Red reflex test screening for neonates: A systematic review and meta analysis

Amar Taksande, Patel Zeeshan Jameel, Bharati Taksande¹, Rewat Meshram

Red reflex test (RRT) screening is yet to be a part of the neonate's normal examination before discharge from hospital in a majority of low- and middle-income countries. The purpose was this review was to systematically evaluate the diagnostic accuracy of RRT for the detection of ocular abnormalities in newborns. PubMed, EMBASE, Scopus, Web of Science, and Cochrane database of systematic reviews were the data sources. Quality of Diagnostic Accuracy Studies-2 (QUADAS-2) was utilized for quality assessment of bias and applicability. Random effects models were used to summarize sensitivities, specificities, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and respective confidence intervals (CI). The pooled sensitivity, calculated from the meta analysis of 11 studies, was 23% (95% CI: 21–24%) and pooled specificity was 98% (95% CI: 98–98%). The PLR was 32.52 (95% CI: 7.89–134.15), NLR was less than 1 (0.69 [95% CI: 0.55–0.88]), and DOR calculated was 138.48 (95% CI: 23.85–803.97). The area under the curve (AUC) and Q* index for RRT were 0.98 ± 0.02 and 0.95 ± 0.045, respectively. The results of our study justify the conclusion that RRT is a highly sensitive and specific test for the detection of anterior segment abnormalities.

Key words: Congenital ocular diseases, neonatal screening, neonates, red reflex testing

World Health Organization (WHO) estimates that around 18.94 million children are suffering from visual impairment, with 1.42 million of them being permanently blind.[1] Few population-based surveys have been carried out for blindness in children. As per some studies, the current prevalence of childhood blindness is 0.8/1000 children.[2,3]

Some of the visual functions may be permanently fixed as early as 6 months of age and if defective, can never be restored to complete normalcy.[4–6] Therefore, the rapid development of the ocular system in the fetal and neonatal period makes the detection of visual system abnormalities imperative. This criticality makes the role of the attending neonatologist/pediatrician invaluable in the early recognition and management of neonatal ocular diseases. The etiology of congenital blindness or poor vision includes congenital cataract, glaucoma, congenital infections, high refractive errors, optic nerve abnormalities (hypoplasia and coloboma), aniridia, albinism, Leber's congenital amaurosis, and other retinal dystrophies.[7] The financial costs of treatment of preventable causes such as childhood cataract was about $1000–6000 million dollars over 10 years.[8]

Red reflex testing (RRT), also known as Brückner eflex, is an essential component of the neonate's physical examination. This screening test is indispensable for early detection of vision and potentially life-threatening abnormalities such as retinal abnormalities, congenital cataracts, glaucoma, retinoblastoma (RB), systemic diseases with ocular abnormalities, and high refractive errors.[9] The American Academy of Paediatrics (AAP) currently recommends the evaluation of an eye in the neonatal period by RRT before discharge from the nursery, and should also be performed on all subsequent routine health visits.[9,10] Most newborns with congenital ocular diseases are usually asymptomatic at birth and maybe missed at birth in the absence of a routine screening examination. Following the publication of several studies evaluating the diagnostic accuracy of the RRT screening, many countries recommend it as routine practice, whereas many more are considering its integration.[9,11] In addition, studies have exhibited that RRT screening is cost-effective, which may have remarkable results in lowering blindness in low-income countries.[12] Our objective was to establish the diagnostic accuracy of RRT screening among the neonatal population. This systematic review's conclusive goal is to provide sufficient evidence, which could guide for policy making aimed at the prevention and effective management of congenital ocular disorders and underpin further research.

Department of Pediatrics, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences, Sawangi Meghe, ¹Department of Medicine, Mahatma Gandhi Institute of Medical Sciences, Sewagram, Wardha, Maharashtra, India

Correspondence to: Dr. Amar Taksande, Department of Pediatrics, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences, Sawangi Meghe, Wardha, Maharashtra, India. E-mail: amar.taksande@gmail.com

Methods

Registration

The protocol for this systematic review and meta-analysis was registered at the International Prospective Register of Systematic Reviews (PROSPERO # CRD42020201918).

This review followed the criteria for reporting systematic literature reviews and meta-analysis as defined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) strategy.[13]

Population type

Neonates who underwent screening with RRT, and who were analyzed for operative characteristics (sensitivity and specificity) were included.

Intervention

RRT screening can be used to detect congenital ocular diseases in an asymptomatic newborn before discharge from the hospital. RRT utilizes transmission of light from an ophthalmoscope through the normally transparent parts of a newborn's eye, which includes tear film, cornea, aqueous humor, crystalline lens, and vitreous humor.[7,9] As the light from the ophthalmoscope passes through the clear media of the anterior as well as the posterior segment of the eye, a characteristic red reflex is produced. This reflex originates from the choroidal pigmentation and vasculature, and not the retina.[7] An abnormal reflex results from any factor that disrupts or blocks the normal transmission of light, which includes mucus or foreign body in the tear film, opacities in the cornea, aqueous and vitreous opacities, cataracts, iris abnormalities affecting the pupillary aperture, unequal or high refractive errors, strabismus, and retinal abnormalities (tumors and chorioretinal coloboma).[7,9] An abnormal RRT screen warrants an immediate referral to an experienced ophthalmologist. This index test screening reduces the number of neonates discharged from the nursery before the diagnosis of any congenital ocular disease, and it can be performed at any stage before or after the routine clinical examination.

Outcome

Congenital ocular diseases/ocular diseases present in the neonatal period.

Literature search

The search strategy was implemented in two stages:
- Bibliographic database search
  The conduct of this systematic review and meta-analysis was based on the Test Accuracy Working Group of the Cochrane Collaboration and the PRISMA of Diagnostic Test Accuracy Studies statement (The PRISMA-DTA Statement) guidelines.[14] Electronic databases (Cochrane Library, PubMed, EMBASE, Scopus, and Web of Science) were used as data sources. We used the following terms for searches: ([Newborn OR Neonate OR Infant OR Term neonate]) AND (Congenital ocular disorders OR congenital ophthalmological disorders OR eye diseases at birth OR corneal opacity OR congenital cataract OR retinoblastoma OR coloboma OR vitreous hemorrhage OR congenital glaucoma OR strabismus OR refractive errors) AND (red reflex or red reflex testing or Bruckner reflex or red reflex screening). The last electronic search was carried out on August 30, 2020.

