Outcome of ovarian cysts diagnosed on prenatal ultrasound: a systematic review and meta-analysis

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Keywords: Ovarian cysts, Ultrasound, Outcome

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/uog.16002

ABSTRACT

Objectives: To explore the outcome of fetuses with a prenatal diagnosis of fetal ovarian cysts.

Methods: Medline and Embase databases were searched. The following outcomes were explored: resolution of the cyst, change of ultrasound pattern, occurrence of ovarian torsion and intra-cystic haemorrhage, need for surgery, need for oophorectomy, detection rate of prenatal ultrasound in correctly identifying ovarian cysts, type of ovarian cyst at histopathological analysis and intra-uterine treatment. Meta-analyses using individual data random-effect logistic regression and meta-analyses of proportion were used to analyse the data. Quality assessment of the included studies was performed using the Newcastle-Ottawa Scale.

Results: Thirty-four studies (954 fetuses) were included. 54.6% (95% CI 47.0-62.0) of the cysts regressed either during pregnancy or after birth. The likelihood of resolution was significantly lower in complex vs simple cysts (OR: 0.15, 95% CI 0.10-0.23) and in those ≥ 40 compared to<40 mm (OR: 0.03, 95% CI 0.01-0.06). Change in ultrasound pattern was associated with an increased risk of ovarian loss (PP: 57.7%, 95% CI 42.9—71.8). The risk of ovarian torsion was significantly higher in cysts ≥ compared to those < 40 mm (OR: 30.8, 95% CI 8.6-110). The risk of having surgery was higher in patients with cysts ≥ compared to <40 mm (OR: 64.4, 95% CI 23.6-175) and in complex cysts compared to simple cysts, irrespective of the cyst size. In cases undergoing prenatal aspiration of the cyst, the rate of recurrence was 37.9% (95% CI 14.8-64.3), while torsion and haemorrhage were diagnosed after birth in 10.8% (95% CI 4.4-19.7) and 9.7% (95% CI 3.7-18.3) of the cases treated. Finally, 17.7% (95% CI 9.3-,28) of fetuses undergoing fetal therapy had surgery after birth.

Conclusion: Cysts size and appearance are the major determinants of perinatal outcome in these anomalies.

INTRODUCTION

Ovarian cysts are the most common abdominal anomalies diagnosed in female fetuses with an estimated incidence of about 1 in 2600 pregnancies[1]. Although the pathophysiology of ovarian cysts has not yet been fully elucidated, they are usually benign functional anomalies resulting from excessive stimulation of fetal ovaries by placental and maternal hormones. Ovarian cysts are common in pregnancies complicated by maternal diabetes, pre-eclampsia or Rhesus isoimmunisation. They are frequently diagnosed during the third trimester, especially after 28 weeks of gestation[1,2]. Ovarian cysts are divided into two categories according to their sonographic appearance. The first category includes simple cysts which are usually anechoic, round, unilocular and thin walled lesions larger than 2 cm. The second category includes complex thick walled, heterogeneous, containing hyperechoic components, free-floating material or intra-cystic septations and is commonly considered the result of torsion or intra-cystic haemorrhage[3].

Optimal management of fetal ovarian cysts is unclear. The evolution of these anomalies is variable Although the majority of them regress either during pregnancy or after birth, torsion and haemorrhage can occur antenatally, thus increasing the risk of surgical intervention and ovarian loss. Pre-natal aspiration of the cyst is occasionally performed, especially in case of large lesions, in order to prevent intra-uterine torsion which may lead to ovarian auto-amputation or the need for oophorectomy. However, whether it improves the neonatal outcome in these fetuses is yet to be established. Furthermore, the accuracy of antenatal ultrasound in correctly identifying ovarian cysts prenatally is unknown. Gastrointestinal, renal and genital anomalies are commonly misdiagnosed as ovarian cysts[2]. Finally, it is yet to be ascertained whether the ultrasound appearance of the cyst can predict the post-natal outcome or be used to guide the prenatal management in these cases.

The aim of this systematic review was to explore the outcome of ovarian cysts diagnosed prenatally and to quantify the accuracy of antenatal ultrasound in correctly identifying these anomalies.

METHODS

Protocol, eligibility criteria, information sources and search

This review was performed according to an a-priori designed protocol and recommended for systematic reviews and meta-analysis[4]. Medline and Embase databases were searched electronically on the 11.02.2016 utilizing combinations of the relevant medical subject heading (MeSH) terms, key words, and word variants for "ovarian cysts", "ultrasound" and "outcome" (Supplementary Table 1). The search and selection criteria were restricted to English language. Reference lists of relevant articles and reviews were hand searched for additional reports. Prisma guidelines were followed[5].

The study was registered with the PROSPERO database (Registration number: CRD42016035594).

Study selection, data collection and data items

Two authors (FB, LM) 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 outcome. Inconsistencies were discussed by the reviewers and consensus reached or 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. For those articles in which information was not reported but the methodology was such that this information would have been recorded initially, the authors were contacted.

Quality assessment of the included studies was performed using the Newcastle-Ottawa Scale (NOS); according to NOS, each study is judged on three broad perspectives: the selection of the study groups; the comparability of the groups; and the ascertainment outcome of interest[6]. Assessment of the selection of a study includes the evaluation of the representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure and the demonstration that outcome of interest was not present at start of study. Assessment of the comparability of the study includes the evaluation of the comparability of cohorts on the basis of the design or analysis. Finally, the ascertainment of the outcome of interest includes the evaluation of the type of the assessment of the outcome of interest, length and adequacy of follow-up[6]. According to NOS a study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

The incidence of the following outcomes was analysed in fetuses with a prenatal diagnosis of an ovarian cyst:

- Resolution of the cyst in utero or after birth.
- Change of ultrasound pattern from simple to complex cyst.
- Occurrence of ovarian torsion and intra-cystic haemorrhage.
- Need for surgery.
- Ovarian loss due to oophorectomy or salpingo-oophorectomy.
- False positive rate of prenatal ultrasound.
- Histopathological type of the ovarian cyst
- Intra-uterine treatment.

Cases undergoing prenatal intervention (cyst aspiration) were evaluated separately in terms of:

- Resolution of the cyst.
- Recurrence of the cyst.
- Increase in cyst size after aspiration.
- Change of ultrasound pattern after intervention.
- Evidence of torsion or haemorrhage after intervention or at birth.
- Need for surgery.
- Preterm birth (PTB) or miscarriage due to the invasive procedure

All these outcomes were assessed in the overall population of fetuses with a prenatal diagnosis of an ovarian cyst. Furthermore, a sub-analysis according to the appearance (simple vs complex) and size of the cyst ($< vs \geq 40$ mm) was also carried out. The choice for this cut-off was based upon the fact that this has been commonly reported to represent the highest centile of cyst size in the published literature.

For the ascertainment of the resolution and the change in ultrasound appearance of the cyst, the anomalies were categorised according to their first ultrasound appearance and size, while the prevalence and risk of torsion, haemorrhage, surgery and need for oophorectomy were ascertained by looking at the post-natal ultrasound examination or, if not available, the last scan in pregnancy.

Cases undergone cyst aspiration in utero were analysed separately and not included in the main analyses. PTB or miscarriage was considered to be caused by fetal therapy whether occurring within 15 days from the intervention.

Only studies reporting a prenatal diagnosis of ovarian cyst were considered suitable for the inclusion in the current systematic review. Post-natal studies or studies from which cases diagnosed

prenatally could not be extracted were excluded. Paediatric and surgical series including only symptomatic cases or patients undergoing surgical treatment were also excluded. Studies published before 2000 were not included, as we considered that advances in prenatal imaging techniques, improvements in the diagnosis and definition of fetal anomalies make these studies less relevant. Finally, studies not providing a clear classification of the anomaly were not considered suitable for the inclusion in the current review.

Only full text articles were considered eligible for the inclusion. Case reports, conference abstracts and case series with fewer than 3 cases of suspected ovarian cysts, irrespective of the fact that the anomalies were isolated or not, were also excluded in order to avoid publication bias.

Statistical analysis

The strength of association between ultrasound characteristics of the cysts and each observed outcome was explored. For the quantification of the incidence of these outcomes, meta-analyses of proportions using random effect model were used to combine data. Funnel plots displaying the outcome rate from individual studies versus their precision (1/standard error) were carried out with an exploratory aim. Tests for funnel plot asymmetry were not used when the total number of publications included for each outcome was less than ten (Supplementary material). In this case, the power of the tests is too low to distinguish chance from real asymmetry.[7-10] Between-study heterogeneity was explored using the I^2 statistic, which represents the percentage of between-study variation that is due to heterogeneity rather than chance[10].

Furthermore, we evaluated separately the association between ovarian cysts type (complex or simple) and size (≥40mm or <40 mm) and six clinical outcomes (change of US pattern: simple cases becoming complex; resolution; torsion; haemorrhage; surgery; ovarian loss / oophorectomy). We also stratified the meta-analyses exploring any combination of cysts type and size, thus performing a total of 8 direct comparisons for each of the outcomes (excluding change of US pattern): (1) complex vs simple cysts; (2) ≥40mm vs <40mm cysts; (3) simple cysts ≥40mm vs <40 mm; (4) complex cysts ≥40mm vs <40 mm; (5) complex cysts ≥40 mm vs simple cysts ≥40mm; (6) complex cysts <40mm vs simple cysts ≥40mm; (7) complex cysts ≥40mm vs simple cysts <40mm; and (8) complex cysts <40mm vs simple cysts <40mm.

We included observational cohort studies in which: (a) many comparisons reported zero events in one groups; (b) several comparisons reported zero events in both groups; (c) exposed and unexposed group sizes were frequently severely unbalanced. In such a case, many of the most

commonly used meta-analytical methods - including those using risk difference (which could be used to handle total zero event studies) - can produce biased estimates when events are rare[11,12]. When many studies are also substantially imbalanced, the best performing methods are the Mantel-Haenszel odds ratio without zero-cell continuity corrections, logistic regression and an exact method[13,14]. Mantel-Haenszel odds ratios cannot be computed in studies reporting zero events in both groups, the exclusion of which may however cause a relevant loss of information and the potential inflation of the magnitude of the pooled exposure effect.[11] Therefore, to keep all studies into the analyses, we performed all meta-analyses using individual data random-effect logistic regression, with single study as the cluster unit. The pooled datasets with individual data were reconstructed using published 2X2 tables. When one of the overall pooled arms showed no events, we used exact logistic regression.

As a likely consequence of non-randomization, dissimilarity of the populations and lack of fixed criteria for when to treat, several of the comparisons showed an extreme imbalance in the success rate between the groups being compared (e.g. 44/67 vs 0/69). Besides the computational issues, in such cases the odds ratios may be of limited interest and sensitivity and specificity may be more informative. We thus computed the overall sensitivity and specificity (and related 95% confidence intervals - CI) for each comparison using according to the efficient-score method (corrected for continuity) described by Newcombe[13].

All analyses were performed using Stata version 13.1 (Stata Corp., College Station, TX, 2013).

RESULTS

Study selection and characteristics

1483 articles were identified, 52 were assessed with respect to their eligibility for inclusion (Supplementary Material 2) and 34 studies included in the systematic review (Table 1, Figure 1)[15-48]. These 34 studies included 954 fetuses with a prenatal diagnosis of ovarian cysts.

Quality assessment of the included studies was performed using Newcastle-Ottawa Scale (NOS) for cohort studies (Table 2). Most of the included studies showed an overall good rate with regard to the selection and comparability of the study groups and for the ascertainment of the outcome of interest. The main weaknesses of these studies were their retrospective design, small sample size and lack of detailed ultrasound characteristics of the cysts for some of the included studies.

Synthesis of the results

Resolution of the cysts

Twenty-nine studies including 784 fetuses with a prenatal diagnosis of an ovarian cyst evaluated the rate of resolution of the cyst. About half of the cysts regress during pregnancy or after birth 53.82% (95% CI 46.0-61.5). Resolution of the cyst occurred in 69.4% (95% CI 59.0-79.0) of simple cysts and in 84.8% (95% CI 70.0-95.2) of those measuring<40 mm. The proportions of resolution of ovarian cysts according to size and appearance are reported in Supplementary Table 3. Complex cysts and those ≥40 mm were less likely to regress than simple cysts or those measuring <40 mm (OR: 0.15, 95% CI 0.10-0.23)and OR: 0.03, 95% CI 0.01-0.06 respectively) (Table 3) (Figure 2).

