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ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

COMPARATIVE SAFETY AND EFFICACY OF PARACETAMOL VERSUS NON-STEROIDAL ANTI-INFLAMMATORY AGENTS IN NEONATES WITH PATENT DUCTUS ARTERIOSUS: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

ΣΥΓΚΡΙΤΙΚΗ ΑΣΦΑΛΕΙΑ ΚΑΙ ΑΠΟΤΕΛΕΣΜΑΤΙΚΟΤΗΤΑ ΤΗΣ ΠΑΡΑΚΕΤΑΜΟΛΗΣ ΕΝΑΝΤΙ ΤΩΝ ΜΗ ΣΤΕΡΟΕΙΔΩΝ ΑΝΤΙΦΛΕΓΜΟΝΩΔΩΝ ΠΑΡΑΓΟΝΤΩΝ ΣΕ ΝΕΟΓΝΑ ΜΕ ΑΝΟΙΧΤΟ ΒΟΤΑΛΕΙΟ ΠΟΡΟ: ΜΙΑ ΣΥΣΤΗΜΑΤΙΚΗ ΑΝΑΣΚΟΠΗΣΗ ΚΑΙ ΜΕΤΑ-ΑΝΑΛΥΣΗ ΤΥΧΑΙΟΠΟΙΗΜΕΝΩΝ ΚΛΙΝΙΚΩΝ ΜΕΛΕΤΩΝ

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Abstract

Introduction: Ibuprofen and indomethacin are the preferred drug treatment for patent ductus arteriosus (PDA) in preterm neonates. The comparative safety and efficacy of paracetamol as an alternative has not yet been well-established.

Objectives: To define the comparative efficacy and safety of paracetamol versus ibuprofen and indomethacin for PDA.

Methods: We performed a systematic literature search in Pubmed, Scopus and Cochrane databases on randomized controlled trials comparing the efficacy and/or the safety of paracetamol versus ibuprofen and/or indomethacin and meta-analyzed the available data.

Results: There were 1718 neonates from 20 eligible studies. Paracetamol did not differ from ibuprofen or indomethacin regarding the primary [OR: 0.933 (95% CI: 0.691-1.260), p-value: 0.650, when compared to ibuprofen, and OR: 0.777 (95% CI: 0.200-3.023), p-value: 0.716, when compared to indomethacin] and overall [OR: 1.166 (95% CI: 0.818-1.662), p-value: 0.394, when compared to ibuprofen, and OR: 1.120 (95% CI: 0.584-2.147), p-value: 0.733, when compared to indomethacin] PDA closure rates. Paracetamol resulted in significantly reduced risk of oliguria and a tendency towards less gastrointestinal bleeding.

Conclusion: There was no significant difference between paracetamol and ibuprofen or indomethacin in the PDA closure rates. However, paracetamol caused less adverse effects.

Keywords: paracetamol; acetaminophen; ibuprofen; indomethacin; patent ductus arteriosus

Περίληψη

Εισαγωγή: Η ιβουπροφαίνη και η ινδομεθακίνη αποτελούν την προτιμώμενη φαρμακευτική θεραπεία για τον ανοιχτό βοτάλειο πόρο σε πρόωρα νεογνά. Η συγκριτική ασφάλεια και αποτελεσματικότητα της παρακεταμόλης ως εναλλακτική θεραπεία δεν είανι ακόμη σαφώς καθορισμένη.

Στόχοι: Να καθοριστεί η συγκριτική ασφάλεια και αποτελεσματικότητα της παρακεταμόλης έναντι της ιβουπροφαίνης και της ινδομεθακίνης όταν δίδεται για την σύγκλειση του ανοιχτού βοτάλειου πόρου.

Μέθοδοι: Πραγματοποιήσαμε συστηματική βιβλιογραφική αναζήτηση στις βάσεις δεδομένων Pubmed, Scopus και Cochrane για τυχαιοποιημένες κλινικές μελέτες που συνέκριναν την αποτελεσματικότητα ή/και την ασφάλεια της παρακεταμόλης έναντι της ιβουπροφαίνης ή/και της ινδομεθακίνης και μετα-αναλύσαμε τα δεδομένα.

Αποτελέσματα: Βρέθηκαν 1718 νεογνά από 20 τυχαιοποιημένες κλινικές μελέτες. Η παρακεταμόλη δεν διέφερε σε βαθμό στατιστικά σημαντικό από την ιβουπροφαίνη ή την ινδομεθακίνη όσον αφορά στον ρυθμό σύγκλεισης πρωτογενώς [OR: 0.933 (95% CI: 0.691-1.260), p-value: 0.650, σε σύγκριση με την ιβουπροφαίνη, και OR: 0.777 (95% CI: 0.200-3.023), p-value: 0.716, σε σύγκριση με την ινδομεθακίνη] ή συνολικά [OR: 1.166 (95% CI: 0.818-1.662), p-value: 0.394, σε σύγκριση με την ιβουπροφαίνη, και OR: 1.120 (95% CI: 0.584-2.147), p-value: 0.733, σε σύγκριση με την ινδομεθακίνη] του ανοιχτού βοτάλειου πόρου. Η χρήση παρακεταμόλης συνοδεύτηκε από σημαντικά μειωμένο αριθμό περιπτώσεων ολιγουρίας και από τάση για μειωμένο αριθμό γαστρεντερικών αιμορραγιών.

Συμπέρασμα: Δεν υπήρχε σημαντική διαφορά όσον αφορά στην αποτελεσματικότητα μεταξύ παρακεταμόλης και ιβουπροφαίνης ή ινδομεθακίνης για την σύγκλειση ανοιχτού βοτάλειου πόρου σε νεογνά. Εντούτοις, η χορήγηση παρακεταμόλης συνοδεύτηκε από λιγότερες ανεπιθύμητες ενέργειες.

Λέξεις κλειδιά: παρακεταμόλη, ακεταμινοφαίνη, ιβουπροφαίνη, ινδομεθακίνη, ανοιχτός βοτάλειος πόρος

Introduction

Ductus arteriosus functionally closes by the 3rd postnatal day in term neonates (1). Gestational age (GA) is inversely correlated with time to ductus closure, remaining patent in the 7th postnatal day in 2%, 65% and 87% of neonates born at 30-37 weeks GA, 25-28 weeks GA and 24th week GA, respectively (2). Patent ductus arteriosus (PDA) constitutes a common cardiovascular problem of prematurity that may lead to pulmonary overcirculation, respiratory distress and increased risk of bronchopulmonary dysplasia (BPD) (3,4).

Non-steroidal anti-inflammatory drugs (NSAIDs) ibuprofen and indomethacin have been used for pharmacological treatment for closure of PDA (5). These agents act on the cyclo-oxygenase cycle, inducing vasoconstriction. On the other hand, this drug-induced vasoconstriction may cause side effects such as renal failure, hepatic failure, necrotizing enterocolitis (NEC) and cerebral hypoperfusion (6). Based on the hypothesis that a big proportion of PDA close spontaneously within a few days, pharmacological therapy tends to be indicated only in hemodynamically significant PDA (hsPDA) defined by clinical and echocardiographic criteria (7,8).

The last decade there has been great interest in the use of paracetamol as an alternative pharmacological agent, which does not interfere with the cyclo-oxygenase cycle and, therefore has a better safety profile when compared to NSAIDs (9).We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) to investigate the safety and efficacy of paracetamol versus NSAIDs in neonates with PDA.

Methods

The methods and the results of this study were carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (PRISMA) (10). The review protocol has been registered to PROSPERO (International Prospective Register of Systematic Reviews) with Identifier (ID) Number: CRD42021270157 (11).

Search strategy

We conducted a systematic search in Medline/Pubmed, Scopus and Cochrane Central Register of Controlled Trials databases using the PICO tool (Patient, Intervention, Comparison, Outcome) (Table 1) (12,13). The keywords were performed through evaluation of the Medical Subject Headings (MeSH): patent ductus arteriosus, paracetamol, acetaminophen, ibuprofen, indomethacin, anti-inflammatory agents, non-steroidal, placebo, safety, efficacy, closure, re-opening, recurrence, liver failure, renal failure, gastrointestinal perforation, gastrointestinal bleeding, bleeding, effective*. The references of systematic reviews and meta-analyses on the same subject, yielded by our search, (labeled as other sources) were also screened for eligible

records. The PICO tool could be used for searching Cochrane systematic reviews only. Specific search strategies can be found in the Appendix Table 1. The search was completed on July21st, 2021.

Eligibility criteria

We considered all RCTs with published full-text articles in English, in which paracetamol was used in the intervention arm for ductal closure in neonates with hemodynamically significant PDA and ibuprofen and/or indomethacin were used in the comparator arm irrespective of dose or route of administration. Studies comparing the efficacy and/or the safety of the above agents were considered. We excluded studies other than RCTs, as well as studies published in languages other than English (Table 2).

Study selection

Two reviewers (G.K. and D.K.) independently screened the literature according to the aforementioned search strategy. Assessment for duplicates was done manually and the remaining records were screened on the basis of their title and abstract using a form with pre-specified fields. Where an abstract was not available, the full-text was assessed for inclusion/exclusion criteria. Finally, full-text read of the remaining records was done to assess for eligibility. When an electronic copy of the record could not be found we contacted the authors via e-mail. We considered for analysis all studies deemed eligible by at least one of the reviewers.

Data extraction

Data extraction was done independently by G.K. and D.K. and any discrepancies were resolved by a third reviewer (V.C.). For all studies, we extracted the following data: the name of the first author, year of publication, country where the study was conducted, the population size, the mean gestational age, the mean birth weight, criteria of PDA severity, the dosage and route of administration of the intervention drug and the comparator drugs and outcome measures.

Risk of bias assessment

In order to assess the risk of bias (methodological quality) of each study included in the review we used the revised Cochrane risk-of-bias tool for randomized trials (RoB2) (14). A fixed set of domains of bias (bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, bias in selection of the reported result) focusing on different aspects of trial design, conduct, and reporting were assessed. Two independent reviewers (G.K. and D.K.) evaluated the included articles and any discrepancies were resolved by a third reviewer (V.C.).

Data analysis

A systematic review was undertaken for the studies that were regarded as eligible according to the inclusion and exclusion criteria. In addition, we performed a meta-analysis using the studies that provided adequate data for statistical comparison ($\geq$ 2 effect sizes for each outcome). The

relative ratios (ORs) were calculated along with the 95% confidence intervals (95% CIs) to assess the comparative safety and efficacy of paracetamol (15). To assess the statistical significance of pooled ORs we performed Z-test. The meta-analysis was performed using the STATA 13 statistical software (16).

The main analysis, along with the pre-specified sub-group analyses, was performed using the Random Effect Model due to the intrinsic heterogeneity of the studies, the large number of studies included and the aim of our meta-analysis which was to generalize the results beyond the included studies (17). Outcomes with zero events in both arms were excluded from the meta-analysis, while a fixed value (0.5) was added in outcomes where zero events were reported only in one arm. The I^2 test was used to assess statistical heterogeneity between the analyzed studies (significance level: $P \leq 0.1$). The I^2 statistic was applied with the following interpretation: for I^2<50%, low heterogeneity; 50–75%, moderate heterogeneity; and >75%, high heterogeneity (18).

Sub-group analyses according to route of drug administration, GA (< 28 and ≥28 weeks mean GA), and body weight (BW) (<1000 gr, 1000-1500 gr, and 1501-2.500 gr) took place in order to assess for any confounding effect of participants' characteristics or route of administration on the effect size of the efficacy outcomes (primary and overall PDA closure). We did not perform sub-group analyses on the safety outcomes given the small event numbers resulting from study heterogeneity regarding the safety outcomes included and the safety outcomes definitions and measures. We also performed sensitivity analysis by excluding studies where the RoB2 yielded a result different from low risk of bias to assess the stability of our results. We only performed sensitivity analysis for the primary and overall PDA closure for the same reason as the one considered above for the sub-group analyses. Additionally, in order to further explore the source of studies heterogeneity (when I^2> 75%), we used Galbraith plot(19,20). Publication bias was assessed when ≥10 studies were available, using Funnel plots and the Egger's and Begg's tests, where a p-value of <0.05 was considered indicative of statistically significant publication bias(21,22). Strength of evidence assessment was conducted using the GRADE reporting system (Grading of Recommendations Assessment Development and Evaluation System)(23).

Results

Search results

The initial total search results per database and other sources (9,24–30) are shown in Figure 1. After the removal of 206 duplicates, 277 studies were screened per Title and Abstract (Figure 2). A total of 31 studies qualified for assessment of eligibility. Finally, 11 studies (5,31-40) were excluded according to the exclusion criteria (Appendix Table 2), while 20 RCTs (41-60) were found eligible for qualitative and quantitative analysis including 1718 randomized

neonates (802 neonates on paracetamol, 722 neonates on ibuprofen and 194 neonates on indomethacin).

Study Characteristics

The majority of the studies (15 of 20) were conducted in Asia (41-45,47,51-58,60), 2 studies (49,50) were conducted in Egypt regarding Africa, 2 studies (48,59) in USA regarding the Americas and one study (46) in Italy regarding Europe. All studies included premature neonates with moderate to severe PDA (Table 3).

With regards to the route of administration of the intervention drug, in 12 studies (41-45,47,49,51,54,56,57,60) paracetamol was administered orally, while in 8 studies (46,48,50,52,53,55,58,59) intravenously (Table 3). In 12 studies (43,46,48-50,53-57,59,60) the dosage of paracetamol was 15mg/kg/6h for 3 days, in 4 studies (44,51,52,58) 15mg/kg/6h for 2 days, in 3 studies (41,42,45) 10mg/kg/6h for 3 days, and in one study (47) 15mg/kg/6h for 7 days (Table 3).

As far as the comparison drugs were concerned, in 14 studies (41-45,49,51,52,54–58,60) ibuprofen was administered orally and in 4 studies (46,50,53,59) intravenously, while in 3 studies (47,48,50) indomethacin was administered intravenously and in one study (55) orally (Table 3). The dosage of ibuprofen was 10mg/kg the first day followed by 5mg/kg for 2 days in 16 studies (42,44-46,49–60), 20mg/kg the first day followed by 10mg/kg for 2 days in one study (43), while in one study (41) both the aforementioned dosages were used (Table 3). The dosage of indomethacin was 0.2mg/kg/12h for 3 doses in one study (50), 0.2mg/kg/24h for 3-5 days in one study (47), 0.2mg/kg/12h for 3 doses or 0.2mg/kg the 1st dose followed by 2 doses of 0.25mg/kg/12h in one study (48), and starting dose of 0.2 mg/kg followed by 0.1 mg/kg for babies <2 days of age, 0.2 mg/kg for 2–7 postnatal days, and 0.25 mg/kg for >7 postnatal days (3 doses at 12 hourly intervals) in one study (55) (Table 3).

Risk of Bias Assessment

For the included RCTs, the results of the risk-of-bias assessment tool are presented in Figures 3 and 4. Some concerns were raised mainly in the "Bias arising from the randomization process" domain due to the fact that, even if the risk was low regarding the allocation sequence in all the included RCTs, in some cases, not enough information was reported on the concealment of allocation sequence process, affecting the overall risk of bias assessment (46,52,55,58–60).

Outcome measures

The efficacy outcomes assessed were primary and overall (following a second course of the same drug) PDA closure, along with PDA constriction and recurrence rate (Table 4). The binary safety outcomes assessed are presented in Table 5, where it is evident that there is a great heterogeneity regarding the selection and reporting of adverse effects. The provided definitions of the efficacy and safety outcomes from the included studies are shown in the Appendix. There

were 37 different safety outcomes assessed additively in different studies along with a significant variability in definitions. For example, 7 studies (41,44,45,47,50,53,60) reported on intraventricular haemorrhage (IVH), 4 studies (41,45,48,54) reported on IVH grade III/IV, one study (56) reported on change in IVH grade and one study (47) reported on IVH all grades and periventricular leukomalacia. In another example, the effect in renal function was expressed in a dichotomous way as renal impairment in 2 records (44,47), renal failure in one record (45), oliguria in 4 records (42,45,54,60), azotemia in one record (54) while in 6 records (42,49,50,55,56,58) the investigators reported on continuous creatinine or blood urea nitrogen (BUN) values.

In almost all studies, follow-up was limited, carried out usually until discharge, but in one study, Oncel et al. (57) followed up the neonates for 18 to 24 months' corrected age to assess for long-term neurodevelopmental outcomes.

Results of Meta-analysis

Paracetamol vs. Ibuprofen

When paracetamol was compared to ibuprofen, 40 out of 41 outcomes were reported, including the 4 efficacy outcomes and 36 safety outcomes (Table 6). In Appendix, the relevant Forest and Funnel plots are shown (Figures 1 to 26). While the results of the study showed no significant differences in the pooled results of the efficacy outcomes, in the subgroup analysis, paracetamol in neonates <1000 gr was shown in one study (49) to be more effective when compared to ibuprofen as assessed by the overall PDA closure [OR: 3.500 (95% CI: 1.111-11.028), p-value = 0.032]. What is more, neonates that received paracetamol were shown to have reduced odds for oliguria [OR: 0.514 (95% CI: 0.272-0.973), p-value: 0.041], while in one study (44) paracetamol was found to cause less renal impairment [OR: 0.270 (95% CI: 0.090-0.800), p-value: 0.019] and in another study (45) paracetamol use resulted in lower risk of hyperbilirubinemia [OR: 0.460 (95% CI: 0.226-0.935), p-value: 0.032] when compared to ibuprofen. There was also a tendency towards less gastrointestinal (GI) bleeding in the paracetamol group, but this did not reach statistical significance [OR: 0.453 (95% CI: 0.174-1.174), p-value: 0.103].

Paracetamol vs. Indomethacin

When paracetamol was compared to Indomethacin, 15 out of 41 outcomes were reported, including 2 efficacy outcomes and 13 safety outcomes (Table 6). In Appendix, the relevant Forest and Galbraith plots are shown (Figures 27 to 39). According to the analysis, there were no significant differences between paracetamol and indomethacin in the analyzed outcomes. There was a tendency towards less NEC in the paracetamol group, but this did not reach statistical significance [OR: 0.440 (95% CI: 0.183-1.058), p-value: 0.067].

Strength of Evidence GRADE reporting system

The results of the quality of evidence assessment regarding the comparison of paracetamol vs ibuprofen are shown in Appendix Table 3. The following outcomes were judged to be of "High" strength of evidence: primary PDA closure, overall PDA closure, oliguria, and hyperbilirubinemia. The following outcomes were judged to be of "Moderate" strength of evidence: mortality, sepsis, NEC, retinopathy of prematurity (ROP), IVH, IVH grade III/IV, renal impairment, and GI bleeding.

The results of the quality of evidence assessment regarding the comparison of paracetamol vs indomethacin are shown in Appendix Table 4. The following outcomes were judged to be of "Moderate" strength of evidence: NEC and ROP.

Discussion

Traditionally, NSAIDs are the standard pharmacological therapy for PDA, but in the last decade they have become controversial because of their adverse effects and their inadequacy in the improvement of long term respiratory, neurodevelopmental, and mortality outcomes (61). The knowledge of the dilatation effect of prostaglandins E_1 and E_2 in the already constricted ductus arteriosus led Friedman et al. (62) in 1976 to use indomethacin as pharmacological therapy for the first time in 6 pre-term neonates with PDA. Their results showed 100% efficacy in PDA closure within 24 hours, with only transient reduction in renal function in 2 neonates. More recently, the deleterious cerebral effect of indomethacin urged Patel et al. (63) in 1995 to use an alternative prostaglandin synthesis inhibitor, ibuprofen, for the first time in 18 pre-term neonates and investigate its efficacy and safety regarding PDA closure and the reduction in cerebral blood volume (CBV), respectively, in comparison to indomethacin (15 pre-term neonates). They found no difference in the rate of PDA closure between the two NSAID agents, but a significant difference in the reduction of CBV was shown, suggesting that ibuprofen may be a safer pharmacological alternative for the treatment of PDA. Subsequently, the adverse effects, due to increased vasoconstriction, of both indomethacin and ibuprofen led Hammerman et al. (64) in 2011 to use for the first time paracetamol in 5 pre-term neonates with hsPDA. Ductal closure was achieved in all treated neonates with no side effects. Since then, lots of randomized and uncontrolled studies, as well as various meta-analyses have tried to clarify if paracetamol is more efficient and safer than NSAIDs in the treatment of PDA (9,24–30,65).

This systematic review and meta-analysis strengthens the evidence derived from previous meta-analyses comparing paracetamol versus non-steroidal anti-inflammatory agents for the treatment of hsPDA as it constitutes an update of previous meta-analyses encompassing recent RCTs investigating this comparison.

We were able to identify 3 dedicated systematic reviews comparing paracetamol with ibuprofen/indomethacin based on RCTs only by Das et al. (65), Huang et al. (24) and Escallon

et al. (30), comprising up to 6 RCTs. Terrinet al. (28) investigated this comparison on the basis of 2 RCTs and 14 uncontrolled studies, Mitra et al. (26) analyzed 5 RCTs, Ohlsson et al. (27) 6 RCTs, Marconi et al.(25) 10 RCTs, Pranata et al. (9) 8 RCTs and 2 uncontrolled studies and Xiao et al. (29) analyzed 11 RCTs comparing paracetamol with ibuprofen/indomethacin.

Our meta-analysis was based on 20 RCTs, reaching a number of 802 neonates on paracetamol and 1718 participants in total. To the best of our knowledge, this is the largest number of randomized participants meta-analyzed so far regarding direct comparison of paracetamol and non-steroidal anti-inflammatory agents for PDA closure in neonates. We opted to include only RCTs and exclude uncontrolled studies in order to reduce the risk of bias and improve the quality of the studies included in the systematic review and meta-analysis. The RoB2 was used to assess the risk of bias and this might have resulted in differences with previous assessments of the same studies, since previously, the criteria listed in the Cochrane Handbook were applied by the investigators to assess the risk of bias, as the revised version of RoB2 tool became available in August 2019 (14).

Previous meta-analyses (9,24–30,65) showed comparable efficacy between paracetamol and ibuprofen or indomethacin. In our study, there was no difference between paracetamol and ibuprofen or indomethacin in the primary [OR: 0.933 (95% CI: 0.691-1.260), p-value: 0.650, when compared to ibuprofen, and OR: 0.777 (95% CI: 0.200-3.023), p-value: 0.716, when compared to indomethacin] and overall [OR: 1.166 (95% CI: 0.818-1.662), p-value: 0.394, when compared to ibuprofen, and OR: 1.120 (95% CI: 0.584-2.147), p-value: 0.733, when compared to indomethacin] PDA closure rate regardless of the route of administration.

Sensitivity analysis performed excluding the studies where the risk of bias was deemed to be more than low was in agreement with the above results for both the primary and overall PDA closure rates and for both comparisons (paracetamol vs ibuprofen and paracetamol vs indomethacin, Table 6). Subgroup analysis did not show any difference between paracetamol and ibuprofen or indomethacin regarding the primary and overall PDA closure rates apart from the study of El-Farrash et al. (49) where ibuprofen was more effective in overall PDA closure in neonates with birth weight<1000gr.

Regarding comparison of safety outcomes, Marconi et al. (25) concluded that paracetamol reduces the risk of oliguria when compared to indomethacin. Das et al. (65) concluded that there was not enough evidence to draw inferences regarding the comparison of paracetamol and ibuprofen, even though in their results there was a lower risk for hyperbilirubinemia and a tendency towards less GI bleeding in the paracetamol group. Terin et al.(28) were in agreement with Das et al. (65) regarding the safety outcomes. Mora-Escallon et al.(30) found that paracetamol is related to a lower risk of GI bleeding but with a tendency for a higher incidence of ROP. Xiao et al. (29) found that paracetamol use resulted in a lower risk of hyperbilirubinemia and a lower percentage of GI bleeding when compared to ibuprofen, but

did not differ from indomethacin in terms of safety. Pranata et al.(9) and Huang et al.(24) concluded that the use of paracetamol carried a lower risk for renal dysfunction and GI bleeding when compared to ibuprofen. Finally, a recent Cochrane review (27) showed that paracetamol carries a lower risk for GI bleeding or stools positive for occult blood (OB) when compared to ibuprofen and is related to lower serum or plasma levels of creatinine, higher urine output and higher platelet counts when compared to ibuprofen or indomethacin. In our study, we confirmed the favorable profile of paracetamol regarding renal function, but we did not establish a statistical significance regarding GI bleeding. Moreover, we did not find any difference between paracetamol and ibuprofen with regards to ROP [OR: 0.900 (95% CI: 0.538-1.505), p-value: 0.687] or ROP requiring treatment [OR: 0.948 (95% CI: 0.411-2.186), p-value: 0.900].

Limitations

This study has several limitations. First, the included studies had variations in the baseline characteristics of the study population. The difference in mode of drug administration, GA and BW may have influenced our effect estimates. We tried to minimize this undesirable effect with sub-group analysis, but due to the great heterogeneity in the reporting of the investigated outcomes of the included RCTs we were able to conduct sub-group analysis only for the main efficacy outcomes. Second, the conducted subgroup analysis was based on mean values regarding GA and BW, as we didn't have the raw data of the analyzed RCTs. Third, we included only RCTs with an available full-text article in English. This way, we might have omitted RCTs in another language and abstracts relevant to our questions. Fourth, most studies didn't have definitions for their secondary outcomes, and there were studies where the outcomes were reported as a continuous variable and these were not included in the meta-analysis. Consequently, the results regarding the safety outcomes should be interpreted with caution. Finally, except for 3 studies (45,50,54), the majority of the included RCTs had small sample sizes, something that may lead to higher variability and subsequently to bias.

Critical outcomes such us mortality, renal and hepatic failure, NEC, IVH, and neurodevelopmental outcome should be examined further by bigger multicenter RCTs. On July 7th 2017, IBUPAR-TRIAL (66), a multicenter RCT with quadruple masking has started, with an estimated study sample size of 300 neonates <30 weeks GA with hsPDA and possible completion date February 27th 2022. The main aim of this study is to assess the efficacy of iv paracetamol vs ibuprofen. What is more, they will follow-up all included neonates until the age of 2 years, and they will investigate many of the aforementioned safety outcomes.

Conclusion

Paracetamol seems to be as efficient as ibuprofen or indomethacin for primary and overall PDA closure. Moreover, paracetamol impairs less the renal function and protects against hyperbilirubinemia when compared to ibuprofen. Overall, there seems to be a great amount of

evidence supporting the efficacy of paracetamol, but more evidence is needed regarding the safety outcomes, both short- and long-term, in comparison to NSAIDs.

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2&rank=1

Table 1. The keywords of PICO tool

Patient	Patent ductus arteriosus
Intervention	Paracetamol OR acetaminophen
Comparison	Ibuprofen OR indomethacin OR anti-inflammatory agents, non-steroidal OR placebo
Outcome	safety OR efficacy OR closure OR re-opening OR recurrence OR liver failure OR renal failure OR gastrointestinal perforation OR gastrointestinal bleeding OR bleeding OR effective*
PICO: Patient, Intervention, Comparison, Outcome	

Table 2. Inclusion and exclusion criteria

	Inclusion criteria	**Exclusion criteria**
Definition	Neonates with PDA	Other CHD
Study type	RCT with published full-text article	Other
Outcome	safety, efficacy, closure, re-opening, recurrence, liver failure, renal failure, gastrointestinal perforation, gastrointestinal bleeding, bleeding, effective*	Other
Language	English	Other

Abbreviations: CHD, congenital heart disease; PDA, patent ductus arteriosus; RCT, randomized controlled trial.

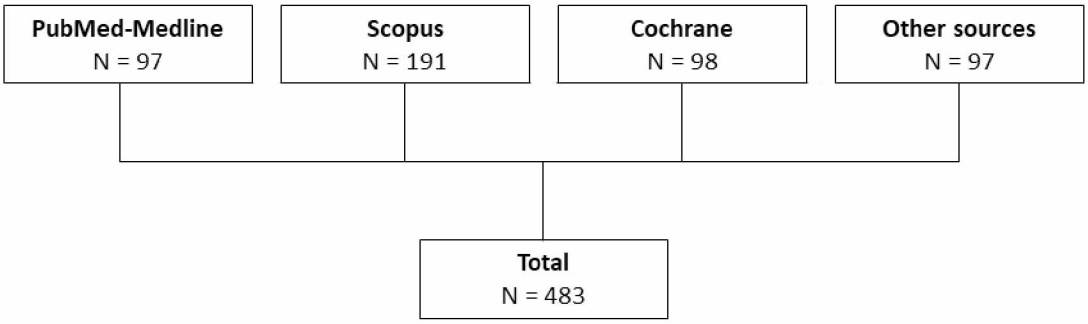

Figure 1. Chart showing the number of results per database, and other sources.

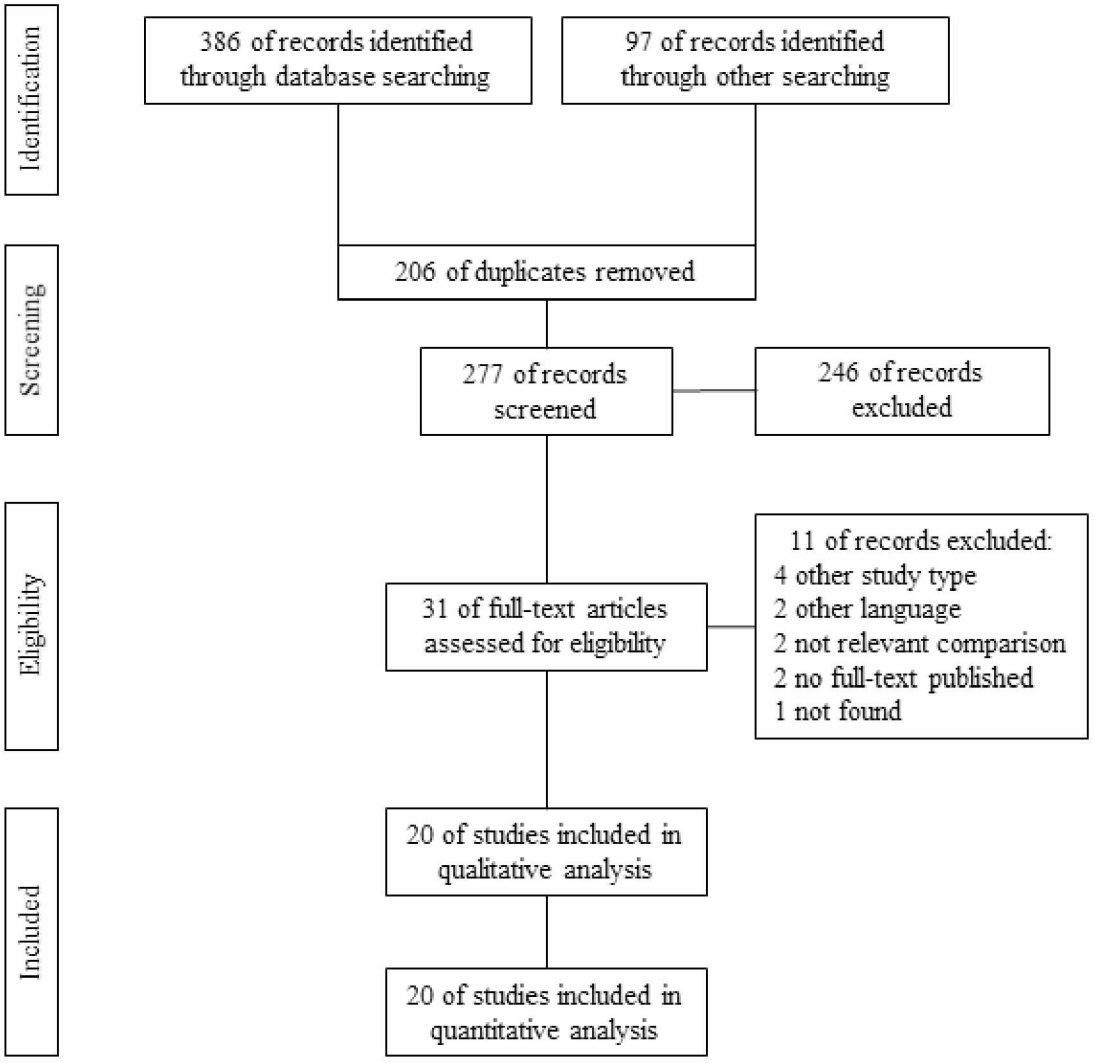

Figure 2. Flow diagram of PRISMA results.