- Searching other sources
  In addition to the databases searched as mentioned above, the references of all the included primary studies relevant to our research question were also searched that might have been missed by the electronic searches

Selection of studies
- Observational studies, detecting RRT in neonates, were deemed acceptable. Inclusion criterion included:
  (1) Studies recruiting neonates (age <1 month),
  (2) Diagnostic test accuracy studies,
  (3) Studies detecting ocular abnormalities by RRT, and
  (4) Studies using ophthalmologist examination for an ocular abnormality as the reference standard.
- Exclusion criterion included:
  (1) Studies unrelated to the accuracy of RRT
  (2) Reviews, proceedings papers, meeting abstracts, letters, notes, and editorial materials, and
  (3) Studies lacking essential data.

No language restriction was practiced for the electronic search databases
- All studies were imported to the literature management software Endnote X7 to eliminate duplicated records. Then, two authors (A.T. and P.Z.J) independently conducted a preliminary screening of studies by reading titles and abstracts. After screening titles and abstracts, the full texts of potentially relevant articles were downloaded. Disagreements between the two reviewers were resolved through discussions and in the absence of consensus, a third review author's (B.T.) opinion was taken. Methods were adapted as per PRISMA guidelines for meta-analyses.[15]

Quality assessment

We adopted the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2)[16] for quality assessment and used Review Manager 5.3[17] for creating the figures of risk of bias and applicability concerns. Two independent reviewers (A.T. and P.Z.J.) assessed the methodological quality of the included studies independently, and disagreements were also resolved through discussions and scientific consultations.

Data extraction and management

A standard data extraction form was used to retrieve relevant information and data from each study included in the analysis. Two review authors (A.T. and P.Z.J.) participated in data extraction independently. A.T. and P.Z.J. extracted data that included primary author, year of publication, country, age, design of the study, testing modality, normal/abnormal red reflex, inclusion or exclusion of neonates, and reference standard. A.T. and P.Z.J. retrieved the data necessary for the construction of a 2 × 2 table: true positive, false positive, true negative, and false negative or if unavailable, other relevant parameters (sensitivity, specificity, positive predictive value, and negative predictive values). Studies with uninterpretable data were excluded from the analysis.

Statistical analysis

We performed statistical analysis using Meta-DiSc software (version 1.4, Clinical Biostatistics Unit, Ramón y Cajal Hospital).[18] Calculations were performed for all included studies. Sensitivity and specificity were calculated from the extracted 2 × 2 contingency tables. Homogeneity among the
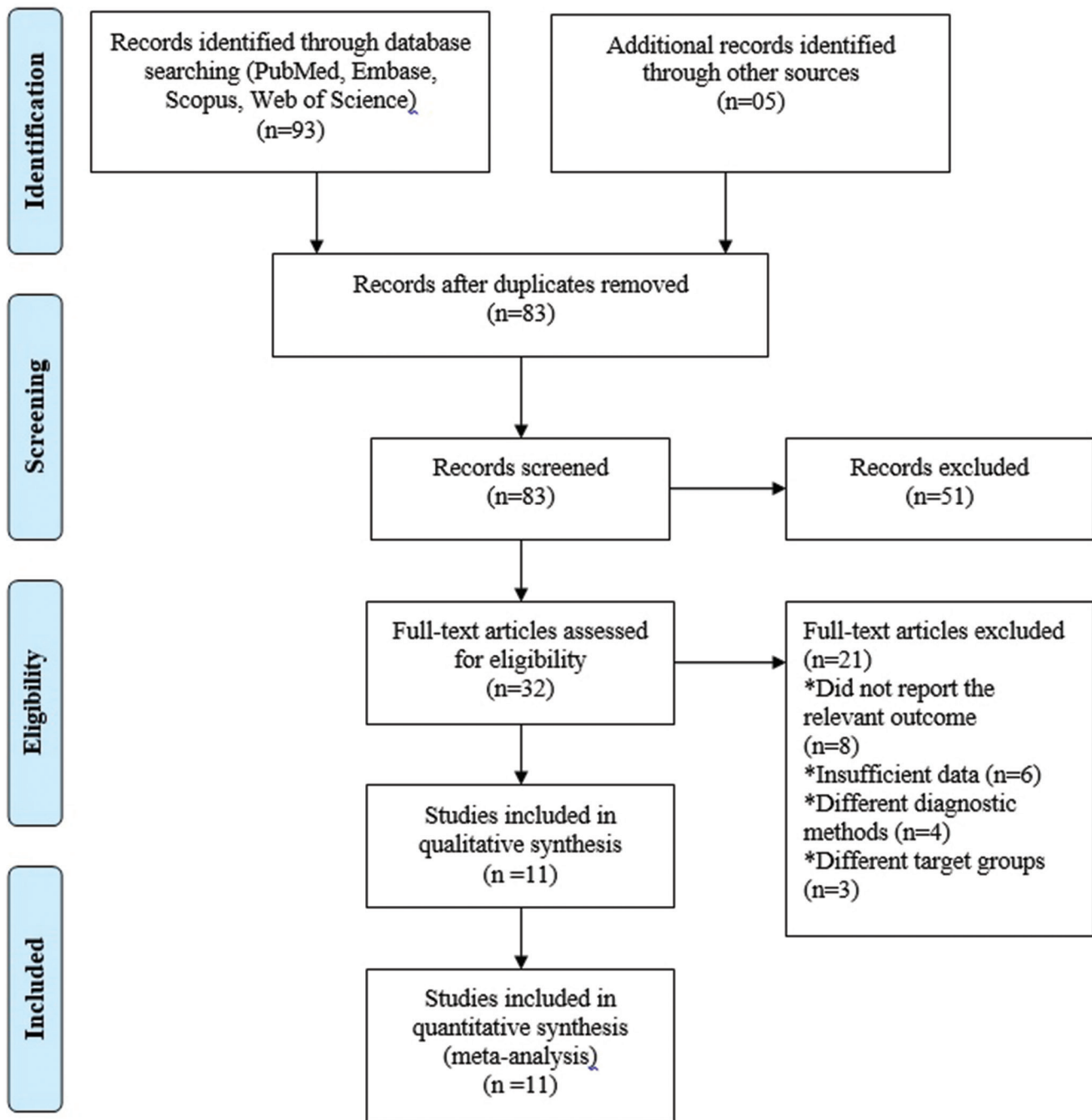
Figure 1: PRISMA flowchart diagram describing the process of identification and selection of studies for inclusion in the review. (PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses)

