

The epidemiology, risk factors, mortality rate, diagnosis, etiologies and treatment of neonatal respiratory distress: a scoping review

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Abstract

Background: Quite a tricky day-to-day clinical condition which may present as the first alarming sign of a life-threatening pathology, neonatal respiratory distress (NRD) remains an emergency until its etiology is diagnosed and appropriate treatment delivered to the neonate. While the prevalence, risk factors, etiologies, diagnosis and management of this potentially fatal neonatal condition has not been examined extensively, the objective of this scoping review is to synthesise contemporary studies on the prevalence, risk factors, etiologies, diagnosis and management of NRD.

Methods: We searched MEDLINE and Google Scholar up to November 13, 2020 for observational and experimental studies and systematic reviews addressing NRD without language restriction. Eight investigators working in four pairs independently selected and extracted relevant data. The methodological quality of all included studies was assessed.

Results: We included 81 studies eligible with a total of 511,158 neonates from 21 countries across the world. The risk of bias was low in 61 (75%), moderate in 14 (17%), and high in six (8%) studies. The prevalence of NRD ranged from 0.21 to 84.8% and the highest prevalence rates were observed in Saudi Arabia (78.5%) and Iraq (84.8%). Its highest reported case fatality rates were in Sudan (36%) and India (47.1%). Predisposing factors included prematurity, male gender, low and high birth weights, low socio-economic status, smoking, infectious anamneses, diabetes mellitus, antepartum haemorrhage, cesarean delivery, fetal distress, anesthetic drugs and meconium stained amniotic fluid. Attending four or more antenatal care visits conveyed protection against NRD. Its diagnosis was mainly clinical using the Silverman-Anderson score. Its leading etiology was neonatal infection followed by transient tachypnoea of the newborn and hyaline membrane disease. With regards to its management, it is widely recommended to start with resuscitation followed by specific management of the etiology of NRD by medical or surgical measures or both.

Conclusion: The prevalence and mortality rates of NRD are alarming, particularly in low- and middle-income countries. Most of its risk factors are preventable. Neonatal infections is the leading cause of NRD. Overall, we have presented an updated overview of NRD which should serve to ameliorate its healthcare.

Background

The term Neonatal Respiratory Distress (NRD), applies to all forms of abnormal gaseous exchange at the level of the lung of a neonate irrespective of the cause (1,2). It is an inability to maintain respiratory homeostasis, leading to impairment of gaseous exchange, ventilation-perfusion mismatch and cerebral anoxia. Its vital risk imposes a rapid diagnosis and an urgent treatment of its etiology (1). NRD is one of the most common clinical manifestation of disease in the early neonatal period (1,3). NRD is a common neonatal emergency worldwide (4).

A tremendous decrease in the NRD case fatality rate has occurred over the last seven decades in high-income countries (5). In 1997, the mortality rate due to NRD in India was between 40 - 60%, which is equivalent to the rate in the United States during the 1950s and 1960s (5). This improvement in neonatal outcome due to NRD in high-income countries is due to several improvements in neonatal care such as the advent of Neonatal intensive care units (NICUs), induction of fetal lung maturation with antenatal steroids, administration of exogenous surfactant to treat immature lungs, the introduction of mechanical ventilation modes like continuous positive airway pressure, which are scarce or non-existent in low-income countries (5,6). Thus, the recommendations are "prevention of NRD by early detection of its risk factors to ensure timely intervention and also the early treatment of its etiologies are crucial in reducing the high NRD specific mortality rate in low resource setting" (4,7-9). The etiologies of NRD are several and are usually divided into medical and surgical causes (2,10), with the medical causes being predominant. NRD can be due to a benign process, such as transient tachypnoea of the newborn (delayed resorption of lung fluid), or could be the first manifestation of serious infection, encephalopathy or congenital malformations (7), which endanger the vital prognosis of the neonate.

With an extensive literature search, there is no comprehensive summary addressing this potentially lethal neonatal emergency (NRD), which continues to plague low- and middle-income countries (LMICs) in particular where it is a major contributor to

the neonatal mortality ratio (4,11) and partly prevents LMICs to attend the sustainable development goal 3 which has as target “fewer than 10 deaths per 1000 live births by 2035” (12). We proposed this review to critically summarize the prevalence, incidence, mortality, risk factor, etiologies, diagnosis and management of NRD.

Methods

We searched two main electronic databases: MEDLINE (via Pubmed) and Google Scholar from inception to November 13, 2020, for observational, and interventional studies addressing the NRD without language restriction. A comprehensive search strategy was conducted using the keywords: “prevalence”, “incidence”, “mortality”, “risk factor”, “etiologies”, “causes”, “diagnosis”, “treatment”, “management”, cross-referenced with the names of all countries to obtain the maximum possible number of studies (Table 1). The reference lists of retrieved articles were scanned to identify any additional relevant studies. One pair of reviewers (JNT and ATS) independently screened records by abstract and title. Subsequently, four pairs of investigators (JNT, ATS, CD, ANM, IK, GA, JRN and MNT) independently screened relevant full texts for articles and reported the prevalence, incidence, mortality, risk factor, etiologies, diagnosis and management of NRD. We only included peer-reviewed observational and interventional studies and systematic reviews. We excluded modeling studies, qualitative studies, letters to the editor and conference proceedings. A standardized and pre-tested data extraction form was used by four pairs of investigators (JNT, ATS, CD, ANM, IK, GA, JRN and MNT) to independently extract bibliometric information (the name of the first author and the country where the study was conducted), the sample size of the study, prevalence, incidence, mortality, risk factors, diagnostic method, etiologies and management of NRD. Discrepancies between the four pairs of authors (JNT, ATS, CD, ANM, IK, GA, JRN and MNT) were solved through consensus and arbitrary by a third reviewer (DHN) when a consensus could not be reached. Eligible studies were scrutinised for quality of their methods using the different Hoy et al tool (13), the SPIRIT 2013 tool (14), and the AMSTAR 2 tool (15) for observational, randomized controlled trials and systematic reviews respectively. Finally, using data retrieved from a myriad of epidemiological studies, interventional studies and systematic reviews, the ensuing results present a narrative synthesis of the most up-to-date and key literature regarding neonatal respiratory distress

Results

Selection

We included 81 studies with a total of 511,158 neonates from 21 countries across the world. The risk of bias was low in 61 (75%), moderate in 14 (17%), and high in six (8%) studies.

Prevalence and incidence of neonatal respiratory distress

There was a high heterogeneity in studies reporting the prevalence rate of NRD due to the large methodological differences, especially in the definition or diagnostic method of NRD between studies. The prevalence of NRD ranged from 0.21 to 84.8% and the highest prevalence rates were observed in Ethiopia (67%) in 2019 (14), Saudi Arabia (78.5%) in 2018 (15) and Iraq (84.8%) in 2019 (16) as illustrated in Table 2.

