal air or bowel content within the concerned hemithorax. AMBU mask ventilation is contraindicated as it causes bowel distension and increases the mediastinal shift with resultant compression of the contralateral lung and also compromises cardiac function. Surgery remains the curative treatment [10].

Oesophageal atresia with or without tracheoesophageal fistula

It is another congenital malformation that causes NRF by the aspiration of saliva or gastric juices into the tracheobronchial tree through a tracheoesophageal fistula (TEF) [10]. Prenatal diagnosis can be made using an antenatal ultrasound for foetal morphology where polyhydramnios is often a sign of oesophageal atresia [191, 193]. After delivery, TEF is suspected clinically when there is an obstruction in the insertion of an orogastric tube in an attempt to perform the "syringe test" which entails the injection of air through the orogastric tube. Other clinical arguments in favour of its diagnosis include NRF with hypersalivation and/or choking during feeds. A lateral radiograph film with an orogastric tube in situ shows a coiled orogastric tube in the upper pouch and an anteroposterior film gives valuable information on the status of the lungs [10]. The definitive curative treatment of oesophageal atresia with or without tracheoesophageal fistula is surgery [10].

From the above, we proposed a simple and practical clinical algorithm to diagnose and manage NRF as illustrated in Supplementary file 3.

Discussion

This review examined the existing contemporary literature on NRF to determine its global prevalence, mortality rate, risk factors, diagnosis, aetiologies and management. We found that the prevalence and mortality rate of NRF was alarming in low-resource settings. RDS was the first NRF aetiology and the most frequent cause of NRF-related deaths. Predictors of NRF could be grouped into foetal, maternal and obstetrical risk factors. We spelled out the current diagnostic and therapeutic modalities of the most frequent aetiologies of NRF and ended up by proposing a simple and practical algorithm for prompt diagnosis/management.

The global prevalence of NRD

These results on the prevalence of NRF reflect a high heterogeneity in the prevalence of NRF amongst the 99 studies retrieved due to several parameters. Firstly, as the aforementioned data on the countries with the highest and lowest prevalence of NRF depict, LMICs especially in Africa and Asia are disproportionately affected by NRF compared with HICs in America and Europe. For instance, between the years 1974 and 2004, the rate tremendously decreased by almost fivefold to 3.8% in HICs like Switzerland [6] due to an improvement in the neonatal outcome of NRF owing to several innovations in neonatology such as the creation of NICUs, induction of foetal lung maturation with antenatal steroids, optimization of neonatal

resuscitation guidelines, administration of exogenous surfactant to treat immature lungs, the provision of affordable caffeine and the introduction of sophisticated modes of respiratory support like CPAP which are insufficient or non-existent in LMICs [223, 224]. Secondly, the high heterogeneity can be explained by differences in study methods with up to 41 different citations for the clinical diagnosis of NRF. The 41 NRF definitions differed in terms of the minimum number of criteria needed for case definition as well as different timing in NRF diagnosis which must have either under-estimated or over-estimated the prevalence of NRF. Thirdly, the heterogeneity in the prevalence of NRF may be explained by the 30 years review period: in eight studies [19–26] published between 1992 and 2001, the prevalence of NRF varied between 0.64 and 60%. From 20 studies [6, 7, 27–32, 34–45] published between 2002 and 2011, the prevalence of NRF varied between 1.6 and 88.4%. Between 2012 and 2022, 71 studies [3, 44, 46–49, 51–115] reported the prevalence rate of NRF to vary between 0.9 and 84.8%. These results show a rise in the prevalence of NRF between the years 1992 and 2022 despite the insidious improvements in neonatal care and health infrastructures over time, globally [3]. Fourthly, this heterogeneity can also be explained by study settings. It is expected that a large proportion of newborns suffering from NRF will be admitted to specialized departments like the NICUs, SBCUs and neonatal units. As such, a high prevalence of NRF was reported between 26.2 and 58.4% for SBCUs [52, 72, 85], 2.2 and 84.8% for neonatal units [3, 22, 23, 25, 26, 36, 41, 43, 49, 53, 58, 61, 66–68, 75, 77–79, 81, 86, 94–96, 109] and 0.9 and 88.4% for NICUs [7, 30, 38, 39, 42, 44–46, 48, 54, 57, 59, 60, 62–65, 69–71, 73, 74, 76, 80, 82–84, 87, 89–91, 93, 97–103, 105–108, 110, 111, 113–115], compared with less specialized units in the management of NRF such as maternities [20, 21, 24, 29, 31, 32, 35, 37, 47, 51, 55, 56, 92, 104, 112] where we observed an NRF prevalence varying between 0.64 and 18.5%. Still, regarding the study setting, it was expected that single-centre studies should have a lower NRF prevalence than multicentre studies. On the contrary, the NRF prevalence rate ranged from 0.9 to 88.4% in single-centre studies compared with lower rates varying between 0.64 and 21% in multicentre studies, probably explained by the fact 82.7% of single-centre studies were carried out in specialized neonatal care centres (NICUs, neonatal units and SCBUs) compared to 66.6% multicentre studies conducted in specialized neonatal care centres (Table 3). Furthermore, the heterogeneity observed in the prevalence rates of NRF across the 99 included studies can be explained by the varying gestational ages in these studies: 17.2–49.6% in premature newborns only [37, 47, 57, 61, 66, 86, 115] versus 1.6–47.2% in term neonates only [30–32, 34, 40, 42, 49, 68, 78, 91, 96, 104, 106, 109]. These findings generally show that the prevalence of NRF decreases with increasing gestational age owing to functional and structural immaturity of the lungs in premature neonates [3].