studies was assessed using a Chi-square test, with $P < 0.05$ considered to denote statistically significant heterogeneity. The percentage of the total variation across studies that was caused by heterogeneity rather than by chance (I^2) was calculated in accordance with the parameters set forth by Higgins *et al.*[19] with I^2 values of 25% or less, 50% or less, and 75% or less used to denote low, moderate, and high heterogeneity, respectively. To account for interstudy heterogeneity, a DerSimonian and Laird random-effects model was applied to pool the sensitivity and specificity data. For studies in which there were no false-positive and no false-negative results, a continuity correction of 0.5 was used. Individual and pooled data, with 95% CIs included, were illustrated using forest plots and a summary receiver operative characteristics (SROC) curve. The area under the curve (AUC), which summarizes the diagnostic performance of a test, was calculated, with an AUC of 1 signifying a perfect test that correctly classifies all cases and with an AUC of 0 signifying a test that never yields a correct diagnosis. The Q* index, which is defined as the point at which sensitivity and specificity are equal, or the point closest to the ideal top-left corner of the SROC space, was also calculated. We also performed subgroup analyses to explore the possible causes of heterogeneity, such

Table 1: Baseline characteristics of the studies included

Authors	Year	Country	Study design	Screening age	Eyes check for RRT	Index Test (RRT)		Reference test (Detail ophthalmological examination)	
						Name of instrument used/ Distance from Eye	Done by	Name	Done by
Cagini *et al.*[20]	2017	Italy	Prospective	<72 h after birth	Simultaneously	DO/45 cm	Pediatrician/Neonatologist	NM	NM
Sun *et al.*[21]	2016	China	Prospective	<48 h after birth	Simultaneously	DO/7 inch	Pediatric Ophthalmologist	Comprehensive eye exam	Ophthalmologist
Ludwig *et al.*[22]	2018	United States	Cohort	<48 h after birth	Simultaneously	NM	Pediatrician	Wide-angle fundus digital imaging	Ophthalmologist
Goyal *et al.*[12]	2018	India	Pilot	<28 days	Simultaneously	Ret Cam 130 LENS	Optometrist	Fundus Imaging	Ophthalmologist
Duret *et al.*[23]	2019	UK	NM	NM	Single eye	DO/50 cm	Medical Student	Slit-lamp biomicroscopy, retinoscopy	Pediatric Ophthalmologist
Baldino *et al.*[24]	2019	Brazil	Cross-sectional	NM	Simultaneously	DO/45 cm	Pediatrician	Indirect binocular ophthalmoscopy	Ophthalmologist
de Aguiar *et al.*[25]	2011	Brazil	Descriptive	NM	Simultaneously	DO	Neonatology Nurse	NM	Ophthalmologist
Eventov-Friedman *et al.*[11]	2010	Israel	Prospective	2nd day of life	Simultaneously	DO/45 cm	Neonatology and pediatric resident	NM	Ophthalmologist
Mussavi *et al.*[26]	2014	Iran	Prospective Analytic	<28 days	Simultaneously	DO	Pediatrician	NM	Ophthalmologist
Ozkurt *et al.*[27]	2018	Turkey	Prospective	NM	Simultaneously	DO/30 cm	Ophthalmologist	NM	Ophthalmologist
Viquez *et al.*[28]	2019	Costa Rica	Prospective	NM	Single eye	DO/45 cm	Ophthalmologist	Fundoscopic examination	Ophthalmologist

DO=Direct ophthalmoscope; NM=Not mentioned; RRT=Red reflex test

Table 2: Characteristic of the studies included in the meta-analysis

Studies	Year	Population	Sample size	True Positives	False Positives	False Negatives	True Negatives
Cagini et al.[20]	2016	Newborn	22,272	3	458	0	21,811
Sun et al.[21]	2016	Newborn	7641	303	267	1875	5196
Ludwig et al.[22]	2018	Newborn	194	0	0	49	145
Goyal et al.[12]	2019	Healthy neonate	1152	170	0	2	980
Duret et al.[23]	2019	Newborn	180 eye examinations (90 newborn)	0	0	9	171
Baldino et al.[24]	2019	Newborn	11,833	16	105	0	11,712
de Aguiar et al.[25]	2011	Newborn with low and medium risk	190	3	0	0	187
Eventov-Friedman et al.[11]	2010	Newborn	11,500	5	7	1	11,487
Mussavi et al.[26]	2014	Neonate	255	51	117	9	78
Ozkurt et al.[27]	2018	Newborn	1358	21	9	0	1328
Viquez et al.[28]	2019	Neonate admitted in ICU with >34 weeks is (GA) and BW >1.5 kg	142 eye examinations (71 neonates)	7	13	24	98

Table 3: Studies showing the number of anterior and posterior segment abnormalities

Studies	Total sample	Anterior segment abnormalities		Posterior segment abnormalities	
		Diagnosed	Missed	Diagnosed	Missed
Cagini et al.[20]	22,272	2	0	1	0
Sun et al.[21]	7641	222	1	81	1874
Ludwig et al.[22]	194	0	0	0	49
Goyal et al.[12]	1152	2	0	170	2
Duret et al.[23]	180 eye examinations (90 newborn)	0	0	0	9
Baldino et al.[24]	11,833	4	0	12	0
Eventov-Friedman et al.[11]	11,500	5	1	0	0
Mussavi et al.[26]	255	0	0	51	9
Ozkurt et al.[27]	1358	18	0	3	0
Viquez et al.[28]	142 eye examinations (71 neonates)	2	0	5	24

as RRT done by (pediatrician or ophthalmologist, or other healthcare professionals). The quality of studies was assessed with the QUADAS-2[16] and the RevMan 5.3 software.[17]

Results

Characteristics of included studies

Initially, a total of 98 articles were identified [Fig. 1]. After the elimination of duplicates, screening titles, and abstracts, 51 papers were found completely irrelevant and excluded. Full texts of the 32 studies were scrutinized for eligibility, among which 21 studies were excluded. There was no disagreement between investigators for full-text selection. Overall, 11 studies were found to be eligible, hence, they were included in the meta-analysis [Fig. 1].