Mortality rate due to neonatal respiratory distress

The neonatal mortality rate due to NRD (case fatality rate) in LMICs was higher compared with high-income countries (3,5,8,9). In Morocco in 2009 (30), Sudan in 2014 (38) and India in 2018 (27) the NRD specific mortality rate was highest; 33.3%, 36% and 47.1% respectively. On the other hand, a tremendous decrease in the NRD specific mortality rate has occurred over the last six decades in high-income countries (5). Between the years 1974 to 2004, the NRD specific mortality rate decreased from 15.5% to 3.5% in Switzerland (6) and it was at 1.2% in Turkey in 2008 (7). In the series by Tochie et al (4) in Cameroon, the NRD mortality rate (24.5%) was twice that of newborn without NRD, $p < 0.001$. The main contributors to the death toll of NRD were neonatal sepsis at 42.7%, respiratory distress syndrome (RDS) or hyaline membrane disease (HMD) at 24.4%, perinatal asphyxia at 15.9%, congenital malformations at 13.4% and meconium aspiration syndrome (MAS) at 3.7%. No death was

recorded in newborns with TTN, neonatal hypoglycaemia and neonatal anaemia. In the series by Fadhil et al in Iraq (16), the causes of death in neonates with respiratory distress were RDS (67.1%), perinatal asphyxia (18.4%), congenital malformations (6.6%), sepsis (4.6%) and MAS (3.3%). Previously cited predictors of NRD-related mortality include a Silverman score > 4 (OR 29.9 CI: 1.601-559.932), convulsion (OR 20.7 CI: 1.259 - 341.616) and being referred from an external health facility (OR 10.4 CI: 1.207-91.238) (19).

Factors associated with neonatal respiratory distress

a. Foetal Risk Factors:

Gestational Age (GA): Studies have demonstrated that respiratory distress of any cause is more common in pre-term neonates than in term and post-term neonates (29,42,43).

Gender: Several studies from Cameroon, Ethiopia, France and South Africa on the risk factors associated with NRD have confirmed the male gender to be an independent risk factor for NRD (4,21,22,37)

Race : The black race has been cited several times to convey protection against NRD (37,44). **Birth weight:** Similarly to gestational age (GA), NRD is inversely related to birth weight (29,45).

b. Maternal Risk Factors:

Socio-economic status: Maternal unemployment, low in-come and unmarried status are all factors that limit a pregnant woman to antenatal care (46,47).

Advanced maternal age : Advanced maternal age has been cited as a risk factor for NRD due to increased incidence of maternal diseases (hypertension, diabetes, placenta praevia or abruptio placentae), high preterm deliveries or cesarean deliveries in older women (29). However, this association is currently doubtful due to some reports refuting a statistical difference between the prevalence of NRD and maternal age (22,28).

Maternal smoking: A few studies, namely that by Siva et al (48) in 2004 and Numan et al (28) in 2007 found a significant risk of NRD when a mother had been a chronic smoker than not.

c. Obstetric Risk Factors:

Infectious Anamneses: Infectious anamnestic risk factors have been shown to predispose a neonate to NRD due to neonatal infection (4,49). Some of these infectious anamnestic risk factors (Table 3) have been put forth by the High French Authority (HAS) which recommend strong clinical suspicion of a latent neonatal sepsis and appropriate diagnostic and therapeutic interventions to be adopted in case a newborn has any infectious anamneses (50).

Maternal diabetes mellitus: Diabetes mellitus whether chronic diabetes or gestational diabetes mellitus has been reported as a major risk factor for NRD in Italy, Egypt and Ethiopia (20,21,29,51).

Antepartum haemorrhage: Many studies have proven placenta praevia and abruptio (independent of caesarean section as a confounder) to be risk factors for NRD (7,22,52,53). **Hypertensive disorders:** We found two studies which highlighted hypertensive disorders in pregnancy are equally a known risk factor for NRD (7,54). By contrast, one study (22) observed that infants born of mothers with hypertensive disorders were not more exposed to NRD than those whose mothers did not have hypertension. Hence, in the absence of a systematic review and meta-analysis, hypertensive disorders during pregnancy still remain controversial as a risk factor for NRD.

Multiple pregnancies: The relationship between NRD and multiple pregnancies is controversial. On the one hand, multiple pregnancies is a risk factor for NRD due to the increased frequency of preterm delivery associated with multiple pregnancies (29). This predisposes the newborn to NRD due to immaturity of fetal lungs. On the other hand, a cross-sectional

French study (22) instead demonstrated multiple pregnancies to convey a protective effect for NRD (OR=0.60, 95% Confidence interval: 0.37 - 0.99), with an unclear pathophysiology.

Mode of Delivery: Cesarean section (CS), especially when elective has been repeated cited by isolated observational studies (4,21,25,33,55) and a systematic review (56).

Non-Reassuring Foetal Status: According to two cross-sectional studies and one cohort study we found, non-reassuring foetal status (NRFS) formerly called acute foetal distress is a significant risk factors for NRD (4,22,23). NRFS exists when there are factors causing cerebral hypoxia, hypo-perfusion of other vital organs and anaerobic metabolism (57). These factors include placental insufficiency (e.g. hypertension), umbilical cord accidents (e.g. cord knot and prolapsed), placental praevia/abruptio, prolonged, rapid and obstructed labour or infections. NRFS is diagnosed on the presence of repetitive variable decelerations foetal tachycardia or bradycardia, late decelerations or a low biophysical profile (58).

Antenatal Drugs: Anesthetic drugs such as hypnotics and neuromuscular blocking agents administered before the clamping of the umbilical cord have been shown to be associated with the incidence of NRD (59). Currently, there are controversial evidence on the use of antenatal glucocorticoids for fetal lung maturation in pre-term pregnancies occurring before 34 weeks of gestation (22,30,60).

Meconium stained amniotic fluid (MSAF): MSAF is present in 8–20% of all deliveries, increasing to 23–52% after 42 weeks of gestation (61,62). About 2–9% of infants born in MSAF develop NRD due to MAS (61,62).

Antenatal Care visits: We found one study conducted in Cameroon which identified attending four or more antenatal care visits to convey protection against NRD (OR: 0.39, 95% CI: 0.16 – 0.98, p: 0.045) (4).