Table 3. Characteristics of the included RCTs.

Author (Year)	Country	Time period	Population size	Inclusion criteria	Post-natal age	PDA severity criteria	BW, Mean (grams)	GA, Mean (weeks)	Intervention	Dosage	Mode of administration	Comparison	Dosage	Mode of administration
Jafari N (2019) (53)	Islamic Republic of Iran	2017-2018	30 (16:14)	28-34 weeks	48-72h	Moderate-to-severe	Unknown	Unknown	Paracetamol	15mg/kg/6h for 3 days (± repeat)	IV	Ibuprofen	10mg/kg 1st day followed by 5mg/kg on the 2nd and 3rd day (± repeat)	IV
Bagheri MM (2016) (43)	Islamic Republic of Iran	2014	129 (67:62) ITT	<37 weeks and ≤14 days	≤14 days	PDA>1.5mm and LA:Ao>1.2	1645	32	Paracetamol	15mg/kg/6h for 3 days	PO	Ibuprofen	20mg/kg 1st day followed by 10mg/kg on the 2nd and 3rd day	PO
Yang B (2016) (60)	People's Republic of China	2012-2015	87 (44:43)	<37 weeks	15h-10 days	PDA>1.4mm, LA:Ao>1.4, diastolic reversal in the PA	2156	34	Paracetamol	15mg/kg/6h for 3 days	PO	Ibuprofen	10mg/kg 1st day followed by 5mg/kg on the 2nd and 3rd day	PO
El-Mashad AE (2016) (50)	Egypt	2012-2015	300 (1:1:1)	<28 weeks or BW<1500gr	≤14 days	PDA>1.5mm, LA:Ao>1.6, diastolic reversal in the PA, end-diastolic flow reversal in the Desc.Ao/mesenteric artery	1067	26	Paracetamol	15mg/kg/6h for 3 days	IV	Ibuprofen	10mg/kg 1st day followed by 5mg/kg on the 2nd and 3rd day	IV
El-Mashad AE (2016) (50)	Egypt	2012-2015	300 (1:1:1)	<28 weeks or BW<1500gr	≤14 days	PDA>1.5mm, LA:Ao>1.6, diastolic reversal in the PA, end-diastolic flow reversal in the Desc.Ao/mesenteric artery	1067	26	Paracetamol	15mg/kg/6h for 3 days	IV	Indomethacin	0.2mg/kg/12h for 3 doses	IV

Oncel MY (2017) (57)	Turkey	2012-2014	61 (30:31)	≤30 weeks and BW ≤1250gr	2-4 days	PDA>1.5mm OR LA:Ao>1.5 OR end-diastolic flow reversal in the Desc.Ao OR HF	986	28	Paracetamol	15mg/kg /6h for 3 days (± repeat)	PO	Ibuprofen	10mg/kg 1st day followed by 5mg/kg on the 2nd and 3rd day (± repeat)	PO
Dash SK (2015) (47)	India	2012-2013	77 (38:39)	preterm neonates and BW ≤1500gr	≤ 48h	PDA>1.5mm, L-to-R shunt across the duct and LA:Ao>1.5	1008	29	Paracetamol	15mg/kg /6h for 7 days	PO	Indomethacin	0.2mg/kg/24h for 3-5 days	IV
Dang D (2013) (45)	People's Republic of China	2012-2013	160 (1:1) PPA	≤34 weeks	≤14 days	significant PDA	1561	31	Paracetamol	10mg/kg /6h for 3 days (± repeat)	PO	Ibuprofen	10mg/kg 1st day followed by 5mg/kg on the 2nd and 3rd day (± repeat)	PO
Al-Lawama M (2018) (41)	Jordan	2015-2016	22 (13:9)	≤32 weeksor BW ≤1500gr	3-5 days	2/3: (SBP-DBP)>1/2SBP, LA:Ao>1.5, LV dilatation, end-diastolic flow reversal in the Desc.Ao	1113	28	Paracetamol	10mg/kg /6h for 3 days	PO	Ibuprofen	20mg/kg 1st day followed by 10mg/kg on the 2nd and 3rd day OR 10mg/kg 1st day followed by 5mg/kg on the 2nd and 3rd day	PO
Asadpour N (2018) (42)	Islamic Republic of Iran	NA	50 (1:1)	<37 weeks	Unknown	Significant PDA	Unknown	Unknown	Paracetamol	10mg/kg /6h for 3 days	PO	Ibuprofen	10mg/kg/12h 1st day followed by 5mg/kg on the 2nd and 3rd day	PO
Balachander B (2018) (44)	India	2014-2016	110 (1:1)	≤37 weeks and BW ≤2500gr	24h-28days	PDA>1.5mm, L-to-R shunt across the duct and any of: LA:Ao>1.5,	1524	32	Paracetamol	15mg/kg /6h for 2 days (±rescue	PO	Ibuprofen	10mg/kg 1st day followed by 5mg/kg on the 2nd	PO

						HF, mechanical ventilation				ibuprofen)			and 3rd day (±coil closure OR surgery OR conservative treatment)	
Oncel MY (2014) (56)	Turkey	2012	90 (1:1)	≤30 weeks and BW ≤1250gr	2-4 days	PDA>1.5mm OR LA:Ao>1.5 OR end-diastolic flow reversal in the Desc.Ao OR HF	952	27	Paracetamol	15mg/kg /6h for 3 days (± repeat)	PO	Ibuprofen	10mg/kg 1st day followed by 5mg/kg on the 2nd and 3rd day (± repeat)	PO
Davidson J (2020) (48)	USA	2016-2018	37 (17:20)	22-32 weeksor BW ≤1500gr	≤21 days	L-to-R shunt across the duct and 2/3: PDA≥1.5, LA:Ao≥1.5, diastolic flow reversal in the abdominal Ao	769	25	Paracetamol	15mg/kg /6h for 3 days	IV	Indomethacin	0.2mg/kg/12h for 3 doses OR 0.2mg/kg 1st dose followed by 2 doses 0.25mg/kg/12h	IV
Ghaderian M (2019) (51)	Islamic Republic of Iran	2017-2018	40 (1:1)	<32 weeksor BW <1500gr	<14 days	PDA≥1.5 and 1 of: LA:Ao≥1.4, ductal velocity<2m/s, antegrade main PA diastolic flow >20 cm/s, E:A>1, IVRT≤40msec, absent or reversed diastolic blood flow pattern in descending thoracic aorta	1178	31	Paracetamol	15mg/kg /6h for 2 days (±repeat for 3 days ± ibuprofen for 3 days ± ibuprofen for 3 days)	PO	Ibuprofen	10mg/kg 1st day followed by 5mg/kg on the 2nd and 3rd day (±repeat for 3 days ± paracetamol for 3 days ± paracetamol for 3 days)	PO
Ghaderian M (2019) (52)	Islamic Republic of Iran	Unknown	40 (1:1)	≤34 weeks and ≥1000gr	Unknown	Unknown	1282	29	Paracetamol	15mg/kg /6h for 2 days (±repeat for 2 days ± ibuprofe	IV	Ibuprofen	10mg/kg 1st day followed by 5mg/kg on the 2nd and 3rd day	PO

										n for 3 days ± ibuprofen for 3 days)			(±repeat for 3 days ± paracetamol for 2 days ± paracetamol for 2 days)	
Meena V (2020) (55)	India	Unknown	105 (1:1:1)	<37 weeks	≤28 days	PDA >1.5 mm, (LA/Ao>1.4), diastolic turbulence (backflow) on Doppler in the pulmonary artery, and reversed end-diastolic flow in the descending aorta/mesenteric artery	1397	32	Paracetamol	15mg/kg /6h for 3 days (± repeat ± rescue drugs)	IV	Ibuprofen	10mg/kg 1st day followed by 5mg/kg on the 2nd and 3rd day (± repeat ± rescue drugs)	PO
Meena V (2020) (55)	India	Unknown	105 (1:1:1)	<37 weeks	≤28 days	PDA >1.5 mm, (LA/Ao>1.4), diastolic turbulence (backflow) on Doppler in the pulmonary artery, and reversed end-diastolic flow in the descending aorta/mesenteric artery	1397	32	Paracetamol	15mg/kg /6h for 3 days (± repeat ± rescue drugs)	IV	Indomethacin	starting dose of 0.2 mg/kg followed by 0.1 mg/kg for babies <2 days of age, 0.2 mg/kg for 2–7 days of postnatal life, and 0.25 mg/kg for >7 days of postnatal life (3 doses at 12 hourly intervals) (± repeat ± rescue drugs)	PO

Kumar A (2020) (54)	India	Unknown	161 (81:80)	<32 weeks	Unknown	PDA≥1.6 mm plus 1 of: LA:Ao≥1.4, transductal blood flow velocity <2 m/s, antegrade main pulmonary artery diastolic flow velocity >20 cm/s, mitral valve inflow E wave:A wave ratio >1, isovolemic relaxation time≥45 ms, and absent or reversed diastolic flow in the descending aorta	1148	29	Paracetamol	15mg/kg /6h for 3 days (± repeat OR rescue drugs)	PO	Ibuprofen	10mg/kg 1st day followed by 5mg/kg on the 2nd and 3rd day (± repeat ±OR rescue drugs)	PO
Dani C (2020) (46)	Italy	Unknown	109 (58:51)	25-32 weeks	24-72h	ductal left-to-right shunt, with a LA:Ao> 1.3 or a ductal size > 1.5 mm and excluding the cases in which the closing flow pattern suggested a restrictive PDA	1044	28	Paracetamol	15mg/kg /6h for 3 days (± ibuprofen)	IV	Ibuprofen	10mg/kg 1st day followed by 5mg/kg on the 2nd and 3rd day (± repeat)	IV
Tauber KA (2020) (59)	USA	2017-2019	10 (1:1)	23-30 weeks	≤14 days	hsPDA	826	26	Paracetamol	15mg/kg /6h for 3 days (± ibuprofen)	IV	Ibuprofen	10mg/kg 1st day followed by 5mg/kg on the 2nd and 3rd day (± repeat)	IV
Shahmirzadi G (2021) (58)	Islamic Republic of Iran	2018-2019	40 (23:17)	premature	<14 days	Asymptomatic (see exclusion ctiteria)	1654	31	Paracetamol	15 mg/kg/6 h for 2 days	IV	Ibuprofen	10 mg/kg, followed by 5 mg/kg every 12 h for 2 days	PO

El-Farrash R (2019) (49)	Egypt	2015-2017	60 (1:1)	≤34	2-7 days	Echocardiographically confirmed hsPDA	`635	31	Paracetamol	15 mg/kg/6 hours for 3 successive days (± repeat)	PO	Ibuprofen	10 mg/kg/d for first day followed by 5 mg/kg/day for the next 2 days (2nd course 5mg/kg/d for 3 days)	PO
Abbreviations: Ao, aorta; DBP, diastolic blood pressure; hsPDA, hemodynamically significant Patent Ductus Arteriosus; IV, intravenous; IVRT, isovolumic relaxation time ; LA, left atrium; LV, left ventricle; L-to-R, left-to-right; NA, not available; PA, pulmonary artery; PO, peros; SBP, systolic blood pressure.														

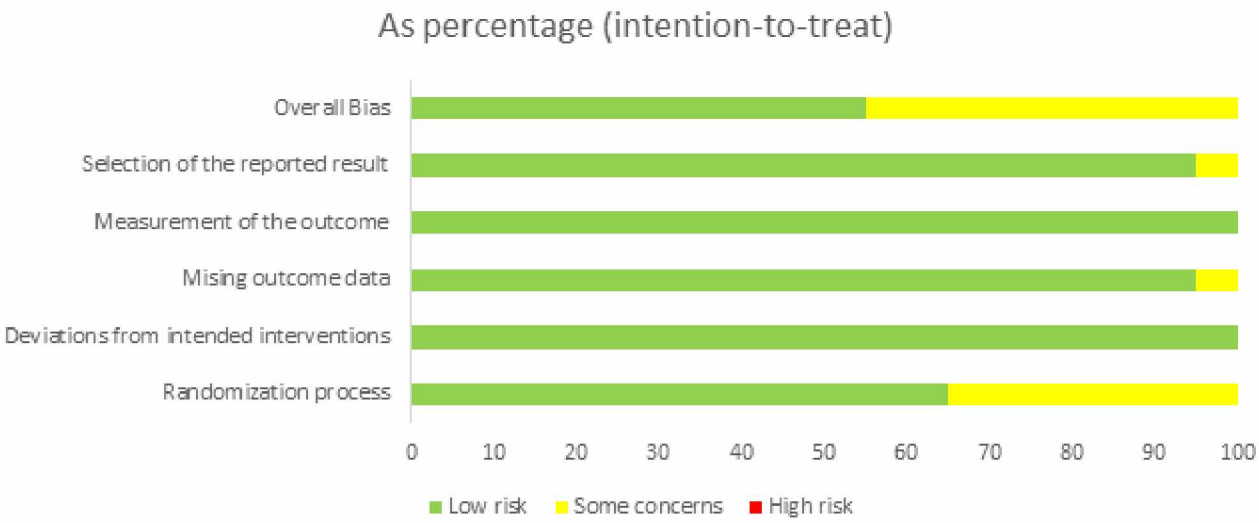

Figure 3. Weighted summary plot of the risk of bias assessment of the included RCTs for primary PDA closure (RoB2 tool).

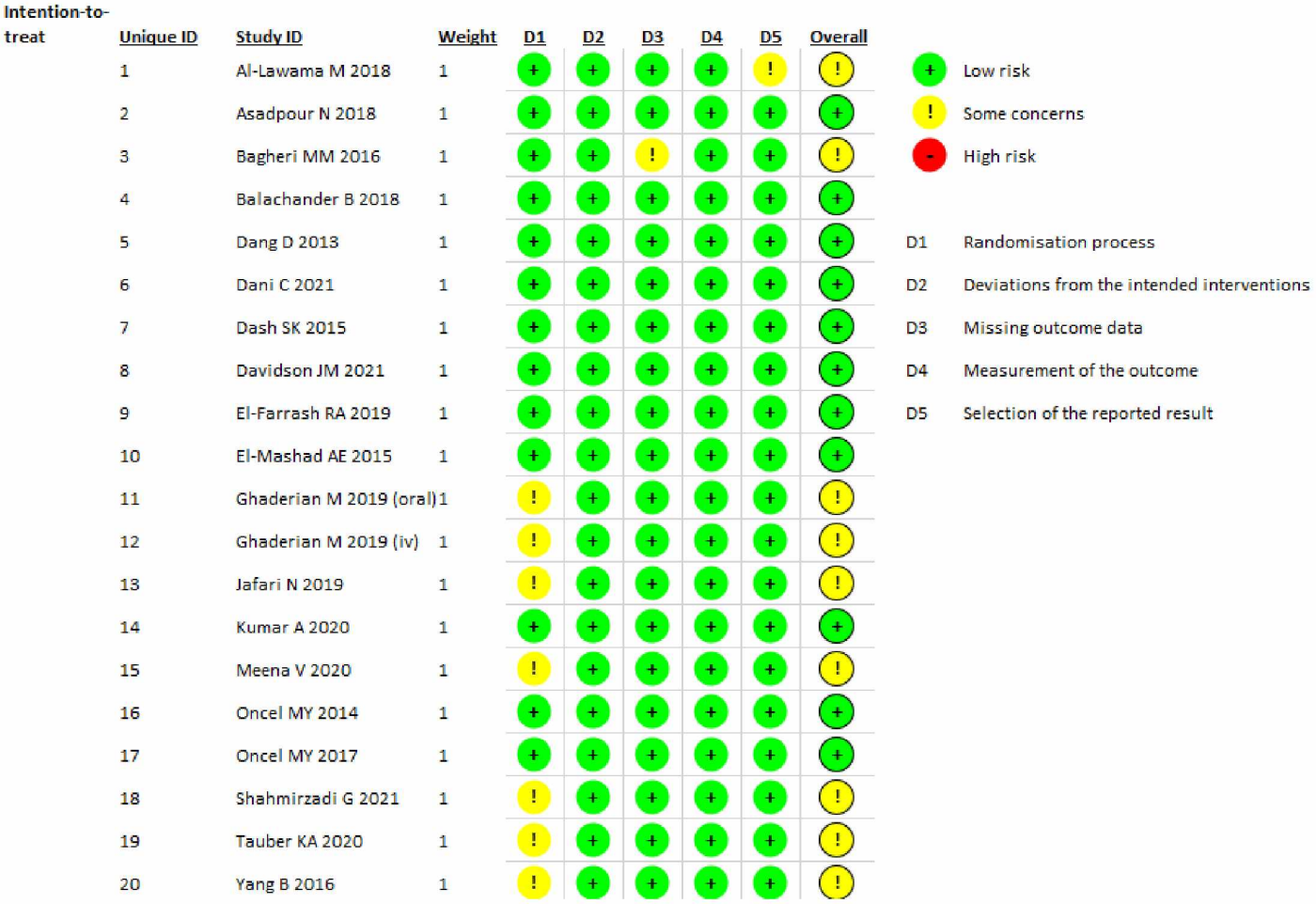

Figure 4. Traffic light plots of the risk of bias assessment of the included RCTs for primary PDA closure (Rob2 tool).

Table 4. Efficacy outcomes of all included RCTs.

	PDA closure rate after 1st course of treatment			PDA constriction after 1st course of treatment			Overall PDA closure rate			PDA recurrence		
	Paracetamol	Ibuprofen	Indomethacin	Paracetamol	Ibuprofen	Indomethacin	Paracetamol	Ibuprofen	Indomethacin	Paracetamol	Ibuprofen	Indomethacin
Asadpour N 2018 (42)	23/25	22/25	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Davidson J 2020(48)	1/17	n/a	11/20	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Meena V 2020(55)	15/35	13/35	8/35	n/a	n/a	n/a	25/35	27/35	24/35	n/a	n/a	n/a
Kumar A 2020(54)	52/81	62/80	n/a	n/a	n/a	n/a	63/71	65/73	n/a	5/57	4/66	n/a
Dani C 2020(46)	27/52	38/49	n/a	42/52	44/49	n/a	n/a	n/a	n/a	14/39	8/43	n/a
Tauber KA 2020(59)	2/5	0/5	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Jafari N 2019(53)	14/16	13/14	n/a	16/16	14/14	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Ghaderian M 2019(51)	14/20	15/20	n/a	n/a	n/a	n/a	18/20	18/20	n/a	n/a	n/a	n/a
Ghaderian M 2019(52)	12/20	13/20	n/a	n/a	n/a	n/a	16/20	17/20	n/a	n/a	n/a	n/a
Shahmirzadi G 2021 (58)	22/23	16/17	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
El-Farrash R 2019(49)	20/30	12/30	n/a	n/a	n/a	n/a	24/30	16/30	n/a	n/a	n/a	n/a
Al-Lawama M 2018(41)	9/13	7/9	n/a	n/a	n/a	n/a	12/13	8/9	n/a	n/a	n/a	n/a
Balachander B 2018(44)	41/55	42/55	n/a	n/a	n/a	n/a	n/a	n/a	n/a	4/41	4/42	n/a
Oncel MY 2017(57)	26/30	23/31	n/a	n/a	n/a	n/a	n/a	n/a	n/a	4/30	4/31	n/a
Bagheri MM 2016(43)	55/67	45/62	n/a	n/a	n/a	n/a	61/67	56/62	n/a	n/a	n/a	n/a
Yang B 2016(60)	31/44	33/43	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
El-Mashad AE 2016(50)	80/100	77/100	81/100	n/a	n/a	n/a	88/100	83/100	87/100	n/a	n/a	n/a
Dash SK 2015(47)	36/38	n/a	35/39	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Oncel MY 2014(56)	29/45	31/45	n/a	n/a	n/a	n/a	n/a	n/a	n/a	7/29	5/31	n/a
Dang D 2013(45)	45/80	38/80	n/a	n/a	n/a	n/a	65/80	63/80	n/a	5/65	6/63	n/a

Abbreviations: n/a, not available; PDA, patent ductus arteriosus; RCT, randomized controlled trial.

Table 5. Safety outcomes of all included RCTs.

Study	Paracetamol	Ibuprofen	Indomethacin
Mortality			
Davidson J 2020(48)	1/17	n/a	3/20
Kumar A 2020(54)	27/81	21/80	n/a
Jafari N 2019(53)	2/16	2/14	n/a
El-Farrash R 2019(49)	2/30	4/30	n/a
Al-Lawama M 2018(41)	3/13	2/9	n/a
Balachander B 2018(44)	12/55	11/55	n/a
Dash SK 2015(47)	8/38	n/a	8/39
Oncel MY 2014(56)	3/45	2/45	n/a
Dang D 2013(45)	10/80	12/80	n/a
RDS			
Al-Lawama M 2018(41)	12/13	6/9	n/a
Surfactant therapy			
Al-Lawama M 2018(41)	9/13	6/9	n/a
Pulmonary haemorrhage			
Meena V 2020(55)	1/35	0/35	1/35
Al-Lawama M 2018(41)	1/13	1/9	n/a
El-Mashad 2016(50)	2/100	5/100	7/100
Dash SK 2015(47)	3/38	n/a	0/39
Oncel MY 2014(56)	1/45	2/45	n/a
BPD			
Davidson J 2020(48)	14/17	n/a	13/20
Kumar A 2020(54)	11/78	6/75	n/a
Jafari N 2019(53)	1/16	1/14	n/a
El-Farrash R 2019(49)	2/30	2/30	n/a
Al-Lawama M 2018(41)	1/13	0/9	n/a
Balachander B 2018(44)	0/55	3/55	n/a
Yang B 2016(60)	5/44	6/43	n/a
Dash SK 2015(47)	5/27	n/a	6/30
Dang D 2013(45)	4/80	5/80	n/a
Hepatotoxicity			
Kumar A 2020(54)	1/78	0/78	n/a
Sepsis			
Davidson J 2020(48)	4/17	n/a	6/20
Al-Lawama M 2018(41)	7/13	4/9	n/a
El-Mashad 2016(50)	15/100	19/100	14/100
Dash SK 2015(47)	21/38	n/a	17/39
Oncel MY 2014(56)	12/45	10/45	n/a
Dang D 2013(45)	18/80	23/80	n/a
NEC			
Davidson J 2020(48)	2/17	n/a	3/20
Meena V 2020(55)	0/35	1/35	2/35
Kumar A 2020(54)	11/73	11/66	n/a
Shahmirzadi G 2021(58)	4/19	0/17	n/a
Al-Lawama M 2018(41)	3/13	2/9	n/a
Balachander B 2018(44)	15/55	12/55	n/a

Yang B 2016(60)	4/44	5/43	n/a
El-Mashad 2016(50)	3/100	6/100	9/100
Dash SK 2015(47)	2/38	n/a	4/39
Oncel MY 2014(56)	3/45	2/45	n/a
Dang D 2013(45)	3/80	2/80	n/a
ROP requiring treatment			
Davidson J 2020(48)	2/17	n/a	1/20
Kumar A 2020(54)	7/76	6/77	n/a
Al-Lawama M 2018(41)	0/9	0/9	n/a
Balachander B 2018(44)	5/55	3/55	n/a
Dash SK 2015(47)	8/29	n/a	7/30
Oncel MY 2014(56)	3/45	7/45	n/a
ROP			
Jafari N 2019(53)	2/16	0/14	n/a
Al-Lawama M 2018(41)	0/9	0/9	n/a
Balachander B 2018(44)	22/55	21/55	n/a
El-Mashad 2016(50)	7/100	10/100	15/100
Dash SK 2015(47)	24/29	n/a	26/30
Dang D 2013(45)	7/80	9/80	n/a
IVH			
Jafari N 2019(53)	1/16	0/14	n/a
Al-Lawama M 2018(41)	7/13	2/9	n/a
Balachander B 2018(44)	5/55	5/55	n/a
Yang B 2016(60)	5/44	4/43	n/a
El-Mashad 2016(50)	5/100	7/100	10/100
Dash SK 2015(47)	8/38	n/a	7/39
Dang D 2013(45)	9/80	10/80	n/a
IVH grade III/IV			
Davidson J 2020(48)	1/17	n/a	3/20
Kumar A 2020(54)	2/71	7/70	n/a
Al-Lawama M 2018(41)	0/13	9/13	n/a
Dang D 2013(45)	3/80	3/80	n/a
Increase in IVH grade			
Oncel MY 2014(56)	2/45	3/45	n/a
PVL			
Kumar A 2020(54)	3/74	0/75	n/a
Al-Lawama M 2018(41)	0/13	0/9	n/a
Dash SK 2015(47)	8/38	n/a	7/39
Dang D 2013(45)	5/80	6/80	n/a
Renal impairment			
Balachander B 2018 (44)	5/55	15/55	n/a
Dash SK 2015 (47)	1/38	n/a	0/39
Azotemia			
Kumar A 2020(54)	12/81	14/79	n/a
Oliguria			
Asadpour N 2018(42)	0/25	0/25	n/a
Kumar A 2020(54)	10/81	16/80	n/a
Yang B 2016(60)	1/44	6/43	n/a
Dang D 2013(45)	6/80	9/80	n/a

Renal failure			
Dang D 2013(45)	0/80	1/80	n/a
GI bleed			
Asadpour N 2018(42)	0/25	5/25	n/a
Meena V 2020(55)	0/35	1/35	1/35
Ghaderian M 2019 (51)	0/20	1/20	n/a
Shahmirzadi G 2021(58)	4/19	1/17	n/a
El-Mashad 2016(50)	1/100	7/100	10/100
Dash SK 2015 (47)	10/38	n/a	7/39
Oncel MY 2014 (56)	0/45	1/45	n/a
Dang D 2013(45)	2/80	8/80	n/a
MV			
Al-Lawama M 2018 (41)	9/13	5/9	n/a
GI perforation			
Davidson J 2020(48)	0/17	n/a	0/20
Postnatal steroids			
Davidson J 2020(48)	4/17	n/a	8/20
Oncel MY 2014 (56)	10/45	16/45	n/a
Pneumothorax			
Jafari N 2019 (53)	0/16	1/14	n/a
Oncel MY 2014 (56)	4/45	2/45	n/a
Feeding intolerance			
Shahmirzadi G 2021(58)	4/18	1/17	n/a
Positive OB test			
Jafari N 2019 (53)	0/16	1/14	n/a
Shahmirzadi G 2021(58)	5/19	3/17	n/a
Yang B 2016(60)	2/44	4/43	n/a
CCF			
Balachander B 2018 (44)	14/55	15/55	n/a
Hyperbilirubineamia			
Dang D 2013(45)	16/80	28/80	n/a
Jaundice requiring phototherapy			
Balachander B 2018 (44)	32/55	25/55	n/a
Cholestasis			
Balachander B 2018 (44)	2/55	2/55	n/a
Bleeding manifestations			
Balachander B 2018 (44)	12/55	11/55	n/a
Thrombocytopenia			
Balachander B 2018 (44)	17/55	16/55	n/a
Screening OAE fail			
Balachander B 2018 (44)	3/55	3/55	n/a
Neurodevelopmental impairment			
Oncel MY 2017(57)	9/30	10/31	n/a
Significant cerebral palsy			
Oncel MY 2017(57)	4/30	2/31	n/a
Blind			
Oncel MY 2017(57)	0/30	1/31	n/a
Deaf			
Oncel MY 2017(57)	0/30	1/31	n/a

Deranged coagulogram			
Kumar A 2020(54)	10/80	9/78	n/a

Abbreviations: BPD, Bronchopulmonary dysplasia; CCF, Congestive Cardiac Failure; GI, Gastrointestinal; IVH, Intraventricular haemmorhage; MV, Mechanical ventilation; NEC, Necrotizing enterocolitis; n/a, not available; OAE, Otoacoustic Emissions; OB, occult blood; PVL, Periventricular leukomalacia; RDS, Respiratory distress syndrome; ROP, Retinopathy of prematurity.

Table 6. The pooled results of Meta-analyses.