Characteristics of eligible studies

The characteristics of the included studies is summarized in Table 1. A total of 56,556 participants were involved in our meta-analysis (range: 71 to 22,272). The 11 included studies were published between 2010 and 2019. Countries

of origin are distributed worldwide, such as India, China, the United Kingdom, Brazil, Israel, Iran, Costa Rica, Turkey, Italy, and the United States of America. The participants were neonates and the screening age ranged from 24 h to 28 days. For every article selected, the ocular abnormalities previously mentioned were considered as outcomes of interest. Detailed ophthalmological examination reference test) by an indirect ophthalmoscope was applied as a pattern of reference in reviews, and its results were assessed independently from the result of the RRT (index test). Details regarding the index (RRT) and reference (detailed ophthalmological examination) tests in the study of this systematic review are summarized in Tables 1 and 2. It is important to mention that in most reviews no aspects were found that might hinder the applicability of the screening both when selecting the population participating in the studies and when performing the screening of the reference pattern.

Methodological quality of included studies assessment

The overall methodological quality of included studies is summarized in Fig. 2. The quality assessment result for the
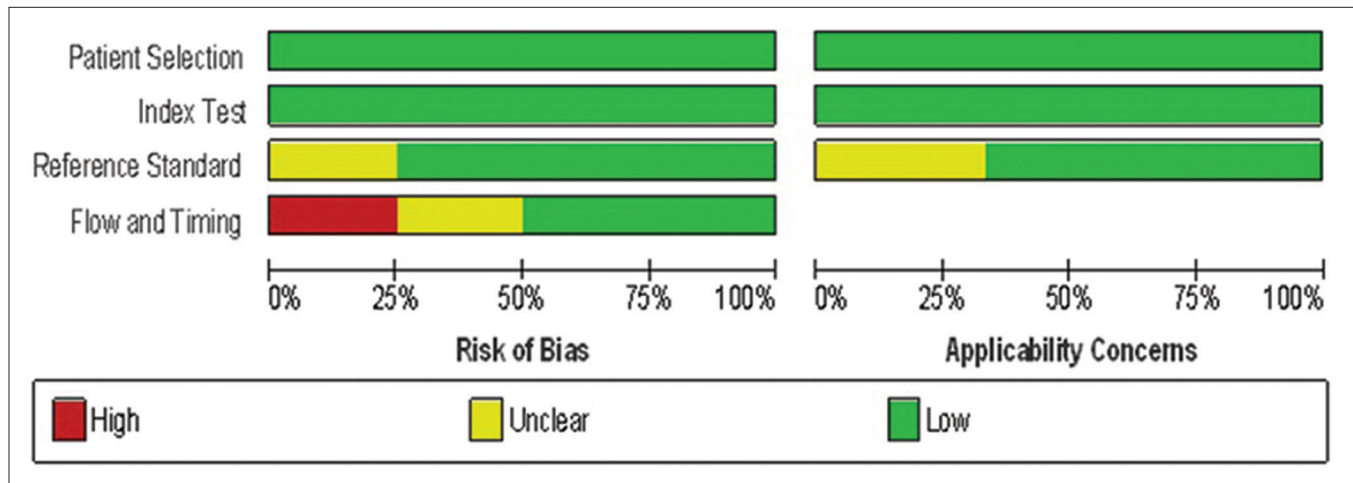
Figure 2: Quality assessment and bias risk according to the QUADAS-2 tool criteria for the diagnostic test studies (QUADAS-2: Quality of Diagnostic Accuracy Studies-2)
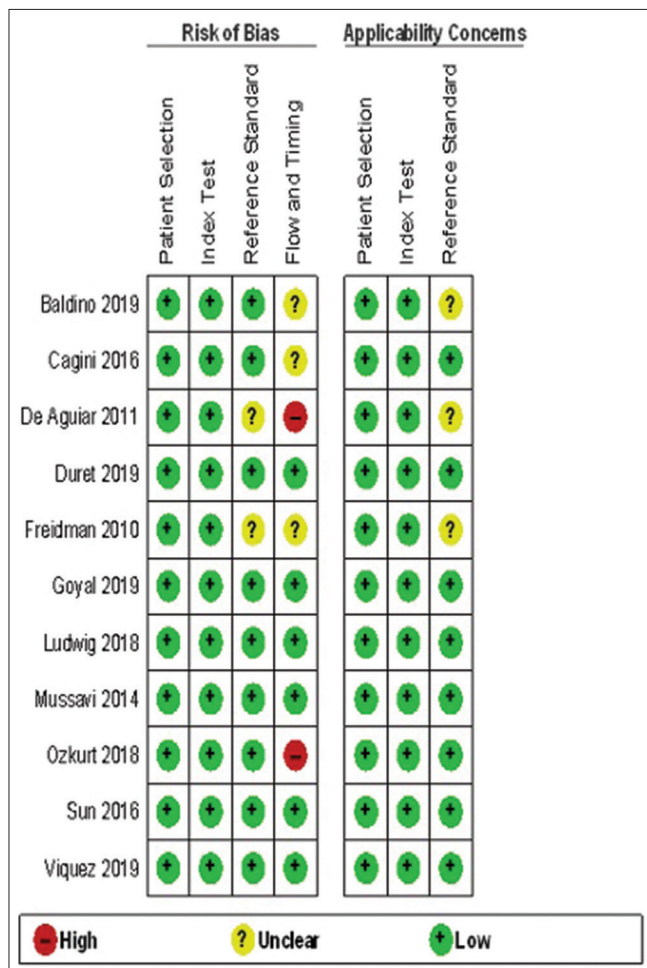

Figure 3: Bias risk and aspects associated with the applicability of every study included

items in QUADAS-2, suggesting that the overall quality of included studies was of moderate-high. Among these 11 included articles, two had a high risk of bias on "flow and timing." Nine out of 11 studies had low applicability concerns in all domains and the overall applicability concern was low.