Change of US pattern, torsion and haemorrhage

More than 20% (22.6%, 95% CI 14.4-34.4) of all simple cysts included in the present systematic review demonstrate change in the ultrasound pattern during pregnancy or at birth. The risk of change in the ultrasound pattern during pregnancy was significantly higher in cysts ≥ compared to those < 40 mm (OR: 3.16, 95% CI 1.02-9.7, I^2: 0%). In those cases, the occurrence of ovarian loss, either due to surgical removal or ovarian autoamputation, was high (pooled proportion: 57.7%, 95% CI 42.9—71.8, I^2: 7.1%) (Figure 2).

The overall incidence of torsion of the cysts was 21.8%, (95% CI 15.2-29.2, (Figure 4). The corresponding figures for simple and complex cysts were 6.0% (95% CI 3.6-8.9) and 44.9% (95% CI 31.7-58.4)(Supplementary Table 4). The risk of ovarian torsion was significantly higher in cysts

≥ compared to those < 40 mm (OR: 30.8, 95% CI 8.6-110). Furthermore, the association between the complex appearance of the cyst at ultrasound and the occurrence of torsion was significantly higher than in case of simple cysts (OR: 16.2, 95% CI 4.3-61.6) . Cysts <40 mm, irrespective of their ultrasound appearance were less likely to be associated with torsion at birth (Table 4).

The risk of haemorrhage was significantly higher in complex vs simple cysts (OR: 28.6, 95% CI 4.9-∞), in those ≥40mm vs <40mm (OR: 31.7, 95% CI 3.71-270) and simple cysts ≥40mm vs <40 mm (OR: 63.4 (10.7-∞ (Table 5)

Surgery

Thirty studies (761 fetuses) explored the incidence of surgery in fetuses with a prenatal diagnosis of ovarian cyst. They reported that 39.50 (95% CI 30.1-49.3of fetuses with a prenatal diagnosis of ovarian cysts confirmed at birth had surgical intervention. The corresponding figures in fetuses with simple and complex ovarian cysts were 24.6 (95% CI 14.2-36.9) and 64.8% (95% CI 52.2-76.3. The risk of having surgery was higher in patients with cysts ≥ compared to <40 mm (OR : 64.4, 95% CI 23.6-175) and in complex cysts compared to simple cysts, irrespective of the cyst size (Table 6).

The ultrasound appearance of the cyst was also associated with the type of surgical intervention and the likelihood of preserving the affected ovary (Supplementary Table 7). Both complex and large cysts (≥ 40 mm) were associated with a significantly increased risk of ovarian loss due to oophorectomy or salpingo-ophoorectomy (OR: 35.1, 95% CI 17.0-72.7)and OR: 58.9, 95% CI 19.2-181, respectively) (Table 7).

Intra-uterine treatment

Twelve studies including 56 fetuses undergoing intra-uterine aspiration of the cyst were included in this systematic review. After aspiration of the cyst, the incidence of recurrence was 37.9% (95% CI 14.8-64.3), while increase in the cyst size occurred in 6.9% (95% CI 2.0-14.5) of the cases. Almost half of the cyst aspirated in utero (48.9%, 95% CI 25.0-74.0) did not recur either during pregnancy or after birth. Change of ultrasound pattern of the cyst from a simple to complex appearance occurred in 7.9% (95% CI 2.6-15.8) of fetuses after aspiration of the cyst, while torsion and haemorrhage were diagnosed after birth in 10.8% (95% CI 4.4-19.7) and 9.7% (95% CI 3.7-18.3) of the cases treated. The rate of preterm birth or miscarriage due to the invasive procedure was 5.10% (95% CI 0.7-13.0); 1/44, I^2:0%). Finally, 21.8% (95% CI 0.9-40) of fetuses undergoing fetal therapy had surgery after birth (Table 8).

False positive rate of prenatal ultrasound and histopathological diagnosis

False positive rate of prenatal ultrasound in detecting ovarian cysts was 7.5% (95% CI 4.4-11.4). Of those cases misdiagnosed as ovarian cysts, almost half were gastrointestinal anomalies (54.1%, 95% CI 28.1-78.9). Furthermore, urogenital and renal anomalies were falsely diagnosed as ovarian cysts in 14.9% (95% CI 6.6-25.6) and 10.3% (95% CI 4.0-19.1) of the cases, respectively (Supplementary Table 8).

Histopathogical assessment of the ovarian cyst following surgery was available for 385 cases. The majority of the cysts were either follicular or theca lutein (93.0%, 95% CI 87.7-96.8)) while cystoadenoma and teratoma were diagnosed in 2.1% (95% CI 0.9-3.7)and 1.5% (95% CI 0.5-2.9) of the cases (Supplementary Table 9).

DISCUSSION

Main findings

The findings from this systematic review showed that a large proportion of fetal ovarian cysts regress either during pregnancy or after birth. Simple cysts may change their ultrasound appearance and become complex during pregnancy and this is associated with an increased risk of ovarian loss. The size and appearance of the cyst are the major determinants of perinatal outcome and are associated with an increased risk of ovarian torsion, haemorrhage and need for oophorectomy. False positive rate of ultrasound in the detection of ovarian cysts is low, although it is not uncommon for gastro-intestinal, renal and urogenital anomalies to be misdiagnosed as ovarian. The very small number of included cases precluded extrapolating a robust evidence on the value of intra-uterine treatment of ovarian cysts.

Strengths and limitations

The small number of cases in some of the included studies, their retrospective non-randomized design, different periods of follow-up, dissimilarity of the populations (due to various inclusion criteria), the lack of fixed criteria for when to treat, and the post-natal confirmation represent the major limitations of this systematic review. The assessment of the potential publication bias was also problematic, both because of the outcome nature (rates with the left side limited to the value zero) which limits the reliability of funnel plots, and because of the scarce number of individual studies, which strongly limits the reliability of formal tests.

Most of the observed outcomes were reported only by a limited proportion of the included studies. Furthermore, we could not stratify the analysis according to different cut-offs for cyst size in view of the fact that the majority of these were reported only by a few studies, thus considerably limiting the interpretation of the results. The ascertainment of some of the outcomes observed, such as surgery or need for oophorectomy was also considerably biased by the peculiar post-natal management adopted in different centers. Large lesions usually undergo surgical intervention irrespective of the presence of symptoms in order to reduce the risk of complications, such as torsion and hemorrhage which may lead to ovarian loss. In this scenario, the results from this systematic review may have over-estimated some of the adverse outcomes associated with ovarian cysts.

The assessment of the role of intra-uterine therapy was also problematic. Ovarian cysts usually regress during pregnancy, thus the role of cyst aspiration in utero in preventing the occurrence of

torsion or haemorrhage could not be completely quantified. Furthermore, the very small number of included cases, different gestational ages at intervention and time points at the post-natal follow-up, lack of ascertainment according to cyst size and appearance did not allow us to draw any conclusion on the role of prenatal cyst aspiration in the management of ovarian cysts. Therefore, an adequately powered randomised control trial is needed in order to ascertain the value of prenatal cyst aspiration.

Despite these limitations, the present review represents the best published estimate of the investigated outcomes in fetuses diagnosed with ovarian cysts.

Implications for clinical practice

Pre and post-natal management of ovarian cysts is challenging. The evidence is sparse and mainly derived from post-natal series reporting high rates of complications and need for surgical intervention.

The findings from this systematic review showed that ultrasound appearance and cyst size are the major determinants of the perinatal outcome in these cases and can be used to tailor the optimal post-natal management of these patients.

Simple cysts may occasionally change their ultrasound appearance and become complex either during pregnancy or after birth, and this was associated with a significantly increased risk of ovarian loss due to surgical oophorectomy or ovarian autoamputation. Ultrasound fetal surveillance should be arranged in order to look for early signs of complications of the cyst, such as an increase in size or appearance of intra-cystic echoes. However, the optimal perinatal management of these cases is controversial[49,50]. Iatrogenic preterm delivery and prompt surgical intervention may further compromise these patients on the basis that ovarian function might have already been compromised. In this scenario, especially in cases remote from term, ultrasound monitoring of the cyst seems the most reasonable and safe option.

Complex cysts have been reported to be strongly associated with ovarian torsion requiring oophorectomy[1,2]. In the present review, the risk of surgical removal of the ovary was higher in large and complex cysts. Despite this, not all complex cysts showed signs of torsion, thus questioning whether immediate postnatal intervention should be arranged immediately after birth in children with complex lesions.

The role of intra-uterine aspiration of ovarian cyst is controversial[51]. The findings from this systematic review suggest that almost half of the ovarian cysts aspirated in utero regress either

during pregnancy or after birth. Furthermore, the risk of torsion, haemorrhage and the need for post-natal surgical intervention is relatively small. However, these findings come from retrospective series mainly including highly selected cases. The very small number of included studies, different time points at fetal intervention and follow-up, variation in cyst size and appearance did not allow us to draw any robust conclusion. Aspiration of the cyst in utero might be considered, especially in case of very large cysts presenting remote from term in order to not compromise the reproductive capacity of the woman or in case of the cyst causing compression on the adjacent structures leading to bowel obstruction or impaired flow in the ductus venosus. However, a randomised and adequately powered control trial is needed in order to ascertain the role, if any, of intra-uterine aspiration of the cyst in the prenatal management of ovarian cysts.

Ovarian cysts are one of the most common abdominal cystic anomalies diagnosed prenatally. The present review showed that a small proportion of renal, gastro-intestinal and genital anomalies can be misdiagnosed as ovarian. Almost 15% of complex urogenital anomalies, such as persistence of urogenital sinus or cloaca, were misdiagnosed as ovarian cysts. Because these anomalies are associated with worse postnatal and surgical outcomes compared to ovarian cysts, a thorough ultrasound examination should be arranged in order to not misdiagnosed them as ovarian cysts.

CONCLUSION

A large proportion of ovarian cysts diagnosed prenatally regress either during pregnancy or after birth. The risk of torsion is particularly high in case of large cysts. The change of ultrasound pattern during pregnancy is associated with a high risk of ovarian loss. The size and appearance of the cysts are the major determinants of perinatal outcome, and are associated with an increased risk of torsion, haemorrhage and need for oophorectomy. Future randomised trials are needed in order to ascertain the role of fetal therapy in the management of these cases.

Conflict of interest statement.

No conflict of interest is declared by any of the authors.

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Table 1. General characteristics of the included studies.

Author	Year	Country	Study Design	Prenatal imaging	Postnatal imaging	GA at diagnosis (w)	Cyst diameter (mm)	Time at surgery	Fetuses (n)	Time at follow-up
Catania[15]	2015	Italy	Retrospective	US	US. MRI	33 (22-39)	NS	NS	25	5y
Thakkar[16]	2015	United Kingdom	Retrospective	US	US	NS	NS	NS	34	NS
Nakamura[17]	2015	Japan	Retrospective	US	US	32 (22-37)	47 (17-79)	NS	33	NS
Marchitelli[18]	2015	France	Retrospective	US	US. MRI	NS	NS	NS	17	NS
Açıkgöz1[19]	2015	Turkey	Retrospective	US	US. MRI	30±6.4	39.8±13.4	NS	17	NS
Jwa[20]	2015	Japan	Retrospective	US. MRI	US	33.9 (29.9-36.9)	37 (15-52)	1d-4m	21	NS
Papic[21]	2014	United Kingdom	Retrospective	US	US	NS	55.1 (24-150)	12w (3-64)	25	NS
Karakus[23]	2014	Turkey	Retrospective	US	US	33.1 (±3.2)	41.5 (10-60)	NS	37	3m
Turgal[22]	2013	Turkey	Retrospective	US	US	28.4 (23-37)	40.9 (11-90)	2-4m	29	2-9m
Amari[24]	2013	Germany	Retrospective	US	NS	32+0 (14+6-39+2)	NS	NS	35	NS
Dimitraki[25]	2012	Greece	Retrospective	US	US	32.4 (30-37)	37.7 (21-74)	1m	16	3-12 m
Gaspari[26]	2012	France	Retrospective	US	US	>32w	52.4 (40-60)	1-3m	5	4.14 y (1.5-6.7)
Lecarpentier[27]	2012	France	Retrospective	US	NS	NS	NS	NS	26	NS
Nemec[28]	2012	Austria	Retrospective	US. MRI	US	31+2 (23+0-35+5)	NS	NS	16	NS
Noia[29]	2012	Italy	Retrospective	US	US	32 (27-36)	46 (31-74)		13	(2m-3y)
Aqrabawi[30]	2011	Jordan	Retrospective	US	US	NS	30-100	NS	12	1m-6y
Akin[31]	2010	Turkey	Retrospective	US	US	34 (32-38)	53.0 (25-80)	1-23d	18	NS
Eleftheriades[32]	2010	Greece	Retrospective	US	US	32 (31+1-32+4)	37 (27-61)	NT	7	NS
Ben-Ami[33]	2010	Israel	Retrospective	US	US	33 (28-37)	42.4 (10-60)	44.2d (1-115)	21	6.6 y (1.3-11.6)
Zampieri[34]	2008	Italy	Retrospective	US	US. MRI	34 (32-37)	50.0 (2.7-7.5)	NS	57	1-5y
Godinho[35]	2008	Portugal	Retrospective	US	US	31.6 (29-35)	38.3 (29-60)	10-11d	5	NS
Shimada[36]	2008	Japan	Retrospective	US	US	III trimester	46.6 (23-75)	Within 10m	16	2m
Monnery-Nochè[37]	2008	France	Retrospective	US	US	33 (24-39)	43.5 (17-130)	3d(0-119d)	65	3m (11d-6y)
Galinier[38]	2008	France	Retrospective	US	US	32 (26-39)	43.5 (20-90)	NS	79	11m (6-10y)

