The histologic fetal inflammatory response and neonatal outcomes: systematic review and meta-analysis

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OBJECTIVE: This study aimed to investigate the prognostic role of concomitant histological fetal inflammatory response with chorioamnionitis on neonatal outcomes through a systematic review and meta-analysis of existing literature.

DATA SOURCES: The primary search was conducted on October 17, 2021, and it was updated on May 26, 2023, across 4 separate databases (MEDLINE, the Cochrane Central Register of Controlled Trials, Embase, and Scopus) without using any filters.

STUDY ELIGIBILITY CRITERIA: Observational studies reporting obstetrical and neonatal outcomes of infant-mother dyads with histological chorioamnionitis and histological fetal inflammatory response vs infant-mother dyads with histological chorioamnionitis alone were eligible. Studies that enrolled only preterm neonates, studies on neonates born before 37 weeks of gestation, or studies on neonates with very low birthweight (birthweight <1500 g) were included. The protocol was registered with the International Prospective Register of Systematic Reviews (registration number: CRD42021283448).

METHODS: The records were selected by title, abstract, and full text, and disagreements were resolved by consensus. Random-effect model-based pooled odds ratios with corresponding 95% confidence intervals were calculated for dichotomous outcomes.

RESULTS: Overall, 50 studies were identified. A quantitative analysis of 14 outcomes was performed. Subgroup analysis using the mean gestational age of the studies was performed, and a cutoff of 28 weeks of gestation was implemented. Among neonates with lower gestational ages, early-onset sepsis (pooled odds ratio, 2.23; 95% confidence interval, 1.76—2.84) and bronchopulmonary dysplasia (pooled odds ratio, 1.30; 95% confidence interval, 1.02—1.66) were associated with histological fetal inflammatory response. Our analysis showed that preterm neonates with a concomitant histological fetal inflammatory response are more likely to develop intraventricular hemorrhage (pooled odds ratio, 1.54; 95% confidence interval, 1.18—2.02) and retinopathy of prematurity (pooled odds ratio, 1.37; 95% confidence interval, 1.03—1.82). The odds of clinical chorioamnionitis were almost 3-fold higher among infant-mother dyads with histological fetal inflammatory response than among infant-mother dyads with histological chorioamnionitis alone (pooled odds ratio, 2.99; 95% confidence interval, 1.96—4.55).

CONCLUSION: This study investigated multiple neonatal outcomes and found association in the case of 4 major morbidities: early-onset sepsis, bronchopulmonary dysplasia, intraventricular hemorrhage, and retinopathy of prematurity.

Key words: bronchopulmonary dysplasia, early-onset sepsis, fetal inflammatory response, fetal inflammatory response syndrome, funisitis, histological chorioamnionitis, intraventricular hemorrhage, intrauterine inflammation, meta-analysis, preterm, sepsis, systematic review

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No ethical approval was required for this systematic review with meta-analysis, as all data had already been published in peer-reviewed journals. No patient was involved in the design, conduct, or interpretation of our study.

The protocol of this systematic review and meta-analysis was registered with the International Prospective Register of Systematic Reviews (registration number: CRD42021283448). The date of registration was October 17, 2021.

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AJOG at a Glance

Why was this study conducted?

Preterm neonates with a history of histological chorioamnionitis (HCA) have worse outcomes than those without HCA. In this association, the effect of histological fetal inflammatory response (FIR) is unclear.

Key findings

The concomitant occurrence of HCA and histological FIR was associated with a higher incidence of intraventricular hemorrhage and retinopathy of prematurity. An elevated incidence of early-onset sepsis and bronchopulmonary dysplasia was found in the group of preterm infants with histological FIR with a mean gestational age of <28 weeks. Our analysis showed higher odds for clinical chorioamnionitis when HCA and histological FIR were present.

What does this add to what is known?

This histological evaluation-based meta-analysis suggests that the presence of histological FIR with HCA is associated with worse outcomes in preterm infants than the presence of HCA alone.

Introduction

Worldwide, 1 in 10 pregnancies ends with preterm birth (PTB). The cause of PTB cannot be specified in most cases[1]; however, intrauterine inflammation is present in approximately 50% of extremely PTBs.[2] The term chorioamnionitis is well known among obstetricians and neonatal specialists and is extensively used to define heterogeneous conditions, such as intrauterine inflammation, intrauterine infection, or both (intrauterine inflammation [IUI]).[3] Chorioamnionitis can be defined by clinical symptoms, although the accuracy of the diagnosis using this approach is only approximately 50%.[4,5]

Histological examination is an objective method to assess the presence of IUI and has higher specificity and sensitivity than clinical predictors.[6,7] The prevalence of histological chorioamnionitis (HCA) in PTBs is inversely related to gestational age (GA).[8] HCA is diagnosed in approximately 50% of PTBs before 28 weeks of gestation.[2] According to Redline et al,[9] during histological examination, maternal inflammatory responses and fetal inflammatory responses (FIRs) can be separated. To draw the line on the origin of the inflammation, the localization of infiltrating neutrophils is crucial. It has been proven that the neutrophils that have migrated to the chorioamnionic membranes are of maternal origin; in contrast, the neutrophil infiltration of the vessels of the chorionic plate or the umbilical cord is mainly of fetal origin.[10−12] Thus, HCA is part of the histological maternal inflammatory response, and funisitis and chorionic vasculitis are the elements of the histological FIR.[10,11,13]

The association between HCA and increased adverse neonatal outcomes has been extensively investigated and demonstrated. These outcomes included mortality, early-onset sepsis (EOS) and late-onset sepsis (LOS), bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), cerebral white matter damage, and long-term neurodevelopmental sequelae.[14−21]

In addition, 50% to 70% of preterm placentas with HCA show signs of FIR as well.[22,23] Over the past few decades, several studies have divided HCA-affected placentas into the following subgroups: placentas with HCA alone and placentas with HCA and FIR. The influence of FIR, in addition to HCA, on neonatal and maternal outcomes is unclear. Some studies showed worse prognosis for preterm infants in the case of HCA and FIR than for preterm infants in the case of HCA alone, whereas other studies reported no difference in neonatal outcomes.[24−29]

Objective

Our objective was to investigate whether HCA with concomitant FIR was accompanied by a higher incidence of adverse neonatal outcomes than HCA without FIR. Therefore, we conducted a systematic review and meta-analysis of the existing literature.

Material and Methods

The protocol of this systematic review and meta-analysis was registered with the International Prospective Register of Systematic Reviews (registration number: CRD42021283448). The study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines.[30]

Sources and search strategy

The literature search was performed in MEDLINE (via PubMed), Embase, the Cochrane Central Register of Controlled Trials, and Scopus on October 17, 2021, and was updated on May 26, 2023. No language restriction was applied. The search key is detailed in the Supplemental Data.

Of note, 3 of the authors (K.K., D.B., and O.K.) independently performed the selection using a reference management tool (Endnote X9 software; Clarivate, Philadelphia, PA). After automatic and manual duplicate removal, the records were screened according to the title, abstract, and full text, based on previously arranged criteria. Disagreements among the 3 reviewers were resolved by discussion. After each step of the selection process, the level of agreement was calculated using the Cohen κ coefficient. The values indicated substantial agreement (0.61−0.80) for title and abstract and full-text selection.[31] References of the included studies were reviewed and, in case of eligibility, added to the pool.

Eligibility criteria

Cohort and case-control studies and case series were considered eligible for inclusion. Animal studies, case reports, or studies without original data were excluded. Our clinical question was

formulated within the Population, Exposure, Comparator, and Outcome framework (Supplemental Table 1).[32]

Our population was defined as preterm infants (born before 37 weeks of gestation) or very low birthweight (VLBW) neonates (birthweight ≤1500 g). We compared the rate of adverse neonatal outcomes in infants with HCA combined with FIR with that of preterm infants who were diagnosed with HCA alone.

We further reviewed the included articles based on the definition of FIR. The group of articles that used the term FIR based on the definition by the Amsterdam Placental Consensus Workshop[33] will be referred to as the "FIR Amsterdam criteria" (FIR-AC) group. In the "FIR-AC" group, the presence of chorionic vasculitis was part of the definition of FIR. The FIR not otherwise specified (FIR-NOS) refers to other publications that either did not specify the definition of FIR or used different terminologies (eg, chorionic vasculitis was not included). Considering these differences, we run 2 analyses for each outcome. All articles were examined in the first analysis, whereas only articles belonging to the FIR-AC group were examined in the second analysis.

The main outcomes were neonatal mortality, EOS, LOS, necrotizing enterocolitis (NEC), and BPD. In addition, we collected data on additional outcomes: retinopathy of prematurity (ROP), IVH, periventricular leukomalacia (PVL), respiratory distress syndrome (RDS), length of hospital stay (LOH), cerebral palsy (CP), neurodevelopmental delay, sensory impairment, and small for gestational age (SGA). Furthermore, we analyzed clinical chorioamnionitis (CCA).

Data extraction

Of note, 2 of the authors (K.K. and O.K.) independently abstracted relevant data into a data sheet (Microsoft Excel 2019; Microsoft Corporation, Redmond, WA), and any mismatch was discussed. Whenever clarification was required, attempts were made to contact the corresponding authors to provide supplemental information.

Risk of bias assessment

According to the recommendations of the Cochrane Prognosis Methods Group, the Quality in Prognosis Studies tool was used.[34] Moreover, 2 of the authors (K.K. and O.K.) independently assessed the risk of bias (RoB) in the included studies for each outcome. Any debates were resolved based on consensus.

Data synthesis

Statistical analyses were performed using package 'meta' of the R statistical software (version 4.1.2.) and the R script of the online tool described by Freeman et al.[35] Statistical analyses were performed according to Harrer et al.[36]

We collected the incidence of different neonatal outcomes among neonates with FIR and HCA and among neonates with HCA alone. Pooled odds ratios (ORs), 95% confidence and prediction intervals, and P values corresponding to the null hypothesis that the OR equals 1 were calculated using the random effect variant of the Mantel-Haenszel method[37,38] implemented in the metabin function. To estimate τ^2, we used the Paule-Mandel method.[39] Moreover, the Hartung-Knapp adjustment[40] was used. In addition to the prediction interval, heterogeneity was assessed by calculating the I^2 measure and its confidence interval (CI) and performing the Cochrane Q test. I^2 values of 25%, 50%, and 75% were considered to indicate low, moderate, and high heterogeneity, respectively. In the presence of zero frequency, the ORs within studies were calculated by adding 0.5 to the cell frequencies; however, to calculate the pooled OR, the exact Mantel-Haenszel method was used, which can handle zero frequencies without the mentioned correction. Whenever we had at least 3 studies in each subgroup, we performed subgroup analysis to assess the effect of GA. We used the mean GA of 28 weeks as the cutoff. Publication bias was assessed visually via funnel plot, and Harbord tests[41] were performed when at least 10 studies were available.

