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Diagnostic accuracy of cell-free DNA in maternal blood in detecting chromosomal anomalies in twin pregnancies: systematic review and meta-analysis

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CONTRIBUTION

What are the novel findings of this work?

In twin pregnancies, cfDNA had a high diagnostic accuracy for Trisomy 13,18 and 21 similar to that reported in singleton and higher compared to what is reported for the combined screening test. The diagnostic performance of cfDNA was similar in DC and MC twins.

What are the clinical implications of this work?

cfDNA can be offered to women carrying twin pregnancies in view of its high diagnostic accuracy.

ABSTRACT

Objectives: To report the diagnostic accuracy of cell-free DNA (cfDNA) in maternal blood in detecting chromosomal anomalies in twin pregnancies.

Methods: Medline, Embase and Cochrane databases were searched. The inclusion criteria were twin pregnancies undergoing cfDNA screening for Trisomies 13, 18, 21, monosomy X0 and other sex chromosomal anomalies (SCA). The index test was represented by a positive results of cfDNA test. The reference standard was represented by the karyotype results (obtained either pre or postnatally) or, in case of negative cfDNA result, by a normal neonatal phenotype. The quality of the studies was assessed using the revised tool for the quality assessment of diagnostic accuracy studies (QUADAS-2). Summary estimates of sensitivity, specificity, positive and negative likelihood ratios (LR+ and LR–) and diagnostic odds ratio (DOR), with the corresponding 95% Confidence Intervals (95% CI), were computed using the bivariate random-effects model.

Results: Thirty-five studies were included. cfDNA had an overall high accuracy in detecting Trisomy 21 in twin pregnancies with a sensitivity of 98.8% (95% CI 96.5-100), a specificity of 100% (95% CI 99.9-100). Sensitivity and specificity were of 94.9% (95% CI 75.6-99.1) and 100 (95% CI 99.9-100) for Trisomy 18, and 84.6% (95% C% 54.6-98.1) and 100% (95% CI 99.9-100) for Trisomy 13 . We could not compute the diagnostic accuracy of cfDNA in detecting monosomy X0 in twins, while cfDNA had a sensitivity of 100% (95% CI 71.5-100) and a specificity of 99.8% (95% CI 99.7-99.9) in detecting other SCA (11 cases). The accuracy of cfDNA in detecting Trisomy 21, 18 and 13 was similar in dichorionic and monochorionic twin pregnancies.

Conclusion: cfDNA has a high diagnostic accuracy in detecting Trisomy 18 and 21 in twin pregnancies, irrespective of chorionicity. Accuracy in the detection of Trisomy 13 and SCA was

limited by the small number of affected cases and the difficulties in the confirmation of false negative cases in case of SCA and requires confirmation in larger studies.

INTRODUCTION

Twin pregnancies are at increased risk of adverse perinatal outcome compared to singletons in view of the higher prevalence of chromosomal and structural anomalies, preterm birth and placental insufficiency[1,2]. Several studies reported that the incidence of chromosomal anomalies in dizygotic twins is higher than that reported in singletons, in view of the presence of two fetuses, each with its own genetic risk, while their occurrence in monozygotic gestations is similar to singletons[3]. Conversely, the risk of chromosomal anomalies in other studies was lower compared to what reported in singletons[4].

Screening for Trisomy 21 in twin pregnancies has been conventionally performed using the combined test, integrating maternal age, nuchal translucency thickness (NT) and if available, biochemical markers (β-hCG and PAPP-A)[5]. Large cohort studies and systematic reviews reported that the efficacy of combined screening in twins was as effective as in singleton despite the higher false positive rates[5]. The introduction of fetal cell-free DNA (cfDNA)-based techniques for the screening of Trisomy 21 and other aneuploidies has completely changed the traditional approach to prenatal screening[6,7].

In 2017 The International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) published a consensus statement endorsing the use of cfDNA in high or intermediate risk singleton pregnancies[8]. Later in 2020, the International Society for Prenatal Diagnosis position statement confirmed the usefulness of cfDNA in screening for common aneuplodies in twins in view of its higher accuracy compared to the combined test[9].