				Test of association				Heterogeneity			Publication bias	
Interventions	**Outcomes**	**Subgroups**	**Effect sizes**	**Pooled OR (95% CI)**	**P-value**	**Model**	**Z test**	**X^2**	**P-value**	**I^2 (%)**	**Egger**	**Begg**
Paracetamol vs. Ibuprofen	**Efficacy**											
	Primary PDA closure		**17**(41–46,49–56,58-60)	0.933 (0.691-1.260)	0.650	RE	0.45	22.42	0.130	28.6	0.784	1.000
		Sensitivity analysis*	**8**(42,44–46,49,50,54,56)	0.880 (0.543-1.426)	0.604	RE	0.52	18.16	**0.011**	61.4		
		Oral	**10**(41–45,49,51,54,56,60)	0.983 (0.670-1.442)	0.930	RE	0.09	14.18	0.116	36.5	0.861	0.655
		IV	**7**(46,50,52,53,55,58,59)	0.841 (0.492-1.439)	0.528	RE	0.63	7.95	0.242	24.6		
		GA <28 weeks	**4**(50,56,58,59)	0.893 (0.488-1.633)	0.714	RE	0.37	3.52	0.318	14.8		
		GA ≥28 weeks	**11**(41,43,60,44–46,49,51,52,54,55)	0.936 (0.634-1.383)	0.742	RE	0.33	18.40	**0.049**	45.7	0.915	0.697
		BW <1000 gr	**4**(49,56,58,59)	1.374 (0.409-4.621)	0.608	RE	0.51	7.61	0.055	60.6		
		BW 1000-1500 gr	**7**(41,46,50–52,54,55)	0.718 (0.469-1.099)	0.127	RE	1.52	8.00	0.238	25.0		
		BW 1501-2500 gr	**4**(43–45,60)	1.205 (0.812-1.789)	0.355	RE	0.93	2.50	0.475	0.0		
	PDA constriction after 1st course of treatment		**1**(46)	0.480 (0.150-1.510)	0.213		1.25					
	Overall PDA closure		**9**(41,43,45,49–52,54,55)	1.166 (0.818-1.662)	0.394	RE	0.85	5.86	0.663	0.0		
		Sensitivity analysis*	**4**(45,49,50,54)	1.347 (0.801-2.267)	0.262	RE	1.12	4.49	0.213	33.2		
		Oral	**7**(41,43,45,49–51,54)	1.270 (0.864-1.867)	0.224	RE	1.22	4.63	0.592	0.0		
		IV	**2**(52,55)	0.731 (0.296-1.801)	0.495	RE	0.68	0.00	0.967	0.0		
		GA <28 weeks	**1**(50)	1.500 (0.678-3.319)	0.317		1.00					
		GA ≥28 weeks	**8**(41,43,45,49,51,52,54,55)	1.096 (0.738-1.628)	0.650	RE	0.45	5.38	0.614	0.0		
		BW <1000 gr	**1**(49)	3.500 (1.111-11.028)	**0.032**		2.14					
		BW 1000-1500 gr	**6**(41,50–52,54,55)	0.990 (0.629-1.560)	0.967	RE	0.04	1.82	0.873	0.0		
		BW 1501-2500 gr	**2**(43,45)	1.146 (0.599-2.192)	0.681	RE	0.41	0.01	0.922	0.0		
	Recurrence		**5**(44–46,54,56)	1.472 (0.845-2.564)	0.172	RE	1.37	2.21	0.698	0.0		
	Safety											
	Mortality		**7**(41,44,45,49,53,54,56)	1.084 (0.712-1.652)	0.707	RE	0.38	2.04	0.916	0.0		
	RDS		**1**(41)	6.000 (0.510-70.629)	0.154		1.42					
	Surfactant therapy		**1**(41)	1.13 (0.180-6.940)	0.896		0.13					
	Pulmonary haemorrhage		**4**(41,50,55,56)	0.524 (0.167-1.648)	0.269	RE	1.11	0.37	0.947	0.0		
	BPD		**7**(41,44,45,49,53,54,60)	1.290 (0.725-2.297)	0.387	RE	0.87	3.21	0.782	0.0		
	Hepatotoxicity		**1**(54)	1.010 (0.061-16.744)	0.994		0.01					

Sepsis	**4**(41,45,50,56)	0.860 (0.554-1.337)	0.504	RE	0.67	1.38	0.709	0.0
NEC	**9**(41,44,45,50,54–56,58,60)	1.060 (0.669-1.681)	0.804	RE	0.25	3.72	0.882	0.0
ROP	**4**(44,45,50,53)	0.900 (0.538-1.505)	0.687	RE	0.40	1.01	0.800	0.0
ROP requiring treatment	**3**(44,54,56)	0.948 (0.411-2.186)	0.900	RE	0.13	2.34	0.310	14.6
IVH	**6**(41,44,45,50,53,60)	1.035 (0.596-1.797)	0.903	RE	0.12	2.56	0.768	0.0
IVH grade III/IV	**3**(41,45,54)	0.248 (0.043-1.412)	0.116	RE	1.57	5.33	0.070	62.5
Increase in IVH grade	**1**(56)	0.650 (0.101-4.167)	0.650		0.45			
PVL	**2**(45,54)	1.127 (0.366-3.469)	0.835	RE	0.21	1.04	0.307	4.0
Renal impairment	**1**(44)	0.270 (0.090-0.800)	**0.019**		2.35			
Azotemia	**1**(54)	0.810 (0.350-1.872)	0.622		0.49			
Oliguria	**3**(45,54,60)	0.514 (0.272-0.973)	**0.041**	RE	2.04	1.72	0.424	0.0
Renal failure	**1**(45)	0.990 (0.061-16.197)	0.994		0.01			
GI bleeding	**7**(42,45,50,51,55,56,58)	0.453 (0.174-1.174)	0.103	RE	1.63	7.59	0.270	21.0
MV	**1**(41)	1.800 (0.309-10.486)	0.513		0.65			
Postnatal steroids	**1**(56)	0.500 (0.191-1.308)	0.158		1.41			
Pneumothorax	**2**(53,56)	1.614 (0.361-7.204)	0.531	RE	0.63	0.32	0.573	0.0
Feeding intolerance	**1**(58)	4.570 (0.458-45.630)	0.196		1.29			
Positive OB test	**3**(53,58,60)	0.906 (0.303-2.712)	0.861	RE	0.18	1.13	0.569	0.0
CCF	**1**(44)	0.910 (0.389-2.127)	0.828		0.22			
Hyperbilirubinemia	**1**(45)	0.460 (0.226-0.935)	**0.032**		2.15			
Jaundice requiring phototherapy	**1**(44)	1.600 (0.755-3.392)	0.220		1.23			
Cholestasis	**1**(44)	1.000 (0.138-7.251)	1.000		0.00			
Bleeding manifestations	**1**(44)	1.120 (0.449-2.794)	0.808		0.24			
Thrombocytopenia	**1**(44)	1.040 (0.460-2.351)	0.925		0.09			
Screening OAE fail	**1**(44)	1.000 (0.191-5.226)	1.000		0.00			
Neurodevelopmental impairment	**1**(57)	0.820 (0.280-2.406)	0.718		0.36			
Significant cerebral palsy	**1**(57)	2.230 (0.378-13.143)	0.376		0.89			
Blind	**1**(57)	1.000 (0.060-16.703)	1.000		0.00			
Deaf	**1**(57)	1.000 (0.060-16.703)	1.000		0.00			
Deranged coagulogram	**1**(54)	1.100 (0.422-2.870)	0.846		0.19			
Paracetamol vs. Indomethacin	**Efficacy**							

Primary PDA closure	**4**(47,48,50,55)	0.777 (0.200-3.023)	0.716	RE	0.36	12.87	**0.005**	76.7
After 1 removed**	**3**(47,50,55)	1.403 (0.696-2.830)	0.344	RE	0.95	2.56	0.278	21.9
Overall PDA closure	**2**(50,55)	1.120 (0.584-2.147)	0.733	RE	0.34	0.00	0.948	0.0
Safety								
Mortality	**2**(47,48)	0.854 (0.312-2.337)	0.759	RE	0.31	0.63	0.426	0.0
Pulmonary haemorrhage	**3**(47,50,55)	0.795 (0.165-3.841)	0.776	RE	0.28	3.10	0.212	35.6
BPD	**2**(47,48)	1.396 (0.509-3.825)	0.517	RE	0.65	0.95	0.330	0.0
Sepsis	**3**(47,48,50)	1.184 (0.682-2.055)	0.548	RE	0.60	0.91	0.634	0.0
NEC	**4**(47,48,50,55)	0.440 (0.183-1.058)	0.067	RE	1.83	0.59	0.900	0.0
ROP requiring treatment	**2**(47,48)	1.420 (0.492-4.095)	0.517	RE	0.65	0.25	0.616	0.0
ROP	**2**(47,50)	0.507 (0.232-1.105)	0.088	RE	1.71	0.39	0.531	0.0
IVH	**2**(47,50)	0.749 (0.294-1.907)	0.544	RE	0.61	1.40	0.236	28.7
IVH grade III/IV	**1**(48)	0.350 (0.030-3.770)	0.395		0.85			
PVL	**1**(47)	1.220 (0.390-3.770)	0.731		0.34			
Renal impairment	**1**(47)	1.050 (0.060-17.470)	0.973		0.03			
GI bleeding	**3**(47,50,55)	0.582 (0.089-3.795)	0.572	RE	0.57	5.60	0.061	64.3
Postnatal steroids	**1**(48)	0.460 (0.110-1.940)	0.289		1.06			

Abbreviations: BPD, Bronchopulmonary dysplasia; CCF, Congestive Cardiac Failure; CI, Confidence Interval; GI, Gastrointestinal; IVH, Intraventricular haemorrhage; MV, Mechanical ventilation; NEC, Necrotizing enterocolitis; OAE, Otoacoustic Emissions; OB, occult blood; OR, Odds Ratio; PDA, Patent Ductus Arteriosus; PVL, Periventricular leukomalacia; RDS, Respiratory distress syndrome; ROP, Retinopathy of prematurity

*Studies with a result in RoB2 different from "low risk of bias" were removed.

**Studies outside the shaded region of Galbaith plot were removed.

Appendix

Table 1. Search strategy per database

Database	Search string
Pubmed-Medline	(((patent ductus arteriosus[Title/Abstract]) AND ((paracetamol[Title/Abstract]) OR (acetaminophen[Title/Abstract]))) AND ((((ibuprofen[Title/Abstract]) OR (indomethacin[Title/Abstract])) OR (placebo[Title/Abstract])) OR (anti-inflammatory agents, non-steroidal[Title/Abstract]))) AND ((((((((((safety[Title/Abstract]) OR (efficacy[Title/Abstract])) OR (closure[Title/Abstract])) OR (re-opening[Title/Abstract])) OR (recurrence[Title/Abstract])) OR (liver failure[Title/Abstract])) OR (renal failure[Title/Abstract])) OR (gastrointestinal perforation[Title/Abstract])) OR (gastrointestinal bleeding[Title/Abstract])) OR (bleeding[Title/Abstract])) OR (effective*[Title/Abstract]))
Scopus	(TITLE-ABS-KEY (patent AND ductus AND arteriosus) AND TITLE-ABS-KEY ((paracetamol) OR (acetaminophen)) AND TITLE-ABS-KEY ((ibuprofen) OR (indomethacin) OR (placebo) OR (anti-inflammatory AND agents, AND non-steroidal)) AND TITLE-ABS-KEY ((safety) OR (efficacy) OR (closure) OR (re-opening) OR (recurrence) OR (liver AND failure) OR (renal AND failure) OR (gastrointestinal AND perforation) OR (gastrointestinal AND bleeding) OR (bleeding) OR (effective*)))
Cochrane Central Register of Controlled Trials	(((patent ductus arteriosus[Title/Abstract]) AND ((paracetamol[Title/Abstract]) OR (acetaminophen[Title/Abstract]))) AND ((((ibuprofen[Title/Abstract]) OR (indomethacin[Title/Abstract])) OR (placebo[Title/Abstract])) OR (anti-inflammatory agents, non-steroidal[Title/Abstract]))) AND ((((((((((safety[Title/Abstract]) OR (efficacy[Title/Abstract])) OR (closure[Title/Abstract])) OR (re-opening[Title/Abstract])) OR (recurrence[Title/Abstract])) OR (liver failure[Title/Abstract])) OR (renal failure[Title/Abstract])) OR (gastrointestinal perforation[Title/Abstract])) OR (gastrointestinal bleeding[Title/Abstract])) OR (bleeding[Title/Abstract])) OR (effective*[Title/Abstract]))

Table 2. List of excluded studies after full-text screening

Study reference	Reason for exclusion
Asad Abbas, Matthew Cawsey. Is intravenous paracetamol as effective as ibuprofen in closing haemodynamically significant patent ductus arteriosus after the first treatment course in preterm babies? Acta Paediatr. 2021 Jun 21. doi: 10.1111/apa.15970.	Not RCT (Review article)
Jennifer Davidson DO; John Ferguson MD; Elizabeth Ivey NNP; Ranjit Philip MD; Mark Weems MD; Bruce Jenkins MD; Ajay Talati MD. A randomized trial of intravenous acetaminophen versus indomethacin for treatment of PDA in VLBW infants. Congenital Heart Disease. 2019; 14: 116-120.	No full-text available (Only abstract available)
Ronald I Clyman, Melissa Liebowitz, Joseph Kaempf, Omer Erdeve, Ali Bulbul, Stellan Håkansson, Johanna Lindqvist, Aijaz Farooqi, Anup Katheria, Jason Sauberan, Jaideep Singh, Kelly Nelson, Andrea Wickremasinghe, Lawrence Dong, Denise C Hassinger, Susan W Aucott, Madoka Hayashi, Anne Marie Heuchan, William A Carey, Matthew Derrick, Erika Fernandez, Meera Sankar, Tina Leone, Jorge Perez, Arturo Serize. PDA-TOLERATE Trial: An Exploratory Randomized Controlled Trial of Treatment of Moderate-to-Large Patent Ductus Arteriosus at 1 Week of Age. J Pediatr. 2019 Feb;205:41-48.e6. doi: 10.1016/j.jpeds.2018.09.012. Epub 2018 Oct 16.	Not relevant comparison
Melissa Liebowitz, Joseph Kaempf, Omer Erdeve, Ali Bulbul, Stellan Håkansson, Johanna Lindqvist, Aijaz Farooqi, Anup Katheria, Jason Sauberan, Jaideep Singh, Kelly Nelson, Andrea Wickremasinghe 8, Lawrence Dong 8, Denise C Hassinger, Susan W Aucott, Madoka Hayashi, Anne Marie Heuchan, William A Carey, Matthew Derrick, Ilene Sue Wolf, Amy Kimball, Meera Sankar, Tina Leone, Jorge Perez, Arturo Serize, Ronald I Clyman. Comparative effectiveness of drugs used to constrict the patent ductus arteriosus: a secondary analysis of the PDA-TOLERATE trial (NCT01958320). J Perinatol. 2019 May;39(5):599-607. doi: 10.1038/s41372-019-0347-4. Epub 2019 Mar 8.	Not relevant comparison
Behzad Mohammadpour Ahranjani, Hosein Dalili, Zeinab Harif Nashtifani, Mamak Shariat, Mohammadrafie Khorgami. The Comparison Between Intravenous Acetaminophen Versus Oral Ibuprofen in Preterm Newborns With Patent Ductus Arteriosus: A Clinical Trial. Acta Med Iran 2020;58(12):631-636.	Not RCT
Mahrus A. Rahman, I Ketut Alit Utamayasa, Agus Cahyono. The Comparison between Acetaminophen and Ibuprofen Effectiveness for Ductus Arterious Closure Therapy in Premature Infants. Journal of International Dental and Medical Research, 2020; Vol. 13, No. 2: 704-707.	Not RCT
Carlo Dani, Chiara Poggi, Ilaria Cianchi, Iuri Corsini, Venturella Vangi, Simone Pratesi. Effect on cerebral oxygenation of paracetamol for patent ductus arteriosus in preterm infants. Eur J Pediatr. 2018 Apr;177(4):533-539. doi: 10.1007/s00431-018-3086-1. Epub 2018 Jan 25.	Not RCT
Parvin Akbari Asbagh M.D., Mohammad Reza Zarkesh M.D., Firoozeh Nili M.D., Fatemeh Sadat Nayeri M.D., Azam Tofighi Naeem M.D. Prophylactic treatment with oral paracetamol for patent ductus arteriosus in preterm infants: a randomized clinical trial. Tehran University Medical Journal, May 2015; Vol. 73, No. 2: 86-92.	Full-text article not in English (Article in Iranian)
Shanshan Wang, Bin Wu, Jiangqin Liu, Yuqi Zhang, Xingyuan Liu. Efficacy and safety of oral drugs in treatment of hemodynamically significant patent ductus arteriosus in extreme premature neonates with gestational age <28 weeks. Chinese Journal of Obstetrics and Gynecology and Pediatrics, 2020, 16 (4), pp. 392-397.	Full-text article not in English (Article in Chinese)
Tim Schindler, John Smyth, Srinivas Bolisetty, Joanna Michalowski, Kylie-Ann Mallitt, Abhijeet Singla, Kei Lui. Early PARacetamol (EPAR) Trial: A Randomized Controlled Trial of Early Paracetamol to Promote Closure of the	Full-text article not found

Ductus Arteriosus in Preterm Infants. Neonatology. 2021;118(3):274-281. doi: 10.1159/000515415. Epub 2021 Apr 12.	
Dr. Morteza Habibi, Dr. Mohammad Nobakht, Dr. Tahereh Jangjoo Pirbazari, Dr. Zohreh Yazdi. The effect of oral ibuprofen and oral acetaminophen in the patent ductus arteriosus (PDA) in preterm infants born in Kouvsar hospital of Qazvin (A comparative study). WJPMR 2016;2:203-7.	No full-text available (Only abstract available)

Efficacy outcomes' definitions

Primary PDA closure: Complete anatomical closure of the PDA after one course of treatment

Overall PDA closure: Complete anatomical closure after 2 courses of treatment

PDA restriction: Complete closure or haemodynamically insignificant PDA after one course of treatment

Recurrence: Reopening of the duct

Safety outcomes' definitions

Azotemia: No definition provided in the published article

Bleeding manifestations: No definition provided in the published article

Blind: No definition provided in the published article

Bronchopulmonary dysplasia (BPD): Oxygen requirement at postmenstrual 36th week or discharge, whichever comes first. **Definition not provided in all articles**

Cholestasis: No definition provided in the published article

Congestive cardiac failure (CCF): No definition provided in the published article

Deaf: No definition provided in the published article

Deranged coagulogram: No definition provided in the published article

Feeding intolerance: No definition provided in the published article

Gastrointestinal (GI) bleeding: No definition provided in the published article

Gastrointestinal (GI) perforation: No definition provided in the published article

Hepatotoxicity: No definition provided in the published article

Hyperbilirubineamia: No definition provided in the published article

Increase in intraventricular haemorrhage (IVH) grade: No definition provided in the published article

Intraventricular haemorrhage (IVH): According to the Papile grading system in one study.
Grade I: Hemorrhage limited to germinal matrix
Grade II: Blood noted within the ventricular system but not distending it
Grade III: Blood in the ventricles with distension of the ventricles
Grade IV: Intraventricular hemorrhage with parenchymal extension
Definition not provided in all articles

Intraventricular haemorrhage (IVH) grade III/IV: No definition provided in the published articles

Jaundice requiring phototherapy: No definition provided in the published article

Mechanical ventilation (MV): No definition provided in the published article

Mortality: Death after starting treatment and until the end of follow-up.

Necrotizing enterocolitis (NEC): Based on Bell's staging criteria or definite and advanced stage per modified Bell staging. **Definition not provided in all articles**

Neurodevelopmental impairment: the presence of any one of the following: (1) moderate-to severe cerebral palsy (CP; hypotonic, spastic diplegia, hemiplegia,or quadriplegia) with functional deficits that required rehabilitative services, or (2) bilateral hearing loss (requiring amplification) and/or blindness in either eye, or (3) MDI or PDI scores < 70.

Oliguria: No definition provided in the published articles

Periventricular leucomalacia (PVL): No definition provided in the published articles

Pneumothorax: No definition provided in the published articles

Positive OB test: Occult blood in stool samples. **Definition not provided in all articles**

Postnatal steroids: Patients with severe (oxygen requirement ≥30% ±positive pressure support) chronic lung disease at postmenstrual week 36 or discharge, whichever comes first. **Definition not provided in all articles**

Pulmonary haemorrhage: No definition provided in the published articles

Renal failure: No definition provided in the published article

Renal impairment: Acute kidney injury but no explicit definition was provided in the published article

Respiratory distress syndrome (RDS): No definition provided in the published article

Retinopathy of prematurity (ROP): According to the International Classification. **Definition not provided in all articles**

Retinopathy of prematurity (ROP) requiring treatment: Patients with pre-threshold type I ROP or who progressed to threshold disease. Pre-threshold type I ROP according to the International Classification is defined as any zone 1 ROP less than threshold, zone 2 stage 2 with plus, zone 2 stage 3 without plus or zone 2 stage 3 with plus but less than 5 contiguous or less than 8 cumulative clock hours of ROP.

Screening OAE fail: No definition provided in the published article

Sepsis: Clinical symptoms and signs of sepsis and a positive blood bacterial culture. **Definition not provided in all articles**

Significant cerebral palsy: Hypotonic, spastic diplegia, hemiplegia,or quadriplegia with functional deficits that required rehabilitative services

Surfactant therapy: No definition provided in the published article

Thrombocytopenia: No definition provided in the published article

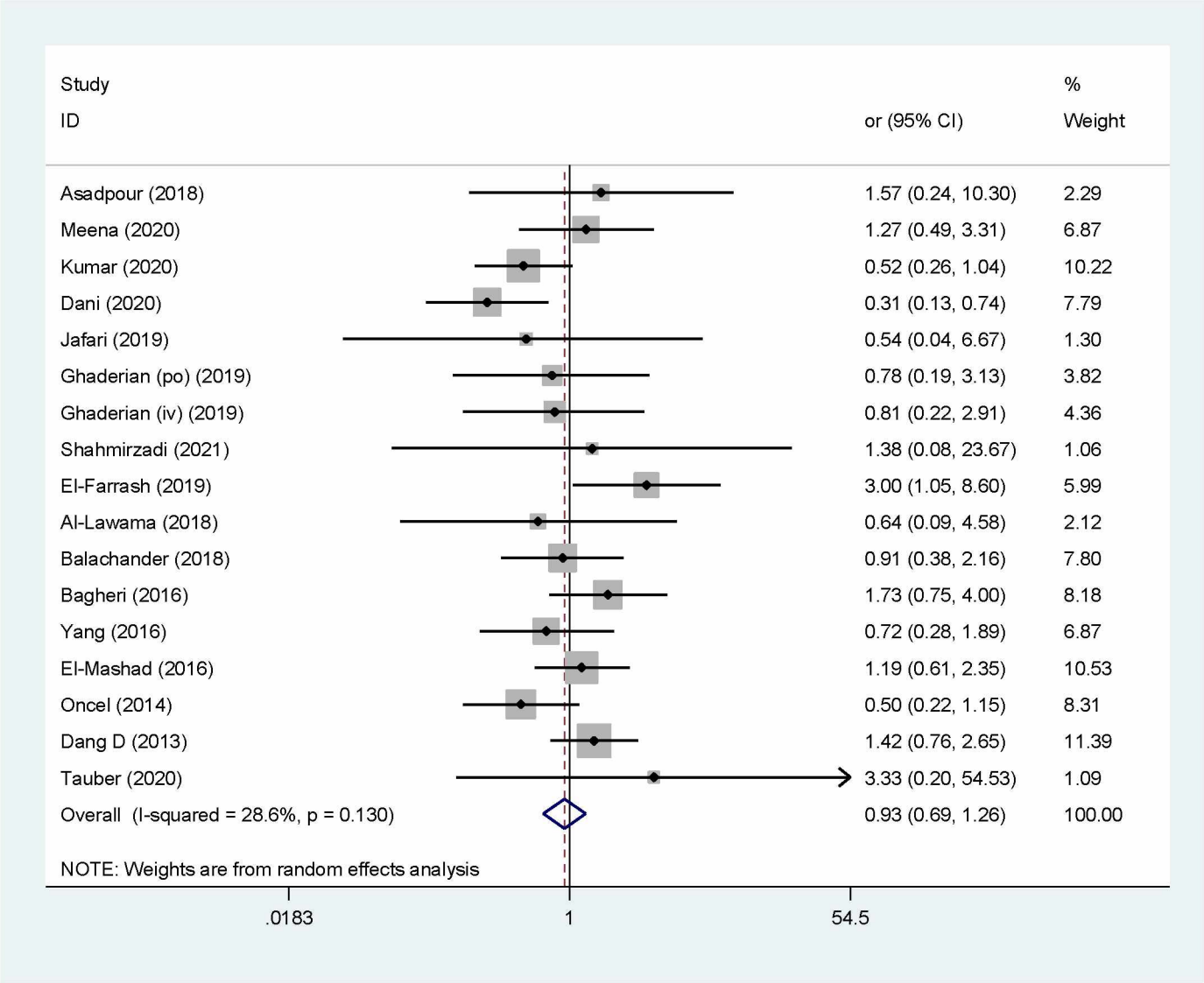

Figure1. Forest plot of studies examining the relationship between paracetamol and primary PDA closure in comparison to ibuprofen.

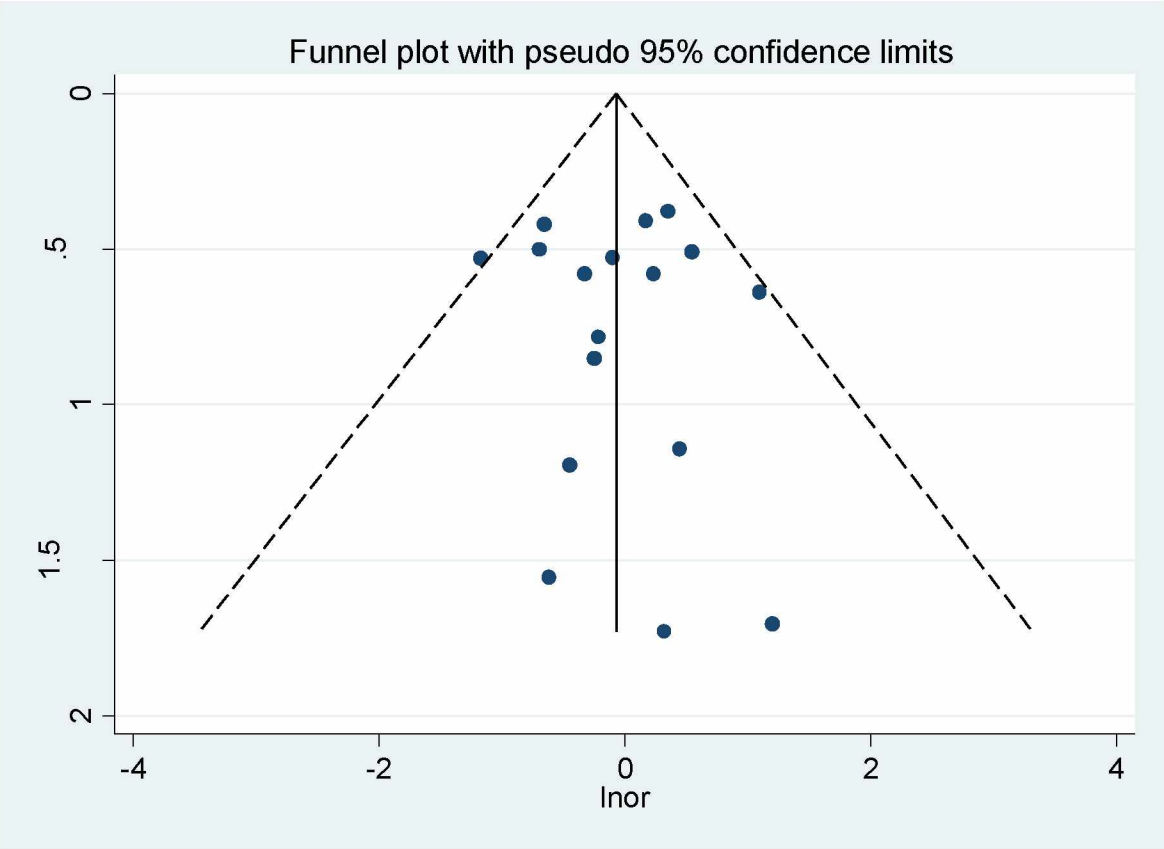

Figure 2. Funnel plot of studies examining the relationship between paracetamol and primary PDA closure in comparison to ibuprofen.

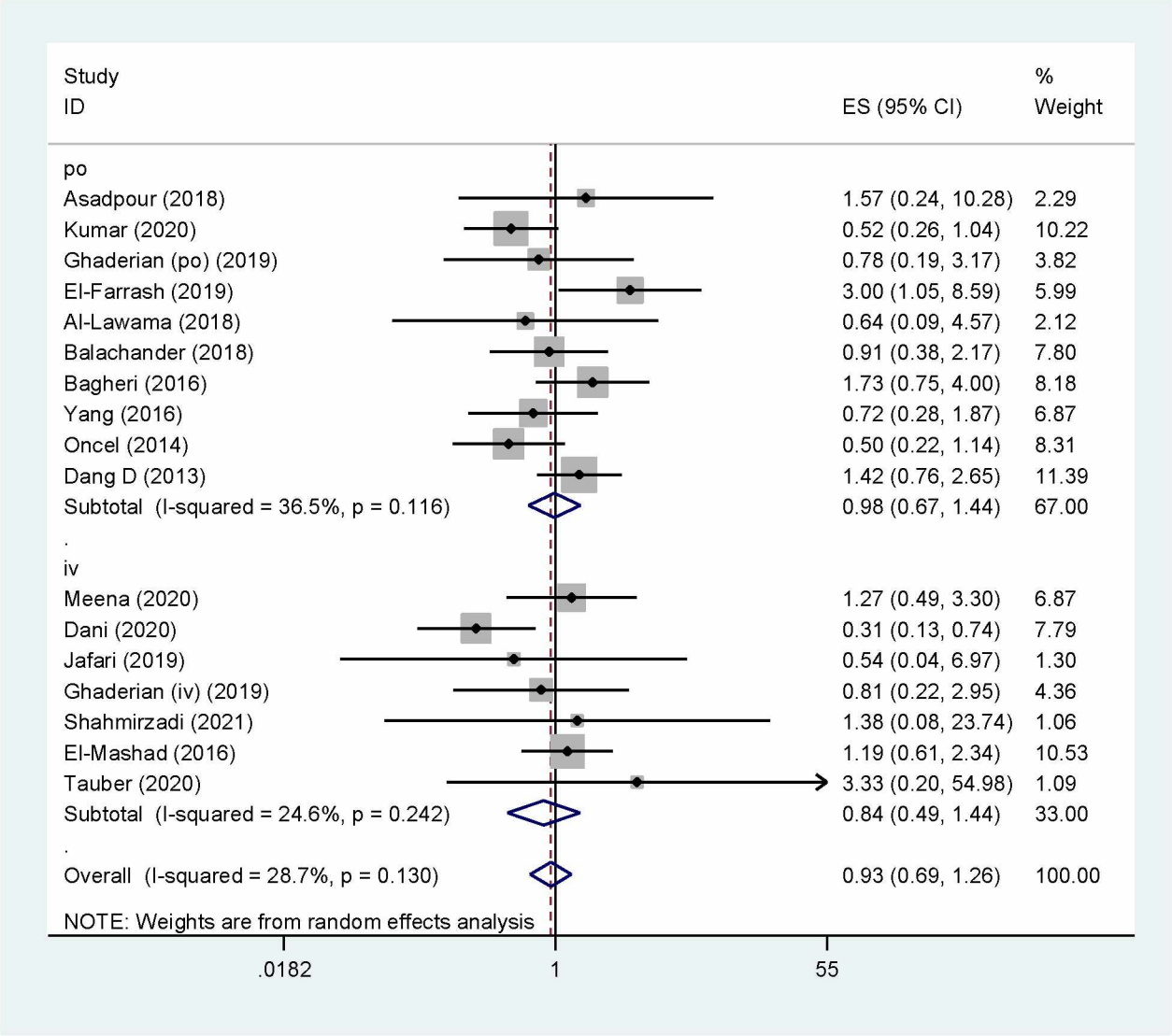

Figure 3. Forest plots of subgroup analysis by mode of drug administration of studies examining the relationship between paracetamol and primary PDA closure in comparison to ibuprofen.