Although our main focus was to provide pooled ORs, we decided to separately pool the 2 proportions behind the OR value as an insightful supplemental analysis. In diagnostic meta-analyses, the usual methodology for providing pooled sensitivity and sensitivity is to fit the random-effect bivariate model.[42] The same bivariate model was used in this study. This approach considers the dependency on the random effect terms between the proportions in the "FIR and HCA" and "HCA alone" groups (see also Riley et al[43]). The advantage of this method is that it provides 95% confidence and prediction regions. We plotted these regions on a 2-dimensional scatter plot, along with the proportions of the included studies and the resulting summary estimates. The confidence region contains the pooled sensitivity and specificity (more exactly 1-specificity) in 95% of the cases. The prediction region contains the true proportion pair of a new study in 95% of the cases; hence, it provides excellent insights into the heterogeneity. In these visualizations, the sizes of the ellipsoids reflect the weights of the studies, calculated according to the method described by Burke et al.[44] We note that the employed bivariate approach is used in Stijnen et al,[45] even for providing pooled ORs (see the "Data analysis" section). Nevertheless, for simplicity, as mentioned above, we decided to use the conventional Mantel-Haenszel method to obtain pooled OR.

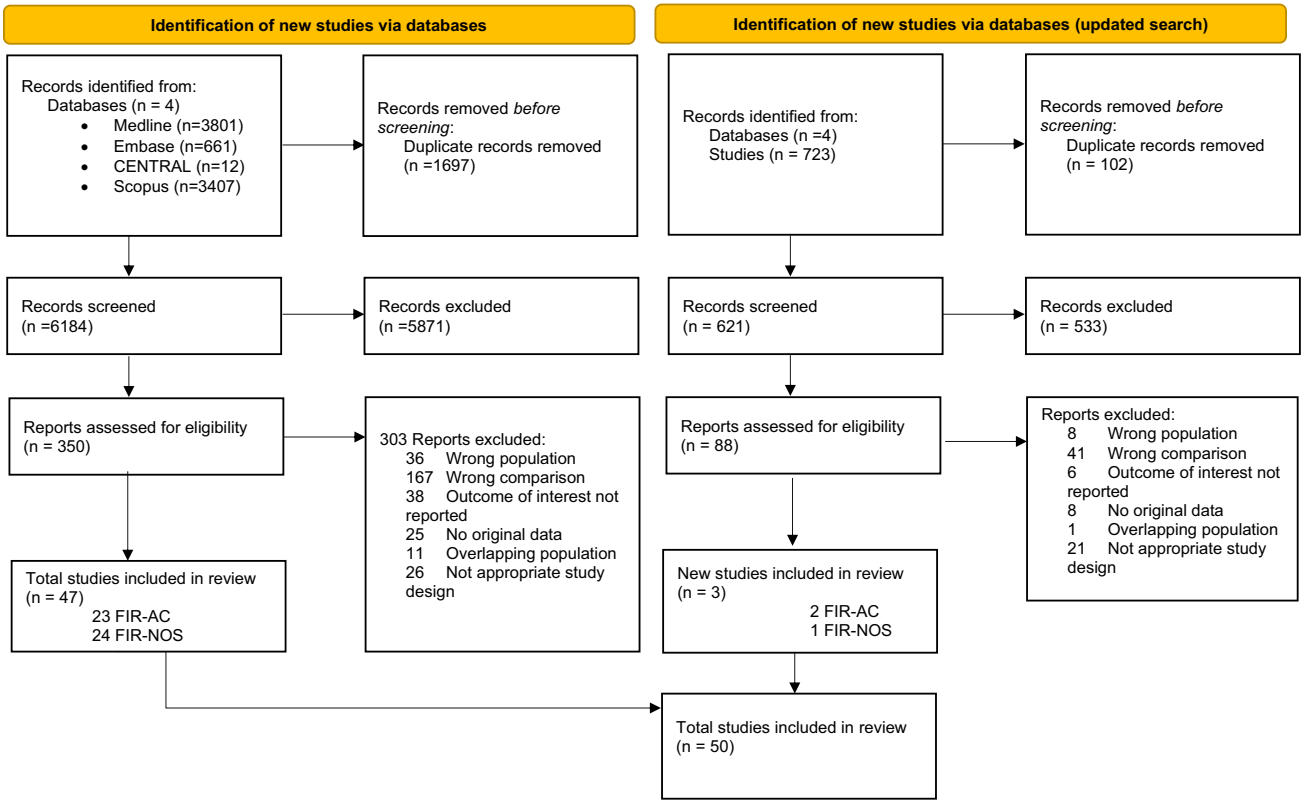
For all statistical analyses, a P value of $<.05$ was considered significant. Because of several outcomes, the number of tests performed is high, so false-positive associations may occur. In this respect, the P value provides useful insights: the smaller the P value, the smaller the probability of a false-positive result.

Results

Study selection

During the initial selection process, we screened 7881 articles. After title and abstract screening and full article review, 47 articles[20,23–29,46–84] met the inclusion criteria for the qualitative synthesis, of which all but one[71] were included in the quantitative synthesis. During the updated search, we identified 3 additional studies.[85–87] Moreover, 25 articles included chorionic vasculitis in their definition of FIR. These studies were

FIGURE 1
Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart



CENTRAL, Cochrane Central Register of Controlled Trials; *FIR-AC*, fetal inflammatory response Amsterdam criteria; *FIR-NOS*, fetal inflammatory response not otherwise specified.

Kovács. The histologic fetal inflammatory response and neonatal outcomes. Am J Obstet Gynecol 2024.

part of the FIR-AC group.[24–29,50–52,54,60–62,64–66,69,72,75,77,79,80,84–86] The PRISMA flow diagram of the search is shown in Figure 1.[88] We did not identify any additional studies from the references of eligible studies.

Study characteristics

An overview of the characteristics of the included studies is presented in the Table. Most of the studies were observational cohort studies, and 1 study was a retrospective case-control study.

Moreover, 25 articles included chorionic vasculitis as part of FIR. The remaining 25 studies either did not report about its status or separated it as a different entity. We included 2 conference abstracts,[48,87] and because of the high RoB, we also performed sensitivity analyses, omitting these articles from the analysis (Supplemental Figures 1–6). To assess the influence of the individual articles, we performed influential analyses in the case of all outcomes (Supplemental Figures 7–20).

Risk of bias and quality assessment

Regarding all outcomes, we also included studies assessed at a moderate or high RoB (Supplemental Figures 21–34). On one hand, the reason was the nature of cohort studies, and on the other hand, most of the studies were not primarily designed to assess the difference between the 2 groups that we investigated. Therefore, there is a lack of information regarding the confounding factors and the differences between the 2 groups. However, the varying—or, in some cases, vague—definitions of the outcomes caused a high RoB.

We were able to assess publication bias in the case of 11 outcomes (Supplemental Figures 35–45). Based on the funnel plot and Harbord test, publication bias was assumed in the case of PVL.

Synthesis of the results

No change in mortality

Of note, 17 studies, including 3547 preterm infants reported mortality rates. A total of 2212 preterm infants (62.4%) had HCA with histological FIR, and 1335 offspring had HCA alone. The overall OR was 1.18 (95% CI, 0.91–1.52; I^2=0%), as shown in Figure 2, A, suggesting that there was no significant association between mortality and the progression of histological intrauterine inflammation. As shown in Figure 2, B, we found similar results in the FIR-AC group, where the OR is 1.19 (95% CI, 0.72–1.97; I^2=27%).

Higher odds of early-onset sepsis

EOS was reported in 9 studies with 1631 neonates of which 1058 (64.9%) had

TABLE
Characteristics of included studies in the meta-analysis and systematic review

Studies	Country	Design	Sample size	No. of cases in exposure/ control group	FIR definition	Inclusion criteria	Mean GA±SD	Outcomes
Al-Mulaabed et al,[48] 2017[a]	United States	Retrospective	85	11/29	FIR-NOS	BW<1500 g	28.40±3.00	NEC
Babnik et al,[67] 2006	Slovenia	Prospective	125	26/21	FIR-NOS	GA<30 wk	27.40±2.00	IVH
Been et al,[26] 2009	The Netherlands	Prospective	301	68/53	FIR-AC	GA≤32 wk	28.31 ±2.01	CCA, SGA, mortality, RDS, EOS, LOS, IVH, cystic PVL, NEC, PDA, BPD
Budal et al,[85] 2023	Norway	Prospective	71	51/20	FIR-AC	GA≤28 wk	25,73	CCA, SGA, mortality, EOS, NEC, ROP, BPD
Burgner et al,[72] 2017	Australia	Retrospective	1218	406/171	FIR-AC	GA<30 wk	27	Mortality
Dessardo et al,[77] 2019	Croatia	Prospective	262	45/60	FIR-AC	GA≤32 wk	29.20±2.30	PDA, BPD
Durrmeyer et al,[78] 2012	France	Prospective	384	85/93	FIR-NOS	GA<28 wk	NA	Mortality, BPD
Gantar et al,[81] 2011	Slovenia	Retrospective	115	28/9	FIR-NOS	GA<30 wk	27.26±1.45	BPD
Gisslen et al,[58] 2016	United States	Prospective	477	31/79	FIR-NOS	GA>32 wk and GA<37 wk	34.71±1.52[b]	CCA; RDS; LOH
Hendson et al,[75] 2011	Canada	Prospective	628	134/95	FIR-AC	GA≤32 wk and BW≤1250 g	26.10±0.10	CP, visual impairment, hearing impairment, mental delay
Holcroft et al,[47] 2004	United States	Retrospective	354	87/59	FIR-NOS	GA<34 wk	28.00±3.06	CCA, mortality, RDS, NEC
Horvath et al,[63] 2012	Hungary	NA	141	14/29	FIR-NOS	BW<1500 g	29.92±6.88	CP
Ikeda et al,[70] 2015	Japan	Retrospective	294	180/50	FIR-NOS	GA<32 wk	27.71±1.63[b]	BPD
Kelly et al,[87] 2022[a]	United States	Retrospective	152	36/24	FIR-NOS	GA<30 wk	NA	RDS, IVH, PVL, NEC, ROP, BPD
Kent and Dahlstrom,[53] 2004	Australia	Retrospective	241	40/40	FIR-NOS	GA<30 wk	27.10±1.95	BPD
Kent et al,[46] 2005	Australia	Retrospective	220	33/39	FIR-NOS	GA<30 wk	27.03±1.89	Mortality, IVH, CP
Kim et al,[76] 2015	Korea	Retrospective	258	34/65	FIR-NOS	BW<1500 g	28.14±2.71	CCA, SGA, mortality, RDS, EOS, LOS, IVH, cystic PVL, NEC, ROP, BPD
Kim et al,[71] 2016	Korea	Retrospective	267	54/74	FIR-NOS	GA≤32 wk	28.32±2.47	Hearing impairment
Lahra et al,[73] 2008	Australia	Prospective	724	219/138	FIR-NOS	GA<30 wk	27.10±1.60	SGA, RDS
Lahra et al,[68] 2009	Australia	Prospective	761	208/140	FIR-NOS	GA<30 wk	27.40±1.50	PDA
Lee et al,[69] 2015	Korea	Retrospective	339	189/29	FIR-AC	GA<34 wk	29.20±2.99	Mortality, CCA, RDS, IVH, PVL, NEC, ROP, BPD
Liu et al,[24] 2012	China	Prospective	216	51/53	FIR-AC	GA<34 wk	31.46±1.64	Mortality, RDS, EOS, LOS, IVH, cystic PVL, NEC, PDA, ROP, BPD

Kovács. The histologic fetal inflammatory response and neonatal outcomes. Am J Obstet Gynecol 2024.