Recent large cohort studies and systematic reviews have confirmed the reliability of cfDNA in screening for Trisomy 21 and other common aneuploidies in twins[10,11]. Despite that, the actual diagnostic accuracy of cfDNA in detecting chromosomal anomalies in twin has not been fully elucidated yet. Previous published studies did not comprehensively report their results in terms of diagnostic accuracy and are limited by the lack of stratification according to chorionicity, gestational age at sampling and cfDNA technique for analysis. The reported number of trisomy-21 cases in twin pregnancy diagnosed using cfDNA testing is far smaller than that in singleton pregnancies.

In this context, we performed a systematic review and meta-analysis to report the diagnostic accuracy of cfDNA in detecting chromosomal anomalies in twin pregnancies.

METHODS

Protocol, information sources and literature search

This review was performed according to an a-priori designed protocol and recommended for systematic reviews and meta-analysis[12-14]. Pubmed, Medline and Embase databases were searched electronically on 24th November 2023 utilizing combinations of the relevant medical subject heading (MeSH) terms, key words, and word variants for "cfDNA", "non-invasive prenatal diagnosis", "" and "aneuploidies" (Table S1). The search and selection criteria were restricted to English language. Reference list of relevant articles and reviews were hand searched for additional reports. Prisma guidelines were followed[15]. The study was registered with the PROSPERO database (registration number: CRD42023485225).

Study selection, data collection, index test and reference standard

The inclusion criteria were twin pregnancies undergoing cfDNA screening for Trisomies 13,18, 21, monosomy X0 and/or other sex-chromosomal anomalies (SCA).

The index test was represented by the positive results of cfDNA test for each of the chromosomal anomalies explored. The reference standard was represented by the karyotype results (obtained either pre or postnatally) or, in case of negative cfDNA result, by a normal phenotype. Furthermore, we planned to perform different subgroup analyses according to chorionicity, gestational age at blood sampling (first vs second trimester) and type of cfDNA analysis (targeted vs massively parallel shotgun sequencing).

Only studies reporting diagnostic accuracy of cfDNA in twin pregnancies for which a pre or post-natal genetic assessment of phenotypic evaluation was reported were considered eligible for the inclusion in the present systematic review. Studies including higher order multiple gestations, fetal anomalies, those from a pre or post-natal confirmation of the aneuploidies explored was not reported and those for which data could not be extrapolated were excluded. Studies published before 2010 were also excluded, as we considered that advances in cfDNA techniques make them less relevant. Studies reporting vanishing twins were also excluded in view of the higher risk of false positive and negative results from the circulating DNA of the demised fetus. Only full text articles were considered eligible for the inclusion; case reports, conference abstracts and case series with fewer than 50 cases were excluded to avoid publication bias.

Two authors (LDV, MP) reviewed all abstracts independently. Agreement regarding potential relevance was reached by consensus. Full text copies of those papers were obtained, and the same two reviewers independently extracted relevant data regarding study characteristics and pregnancy outcomes. Inconsistencies were discussed by the reviewers and consensus reached or by discussion with a third author (FDA). If more than one study was published for the same cohort with identical endpoints, the report containing the most comprehensive information on the population was included to avoid overlapping populations.

Quality assessment, risk of bias and statistical analysis

The quality of the studies was assessed using the revised tool for the quality assessment of diagnostic accuracy studies (QUADAS-2), which consists of four key domains covering patient selection, index test, reference standard, and flow of patients through the study and timing of the index test and reference standard[16]. Each domain is assessed in terms of the risk of bias, and the first three are also assessed in terms of concerns regarding applicability. Each item was scored as having high or low risk, or unclear risk if there was insufficient information to make an accurate judgment[16].

The overall accuracy of cfDNA to predict the selected chromosomal anomalies in twin pregnancies was assessed computing summary estimates of sensitivity, specificity, positive and negative likelihood ratios (LR+ and LR–) and diagnostic odds ratio (DOR) - and the corresponding 95% confidence intervals (95% CI) - using a bivariate random-effects model [17]. The DOR is defined as the ratio of the odds of the test being positive if the subject has a disease, relative to the odds of the test being positive if the subject does not have the disease, i.e. LR+/LR–[18,19].