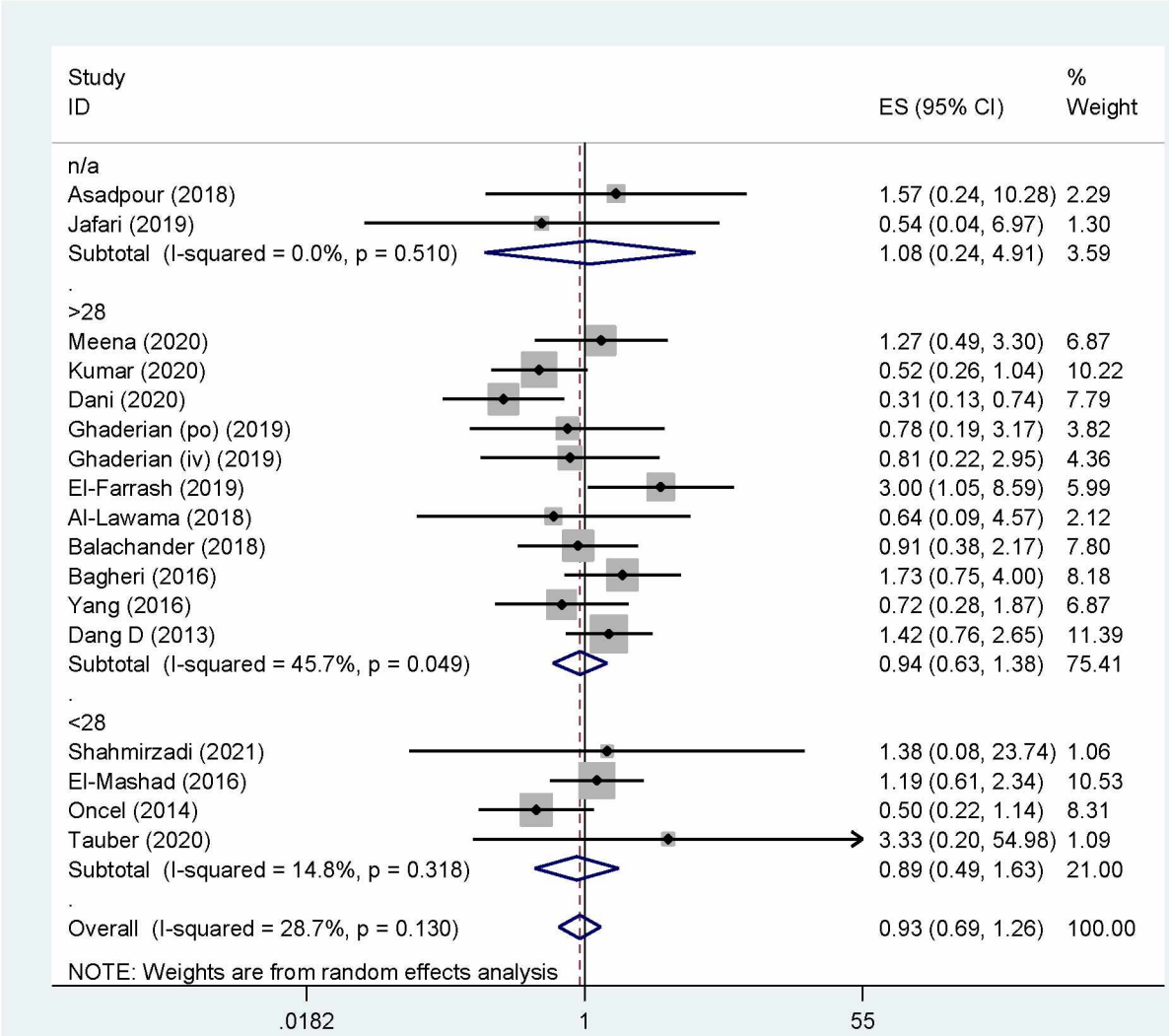

Figure 4. Forest plots of subgroup analysis by gestational age of studies examining the relationship between paracetamol and primary PDA closure in comparison to ibuprofen.

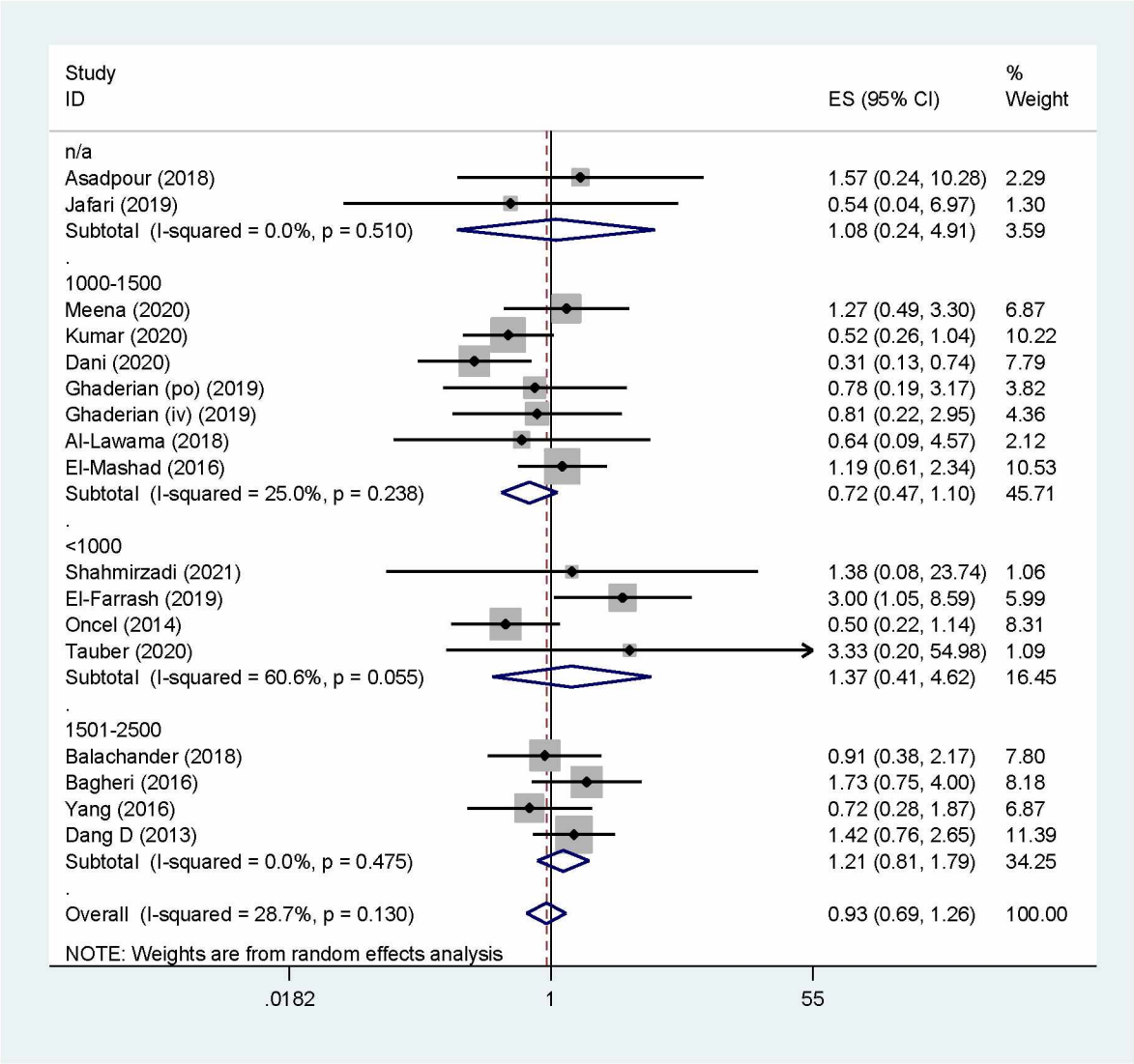

Figure 5. Forest plots of subgroup analysis by body weight of studies examining the relationship between paracetamol and primary PDA closure in comparison to ibuprofen.

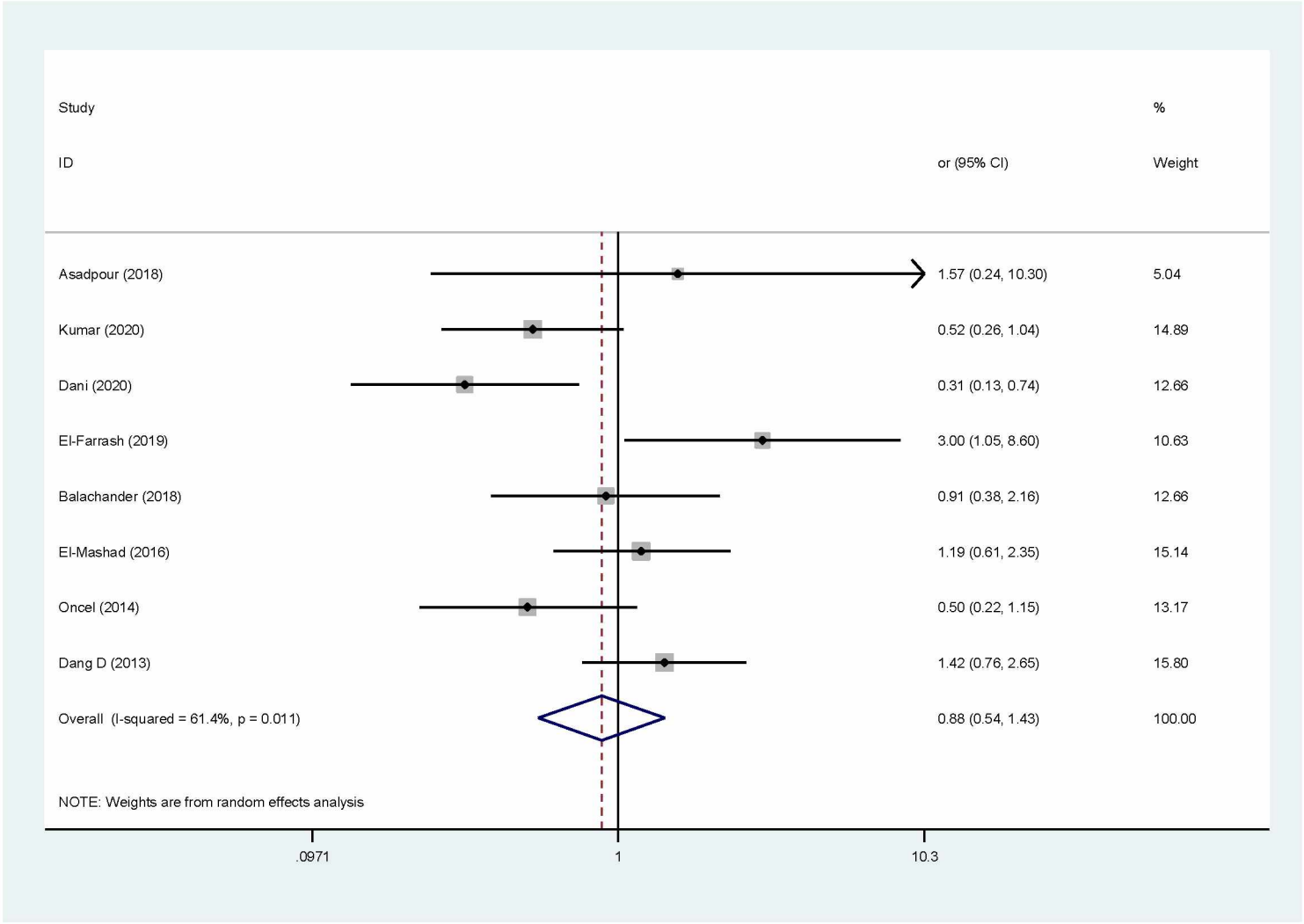

Figure 6. Forest plot of studies examining the relationship between paracetamol and primary PDA closure in comparison to ibuprofen, after sensitivity analysis.

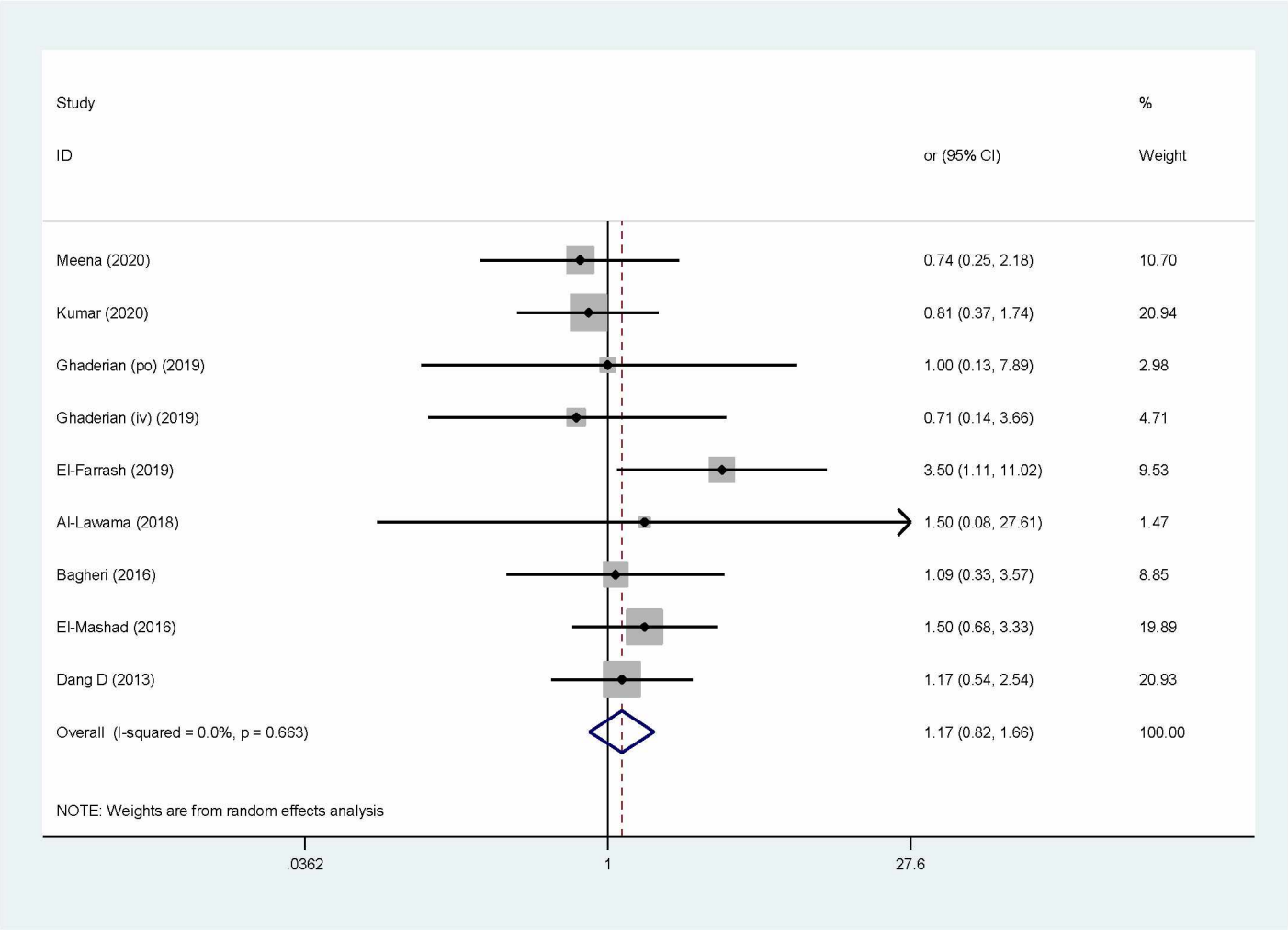

Figure 7. Forest plot of studies examining the relationship between paracetamol and overall PDA closure in comparison to ibuprofen.

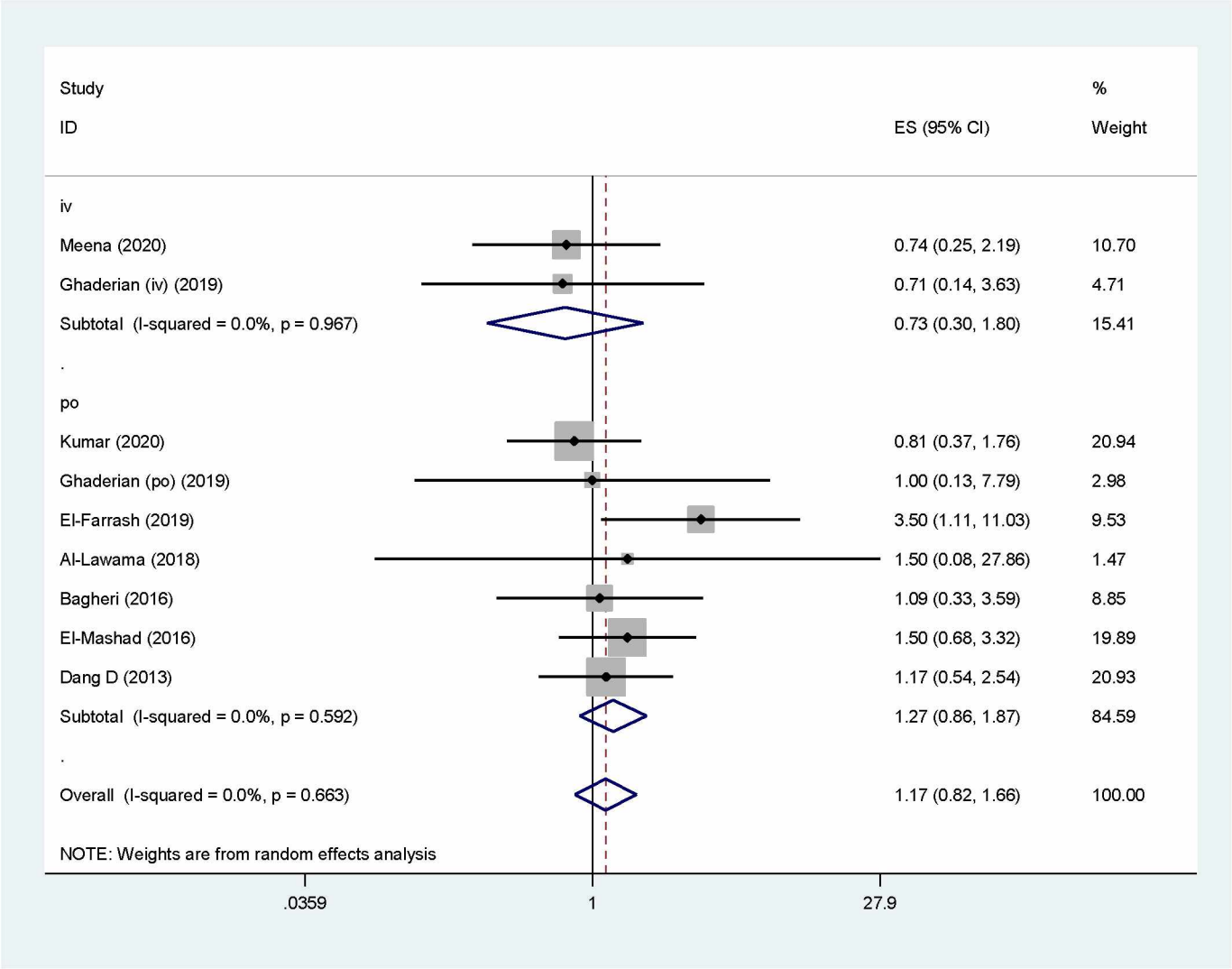

Figure 8. Forest plots of subgroup analysis by mode of drug administration of studies examining the relationship between paracetamol and overall PDA closure in comparison to ibuprofen.

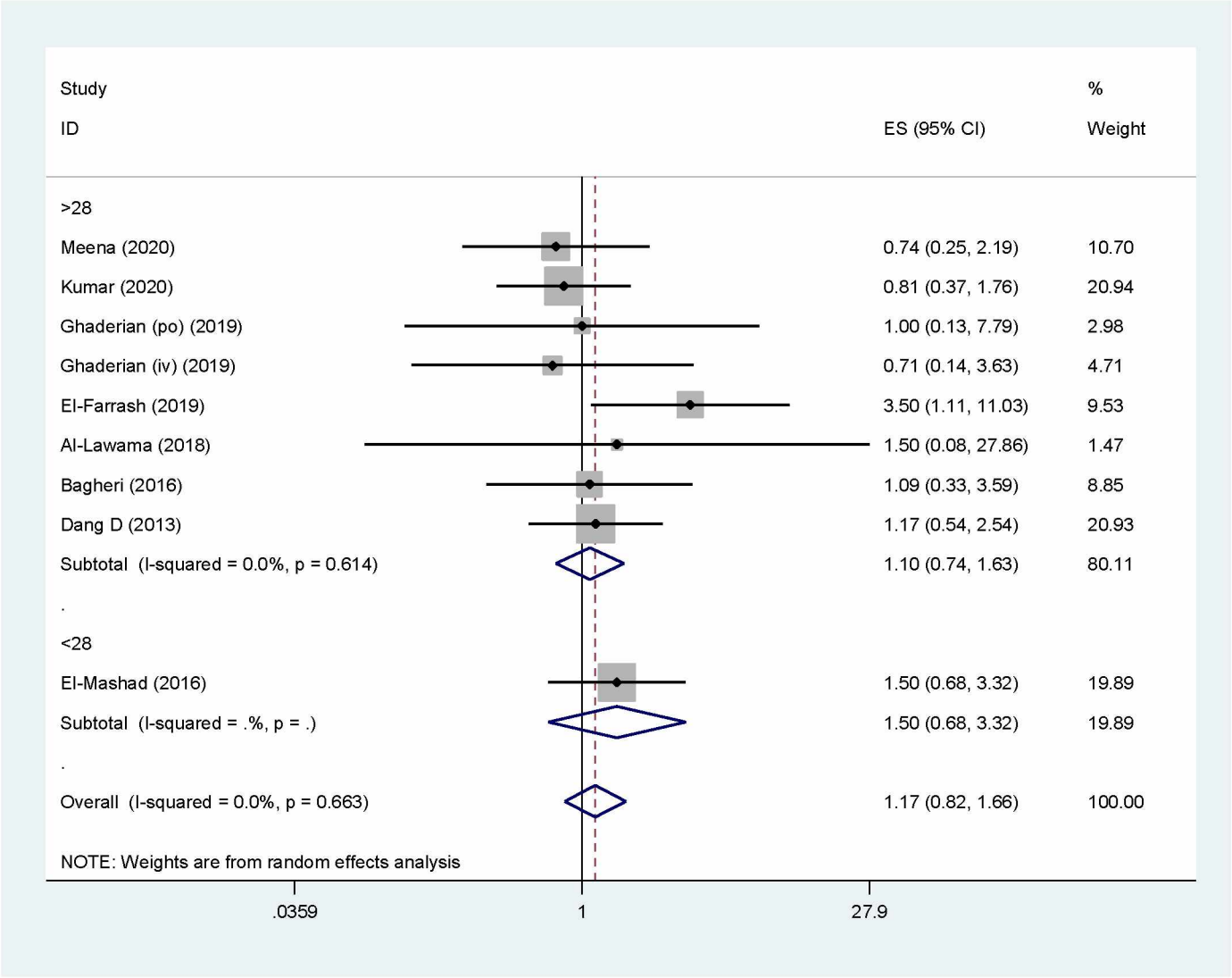

Figure 9. Forest plots of subgroup analysis by gestational age of studies examining the relationship between paracetamol and overall PDA closure in comparison to ibuprofen.

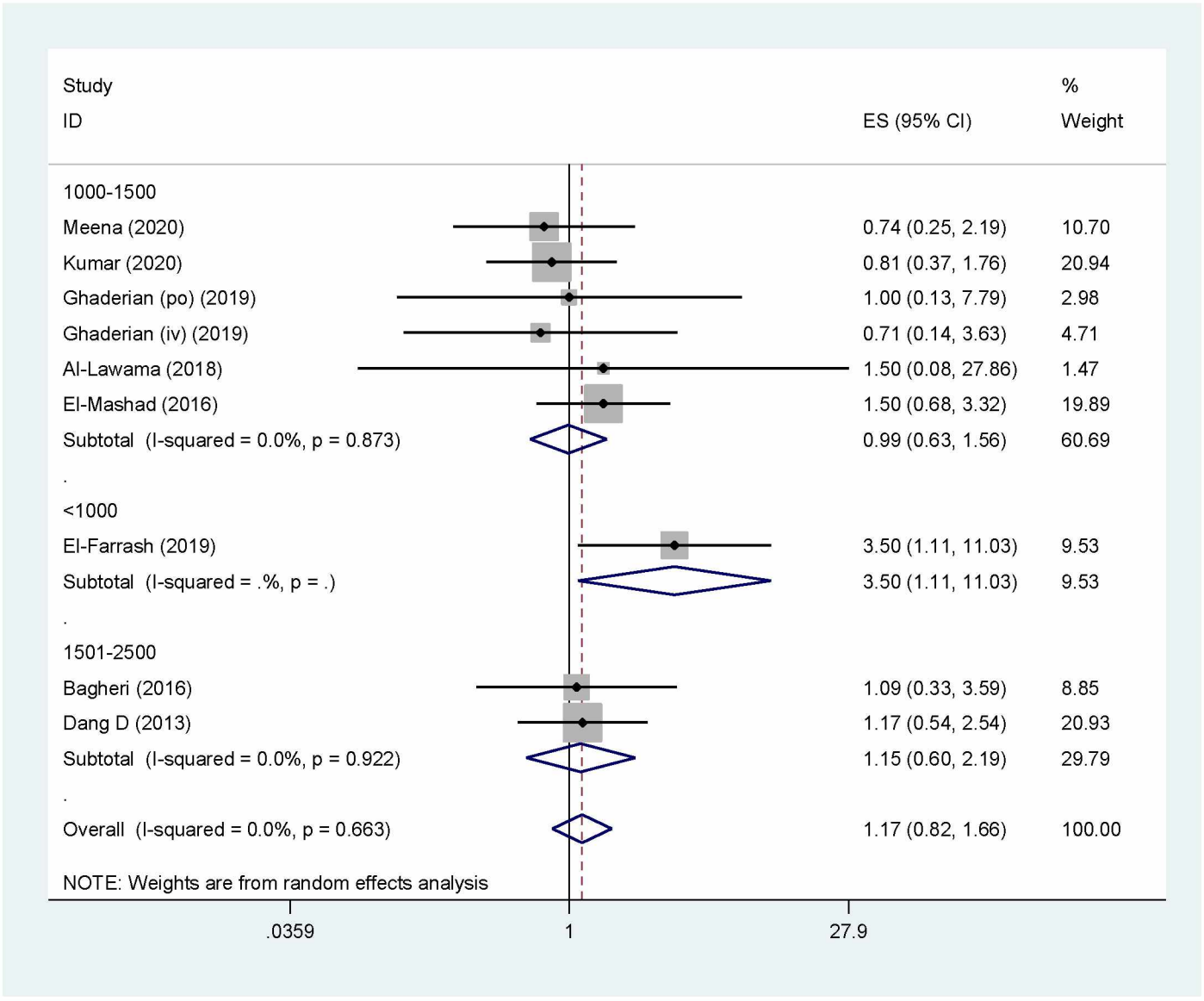

Figure 10. Forest plots of subgroup analysis by body weight of studies examining the relationship between paracetamol and overall PDA closure in comparison to ibuprofen

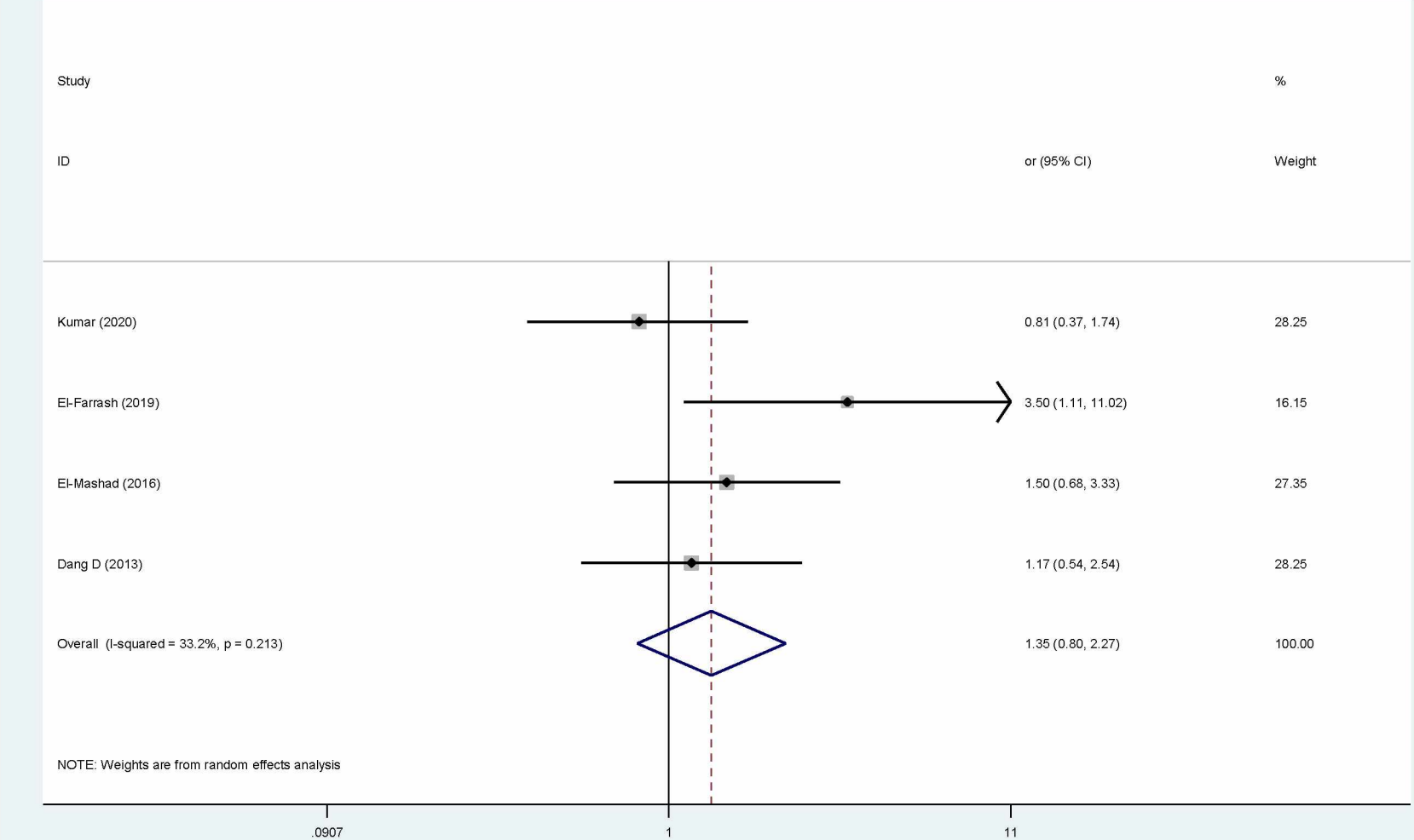

Figure 11. Forest plot of studies examining the relationship between paracetamol and overall PDA closure in comparison to ibuprofen, after sensitivity analysis.