(continued)

TABLE

Characteristics of included studies in the meta-analysis and systematic review *(continued)*

Studies	Country	Design	Sample size	No. of cases in exposure/ control group	FIR definition	Inclusion criteria	Mean GA±SD	Outcomes
Lynch et al,[84] 2017	United States	Retrospective	1217	305/82	FIR-AC	GA≤30 wk or BW≤1500 g	29.00±2.50	ROP
Maisonneuve et al,[50] 2020	France	Prospective	1470	217/211	FIR-AC	GA<32 wk	NA	CP
Matulova et al,[86] 2022	Czech Republic	Retrospective	818	343/151	FIR-AC	GA<37 wk	33[c]	Mortality, RDS, EOS, LOS, IVH, NEC, ROP, BPD, SGA
Mestan et al,[29] 2010	United States	Prospective	256	54/40	FIR-AC	GA<37 wk	28.75±2.70	CCA, IVH, NEC, BPD
Mir et al,[66] 2019	United States	Retrospective	241	75/42	FIR-AC	GA<29 wk	26.00±1.53	BPD
Park et al,[74] 2015	Korea	NA	378	125/94	FIR-NOS	GA≤34 wk	30.20±2.29[b]	RDS
Cortelyou et al,[80] 2020	United States	Retrospective	255	61/21	FIR-AC	GA<33 wk	28.60±2.00	IVH
Perniciaro et al,[55] 2020	Italy	Retrospective	162	17/31	FIR-NOS	BW<1500 g	28.70±3.10	SGA, PDA, BPD
Pietrasanta et al,[28] 2019	Italy	Prospective	807	61/73	FIR-AC	GA<35 wk and/or BW≤1500 g	30.14±3.32	CCA, SGA, mortality, RDS, EOS, LOS, IVH, PDA, ROP, BPD
Plakkal et al,[27] 2013	Canada	Retrospective	529	186/84	FIR-AC	GA<29 wk	25.70±1.60	CCA, SGA, mortality, RDS, NEC, PDA, BPD, LOH
Richardson et al,[82] 2006	United Kingdom	Prospective	660	178/114	FIR-NOS	GA<34 wk	29.44±2.64	Mortality, CCA, RDS, IVH, cystic PVL, BPD
Rocha et al,[52] 2007	Portugal	Retrospective	452	81/44	FIR-AC	GA<34 wk	29.80±1.73[b]	IVH, cystic PVL
Rovira et al,[23] 2011	Spain	Prospective	177	45/42	FIR-NOS	GA<32 wk or BW<1500 g	28.30±2.50	Mortality, IVH, cystic PVL, CP, visual impairment, hearing impairment, mental delay
Salas et al,[61] 2013	United States	Retrospective	347	110/38	FIR-AC	GA<19 wk	25.35±2.31[b]	CCA, RDS, CP, visual impairment, hearing impairment, mental delay
Sharma et al,[54] 2021	United States	Retrospective	246	127/34	FIR-AC	GA<28 wk	25.23±1.22	BPD
Smit et al,[51] 2015	The Netherlands	Retrospective	300	55/80	FIR-AC	GA≤32 wk	28.84±2.08	RDS, IVH, cystic PVL, NEC, PDA, BPD
Soraisham et al,[20] 2013	Canada	Retrospective	384	140/57	FIR-NOS	GA<29 wk	26.60±1.30	CP, visual impairment, hearing impairment, mental delay
Strunk et al,[62] 2019	Australia	Retrospective	1089	396/131	FIR-AC	GA<30 wk	26.52±1.94	EOS, LOS, NEC, PDA, ROP, BPD
Torchin et al,[60] 2017	France	Prospective	1731	269/250	FIR-AC	GA<30 wk	29.10±2.52[b]	BPD, mortality
Trevisanuto et al,[25] 2013	Italy	Prospective, case-control	320	44/27	FIR-AC	GA<32 wk	27.76±2.73	CCA, SGA, EOS, LOS, mortality, IVH, cystic PVL, NEC, BPD, LOH

Kovács. The histologic fetal inflammatory response and neonatal outcomes. Am J Obstet Gynecol 2024.

(continued)

TABLE
Characteristics of included studies in the meta-analysis and systematic review *(continued)*

Studies	Country	Design	Sample size	No. of cases in exposure/ control group	FIR definition	Inclusion criteria	Mean GA±SD	Outcomes
Tsiartas et al,[49] 2013	Czech Republic	NA	231	45/97	FIR-NOS	GA<37 wk	32.00[c]	PDA
van Doorn et al,[57] 2022	The Netherlands	Retrospective	1014	168/72	FIR-NOS	GA≤32 wk or BW<1500 g	29.00±2.10	LOS
Vergani et al,[83] 2000	Italy	Retrospective	88	5/37	FIR-NOS	GA<32 wk	28.03±2.22	IVH
Woo et al,[56] 2012	Korea	Retrospective	246	35/52	FIR-NOS	GA≤32 wk	29.20±1.90	ROP
Yamada et al,[65] 2015	Japan	NA	272	93/19	FIR-AC	GA<34 wk	25.00	Mortality, IVH, NEC, BPD
Ykema et al,[79] 2018	The Netherlands	Retrospective	88	12/3	FIR-AC	GA<32 wk	28.40±5.43[b]	EOS
Zanardo et al,[64] 2008	Italy	Prospective	287	16/52	FIR-AC	GA<32 wk	31.70±5.10	IVH
Zanardo et al,[59] 2011	Italy	Prospective	234	71/46	FIR-NOS	GA<32 wk	27.67±3.00[b]	RDS

BPD, bronchopulmonary dysplasia; *BW*, birthweight; *CCA*, clinical chorioamnionitis; *CP*, cerebral palsy; *EOS*, early-onset sepsis; *FIR-AC*, fetal inflammatory response Amsterdam criteria; *FIR-NOS*, fetal inflammatory response not otherwise specified; *GA*, gestational age; *IVH*, intraventricular hemorrhage; *LOH*, length of hospital stay; *LOS*, late-onset sepsis; *NA*, not applicable; *NEC*, necrotizing enterocolitis; *PDA*, patent ductus arteriosus; *PVL*, periventricular leukomalacia; *RDS*, respiratory distress syndrome; *ROP*, retinopathy of prematurity; *SD*, standard deviation; *SGA*, small for gestational age.

[a] Conference abstract; [b] Estimated from the median; [c] Median.

Kovács. The histologic fetal inflammatory response and neonatal outcomes. Am J Obstet Gynecol 2024.

HCA with concomitant FIR (Figure 3, A). We observed a difference between the 2 groups with higher odds of EOS in the exposure group (OR, 1.84; 95% CI, 1.00−3.40; I^2=44%), and this was statistically significant in the subgroup with lower GA (OR, 2.23; 95% CI, 1.76−2.84; I^2=0%). Similar results were observed in the FIR-AC population, as shown in Figure 3, B.

No difference in case of late-onset sepsis

Of note, 8 studies included LOS as an outcome, including 1781 neonates, among which 1161 (65.2%) were diagnosed with concomitant FIR (Figure 4, A and B). There was no difference in the rate of LOS between the 2 groups, neither in the analysis of all included studies (OR, 1.18; 95% CI, 0.81−1.72; I^2=14%) nor in the case of the FIR-AC group (OR, 1.31; 95% CI, 0.91−1.88; I^2=0%).