Meta-Disc, version 1.4, was used to analyze the data.

RESULTS

Study selection and characteristics

497 articles were identified, 59 were assessed with respect to their eligibility for inclusion and 35 studies were included in the systematic review (Figure 1 and Table 1)[10,20-53]. These studies included (after removing the studies including overlapped cases) 35046 twin pregnancies undergoing cfDNA for the detection of Trisomy 21, 28469 for Trisomy 18, 16308 for Trisomy 13, 4811 for monosomy X0 and 6335 for other SCA. Failure rate of cfDNA in twin pregnancies was 1.28% (95% CI 1.1-1.5%). The results of the quality assessment of the included studies using QUADAS-2 tool are presented in Table 2. Most studies were of moderate quality. The major weaknesses of the studies were the different gestational ages at blood analysis, lack of stratification of the analysis according to chorionicity for some of the included studies and lack of confirmation of false negative cases in case of SCA. For meta-analyses including ≥ 10 individual studies, Deek's funnel plot asymmetry test did not show any significant publication bias.

Synthesis of the results

Thirty studies including 35046 women with twin pregnancies reported the accuracy of cfDNA in identifying Trisomy 21 (253 affected cases). When considering all twin pregnancies, cfDNA had an overall high accuracy in detecting Trisomy 21 in twin pregnancies with a sensitivity of 98.8% (95% CI 96.5-100), a specificity of 100% (95% CI 99.9-100), a LR+ of 631 (95% CI 432-921), a LR- of 0.08 (95% CI 0.05-0.12) and a DOR of 9623 (95% CI 4990-18560). Similarly, cfDNA had a high accuracy in identifying fetuses with Trisomy 18 (63 affected cases) in the setting of a twin pregnancies, with a sensitivity of 94.9% (95% CI 75.9—99.1), a specificity of 100% (95% CI 99.9-100), a LR+ of 2698 (95% CI 1346-5408), a LR- of 0.05 (95% CI 0.02-0.016) and a DOR of 52048 (95% CI 13946-194257) (Table 3), while the corresponding figures for Trisomy 13 (12 affected cases) were 84.6% (95% CI 54.6-98.1), 100% (95% CI 99.9-100), 1012 (95% CI 473-2175), 0.30 (95% C% 0.2-0.6) and 3368 (95% CI 918-12359) (Figure S1)

We could not compute the figures for the diagnostic accuracy of cfDNA in detecting monosomy X0 as there was no true positive case was reported in the included studies, while the sensitivity and specificity for other SCA (11 affected cases) were 100 (95% CI 71.5-100) and 99.8% (95% CI 99.7-99.9) respectively.

When considering MC and DC gestations separately, the sensitivity and specificity of cfDNA in detecting Trisomy 21 was 98.5% (95% CI 94.7-98.8) and 99.9% (95% CI 99.9-100) in DC and 100% (95% CI 75.3-100) and 100 (95% CI 99.0-100) in MC pregnancies. The sensitivity for Trisomy 18 was 92.6% (95% CI 75.7-99.1) in DC and 100% (95% CI 39.8-100) in MC, while the corresponding figures for specificity were 100% (95% CI 99.8-100) and 99.8% (95% 99.1-100), respectively. Sensitivity and specificity for Trisomy 13 were 88.9% (955 CI 51.8-99.7) and 100% (95% CI 99.9-100) in DC pregnancies, and 100% (95% CI 2.5-100) and 100% (95% CI 98.8-100) in MC pregnancies.

DISCUSSION

Summary of the main findings

The findings from this study showed that in twin pregnancies, cfDNA had a high diagnostic accuracy for Trisomy 18 and 21. The diagnostic performance of cfDNA was similar in DC and MC twins. However, the very small number of affected cases for Trisomy 13, monosomy XO and other SCA limits the robustness of the results.