Meta-analysis

The pooled sensitivity and specificity of RRT for diagnosing ocular abnormalities were 23% (95% CI: 21–24%) and 98% (95% CI, 98–98%), respectively [Fig. 4]. Diagnostic odds ratio (DOR), positive likelihood ratio (PLR), and negative likelihood ratio (NLR), unlike positive predictive value (PPV) and negative predictive value (NPV) are independent of the prevalence of the disease among the population being investigated. Farther the PLR from 1, the stronger the evidence for the presence of the disease.[29] In our meta-analysis, PLR was 32.52 (95% CI: 7.89–134.15), which further supplements the strong evidence for RRT-positive newborns with disease. NLR was less than 1 [0.69 (95% CI: 0.55–0.88)] suggesting a low false-negative value of RRT. DOR calculated was 138.48 (95% CI: 23.85–803.97), which further implies that RRT has high discriminatory power for the detection of an abnormal ophthalmological condition. Fig. 5 shows the ROC-AUC for RRT. The mean (± SD) AUC and Q* index were 0.98 ± 0.02 and 0.95 ± 0.045, respectively, for the RRT. The ROC curve generated from the binary results of RRT showed an AUC of 0.98 ± 0.02, which implies that RRT is a very good discriminator of neonates with ophthalmological abnormalities versus neonates without ophthalmological abnormalities. A value of more than 0.9 is considered outstanding.[30] Statistically significant heterogeneity was observed for the calculation of the sensitivity ($\chi^2 = 849.01$, $P = 0.000$) and specificity ($\chi2 = 1395.21$, $P = 0.000$) among all studies included in the analysis, as well as for the calculation of specificities and sensitivities in the subgroup analyses. High variation was observed in the calculation of sensitivity ($I^2 = 98.8\%$) and specificity ($I^2 = 99.3\%$) calculation.

Subgroup analysis

In the subgroup analysis of studies that mainly focused on RRT done by pediatricians only,[11,20,22,24,26] the pooled sensitivity and specificity were 56% (95% CI, 47–64%) and 97% (95% CI, 97–97%),
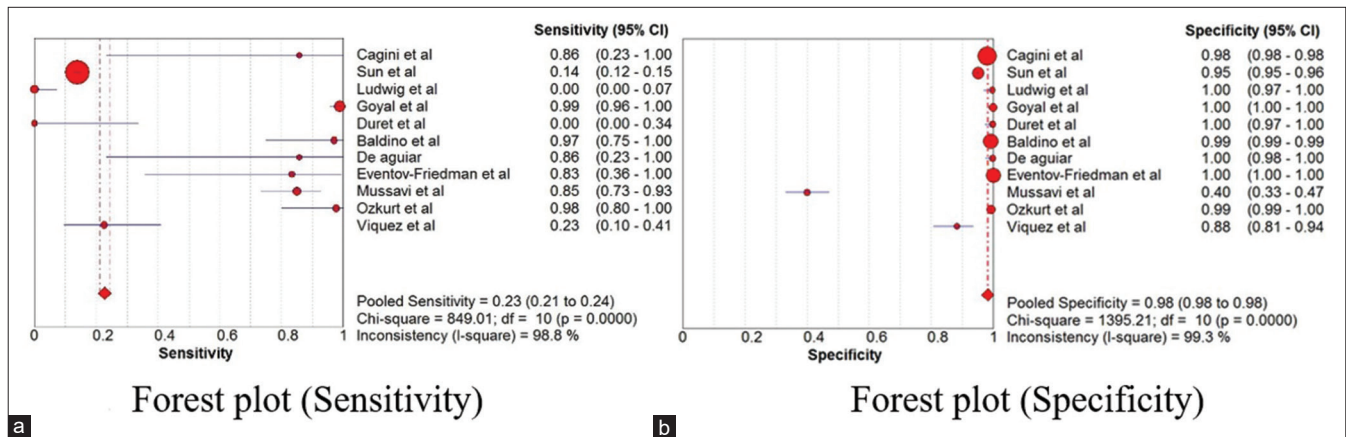
individual studies is shown in Fig. 3. It shows the risk of bias and applicability concerns in different domains. The majority of all included articles in the current meta-analysis met most

Figure 4: Forest plot of sensitivity (a) and specificity (b) of RRT for diagnosing ocular abnormalities of all the included studies
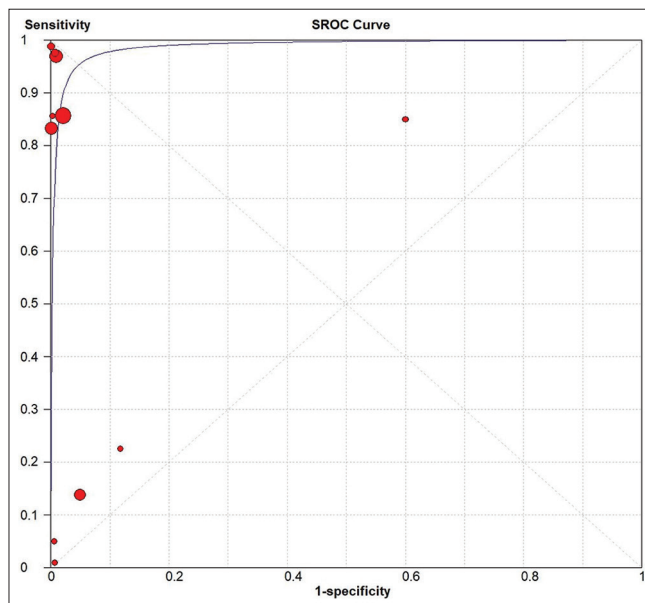

Figure 5: Summary ROC (SROC) curve for diagnostic accuracy of RRT for diagnosing ocular abnormalities. *Red circles represent the individual studies*

respectively. The pooled sensitivity of studies where RRT was done by ophthalmologist[21,27,28] was 15% (95% CI: 13–16%), whereas the specificity was 96% (95% CI: 95–96%). In the studies where the RRT was performed by other medical trained health professionals (nurse, medical students, optometrists),[12,23,25] the pooled sensitivity and specificity were 94% (95% CI: 89–97%) and 100% (95% CI: 100–100%), respectively. This pooled analysis has been represented with a forest plot in Fig. 6.