Kwak[39]	2006	South Korea	Retrospective	US	US	34.0 (30-38)	49 (33-78)	1d-3w	17	1-24m
Foley[40]	2005	Australia	Retrospective	US	US	II-III trimester	39.6 (0.7-7.0)	7-8m	11	12.9 m (3m-6y)
Enriquez[41]	2005	Spain	Retrospective	US. MRI	US. MRI	(33-37)	(2.4-11.2)	NS	18	(3-15m)
Comparetto[42]	2005	Italy	Retrospective	US	US	34 (32-37)	(27-75)	NS	32	1-5y
Quarello[43]	2003	France	Retrospective	US	US	31	NS	NS	12	NS
Mittermayer[44]	2003	Germany	Retrospective	US	US	32 (24-38)	42 (±12)	2h-6w	61	(7d-12m)
Heling[45]	2002	Germany	Retrospective	US	US	35 (26-40)	32 (17.5-55.0)	1-14d	64	NS
Bagolan[46]	2002	Italy	Prospective	US	US	33.6 (23-39)	39 (23-.85)	NS	80	NS
Perrotin[47]	2000	France	Retrospective	US	US	31 (29-32)	31 (16-44)	No surgery	3	2-4w
Luzzatto[48]	2000	Italy	Retrospective	US	US	33 (28-36)	43.3 (24-77)	0-17m	27	(3m-9y)

NS: NS

Table 2. Quality assessment of the included studies according to Newcastle-Ottawa Scale (NOS) a study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Author	Year	Selection	Comparability	Outcome
Catania[15]	2015	★★	★	★★
Thakkar[16]	2015	★★★	★★	★★
Nakamura[17]	2015	★★	★	★
Marchitelli[18]	2015	★★	★	★
Açıkgöz1[19]	2015	★★	★	★★
Jwa[20]	2015	★★	★	★★
Papic[21]	2014	★★	★	★★
Karakus[23]	2014	★★	★	★★
Turgal[22]	2013	★★	★	★
Amari[24]	2013	★	★	★
Dimitraki[25]	2012	★★	★	★
Gaspari[26]	2012	★★	★	★★
Lecarpentier[27]	2012	★★	★	★★
Nemec[28]	2012	★★	★	★★
Noia[29]	2012	★★	★	★
Aqrabawi[30]	2011	★★	★	★★
Akin[31]	2010	★★	★	★★
Eleftheriades[32]	2010	★★	★	★★
Ben-Ami[33]	2010	★★	★	★★
Zampieri[34]	2008	★★	★	★★
Godinho[35]	2008	★★	★	★★
Shimada[36]	2008	★★	★	★
Monnery-Nochè[37]	2008	★★	★	★★
Galinier[38]	2008	★★	★	★★
Kwak[39]	2006	★★	★	★★
Foley[40]	2005	★★	★	★★
Enriquez[41]	2005	★★	★	★★
Comparetto[42]	2005	★★	★	★★
Quarello[43]	2003	★★	★	★★
Mittermayer[44]	2003	★★	★★	★★★
Heling[45]	2002	★★	★	★
Bagolan[46]	2002	★★	★★	★★
Perrotin[47]	2000	★★	★	★★
Luzzatto[48]	2000	★★	★★	★★

Table 3: Pooled odd ratios showing the likelihood of resolution of fetal ovarian cysts according to cysts size and/or US appearance.

	Studies (n)	Fetuses (n/N Vs n/N)	Pooled OR (95% CI)	p	Sensitivity* (95% CI)	Specificity* (95% CI)
Complex vs simple cysts	20	68/224 vs 231/341	0.15 (0.10-0.23)	<0.001	58.6 (52.5-64.6)	77.3 (72.0-81.8)
≥40mm vs <40mm cysts	16	60/192 vs 149/168	0.03 (0.01-0.06)	<0.001	87.4 (80.8-92.1)	71.3 (64.6-77.2)
Simple cysts ≥40mm vs <40 mm	16	45/134 vs 140/156	0.02 (0.00-0.06)	<0.001	84.8 (76.1-90.8)	75.7 (68.7-81.5)
Complex cysts ≥40mm vs <40 mm	9	(17/54 vs 25/28)	0.06 (0.01-0.21)	<0.001	92.5 (78.5-98.0)	59.5 (43.3-74.0)
Complex cysts ≥40 mm vs simple cysts ≥40mm	11	(19/60 vs 42/83)	0.40 (0.18-0.88)	0.022	50.0 (38.8-61.2)	68.9 (55.6-79.8)
Complex cysts <40mm vs simple cysts ≥40mm	11	(26/30 vs 39/73)	4.93 (1.36-17.8)	0.015	10.5 (3.0-25.7)	60.0 (47.1-71.7)
Complex cysts ≥40mm vs simple cysts <40mm	12	(20/62 vs 71/83)	0.04 (0.01-0.12)	<0.001	77.8 (64.1-87.5)	78.0 (67.9-85.7)
Complex cysts <40mm vs simple cysts <40mm	11	(26/30 vs 64/74)	0.56 (0.09-3.38)	0.5	25.6 (9.6-58.0)	71.1 (60.5-79.9)

* Both sensitivity and specificity have been computed for the reversed outcome "No resolution".

Table 4: Pooled odd ratios showing the likelihood of torsion of fetal ovarian cysts according to cysts size and/or US appearance.

	Studies (n)	Fetuses (n/N Vs n/N)	Pooled OR (95% CI)	p	Sensitivity (95% CI)	Specificity (95% CI)
Complex vs simple cysts	19	139/253 vs 7/242	59.1 (24.7-141)	<0.001	95.2 (90.0-97.9)	67.3 (62.1-72.2)
≥40mm vs <40mm cysts	13	45/116 vs 3/121	30.8 (8.6-110)	<0.001	93.8 (81.8-98.4)	62.4 (55.1-69.3)
Simple cysts ≥40mm vs <40 mm	12	(14/82 vs 1/123)	26.7 (3.3-214)	0.002	93.3 (66.0-99.7)	64.2 (56.9-70.9)
Complex cysts ≥40mm vs <40 mm	9	(37/61 vs 3/33)	16.2 (4.3-61.6)	<0.001	92.5 (78.5-98.0)	55.6 (41.5-68.8)
Complex cysts ≥40 mm vs simple cysts ≥40mm	9	(37/61 vs 1/40)	82.0 (9.1-743)	<0.001	97.4 (84.6-99.9)	61.9 (48.8-73.6)
Complex cysts <40mm vs simple cysts ≥40mm	9	(3/35 vs 2/38)	1.8 (0.2-13.7)	0.6	60.0 (17.0-92.7)	52.9 (45.0-65.0)
Complex cysts ≥40mm vs simple cysts <40mm	11	(38/66 vs 0/62)	114 (19.3-∞) *	<0.001	100.0 (88.6-100.0)	68.9 (58.1-78.0)
Complex cysts <40mm vs simple cysts <40mm	10	(3/39 vs 0/60)	6.2 (0.6-∞) *	0.11	100.0 (31.0-100.0)	62.5 (52.0-72.0)

* Exact logistic regression, as no logistic regression model was possible due to zero event in the reference group (∞ = infinite).

Table 5: Pooled odd ratios showing the risk of haemorrhage of fetal ovarian cysts according to cysts size and/or US appearance.

	Studies (n)	Fetuses (n/N Vs n/N)	Pooled OR (95% CI)	p	Sensitivity (95% CI)	Specificity (95% CI)
Complex vs simple cysts	17	19/210 vs 0/205	28.6 (4.9-∞)*	<0.001	100.0 (79.1-100.0)	51.8 (46.7-56.8)
≥40mm vs <40mm cysts	12	2/15 vs 0/35	31.7 (3.71-270)	0.002	100.0 819.8-100.0)	72.9 (57.9-84.3)
Simple cysts ≥40mm vs <40 mm	10	(20/70 vs 0/115)	63.4 (10.7-∞) *	<0.001	100.0 (80.0-100.0)	69.7 (62.0-76.5)
Complex cysts ≥40mm vs <40 mm	7	(5/44 vs 1/26)	2.8 (0.3-28.5)	0.4	83.3 (36.5-99.1)	39.1 (27.4-52.1)
Complex cysts ≥40 mm vs simple cysts ≥40mm	7	(5/44 vs 0/28)	4.64 (0.60-∞) *	0.16	100.0 (46.3-100.0)	41.8 (30.1-54.5)
Complex cysts <40mm vs simple cysts ≥40mm	7	(1/28 vs 0/26)	0.9 (0.0-∞) *	0.9	100.0 (5.5-100.0)	49.1 (35.3-63.0)
Complex cysts ≥40mm vs simple cysts <40mm	9	(7/49 vs 0/54)	11.9 (1.72-∞) *	0.009	100.0 (56.1-100.0)	56.3 (45.8-66.2)
Complex cysts <40mm vs simple cysts <40mm	8	(1/32 vs 0/52)	1.6 (0.0-∞) *	0.8	100.0 (5.5-100.0)	62.7 (51.3-72.8)

* Exact logistic regression, as no logistic regression model was possible due to zero event in the reference group (∞ = infinite).

Table 6: Pooled odd ratios showing the likelihood of surgery according to cysts size and/or US appearance.

	Studies (n)	Fetuses (n/N Vs n/N)	Pooled OR (95% CI)	p	Sensitivity (95% CI)	Specificity (95% CI)
Complex vs simple cysts	22	(197/290 vs 77/292)	14.6 (8.53-24.8)	<0.001	71.9 (66.1-77.1)	69.8 (64.3-74.8)
≥40mm vs <40mm cysts	15	(96/138 vs 9/140)	64.4 (23.6-175)	<0.001	91.4 (83.9-95.8)	75.7 (68.5-81.8)
Simple cysts ≥40mm vs <40 mm	14	(67/90 vs 1/133)	3998 (233-68,626)	<0.001	98.5 (91.0-99.9)	85.2 (78.4-90.2)
Complex cysts ≥40mm vs <40 mm	11	(56/75 vs 7/42)	48.8 (10.4-229)	<0.001	88.9 (77.8-95.0)	64.8 (50.6-77.0)
Complex cysts ≥40 mm vs simple cysts ≥40mm	11	(75/58 vs 23/48)	17.7 (4.39-71.3)	<0.001	71.6 (60.3-80.8)	59.5 (43.3-74.0)
Complex cysts <40mm vs simple cysts ≥40mm	11	(7/44 vs 23/46)	0.22 (0.06-0.76)	0.016	23.3 (10.6-42.7)	38.3 (26.4-51.8)
Complex cysts ≥40mm vs simple cysts <40mm	13	(61/80 vs 1/72)	2015 (71.0-57,179)	<0.001	98.4 (90.2-99.9)	78.9 (68.8-86.5)
Complex cysts <40mm vs simple cysts <40mm	12	(7/48 vs 1/70)	45.3 (1.2-1722)	0.040	87.5 (46.7-99.3)	80.5 (74.3-85.5)

Table 7: Pooled odd ratios showing the likelihood of ovarian loss at surgery (due to oophorectomy or salpingo-oophorectomy) according to cysts size and/or US appearance.

