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Article type : Systematic review

Prenatal detection of esophageal atresia: a systematic review and meta-analysis

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Conflict of interest: none.

ABSTRACT

Introduction: The primary aim of this systematic review was to quantify the diagnostic performance of ultrasound, MRI and amniotic fluid analysis in detecting esophageal atresia (EA) prenatally. The secondary aim was to explore the accuracy of individual imaging signs in identifying this anomaly. **Material and methods:** Medline, Embase and Cochrane databases were searched. The quality of 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 for the predictive accuracy of ultrasound, MRI and amniotic fluid analysis in detecting EA were computed using the hierarchical summary receiver operating characteristic (HSROC) or DerSimonian-Laird random-effect model, according to the number of studies included in each analysis. PROSPERO registration number: CRD42017055828. **Results**: Twenty studies (73246 fetuses, 1760 affected by EA) were included. Overall, prenatal ultrasound had a sensitivity of 31.7%. Only 2 studies reported all data for diagnostic accuracy, and based on these studies prenatal ultrasound had a sensitivity of 41.9%, a specificity of 99.9%, a LR+ of 88.1, a LR- of 0.58 and a diagnostic odds ratio of 153.7. Prenatal ultrasound correctly identifies 77.9% of cases with EA and 21.9% EA with an associated trachea-esophageal fistula. Polyhydramnios was present in 56.3% of cases affected by EA, while a small or absent stomach was identified in 50.0% cases. When performed following a suspicious ultrasound, fetal MRI had an overall good diagnostic accuracy for EA, with a sensitivity of 94.7%, a specificity of 89.3%, a +LR of 8.8, a -LR of 0.06, and a diagnostic odds ratio of 149.3. Finally, amniotic fluid analysis with an esophageal atresia index ≥3 had a sensitivity of 89.9% and a specificity of 99.6% in detecting EA. **Conclusions:** Ultrasound alone is a poor diagnostic tool for identifying EA prenatally, and has a high rate of false positive diagnoses. MRI and amniotic fluid analysis have high diagnostic accuracy for EA. We would recommend their use following a suspicious ultrasound.

Key words

esophageal atresia, prenatal diagnosis, ultrasound, MRI, amniotic fluid analysis

Abbreviations:

AF: amniotic fluid

DOR diagnostic odds ratio

EA: esophageal atresia

GGTP γ-glutamyl transpeptidase

HSROC hierarchical summary receiver operating characteristic

LR- negative likelihood ratio

LR+ positive likelihood ratio

MoM multiple of median

MRI: magnetic resonance imaging

QUADAS-2 Quality Assessment of Diagnostic Accuracy Studies

ROC receiver operating characteristic

Key message

Prenatal detection of esophageal atresia is poor, particularly in the presence of an associated tracheo-esophageal fistula. The sonographic 'pouch sign' and 'distended fetal hypopharynx', as well as MRI and amniotic fluid analysis following a suspicious ultrasound, improve detection rate.

INTRODUCTION

Esophageal atresia (EA) comprises a spectrum of congenital anomalies characterized by a lack of continuity of the esophagus (atresia) with or without the presence of one or more abnormal connections with the trachea (tracheo-esophageal fistula), (Figure 1). Recent large studies have identified the prevalence of EA to be 2.3-2.4 cases per 10000 births (1, 2). In the last decade, survival has increased to 91-98%(3-7). EA has a high incidence of associated anomalies, ranging from 31-59%(1, 4, 6, 8, 9). Mortality is primarily related to the associated anomalies and genetic syndromes(8), reducing survival to as low as 51%, and resulting in increased overall morbidity in the short and long term.

Prenatal diagnosis of EA remains challenging, ranging from 24-32%(10-12). The main signs detected on routine prenatal ultrasound are polyhydramnios, a small or absent stomach bubble, and a blind-ending dilated upper esophageal pouch ('pouch sign'). The use of

ultrasound for the prenatal diagnosis of EA is limited by the fact that these signs are operator dependent, can be non-specific(13), and transient(14).

More recently, the role of fetal magnetic resonance imaging (MRI) (11, 15-18) and amniotic fluid (AF) analysis(11, 15, 19, 20) in the diagnosis of EA have been investigated as a potential tool to increase prenatal detection. γ-glutamyl transpeptidase (GGTP) is an amniotic fluid digestive enzyme, secreted by microvilli. Fetal swallowing of amniotic fluid initially results in accumulation of GGTP in the gastrointestinal tract. Once the anal membrane opens, GGTP is released into the amniotic fluid. Following maturation of the anal sphincter, digestive enzymes accumulate in meconium, with associated reduced amniotic fluid levels. However, in esophageal atresia, fetal vomiting results in the accumulation of GGTP in the amniotic fluid(21). Measurements of GGTP and alpha fetoprotein [expressed as multiple of median (MoM) corresponding to the ratio between observed raw value and median raw value defined for that gestational age], have been used to produce an amniotic fluid index: alpha fetoprotein (MoM) x GGTP (MoM). A cutoff of ≥3 is suggestive of a diagnosis of EA(20).

Currently, even in high volume tertiary fetal medicine centers, MRI and AF analysis are rarely used to supplement routine ultrasound screening, in order to improve the poor prenatal detection rate of EA. Increased prenatal detection of EA prompts careful assessment for associated anomalies, provides the opportunity for effective prenatal counseling, and has been shown to result in fewer postnatal transfers(10).

The primary aim of this systematic review was to quantify the diagnostic accuracy of ultrasound, MRI and AF analysis in detecting EA prenatally. The secondary aims were to explore the diagnostic performance of different imaging signs in detecting this condition.

MATERIAL AND METHODS

This review was performed according to a priori designed protocol using methods recommended for systematic reviews and meta-analysis(22, 23). Databases searched electronically included Medline, Embase, the Cochrane Library (including The Cochrane Database of Systematic Reviews and The Cochrane Central Register of Controlled Trials), the Database of Abstracts of Reviews of Effects, the Healthy Technology Assessment Database and the NHS Economic Evaluation Database. The search was undertaken in July

2018 using combinations of the relevant subject heading (MeSH) terms, key words and word variants for ‘esophageal atresia’ and ‘antenatal’ (Supporting Information Table S1). The search and selection criteria were restricted to English language, and papers published after 2000. Animal studies, case series with less than 5 cases, review articles and questionnaires were excluded. Reference lists from relevant papers were hand searched for additional reports. The study was registered with the PROSPERO database (registration number CRD42017055828).