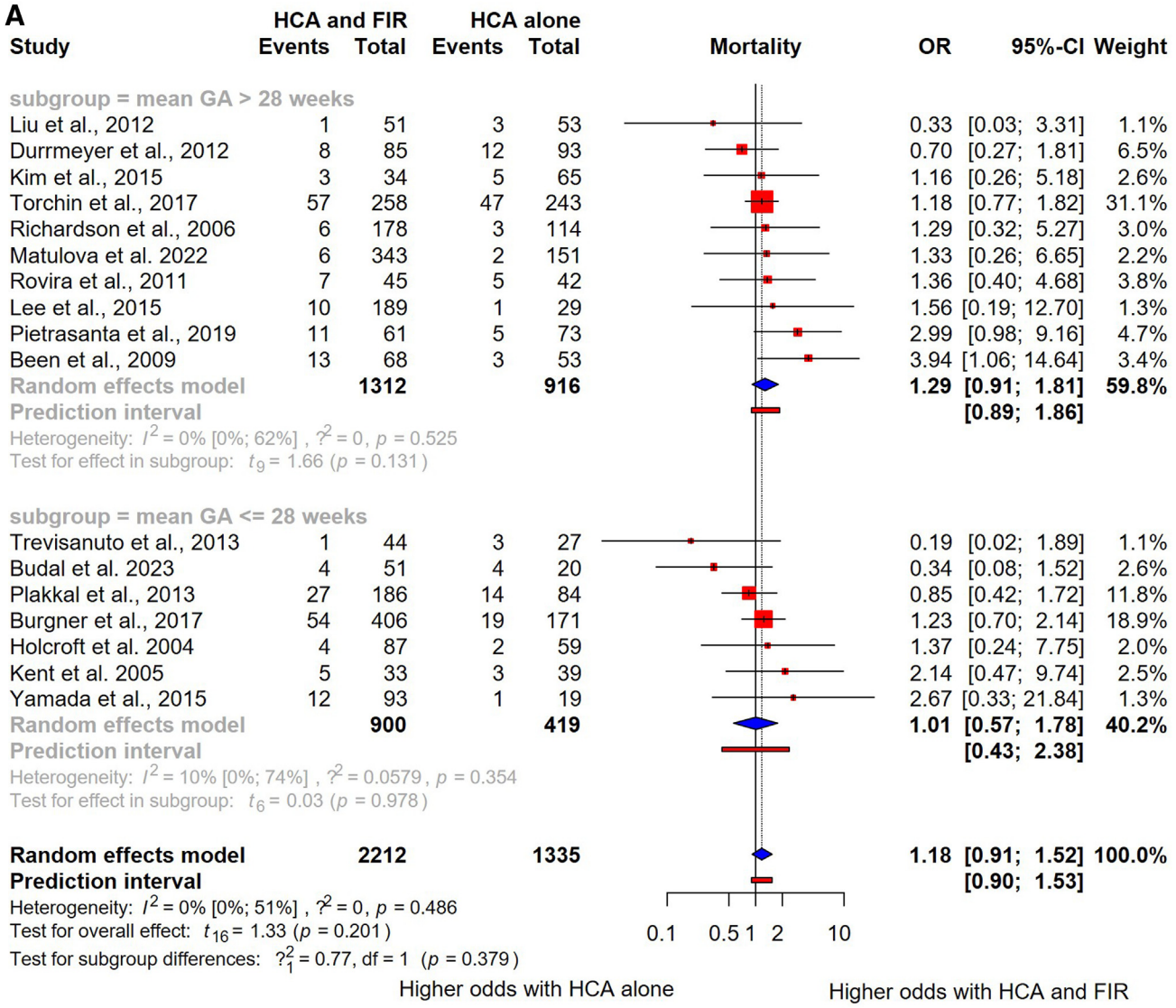
Necrotizing enterocolitis

NEC was analyzed in 15 publications involving 2555 preterm infants, of which 1694 (66.3%) had HCA with FIR. According to our analysis, we found no significant association between NEC and the presence of FIR (OR, 0.94; 95% CI, 0.62−1.40; I^2=4%) (Figure 5, A). However, in the subgroup of neonates with lower GA, we found significantly lower odds of NEC in the group of preterm infants with FIR (OR, 0.60; 95% CI, 0.41−0.90; I^2=0%) (Figure 5, A). Similar results were observed in the FIR-AC population, as shown in Figure 5, B (OR, 0.74; 95% CI, 0.50−1.08; I^2=0%).

Higher incidence of bronchopulmonary dysplasia among extremely preterm infants with fetal inflammatory response

Of note, 22 studies reported the incidence of BPD, including 4063 preterm infants, of which 2581 (63.5%) had chorioamnionitis with FIR. According to our analysis, there was no significant difference in the odds of BPD between the 2 investigated populations (OR, 1.32; 95% CI, 0.95−1.82; I^2=56%) (Figure 6, A). However, in the subgroup with lower mean GA, we found a significant increase in the odds of BPD among

FIGURE 2
The odds of mortality among preterm neonates with HCA and FIR vs with HCA alone



There is no change in the case of mortality. **A,** All studies. **B,** Fetal inflammatory response Amsterdam criteria group.

CI, confidence interval; *FIR*, fetal inflammatory response; *GA*, gestational age; *HCA*, histological chorioamnionitis; *OR*, odds ratio.

Kovács. The histologic fetal inflammatory response and neonatal outcomes. Am J Obstet Gynecol 2024.

neonates with concomitant FIR (OR, 1.30; 95% CI, 1.02−1.66; I^2=0%) (Figure 6, A). In the FIR-AC group, the subgroup analysis showed similar results (Figure 6, B).

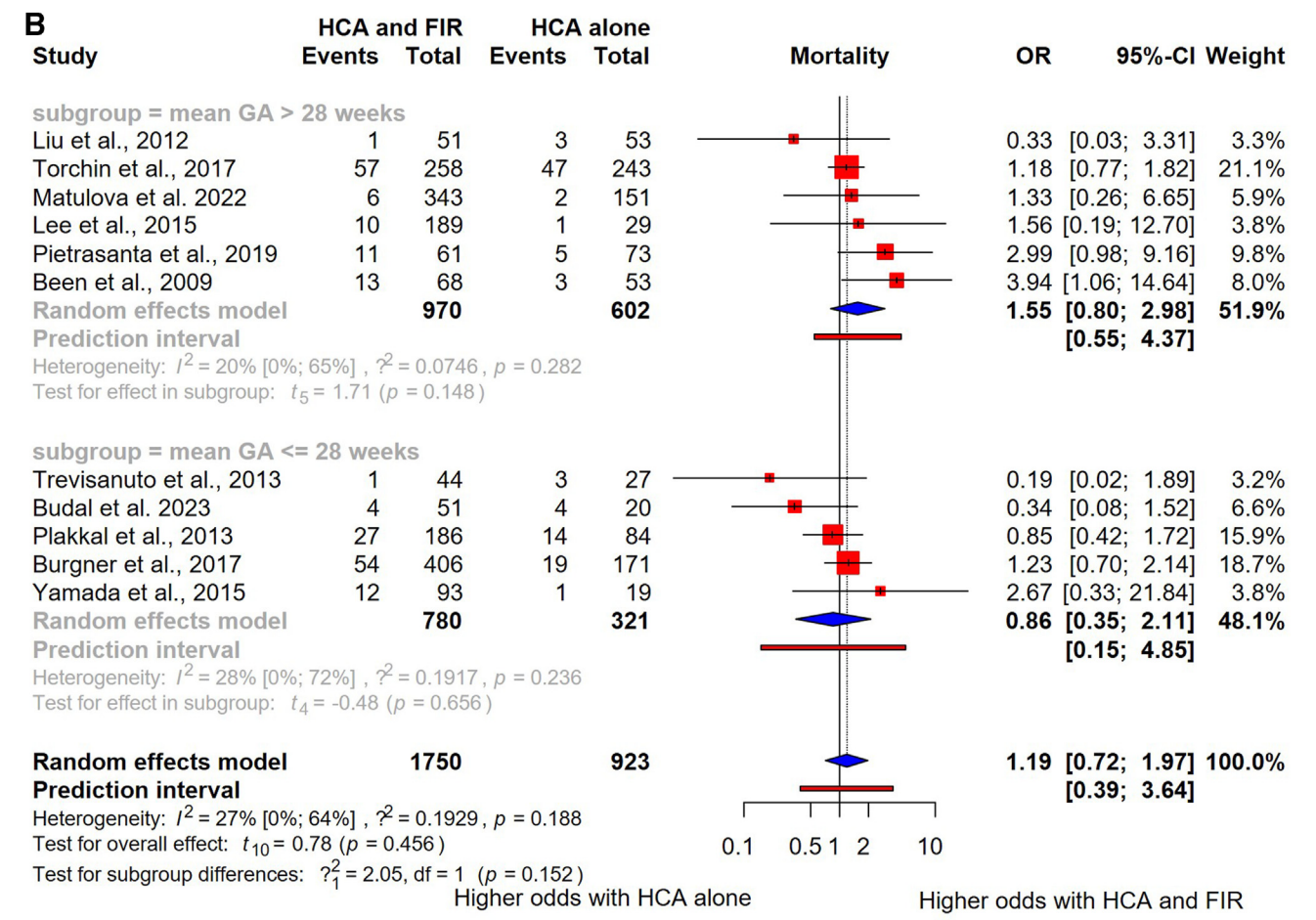
Higher rates of intraventricular hemorrhage and retinopathy of prematurity and no change in cases of periventricular leukomalacia and cerebral palsy

We analyzed several neurologic outcomes. In the case of IVH, we extracted the data separately according to the severity. We found a significant association between IVH and the presence of FIR (OR, 1.54; 95% CI, 1.18−2.02; I^2 =0%); however, this association with severe IVH was not observed (Supplemental Figures 46 and 47). Our analysis showed a significant association between ROP and the presence of FIR with chorioamnionitis. We found no significant difference between the 2 investigated populations in cases of ROP, PVL, and CP (Supplemental Figures 48−50). Our analysis showed a significant association between ROP and the presence of FIR with chorioamnionitis (Supplemental Figure 48, OR, 1.37; 95% CI, 1.03−1.82; I^2 =0%). We found no significant difference between the 2 investigated populations in cases of PVL, and CP (Supplemental Figures 49 and 50).

Three-fold elevated clinical chorioamnionitis

In both analyses, the presence of CCA was significantly elevated in the group of preterm infants with FIR (OR, 2.99; 95% CI, 1.96−4.55; I^2 =55%). Interestingly,

FIGURE 2
Continued



Kovács. The histologic fetal inflammatory response and neonatal outcomes. Am J Obstet Gynecol 2024.

according to the subgroup analysis, this elevation was not significant in groups of infant-mother dyads with lower mean GA (Supplemental Figure 51).

Respiratory distress syndrome, patent ductus arteriosus, and small for gestational age

Our analysis showed no association between FIR and RDS (Supplemental Figure 52). In the case of patent ductus arteriosus (PDA), we found no significant difference between the 2 groups of neonates. Moreover, we assessed the incidence of SGA, and our data suggest that there was no difference between the cases associated with FIR and the comparison group (Supplemental Figures 53 and 54).

Systematic review

Of note, 4 studies[20,23,61,75] reported neurodevelopmental impairments, and none of the studies showed significant differences between the 2 groups of neonates. Hearing impairment or deafness was analyzed in 5 studies,[20,23,61,71,75] and visual impairment was analyzed in 4 studies,[20,23,61,75] none of which found an association with the exposure. However, the results for the different endpoints could not be included in the quantitative synthesis because of heterogeneity.

The LOH was analyzed in 3 studies[25,27,58]; however, although it was included as an outcome of our protocol, analyzing it was not reasonable because of the differences between institutional protocols and capacities.

Meta-analysis of proportions

In addition, we conducted a study of proportions, which are shown in Supplemental Figures 55 to 68 and Supplemental Table 2.