	Studies (n)	Fetuses (n/N Vs n/N)	Pooled OR (95% CI)	p	Sensitivity (95% CI)	Specificity (95% CI)
Complex vs simple cysts	20	(139/263 vs 17/276)	35.1 (17.0-72.7)	<0.001	89.9 (82.9-93.3)	67.6 (62.4-72.2)
≥40mm vs <40mm cysts	15	(76/138 vs 5/140)	58.9 (19.2-181)	<0.001	93.8 (85.6-97.8)	68.5 (61.5-74.8)
Simple cysts ≥40mm vs <40 mm	13	(26/84 vs 0/129)	80.3 (13.8-∞) *	<0.001	100.0 (84.0-100.0)	69.0 (61.8-75.4)
Complex cysts ≥40mm vs <40 mm	10	(42/62 vs 4/38)	21.8 (5.8-81.9)	<0.001	91.3 (78.3-97.2)	63.0 (48.7-75.4)
Complex cysts ≥40 mm vs simple cysts ≥40mm	10	(42/62 vs 10/62)	35.0 (5.93-206)	<0.001	80.8 (67.0-89.9)	72.2 (60.2-81.8)
Complex cysts <40mm vs simple cysts ≥40mm	10	(4/40 vs 10/40)	1.6 (0.2-13.8)	0.7	28.6 (9.6-58.0)	45.5 (33.3-58.1)
Complex cysts ≥40mm vs simple cysts <40mm	12	(44/67 vs 0/68)	∞ (500-∞) *	<0.001	100.0 (89.9-100.0)	74.7 (64.3-83.0)
Complex cysts <40mm vs simple cysts <40mm	11	(4/44 vs 0/66)	8.4 (1.0-∞) *	0.047	100.0 (39.6-100.0)	62.3 (52.3-71.3)

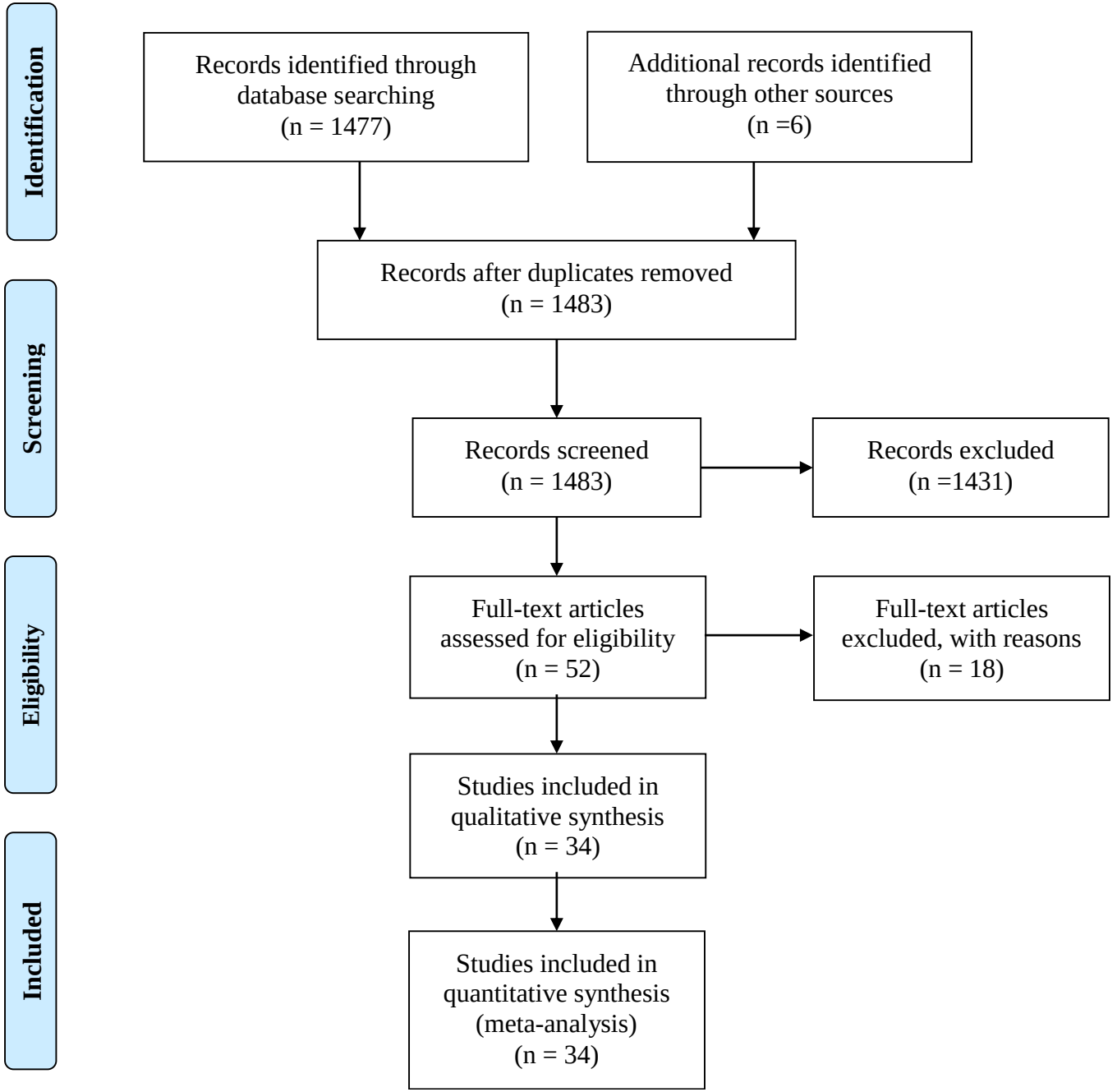
* Exact logistic regression, as no logistic regression model was possible due to zero event in the reference group (∞ = infinite)

Table 8: Pooled proportions for the different outcomes observed in fetal ovarian cysts treated pre-natally.

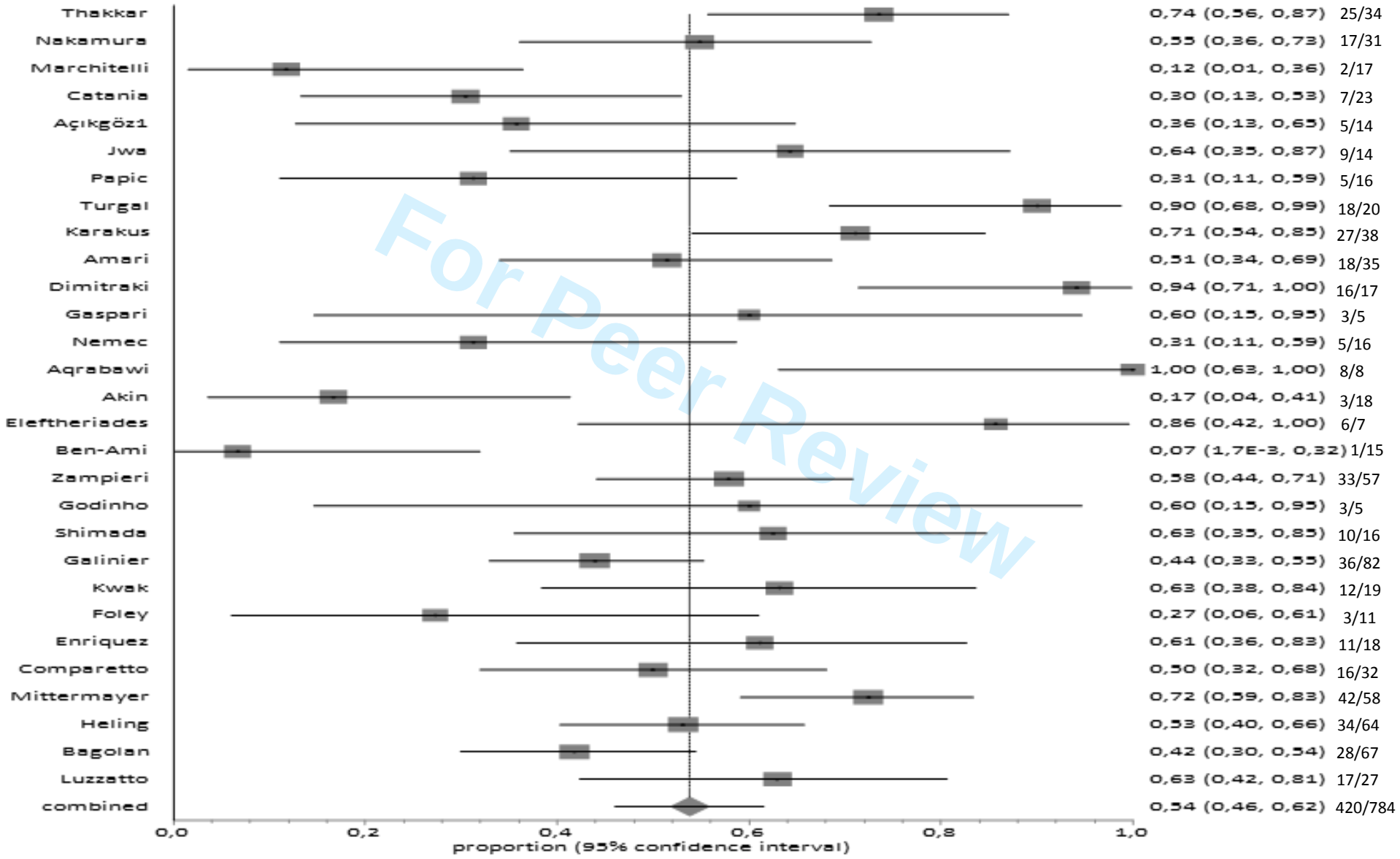
	Studies (n)	Fetuses (n/N)	Raw proportions (95% CI)	I^2	Pooled proportion (95% CI)
Recurrence	12	19/56	33.93 (21.8-47.8)	74	37.88 (14.8-64.3)
Resolution	12	31/56	55.36 (41.5-68.7)	70	48.86 (25.0-74.0)
Increase of cyst size	12	2/56	3.57 (0.4-12.3)	0	6.90 (2.0-14.5)
Change of US pattern	12	3/56	5.36 (1.1-14.9)	0	7.90 (2.6-15.8)
Torsion	12	4/56	7.14 (2.0-17.0)	0	10.83 (4.4-19.7)
Haemorrhage	12	5/56	8.93 (3.0-19.6)	35.3	9.72 (3.7-18.3)
Surgery	12	9/56	16.07 (7.6-28.3)	40.5	21.81 (0.9-40)
Preterm birth	6	1/44	2.27 (0.1-12)	0	5.10 (0.7-13.0)

FIGURE LEGEND

Figure 1. Systematic review flowchart.
Figure 2 (a-b). Pooled proportions for the occurrence of (a) resolution, (b) change of ultrasound pattern from simple to complex in fetuses with ovarian cysts.
Figure 3 (a-d). Pooled proportions for the occurrence of (a) torsion, (b) haemorrhage (c) surgery and (d) need for oophorectomy in fetuses with ovarian cysts.
Figure 4 (a-h). Pooled proportions for the occurrence of different perinatal outcomes in fetuses with ovarian cyst undergoing intra-uterine aspiration.