Index tests were the diagnostic accuracy performance of ultrasound, MRI and AF analysis for the prenatal detection of EA.

The diagnostic accuracy of the following ultrasound signs suggestive of EA were explored:

- Polyhydramnios - defined either as an amniotic fluid index (AFI) >18 cm or a deepest vertical pocket (DVP) > 8 cm.
- Absent fetal stomach - defined as the non-visualization of fetal stomach on the scan after prolonged observation (>30 minutes)
- Small fetal stomach - defined as the presence of a fetal stomach of reduced size according to the published fetal normograms or upon subjective assessment.
- Pouch sign - defined as visualization of a fluid-filled, blind ending esophagus during fetal swallowing.

A separate sensitivity analysis for pure EA and EA with tracheo-esophageal fistula was planned. The reference standard was the presence of EA confirmed at the time of surgery, or at post-mortem.

Two authors (CP, FD) reviewed all abstracts independently. Agreement regarding potential relevance was reached by consensus; full text copies of those articles were obtained, and the same two reviewers independently extracted relevant data regarding study characteristics and the explored outcomes. Inconsistencies were discussed, and consensus was reached, or the dispute was resolved by discussion with a third author. 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.

The quality of studies was assessed using the revised tool for the quality assessment of diagnostic accuracy studies (QUADAS-2). It consisted 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. Each domain was assessed in terms of the risk of bias and the first three were also assessed in terms of concerns regarding applicability. Each item was scored a ‘‘yes’’, ‘‘no’’, or ‘‘unclear’’ if there was insufficient information to make an accurate judgment(24).

Summary estimates of sensitivity, specificity, positive and negative likelihood ratios (LR+ and LR-) and diagnostic odds ratio (DOR) for the predictive accuracy of ultrasound, MRI and AF analysis in detecting EA, were computed using the hierarchical summary receiver operating characteristic (HSROC) model(25). 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 (LR+/LR-)(26). Rutter and Gatsonis HSROC parameterization was used because it models functions of sensitivity and specificity to define a summary receiver operating characteristic (ROC) curve, and its hierarchical modeling strategy can be used for comparisons of test accuracy when there is variability in threshold between studies(27). However, when the number of studies is small, the uncertainty associated with the estimation of the shape parameter could be very high, and models may fail to converge(28). Thus, for all meta-analyses in which less than 4 study estimates could be pooled, the DerSimonian-Laird random-effect model was used.

For those meta-analyses including ≥10 individual studies we aimed to assess the publication bias using Deeks funnel plot asymmetry test(29). Meta-Disc 1.4 (http://www.hrc.es/investigacion/metadisc_en.htm) and Stata command metandi 2013 (Stata Corp. College Station, TX, USA) were used to analyze the data(25, 30).

RESULTS

The search yielded 782 possible citations. Twelve were identified as duplicates and excluded, and 732 were excluded by reviewing the title or the abstract, as they did not meet the selection criteria. The remaining 38 full-text manuscripts were reviewed and a total of 20 studies were finally included (Figure 2). These 20 studies included 73246 fetuses undergoing prenatal ultrasound; of these 1760 had confirmed EA. A summary of the identified studies is shown in Table 1.

The quality assessment based on QUADAS-2 is reported in Figure 3. The large majority of the included studies did not report all the figures for the diagnostic accuracy, thus making it impossible to perform a pooled analysis computing both sensitivity and specificity. In view of such limitations, the results were also reported as proportions.

Sixteen studies reported information on diagnostic accuracy of ultrasound for EA. Unfortunately, crude values for all the figures of diagnostic accuracy were not consistently reported by all the included studies. Eleven studies explored the sensitivity of ultrasound in detecting EA. Overall, ultrasound had a sensitivity of 31.7% (95% confidence interval (CI) 19.9 to 44.7, 384/1520; I^2=96.0%) in detecting EA (Figure 4). However, all data for diagnostic accuracy were reported only by two studies(31, 32) (70967 fetuses, of whom 117 had EA). Based on these studies, prenatal ultrasound had a sensitivity of 41.9% (95% CI 32.8 to 51.4), a specificity of 99.9% (95% CI 99.9 to 99.9), a LR+ of 88.1 (95% CI 78.6 to 9878.0), a LR- of 0.58 (0.3 to 1.0) and a DOR of 153.7 (95% CI 2.1 to 11483.3). The individual figures for diagnostic accuracy from each included study are provided in Table 2.

Eight studies including 1210 cases compared the prenatal diagnosis of EA and EA with tracheo-esophageal fistula. Prenatal ultrasound correctly identifies 77.9% (95% CI 59.5 to 91.9; 100/134, I^2: 79.1%, eight studies) of cases of EA, but only 21.9% (95% CI 15.2 to 29.5; 182/1053, I^2: 80.9%, eight studies) of those with EA and tracheo-esophageal fistula.

Five studies (99 fetuses) explored the diagnostic performance of MRI, in fetuses who had sonographic signs suspicious for EA. MRI had good diagnostic accuracy for EA, with a sensitivity of 94.7% (95% CI 71.4 to 99.2), a specificity of 89.3% (95% CI 38.6 to 99.0), a LR+ of 8.8 (95% CI 0.9 to 85), a LR- of 0.06 (95% CI 0.09 to 0.4) and a DOR of 149.3 (95% CI 9.6 to 233.6) (Figure 5). The individual diagnostic accuracy of fetal MRI in detecting EA is reported in Table 3.

Three studies explored the diagnostic accuracy of amniotic fluid analysis in 523 fetuses suspected to be affected by EA. An amniotic fluid EA index of ≥3 had a sensitivity of 89.9% (95% CI 80.2 to 95.8), a specificity of 99.6 (95% CI 98.7 to 100), a LR+ of 54.7 (95% CI 0.6 to 5375.5), a LR- of 0.13 (95% CI 0.02 to 0.8) and a DOR of 462.5 (95% CI 11.4 to 18701.6) (Figure 6).

Unfortunately, due to the lack of information on false positive and true negative diagnoses, it was not possible to perform a pooled analysis reporting all the figures of the diagnostic accuracy of the ultrasound signs suggestive of EA explored in the present systematic review. Therefore, the results were reported as proportions (detection rate and false positive rates when possible). Only 2 studies (Garabedian et al. (10) and Langer et al.(18)) reported sonographic detection rate of the pouch sign, which precluded statistical analysis.