Sensitivity analysis

We conducted the following additional sensitivity analysis of the RRT for diagnosing ocular abnormalities removing studies with a high risk of selection bias and including studies with low- and moderate-risk bias. Nine studies with low-risk bias were included in the sensitivity analysis. The pooled sensitivity for RRT was 0.22 (95% CI: 0.20–0.24) and the specificity was 0.98 (95% CI: 0.98–0.98) [Fig. 7]. The PLR was 21.98 (95% CI: 4.71–102.57). The NLR was 0.74 (95% CI: 0.59–0.92). The DOR was 71.30 (95% CI, 11.99-423.93). The AUC was 0.976.

Discussion

Ocular abnormalities are a considerable cause of morbidity in newborns. A screening strategy involving RRT is essential in early diagnosis. This helps to achieve the ultimate goal by preventing late diagnosis and eventually complete blindness and cognitive sequelae in newborns. Eleven studies met the inclusion criteria of this systematic review with a total of 56,556 neonates who underwent RRT.

The prevalence rates for ocular abnormalities in the included studies varied from 0.01% to 30.9%. Five studies were from Asia, two from Europe, and four from the American continents. Individuals (pediatrician, ophthalmologist, neonatologist, etc.) performing the RRT differed among the studies as described in Table 1. A screening test should have 100% sensitivity and specificity to be accepted as the "gold standard," although the practicality of such a screening modality is almost next to impossible. Our meta-analysis showed that RRT has a poor pooled sensitivity of 23% (95% CI: 21–24%). A high variance was seen among the studies in reporting sensitivity (0% to 99%). Only three studies have reported a sensitivity greater than 90%,[12,24,27] whereas four studies have sensitivity less than 50%.[21-23,28] This high degree of variation was statistically significant ($P = 0.00$; $I^2 = 98.8\%$). Among the studies reporting poor sensitivities, Ludwig *et al.*[22] found that the poor sensitivity of RRT was attributable to the high number of false-negative cases of posterior segment abnormalities detected by this screening test. Sun *et al.*,[21] also supported the finding that RRT had a high rate of false-negative with a sensitivity of only 4.1% for detection of posterior segment abnormalities, whereas the sensitivity for detection for the anterior segment was 99.6%. Study by Viquez *et al.*[28] also determined that RRT had poor sensitivity in the detection of posterior segment abnormalities in contrast to anterior segment (54.7% vs. 100%). Duret *et al.*,[23] in their examination of 90 neonates, determined that RRT had 0% sensitivity in comparison with IR-reflex imaging that picked up subtle ocular media opacities in nine eyes. Even though with such a poor sensitivity, specificity for RRT was 100% as there were no false positives in the study.

The pooled specificity of RRT calculated was 98% (95% CI: 98–98%). Nine of the included studies have shown high specificity of this screening test (>95%). Viquez *et al.*[28] had an acceptable specificity of 88%. The specificity of RRT in the
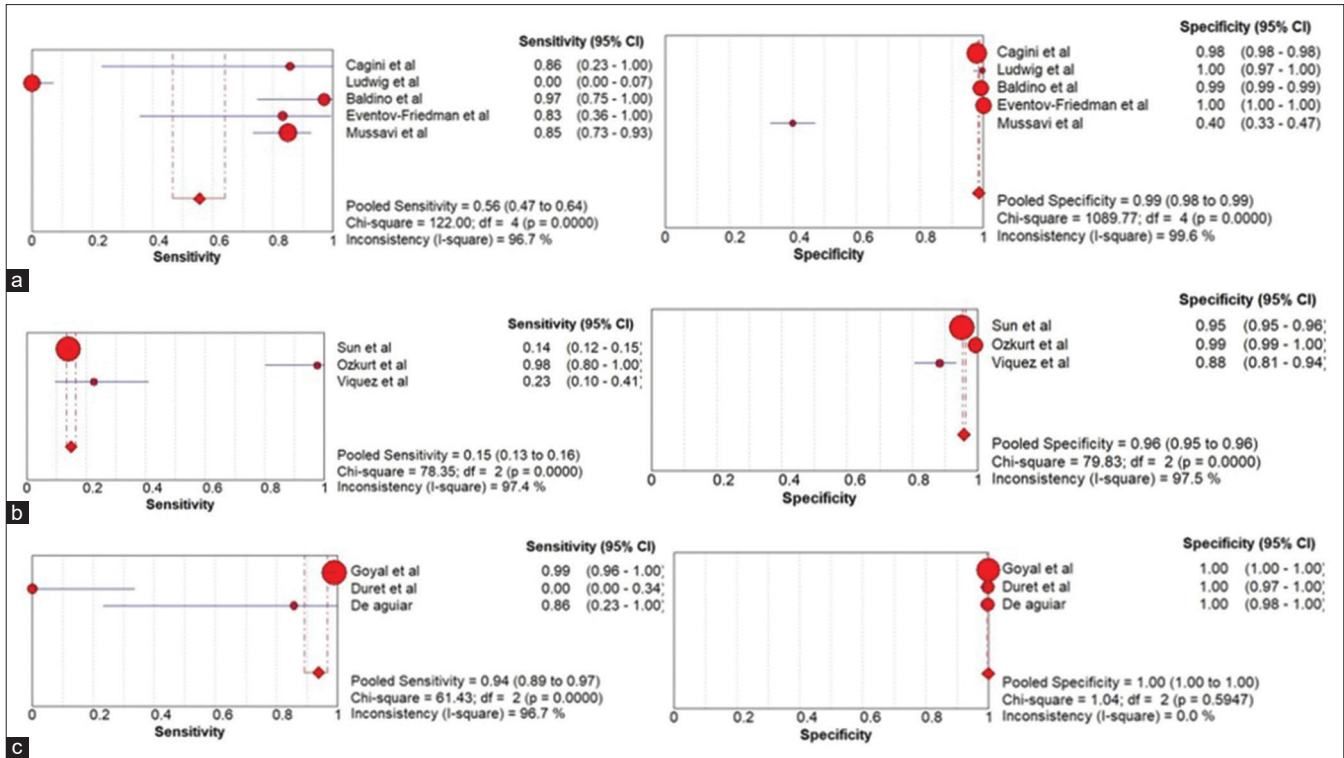
Figure 6: The forest plot of sensitivity and specificity of RRT for diagnosing ocular abnormalities in the included studies by pediatrician/ neonatologist (a), an ophthalmologist (b), and other healthcare professionals (medical students, optometrist, and trained nurse) (c)
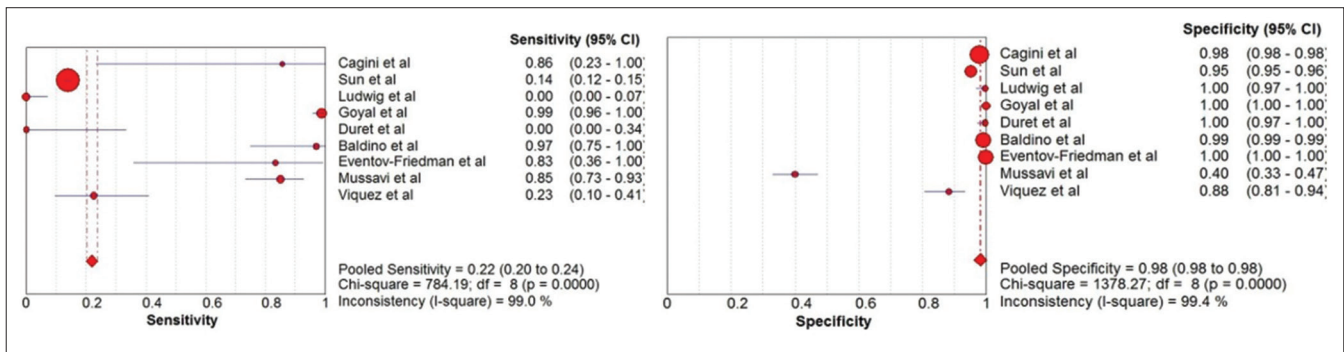