Resolution



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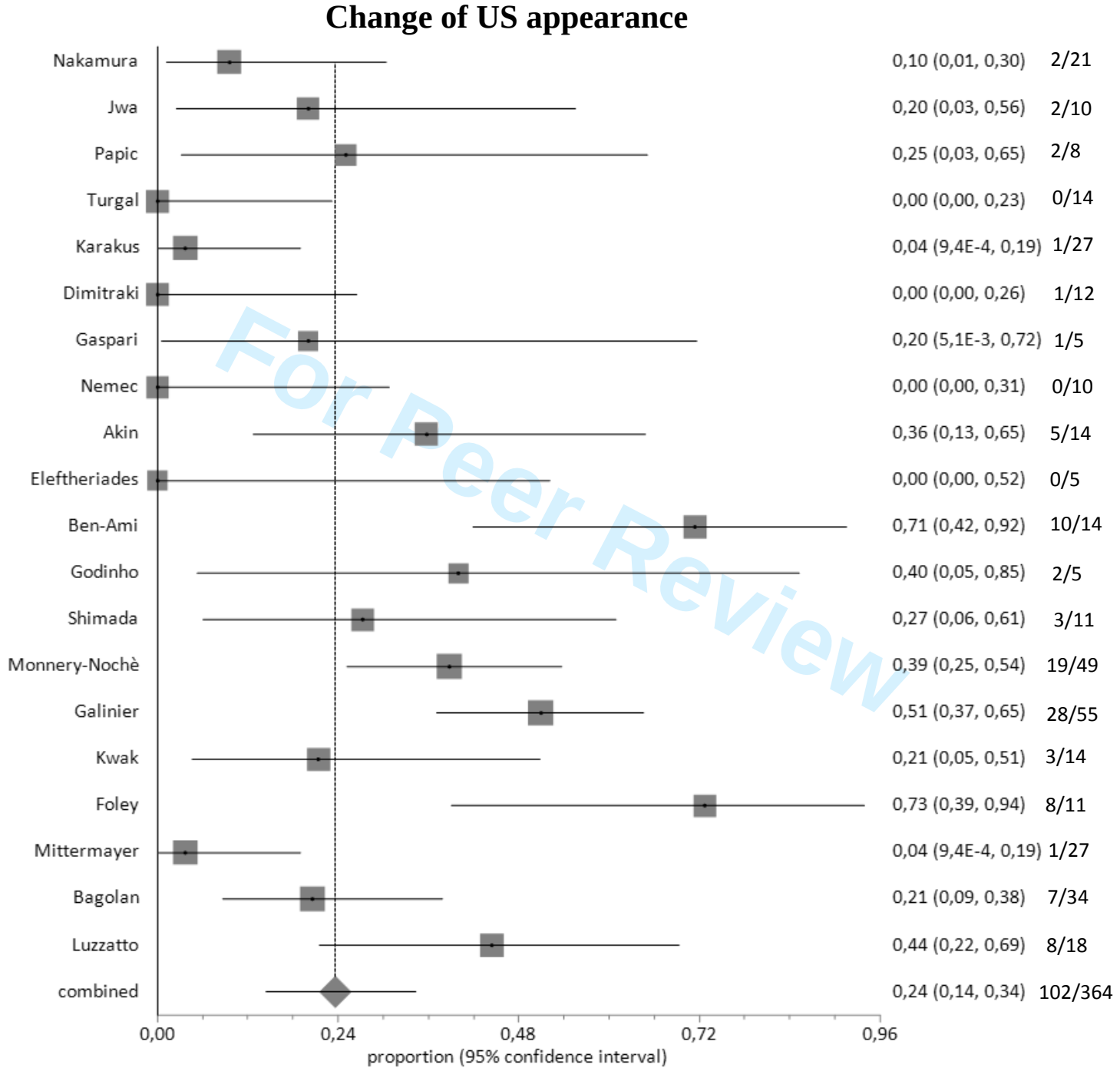

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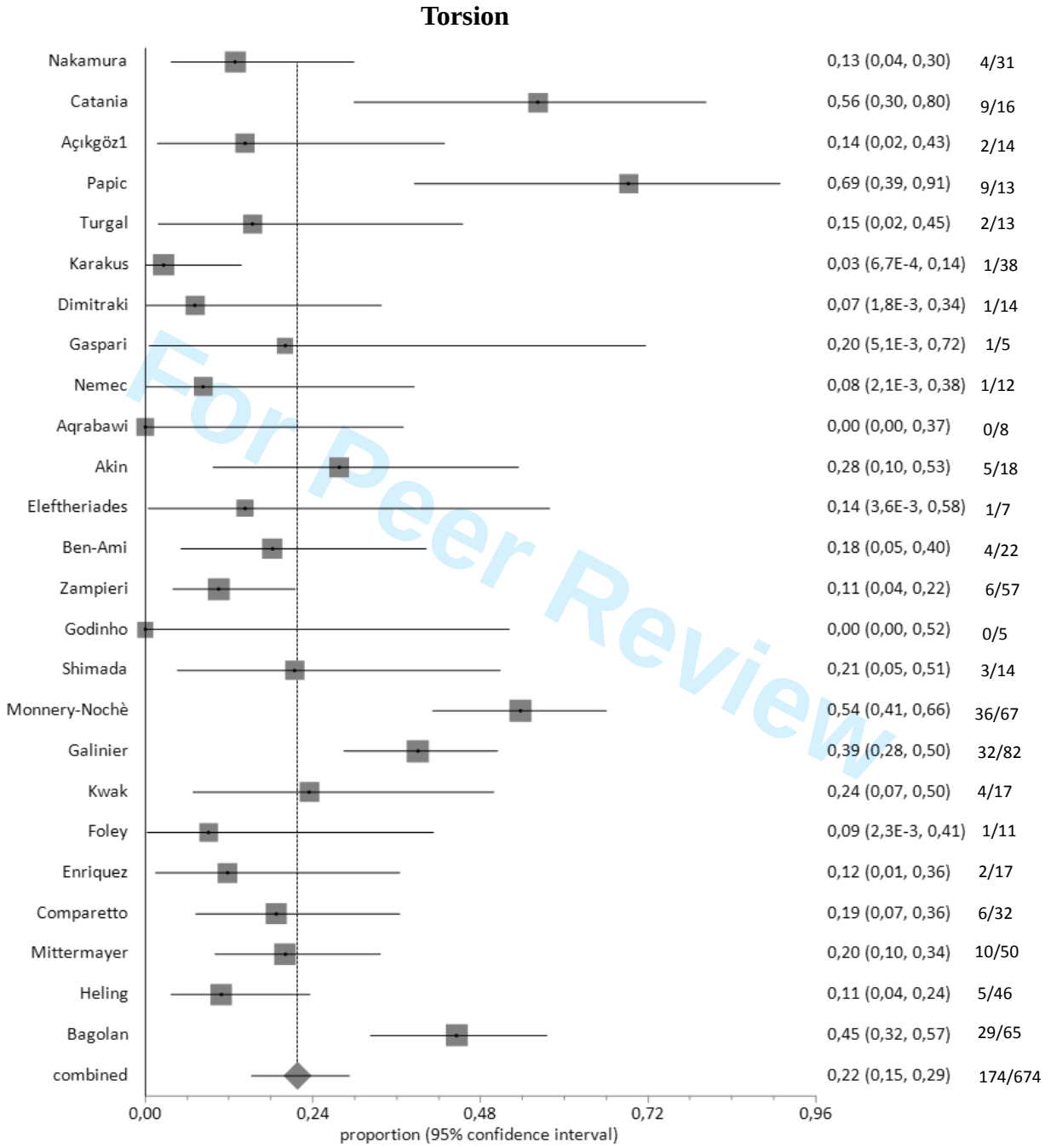