Nine studies (853 fetuses) explored the prevalence of polyhydramnios in fetuses affected by EA. Polyhydramnios was present in 56.3% (95% CI 44.0-68.3; I^2=88.6%) of cases affected by EA. A sub-analysis of the distribution of polyhydramnios according to the type of anomaly (pure EA vs EA with tracheo-esophageal fistula) was not possible due to the lack of data which precluded to perform a meaningful data synthesis. Only three studies (Ethun *et al.*, (17) Kunisaki *et al.* (33) and Borsellino *et al.(34))* reported the incidence of polyhydramnios in fetuses affected by EA/EA with tracheo-esophageal fistula. Overall the rate of false positive diagnoses was 66.2% (95% CI 45.1 to 84.4; I^2=19.7%).

Nine studies (743 fetuses) explored the detection rate of an absent/small stomach bubble in identifying EA antenatally. A small or absent stomach was present in 50.0% cases (95% CI 33.6 to 66.9; I^2=92.1%), while only 4 studies (Ethun *et al.*(17), Kunisaki *et al.*(33), Borsellino *et al.*(34), Langer *et al.(18))* explored the distribution of such signs in fetuses not affected by the anomaly, reporting an incidence of false positive diagnoses of 71.8% (95% CI 38.8 to 95.2; I^2=71.8%). In view of the small number of included cases, it was not possible to perform a subgroup analysis according to the type of EA.

DISCUSSION

This systematic review confirms that prenatal ultrasound has poor diagnostic accuracy for detecting EA, with only a third of cases identified, and a high rate of false positive diagnosis. The poor diagnostic performance of ultrasound for prenatal detection of EA is due to the sonographic signs suggestive of EA being neither sensitive nor specific.

Polyhydramnios is present in approximately 10% of pregnancies(31), and is most commonly idiopathic. It can be associated with a wide range of congenital anomalies in which fetal swallowing is either impaired or absent (13). It is therefore not surprising that

polyhydramnios, in the context of prenatal diagnosis of EA, is associated with a high rate of false positive diagnosis (66.2%).

Polyhydramnios was present in over half of confirmed cases (56.3%) of EA. This may be influenced by the timing of the prenatal ultrasound, as fetal swallowing is not established until the 5th month of gestation(35), and polyhydramnios is rarely diagnosed earlier than 24 weeks(14).

A small or absent stomach was identified in half of cases of confirmed EA. This sign is subjective, with no consensus at present with respect to the classification of a 'small' stomach. It is also difficult to determine, as visualization of the stomach bubble may be transient due to the intermittent nature of fetal swallowing. Even in the absence of a fistula, the stomach may still be visualized as a result of secretions from the gastric mucosa(36). The combination of polyhydramnios and a small or absent stomach bubble has been shown to increase the accuracy of prenatal diagnosis of EA(13).

Both polyhydramnios and a small or absent stomach bubble have been found to be associated with a higher incidence of false positive diagnosis of EA in the context of associated anomalies(12).

EA is most commonly associated with a distal fistula (85% cases)(37). These cases represent a significant diagnostic challenge, based on the sonographic signs of polyhydramnios and small or absent stomach bubble. This is because the presence of a distal fistula may result in the stomach still being visualized, with normal volume of amniotic fluid, due to the aspiration of amniotic fluid with reflux into the stomach via the fistula(38).

The 'pouch sign' and the 'distended fetal hypopharynx' (DHP)(39) are more recent additions to the sonographic signs used to identify EA. A significant benefit of both is that they are well visualized in EA and EA with tracheo-esophageal fistula. The pouch sign has been proposed as the most reliable sign for the diagnosis of EA(40), particularly when identified using MRI rather than ultrasound (41). However, it is recognized to be a late sign not seen before 26 weeks' gestation(42). The distended fetal hypopharynx has been identified at an earlier gestational age than the pouch sign, and found to be more sensitive (86% vs. 62%), but less specific (67% vs. 97%) for EA(39).

The use of fetal MRI for the detection of the pouch sign, and amino acid analysis using the esophageal atresia index, both have good diagnostic performance for the prenatal detection of EA. Fetal MRI has the highest sensitivity (94.7%) of the three investigations studied, and therefore appears to be an important non-invasive tool for improving the prenatal diagnostic accuracy of EA. The value of MRI appears to be its accurate identification of the pouch sign, which unlike the sonographic signs of polyhydramnios and a small or absent stomach bubble, is not affected by the presence of a tracheo-esophageal fistula, or other associated congenital anomalies. The cost of an MRI to the National Health System in the UK is estimated to be £130 (144€) (43).

The amniotic fluid esophageal index presents a promising marker with a slightly lower sensitivity that MRI (89.9%), but a higher specificity (99.6% vs. 89.3%). However, further studies are required to further evaluate its use. Given that the risk of miscarriage associated with amniocentesis prior to 24 weeks' gestation has been identified to be much lower than previously thought (0.81%)(44), the increased detection rate of EA together with the opportunity for karyotyping might justify this risk. Certainly, when amniocentesis is clinically indicated, AF analysis for the prenatal detection of EA should be performed. At present, to our knowledge, AF analysis is available at only one center in Europe (Hôpital Robert Debré, Paris) and the cost is around €200 (£180). A recent publication however, highlighted a case of EA with an associated trachea-esophageal atresia, which was not diagnosed antenatally, despite combined screening with ultrasound, MRI and AF analysis(45).

This review represents the most comprehensive estimate of the diagnostic accuracy of prenatal investigation to detect EA. The major limitation of this systematic review was the small number of studies included, their retrospective design and the limited raw data presented. The studies included had variation in the gestational age at ultrasound, heterogeneity in the time intervals between the last scan and delivery, and lack of stratification according to the type of EA, and the presence of associated fetal anomalies.

The vast majority of studies retrospectively reviewed prenatal signs present in postnatally confirmed cases, making it difficult to exclude the presence of these signs in the investigations of normal fetuses. Only 2 of the 14 papers investigating the use of prenatal ultrasound for the diagnosis of EA provided a figure for the true negative scans, and one of these two studies was a calculated estimate. Computation of HSROC for the diagnostic

accuracy of ultrasound could not be performed because only two studies with different designs reported the raw data for all the figures of diagnostic accuracy.