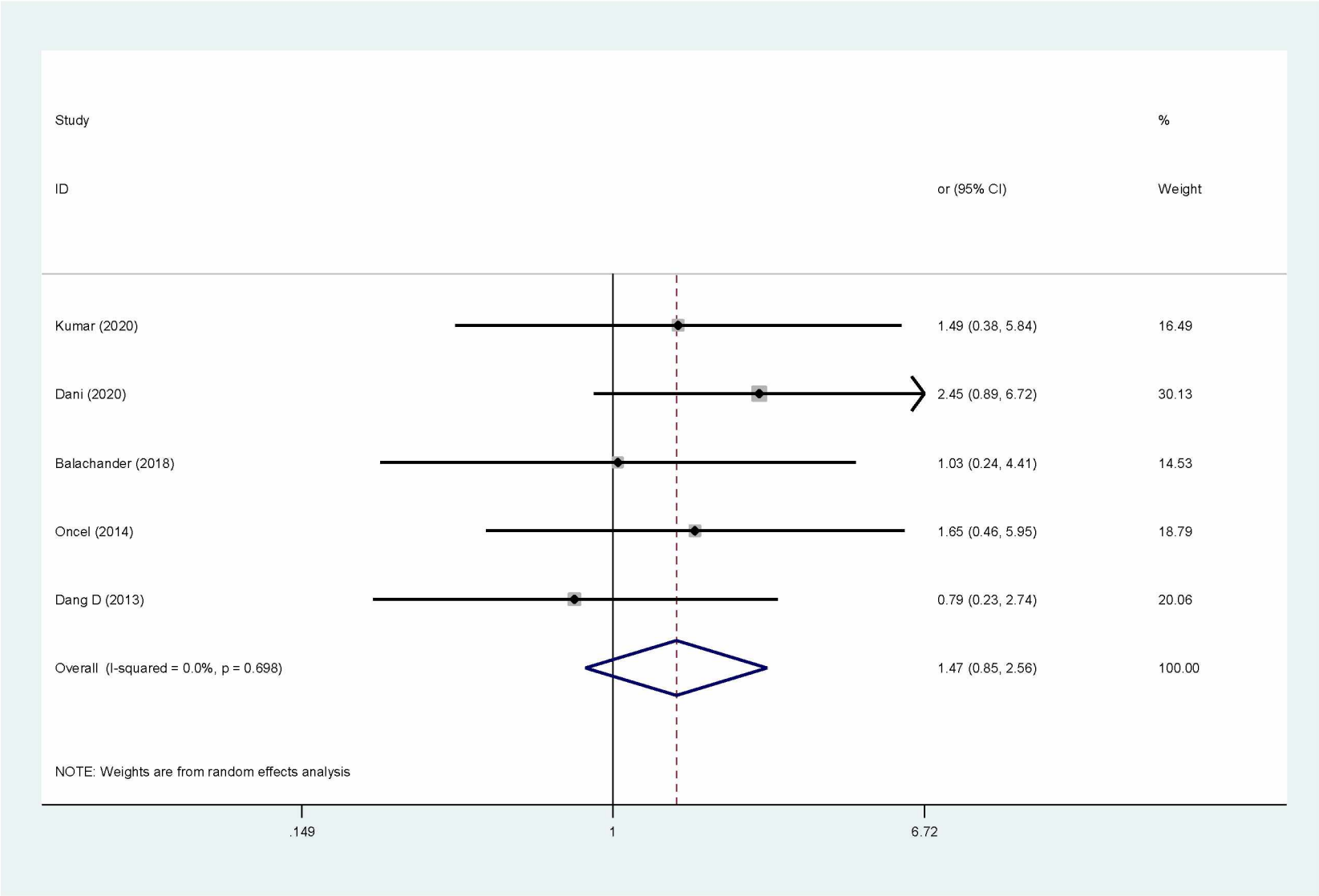

Figure 12. Forest plot of studies examining the relationship between paracetamol and recurrence of PDA in comparison to ibuprofen.

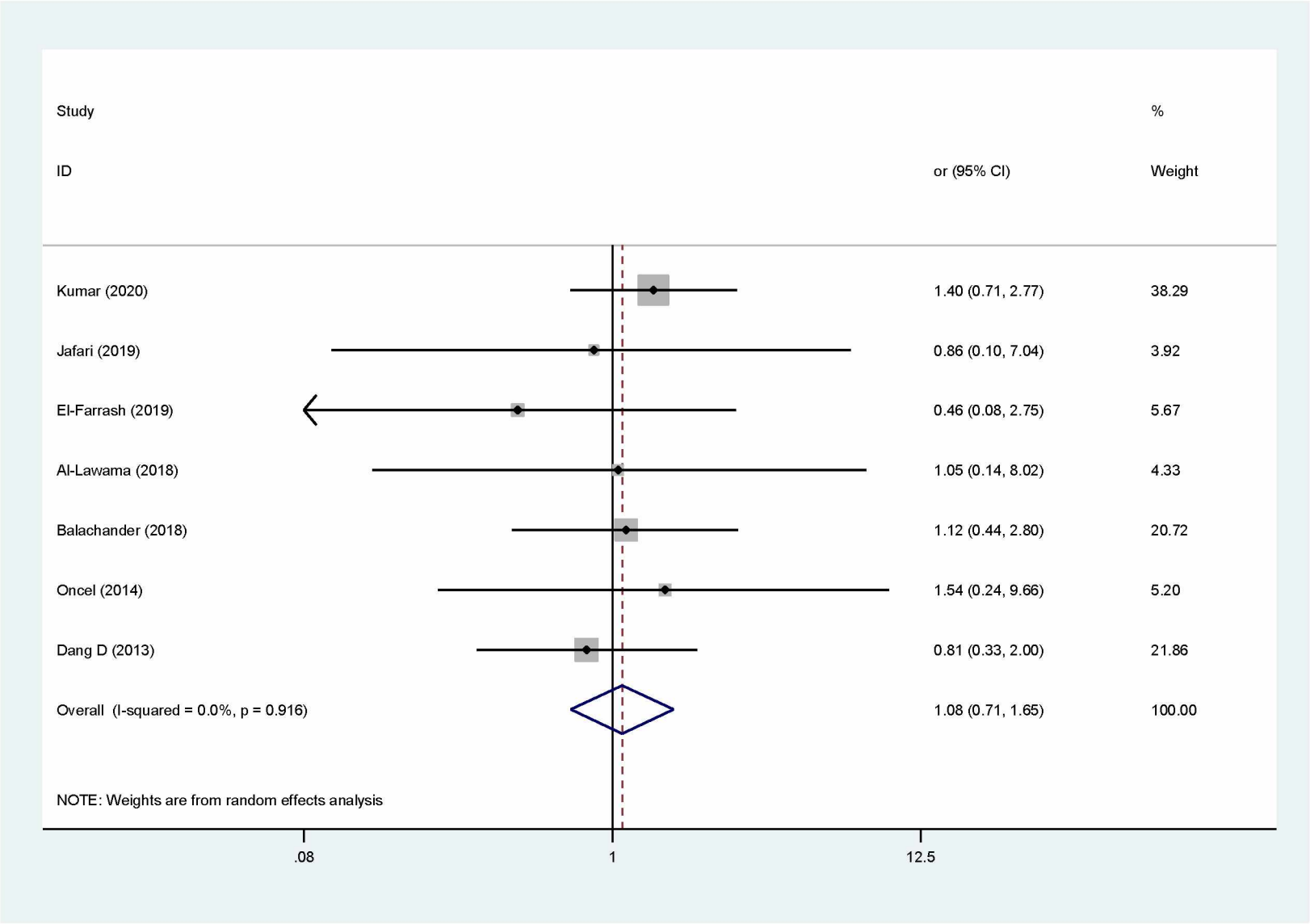

Figure 13. Forest plot of studies examining the relationship between paracetamol and mortality in comparison to ibuprofen.

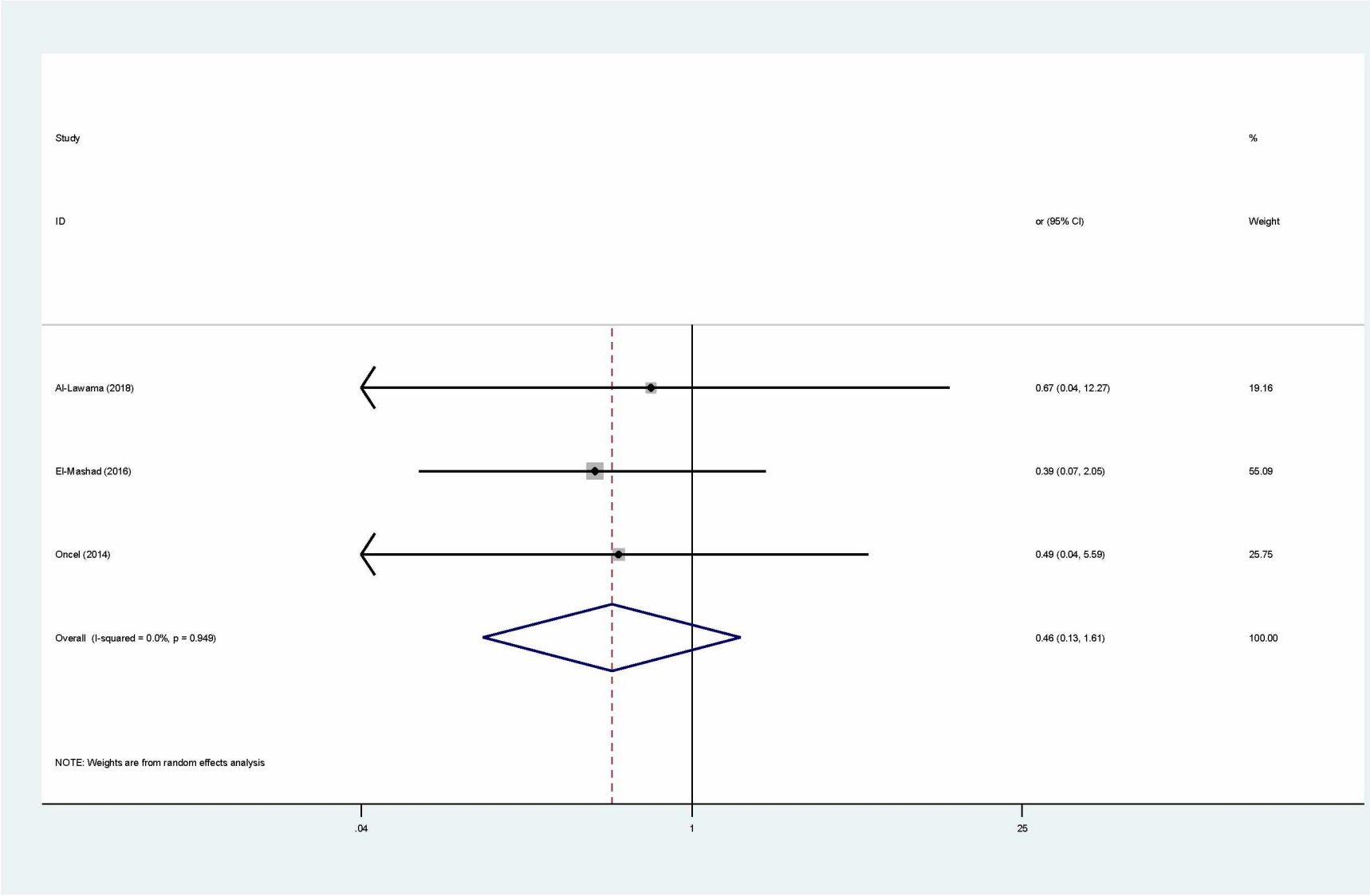

Figure 14. Forest plot of studies examining the relationship between paracetamol and pulmonary haemorrhage in comparison to ibuprofen.

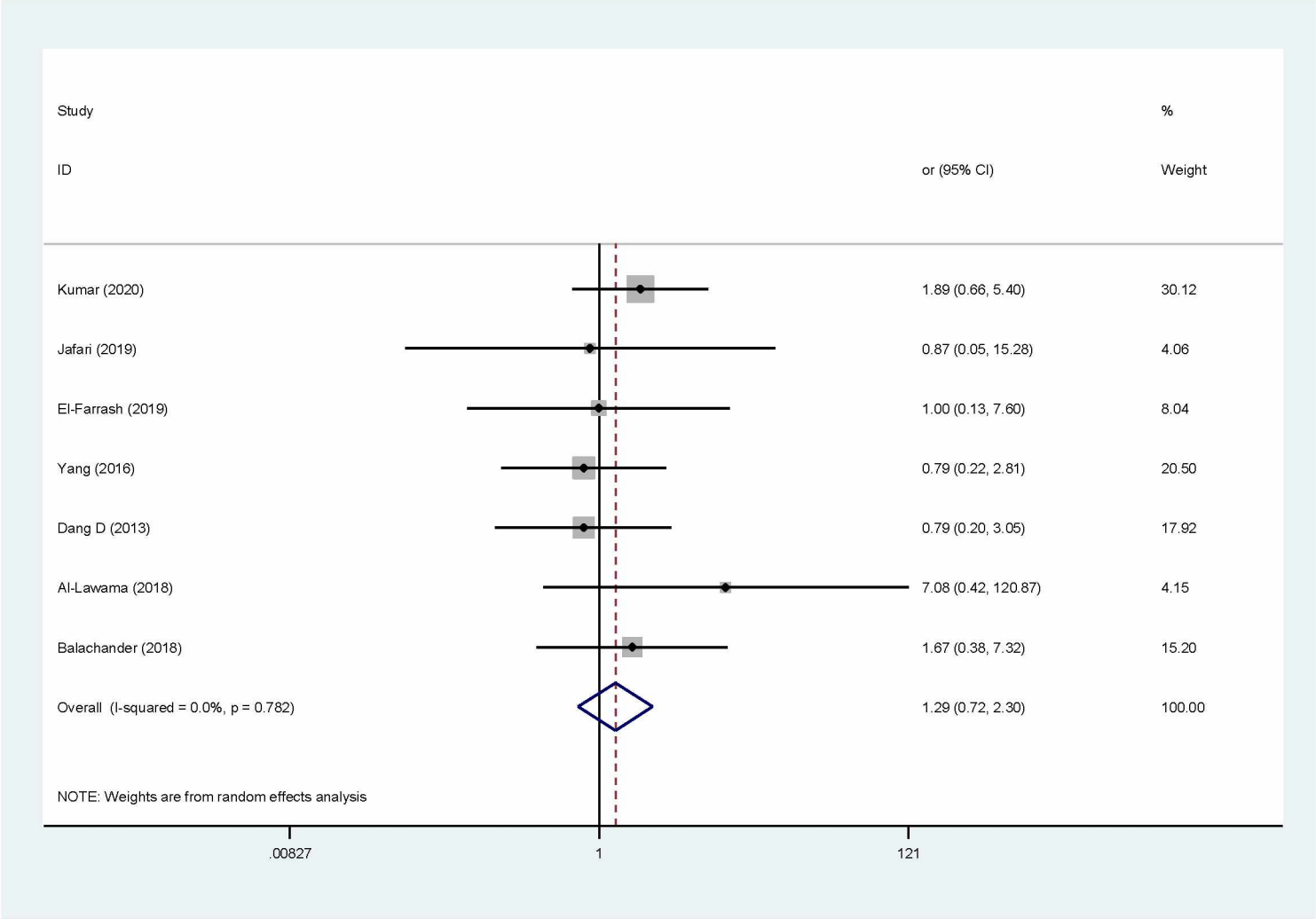

Figure 15. Forest plot of studies examining the relationship between paracetamol and BPD in comparison to ibuprofen.

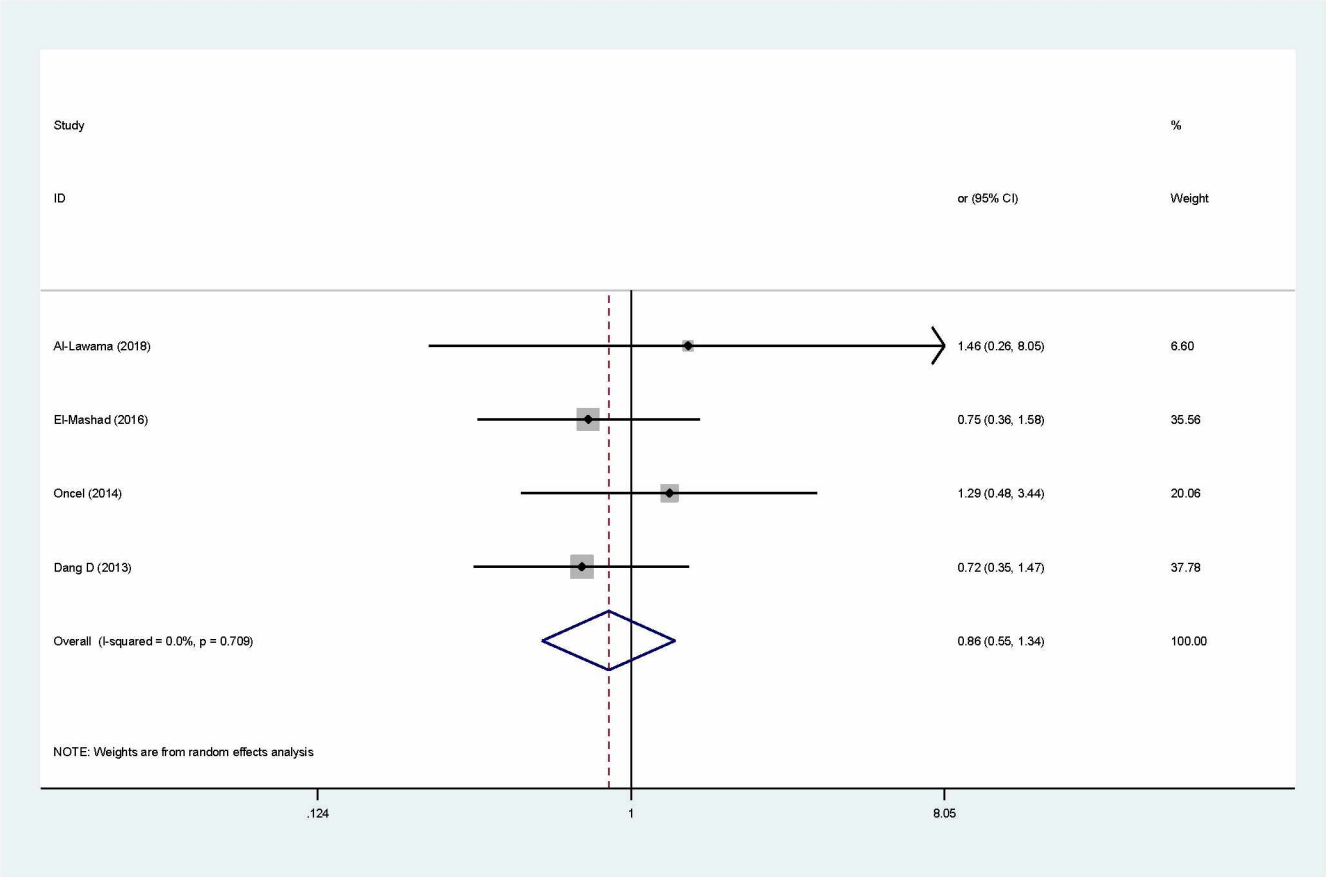

Figure 16. Forest plot of studies examining the relationship between paracetamol and sepsis in comparison to ibuprofen.

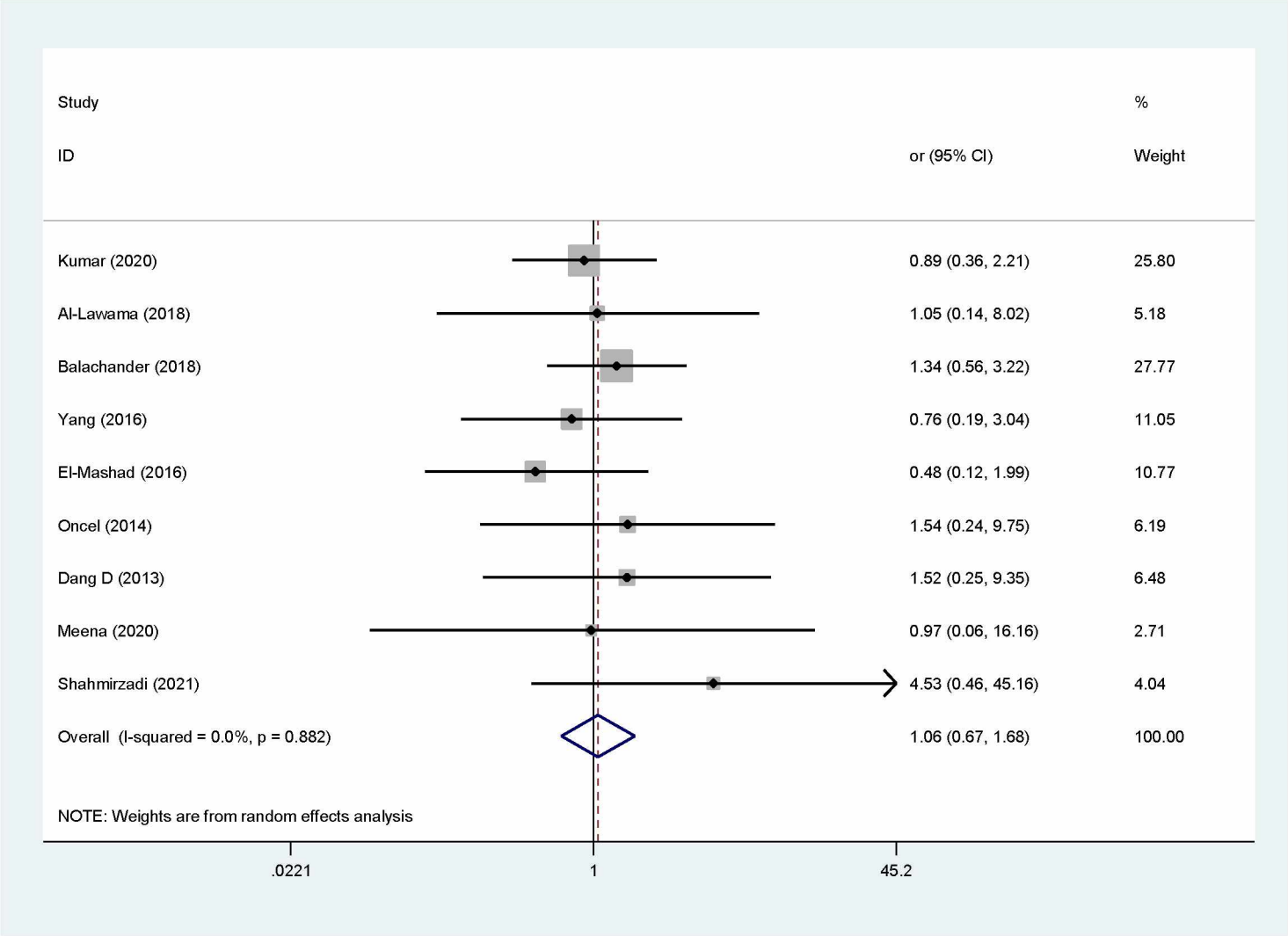

Figure 17. Forest plot of studies examining the relationship between paracetamol and NEC in comparison to ibuprofen.

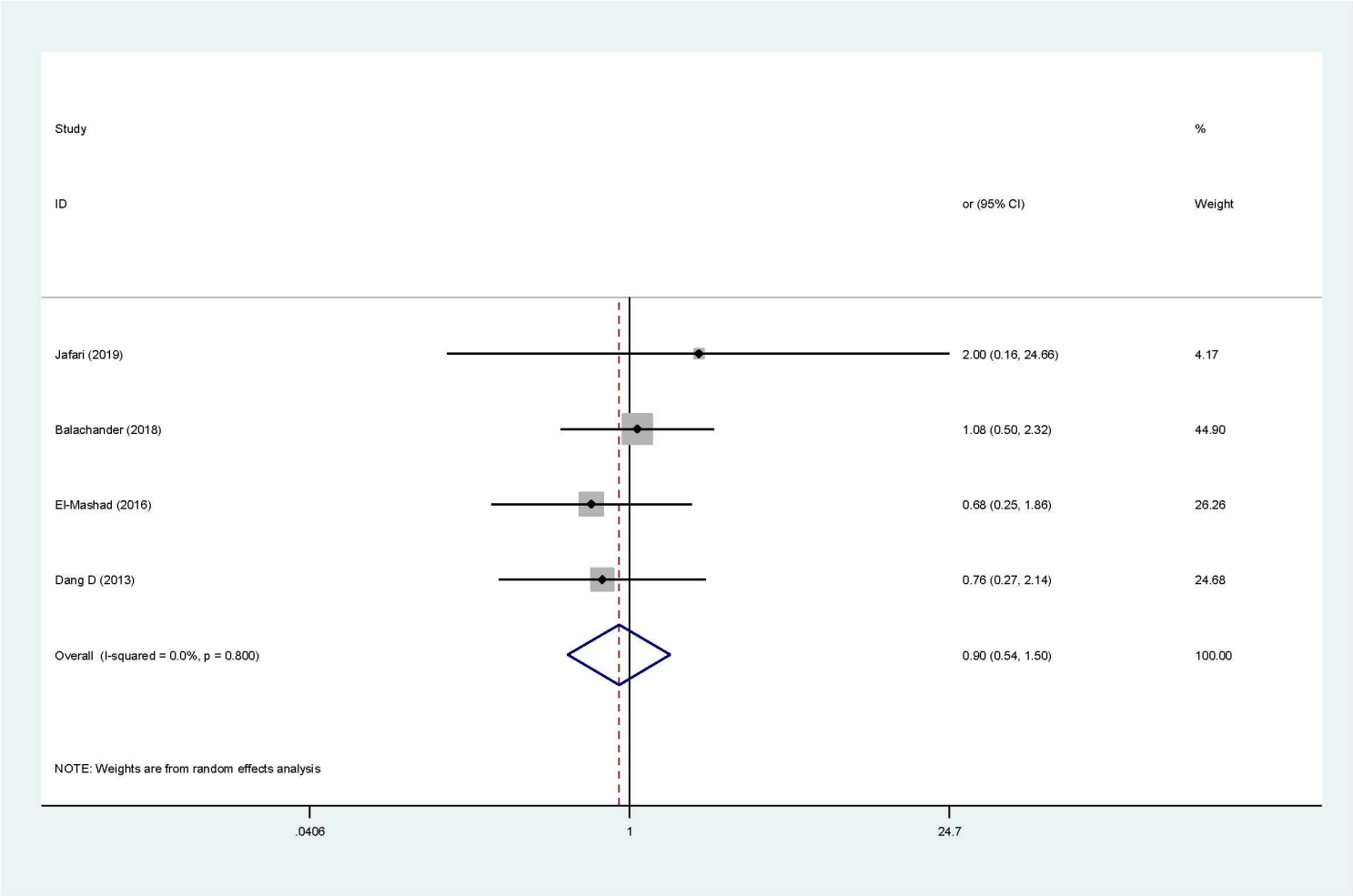

Figure 18. Forest plot of studies examining the relationship between paracetamol and ROP in comparison to ibuprofen.

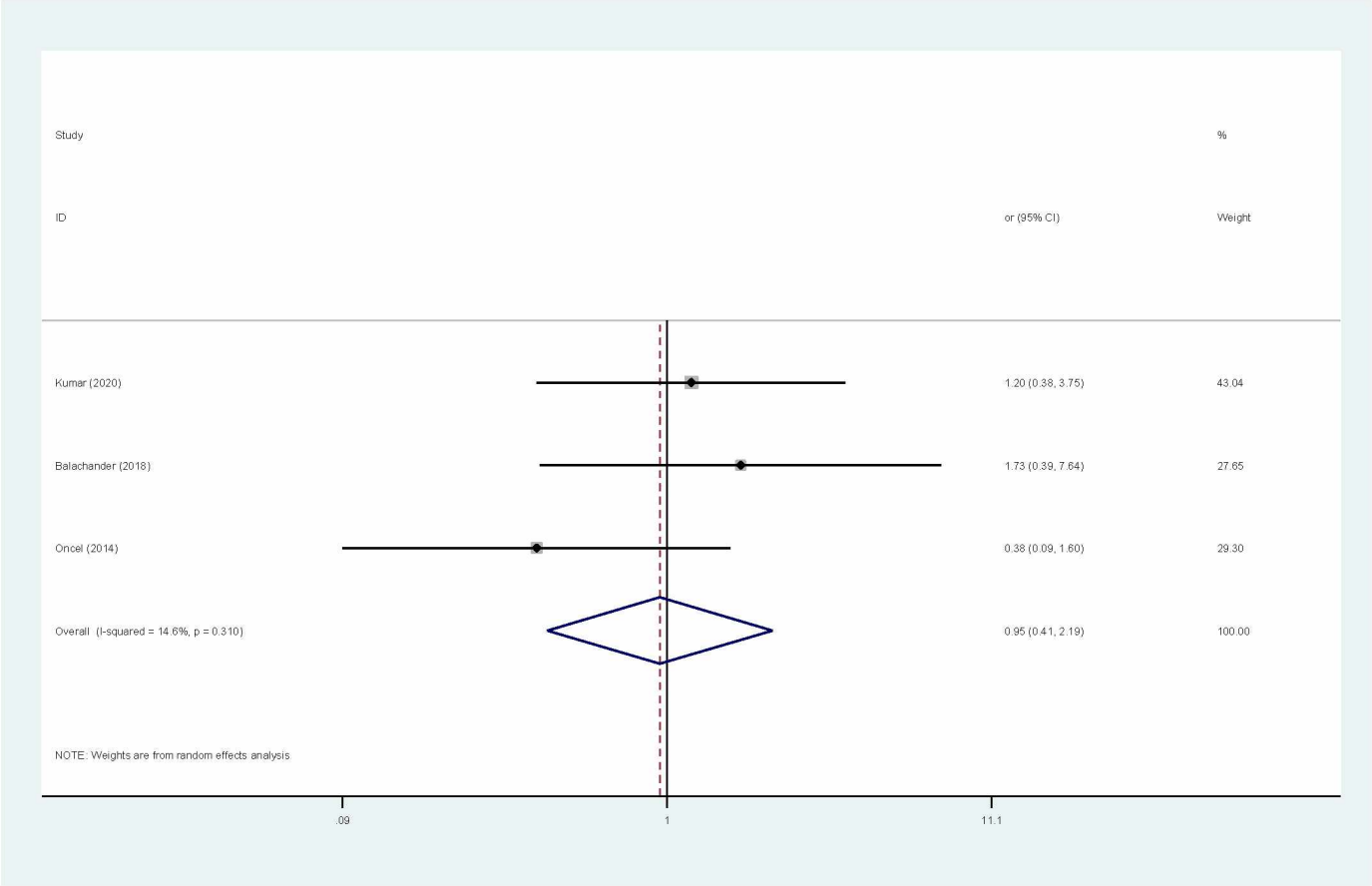

Figure 19. Forest plot of studies examining the relationship between paracetamol and ROP requiring treatment in comparison to ibuprofen.