Strengths and limitations, comparison with other systematic reviews

Thorough literature search, large sample size and stratification of the results according to chorionicity represent the main strengths of the present review. Furthermore, we reported all the figures for diagnostic accuracy of cfDNA in detecting chromosomal anomalies in twins. The retrospective design of some of the included studies, heterogeneity in the population analyzed, lack of information on ultrasound assessment of the included cases and stratification according to chorionicity, gestational age at blood sampling and techniques of cfDNA analyses in most of the included studies represent the major weaknesses of the present systematic review. Furthermore, the relatively very small number of some of the chromosomal anomalies considered compared to studies including singletons represents another source of bias potentially affecting the figures of diagnostic accuracy reported in the present study. Validation of the cfDNA results in case of SCA represented another peculiar issue. SCA did not commonly show anomalies at ultrasound and the phenotypic recognition of such cases is difficult, thus making the computation of the false negative challenging.

The findings from the present systematic review are generally in line with those in singletons.

Gil et al. reported a detection rate of 98.2% and 88.9% for Trisomy 21 and 18 with a 0.05% and 0.03% false positive rate respectively, while the very small number of cases affected by Trisomy 13 did not allow computation of diagnostic accuracy for this aneuploidy[9].

Shear et al. a sensitivity and specificity of 98.8% and 99.4% for 45X0, 100% and 100% for 47,XXY and 100% and 99.9% for 47,XXX. Another systematic review including a12 studies and 8000 twin pregnancies reported a detection rate of 99%, 93% and 93% for Trisomy 21, 18 and 13 respectively, while the corresponding figures for false positive rate were 0.01%, 0.01% and 0.1%[54]. Compared to that study, the present systematic reviews included a larger cohort of twins and reported all the figures of diagnostic accuracy, including specificity, LR+ and LR- and DOR.

Clinical and research implications

Screening for aneuploidies in twins is more complex than in singletons. Accurate prenatal counselling is crucial and should highlight the potential limitations of the screening test, higher risk of invasive procedures compared to singleton and the potential risks associated with selective termination[,55,56].

Estimating the actual risk of aneuploidies in twins is also challenging and is related to maternal age and zygosity. In dizygotic twins, each twin has an independent risk of aneuploidy as they derive for the fertilization of two separate ova, thus making the risk for at least one twin to be affected theoretically higher than singletons. Conversely, in monozygotic twin the risk is theoretically the same as they are derived by the fertilization of a single oocyte. Despite this assumption, large cohort studies have reported a lower-than-expected risk of aneuploidies in twin pregnancies independent of maternal age[3]. One of the likely explanations for this phenomenon may be the higher early fetal loss rate observed in twins compared to singleton.

Screening for the most common aneuploidies in twins had been classically carried out with the combined screening test, integrating maternal age, nuchal translucency and biochemical markers.

Placental cfDNA circulating in maternal blood has become widely used for aneuploidy screening in singleton pregnancies. Gil et al. reported a detection rate of 98.2% and 88.9% for Trisomy 21 and 18 with a 0.05% and 0.03% false positive rate respectively, while the very small number of cases affected by Trisomy 13 did not allow computation of diagnostic accuracy[9].

Diagnostic performance of cfDNA in twins has always been a matter of debate. The American College Obstetricians and Gynecologist and the international Society for Prenatal Diagnosis state that cfDNA is an appropriate test for aneuploidy screening in twin pregnancies, although both societies highlight the potential limitations of the test in identifying Trisomy 18 and 13 in view of the very small number of cases included in previously published studies[8,57]. In the present systematic review, cfDNA showed an overall high diagnostic accuracy in identifying fetuses with Trisomy 13 and 18. Despite being higher than individual study, the overall prevalence of Trisomy 13 and 18 was lower compared to that reported in studies on singletons thus potentially affecting the robustness of the reported results. However, Trisomies 13 and 18 are almost invariably associated with ultrasound anomalies presenting since the very early stages of pregnancies, and it may be argued that the contribution of cfDNA in such cases is less significant as a significant proportion of, if not all, these cases are potentially suspected at ultrasound and confirmed after invasive procedure.