The figures of diagnostic accuracy for fetal MRI and AF analysis reported in the present systematic review are likely to be biased by the fact that these were secondary investigations performed in fetuses identified to have high suspicion of the anomaly on ultrasound. However, this reflects current clinical practice, as fetal MRI is currently not offered as a screening test in all pregnancies. It is important to note that in the studies included in this review, MRI was performed at a relatively late gestation (30-32 weeks'), which is also likely to increase its diagnostic accuracy.

As the use of MRI and AF analysis is a more recent addition to the traditional sonographic diagnosis of EA, the number of studies and cases are few, preventing any robust conclusions being drawn from our analysis.

CONCLUSION

Ultrasound is a relatively poor diagnostic tool for the prenatal diagnosis of EA. MRI and AF analysis have high diagnostic accuracy when EA is suspected. The non-invasive nature of MRI offers an advantage over amniotic fluid analysis. However, when amniocentesis is indicated clinically, AF analysis may improve the prenatal detection of EA. We would recommend more extensive use of these advanced prenatal investigations, particularly in the context of comprehensive prospective studies.

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

Author (Ref)	Year	Country	Study Design	Investigation	Reference Standard	Fetuses	Cases of esophageal atresia	Additional anomalies
Lal(46)	2017	US	Retrospective multicentre cohort study	US	Findings at surgery	396	396	Yes
Kunisaki (33)	2014	US	Retrospective single centre	US	Not specified	81	70	Yes
Bradshaw (31)	2016	UK	Retrospective single centre	US	Not specified	70 500 (estimate)	58	Yes
Hoopman (32)	2015	Germany	Retrospective single centre	US	Not specified	433	59	Not specified
Spaggiari (11)	2015	France	Retrospective single centre	US, MRI, AF analysis	Not specified	122	122	Yes
Garabedian (10)	2015	France	Retrospective multicentre	US, MRI	Not specified	469	469	Yes
Allaf (19)	2015	France	Retrospective cohort study	US, AF analysis	Not specified	464	15	Not specified
Hochart (16)	2015	France	Retrospective single centre	MRI	Not specified	18	11	Yes
Garabedian (15)	2014	France	Retrospective single centre	US, MRI, AF analysis	Findings at birth/surgery/ post-mortem	15	10	Yes
Fallon(47)	2014	US	Retrospective single centre	US, MRI	Identified from database	91	91	Yes
Ethun (17)	2014	US	Retrospective single centre	US, MRI	CXR, findings at surgery	28	15	Yes
Czerkiewicz (20)	2011	France	Retrospective single centre	US, AF analysis	Not specified	44	44	Yes
Quarello(48)	2011	France	Case report	US	Findings at surgery/ post-mortem	7	6	Yes
de Jong(49)	2010	Netherlands	Retrospective single centre	US	Findings at surgery/post-mortem	79	79	Yes
Choudhry (12)	2007	UK	Retrospective single centre	US	Findings at surgery/ post-mortem	62	32	Yes
Borsellino (34)	2006	Italy	Retrospective single centre	US	Findings at delivery/ post-mortem	157	8	Not specified
Kalish(50)	2003	US	Retrospective single centre	US	Not specified	22	22	Yes
Khorshid(51)	2003	Saudi Arabia	Retrospective single centre	US	Not specified	78	78	Yes
Langer (18)	2001	US	Prospective single centre	US, MRI	Not specified	10	5	Yes
Sparey (36)	2000	UK	Retrospective multicentre	US	Not specified	170	170	Yes

US, ultrasound; MRI, magnetic resonance imaging; AF, amniotic fluid.

REFERENCES

1. Pedersen RN, Calzolari E, Husby S, Garne E, group EW. Oesophageal atresia: prevalence, prenatal diagnosis and associated anomalies in 23 European regions. Arch Dis Child. 2012;97:227-32.
2. Lupo PJ, Isenburg JL, Salemi JL, Mai CT, Liberman RF, Canfield MA, et al. Population-based birth defects data in the United States, 2010-2014: A focus on gastrointestinal defects. Birth defects research. 2017;109:1504-14.
3. Koivusalo AI, Sistonen SJ, Lindahl HG, Rintala RJ, Pakarinen MP. Long-term outcomes of oesophageal atresia without or with proximal tracheooesophageal fistula - Gross types A and B. Journal of pediatric surgery. 2017;52:1571-5.
4. Koivusalo AI, Pakarinen MP, Rintala RJ. Modern outcomes of oesophageal atresia: single centre experience over the last twenty years. Journal of pediatric surgery. 2013;48:297-303.
5. Lilja HE, Wester T. Outcome in neonates with esophageal atresia treated over the last 20 years. Pediatric surgery international. 2008;24:531-6.
6. Konkin DE, O'Hali W A, Webber EM, Blair GK. Outcomes in esophageal atresia and tracheoesophageal fistula. Journal of pediatric surgery. 2003;38:1726-9.
7. Lopez PJ, Keys C, Pierro A, Drake DP, Kiely EM, Curry JI, et al. Oesophageal atresia: improved outcome in high-risk groups? Journal of pediatric surgery. 2006;41:331-4.
8. Deurloo JA, Ekkelkamp S, Schoorl M, Heij HA, Aronson DC. Esophageal atresia: historical evolution of management and results in 371 patients. Ann Thorac Surg. 2002;73:267-72.
9. Saing H, Mya GH, Cheng W. The involvement of two or more systems and the severity of associated anomalies significantly influence mortality in esophageal atresia. Journal of pediatric surgery. 1998;33:1596-8.
10. Garabedian C SR, Langlois C, Bonnard A, Khen-Dunlop N, Gelas T, Michaud L, Auber F, Gottrand F, Houfflin-Debarge V. Does prenatal diagnosis modify neonatal treatment and early outcome of children with esophageal atresia? American Journal of Obstetrics and Gynecology. 2015;212:340.
11. Spaggiari E, Faure G, Rousseau V, Sonigo P, Millischer-Bellaiche AE, Kermorvant-Duchemin E, et al. Performance of prenatal diagnosis in esophageal atresia. Prenat Diagn. 2015;35:888-93.
12. Choudhry M, Boyd PA, Chamberlain PF, Lakhoo K. Prenatal diagnosis of tracheo-oesophageal fistula and oesophageal atresia. Prenat Diagn. 2007;27:608-10.
13. Houben CH, Curry JI. Current status of prenatal diagnosis, operative management and outcome of esophageal atresia/tracheo-esophageal fistula. Prenat Diagn. 2008;28:667-75.
14. Solt I, Rotmensch S, Bronshtein M. The esophageal 'pouch sign': a benign transient finding. Prenat Diagn. 2010;30:845-8.
15. Garabedian C VP, Czerkiewicz I, Langlois C, Muller F, Avni F, Bigot J, Sfeir R, Vaast P, Coulon C, Subtil D, Houfflin-Debarge V. Does a combination of ultrasound, MRI, and biochemical amniotic fluid analysis improve prenatal diagnosis of esophageal atresia? Prenat Diagn. 2014;34:839-42.