Aetiologies of NRF and NRF-related in-hospital mortality

The persistence of RDS as lead NRF aetiology and cause of NRF-related in-hospital death as far back as the year 1995 [117] to as recent as the year 2021 [108, 110] may imply that despite the progress made in NRF management over the last four decades, more therapeutic advances still need to be made. These efforts need to be particularly allocated to the Americas and Asia where neonates are disproportionately affected by RDS. As expected, neonatal sepsis is a still major global health concern in Africa. A preponderance of TTN in Europe and the Middle East may reflect high rates cesarean deliveries. The in-hospital mortality rate due to NRF in LMICs was higher compared to HICs, re-inforcing claims of NRF being a public health condition disproportionately affecting LMICs, especially in Sub-Saharan Africa (SSA) [3, 8, 99].

Predictors or risk factors associated with NRF

With regards to the foetal risk factors, the role played by prematurity as a risk factor for NRF can be explained by a primary surfactant deficiency due to structural and functional immaturity of the foetal lung [171, 246]. Male neonates have a higher prevalence of NRF due to slower lung maturation by delayed pulmonary biomechanics and delayed pulmonary vascular development induced by the higher concentration of serum androgens in males compared with their female counterparts [247, 248]. Indeed, testosterone regulates the transduction of epidermal growth factor, the transformation of growth factor-β, hence, delaying foetal lung maturation. Foetal androgens also slow the growth of type II pneumocytes and the secretion of fibroblast-pneumocyte factor, thus, reducing the secretion of foetal lung surfactant [249, 250]. Meanwhile, oestrogen enhances the growth of synthesis of type II pneumocytes and increases the secretion of foetal pulmonary surfactant as a whole by promoting the synthesis of surfactant components such as lecithin, phospholipids and surfactant protein A or B [249, 250]. Black neonates have a reduce NRF risk due to an intrinsic accelerated timing of lung maturation [147–152] evidenced by higher lecithin/sphingomyelin ratios in black neonates compared with Caucasians [147]. Contradicting findings [30] of LBW not being a risk factor for NRF could be explained by the presence of intrauterine stressful conditions associated with LBW/small for gestational age, which enhances surfactant secretion and foetal lung maturation in LBW neonates with IUGR. The pathophysiology of NRF in high birth weight neonates is attributed to its frequent association with maternal diabetes and other obstetrical complications such as acute foetal distress, shoulder dystocia and hypoglycaemia [251]. Advanced maternal age is associated with NRF due to increased incidence of high-risk pregnancies (hypertensive diseases of pregnancy,