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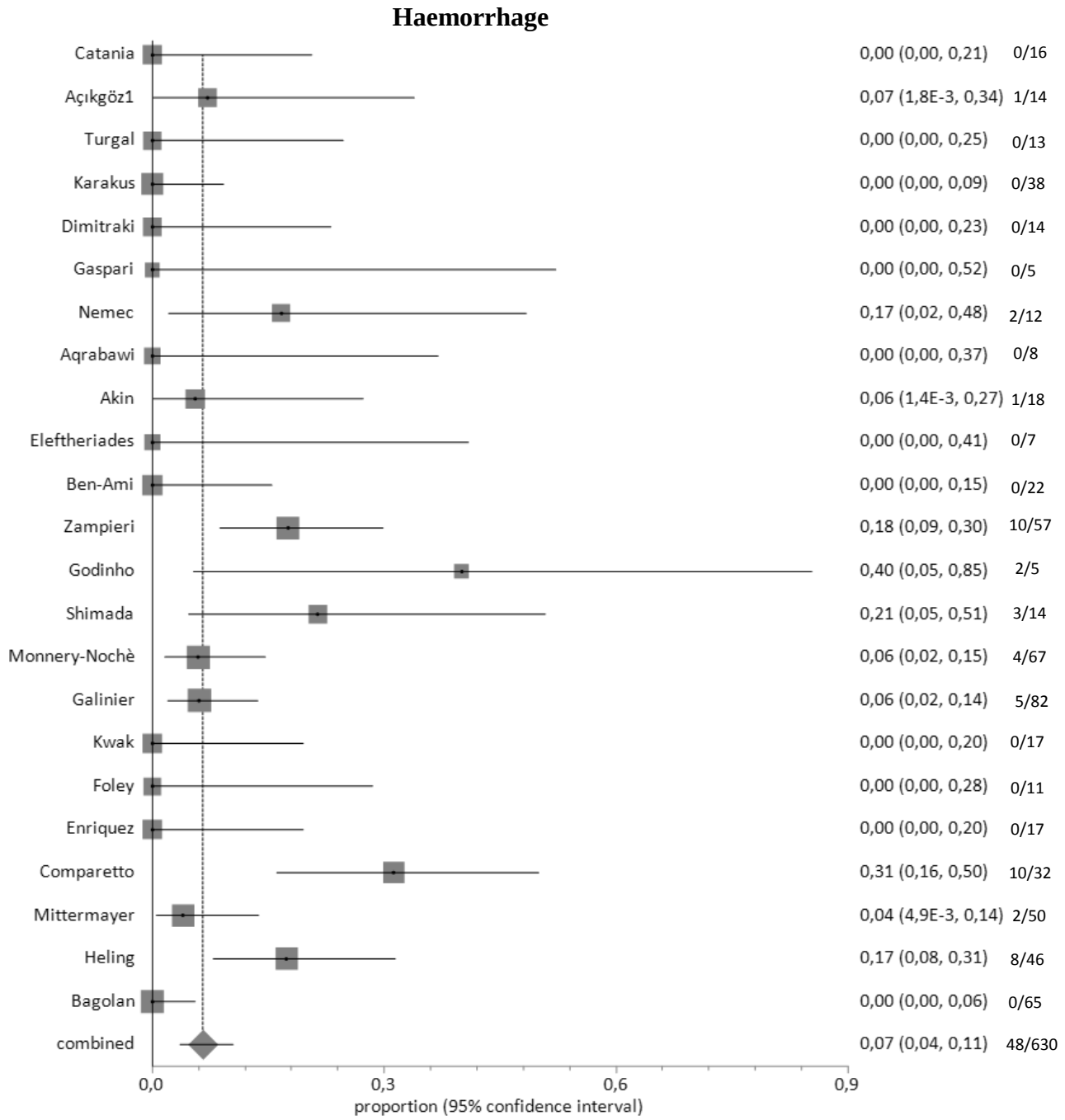
Haemorrhage
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Açıkgöz1
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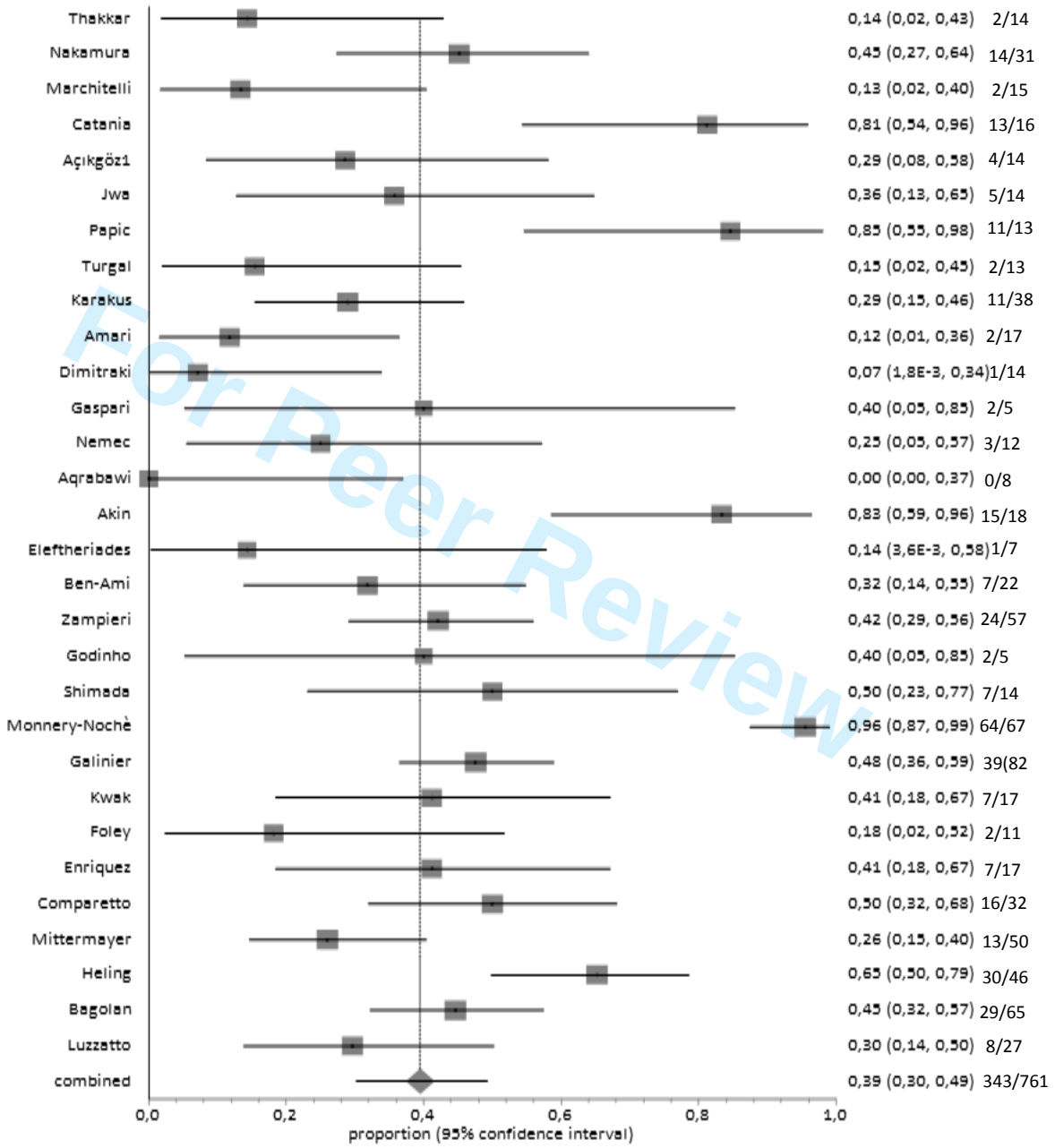
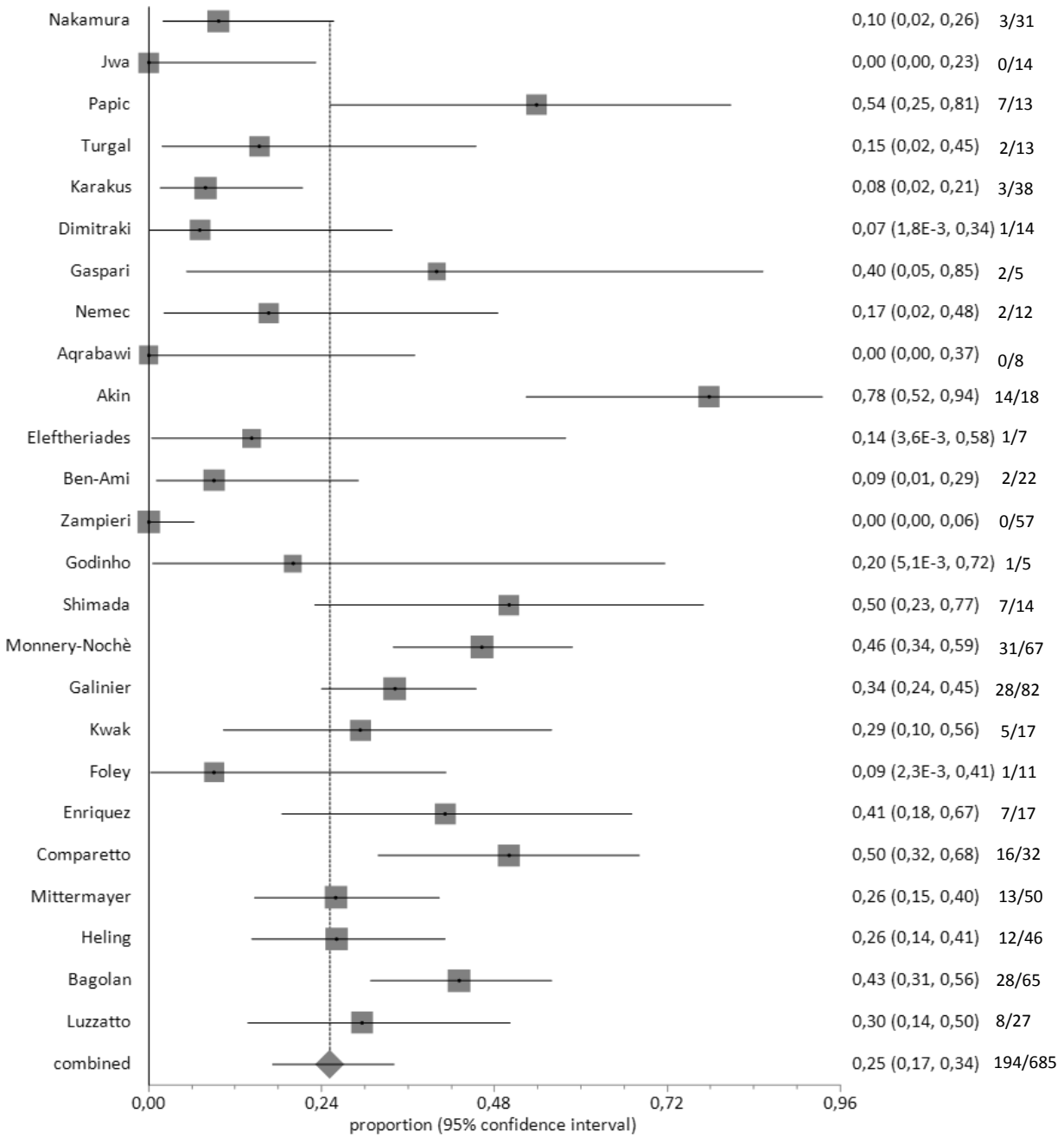
Karakus
Dimitraki
Gaspari
Nemec
Aqrabawi
Akin
Eleftheriades
Ben-Ami
Zampieri
Godinho
Shimada
Monnery-Nochè
Galinier
Kwak
Foley
Enriquez
Comparetto
Mittermayer
Heling
Bagolan
combined
0,00 (0,00, 0,21) 0/16
0,07 (1,8E-3, 0,34) 1/14
0,00 (0,00, 0,25) 0/13
0,00 (0,00, 0,09) 0/38
0,00 (0,00, 0,23) 0/14
0,00 (0,00, 0,52) 0/5
0,17 (0,02, 0,48) 2/12
0,00 (0,00, 0,37) 0/8
0,06 (1,4E-3, 0,27) 1/18
0,00 (0,00, 0,41) 0/7
0,00 (0,00, 0,15) 0/22
0,18 (0,09, 0,30) 10/57
0,40 (0,05, 0,85) 2/5
0,21 (0,05, 0,51) 3/14
0,06 (0,02, 0,15) 4/67
0,06 (0,02, 0,14) 5/82
0,00 (0,00, 0,20) 0/17
0,00 (0,00, 0,28) 0/11
0,00 (0,00, 0,20) 0/17
0,31 (0,16, 0,50) 10/32
0,04 (4,9E-3, 0,14) 2/50
0,17 (0,08, 0,31) 8/46
0,00 (0,00, 0,06) 0/65
0,07 (0,04, 0,11) 48/630
0,0
0,3
0,6
0,9
proportion (95% confidence interval)