Conclusion

cfDNA shows a high diagnostic performance in identifying fetuses with Trisomy 21, 18 and 13 in twins, higher than the combined test and similar to that reported in singletons, although the overall number of affected cases was significantly lower compared to previous meta-analysis on singletons, thus limiting the robustness of these results. Similarly, the diagnostic performance in identifying SCA was high but limited by the very small number of affected cases and requires confirmation in large prospective series.

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Figure legend

Figure 1. Systematic review flowchart

Table 1: General characteristics of the studies included in the present systematic review.

Author	**Year**	**Country**	**Study design**	**Period considered**	**GA at testing (weeks)**	**cfDNA analysis**	**Chorionicity**	**Population**	**Aneuploidies tested**	**Pregnancies (n)**
Eiben[20]	2023	Germany	Retrospective cohort	2017-2022	12.8 ±0.31	MPSS	NR	High-risk	T13, T18, T21	1658
Dugoff[21]	2023	United States	Retrospective cohort	2011-2020	12.3 (11.4-13.6)	MPSS	MC, DC	High and low risk	T13, T18, T21	1764
De Falco[22]	2023	Italy	Retrospective cohort	2020-2022	11.54	MPSS	MC, DC	High and low risk	T13, T18, T21	1254
Wang[23]	2023	China	Retrospective cohort	2015-2020	17.04±4.03	MPSS	MC, DC	High and low risk	T13, T18, T21, SCA	2010
Claudel[24]	2023	France	Retrospective cohort	2017-2019	16.2±4.2	MPSS	MC, DC	Low risk	T21	2577

Yuan[25]	2023	China	Retrospective cohort	2018-2022	16.9± 2.0	MPSS	MC, DC	High and low risk	T13, T18, T21, SCA	1754
Chen[26]	2022	China	Retrospective cohort	2016-2017	16.8 (12-24)	MPSS	NR	NR	T13, T18, T21	6471
Yang[27]	2022	China	Retrospective cohort	2019-2020	15 (12-21)	MPSS	DC	High-risk	T13, T18, T21	474
La Verde[28]	2021	Italy	Retrospective cohort	2017-2019	12+3 (10+1-19+6)	MPSS	MC, DC	High and low risk	T13, T18, T21, SCA	800
Xu[29]	2021	China	Retrospective cohort	2015-2019	NR	MPSS	NR	High-risk	T13, T18, T21	2399
Bai[30]	2021	China	Retrospective cohort	2017-2018	16.8 (15.9-17.8)	MPSS	MC, DC	High and low risk	T13, T18, T21, SCA	5469
Gottard[i31]	2021	France	Retrospective cohort	2017-2018	<14	MPSS	MC, DC	High and low risk	T13, T18, T21	719

Cheng[32]	2021	China	Prospective cohort	2016-2020	16 (12-28)	MPSS	MC, DC	High and low risk	T13, T18, T21, SCA	1048
van Riel[33]	2021	Belgium	Retrospective cohort	2013-2020	From 10 weeks	MPSS	MC, DC	High and low risk	T13, T18, T21	4150
Khalil[34]	2021	United Kingdom	Prospective cohort	2015-2018	10 to 36	MPSS	MC, DC	High and low risk	T13, T18, T21	1003
Yang[35]	2021	China	Retrospective cohort	2015-2019	NR	MPSS	NR	NR	SCA	1530
Judah[10]	2021	United Kingdom	Prospective cohort	2012-2020	10+0 -14+1	Targeted	MC, DC	High and low risk	T13, T18, T21	1442
Jin[36]	2021	China	Retrospective cohort	2015-2019	12- 26+6	MPSS	NR	High-risk	T13, T18, T21	978
He[37]	2020	China	Prospective cohort	2016-2018	16.1 (10-23)	MPSS	MC, DC	High and low risk	T13, T18, T21	146