gestational diabetes mellitus, placenta praevia or abruptio placentae), high preterm deliveries or caesarean deliveries in older women [171]. The role played by maternal smoking in predisposing neonates to NRF is yet to be elucidated. Neonatal sepsis anamnestic criteria except PROM have been shown to predispose a neonate to NRF. PROM is hypothesized to decrease the incidence of NRF due to a foetal inflammatory syndrome induced by PROM which accelerates foetal pulmonary maturation [252]. However, this remains controversial, because PROM leads to oligo-hydramnios which can cause pulmonary hypoplasia [252]. GDM and PGDM lead to intra-uterine exposure to maternal hyperglycaemia resulting in an increased trans-placental transfer of glucose to the foetus leading to foetal hyperglycaemia [253]. Foetal hyperglycaemia, in turn, stimulates the secretion of insulin by foetal pancreatic β-cells leading to hyperinsulinism which inhibits the synthesis of foetal lung surfactant [253]. The negative feedback effects of foetal hyperinsulinism also ends in foetal hypoglycaemia with a resultant surge in metabolic demands leading to increase respiratory efforts [253]. Antepartum haemorrhage exerts its effect as a risk factor via foetal anaemia from low uteroplacental blood flow to the foetus leading to foetal hypoxia [254, 255]. Hypertensive disorders during pregnancy are associated with NRF due to abnormal placentation (characterized by shallow invasion of the maternal arteries), placental hypoperfusion or uteroplacental insufficiency with resultant compromised blood flow to the foetus (critical in the maintenance of foetal pulmonary alveolarization leading to an anti-angiogenic effect with impaired foetal pulmonary vascular and alveolar development), IUGR and preterm birth with surfactant deficiency and lung immaturity [160, 165, 256]. The pathophysiology underlining the association between NRF and multiple pregnancies is still to be elucidated. Caesarean section impairs the physiological changes (secretion of catecholamines and glucocorticoids which trigger pulmonary fluid resorption, secretion of surfactant and pulmonary vasodilatation) occurring during labour and necessary for the normal cardiorespiratory adaptation of the newborn [173, 257, 258]. Hence, elective CS before the onset of labour is more related to TTN. Meanwhile, emergency CS due to foetal distress is related to intrapartum asphyxia or HIE [3]. Hypnotics administered during general anaesthesia for caesarean delivery induce central nervous system depression with resultant NRF. Local anaesthetics used for spinal anaesthesia during CS decrease the uteroplacental blood flow leading to NRF [182]. Undoubtedly, antenatal corticosteroids reduce the risk of NRF via a process entailing the acceleration of foetal lung maturation [187, 188]. NRFS, MSAF and APGAR score at birth often share a linked or chained mechanism in their prediction of NRF. An abnormal intrapartum foetal heart monitoring (NRFS) reflects ongoing foetal cerebral hypoxia, hypoperfusion of other vital organs and anaerobic metabolism due to placental insufficiency, umbilical cord accidents, antepartum haemorrhage and rapid, prolonged or obstructed labour [259]. NRFS leads to NRF due to pulmonary arterial hypertension, ischaemic heart disease and heart failure but more frequently due to perinatal asphyxia [259, 260]. Asphyxiated foetuses usually emit meconium in amniotic fluid, indicative of foetal distress and would be delivered as a low-APGAR neonate with poor respiratory vital signs [144]. Attending four or more antenatal care visits is suggestive of an adequate or good pregnancy follow-up with a subsequent reduction in the incidence of obstetrical complications such as maternal diabetes/GDM, hypertensive disorders of pregnancy and antepartum haemorrhage which predispose to NRF [3].

Diagnosis of NRF

The use of Downes' score to assess the clinical severity of NRF needs emphasis due to its better diagnostic performance and clinical applicability than Silverman-Anderson score [205]. In the current era of precision medicine, the use of novel externally validated diagnostic and monitoring tests such as serum malondialdehyde, superoxide dismutase, lactate dehydrogenase and lung ultrasound to predict or rule in/out differential NRF aetiologies is the standard good clinical practice [210–213]. However, the utility of these relatively expensive tests demanding skilled labour is limited in LMICs [3, 8]. Finally, we proposed a simple and practical diagnostic and management algorithm in Supplementary material S3 for NRF. The clinical use of this clinical algorithm may promote timely diagnosis and management of NRF and improve the overall neonatal outcome or prognosis. This would of course need further exploration in large cohorts of neonates with NRF.

Study limitations and strengths

The main drawback of the current study is the heterogeneity across all the studies included, which hindered a meta-analysis. Indeed, carrying out a meta-analysis with a pooled prevalence, mortality rate of NRF and risk estimate was inappropriate because of a variety of methodological differences between the included studies. Nonetheless, the current scoping review is a reference-contemporary document of citations over the last three decades on the global scene of NRF and it sets the pace to conduct a proper systematic review and meta-analysis of epidemiological studies on NRF.

Conclusion

NRF has an alarming prevalence especially in LMICs of Asia and Africa where RDS and neonatal sepsis respectively represent major NRF plagues. Most of its identified

predictors (e.g. gestational age, birth weight, maternal smoking, pregestational/gestational diabetes mellitus, infectious anamneses, gestational hypertensive disorders, foetal distress, APGAR score, meconium-stained amniotic fluid and pregnancy follow-up) are modifiable. Hence, we recommend a change of maternal life style habits, adequate antenatal care, intra-partum care and postnatal care to advert these risk factors as well as for a better anticipation of the management of NRF. Meanwhile, the urgent need for more aggressive treatment and innovations targeted towards RDS, preferably subsidized in resource-constrained settings, cannot be over emphasized in a step forward to curb the high NRF-related mortality.

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Authors' contributions Study conception by Joel Noutakdie Tochie. Study search, data extraction and charting, assessment of methodology quality and sub-analyses by Joel Noutakdie Tochie and Aurelie T Sibetcheu. The first draft of the manuscript was written by Joel Noutakdie Tochie. Interpretation of data and critical revisions by Joel Noutakdie Tochie, Aurelie T Sibetcheu and Pascal Ebot Arrey-Ebot. Critical revisions for important intellectual content and supervision of the study by Simeon-Pierre Choukem. Joel Noutakdie Tochie is the guarantor of the review. All authors read and approved the final manuscript.

Data availability All data generated or analysed during this study are included in this published article.

Declarations

Ethics approval This article is a review; consequently, there is no ethical statement required.

Consent to participate This article is a review; consequently, there is no consent to participate required.

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