Diagnosis of Neonatal Respiratory Distress

a. Clinical diagnosis

All included studies diagnosed NRD clinically. The most frequent diagnosis in the majority of studies was either the presence of at least one or two of the elements of the following three signs: an abnormal respiratory rate (tachypnoea [respiratory rate above 60 breaths/minute], bradypnoea [respiratory rate less than 30 breaths/minutes], respiratory pauses [an absence of breathing movements for a period less than 20 seconds] and apnoea [an absence of breathing movements for a period greater than 20 seconds]), signs of laboured breathing (expiratory grunting, nasal flaring, intercostal recessions, xiphoid recession and thoraco-abdominal asynchrony) best evaluated with the Silvermann-Anderson score (Table 4) and generalised or localised cyanosis (1,3,4,8,16,19,21,25,27,31–33,35,53,63–65).

b. Investigations

Leucocytosis, leucopaenia, raised C-reactive proteins (CRP), elevated procalcitonin and a positive blood, urine or cerebrospinal fluid culture confirm the diagnosis of a neonatal infection. While low blood glucose level may be indicative of hypoglycaemia as the cause of NRD and low haemoglobin level may suggest anaemia as the etiology (66,67). The first imaging study of choice is a chest x-ray ideally carried out at the neonate's bedside in the antero-posterior view taken in inspiration with a gastric tube in situ. Here, a gastric tube coiled in the oesophagus or found in the trachea indicates oesophageal atresia or trachea-oesophageal fistula respectively. The presence of loops of intestines, usually in the left hemi-thorax affirms the diagnosis of CDH (66,67). An echocardiography would help confirm the diagnosis of CHDs and a transfontanel ultrasound is not diagnostic of perinatal asphyxia but may help diagnose its complications such as intracranial hemorrhage, periventricular leucomalacia which may indirectly suggest the presence of perinatal asphyxia.

c. Signs of the severity of NRD

These include a Silverman score ≥ 7 , cyanosis refractory to supplementary oxygen, and haemodynamic instability; tachycardia above 160/min, capillary refill time (CRT) > 3 sec, hypotension, hypoxaemia, respiratory acidosis, hypercapnia, low ejection fraction, pulmonary hypertension, severe congenital heart defect (66,67).

Causes of Neonatal Respiratory Distress

Our search strategy retrieved a total of 16 articles which reported the etiologies of NRD according to their frequency in neonates admitted for respiratory distress. The leading etiology of NRD was neonatal infection, followed by transient tachypnoea of the newborn and then, hyaline membrane disease. All etiologies were evenly distributed around the globe (See Table 5).

Some Common Etiologies of Neonatal Respiratory Distress: essentials of their diagnosis and management

Neonatal Infection

NRD is frequently the clinical manifestation of pathological processes by micro-organisms (bacteria, viruses, parasites) acquired transplacentally through the ascending route from the birth canal (often favoured by prolonged rupture of membranes) or from the birth canal (vagina) during childbirth (69). According to the 2004 Demographic Health Survey in Cameroon, neonatal infections are responsible for 25% of neonatal deaths (70). Meanwhile, the prevalence of neonatal infection at the neonatal unit of the Yaoundé Gynaeco-Obstetric and Pediatric Hospital of Cameroon in 2011 and the Douala General Hospital of Cameroon in 2016 was 34.7% (49) and 31% (4). Hence, neonatal infection can be rated as a public health problem. Thus, prevention of its risk factors is primordial (70). Neonatal infection has no pathognomonic sign or symptom. Respiratory distress has been reported as the second (31%) most frequent clinical sign of infection after hyperthermia-hypothermia by Chiabi et al (49). A characteristic neonate with NRD due to neonatal infection has infectious anamneses enumerated in Table 3, clinical signs of infection (jaundice, pallor, fever, hypothermia, refusal to feed, abdominal distension, vomiting, hypotonia, irritability, altered consciousness, convulsions, coma), and any of the followings: leucocytosis $> 25,000/\text{mm}^3$, leucopenia $< 5,000/\text{mm}^3$, myeloma (more than 10% of leucocyte counts is made of immature leucocytes), platelets count $< 150,000/\text{mm}^3$, CRP $> 20\text{mg/l}$, elevated procalcitonin levels and positive bacterial culture from blood, urine or cerebrospinal fluid sample (4,71). The mainstay of the treatment of neonatal infection is through the intravenous administration of at least two antibiotics (either ampicillin plus gentamycin or a third generation cephalosporin plus gentamycin) in conformity with HAS guidelines of 2017 on the management of neonatal infection (50).

Transient Tachypnoea of the Newborn

TTN is a benign condition and one of the most common causes of NRD, irrespective of GA and it is due to delayed in the resorption of pulmonary fluid after birth (72). As a result, it is also called Wet lung Syndrome. CS, especially when performed electively is the most important risk factor associated with TTN (73). Several authors namely Atiye et al in Turkey (7), Dawodu et al in Ngeria (31), Abdelrahman et al in Sudan (38) and Kommawar et al in India (68) reported it to be the first etiology of NRD. A neonate with TTN typically presents with tachypnoea, diffuse fine crackles on lung auscultation usually immediately after birth or within the first two hours of life (72). There is mild oxygen dependence and no acidosis. The clinical signs usually disappear within 24 – 48 hours (2). Radiological findings are non-specific and show interstitial opacities and occasionally fluid in the interlobular fissures (2). No specific test is yet available. A complete blood count (CBC), CRP and blood glucose test are usually normal, unless TTN is associated with neonatal infection or hypoglycaemia (4). TTN is a benign self-limiting disease, thus, its treatment is mainly symptomatic (67). As stated earlier, symptoms usually resolve completely after 24 - 48 hours of supplementary oxygen (67).

Hyaline Membrane Disease

HMD is also called Respiratory Distress Syndrome (RDS). It is NRD due to a structural and functional pulmonary immaturity stemming from a deficiency in pulmonary surfactant (74). Thus, usually more common in pre-term newborns (74). HMD is due

to a quantitative and qualitative deficiency in surfactant, leading to alveolar atelectasis (2). The resultant atelectasis causes pulmonary hypo-perfusion, hypoxaemia and ischaemia. Hyaline membranes form through the accumulation of sloughed epithelia, eosinophiles, proteins and oedema at the level of the alveoli (2). Clinically, it often presents as an acute NRD immediately at birth or within the first hour of life with exacerbation and oxygen needs within the first 24-48 hours of life followed by a stable phase till 72 hours, then rapid frank amelioration of NRD between the 3rd and 6th day (74). Expiratory grunting is usually the first sign while an abnormal respiratory rate (usually tachypnoea) is predominant (74). Chest x-ray findings are not specific and include a fine reticulo-granular pattern, a 'ground glass appearance' representing diffuse atelectasis and air bronchogramme. With time there is a confluent opacity with loss of the cardiac, mediastinal and pulmonary contours resulting in complete bilateral opacity (74). Blood gases show hypoxaemia, hypercapnia and respiratory acidosis (74). Antenatal tests like amniocentesis for lecithin-sphingomyelin ratio (a ratio < 2 is significant) and prostaglandins levels also add more clues to its diagnosis (74). Preventive treatment by antenatal glucocorticoids to pregnant women at risk for preterm delivery is still recommended although there are controversial evidence on its benefits (60). Supportive treatment by supplementary oxygen with continuous positive airway pressure (CPAP), and assisted ventilation if no respiratory autonomy by the neonate (67). Its definitive treatment entails administering exogenous surfactant (67).