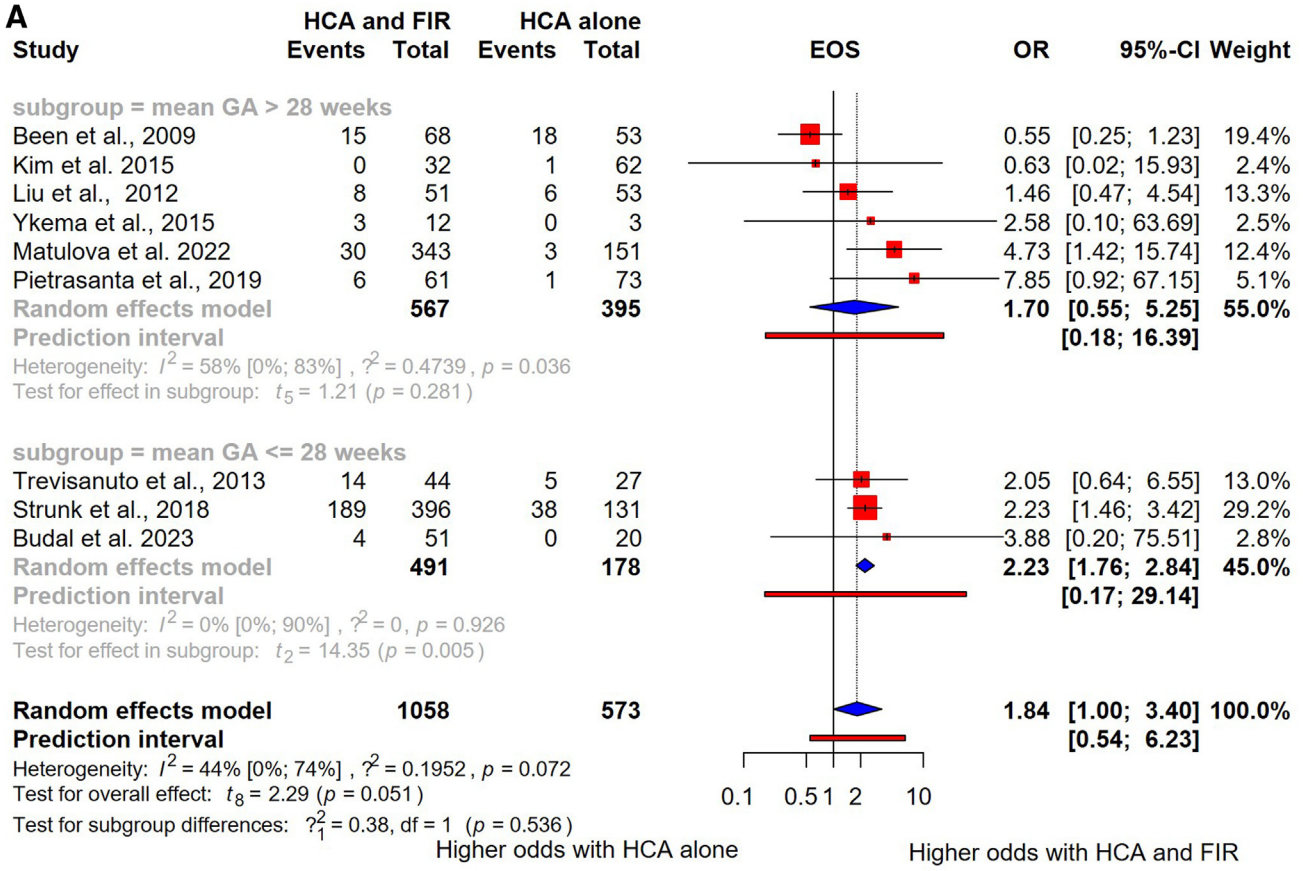
Comment

Principal findings

We performed a meta-analysis of 47 observational studies to assess the influence of the concomitant presence of histological FIR with HCA vs HCA alone on the complications of prematurity. This analysis was based on unadjusted data, using the mean GAs to perform a subgroup analysis.

The main result of our study was that the incidence of IVH was significantly higher in the group of preterm infants with HCA and histological FIR than in the group of preterm infants with HCA alone. Moreover, a similar comparison in the subgroup of preterm infant

FIGURE 3
The odds of EOS with HCA and FIR vs with HCA alone



There is no significant difference in the case of EOS. **A,** All studies included. **B,** Fetal inflammatory response Amsterdam criteria group.

CI, confidence interval; *EOS*, early-onset sepsis; *FIR*, fetal inflammatory response; *GA*, gestational age; *HCA*, histological chorioamnionitis; *OR*, odds ratio.

Kovács. The histologic fetal inflammatory response and neonatal outcomes. Am J Obstet Gynecol 2024.

populations with a mean GA of <28 weeks showed a significantly higher incidence of EOS and BPD but a lower incidence of NEC in the cases of HCA and histological FIR. In addition, we found nearly 3-fold higher odds for clinically apparent HCA when HCA and histological FIR were present.

The rate of all other investigated complications in preterm infants, including severe IVH, did not differ by the presence of histological FIR with HCA.

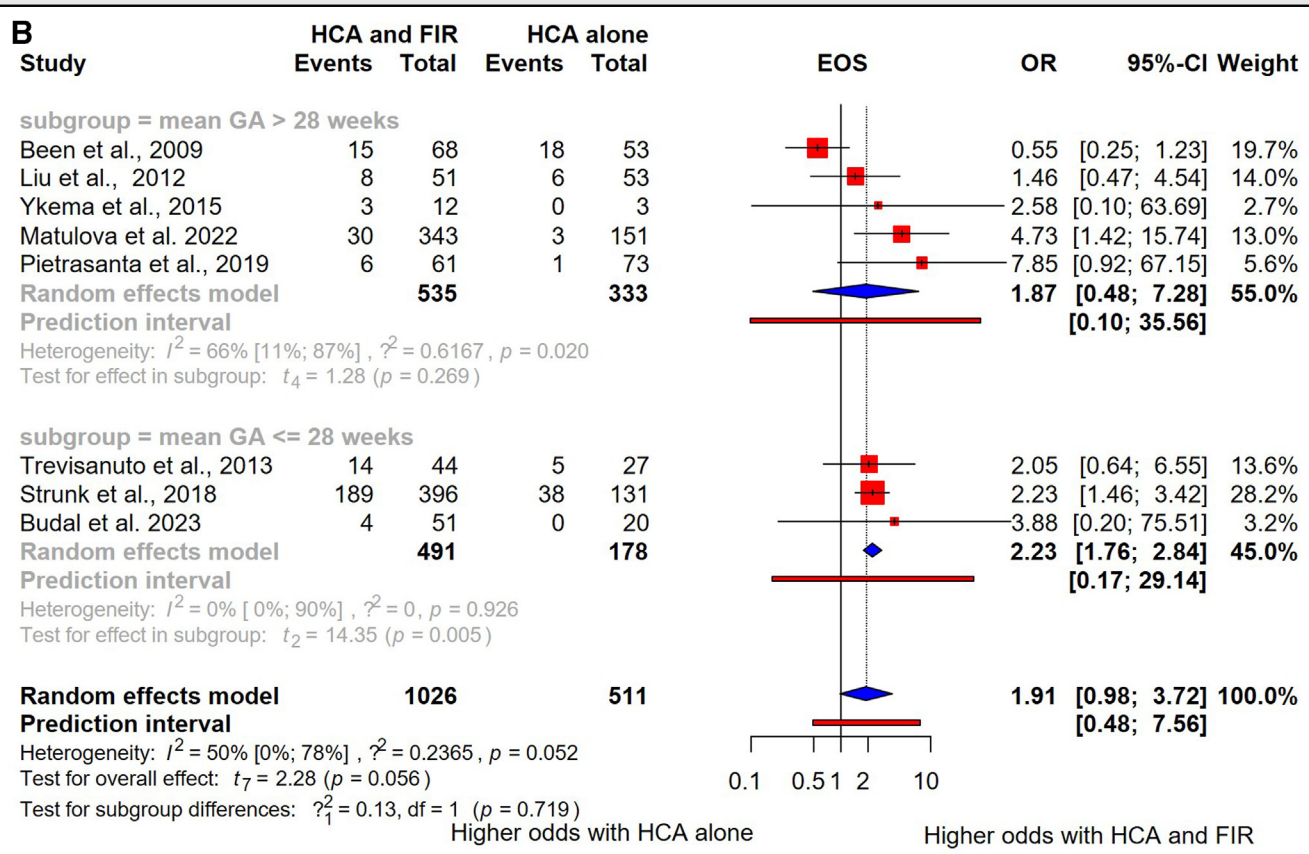
Comparison with the existing literature

Several meta-analyses deal with the association of chorioamnionitis and adverse outcomes of preterm infants, and some of them also included the effect of histological FIR in the investigation.[15–19,89–91] This review is strictly based on histological evaluation vs other systematic reviews investigating histological FIR as a part of the FIR syndrome (FIRS).[92]

In the subgroup of preterm infants with a mean GA of <28 weeks, an elevated rate of BPD was observed. This correlation was statistically significant only in the FIR-AC group. Similar to our findings, the results in the literature are also inconsistent. Most cohort studies and meta-analyses have found an association between BPD and IUI; however, its role as an independent risk factor has not been proven.[15] BPD has been the subject of extensive research during the past few decades, and it is no longer considered that immature lungs and aggressive ventilation alone would be responsible for the development of BPD. As one of the first organs to encounter the amniotic fluid, the fetal lung might be one of the first organs to initiate FIR as well. In an experimental setting, the exposure of the fetal lung to lipopolysaccharide (LPS) initiated FIR.[93] Inflammation and microbial particles facilitate lung maturation.[94] However, this accelerated maturation induces anatomic and structural changes within the lung tissue, turning this benefit into a disadvantage, an impaired lung function.[95,96]

In the subgroup with lower GA, we also found an association between the presence of histological FIR and EOS

FIGURE 3
Continued



Kovács. The histologic fetal inflammatory response and neonatal outcomes. Am J Obstet Gynecol 2024.

in contrast to other meta-analyses focusing on this topic.[16] This discrepancy could be due to more recent publications or the excluded articles because of the different populations and designs.

Surprisingly, our analysis showed a reduced incidence of NEC in the group of preterm infants with histological FIR in the subgroup with lower mean GA. Another meta-analysis conducted in 2013[18] found no significant association between HCA and NEC. The pathogenesis of NEC is still not fully elucidated. Risk factors include immaturity, hypoxic-ischemic states, abnormal microbiological colonization, and formula feeding.[97] Therefore, local protocols for antibiotic prophylaxis and enteral feeding may have affected the incidence of NEC in different studies.[98,99]

In the case of LOS and PDA, we found no significant association, similar to other meta-analyses.[16,90,91] Villamor-Martinez et al[89] detected a higher risk of ROP among neonates with histological FIR, and we could substantiate this by analyzing a larger number of studies.