Chibuk[38]	2020	United States	Retrospective cohort	2013-2018	12 (9-34)	MPSS	NR	High-risk	T13, T18, T21	422
Motevasselian[39]	2020	Iran	Prospective cohort	2016-2018	15+4± 5d	Targeted, MPSS	MC, DC	High-risk	T13, T18, T21	500
Dyr[40]	2019	United States	Retrospective cohort	2011-2017	13+5 (9-38)	MPSS	NR	High and low risk	Trisomy 13,18,21, SCA	30826
Norwitz[41]	2019	United States, Turkey, Italy	Prospective cohort	2013-2017	15.5± 4.7	Targeted	MC, DC	High and low risk	T13, T18, T21	117
Yu[42]	2019	China	Prospective cohort	2015-2017	18.1 (8-30)	MPSS	MC, DC	High and low risk	T13, T18, T21, SCA	1160
Milan[43]	2018	Spain	Retrospective cohort	2015-2017	13.4± 2.5	MPSS	NR	High and low risk	T13	706

Yang[44]	2018	China	Prospective cohort	2015-2016	from 9 weeks	MPSS	MC, DC	High and low risk	T13, 18, 21, SCA	432
Garshasbi[45]	2018	Iran	Prospective cohort	2015-2016	NR	MPSS	NR	High and low risk	T13, T18, T21, SCA	443
Le Conte[46]	2018	France	Retrospective cohort	2013-2015	16.3 (10.2-35.5)	MPSS	MC, DC	High and low risk	T13, T18, T21	492
Takeda[47]	2018	Japan	Prospective cohort	2013-2016	13.8 (+-) 1.2	MPSS	MC, DC	High and low risk	T13, T18, T21	60
Chen[47]	2018	China	Retrospective cohort	2013-2015	18 (12-35)	MPSS	MC, DC	High and low risk	T13, T18, T21, SCA	384
Fosler[49]	2017	United States	Prospective cohort	2010-2011	15.2±5.9	MPSS	NR	High-risk	T13, T18, T21, SCA	602
Du[50]	2017	China	Retrospective cohort	2013-2016	17.9 (14-23)	MPSS	MC, DC	High-risk	T13, T18, T21	92

Tan[51]	2016	China	Retrospective cohort	2012-2013	12 (11-28)	MPSS	MC, DC	High and low risk	T21	565
Huang[52]	2014	China	Prospective cohort	NR	19 (11-36)	MPSS	MC, DC	High-risk	T18, T21	189
Grömminger[53]	2014	United States	Retrospective cohort	2012-2013	9+3 -23+0	MPSS	MC, DC	NR	T21	54

MPSS: massively parallel shotgun sequencing

Table 2. Quadas-2 assessment of the included studies.

Study	RISK OF BIAS				APPLICABILITY CONCERNS		
	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD
Eiben[20]	?	☺	☺	☺	?	☺	☺
Dugoff[21]	?	☺	☺	☺	?	☺	☺
De Falco[22]	☺	☺	?	☺	☹	☺	☺
Wang[23]	?	☺	☺	☺	?	☺	?
Claudel[24]	☹	☺	☺	☺	?	☺	?
Yuan[25]	☹	☺	?	☹	☹	☺	?
Chen[26]	?	☺	☺	☺	☹	☺	☺
Yang[27]	☹	☺	?	☹	?	☺	☺

La Verde[28]	☺	☺	?	☺	☹	☺	☺
Xu[29]	?	☺	☺	☹	?	☺	☺
Bai[30]	?	☺	☺	☹	?	☺	☺
Gottardi[31]	☺	☺	☺	☺	☺	☺	☺
Cheng[32]	☺	☺	?	☹	☺	☺	☺
van Riel[33]	☺	☺	☺	☺	☺	☺	☺
Khalil[34]	☺	☺	☺	☺	☺	☺	☺
Yang[35]	☹	☺	?	☹	☺	☺	?
Judah[10]	☺	☺	☺	☺	☺	☺	☺
Jin[36]	☹	☺	☺	☺	☺	☺	☺
He[37]	☺	☺	☺	☺	☺	☺	☹
Chibuk[38]	☺	☺	?	☹	☺	☺	☺
Motevasselian[39]	☺	☺	?	☹	☺	☺	?
Dyr[40]	?	☺	?	☹	☺	☺	☺