Meconium Aspiration Syndrome

MAS is defined as respiratory distress due to inhalation of MSAF (61). The prevalence of MAS in childbirth with MSAF from a recent prospective cohort study was 2.34% (62). The excretion of meconium into amniotic fluid occurs by three main mechanisms: physiological maturation of the fetal gastrointestinal tract or acute or chronic hypoxic events (61). Inhalation of meconium causes NRD by the following mechanisms (61); (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 fetal pancreatic enzymes contained in meconium. (c) Surfactant inactivation by proteins and fatty acids contained in meconium. (d) Chemical pneumonitis: meconium is a chemo-attractant for neutrophils and macrophages and also a source for pro-inflammatory mediators such as interleukins and tumour necrosis factors. MAS presents clinically as an early onset of NRD in a neonate born in MSAF with or without an antenatal history of foetal distress. There is hyper-inflated or 'barrel' chest, diffused crackles, and sometimes a poor neonatal adaptation (due to low APGAR score caused by perinatal asphyxia) on physical examination (2,61). A chest x-ray shows a coarse nodular opacity, areas of hyperinflation and atelectasis (61). The management of MAS currently recommended by the Neonatal resuscitation program (NRP) entails supplementary oxygen and assisted ventilation if necessary by endotracheal intubation and direct endotracheal suction soon after delivery for non-vigorous neonate born in MSAF who have respiratory distress, poor muscle tone, and/or heart rate less than 100/minute (75,76). Previous treatment measures which are now contraindicated include routine intra-partum oropharyngeal and nasopharyngeal suctioning after delivery of the head for infants born with clear or MSAF (76,77). Also, ventilation before aspiration is contraindicated (61) and prophylactic use of antibiotics in MAS is only indicated in case of definite perinatal risks factors for infection (78).

Perinatal asphyxia

According to WHO estimates, 3% of the 120 million neonates born annually in developing countries have NRD due to moderate to severe perinatal asphyxia (79). Prevention of its risk factors and causes is more important than treatment. In a low-income country like Cameroon, the need for this risk assessment is thus obvious. Many studies have been carried out to put forth reliable clinical diagnostic criteria for neonatal asphyxia. Amongst these studies, we distinguish that of the American Academy of Paediatrics (AAP), and the American college of obstetricians and Gynaecologists (ACOG) which both highlighted four clinical criteria to characterise perinatal asphyxia (80): a pH < 7 (from umbilical arterial blood samples); an APGAR score between 0 – 3 at the fifth minute; the presence of neurological signs in the immediate neonatal period (hypotonia, convulsion and coma); 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 outcome of the newborn, and many considered it obsolete, few would deny that its application at one and five minutes of life accomplishes a vital goal of focusing attention the infant immediately after birth (81–83). The APGAR score is still the most feasible and practical to

perform in the delivery room (84). The APGAR score is still a valid and rapid index for assessing cardiorespiratory adaptation at birth and the effectiveness of resuscitative efforts (85). However, the SARNAT Score developed after the APGAR score has shown more merits in the diagnosis of perinatal asphyxia and it is becoming more frequently used. The management of perinatal asphyxia includes admission into a neonatal unit, preferably in the neonatal intensive care unit (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, hypernatraemia, hypoglycaemia, hyperglycaemia as these are deleterious for the injured brain; treating any comorbidities such as sepsis; neuroprotection by maintenance of a body temperature between 36 - 36.5°C; administering anticonvulsants in case of convulsions (67).

Congenital Heart Diseases

CHD could be cyanotic or acyanotic heart diseases (86). In both cases, the newborn can present with NRD, a heart murmur, cardiomegaly and/or signs of heart failure depending on the severity of the CHD (4). However, cyanosis and hypoxaemia refractory to supplementary oxygen are solely features of cyanotic heart diseases (86). A heart ultrasound often confirms the diagnosis by identifying the type of CHD and its severity such as a low ejection fraction (4). The treatment of CHD can be medical or surgical depending on its severity and the type of CHD (86).

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 breaths exclusively through the nostrils (10). The diagnosis is suspected clinically in case of impossibility of passing a nasogastric tube through the nostrils into the nasopharynx and NRD which improves when the baby cries. The diagnosis can be confirmed by computerised tomography scan (CT-scan) (4,10). The definitive treatment till date is surgery. While waiting for surgery, securing the oropharyngeal airway with a Guedel cannula is recommended (10).

Congenital Diaphragmatic Hernia

Its incidence is 1 in 2000 to 1 in 5000 live births. It is one of the most difficult challenges in the realm of pediatric surgery (10). CDH is a congenital anomaly caused by the herniation of abdominal visceral contents through the diaphragm (usually at the posterolateral foramen of Bochdalek or the anterior foramen of Morgagni) which leads to pulmonary compression and pulmonary hypoplasia resulting in NRD (10). The clinical diagnosis is evoked in the presence of NRD associated with a scaphoid abdomen, a displaced apex heart beat, absence of breath sounds on the affected side and bowel sounds in chest (2,10). A history of polyhydramnios is noted in approximately 80 % and prematurity is frequent (10). A chest radiograph shows air-filled bowel loops in the affected hemithorax (usually the left hemithorax) with non-visualization of diaphragmatic margin, mediastinal shift and a relative paucity of abdominal gas. A small portion of the ipsilateral lung may be visible superiorly. An echocardiogram should be performed to exclude associated congenital anomalies such as congenital heart defects (10). The routine neonatal management measures include nasogastric tube insertion and drainage. Bag and mask ventilation is contraindicated as it causes bowel distension and increases the mediastinal shift further which compresses the contralateral lung and also compromises cardiac function. The definitive treatment is surgery (10).

Oesophageal Atresia with or without Tracheoesophageal Fistula

It is another congenital malformation that causes NRD by aspiration of saliva or gastric juices into the tracheobronchial tree through a tracheoesophageal fistula (TEF) (10). It is suspected clinically by an obstruction to the passage of an orogastric tube at an attempt to perform the "syringe test" which entails injection of air through the orogastric tube. The air should normally be heard on auscultation at the epigastrium of the newborn. If air is heard in the lungs, a TEF is suspected. The test is routinely recommended at the birth of all neonates to rule out oesophageal atresia and TEF. Other elements of clinical diagnosis include NRD with hypersalivation or choking with attempted feeds. A lateral chest x-ray 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 treatment is surgical (10).

Grosso modo, Figure 1 below illustrate a diagnostic and therapeutic approach for NRD

Complications of Neonatal Respiratory Distress

Early complications include pneumothorax and pneumomediastinum, usually seen in neonates on artificial ventilation with high pressures (87).

Late complications include bronchopulmonary dysplasia (BPD), retinopathy of prematurity (due to oxygen toxicity and can be prevented by avoiding PaO₂ above 75mmHg in the newborn), persistent ductus arteriosus and sequelae of cerebral anoxia such as cerebral palsy (87).