According to our results, there was an increased occurrence of IVH in the presence of HCA with histological FIR, in contrast to the results of Villamor-Martinez et al.[19] This finding may be explained by the larger number of included studies and the design focused on answering the particular question of the role of histological FIR with HCA. According to our results, this significant association was not demonstrated in the case of severe IVH. The discrepancy between the 2 analyses regarding all IVH and severe IVH-only cases can easily be caused by the different grading systems[100,101] or the potentially different etiology of intraparenchymal bleeding.[100,102]

Our analysis showed a 3-fold increase in CCA among infant-mother dyads with HCA and histological FIR. More than 90% of pregnant women diagnosed with CCA are expected to deliver within the next 12 hours.[103] Based on these results, HCA is more likely to be clinically silent than additional histological FIR. This association could support the understanding that fetal inflammation develops later, depending on the duration and intensity of the exposure to inflammation. However, this also raises the possibility of further explanation. For example, in the case of HCA, bacteria are more commonly identified when CCA is present.[104] As specific inflammatory patterns have been described in the cord, several pathogens have been proposed to

FIGURE 4
The odds of LOS with HCA and FIR vs with HCA alone

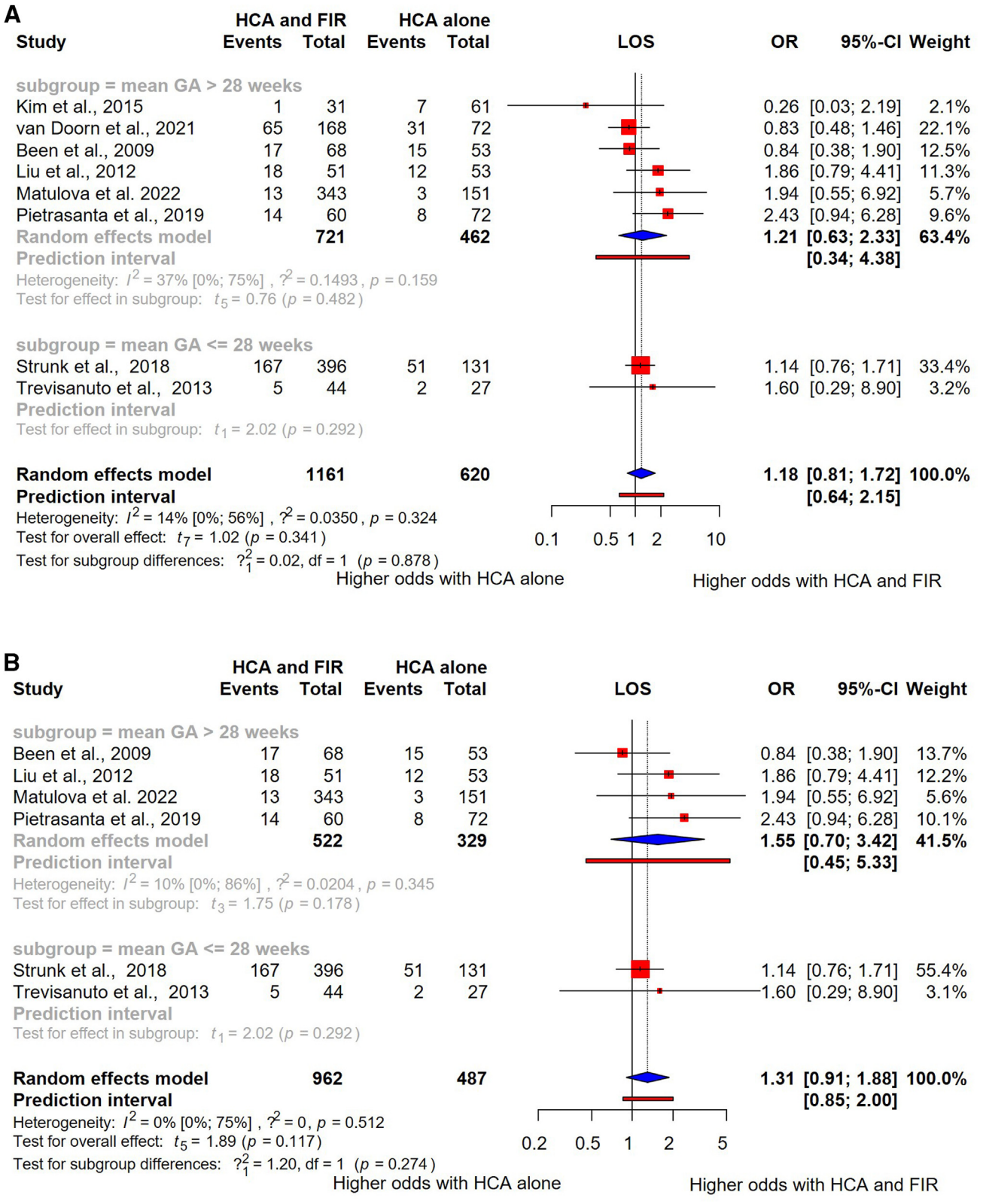
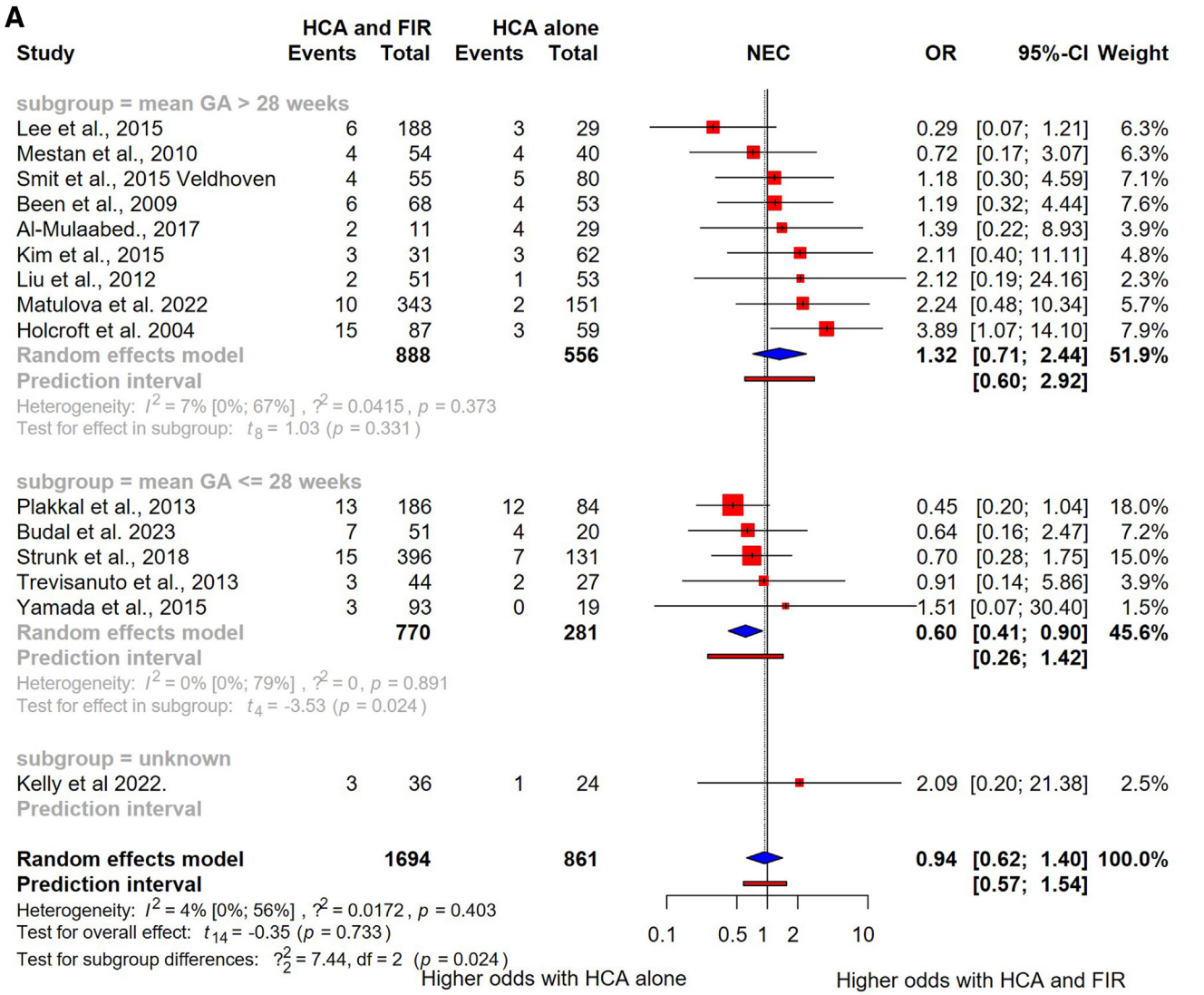


FIGURE 5
The odds of NEC with HCA and FIR vs with HCA alone



There is no significant difference in the case of NEC. **A,** All studies. **B,** Fetal inflammatory response Amsterdam criteria group.

CI, confidence interval; *FIR*, fetal inflammatory response; *GA*, gestational age; *HCA*, histological chorioamnionitis; *NEC*, necrotizing enterocolitis; *OR*, odds ratio.

Kovács. The histologic fetal inflammatory response and neonatal outcomes. Am J Obstet Gynecol 2024.

play a role in the development of histological FIR.[105] It would be reasonable that certain pathogens could induce an FIR, leading to a higher rate of CCA.