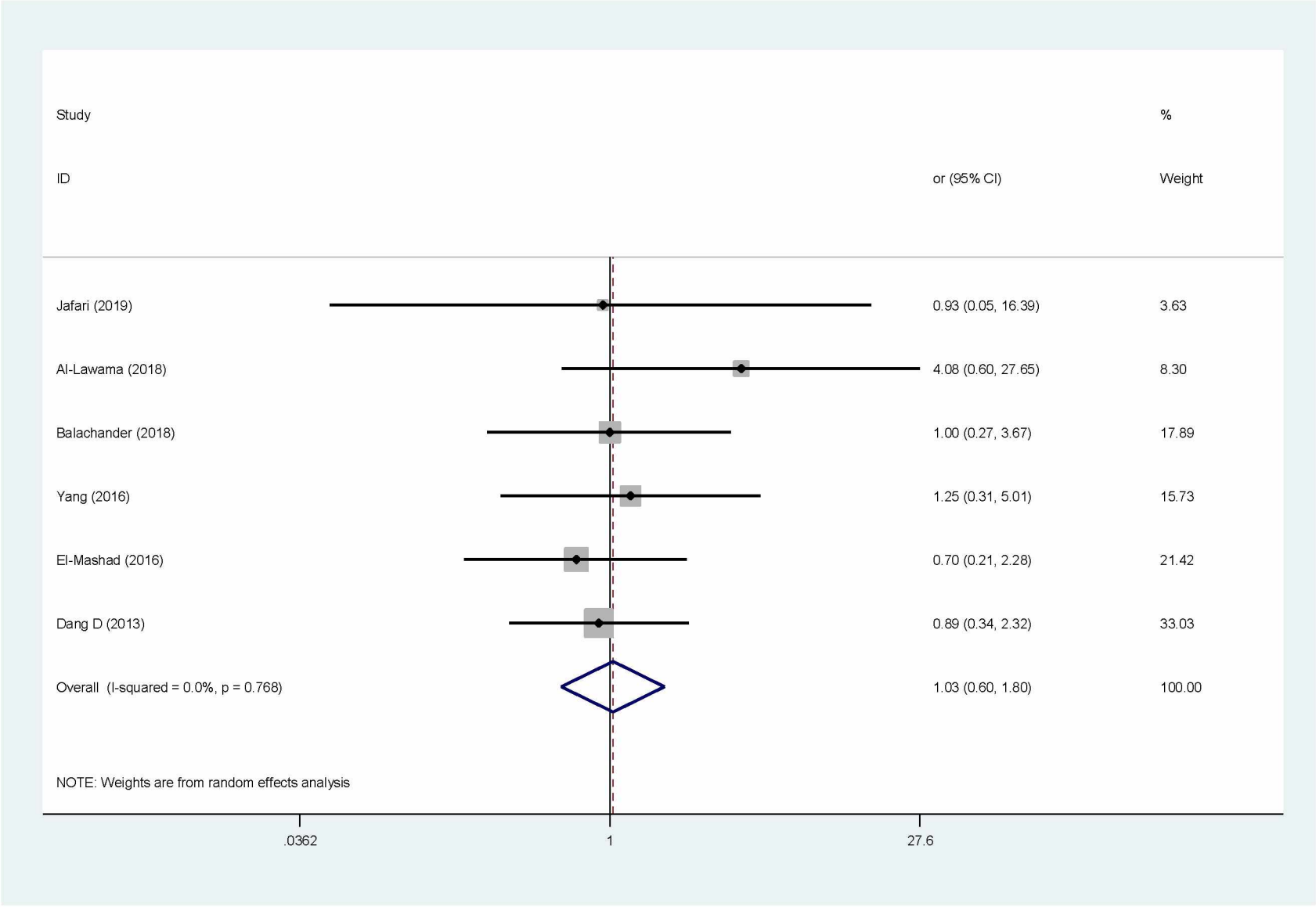

Figure 20. Forest plot of studies examining the relationship between paracetamol and IVH in comparison to ibuprofen.

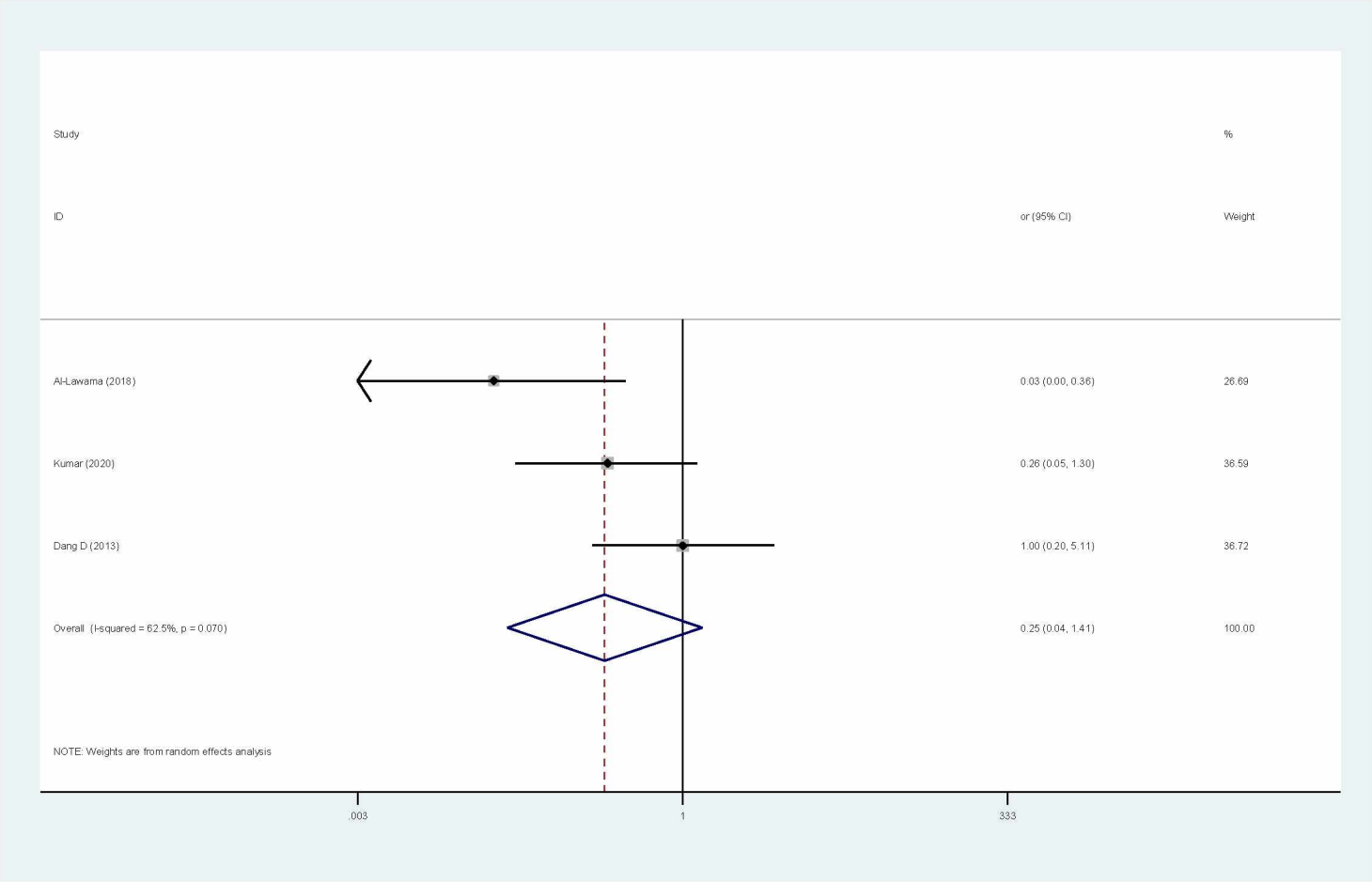

Figure 21. Forest plot of studies examining the relationship between paracetamol and IVH grade III/IV in comparison to ibuprofen.

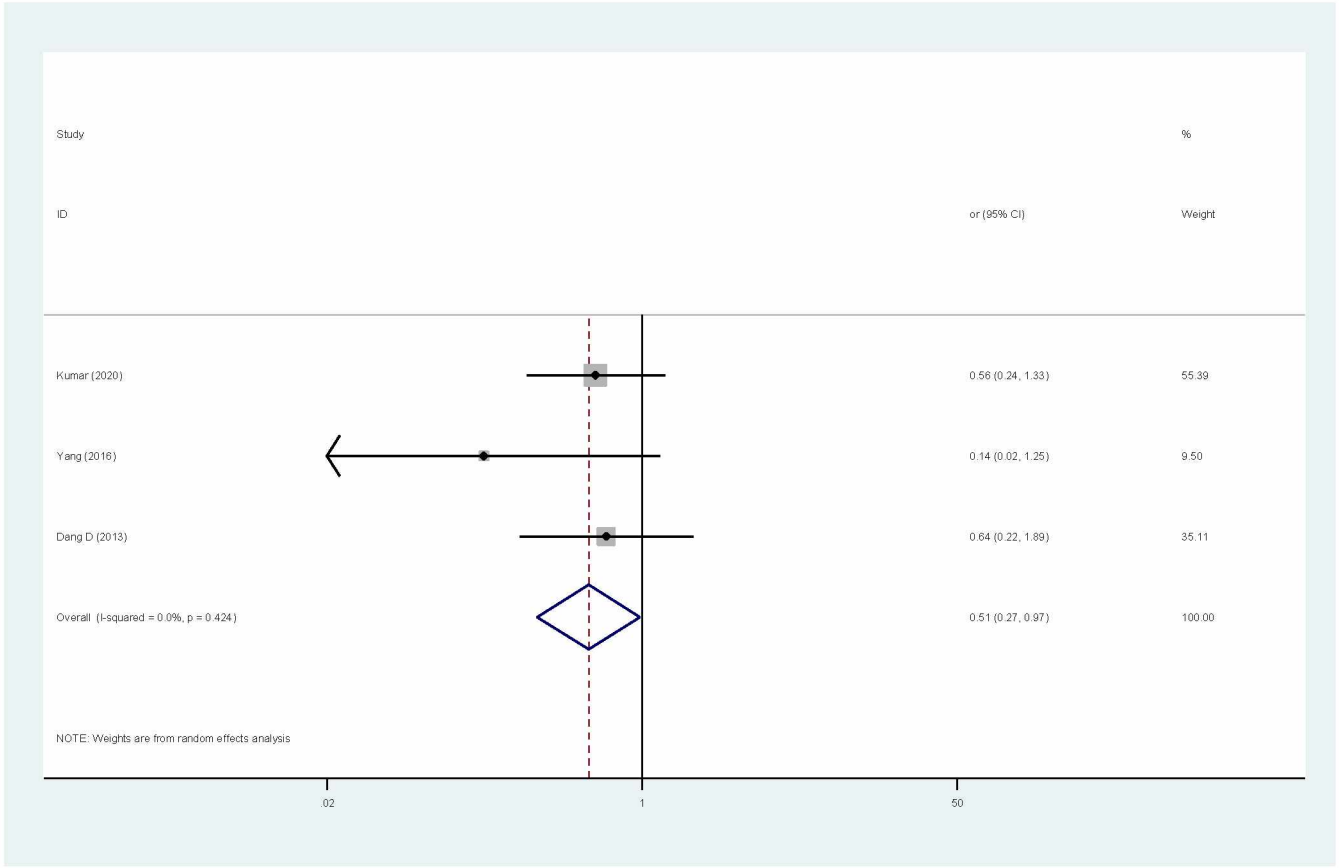

Figure 22. Forest plot of studies examining the relationship between paracetamol and oliguria in comparison to ibuprofen.

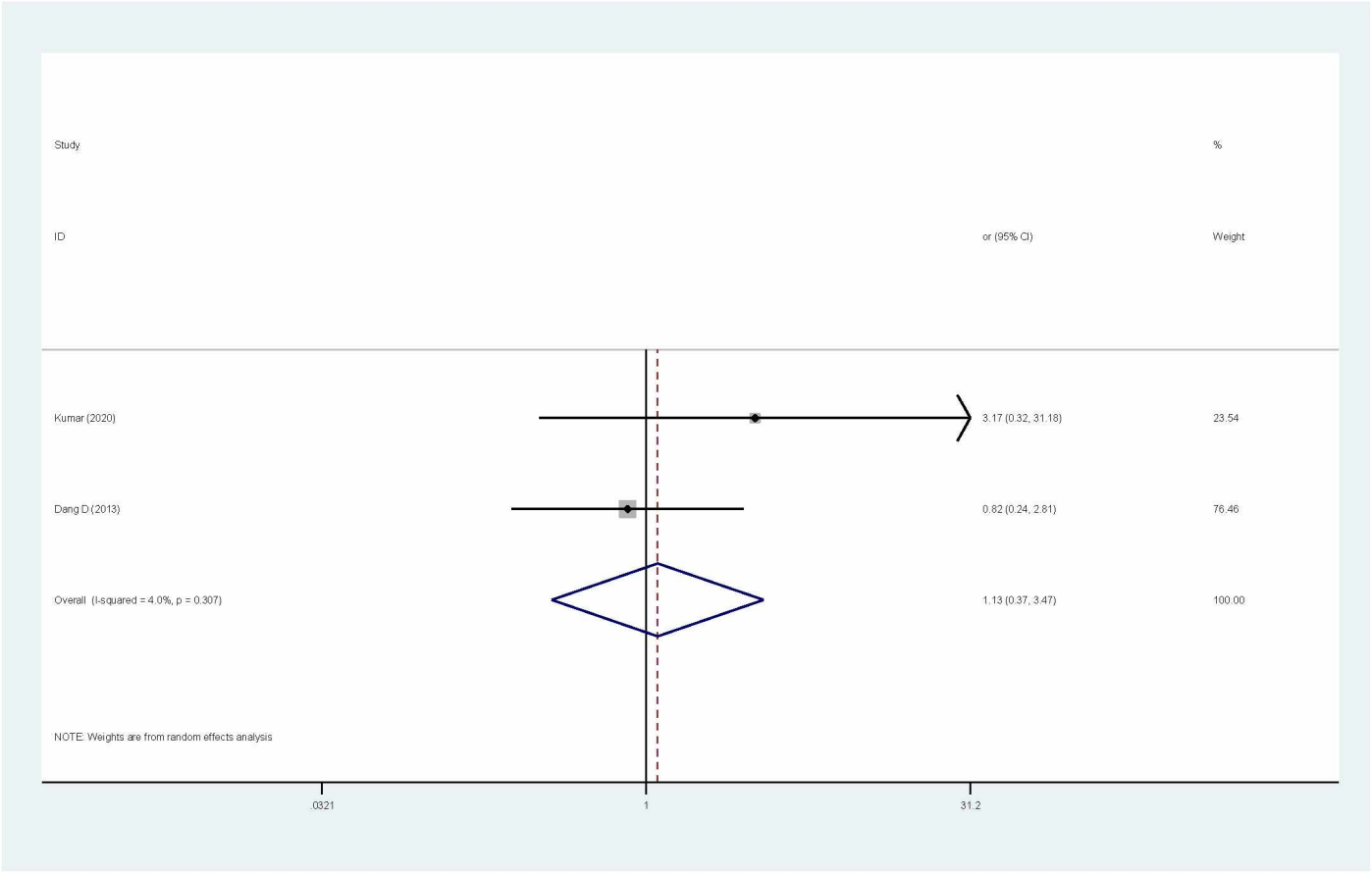

Figure 23. Forest plot of studies examining the relationship between paracetamol and PVL in comparison to ibuprofen.

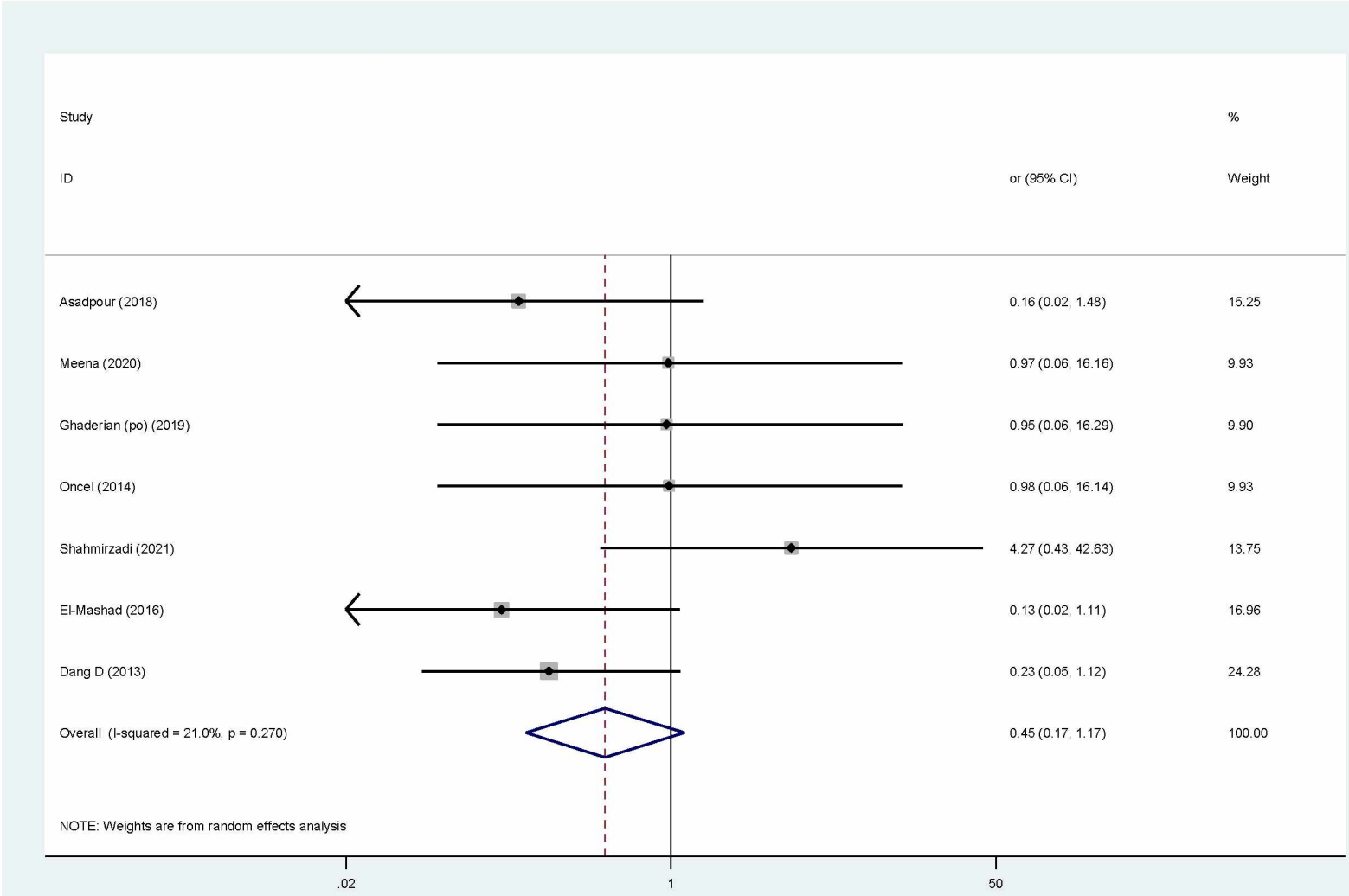

Figure 24. Forest plot of studies examining the relationship between paracetamol and GI bleeding in comparison to ibuprofen.

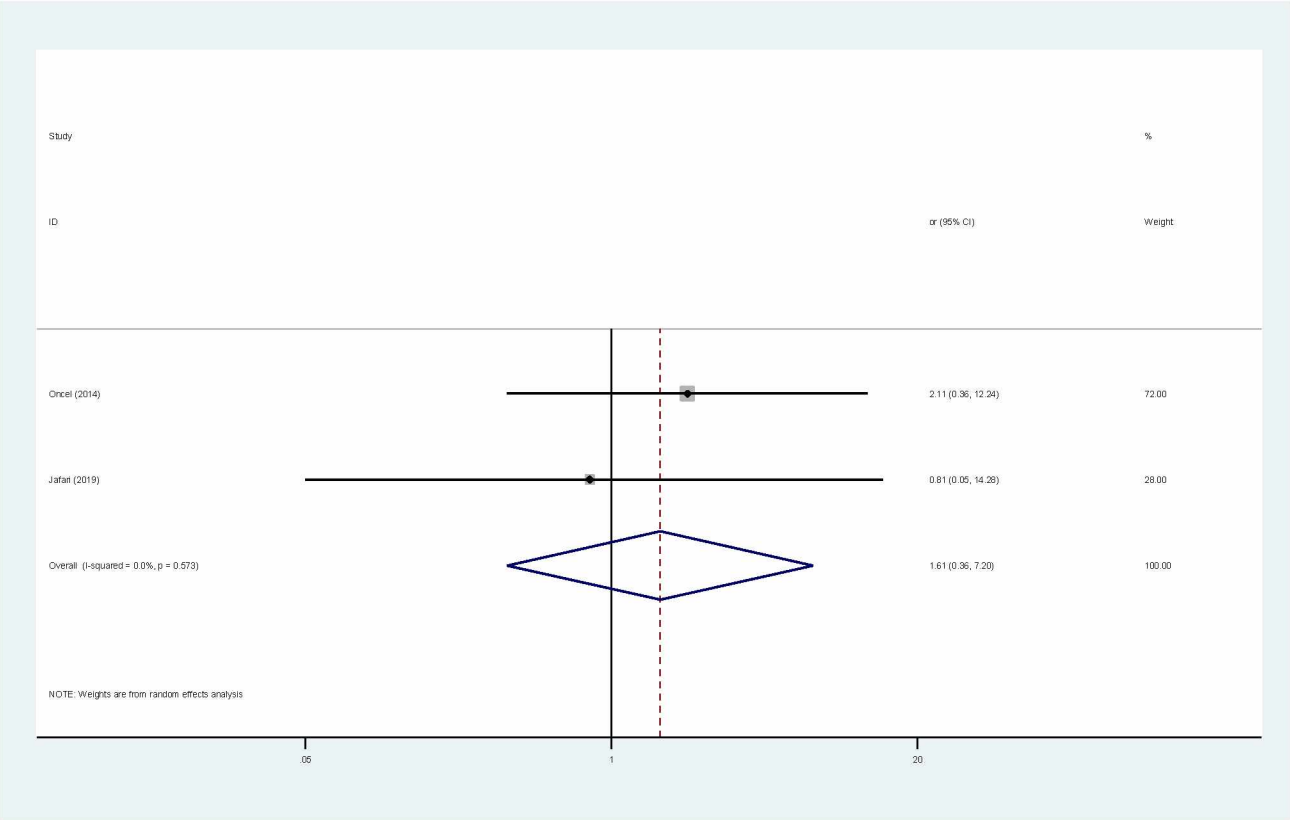

Figure 25. Forest plot of studies examining the relationship between paracetamol and pneumothorax in comparison to ibuprofen.

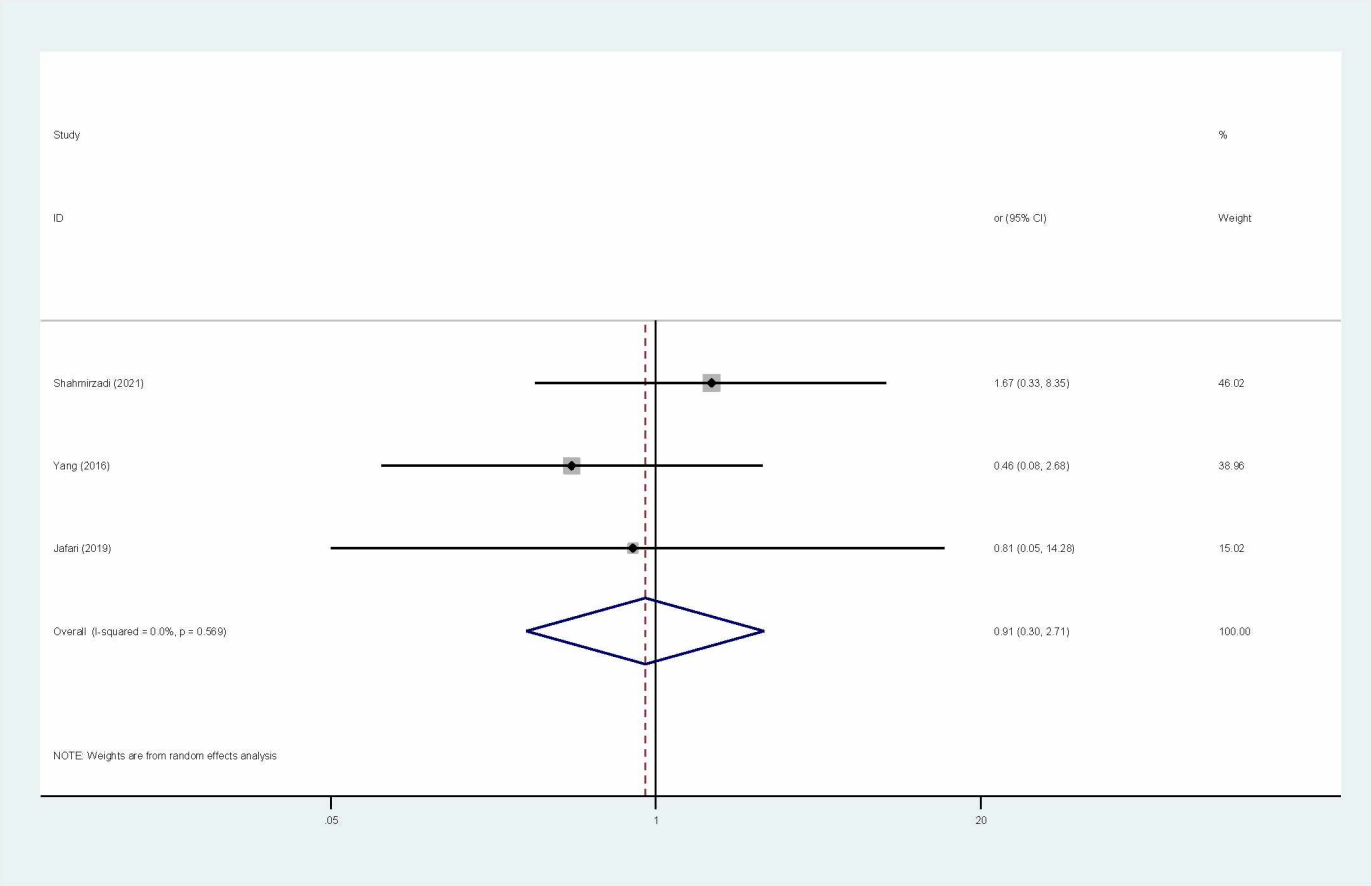

Figure 26. Forest plot of studies examining the relationship between paracetamol and positive OB test in comparison to ibuprofen.

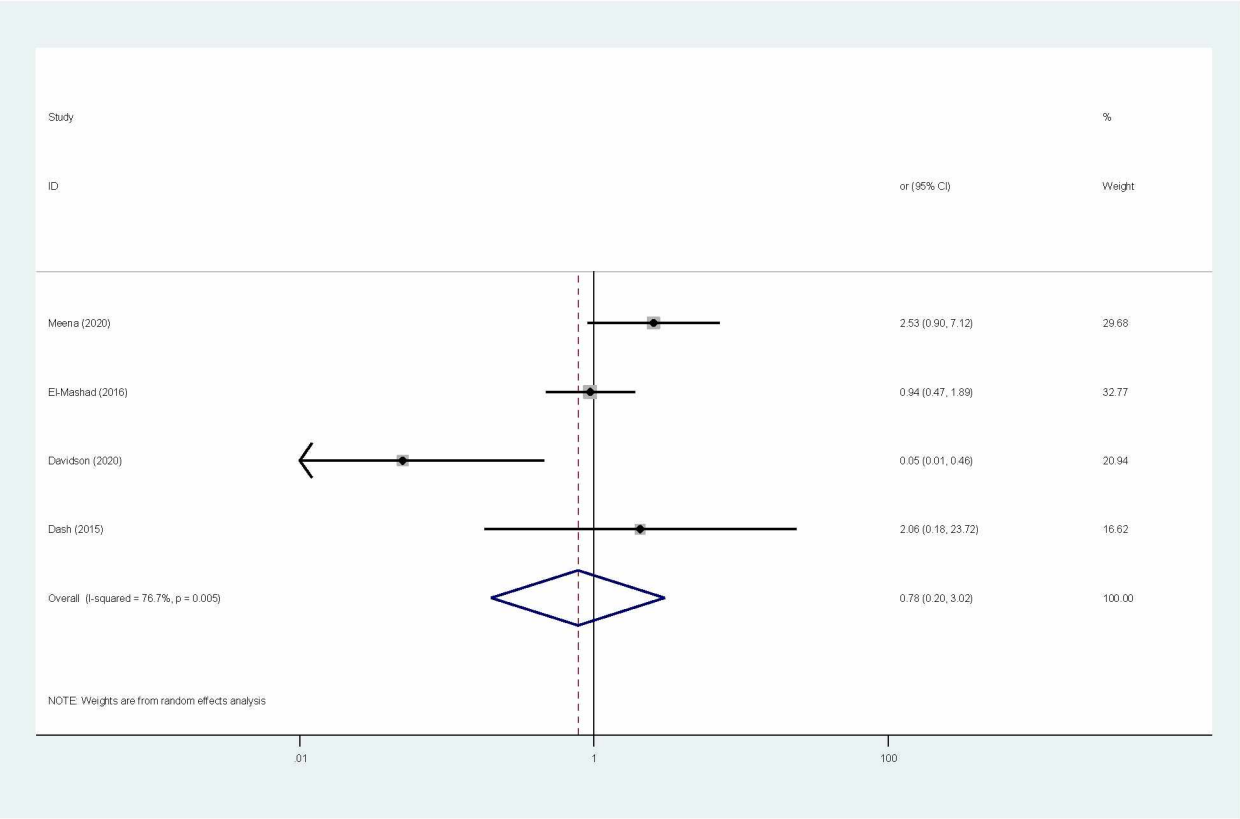

Figure 27. Forest plot of studies examining the relationship between paracetamol and primary PDA closure in comparison to indomethacin.