Discussion

This scoping review with data from 81 studies with a total of 511,158 neonates found an overall high prevalence mortality rates of NRD evenly distributed round the world, though more frequent in LMICs. We also found that the risk factors for NRD were diverse and could be grouped into foetal, maternal and obstetrical factors such as prematurity, male gender, low and high birth weights, low socio-economic status, smoking, infectious anamneses, diabetes mellitus, antepartum haemorrhage, cesarean delivery, fetal distress, anesthetic drugs and meconium stained amniotic fluid. On the other hand, attending four or more antenatal care visits conveyed protection against NRD. Controversial risk factors for NRD still needing to be elucidated included hypertensive disorders of pregnancy and antenatal glucocorticoids for fetal lung maturation. Other findings included clinical diagnosis of NRD as the most universally accepted definition. Its leading aetiology was neonatal sepsis, followed by transient tachypnoea of the newborn and then, hyaline membrane disease. The treatment of NRD was recommended to me categorized into a resuscitation phase firstly followed by a specific management according to the etiology of NRD.

represents the aetiology of stroke in 11 out of 1000 patients and is fatal in 56 out of 1000 cases, with superior sagittal sinus been the most affected venous sinus.

There was a high heterogeneity in studies reporting the prevalence rate of NRD due to the large methodological differences, especially in the definition or diagnostic method of NRD between studies. Some studies define NRD as the presence of at least one of the following signs tachypnoea, expiratory grunting, nasal flaring, intercostal recessions, xiphoid recession, thoraco-abdominal asynchrony and cyanosis (3,9,28). While other studies define NRD as the presence of at least two elements of the following group of signs: signs of an abnormal respiratory rate (tachypnoea [respiratory rate above 60 breaths/minute], bradypnoea [respiratory rate less than 30 breaths/minutes], respiratory pauses [an absence of breathing movements for a period less than 20 seconds] and apnoea [an absence of breathing movements for a period greater than 20 seconds]), signs of laboured breathing (expiratory grunting, nasal flaring, intercostal recessions, xiphoid recession and thoraco-abdominal asynchrony) and generalised or localised cyanosis (4,19). However, we observed the prevalence was evenly distributed between high-income countries and LMICs. This re-iterates NRD as a frequent neonatal condition in day-to-day clinical practice. The case fatality rate due to NRD was higher LMICs compared with high-income countries (3,5,8,9). These re-enforces claims of NRD being a public health condition disproportionately affecting LMICs especially in SSA where it has been reported that every one out of two neonates admitted to the neonatal unit present with NRD and every one out of four neonates with NRD have a fatal outcome(4).

The most accepted diagnosis for NRD was based on the clinical presence of at least one or two of the elements of the following three signs: an abnormal respiratory rate (tachypnoea [respiratory rate above 60 breaths/minute], bradypnoea [respiratory rate less than 30 breaths/minutes], respiratory pauses [an absence of breathing movements for a period less than

20 seconds] and apnoea [an absence of breathing movements for a period greater than 20 seconds]), signs of laboured breathing (expiratory grunting, nasal flaring, intercostal recessions, xiphoid recession and thoraco-abdominal asynchrony) and generalised or localised cyanosis (1,3,4,8,16,19,21,25,27,31–33,35,53,63–65). The rest of the clinical examination is aimed at investigating the aetiology of NRD. The presence haemodynamic instability (hypotension and a fast low-volume pulse abnormal for age, capillary refill time [CRT] > 3 seconds), irritability, jaundice, watery stools, abdominal distension can be suggestive of neonatal sepsis. The presence of fine crackles is suggestive of TTN, MAS or neonatal infection. Cardiac arrhythmia, heart murmurs or cyanosis refractory to supplementary oxygen are indicative of a congenital heart disease (CHD). A neurological abnormality (reduced alertness, coma, convulsion, irritability, a swollen fontanel, hypertonic or hypotonic primitive reflexes) is often present in neonates with NRD irrespective of the etiology of NRD due to cerebral hypoxia. However, a neonatal infection or perinatal asphyxia should be ruled out in all newborns with NRD and a poor neurological state. Complete or partial im-permeability of the choanae and oesophagus should point towards choanal atresia or oesophageal atresia. Hypersalivation, choking or regurgitation of milk after feeding are often indicative of a trachea-oesophageal fistula. Hemi-thoracic distension with asymmetric auscultation is suggestive of a pneumothorax or congenital diaphragmatic hernia (CDH) (64,87).

We found several risk factors associated with NRD which we classified into foetal, maternal and obstetrical. With regards to the foetal risk factors, we found prematurity, the male gender, racial background, low and high birth weights to be independent risk factors for NRD. The role played by prematurity as a risk factor for NRD can be explained by structural and functional immaturity of the fetal lung (29,43). For example, the incidence of NRD due to HMD was reported at 60-80% in newborns < 28 weeks of GA, 15-30% when the GA was between 32-36 weeks, 5% when the GA > 37weeks and rarely at term (43). Sathenahalli et al in India (53), Tochie et al in Cameroon (4), Adebami et al in Nigeria (32), Aynalem et al in Ethiopia (21) and Baseer et al in Egypt (20) found that prematurity was an independent risk factor for NRD. Also, post-term GA has been established as a risk factor for NRD due to the considerable intrauterine excretion of meconium by the fetus, subsequently leading to MAS (61). Male neonates have a higher prevalence of NRD due to slower lung maturation induced by the higher concentration of androgens in males compared with their female counterparts (30,88). The mechanism which can explain the black ethnicity to be at a lower risk of NRD compared to Caucasians is not yet well understood. But hypotheses include an inherent faster pulmonary maturation in the black fetus compared with Caucasians (44). It has been demonstrated that black newborns have a lower prevalence of NRD compared to their Caucasian counterparts in South Africa (50). With regards to birth weight as a risk factor for NRD, Dani et al in Italy (29), Njim et al in Cameroon (89) and Sathenahalli et al in India (53) found a statistically significant association between low birth weight (birth weight < 2500 grams) and NRD (89). On the other hand, Numan et al in Iraq (28), did not find low birth weight a risk factor for NRD because of the presence of intrauterine stressful conditions enhancing surfactant secretion and maturation of the lungs in low birth weight neonates. Unexpectedly, Tochie et al in Cameroon observed that a birth weight \geq 4000 grams as an independent risk factor for NRD (OR: 2.27, 95% CI: 1.06 – 4.87, p: 0.034) (4). The pathophysiology here was attributed to complications of high birth weight, such as acute foetal distress, shoulder dystocia, hypoglycaemia also described by Obama et al more than two decades ago (90). Obvious maternal risk factors associated with NRD included low socio-economic status and maternal smoking. Advanced maternal age due to its positive correlation with poverty and illiteracy leading to the under-diagnosis and under-treatment of pregnancy diseases (diabetes, hypertensive disorders, genitourinary infections, etc) with can predispose the newborn to NRD. It is currently unclear whether advanced maternal age predisposes to NRD due to some reports which show no statistical difference between the prevalence of NRD and maternal age (22,28). The role played by maternal smoking in predisposing neonates to respiratory distress is yet to be elucidated. Clear obstetrical risk factors found to be associated with NRD were infectious anamneses, maternal diabetes mellitus, antepartum haemorrhage, cesarean section delivery, non-reassuring foetal status (NRFS), antenatal drugs, meconium stained amniotic fluid (MSAF), and antenatal care visits. A neonate with any infectious anamneses is at risk of NRD due to neonatal infection (50). Chiabi et al in Cameroon found that NRD was the second most frequent clinical manifestation of neonatal infection and statistically significant risk factors for NRD due to neonatal infection (49). Here, some infectious anamnestic risk factors cited by Chiabi et al were unexplained prematurity < 35 weeks of gestation and prolonged membrane rupture (>12 hours) (49). In contrast, Chalacon et al (22) in France, Tochie et al in Cameroon (4), Sathenahalli et al in India (53) and Baseer et al in Egypt (20) reported prolonged rupture of