16. Hochart V, Verpillat P, Langlois C, Garabedian C, Bigot J, Debarge VH, et al. The contribution of fetal MR imaging to the assessment of oesophageal atresia. European radiology. 2015;25:306-14.
17. Ethun CG, Fallon SC, Cassady CI, Mehollin-Ray AR, Olutoye OO, Zamora IJ, et al. Fetal MRI improves diagnostic accuracy in patients referred to a fetal center for suspected esophageal atresia. Journal of pediatric surgery. 2014;49:712-5.
18. Langer JC, Hussain H, Khan A, Minkes RK, Gray D, Siegel M, et al. Prenatal diagnosis of esophageal atresia using sonography and magnetic resonance imaging. Journal of pediatric surgery. 2001;36:804-7.
19. Allaf B, Dreux S, Schmitz T, Czerkiewicz I, Le Vaillant C, Benachi A, et al. Amniotic fluid biochemistry in isolated polyhydramnios: a series of 464 cases. Prenat Diagn. 2015;35:1331-5.
20. Czerkiewicz I, Dreux S, Beckmezian A, Benachi A, Salomon LJ, Schmitz T, et al. Biochemical amniotic fluid pattern for prenatal diagnosis of esophageal atresia. Pediatric research. 2011;70:199-202.
21. Muller C, Czerkiewicz I, Guimiot F, Dreux S, Salomon LJ, Khen-Dunlop N, et al. Specific biochemical amniotic fluid pattern of fetal isolated esophageal atresia. Pediatric research. 2013;74:601-5.
22. Henderson LK, Craig JC, Willis NS, Tovey D, Webster AC. How to write a Cochrane systematic review. Nephrology (Carlton, Vic). 2010;15:617-24.
23. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, 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.
24. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Annals of internal medicine. 2011;155:529-36.
25. Harbord RM WP. metandi: Meta-analysis of diagnostic accuracy using hierarchical logistic regression. The Stata Journal. 2009;9:211-29.
26. Glas AS, Lijmer JG, Prins MH, Bonsel GJ, Bossuyt PM. The diagnostic odds ratio: a single indicator of test performance. Journal of clinical epidemiology. 2003;56:1129-35.
27. Rutter CM, Gatsonis CA. A hierarchical regression approach to meta-analysis of diagnostic test accuracy evaluations. Statistics in medicine. 2001;20:2865-84.
28. Macaskill P GC, Deeks JJ, Harbord RM, Takwoingi Y. Chapter 10: Analysing and Presenting Results. In: Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy Version 1.0. In: Deeks JJ BP, Gatsonis C, (ed). The Cochrane Collaboration, 20102010.
29. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ (Clinical research ed). 1997;315:629-34.
30. Zamora J, Abraira V, Muriel A, Khan K, Coomarasamy A. Meta-DiSc: a software for meta-analysis of test accuracy data. BMC medical research methodology. 2006;6:31.
31. Bradshaw CJ, Thakkar H, Knutzen L, Marsh R, Pacilli M, Impey L, et al. Accuracy of prenatal detection of tracheoesophageal fistula and oesophageal atresia. Journal of pediatric surgery. 2016;51:1268-72.
32. Hoopmann M, Kagan KO, Borgmeier F, Seitz G, Arand J, Wagner P. Measurement of Gastric Circumference in Foetuses with Oesophageal Atresia. Geburtshilfe und Frauenheilkunde. 2015;75:1148-52.

33. Kunisaki SM, Bruch SW, Hirschl RB, Mychaliska GB, Treadwell MC, Coran AG. The diagnosis of fetal esophageal atresia and its implications on perinatal outcome. Pediatric surgery international. 2014;30:971-7.
34. Borsellino A, Zaccara A, Nahom A, Trucchi A, Aite L, Giorlandino C, et al. False-positive rate in prenatal diagnosis of surgical anomalies. Journal of pediatric surgery. 2006;41:826-9.
35. TW S. Third Month to Birth: The Fetus and Placenta. Langman's Medical Embryology. 12th ed. Philadelphia: Lippincott Williams & Wilkins; 2012.
36. Sparey C, Robson SC. Oesophageal atresia. Prenat Diagn. 2000;20:251-3.
37. Harmon C CG. Pediatric Surgery. 6th ed. Philadelphia: Mosby; 2006.
38. Pretorius DH, Drose JA, Dennis MA, Manchester DK, Manco-Johnson ML. Tracheoesophageal fistula in utero. Twenty-two cases. Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine. 1987;6:509-13.
39. Tracy S, Buchmiller TL, Ben-Ishay O, Barnewolt CE, Connolly SA, Zurakowski D, et al. The Distended Fetal Hypopharynx: A Sensitive and Novel Sign for the Prenatal Diagnosis of Esophageal Atresia. Journal of pediatric surgery. 2018;53:1137-41.
40. Kalache KD, Chaoui R, Mau H, Bollmann R. The upper neck pouch sign: a prenatal sonographic marker for esophageal atresia. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 1998;11:138-40.
41. Salomon LJ, Sonigo P, Ou P, Ville Y, Brunelle F. Real-time fetal magnetic resonance imaging for the dynamic visualization of the pouch in esophageal atresia. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2009;34:471-4.
42. Kalache KD, Wauer R, Mau H, Chaoui R, Bollmann R. Prognostic significance of the pouch sign in fetuses with prenatally diagnosed esophageal atresia. Am J Obstet Gynecol. 2000;182:978-81.
43. The Bill of Health. https://www.gocompare.com/health-insurance/the-bill-of-health/2018.
44. Akolekar R, Beta J, Picciarelli G, Ogilvie C, D'Antonio F. Procedure-related risk of miscarriage following amniocentesis and chorionic villus sampling: a systematic review and meta-analysis. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2015;45:16-26.
45. Garabedian C, Vaast P, Verpillat P, Sfeir R, Coulon C, Houfflin-Debarge V. Prenatal diagnosis of esophageal atresia: A case of triple negative screening. Journal of gynecology obstetrics and human reproduction. 2018;
46. Lal DR, Gadepalli SK, Downard CD, Ostlie DJ, Minneci PC, Swedler RM, et al. Perioperative management and outcomes of esophageal atresia and tracheoesophageal fistula. Journal of pediatric surgery. 2017;52:1245-51.
47. Fallon SC, Ethun CG, Olutoye OO, Brandt ML, Lee TC, Welty SE, et al. Comparing characteristics and outcomes in infants with prenatal and postnatal diagnosis of esophageal atresia. J Surg Res. 2014;190:242-5.
48. Quarello E, Saada J, Desbriere R, Rousseau V, De Lagausie P, Benachi A. Prenatal diagnosis and evaluation of defect length in esophageal atresia using direct and indirect (tracheal print) signs. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2011;38:225-8.