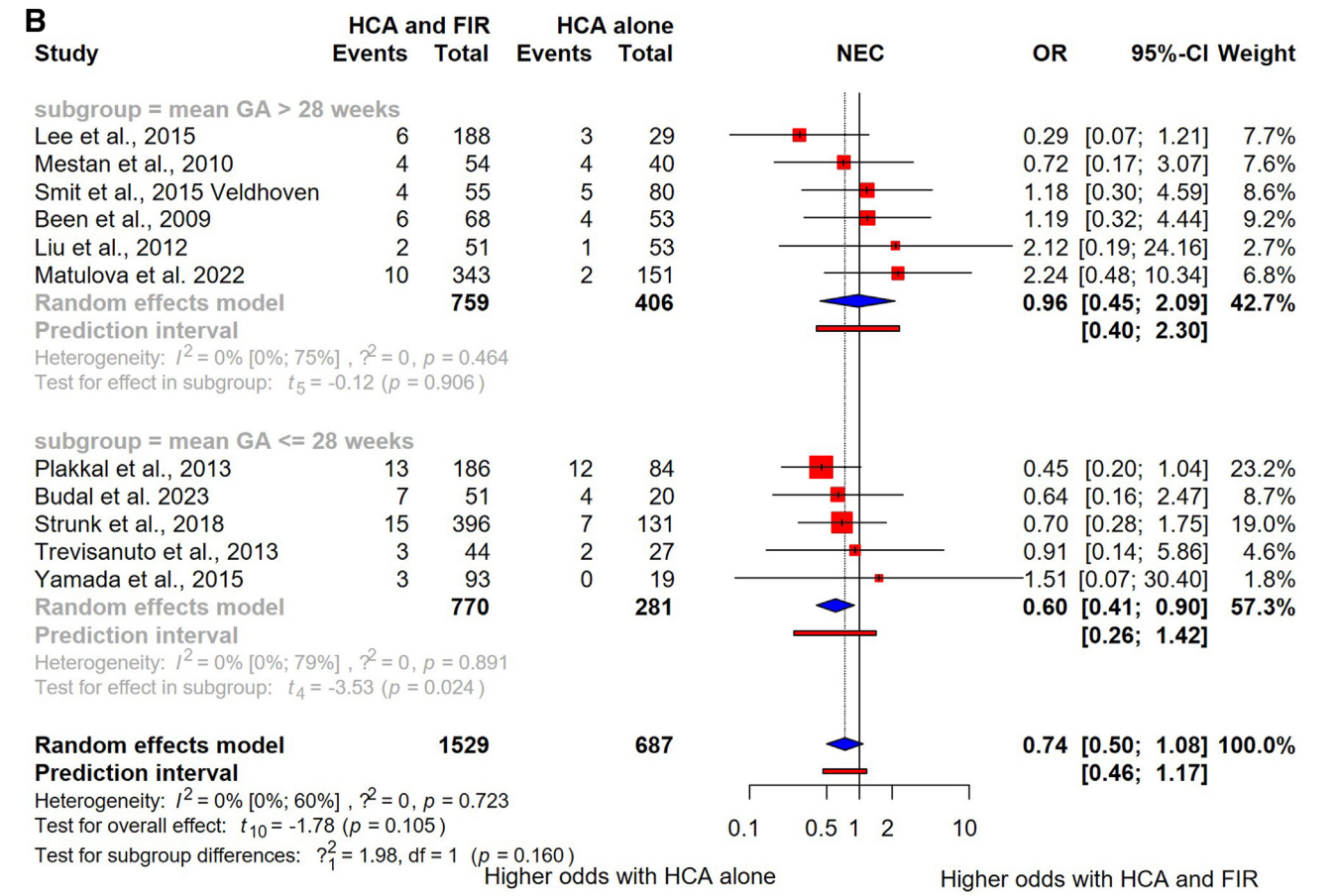
As discussed in the literature, histological FIR is the morphologic equivalent of the clinical FIRS.[106] With the clear effect of HCA on nearly all adverse neonatal outcomes, the presence of histological FIR may propose a more extensive inflammation that brings even worse odds for neonatal mortality and morbidity. Based on animal studies, the progression of HCA occurs chronologically from stage 1 to stage 3 after an inflammatory stimulus.[107] A parallel between the manifestation and advancement of histological FIR is less

There is no significant difference in the case of LOS. **A,** All studies. **B,** Fetal inflammatory response Amsterdam criteria group.

CI, confidence interval; *FIR*, fetal inflammatory response; *HCA*, histological chorioamnionitis; *LOS*, late-onset sepsis; *OR*, odds ratio.

Kovács. The histologic fetal inflammatory response and neonatal outcomes. Am J Obstet Gynecol 2024.

FIGURE 5
Continued



Kovács. The histologic fetal inflammatory response and neonatal outcomes. Am J Obstet Gynecol 2024.

clear.[104] According to the literature, FIR usually presents with a higher stage of maternal chorioamnionitis.[108,109] Furthermore, when comparing HCA alone with HCA with histological FIR, the levels of several interleukins and tumor necrosis factor alpha in the amniotic fluid were significantly higher in the latter group. These findings suggest a progressed level of inflammation reaching the chorionic vessels and the umbilical vein and arteries.[110] Therefore, histological FIR is considered an "advanced stage" of HCA.[111]

However, this equation might be more complicated. Experimental fetal inflammation can induce functional maturation and activation of monocytes and macrophages. Activated fetal cells may alter the intrauterine response of the fetus during intrauterine inflammation.[111] The nature of these complex immunologic mechanisms in the fetus may explain why HCA with histological FIR is not always associated with worse neonatal outcomes but might influence the course of CCA.

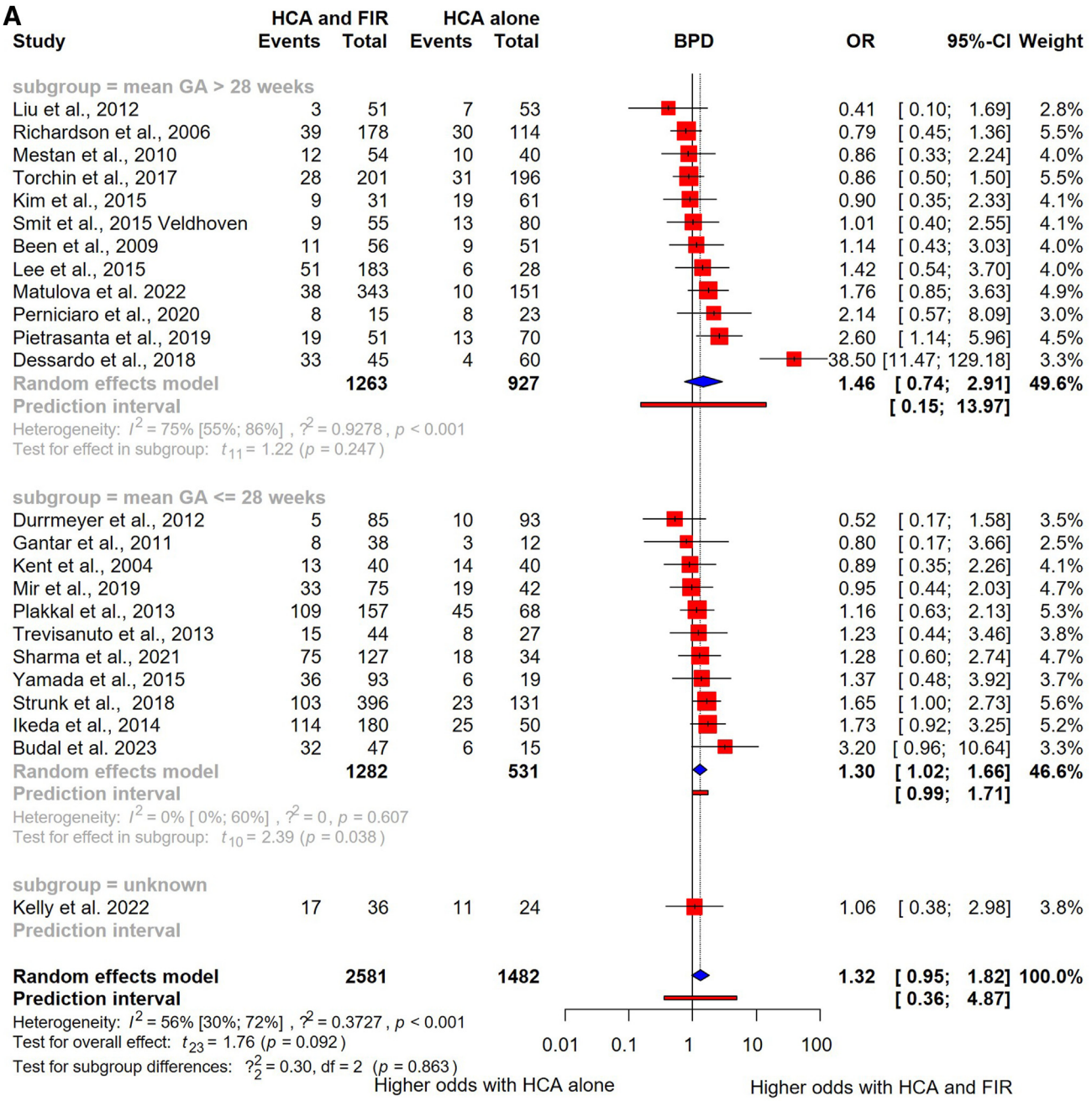
Strengths and limitations

This was a meta-analysis that focused on the consequences of the presence of histological FIR with HCA in a wide range of neonatal outcomes. We only included articles that defined chorioamnionitis based on histological examination. Furthermore, we have a selected population of articles with uniform histological classification. To decrease the possible influence of GA on outcomes, subgroup analyses were performed on the basis of the mean GA.

Our study has some limitations. All of the included studies were observational studies, mainly with a moderate to high RoB because of our particular research question. Our population consists of preterm infants or VLBW neonates, and we did not make any other restrictions. This resulted in a rather heterogeneous population. The definitions of the outcomes differed in certain articles or were described only vaguely.