membranes (regardless of the presence of chorioamnionitis) to have a protective role or decrease the incidence of NRD due to a fetal inflammatory syndrome secondary induced by prolonged rupture of membranes which accelerates fetal pulmonary maturation (91). However, this remains controversial, because prolonged rupture of membranes leads to oligohydramnios which can cause pulmonary hypoplasia and thus, NRD (91). Maternal diabetes mellitus is an independent predictor of NRD due to delayed fetal pulmonary maturity induced by hyperglycaemia during gestation. Results from other authors from France in 2012 and Iraq 2007 show that neonates born of mothers with diabetes are not more exposed to NRD than those whose mothers did not have diabetes or hypertension (22,28). However, more conclusive results from a meta-analysis of 24 cohort and case-control studies depict an association between maternal diabetes mellitus and the risk of NRD with a pooled OR of the risk of NRDS of 1.57 (95% CI 1.28–1.93) for gestational diabetes mellitus and 2.66 (95% CI 2.06–3.44) for pre-gestational diabetes mellitus (92). The pathophysiology hypothesized to explain antepartum haemorrhage as a risk factor for NRD include foetal anaemia from low utero-placenta blood flow to the fetus leading to fetal hypoxia and eventually NRD at birth (7,22,52,53). Cesarean 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 normal cardiorespiratory adaptation of the newborn (73,93). This predisposes the newborn to NRD caused by TTN as observed by Aynalem et al in 2020 in Ethiopia (21), Rijal et al in 2018 in Nepal (33) and Swarnkar et al in India in 2015 (25). In a prospective cohort study by Hansen et al (93) in Denmark and a retrospective case-control study by Zanardo et al (55) in Italy which compared the neonatal respiratory morbidity following vaginal delivery and CS, both studies found that neonates born through CS had a two to four-fold risk of NRD compared to those born through vaginal delivery and the risk increased with a decrease in GA. In the same vein, a Cameroonian study found that elective CS increased the odds of NRD (OR: 3.61, 95% CI : 2.01 – 4.08, p: 0.004) (4). More so, in Cameroon, Forsah et al in 2012 described NRD as a frequent adverse neonatal outcome following CS (94). More conclusive evidence has been demonstrated in a systematic review and meta-analysis of 26 studies published in 2018 by Li et al (56). Here, both emergency and elective CS were shown through a pooled odds ratio of the risk of neonatal RDS of 2.38 (95% CI 1.89–2.99) for elective CS and 1.85 (95% CI 1.34–2.56) for emergency CS (56). Non-Reassuring Foetal Status is a predisposes to NRD due to pulmonary hypertension, myocardial infarction, heart failure but more frequently due to perinatal asphyxia (57,58). In a descriptive study carried out in Gabon by Minko et al (23) on the clinical presentation of neonates delivered following NRFS, NRD had a frequency of 20%. Chalancon et al (22) observed NRFS to double the risk of NRD (OR= 2.70, 95% Confidence interval: 1.28-5.69). Furthermore, in cross-sectional study determining the risk factors for NRD in Cameroon, acute foetal distress or Non-Reassuring Foetal Status (OR: 5.59, 95% CI : 3.84 – 8.14, p < 0.001) was an independent risk factor for NRD following multivariate analysis (4). Anesthetic drugs such as hypnotics administered during cesarean delivery have been reported to predisposes to NRD either by central nervous system depression in case of general anesthesia or by a decreased in utero-placental blood flow in case of spinal anesthesia (59). Evidence from a meta-analysis of randomised trials carried out between 1974 and 1994 clearly demonstrates that the administration of antenatal glucocorticoids to pregnant women at risk for pre-term delivery prior to **34 weeks of gestation** decreases both the incidence of HMD by 50% as well as its severity in neonates (60). The latter study has long been the scientific evidence of reference used by the **American College of Obstetricians and Gynecologists (ACOG)** and **Royal College of Medicine** in recommending the administration of synthetic glucocorticoids (dexamethasone and betamethasone) within 24 to 48 hours to no longer than seven days to accelerate fetal lung maturation by increasing the formation and release of surfactant in case of pre-term labour occurring before 34 weeks of gestation, the term before fetal lung maturation is complete (60). However, in a prospective cohort study carried out in France in 2012 to determine both risk factors and protective factors for NRD in moderate pre-term neonates (32 to less than 34 completed weeks) using a logistic regression analysis, the administration of antenatal steroids showed no protective effect for the development of NRD (22). Chakrouni et al in 2009 in a cross-sectional study had similar findings which was attributed to a low rate (26%) of administration of antenatal corticosteroids in Moroccan neonates with NRD born following preterm labour due to the short duration between the admission of the pregnant women-parenteral administration of the two recommended consecutive doses of betamethasone over two consecutive days and preterm delivery (30). In the absence of an updated systematic review on the effect of antenatal synthetic glucocorticoids on the incidence of NRD, the routine use of antenatal parenteral synthetic glucocorticoids in pre-term labour occurring before 34 weeks of pregnancy remains doubtful. MSAF is indicative of either acute or chronic fetal distress or maturation of the digestive system (61), thus, neonates with a history of delivery in MSAF might have NRD due to

MAS, perinatal asphyxia or neonatal infection, because meconium is a good medium for bacterial culture (61). In a multicentre retrospective study by Wiswell et al (78) involving 176,790 live births in the USA, the frequency of MSAF was 13%, of which 5% out of the 13% cases of MSAF had NRD due to MAS. Likewise, Sathenahalli et al reported similar findings in India (53). Attending four or more antenatal care visits to convey protection against NRD due to a good follow-up of pregnancy with a subsequent reduction in the incidence of obstetrical complications such as maternal diabetes, hypertensive disorders of pregnancy and antepartum haemorrhage which predispose to NRD (4).