3b

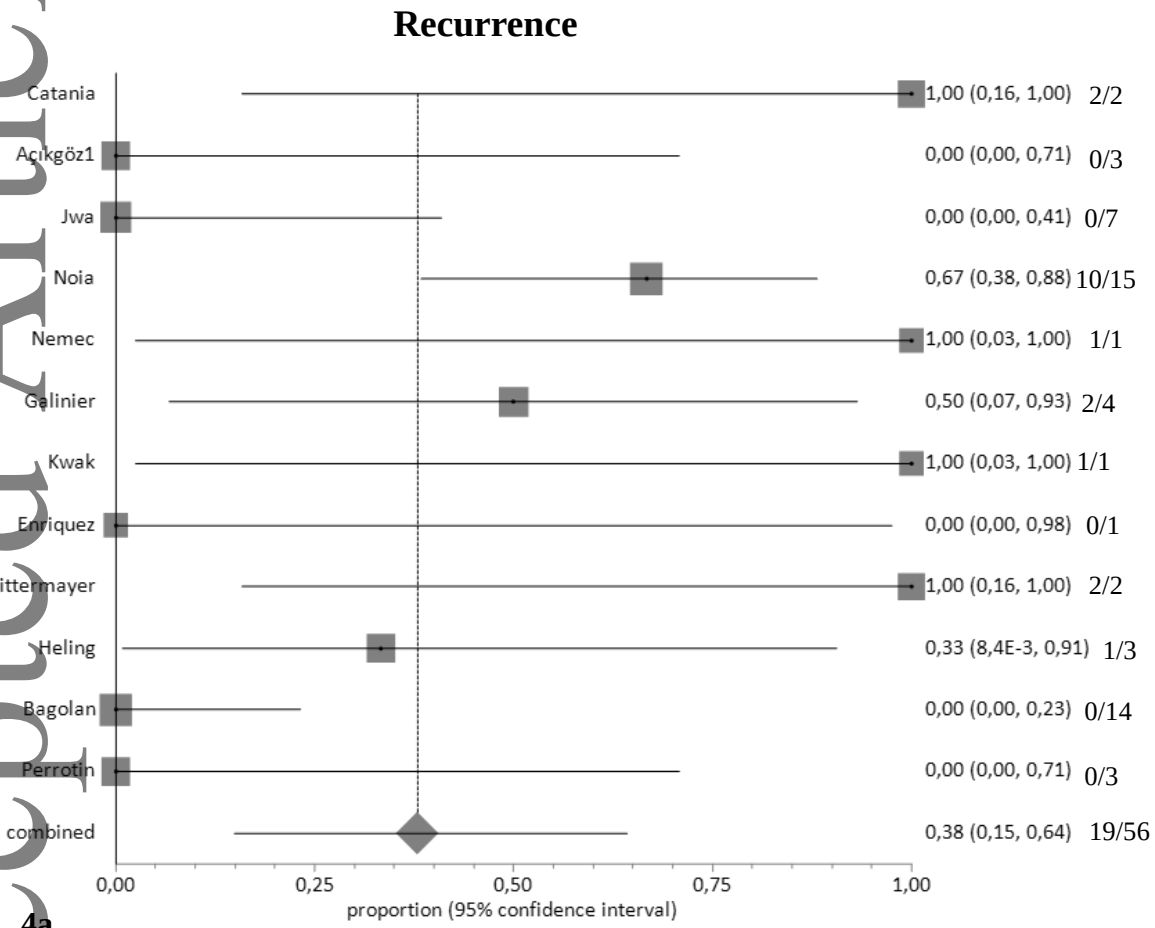
Surgery



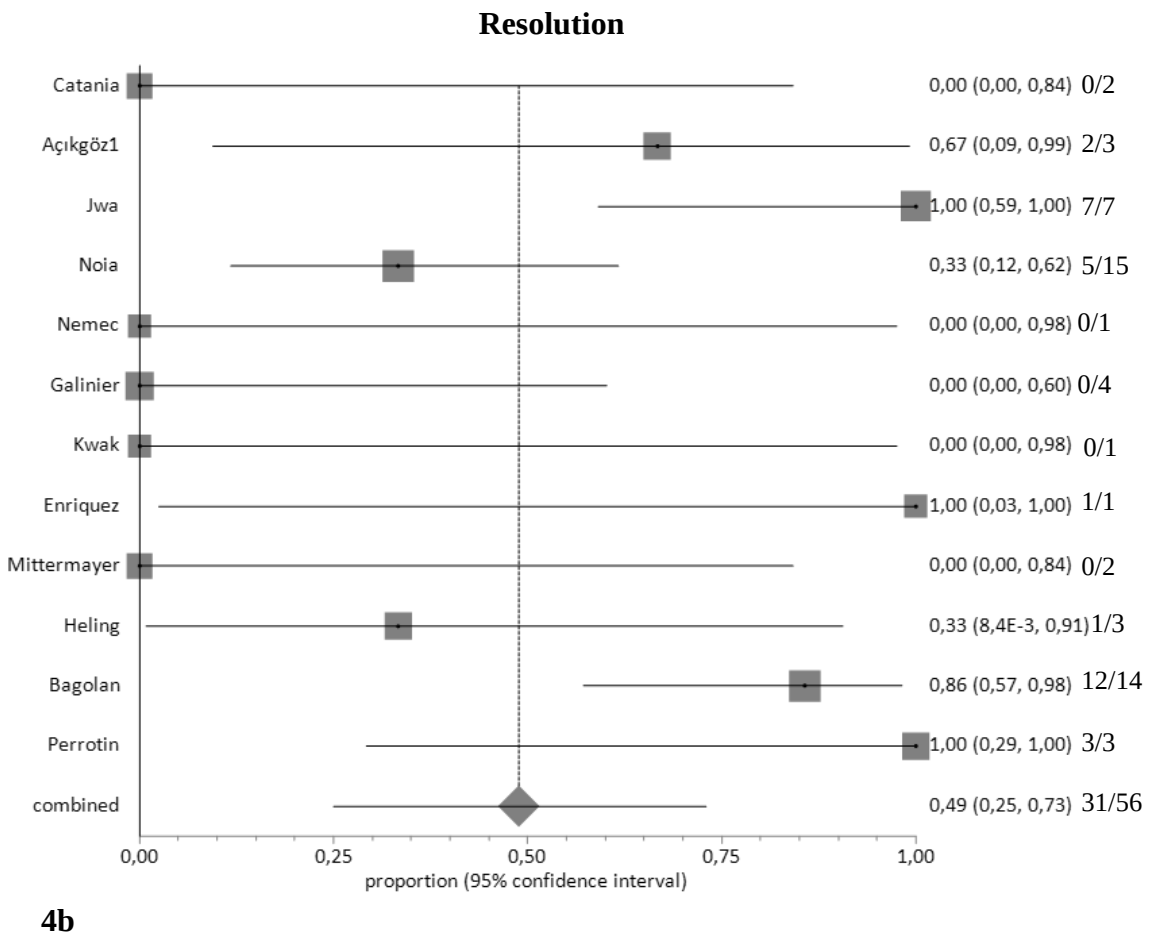
3c


Ovarian loss
Nakamura 0,10 (0,02, 0,26) 3/31
Jwa 0,00 (0,00, 0,23) 0/14
Papic 0,54 (0,25, 0,81) 7/13
Turgal 0,15 (0,02, 0,45) 2/13
Karakus 0,08 (0,02, 0,21) 3/38
Dimitraki 0,07 (1,8E-3, 0,34) 1/14
Gaspari 0,40 (0,05, 0,85) 2/5
Nemec 0,17 (0,02, 0,48) 2/12
Aqrabawi 0,00 (0,00, 0,37) 0/8
Akin 0,78 (0,52, 0,94) 14/18
Eleftheriades 0,14 (3,6E-3, 0,58) 1/7
Ben-Ami 0,09 (0,01, 0,29) 2/22
Zampieri 0,00 (0,00, 0,06) 0/57
Godinho 0,20 (5,1E-3, 0,72) 1/5
Shimada 0,50 (0,23, 0,77) 7/14
Monnery-Nochè 0,46 (0,34, 0,59) 31/67
Galinier 0,34 (0,24, 0,45) 28/82
Kwak 0,29 (0,10, 0,56) 5/17
Foley 0,09 (2,3E-3, 0,41) 1/11
Enriquez 0,41 (0,18, 0,67) 7/17
Comparetto 0,50 (0,32, 0,68) 16/32
Mittermayer 0,26 (0,15, 0,40) 13/50
Heling 0,26 (0,14, 0,41) 12/46
Bagolan 0,43 (0,31, 0,56) 28/65
Luzzatto 0,30 (0,14, 0,50) 8/27
combined 0,25 (0,17, 0,34) 194/685
0,00
0,24
0,48
0,72
0,96
proportion (95% confidence interval)