49. de Jong EM, de Haan MA, Gischler SJ, Hop W, Cohen-Overbeek TE, Bax NM, et al. Pre- and postnatal diagnosis and outcome of fetuses and neonates with esophageal atresia and tracheoesophageal fistula. Prenat Diagn. 2010;30:274-9.
50. Kalish RB, Chasen ST, Rosenzweig L, Chervenak FA. Esophageal atresia and tracheoesophageal fistula: the impact of prenatal suspicion on neonatal outcome in a tertiary care center. Journal of perinatal medicine. 2003;31:111-4.
51. Khorshid EA, Dokhan AL, Turkistani AF, Shadi SM, Hassab MH. Five year experience in prenatal ultrasound diagnosis of esophageal atresia in Saudi Arabia. Annals of Saudi medicine. 2003;23:132-4.

Supporting Information legend:

Table S1. Search Strategy run on 25 July 2018.

Legends to figures and tables:

Figure 1. Gross classification of esophageal atresia.

Figure 2. Systematic review flowchart.

Figure 3. Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) assessment of the included studies.

Figure 4. Sensitivity of ultrasound in detecting esophageal atresia prenatally.

Figure 5. Hierarchical receiver operating characteristic curve (HSROC) showing the diagnostic performance of fetal magnetic resonance imaging in detecting esophageal atresia.

Figure 6. Der-Sirmonian summary receiver operating characteristic curve (SROC) showing the diagnostic performance of amniotic fluid analysis in detecting esophageal atresia.

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

Table 2: Diagnostic accuracy of ultrasound in detecting esophageal atresia among the different studies.

Table 3: Diagnostic accuracy of MRI in detecting esophageal atresia in the different studies.

Table 2: Diagnostic accuracy of ultrasound in detecting esophageal atresia among the different studies.

Author (Ref)	Year	Sensitivity	Specificity	PPV	NPV	LR+	LR-
Lal (46)	2017	13.38 (10.2-17.1)	-	-	-	-	-
Bradshaw (31)	2016	25.86 (15.3-39.0)	99.96 (99.9-100)	34.88 (1.1-50.9)	99.94 (99.9-100)	650.9 (363.7-1125.0)	0.74 (0.6-0.8)
Hoopman (32)	2015	57.63 (44.1-70.4)	95.19 (92.5-97.1)	65.38 (50.9-78.0)	93.44 (90.5-95.7)	11.97 (7.3-19.6)	0.45 (0.3-0.6)
Spaggiari (11)	2015	31.97 (23.8-41.0)	-	-	-	-	-
Garabedian (10)	2015	24.31 (20.5-28.5)	-	-	-	-	-
Garabedian (15)	2014	-	-	66.67 (38.4-88.2)	-	-	-
Fallon (47)	2014	16.48 (9.5-25.7)	-	-	-	-	-
Ethun (17)	2014	-	-	45.45 (28.1-63.6)	-	-	-
Quarello(48)	2011	-	-	85.71 (42.1-99.6)	-	-	-
Choudhry (12)	2007	31.25 (16.1-50.0)	-	25.0 (12.7-41.2)	-	-	-
Borsellino (34)	2006	-	-	72.73 (39.0-94.0)	-	-	-
Kalish (50)	2003	40.91 (20.7-63.6)	-	-	-	-	-
Khorshid (51)	2003	89.74 (80.8-95.5)	-	-	-	-	-
Langer (18)	2001	-	-	50.0 (18.7-82.3)	-	-	-
Sparey (36)	2000	11.38 (6.3-18.4)	-	43.75 (26.4-62.3)	-	-	-

PPV, positive predictive value; NPV, negative predictive value; LR+, positive likelihood ratio; LR-, negative likelihood ratio.

Table 3: Diagnostic accuracy of magnetic resonance imaging in detecting esophageal atresia in the different studies.

Author (Ref)	Year	Sensitivity	Specificity	PPV	NPV	LR+	LR-
Spaggiari (11)	2015	67.86 (47.6-84.1)	-	100 (82.4-100)	-	-	-
Hochart (16)	2015	90.91(58.7-99.8)	100 (59.4-100)	100 (69.2-100)	87.50 (47.4-99.7)	∝ (2.5-∝)	0.09 (0.02-0.4)
Garabedian (15)	2014	80.0 (44.4-97.5)	100 (47.8-100)	100 (63.1-100)	71.43 (63.1-100)	∝ (1.7-∝)	0.2 (0.06-0.7)
Ethun (17)	2014	100 (78.2-100)	46.15 (19.2-74.9)	68.18 (45.1-86.1)	100 (54.1-100)	1.86 (1.2-3.3)	* (0-0.5)
Langer (18)	2001	100 (47.8-100)	80.0 (28.4-99.5)	83.33 (35.9-99.6)	100 (39.8-100)	5 (1.2-25.4)	* (0-0.6)

PPV, positive predictive value; NPV, negative predictive value; LR+, positive likelihood ratio; LR-, negative likelihood ratio.