Conclusion

This review examined the contemporary literature published till November 13, 2020, on NRD to determine its prevalence, mortality rate, diagnosis, etiologies and management. We found an alarming prevalence and case fatality of NRD which was evenly distributed between high-income countries and LMICs. The etiologies of NRD were dominated by neonatal infections despite several progresses made in its management. To reduce the burden of NRD especially in LMICs, we recommend: (1) A good history taking and neonatal assessment taking into consideration the risk factors we identified plus the diagnostic and management algorithms suggested in this review. (2) Early diagnosis and treatment of those risk factors, especially infectious risk factors and a timely septic screen against neonatal infection which is the leading etiology of NRD. (3) The benefits of normal labor against the risk of NRD following cesarean section should meticulously be weighed to prevent transient tachypnoea of the newborn (4). Adequate fetal monitoring during childbirth for early detection of fetal distress and timely intervention to prevent both meconium aspiration syndrome and perinatal asphyxia. (5) Routine physical examination of the neonate in the delivery room entailing passing a nasogastric tube through the nostrils and performing the syringe test to timely diagnose and treat choanal atresia and oesophageal atresia respectively.

The main drawback of the current study is the heterogeneity across all the studies included, which hindered a meta-analysis.

List Of Abbreviations

ACOG: American College of Obstetricians and Gynecologists; CRT: Capillary refill time; CS: Cesarean section; CBC: Complete blood count; CDH: Congenital Diaphragmatic Hernia; CHD: Congenital Heart Diseases; CPAP: Continuous positive airway pressure; CRP: C-reactive proteins; GA: Gestational age; IV: intravenous; HAS: Haute Autorité de Santé; HMD: Hyaline Membrane Disease; LMICs: Low- and middle-income countries; MAS: Meconium aspiration syndrome; MSAF: Meconium stained amniotic fluid; NI: Neonatal Infection; NICU: Neonatal Intensive Care Unit; NRD: Neonatal respiratory distress; NRFS: Non-reassuring foetal status; RDS: respiratory distress syndrome; TTN: Transient tachypnoea of the newborn; TEF: Tracheoesophageal fistula; OAWOWTE: Oesophageal Atresia with or without Tracheoesophageal Fistula.

Declarations

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Authors' contributions

JNT conceived and designed the study, run the preliminary search. JNT, ATS, CD, ANM, IK, GA, JRN and MNT performed the study selection and data extraction. DHN served as an arbitrary resolving discrepancies between authors who performed the study selection and data extraction. JNT wrote the first draft of the manuscript, subsequently reviewed and revised by ATS, CD, ANM, IK, GA, JRN, DHN and MNT. All authors approved the final manuscript. JNT is the guarantor for this study.

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Tables

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 distress [MESH] OR Respiratory difficulties [tiab] OR Respiratory problems[tiab] OR Breathing difficulties[tiab] OR Breathing problem[tiab] OR Breathlessness[tiab] OR Abnormal breathing [tiab]
#3	Prevalence [MESH] OR Incidence [MESH] OR Mortality[MESH] OR Fatality OR Neonatal Death[tiab] OR Risk factor[tiab] OR Determinants[tiab] OR Etiologies[tiab] OR Aetiologies[tiab] OR Causes[tiab] OR management Treatment[tiab]
#4	#1 AND #2 AND #3 AND #4
#5	Limits: up to 13/11/2020 with no language restriction

Table 2: Global Trends in the Prevalence of Neonatal Respiratory Distress.

YEAR OF PUBLICATION	AUTHORS	COUNTRIES	STUDY DESIGN	SAMPLE SIZE	PREVALENCE OR INCIDENCE OF NRD (%)	MORTALITY RATE OF NRD (%)
1991	Dan et al (17)	Benin	Cross-sectional	4428	10.3	No data
1997	Kam et al (9)	Burkina Faso	Cross-sectional	951	14.5	No data
2016	Tochie et al (4)	Cameroon	Cross-sectional	703	47.5	24.5
2017	Ndombo et al (18)	Cameroon	Cross-sectional	332	2.4	No data
2019	Kedy et al (19)	Cameroon	Cross-sectional	499	34.5	No data
2020	Baseer et al (20)	Egypt	Cross-sectional	312	46.5	26.2
2019	Bayana et al (14)	Ethiopia	Cross-sectional	341	67	No data
2020	Aynalem et al (21)	Ethiopia	Cohort	571	42.9	No data
2012	Chalacón et al (22)	France	Cohort	579	18.5	No data
2004	Minko et al (23)	Gabon	Cross-sectional	61955	20	No data
1996	Kumar et al (24)	Indian	Cross-sectional	4505	6.7	No data
2015	Swarnkar et al (25)	India	Cross-sectional	855	16.4	22.86
2017	Kannan et al (26)	India	Cross-sectional	3623	27.4	No data
2018	Verma et al (27)	India	Cohort	1424	39	47.1
2007	Numan et al (28)	Iraq	Cross-sectional	2312	2.1	No data
2019	Fadhil et al (16)	Iraq	Cross-sectional	870	84.8	21
1995	Dani et al (29)	Italy	Cross-sectional	63537	0.21	No data
1992	Lasme et al (8)	Ivory Coast	Cross-sectional	273	23	No data
2009	Chakrouni et al (30)	Morocco	Cross-sectional	763	9.83	33.3
1984	Dawodu et al (31)	Nigeria	Cross-sectional	312	33	No data
2017	Adebami et al (32)	Nigeria	Cross-sectional	625	26.2	No data
2018	Rijal et al (33)	Nepal	Cross-sectional	317	34.3	12.8
2013	Saeed et al (34)	Pakistan	Cross-sectional	659	4.24	No data
2015	Parkash et al (35)	Pakistan	Cross-sectional	615	33.3	No data
2018	NiesBuchowska-Hoxha et al (36)	Poland	Cross-sectional	175	54.3	No data
2018	Qari et al (15)	Saudi Arabia	Cross-sectional	503	78.5	No data
1996	Rinjswijk et al (37)	South Africa	Cross-sectional	7539	0.6	2.1/1000 live births
2014	Abdelrahman et al (38)	Sudan	Cross-sectional	177	56.5	36
2007	Ersch et al (6)	Switzerland	Cohort	315279	3.8	No data
2011	Atiye et al (7)	Turkey	Cross-	390	61.5	

			sectional			No data
2020	Egesa et al (39)	Uganda	Cohort	351	43	No data
1995	Morrison et al (40)	UK	Cross-sectional	33289	7.9/1000 deliveries	No data
2000	Wiswell et al (41)	US	Clinical trial	2094	7.1	No data

Table 3: Anamnestic criteria for Neonatal infection According to HAS in 2017 (50).