The morbidities of preterm infants are multifactorial and highly influenced by several confounding factors, such as maternal medical complications, premature rupture of membranes, antenatal steroid prophylaxis, GA, or surfactant therapy. Here, data were not adjusted for

FIGURE 6
The odds of BPD with HCA and FIR vs with HCA alone



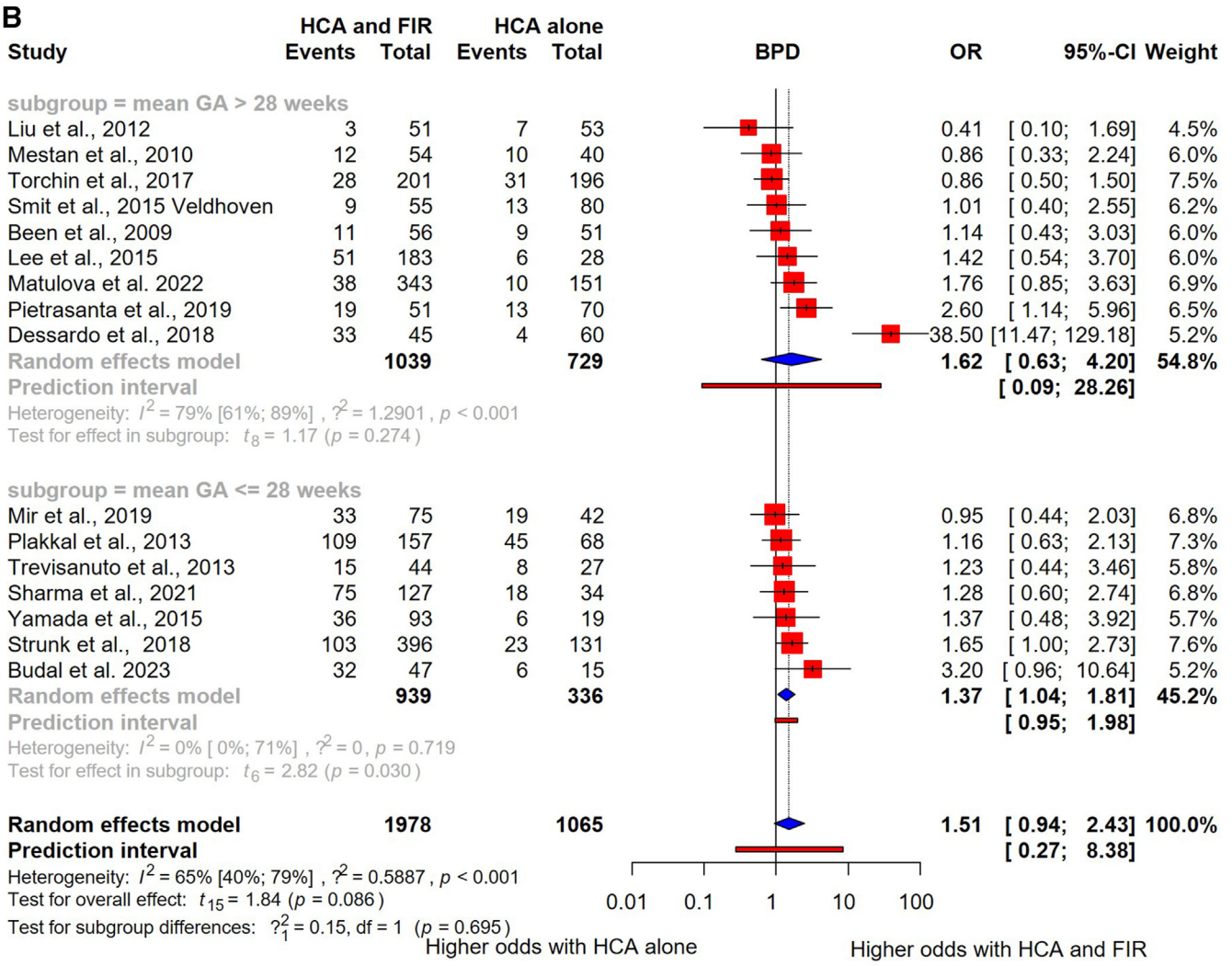
There is higher incidence of BPD among extremely preterm infants with FIR. **A,** All studies. **B,** Fetal inflammatory response Amsterdam criteria group.

BPD, bronchopulmonary dysplasia; *CI*, confidence interval; *FIR*, fetal inflammatory response; *GA*, gestational age; *HCA*, histological chorioamnionitis; *OR*, odds ratio.

Kovács. The histologic fetal inflammatory response and neonatal outcomes. Am J Obstet Gynecol 2024.

these factors. In addition, in some studies where the baseline characteristics were available separately in the HCA alone and HCA with FIR groups, significant differences were observed regarding these characteristics.[28,29,77] Regarding long-term outcomes, we could only make a meta-analysis in the case of CP. In the case of other outcomes, such as hearing or visual impairment or neurodevelopmental delay, the different effect measurements were not suitable for merging. Therefore, to avoid protocol deviation, we cover this topic in the narrative review section. Moreover, we

FIGURE 6
Continued



Kovács. The histologic fetal inflammatory response and neonatal outcomes. Am J Obstet Gynecol 2024.

did not have a histologically negative population, which is a substantial limitation. Defining the FIR-AC group was necessary to differentiate articles with precise histological descriptions. Because of the vague definitions used by some articles, we cannot ensure that all articles referred to as FIR-NOS are not based on the same criteria as the FIR-AC group.

Conclusion and implication

Higher rates of EOS, BPD, IVH, and ROP provide further information for prognostic evaluation. Histological examination of the umbilical cord can provide an additional element in the diagnostic workup of EOS and could be a helpful guide in clinical decision-making. Based on our results, the presence of CCA—a more advanced stage of intrauterine inflammation—should be suspected.

In our comparison, there was no histologically negative population. To obtain a better understanding, a meta-analysis comparing HCA alone with a histologically negative population should be performed. To decrease the influence of confounding factors in the analyses, original datasets should be made available in future studies. ■

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Appendix

SUPPLEMENTARY TABLE 1
Clinical question according to PECO framework (Population, Exposure, Comparison, Outcome)

Population	**Preterm neonates (born before the 37th completed gestational week) or very low birth weight neonates (birth weight ≤1500 g).**
Exposure	Preterm neonates with histological chorioamnionitis but no histological signs of fetal inflammatory response.
Comparison	Preterm neonates with histological chorioamnionitis and the presence of histological signs of fetal inflammatory response. FIR-AC group: FIR definition based on the Amsterdam Placental Consensus Workshop FIR-NOS group: FIR defined only with funisitis or not otherwise specified
Outcomes	Primary outcomes: neonatal mortality, early-onset sepsis, late-onset sepsis, necrotizing enterocolitis, and bronchopulmonary dysplasia. Additional outcomes: retinopathy of prematurity; intraventricular hemorrhage; periventricular leukomalacia; respiratory distress syndrome; length of hospital stay; cerebral palsy; neurodevelopmental delay; sensory impairment; small for gestational age; clinical chorioamnionitis.

Kovács. The histologic fetal inflammatory response and neonatal outcomes. Am J Obstet Gynecol 2024.

SUPPLEMENTARY TABLE 2
Meta-analysis of proportions

Outcomes	value	lower CI	upper CI
Mortality GA>28 HCA and FIR	0.081070254	0.047920021	0.133927332
Mortality GA>28 HCA alone	0.066397704	0.038433546	0.112331592
Mortality GA<=28 HCA and FIR	0.105386926	0.074307628	0.147395406
Mortality GA<=28 HCA alone	0.098536878	0.065329232	0.145987882
EOS GA>28 HCA and FIR	0.115482579	0.072606327	0.178797042
EOS GA>28 HCA alone	0.049390531	0.013661988	0.16310459
EOS GA<=28 HCA and FIR	0.257986496	0.0959882	0.53237881
EOS GA<=28 HCA alone	0.103838846	0.018214591	0.419844816
LOS GA>28 HCA and FIR	0.179552903	0.091244285	0.322955353
LOS GA>28 HCA alone	0.149885812	0.064412896	0.311067478
NEC GA>28 HCA and FIR	0.069391085	0.042985364	0.110150723
NEC GA>28 HCA alone	0.053231591	0.034342886	0.081630936
NEC GA<=28-HCA and FIR	0.056804107	0.034547944	0.092031203
NEC GA<=28 HCA alone	0.088450943	0.045119801	0.166154511
BPD GA>28 HCA and FIR	0.242172659	0.158971341	0.350758346
BPD GA>28 HCA alone	0.176947096	0.133761662	0.230367219
BPD GA<=28 HCA and FIR	0.408204906	0.284678985	0.544528436
BPD GA<=28 HCA alone	0.347622638	0.241742724	0.471066709
IVH GA>28 HCA and FIR	0.251654505	0.201335516	0.309673306
IVH GA>28 HCA alone	0.187873512	0.146943901	0.237035802
Severe IVH GA>28 HCA and FIR	0.069666992	0.045139074	0.106042859
Severe IVH GA>28 HCA alone	0.054804329	0.028582859	0.102541731
Severe IVH GA<=28 HCA and FIR	0.127262001	0.044086874	0.315556164
Severe IVHGA<=28 HCA alone	0.085529519	0.034076287	0.198692857
ROP GA>28 HCA and FIR	0.145603238	0.054118183	0.336691477
ROP GA>28 HCA alone	0.094841791	0.031162837	0.25446687
PVL GA>28 HCA and FIR	0.029549078	0.015177863	0.056743696
PVL GA>28 HCA alone	0.01705803	0.004281642	0.065452968
CP GA<=28 HCA and FIR	0.088147665	0.051729895	0.146249396
CP GA<=28 HCA alone	0.106318279	0.0706149	0.15702359
CCA GA>28 HCA and FIR	0.456744715	0.269213428	0.657395147
CCA GA>28 HCA alone	0.183363328	0.0816588	0.361830053
CCA GA<=28 HCA and FIR	0.336183355	0.283923069	0.392786504
CCA GA<=28 HCA alone	0.143342357	0.056401787	0.318992583
RDS GA>28 HCA and FIR	0.376518379	0.215615416	0.570207612
RDS GA>28 HCA alone	0.352553837	0.229026935	0.499537303
RDS GA<=28 HCA and FIR	0.73455352	0.504149129	0.882788157
RDS GA<=28 HCA alone	0.818103789	0.675358437	0.906750111
SGA GA>28 HCA and FIR	0.078689978	0.046623283	0.129808669

Kovács. The histologic fetal inflammatory response and neonatal outcomes. Am J Obstet Gynecol 2024. *(continued)*

SUPPLEMENTARY TABLE 2
Meta-analysis of proportions *(continued)*

Outcomes	value	lower CI	upper CI
SGA GA>28 HCA alone	0.140742933	0.100909605	0.192926151
SGA GA<=28 HCA and FIR	0.054	0.037288458	0.077597458
SGA GA<=28 HCA alone	0.040892193	0.022787722	0.072315942
PDA GA>28 HCA and FIR	0.266301567	0.154617254	0.418702829
PDA GA>28 HCA alone	0.166314051	0.082335129	0.30726789
PDA GA<=28 HCA and FIR	0.256942568	0.044165293	0.72127689
PDA GA<=28 HCA alone	0.303561884	0.058363734	0.754014215

Point estimates and confidence intervals.

CI, confidence interval; GA, gestational age; HCA, histological chorioamnionitis; FIR, fetal inflammatory response; EOS, early onset sepsis; LOS, late-onset sepsis; NEC, necrotizing enterocolitis; BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; ROP, retinopathy of prematurity; PVL, periventricular leukomalacia; CP, cerebral paresis; CCA, clinical chorioamnionitis; RDS, respiratory distress syndrome; PDA, patent ductus arteriosus; SGA, small for gestational age.

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