Figure 7: Forest plot for individual studies and pooled sensitivity and specificity for RRT who reported the low-risk studies

study by Mussavi *et al.*[26] was a low 40% in the nonstandard condition in stark contrast to 92.6% when the test was done under standard condition. The possible causes of this disparity could be the fact that initial screening was under a nonideal scenario (nondilated eyes, bedside/delivery room examination) and by a pediatrician although trained. Overall, the specificity was high for RRT independent of the abnormality being in the anterior segment or posterior segment as was observed in the analysis of sensitivity. The distribution of true positives and false negatives being expressed in terms of the ability of RRT to detect anterior segment abnormalities as well as posterior segment abnormalities is shown in Table 3.

In all the studies included except one,[25] the diagnosis of all the neonates with an abnormal RRT was specified. When the diagnostic ability of RRT is considered for anterior segment abnormalities, RRT detected 255/257 (99.22%) cases, whereas

for posterior segment abnormalities RRT could detect only 323/2290 (14.10%) cases. Thus, we can conclusively say that RRT is an excellent tool for the diagnosis of anterior segment diseases when compared with posterior segment diseases.

Overall, the quality of the included studies was good with the risk of bias being low risk for six studies, unclear risk for three, and high risk for two studies. Both sensitivity and specificity have shown a high degree of variation in our meta-analysis. The subgroup analyses were done, to compare if the heterogeneity was dependent on the person (pediatrician vs. ophthalmologist vs. other trained professional) performing the screening test, showed a huge range of sensitivities (56% vs. 15% vs. 94%) and specificities (99% vs. 96% vs. 100%). However, the degree of heterogeneity observed among the different study estimates is statistically significant; this variability might be attributed to the nonhomogeneity of

individuals performing the RRT. Thus, the results of the pooled analysis have to be taken with a certain degree of discretion. The other major reason could be the large diversity of sample size found in each study accounting for variability between studies. Although this variation is meaningful from the statistic perspective, its clinical importance regarding diagnostic performance of physical examination and RRT is objectionable due to the operative characteristics already described and its diagnostic accuracy in the detection of ocular abnormalities. Likewise, the low sensitivity of RRT found in some of the included articles may also influence the global estimate for heterogeneity.

With regards to the clinical implication of including RRT in ocular abnormalities screening, we may conclude that it contributes to the early diagnosis of few cases, thus reducing the number of false-negative results of the RRT and with it the economic burden. Goyal et al.[12] calculated the financial loss incurred for a child going blind at US $75,224. Such a huge amount and resource expenditure can be brought down by the application of universal newborn screening by RRT. However, more studies are needed to evaluate the financial gains of the application of this screening modality for a final comment on the feasibility of RRT. There has been significant concern regarding the higher incidence of neonatal conjunctivitis among those who have undergone RRT. Ulanovsky et al.[31] and Smolkin et al.[32] have reported a higher, significant relationship of clinical neonatal conjunctivitis and performance of RRT. However, this complication could be prevented by the application of hand hygiene using the alcohol-based gel as a disinfectant.[32]

Strengths and limitations

The strengths of this review include a rigorous, comprehensive search conducted to incorporate all relevant studies with no language restrictions and the standardized quality assessment with risk of bias assessment performed on all the articles included using the QUADAS-2 tool. This review has tried to explore all the possible causes of heterogeneity and quantify them. The calculation of DOR, PLR, and NLR along with a diagrammatic depiction of the AUC of the ROC curve further consolidates the objective of the study. The limitations of our review include the small number of studies evaluating the use of RRT as a screening strategy for the detection of ocular abnormalities. A major limitation was the nonuniformity of the individuals performing the RRT among the included studies. A certain level of expertise is required to use, perform, and interpret the results of the RRT efficiently, which was lacking in some studies. This could have potentially lead to a higher rate of false positives and false negatives, thus, impacting the accuracy of the screening test. We cannot rule out the presence of unexplained heterogeneity in this accuracy index, even though it is possible that some of the variations observed in sensitivities of individual studies could be explained by the paucity of abnormal ophthalmological cases as well as a large variation in the sample sizes.

Conclusion

From this systematic review and meta-analysis, we conclude that the use of RRT has a high specificity, thus, aiding in ruling out neonates with ocular abnormalities, without significantly increasing the number of false-positive results. The pooled

sensitivity may be low, but with the data currently available, we recommend RRT as a highly sensitive test for the detection of anterior segment abnormalities. The specificity of RRT was found to be similar and independent of abnormalities of the anterior segment or posterior segment. However, the nonuniformity of the individuals performing the RRT, studies with a large percentage of posterior segment abnormalities, and large variation in sample size among the included studies make for a careful interpretation of results. This review sets the basis for determining whether the impact of including this noninvasive technology as part of newborn screening is cost-effective in low- and middle-income countries.