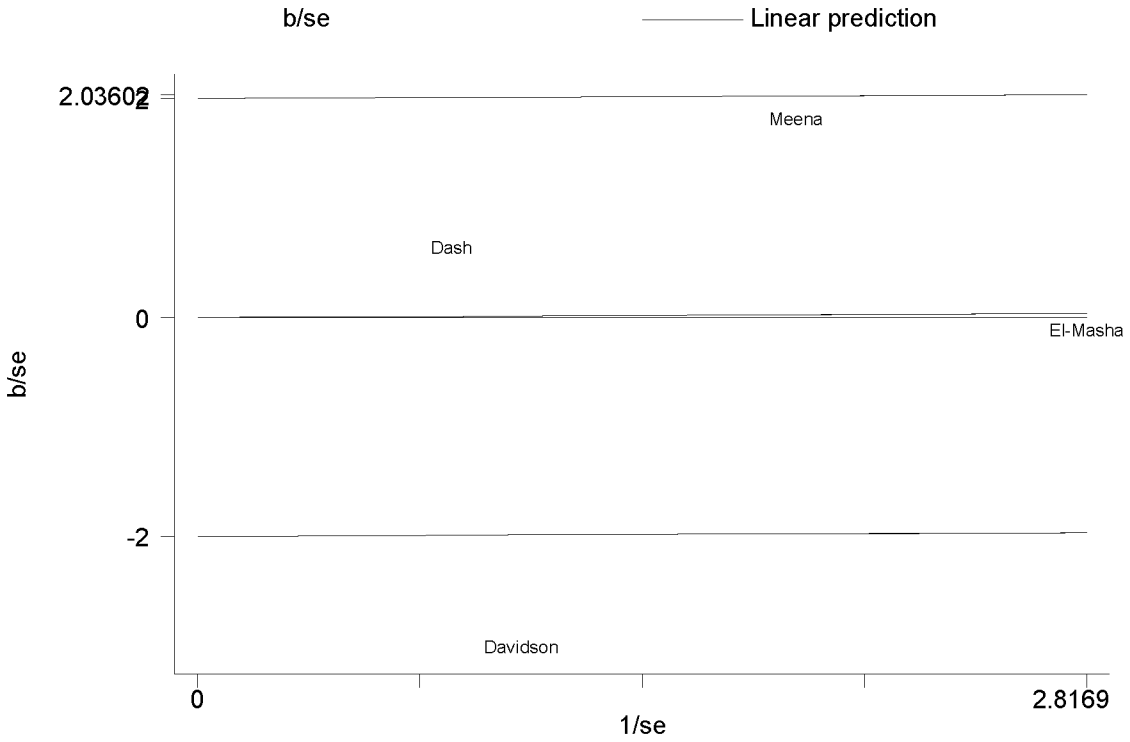

Figure 28. Galbraith plot of studies examining the relationship between paracetamol and primary PDA closure in comparison to indomethacin.

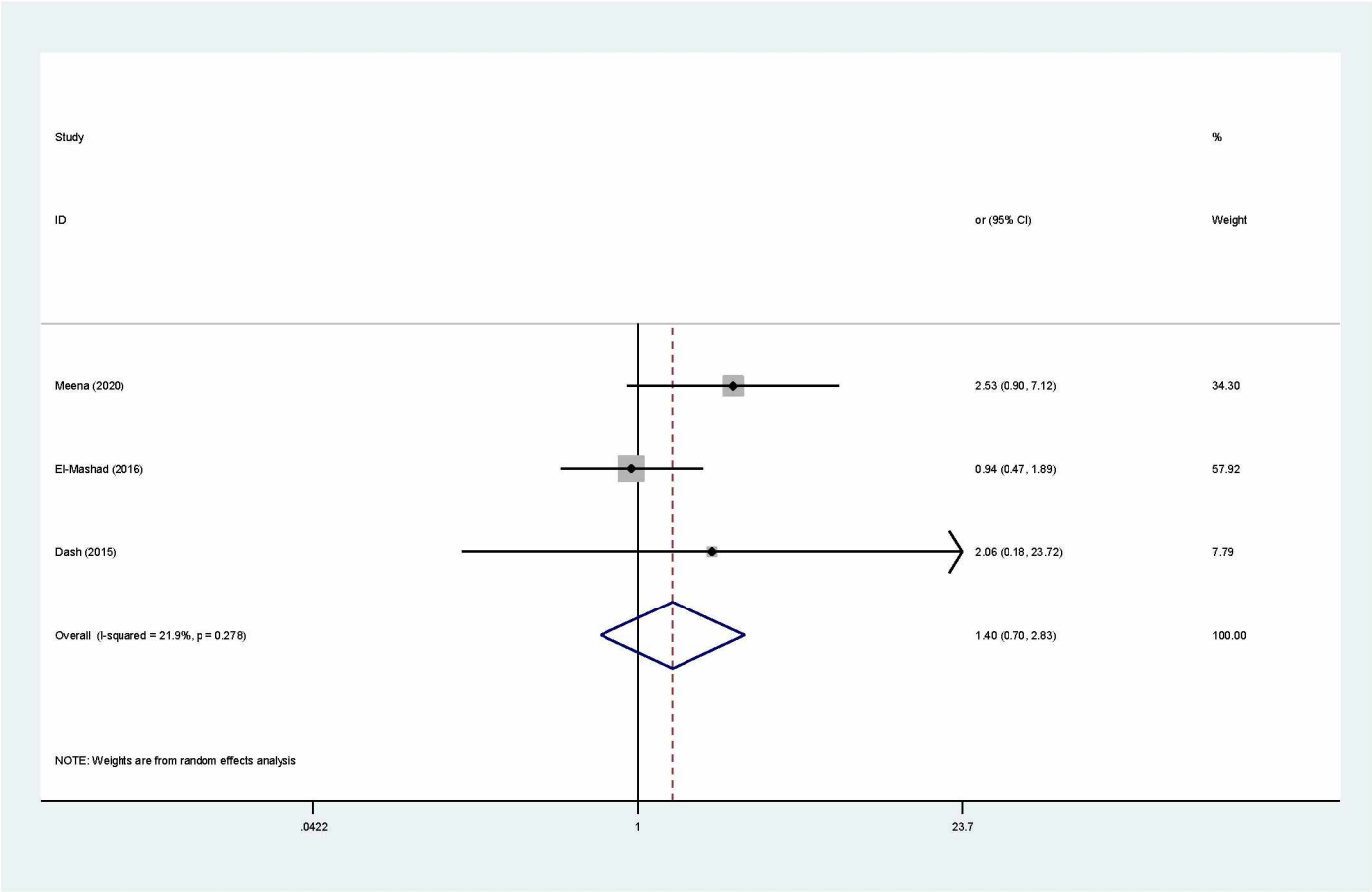

Figure 29. Forest plot of studies examining the relationship between paracetamol and primary PDA closure in comparison to indomethacin, after the removal of one study.

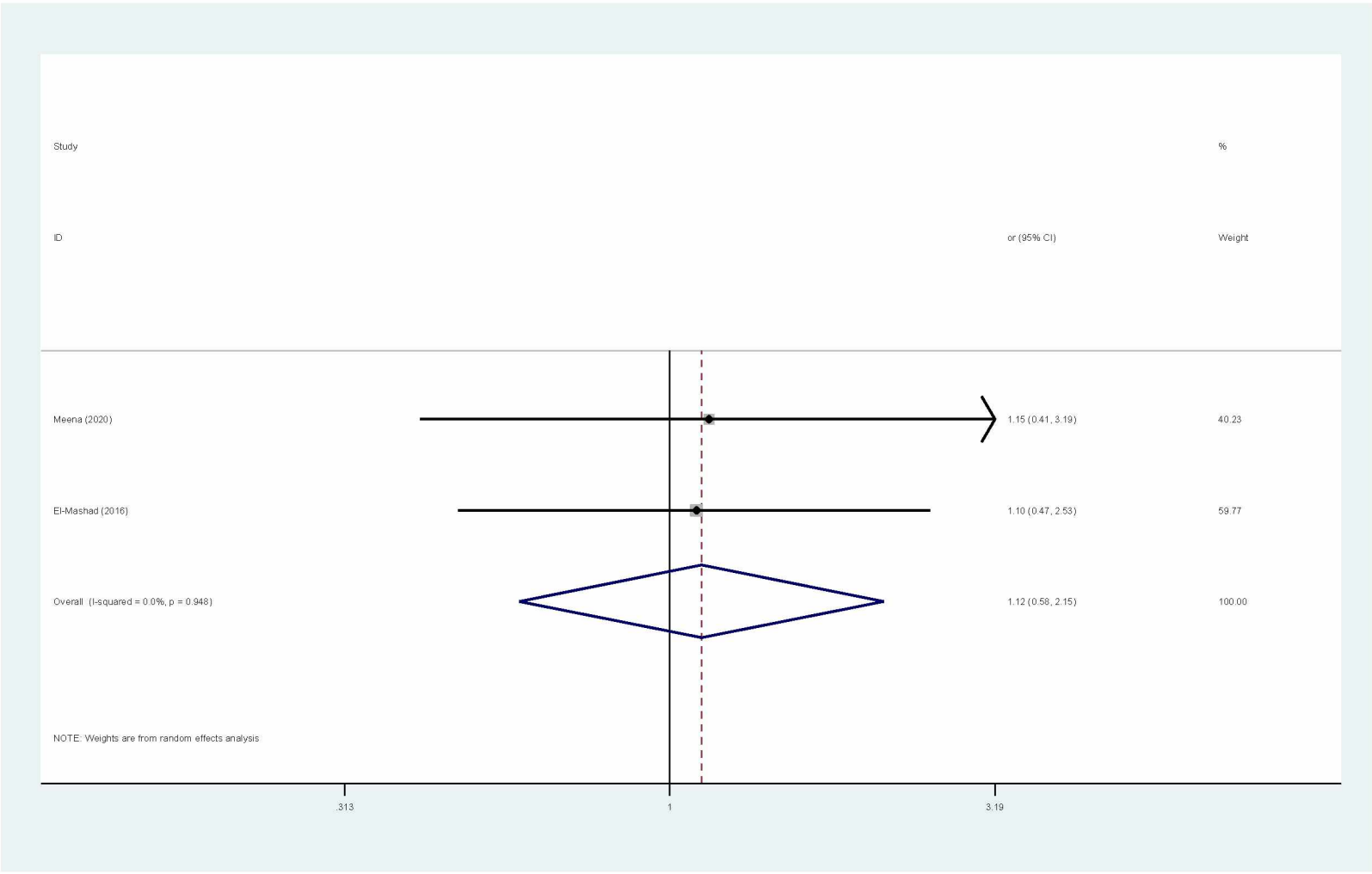

Figure 30. Forest plot of studies examining the relationship between paracetamol and overall PDA closure in comparison to indomethacin.

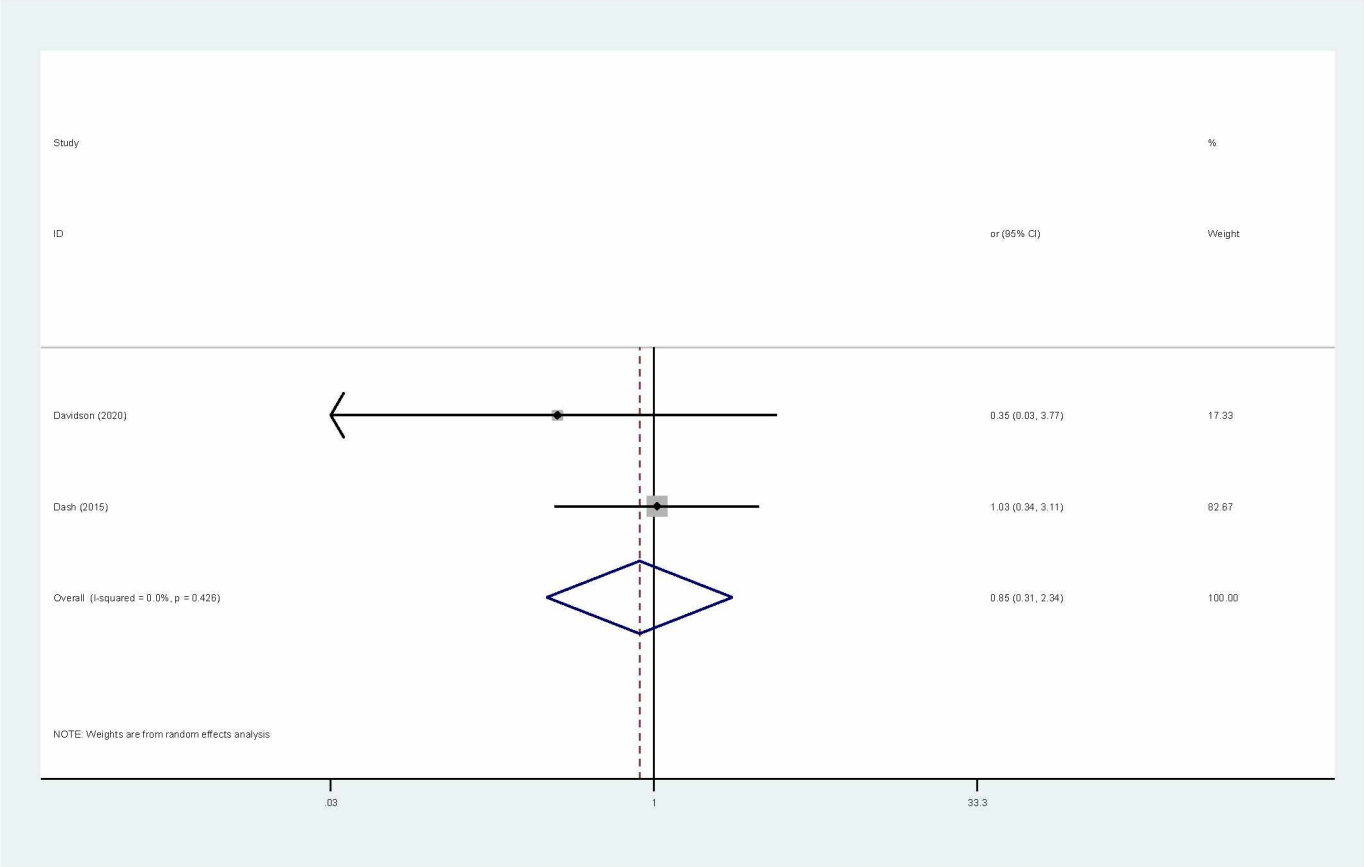

Figure 31. Forest plot of studies examining the relationship between paracetamol and mortality in comparison to indomethacin.

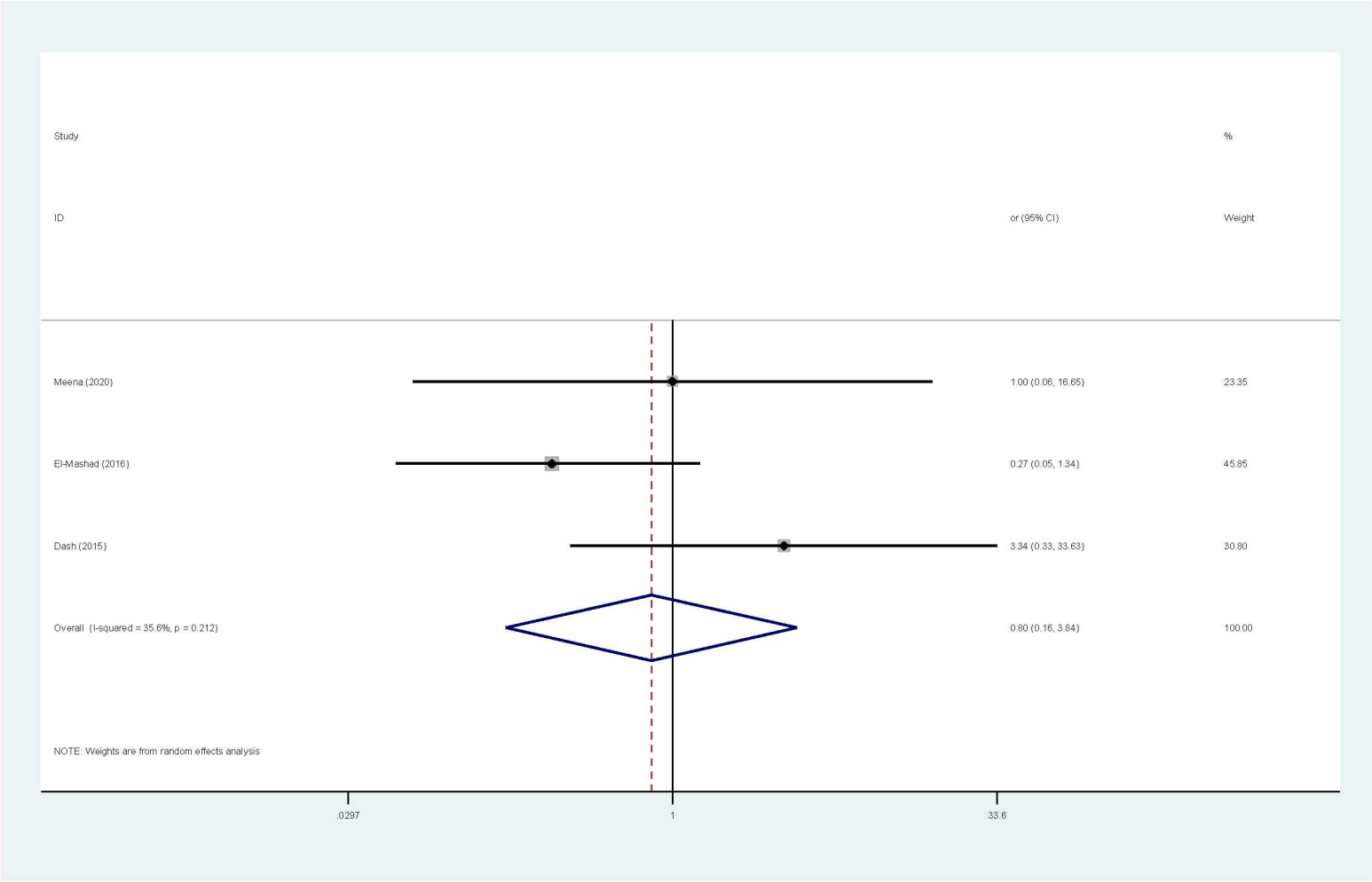

Figure 32. Forest plot of studies examining the relationship between paracetamol and pulmonary haemorrhage in comparison to indomethacin.

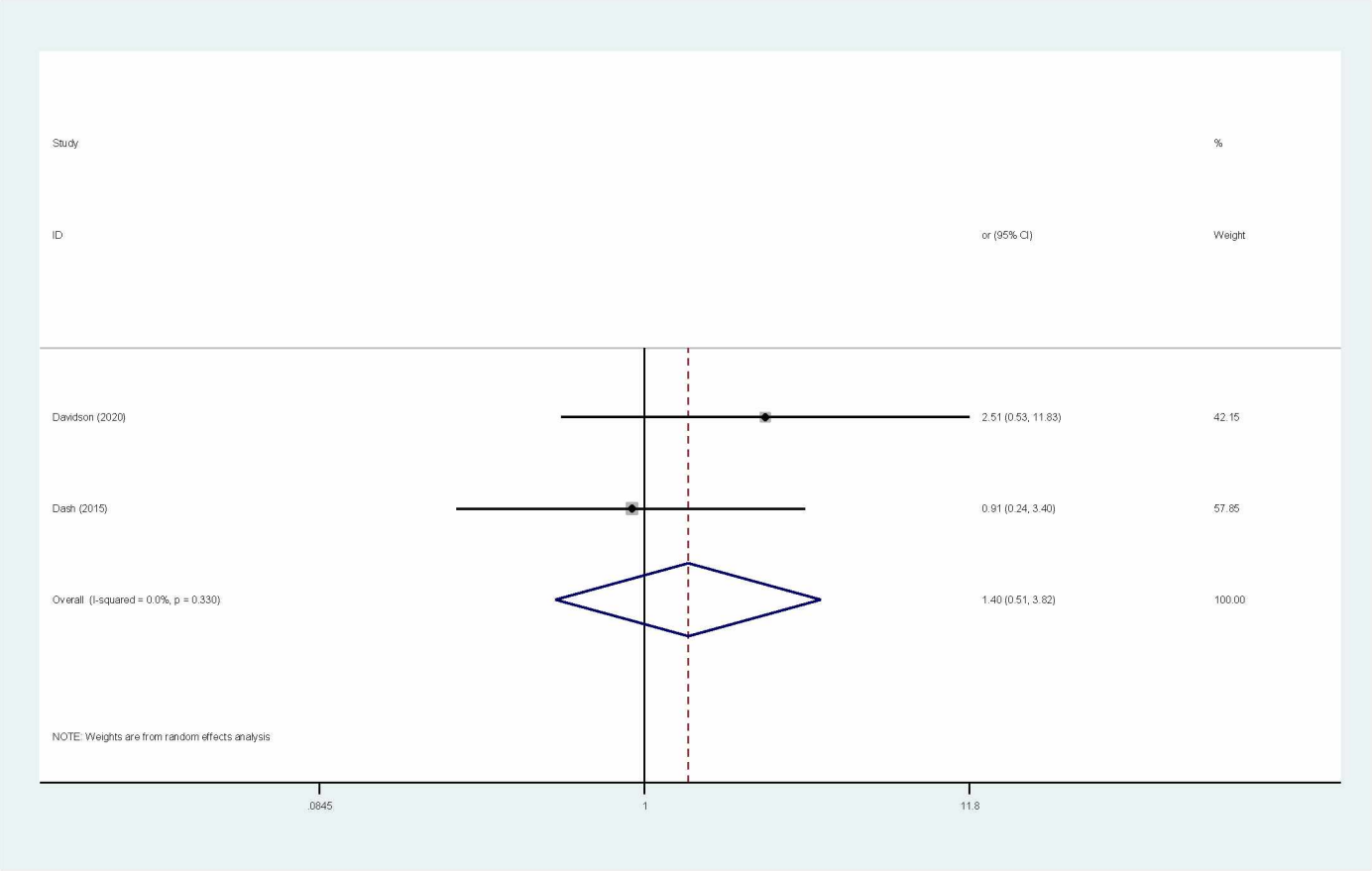

Figure 33. Forest plot of studies examining the relationship between paracetamol and BPD in comparison to indomethacin.

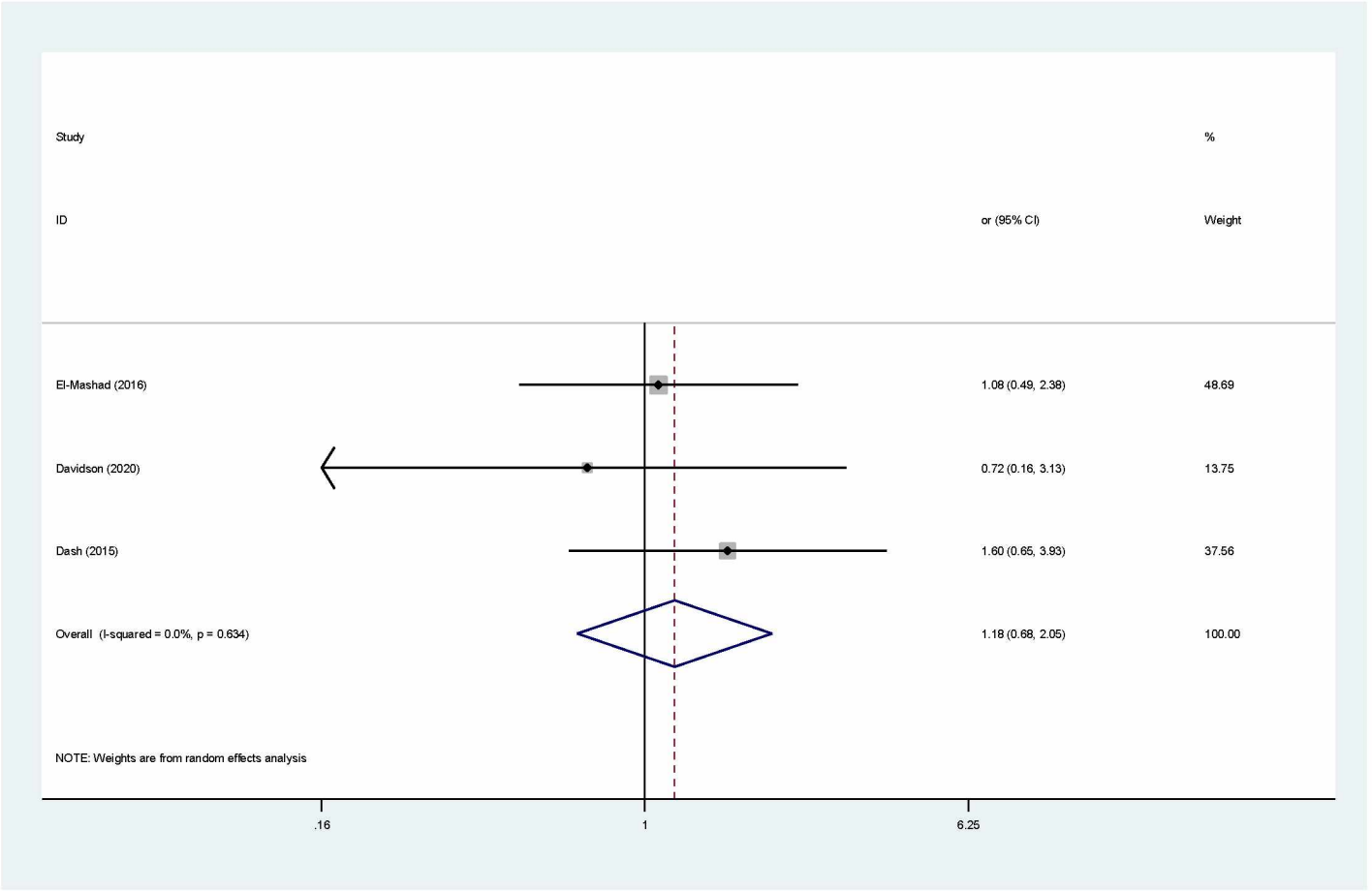

Figure 34. Forest plot of studies examining the relationship between paracetamol and sepsis in comparison to indomethacin.

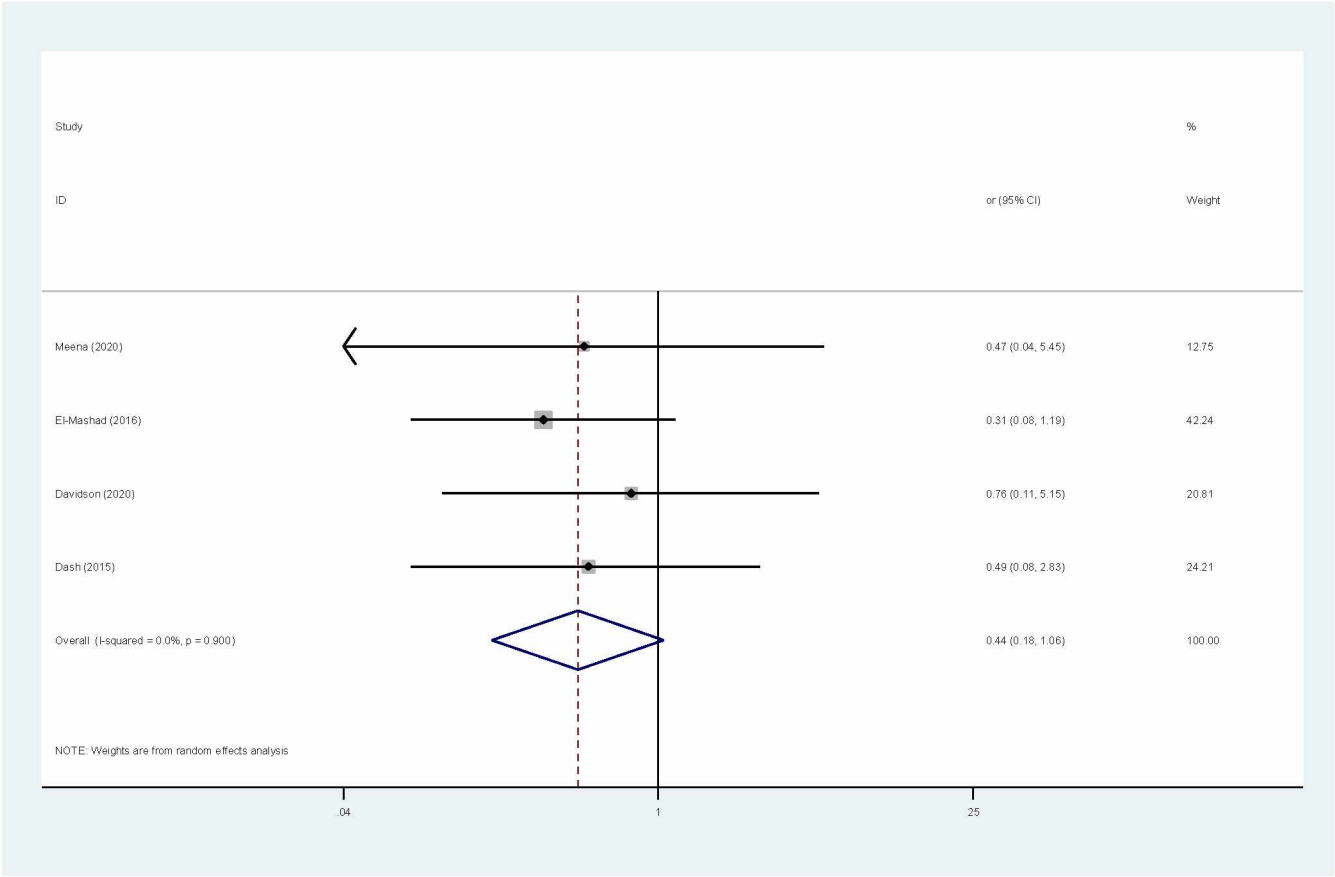

Figure 35. Forest plot of studies examining the relationship between paracetamol and NEC in comparison to indomethacin.