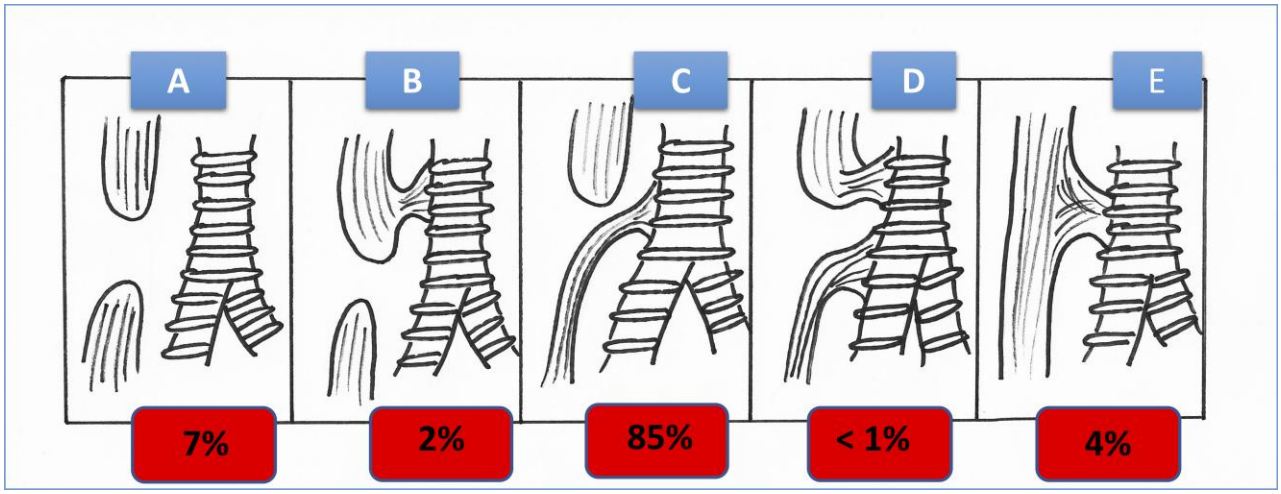

Figure 1. Gross classification of esophageal atresia.

Figure 2. Systematic review flowchart.

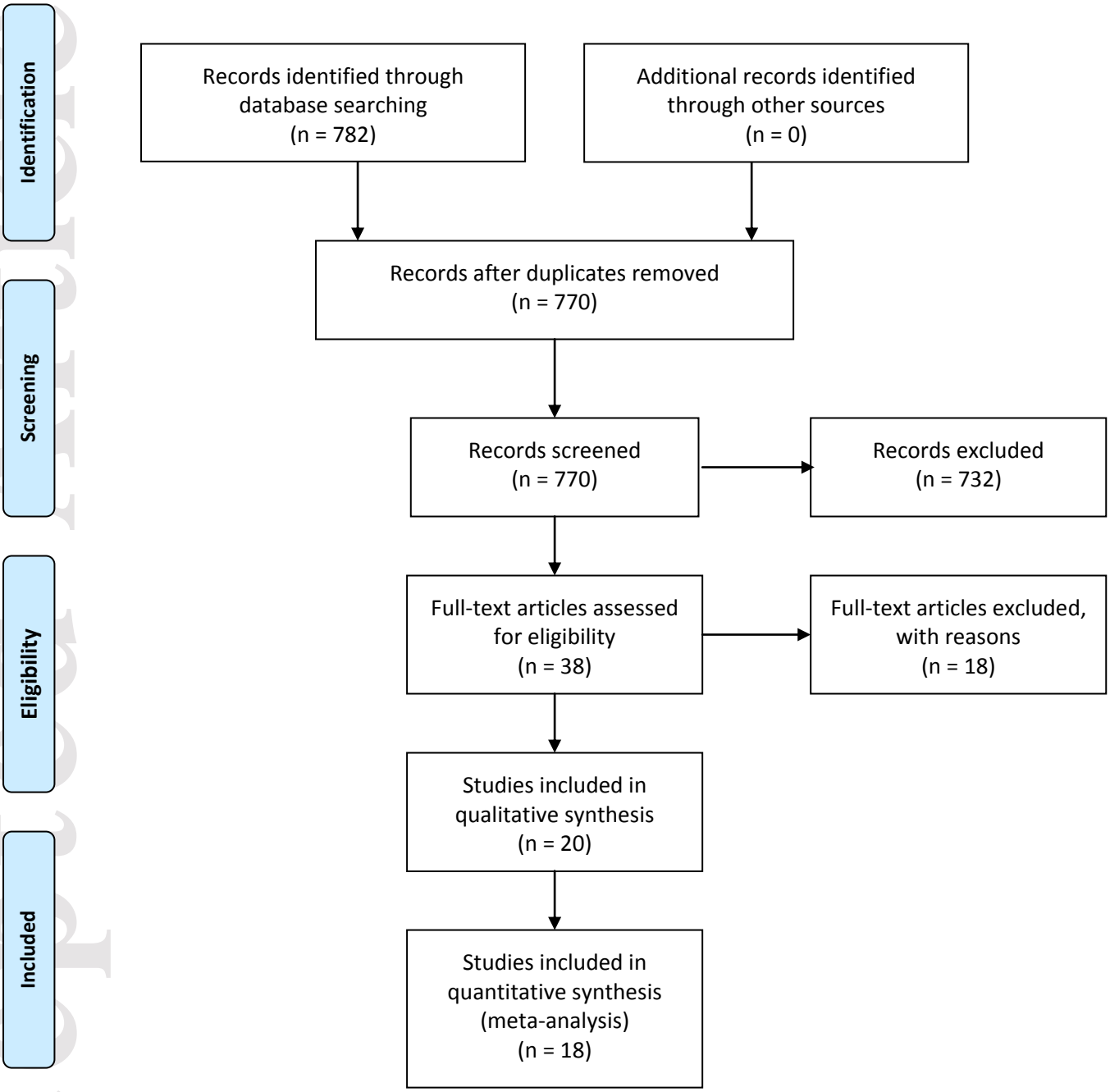

Figure 3. QUADAS-2 assessment of the included studies.

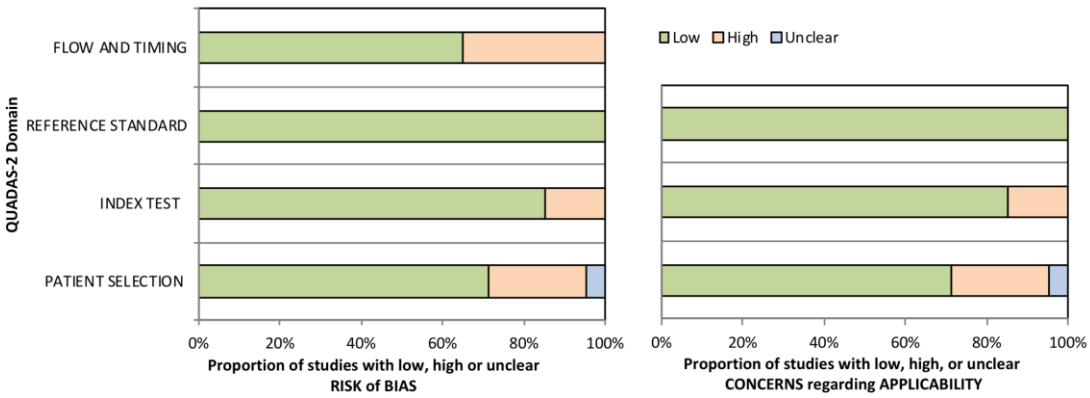

Figure 4. Sensitivity of ultrasound in detecting EA prenatally.