Norwitz[41]	☺	☺	☺	☺	☺	☺	?
Yu[42]	☺	☺	?	☹	☺	☺	☺
Milan[43]	☺	☺	?	☹	☺	☺	☺
Yang[44]	☺	☺	?	☹	☺	☺	☹
Garshasbi[45]	☺	☺	?	☹	☺	☺	☺
Le Conte[46]	☺	☺	☺	☺	☺	☺	☹
Takeda[47]	☺	☺	☺	☹	?	☺	?
Chen[47]	☺	☺	?	☹	☺	☺	?
Fosler[49]	☹	☺	?	☹	☹	☺	☺
Du[50]	☺	☺	☺	☹	?	☺	?
Tan[51]	☹	☺	☺	☹	☺	☺	?
Huang[52]	☺	☺	☺	☹	?	☺	☺
Grömminger[53]	☺	☺	☺	☹	☺	☺	☺

☺Low Risk ☹High Risk ? Unclear Risk

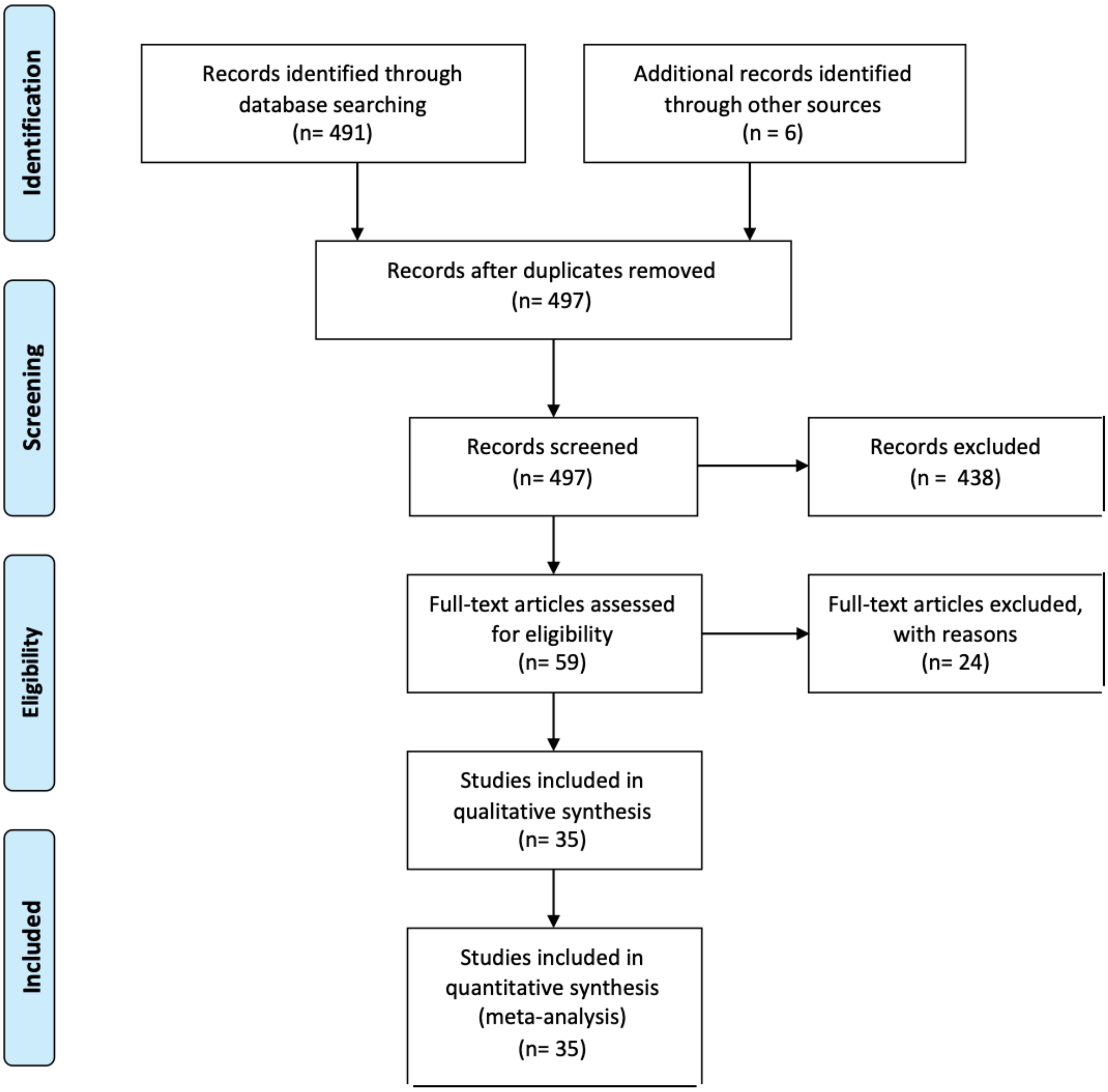
Table 3. Summary estimates and 95% Confidence Interval (95% CI) of sensitivity, specificity, positive and negative likelihood ratios (LR+ and LR-) and diagnostic odds ratio (DOR) of cfDNA in detecting Trisomy 21, 18, 13 and SCA in twin pregnancies.