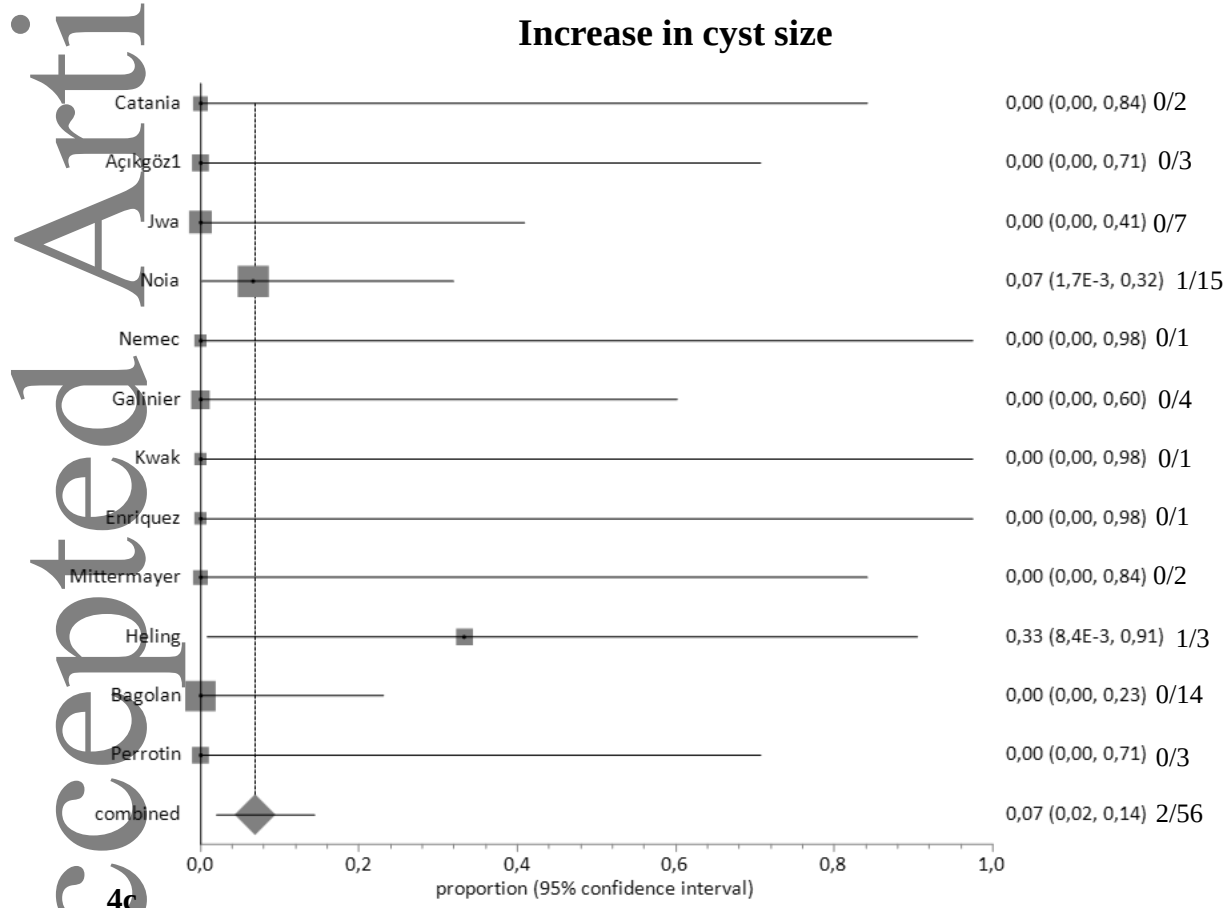
3d



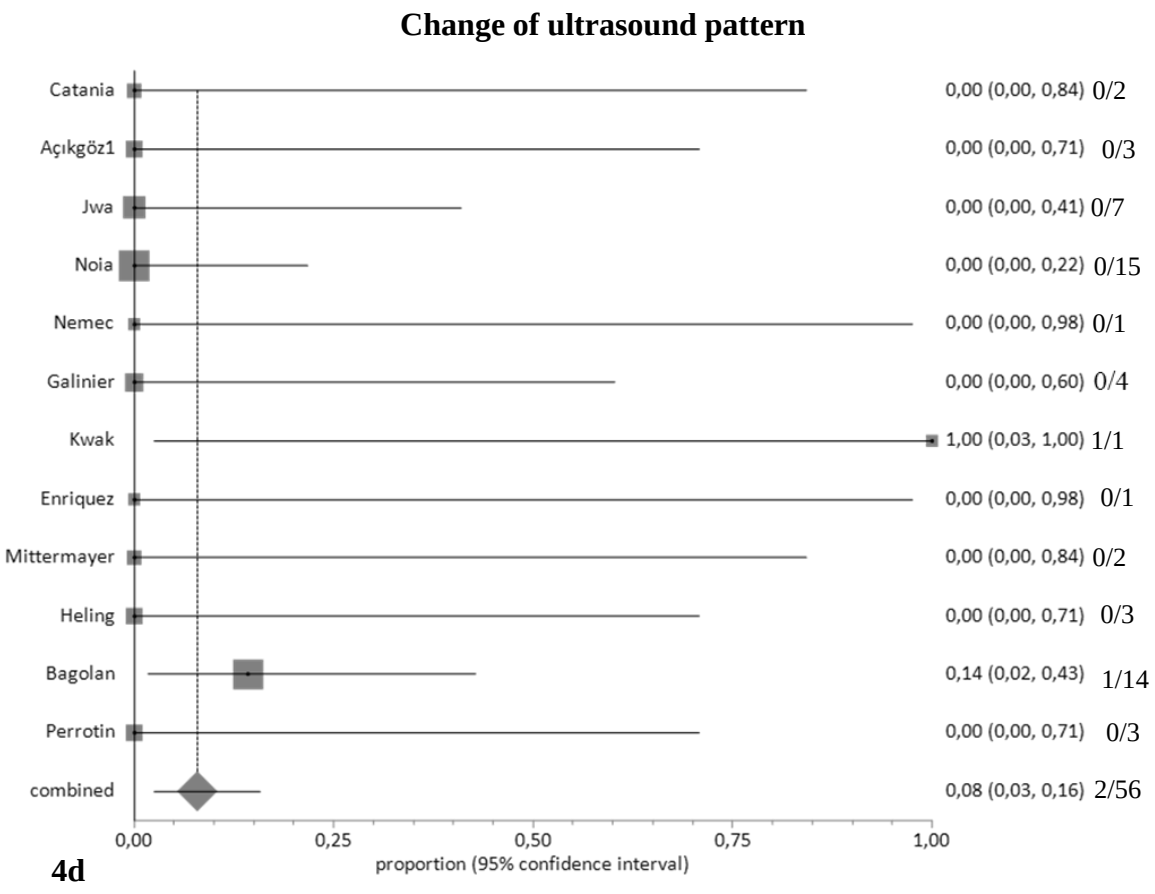
4a



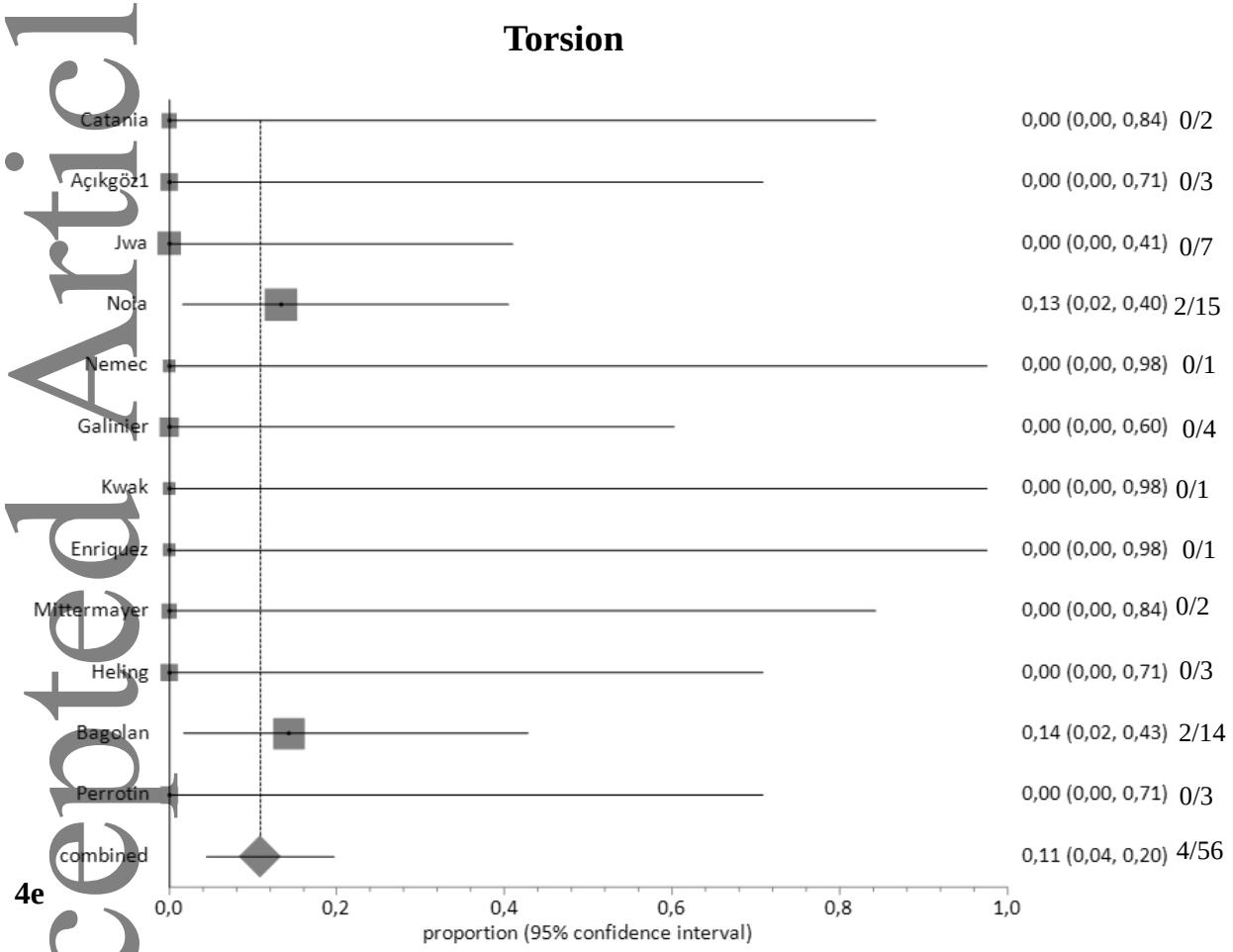
4b



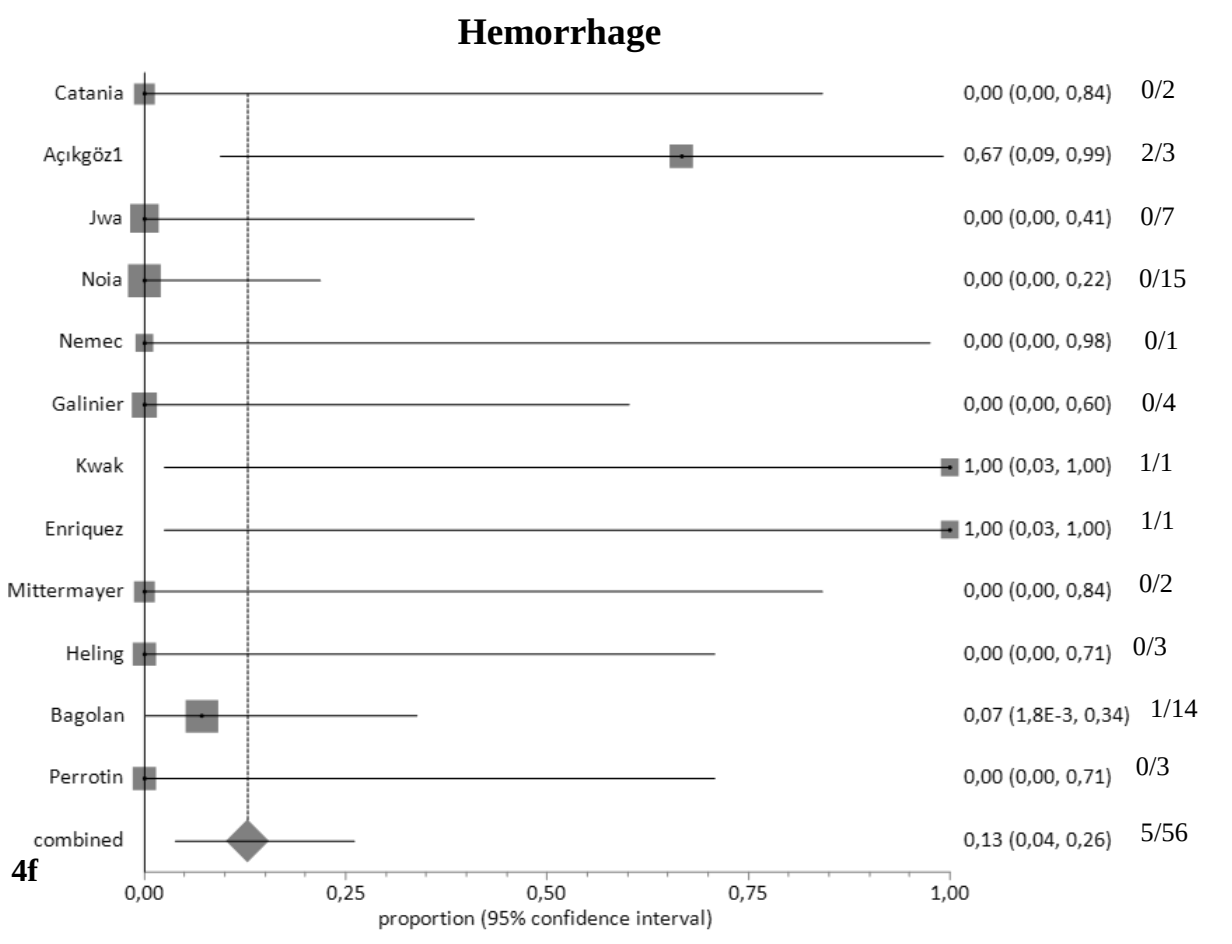
4c



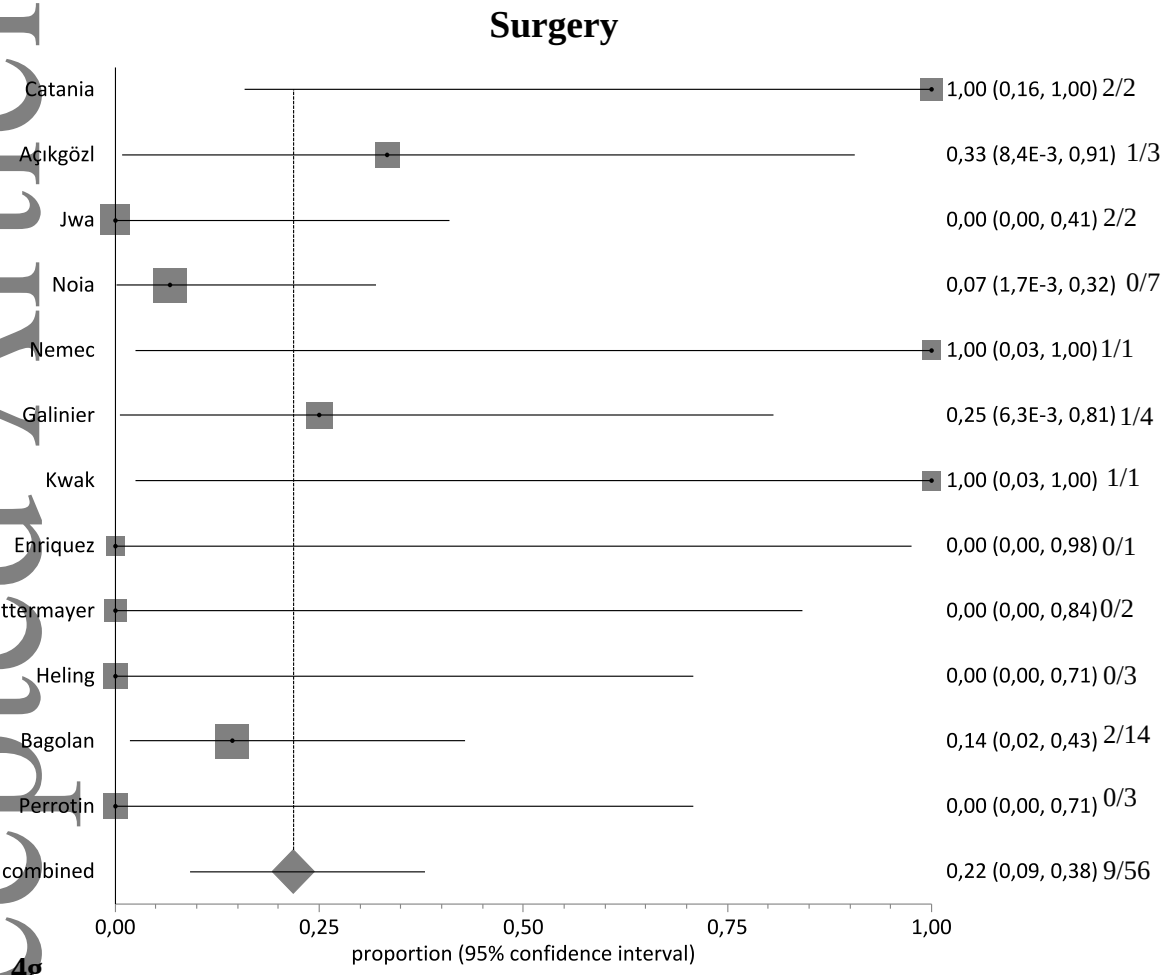
4d



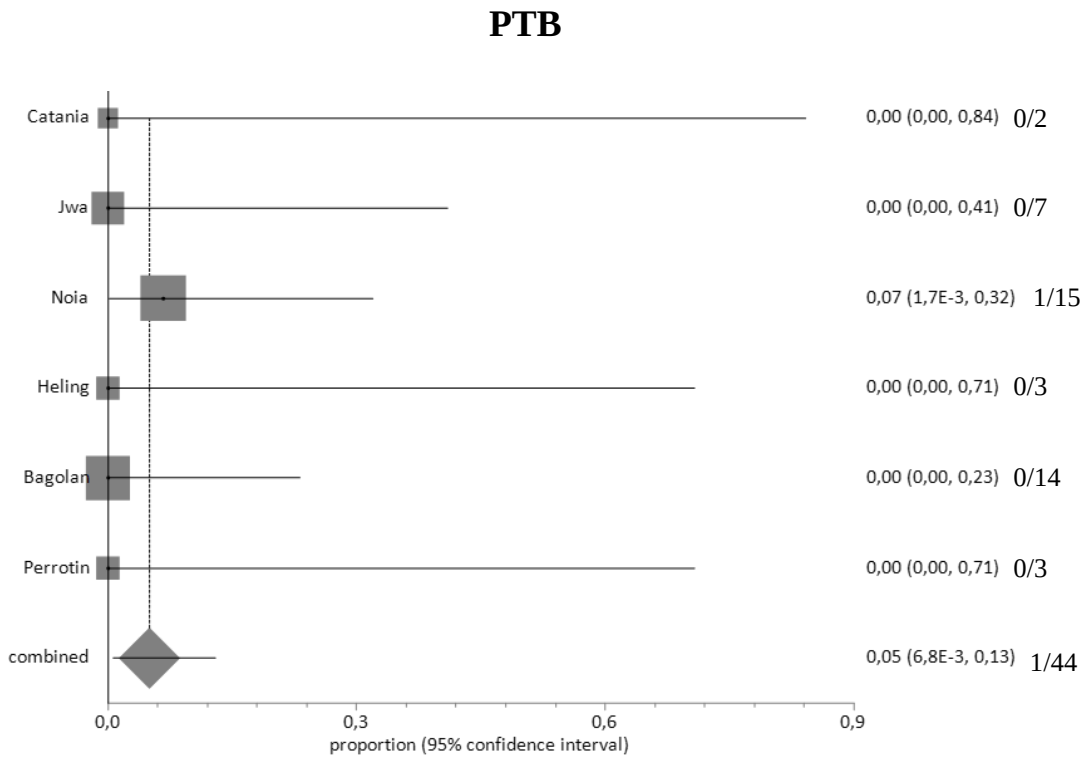
4e



4f



4g



4h