Conflicts of interest

There are no conflicts of interest.

References

1. Pascolini D, Mariotti SP. Global estimates of visual impairment: 2010. Br J Ophthalmol 2012;96:614-8.

2. Dandona L, Williams JD, Williams BC, Rao GN. Population-based assessment of childhood blindness in southern India. Arch Ophthalmol Chic Ill 1960 1998;116:545–6.

3. Gudlavalleti VSM. Magnitude and temporal trends in avoidable blindness in children (ABC) in India. Indian J Pediatr 2017;84:924–9.

4. Mayer DL, Beiser AS, Warner AF, Pratt EM, Raye KN, Lang JM. Monocular acuity norms for the Teller Acuity Cards between ages one month and four years. Invest Ophthalmol Vis Sci 1995;36:671–85.

5. Salomão SR, Ventura DF. Large sample population age norms for visual acuities obtained with Vistech-Teller Acuity Cards. Invest Ophthalmol Vis Sci 1995;36:657–70.

6. Solebo AL, Teoh L, Rahi J. Epidemiology of blindness in children. Arch Dis Child 2017;102:853.

7. De Alba Campomanes AG, Binenbaum G. Eye and vision disorders. In: Avery's Diseases of the Newborn. 10th ed. Philadelphia: Elsevier; 2018. p. 1536–57.

8. Gilbert C, Foster A. Childhood blindness in the context of VISION 2020--The right to sight. Bull World Health Organ 2001;79:227–32.

9. American Academy of Pediatrics; Section on Ophthalmology; American Association for Pediatric Ophthalmology and Strabismus; American Academy of Ophthalmology; American Association of Certified Orthoptists. Red reflex examination in neonates, infants, and children. Pediatrics 2008;122:1401-4.

10. Donahue S, Nixon C, Section on Opthamology, American Academy of Pediatrics, Committee on Practice and Ambulatory Medicine, American Academy of Pediatrics, American Academy of Ophthalmology, American Association for Pediatric Ophthalmology and Strabismus, et al. Visual system assessment in infants, children, and young adults by pediatricians. Pediatrics 2016;137:28–30.

11. Eventov-Friedman S, Leiba H, Flidel-Rimon O, Juster-Reicher A, Shinwell E. The red reflex examination in neonates: An efficient tool for early diagnosis of congenital ocular diseases. Isr Med Assoc J 2010;12:259-61.

12. Goyal P, Padhi TR, Das T, Pradhan L, Sutar S, Butola S, et al. Outcome of universal newborn eye screening with wide-field digital retinal image acquisition system: A pilot study. Eye 2018;32:67–73.

13. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate

health care interventions: Explanation and elaboration. PLoS Med 2009;6:e1000100.

14. McInnes MDF, Moher D, Thombs BD, McGrath TA, Bossuyt PM, and the PRISMA-DTA Group. Preferred reporting items for a systematic review and meta-analysis of diagnostic test accuracy studies: The PRISMA-DTA statement. JAMA 2018;319:388–96.

15. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. BMJ 2009;339. doi: 10.1136/bmj.b2535.

16. Whiting PF, Rutjes AWS, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, *et al*. QUADAS-2: A revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011;155:529–36.

17. Nordic Cochrane Centre The Cochrane Collaboration. Review manager (*RevMan*) [*computer program*] Version 53. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

18. Zamora J, Abraira V, Muriel A, Khan K, Coomarasamy A. Meta-DiSc: A software for meta-analysis of test accuracy data. BMC Med Res Methodol 2006;6:31.

19. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.

20. Cagini C, Tosi G, Stracci F, Rinaldi VE, Verrotti A. Red reflex examination in neonates: Evaluation of 3 years of screening. Int Ophthalmol 2017;37:1199-204.

21. Sun M, Ma A, Li F, Cheng K, Zhang, Yang H, *et al*. Sensitivity and specificity of red reflex test in newborn eye screening. J Pediatr 2016;179:192-6.e4.

22. Ludwig CA, Callaway NF, Blumenkranz MS, Fredrick DR, Moshfeghi DM. Validity of the red reflex exam in the newborn eye screening test cohort. Ophthalmic Surg Lasers Imaging Retina 2018;49:103–10.

23. Duret A, Humphries R, Ramanujam S, Te Water Naudé A, Reid C, Allen LE. The infrared reflex: A potential new method for congenital cataract screening. Eye Lond Engl 2019;33:1865–70.

24. Baldino VMCL, Eckert GU, Rossatto J, Wagner MB. Red reflex test at the maternity hospital: results from a tertiary hospital and variables associated with inconclusive test results. Jornal de Pediatria. 2020;96:748–54.

25. de Aguiar AS, Ximenes LB, Lúcio IL, Pagliuca LM, Cardoso MV. Association of the red reflex in newborns with neonatal variables Rev Lat Am Enfermagem 2011;19:309-16.

26. Mussavi M, Asadollahi K, Janbaz F, Mansoori E, Abbasi N. The evaluation of red reflex sensitivity and specificity test among neonates in different conditions. Iran J Pediatr 2014;24:697–702.

27. Ozkurt Z, Balsak S, Yildirim Y, Yuksel H, Caca I. Associations between red reflex abnormality, consanguinity and intensive care hospitalization of newborns in Turkey. East Mediterr Health J 2018;24:631–6.

28. Viquez MV, Wu L. Sensitivity and specificity of the red reflex in Costa Rican newborns. Arch Soc Esp Oftalmol (Engl Ed) 2020;95:4-8.

29. Eusebi P. Diagnostic accuracy measures. Cerebrovasc Dis 2013;36:267–72.

30. Hosmer D, Lemeshow S. Applied Logistic Regression. In: 2nd ed. New York, NY: John Wiley and Sons; 2000. p. 160–4.

31. Ulanovsky I, Shnaider M, Geffen Y, Smolkin T, Mashiach T, Blazer S, *et al*. Performing red reflex eye examinations increases the rate of neonatal conjunctivitis. Acta Paediatr 2015;104:e541-5.

32. Smolkin T, Roth-Ahronson E, Kranzler M, Geffen Y, Mashiach T, Kugelman A, *et al*. Optimizing accessibility of a hand-wash gel to infant's cradle: Effect on neonatal conjunctivitis. Pediatr Infect Dis J 2019;38:e7–11.