MAJOR ANAMNESTIC CRITERIA (GRADE A)	Maternal Group B Streptococcal genital tract infection
	Past history of maternal Group B Streptococcal genital tract infection
	Maternal temperature $\geq 38^{\circ}\text{C}$ during labour or following the next two hour after delivery
	Unexplained spontaneous prematurity < 37 weeks of gestation
	Duration of rupture of membranes > 12 hours
	Premature rupture of membranes before 37 weeks
	Past history of neonatal sepsis by Group B streptococcus(GBS)

Table 4: Silverman Score (63)

Points		0	1	2
Signs				
Inspiration	Nasal flaring	Absent	Mild	Marked
	Intercostal retraction	Absent	Mild	Marked
	Xiphoid retraction	Absent	Mild	Marked
	Thoracoabdominal movement	Synchronous	Chest lags on inspiration	See-saw movement
Expiration	Expiratory grunting	Absent	Heard only with stethoscope	Heard with Naked ear

Score 0 - 3: Mild NRD, Score 4 - 6: Moderate NRD, Score > 6: Severe NRD with impending respiratory failure

Table 5: Causes or etiologies of NRD in the world

Causes of NRD by author and country	TTN	HMD or RDS	MAS	Neonatal infection	Perinatal asphyxia	Choanal atresia	CHD	CDH	OAWOWTEF
Tochie et al Cameroon (4)	2 nd	3 rd	4 th	1 st	5 th	9 th	6 th	7 th	8 th
Kedy et al in Cameroon (19)	3 rd	-	4 th	1 st	2 nd	-	5 th	-	-
Baseer et al in Egypt (20)	2 nd	1 st	4 th	3 rd	-	-	-	-	-
Bayana et al Ethiopia (14)	-	2 nd	4 th	1 st	-	-	-	-	-
Sévère et al in Haiti (3)	3 rd	-	2 nd	1 st	-	-	-	-	-
Swarnkar et al, India (25)	2 nd	1 st	4 th	5 th	3 rd	-	8 th	-	-
Verma et al India (27)	2 nd	1 st	3 rd	4 th	-	-	-	-	-
Kommawar et al in India (68)	1 st	2 nd	4 th	-	3 rd	-	5 th	-	-
Fadhil et al in Iraq (16)	2 nd	1 st	5 th	6 th	3 rd	-	4 th	-	-
Rijal et al in Nepal (33)	3 rd	4 th	1 st	2 nd	4 th	-	5 th	-	-
Adebami et al in Nigeria (32)	4 th	3 rd	5 th	1 st	2 nd	-	-	-	-
Dawodu et al in Ngeria (31)	1 st	4 th	3 rd	2 nd	-	-	-	-	-
Parkash et al in Pakistan (35)	4 th	2 nd	3 rd	1 st	5 th	-	-	-	-
Rinjswijk et al in South Africa (37)	3 rd	2 nd	-	1 st	-	-	-	-	-
Abdelrahman et al in Sudan (38)	1 st	3 rd	4 th	2 nd	-	-	-	-	-
Atiye et al in Turkey (7)	1 st	3 rd	2 nd	-	-	-	-	-	-
Total of the pathology cited as the 1st etiology of NRD	4	4	1	7	0	0	0	0	0
Total of the pathology cited as the 2nd etiology of NRD	5	4	2	2	2	0	0	0	0
Total of the pathology cited as the 3rd etiology of NRD	4	3	3	1	3	0	0	0	0

TTN: Transient tachypnean of the newborn; HMD: Hyaline Membrane Disease; NRS: Neonatal respiratory distress; CHD: Congenital heart diseases; CDH: Congenital Diaphragmatic Hernia; OAWOWTEF: Oesophageal Atresia with or without Tracheoesophageal Fistula; NRD: Neonatal respiratory distress

Figures

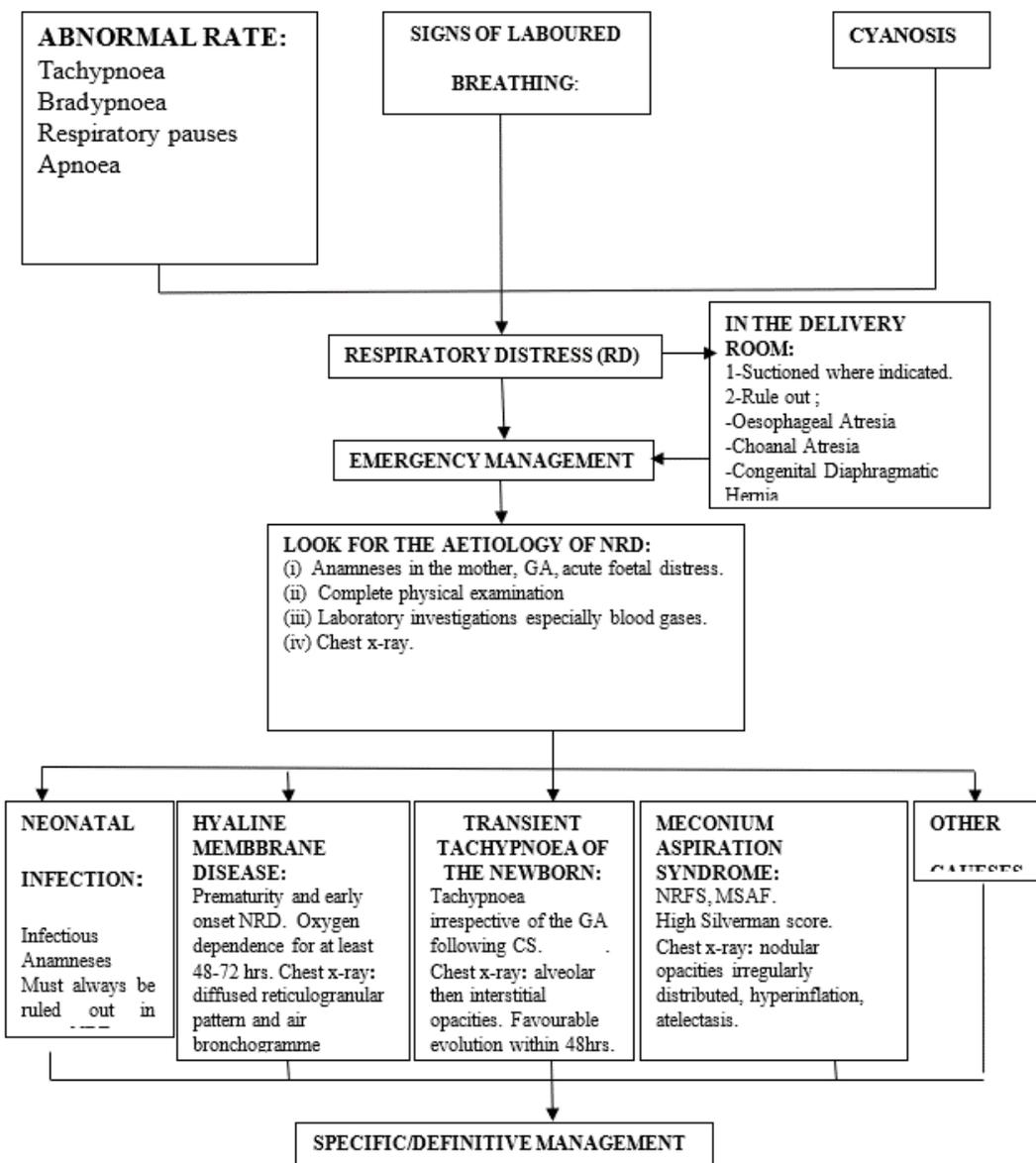


Figure 1

Diagnostic and Management Algorithm of Neonatal Respiratory Distress.