Anomaly	N. studies	Total Sample	Events	Sensitivity % (95% CI)	Specificity % (95% CI)	DOR (95% CI)	LR+ (95% CI)	LR- (95% CI)	I^2 (%)*
All twin pregnancies									
Trisomy 21	30	35,046	253	98.8 (96.5-100)	100 (99.9-100)	9623 (4990-18,560)	631 (432-921)	0.08 (0.05-0.12)	0.0; 11.0
Trisomy 18	23	28,469	63	94.9 (75.9-99.1)	100 (99.9-100)	52048 (13945-19457)	2698 (1346-5408)	0.05 (0.02-0.16)	0.0; 0.0
Trisomy 13	8	16,308	12	84.6 (54.6-98.1)	100 (99.9-100)	3368 (918-12,359)	1012 (473-2165)	0.30 (0.15-0.60)	0.0; 48.6
Monosomy X0	3	4811	0	--	--	--	--	--	--
Other SCA	4	6335	11	100 (71.5-100)	99.8 (99.7-99.9)	3468 (659-18,244)	416 (233-742)	0.14 (0.04-0.50)	0.0; 0.0

Dichorionic pregnancies									
Trisomy 21	18	12,442	133	98.5 (94.7-98.8)	99.9 (99.9-100)	4998 (2079-12,014)	403 (239-679)	0.10 (0.06-0.18)	0.0; 12.2
Trisomy 18	12	9233	27	92.6 (75.7-99.1)	100 (99.9-100)	3027 (947-9679)	660 (290-1505)	0.33 (0.19-0.58)	0.0; 0.0
Trisomy 13	5	5190	8	88.9 (51.8-99.7)	100 (99.9-100)	3797 (675-21,347)	962 (315-2943)	0.25 (0.10-0.62)	0.0; 0.0
Monosomy X0	2	1390	0	--	--	--	--	--	--
Other SCA	2	710	4	100 (29.2-100)	99.7 (99.2-99.9)	1070 (81.2-14,090)	197 (67.8-575)	0.21 (0.04-1.18)	0.0; 27.5
Monochorionic pregnancies									

Trisomy 21	9	2373	13	100 (75.3-100)	100 (99.8-100)	925 (235-3634)	193 (73.2-510)	0.22 (0.10-0.49)	0.0; 0.0
Trisomy 18	3	619	4	100 (39.8-100)	99.8 (99.1-100	693 (70.9-6769)	149 (39.2-565)	0.22 (0.05-0.91)	0.0; 0.0
Trisomy 13	1	308	1	100 (2.5-100)	100 (98.8-100)	1845 (26.7-130,000)	462 (25.9-8253)	0.25 (0.02-2.76)	--
Monosomy X0	0	--	--	--	--	--	--	--	--
Other SCA	1	159	1	100 (2.5-100)	100 (97.7-100)	951 (13.7-65,800)	239 (13.4-4252)	0.25 (0.02-2.77)	--

**: I^2 computed for sensitivity and specificity respectively.*



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