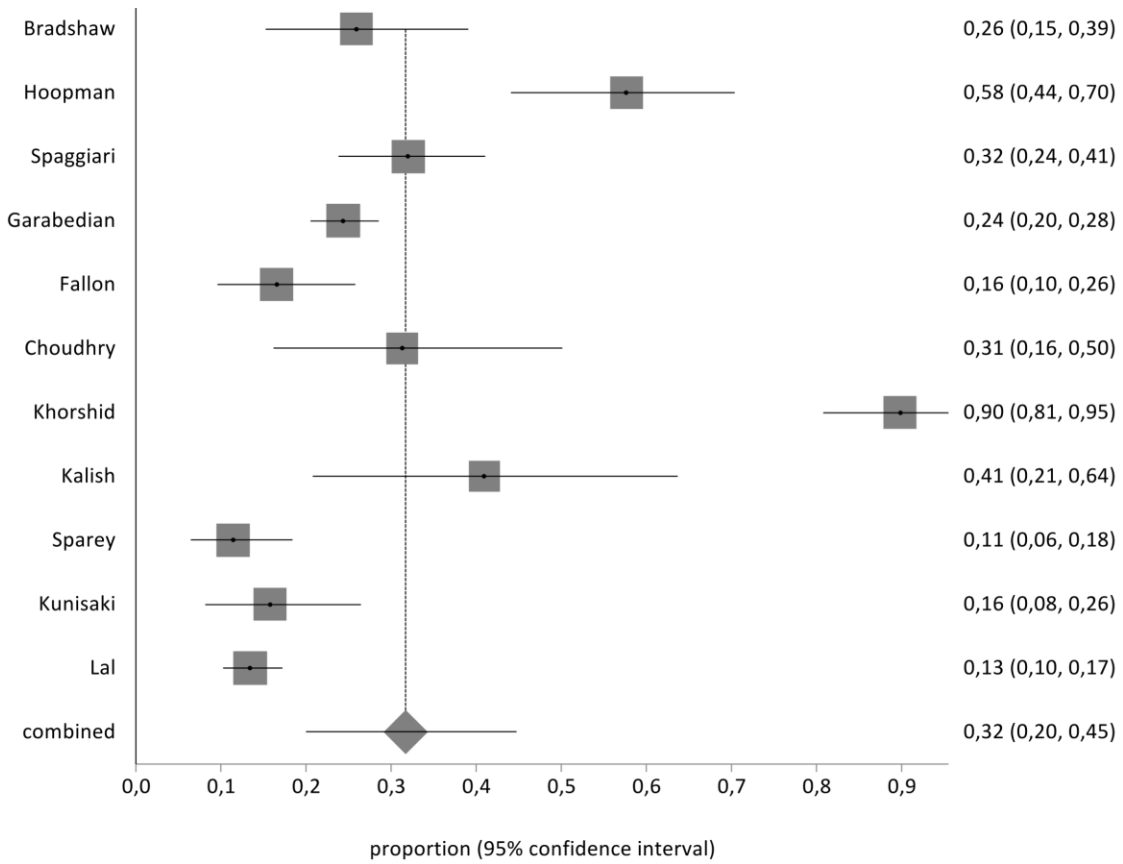

Figure 5. Hierarchical receiver operating characteristic curve (HSROC) showing the diagnostic performance of fetal MRI in detecting EA.

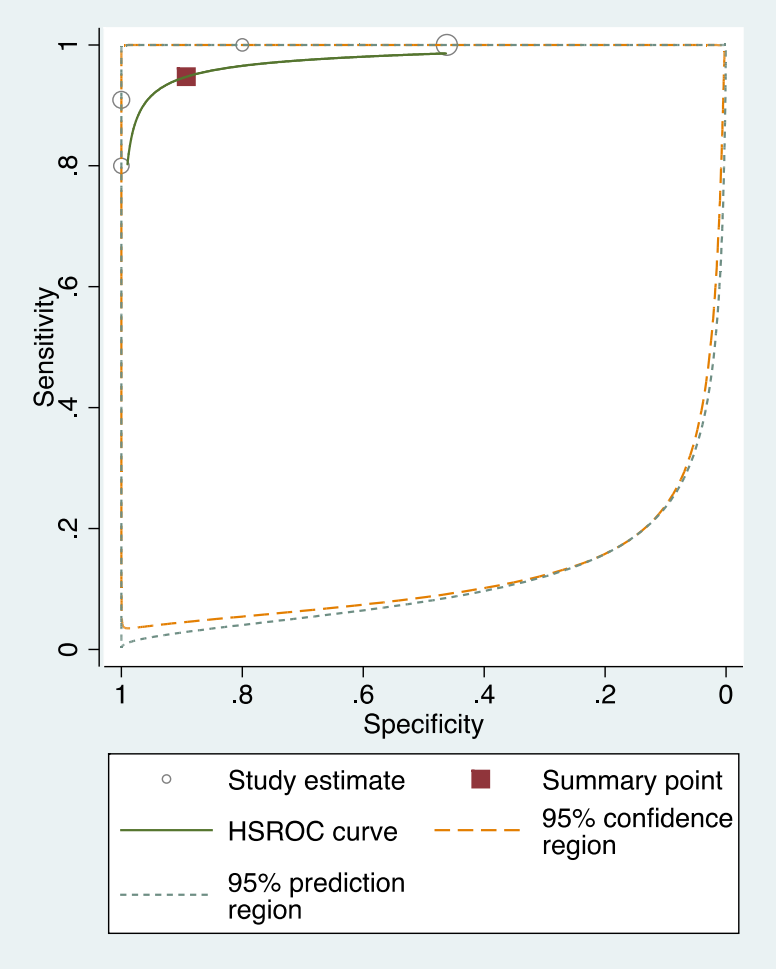

Figure 6. Der-Sirmonian summary receiver operating characteristic curve (SROC) showing the diagnostic performance of amniotic fluid analysis in detecting EA.