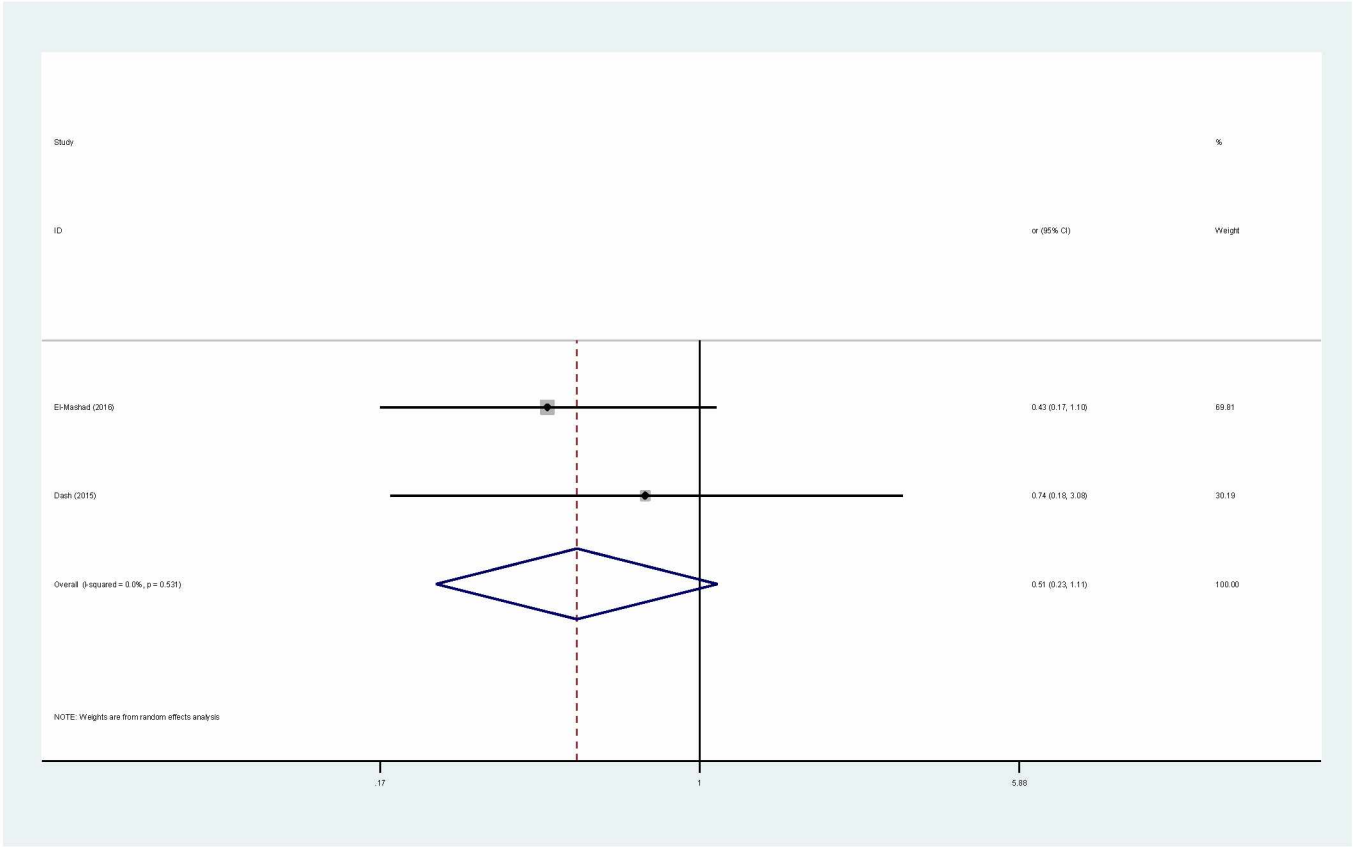

Figure 36. Forest plot of studies examining the relationship between paracetamol and ROP in comparison to indomethacin.

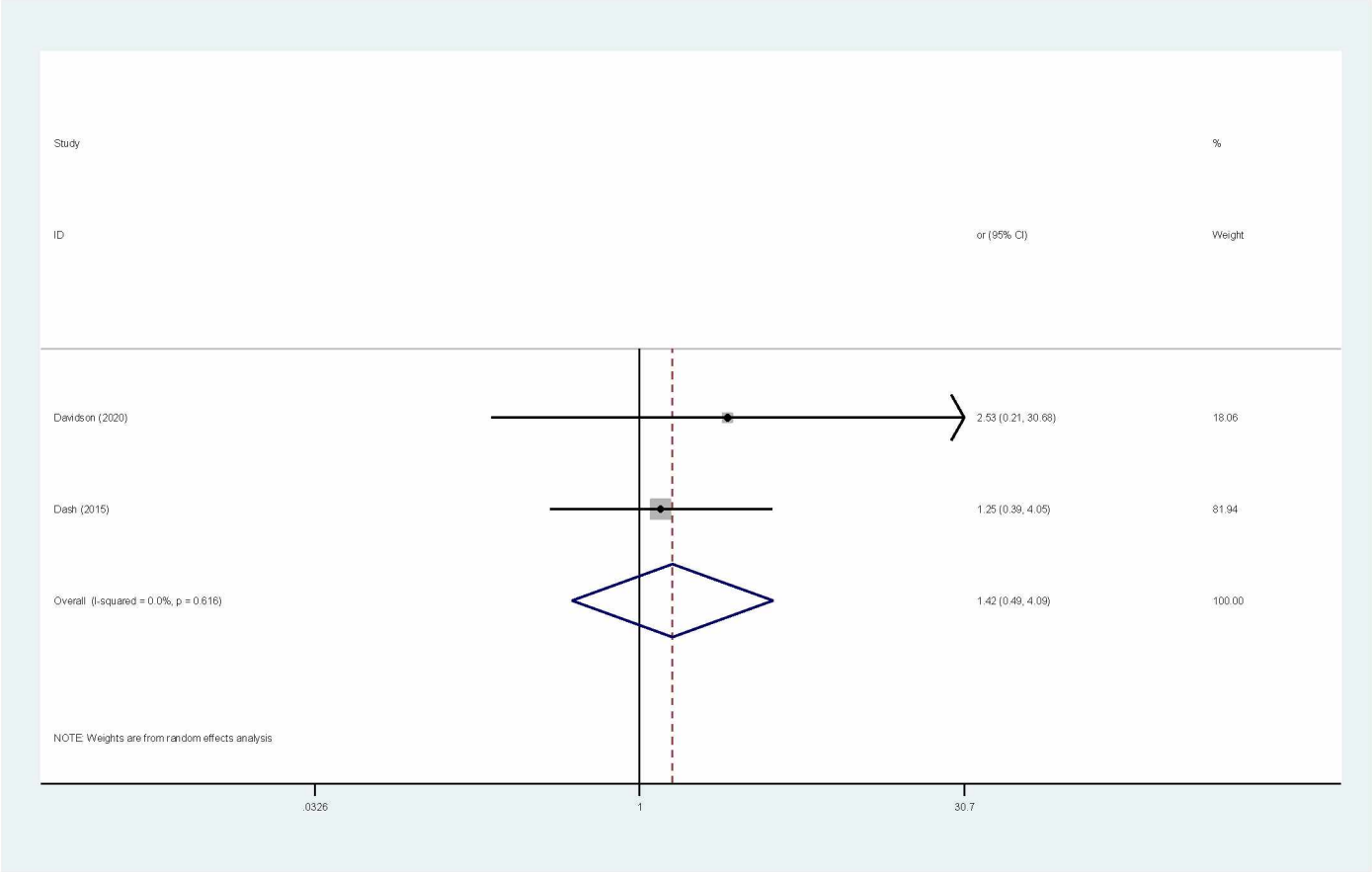

Figure 37. Forest plot of studies examining the relationship between paracetamol and ROP requiring treatment in comparison to indomethacin.

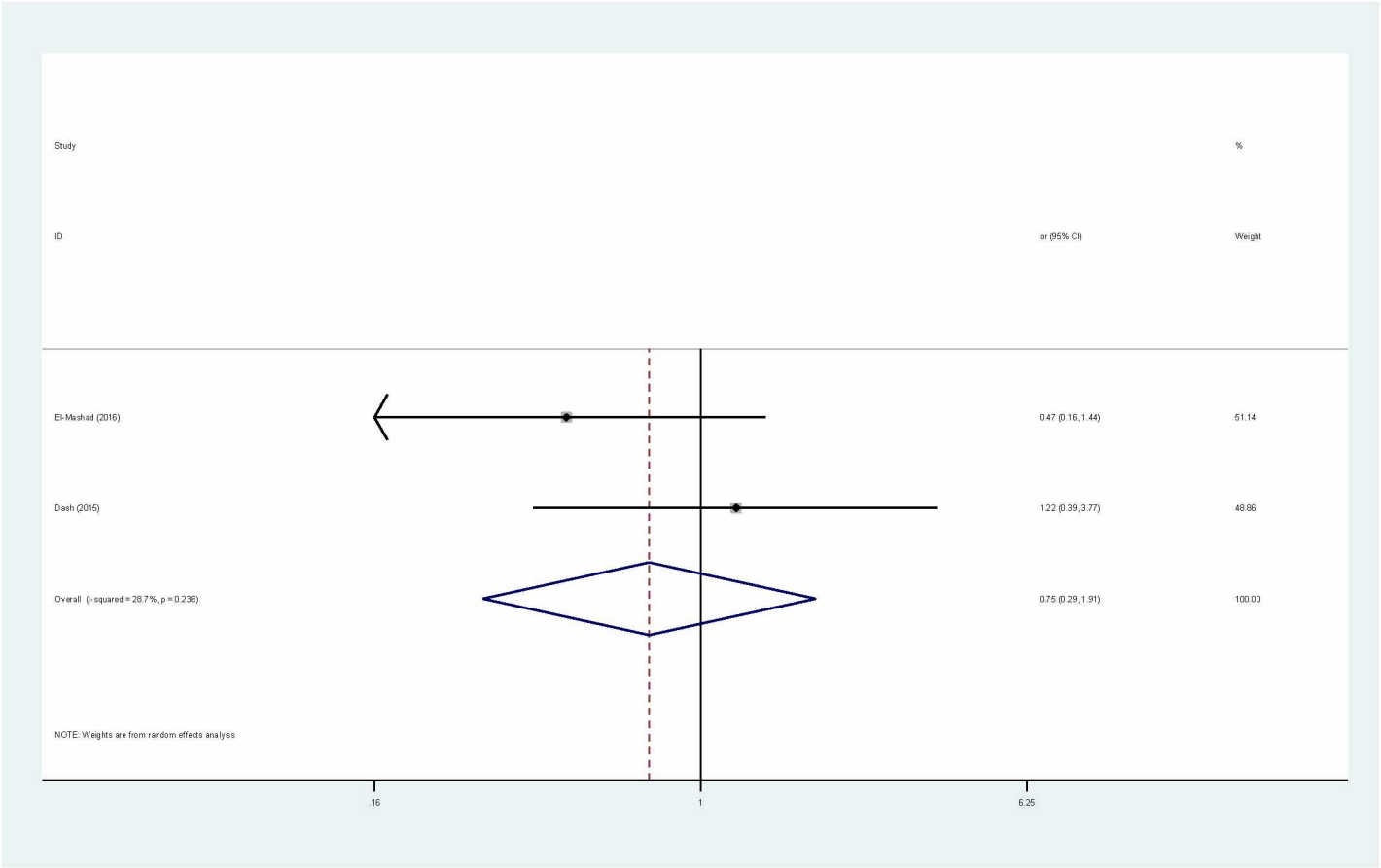

Figure 38. Forest plot of studies examining the relationship between paracetamol and IVH in comparison to indomethacin.

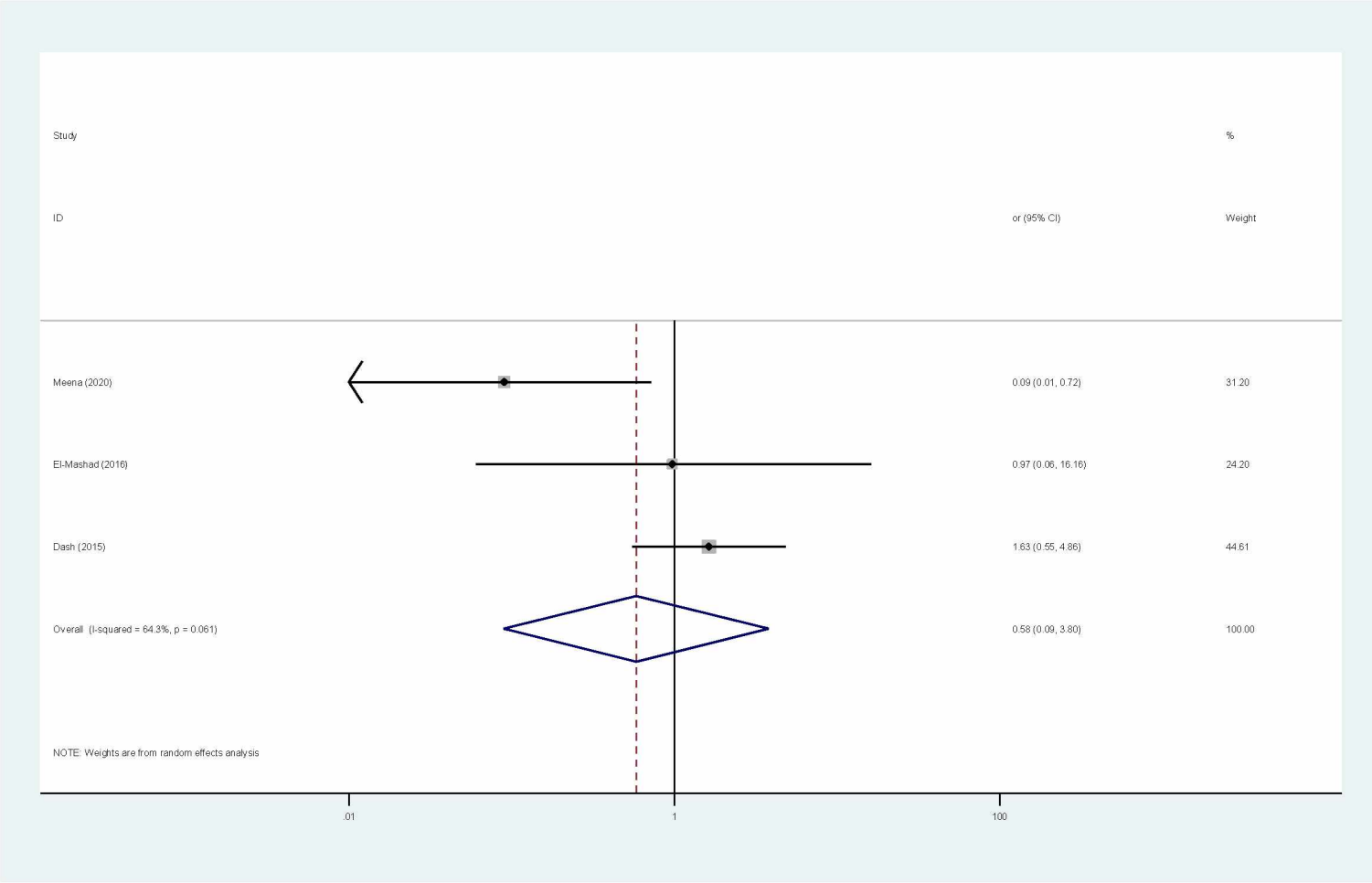

Figure 39. Forest plot of studies examining the relationship between paracetamol and GI bleeding in comparison to indomethacin.

Table 3. GRADE Summary of findings in the effect estimates of the outcomes regarding the comparison of paracetamol vs ibuprofen in PDA closure.

	N of patients		Effect		Certainty
N of studies	**Paracetamol**	**Ibuprofen**	**Relative (95% CI)**	**Absolute (95% CI)**	
Primary PDA closure					
17	489/749 (65.3%)	477/720 (66.3%)	**OR 0.933** (0.691 to 1.260)	**16 fewer per 1.000** (from 87 fewer to 50 more)	⊕⊕⊕⊕ HIGH
PDA constriction after 1st course of treatment					
1	42/52 (80.8%)	44/49 (89.8%)	**OR 0.48** (0.15 to 1.51)	**89 fewer per 1.000** (from 329 fewer to 32 more)	⊕⊕◯◯ [a] LOW
Overall PDA closure					
9	372/436 (85.3%)	345/429 (80.4%)	**OR 1.166** (0.818 to 1.662)	**23 more per 1.000** (from 34 fewer to 68 more)	⊕⊕⊕⊕ HIGH
Recurrence					
5	39/261 (14.9%)	31/276 (11.2%)	**OR 1.472** (0.845 to 2.564)	**45 more per 1.000** (from 16 fewer to 133 more)	⊕⊕◯◯ [a] LOW
Mortality					
7	67/320 (20.9%)	54/313 (17.3%)	**OR 1.084** (0.712 to 1.652)	**12 more per 1.000** (from 43 fewer to 84 more)	⊕⊕⊕◯ [b] MODERATE
RDS					
1	12/13 (92.3%)	6/9 (66.7%)	**OR 6.000** (0.510 to 70.629)	**256 more per 1.000** (from 162 fewer to 326 more)	⊕⊕◯◯ [a] LOW
Surfactant therapy					
2	16/29 (55.2%)	13/23 (56.5%)	**OR 0.900** (0.289 to 2.804)	**26 fewer per 1.000** (from 292 fewer to 220 more)	⊕⊕◯◯ [a] LOW
Pulmonary hemorrhage					
4	5/193 (2.6%)	8/189 (4.2%)	**OR 0.524** (0.167 to 1.648)	**20 fewer per 1.000** (from 35 fewer to 26 more)	⊕⊕◯◯ [a] LOW
BPD					

7	24/316 (7.6%)	23/306 (7.5%)	**OR 1.290** (0.725 to 2.297)	**20 more per 1.000** (from 20 fewer to 82 more)	⊕⊕◯◯ [a] LOW
Hepatotoxicity					
1	1/78 (1.3%)	0/78 (0.0%)	**OR 1.010** (0.061 to 16.744)	**0 fewer per 1.000** (from 0 fewer to 0 fewer)	⊕⊕◯◯ [a] LOW
Sepsis					
4	52/238 (21.8%)	56/234 (23.9%)	**OR 0.860** (0.554 to 1.337)	**26 fewer per 1.000** (from 91 fewer to 57 more)	⊕⊕⊕◯ [b] MODERATE
NEC					
9	46/464 (9.9%)	41/450 (9.1%)	**OR 1.060** (0.669 to 1.681)	**5 more per 1.000** (from 28 fewer to 53 more)	⊕⊕⊕◯ [b] MODERATE
ROP					
4	38/251 (15.1%)	40/249 (16.1%)	**OR 0.900** (0.538 to 1.510)	**14 fewer per 1.000** (from 67 fewer to 64 more)	⊕⊕⊕◯ [b] MODERATE
ROP requiring treatment					
3	15/176 (8.5%)	16/177 (9.0%)	**OR 0.948** (0.411 to 2.186)	**4 fewer per 1.000** (from 51 fewer to 88 more)	⊕⊕◯◯ [a] LOW
IVH					
6	40/308 (13.0%)	28/301 (9.3%)	**OR 1.035** (0.596 to 1.797)	**3 more per 1.000** (from 35 fewer to 63 more)	⊕⊕⊕◯ [b] MODERATE
IVH grade III/IV					
3	5/164 (3.0%)	19/163 (11.7%)	**OR 0.248** (0.043 to 1.412)	**85 fewer per 1.000** (from 111 fewer to 40 more)	⊕⊕⊕◯ [b] MODERATE
Increase in IVH grade					
1	2/45 (4.4%)	3/45 (6.7%)	**OR 0.650** (0.101 to 4.167)	**22 fewer per 1.000** (from 60 fewer to 163 more)	⊕⊕◯◯ [a] LOW
PVL					
2	8/154 (5.2%)	6/155 (3.9%)	**OR 1.127** (0.366 to 3.469)	**5 more per 1.000** (from 24 fewer to 84 more)	⊕⊕◯◯ [a] LOW
Renal impairment					

1	5/55 (9.1%)	15/55 (27.3%)	**OR 0.27** (0.09 to 0.80)	**181 fewer per 1.000** (from 240 fewer to 42 fewer)	⊕⊕⊕◯ [b] MODERATE
Azotemia					
1	12/81 (14.8%)	14/79 (17.7%)	**OR 0.810** (0.350 to 1.872)	**29 fewer per 1.000** (from 107 fewer to 110 more)	⊕⊕◯◯ [a] LOW
Oliguria					
3	17/205 (8.3%)	31/203 (15.3%)	**OR 0.514** (0.272 to 0.973)	**68 fewer per 1.000** (from 106 fewer to 4 fewer)	⊕⊕⊕⊕ HIGH
Renal failure					
1	0/80 (0.0%)	1/80 (1.3%)	**OR 0.990** (0.061 to 16.197)	**0 fewer per 1.000** (from 12 fewer to 158 more)	⊕⊕◯◯ [a] LOW
GI bleeding					
7	17/404 (4.2%)	25/402 (6.2%)	**OR 0.453** (0.174 to 1.174)	**33 fewer per 1.000** (from 51 fewer to 10 more)	⊕⊕⊕◯ [b] MODERATE
MV					
1	9/13 (69.2%)	5/9 (55.6%)	**OR 1.800** (0.309 to 10.486)	**137 more per 1.000** (from 277 fewer to 374 more)	⊕⊕◯◯ [a] LOW
Postnatal steroids					
1	10/45 (22.2%)	16/45 (35.6%)	**OR 0.500** (0.191 to 1.308)	**139 fewer per 1.000** (from 260 fewer to 64 more)	⊕⊕⊕◯ [b] MODERATE
Pneumothorax					
2	4/61 (6.6%)	3/59 (5.1%)	**OR 1.614** (0.361 to 7.204)	**29 more per 1.000** (from 32 fewer to 228 more)	⊕⊕◯◯ [a] LOW
Feeding intolerance					
1	4/18 (22.2%)	1/17 (5.9%)	**OR 4.570** (0.458 to 45.630)	**163 more per 1.000** (from 31 fewer to 682 more)	⊕⊕◯◯ [a] LOW
Positive OB test					
3	7/69 (10.1%)	8/64 (12.5%)	**OR 0.906** (0.303 to 2.712)	**10 fewer per 1.000** (from 84 fewer to 154 more)	⊕⊕◯◯ [a] LOW
CCF					

1	14/55 (25.5%)	15/55 (27.3%)	**OR 0.910** (0.389 to 2.127)	**18 fewer per 1.000** (from 145 fewer to 171 more)	⊕⊕◯◯ [a] LOW
Hyperbilirubinemia					
1	16/80 (20.0%)	28/80 (35.0%)	**OR 0.460** (0.226 to 0.935)	**151 fewer per 1.000** (from 242 fewer to 15 fewer)	⊕⊕⊕⊕ HIGH
Jaundice requiring phototherapy					
1	32/55 (58.2%)	25/55 (45.5%)	**OR 1.600** (0.755 to 3.392)	**117 more per 1.000** (from 68 fewer to 284 more)	⊕⊕◯◯ [a] LOW
Cholestasis					
1	2/55 (3.6%)	2/55 (3.6%)	**OR 1.000** (0.138 to 7.251)	**0 fewer per 1.000** (from 31 fewer to 178 more)	⊕⊕◯◯ [a] LOW
Bleeding manifestations					
1	12/55 (21.8%)	11/55 (20.0%)	**OR 1.120** (0.449 to 2.794)	**19 more per 1.000** (from 99 fewer to 211 more)	⊕⊕◯◯ [a] LOW
Thrombocytopenia					
1	17/55 (30.9%)	16/55 (29.1%)	**OR 1.040** (0.460 to 2.351)	**8 more per 1.000** (from 132 fewer to 200 more)	⊕⊕◯◯ [a] LOW
Screening OAE fail					
1	3/55 (5.5%)	3/55 (5.5%)	**OR 1.000** (0.191 to 5.226)	**0 fewer per 1.000** (from 44 fewer to 177 more)	⊕⊕◯◯ [a] LOW
Neurodevelopmental impairment					
1	9/30 (30.0%)	10/31 (32.3%)	**OR 0.820** (0.280 to 2.406)	**42 fewer per 1.000** (from 205 fewer to 211 more)	⊕⊕◯◯ [a] LOW
Significantcerebral palsy					
1	4/30 (13.3%)	2/31 (6.5%)	**OR 2.230** (0.378 to 13.143)	**69 more per 1.000** (from 39 fewer to 411 more)	⊕⊕◯◯ [a] LOW
Blind					
1	0/30 (0.0%)	1/31 (3.2%)	**OR 1.000** (0.060 to 16.703)	**0 fewer per 1.000** (from 30 fewer to 325 more)	⊕⊕◯◯ [a] LOW
Deaf					

1	0/30 (0.0%)	1/31 (3.2%)	**OR 1.000** (0.060 to 16.703)	**0 fewer per 1.000** (from 30 fewer to 325 more)	⊕⊕◯◯ [a] LOW
Deranged coagulogram					
1	10/80 (12.5%)	9/78 (11.5%)	**OR 1.100** (0.422 to 2.870)	**10 more per 1.000** (from 63 fewer to 157 more)	⊕⊕◯◯ [a] LOW

Abbreviations: BPD, Bronchopulmonary dysplasia; CCF, Congestive Cardiac Failure; CI, Confidence Interval; GI, Gastrointestinal; GRADE, Grading of Recommendations; Assessment Development and Evaluation System IVH, Intraventricular haemorrhage; MV, Mechanical ventilation; NEC, Necrotizing enterocolitis; OAE, Otoacoustic Emissions; OB, occult blood; OR, Odds Ratio; PDA, Patent Ductus Arteriosus; PVL, Periventricular leukomalacia; RDS, Respiratory distress syndrome; ROP, Retinopathy of prematurity

Explanations

Where there were "Some concerns" in the risk of bias assessment of the studies, we decided not to downgrade the quality of evidence.

Where < 10 studies were included, we did not construct a funnel plot regarding the publication bias assessment.

[a] Because the point estimate was not precise with a very wide 95% CI we downgraded the quality of the evidence by 2 steps.

[b] Because the point estimate was not precise with a wide 95% CI we downgraded the quality of the evidence by 1 step.

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

Table 4. GRADE Summary of findings in the effect estimates of the outcomes regarding the comparison of paracetamol vs indomethacin in PDA closure.

	N of patients		Effect		Certainty
N of studies	**Paracetamol**	**Ibuprofen**	**Relative (95% CI)**	**Absolute (95% CI)**	
Primary PDA closure					
4	132/190 (69.5%)	135/214 (63.1%)	**OR 0.777** (0.200 to 3.023)	**60 fewer per 1.000** (from 376 fewer to 207 more)	⊕◯◯◯[a,b] VERY LOW
Overall PDA closure					
2	113/135 (83.7%)	111/135 (82.2%)	**OR 1.120** (0.584 to 2.147)	**16 more per 1.000** (from 92 fewer to 86 more)	⊕⊕◯◯[b] LOW
Mortality					
2	9/55 (16.4%)	11/59 (18.6%)	**OR 0.854** (0.312 to 2.337)	**23 fewer per 1.000** (from 120 fewer to 162 more)	⊕⊕◯◯[b] LOW
Pulmonary hemorrhage					
3	6/172 (3.5%)	8/174 (4.6%)	**OR 0.795** (0.165 to 3.841)	**9 fewer per 1.000** (from 38 fewer to 110 more)	⊕⊕◯◯[b] LOW
BPD					
2	19/44 (43.2%)	19/50 (38.0%)	**OR 1.396** (0.509 to 3.825)	**81 more per 1.000** (from 142 fewer to 321 more)	⊕⊕◯◯[b] LOW
Sepsis					
3	40/155 (25.8%)	37/159 (23.3%)	**OR 1.184** (0.682 to 2.055)	**32 more per 1.000** (from 61 fewer to 151 more)	⊕⊕◯◯[b] LOW
NEC					
4	7/190 (3.7%)	18/194 (9.3%)	**OR 0.440** (0.183 to 1.058)	**50 fewer per 1.000** (from 74 fewer to 5 more)	⊕⊕⊕◯[c] MODERATE
ROP requiring treatment					
2	10/46 (21.7%)	8/50 (16.0%)	**OR 1.420** (0.492 to 4.095)	**53 more per 1.000** (from 74 fewer to 278 more)	⊕⊕◯◯[b] LOW
ROP					

2	31/129 (24.0%)	41/130 (31.5%)	**OR 0.507** (0.232 to 1.105)	**126 fewer per 1.000** (from 219 fewer to 22 more)	⊕⊕⊕◯ [c] MODERATE
IVH					
2	13/138 (9.4%)	17/139 (12.2%)	**OR 0.749** (0.294 to 1.907)	**28 fewer per 1.000** (from 83 fewer to 88 more)	⊕⊕◯◯ [b] LOW
IVH grade III/IV					
1	1/17 (5.9%)	3/20 (15.0%)	**OR 0.35** (0.03 to 3.77)	**92 fewer per 1.000** (from 145 fewer to 250 more)	⊕⊕◯◯ [b] LOW
PVL					
1	8/38 (21.1%)	7/39 (17.9%)	**OR 1.22** (0.39 to 3.77)	**31 more per 1.000** (from 101 fewer to 272 more)	⊕⊕◯◯ [b] LOW
Renal impairment					
1	1/38 (2.6%)	0/39 (0.0%)	**OR 1.05** (0.06 to 17.47)	**0 fewer per 1.000** (from 0 fewer to 0 fewer)	⊕⊕◯◯ [b] LOW
GI bleeding					
3	11/173 (6.4%)	18/174 (10.3%)	**OR 0.582** (0.089 to 3.795)	**41 fewer per 1.000** (from 93 fewer to 201 more)	⊕⊕◯◯ [b] LOW
Postnatal steroids					
1	4/17 (23.5%)	8/20 (40.0%)	**OR 0.46** (0.11 to 1.94)	**165 fewer per 1.000** (from 332 fewer to 164 more)	⊕⊕◯◯ [b] LOW

Abbreviations: BPD, Bronchopulmonary dysplasia; CCF, Congestive Cardiac Failure; CI, Confidence Interval; GI, Gastrointestinal; GRADE, Grading of Recommendations; Assessment Development and Evaluation System; IVH, Intraventricular haemorrhage; NEC, Necrotizing enterocolitis; OR, Odds Ratio; PDA, Patent Ductus Arteriosus; PVL, Periventricular leukomalacia; ROP, Retinopathy of prematurity

Explanations

Where there were "Some concerns" in the risk of bias assessment of the studies, we decided not to downgrade the quality of evidence.

Where < 10 studies were included, we did not construct a funnel plot regarding the publication bias assessment.

[a] Due to the high statistical heterogeneity between studies as evidenced by an I2 greater than 75%, we downgraded the quality of evidence by 1 step.

[b] Because the point estimate was not precise with a very wide 95% CI we downgraded the quality of the evidence by 2 steps.

[c] Because the point estimate was not precise with a wide 95% CI we downgraded the quality of the evidence by 1 step.

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.