Fetal Diagnosis and Therapy

Review Article

Fetal Diagn Ther 2021;48:81–87
DOI: 10.1159/000510648

Received: June 22, 2020
Accepted: August 3, 2020
Published online: February 8, 2021

The Novel Ultrasonographic Marker of Uterocervical Angle for Prediction of Spontaneous Preterm Birth in Singleton and Twin Pregnancies: A Systematic Review and Meta-Analysis

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Keywords
Pregnancy · Preterm birth · Singleton · Twin · Uterocervical angle

Abstract
The alteration of the uterocervical angle (UCA) has been proposed to play an important role in spontaneous preterm birth (sPTB). The aim of this systematic review and meta-analysis was to evaluate the evidence on the UCA predictive role in sPTB. In this study, PubMed, Web of Science, Scopus, and Google scholar were systematically searched from inception up to June 2020. Inter-study heterogeneity was also assessed using Cochrane's Q test and the I^2 statistic. Afterward, the random-effects model was used to pool the weighted mean differences (WMDs) and the corresponding 95% confidence intervals (CIs). Eleven articles that reported second-trimester UCA of 5,061 pregnancies were included in this study. Our meta-analysis results indicate that a wider UCA significantly increases the risk of sPTB in following cases: all pregnancies (WMD = 15.25, 95% CI: 11.78–18.72, $p < 0.001$; $I^2 = 75.9\%$, $p < 0.001$), singleton (WMD = 14.43, 95% CI: 8.79–20.06, $p < 0.001$; $I^2 = 82.4\%$, $p < 0.001$), and twin pregnancies (WMD = 15.14, 95% CI: 13.42–16.87, $p < 0.001$; $I^2 = 0.0\%$, $p = 0.464$). A wider ultrasound-measured UCA in the second trimester seems to be associated with the increased risk of sPTB in both singleton and twin pregnancies, which reinforces the clinical evidence that UCA has the potential to be used as a predictive marker of sPTB.

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Background

Spontaneous preterm birth (sPTB), which was estimated to complicate up to 13% of all pregnancies, represents a major challenge in obstetrics and pediatrics healthcare [1]. Moreover, sPTB is one of the main causes of morbidity and mortality among newborns and is also associated with an annual economic burden estimated around 25 billion US dollars in the USA [2]. In addition to neonatal complications associated with sPTB, previous

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reports have also shown that premature born children suffer from various short- and long-term morbidities and adverse outcomes in later years of their lives such as neurologic deficits, learning disabilities, and various respiratory problems [3].

Many strategies have been proposed for early prediction of sPTB; therefore, physicians would be able to take preventive measures to improve the pregnancy outcome. In the current medical practice, a previous history of sPTB in obstetrical history and a short cervical length (CL) in ultrasound examination that are among the most commonly used predictive tools, were applied to evaluate the risk of sPTB [4]. However, CL has been shown to have a limited value in the prediction of sPTB among those women who have a history of preterm delivery in previous pregnancies [5]. Furthermore, there is inadequate evidence to recommend the widespread screening of CL for identifying the women who are at the risk of sPTB [5]. Recent research has also focused on maternal serum, amniotic fluid, and cervicovaginal fluid inflammatory biomarkers for predicting sPTB; however, their utilization and cost-effectiveness are not sufficient for most of the current clinical settings [6].

According to the abovementioned reasons, developing some new predictive methods for the identification of women at risk of sPTB seems necessary. In the recent years, the ultrasonographic measurement of uterocervical angle (UCA), which is the angle formed between the cervical canal and anterior uterine wall, has been recommended to be a predictive measurement for sPTB [7].

Several underlying biological and anatomical pathways leading to sPTB are complex. During pregnancy, cervix experiences pressure from adjacent organs and also withstands the force from the gravid uterus. In this regard, the adjacent pressure and distinct uterine anatomy affect the internal os and cervical function [8]. Moreover, the function of cervix during gestation could be assessed through performing the ultrasound measurement of CL or UCA. Notably, the underlying mechanism supporting the utility of UCA for prediction of sPTB is built on the rules of physics. The downward uterine force on an acute UCA supports endocervical canal closure, while the same force on an obtuse UCA has the potential of facilitating cervical dilation, which seems to be more pronounced in twin gestations due to uterine over distention [9, 10]. In other word, it has been hypothesized that UCA may act as a mechanical barrier affecting the progress of labor [11]. Thus, a number of studies have assessed the UCA predictive value, mostly measured at the 2nd trimester, at the same time with CL screening, for early identification of women at risk for sPTB. However, their findings seem to be conflicting [12–14].

Given the fact that the conflict exist in the findings of previous reports may be partly explained by some variations in the number of participants, study design, etc.; therefore, it seems necessary to carry out a meta-analysis to provide a more reliable comment on this issue. Thus, we undertook a systematic review and meta-analysis to provide a more comprehensive conclusion on the association between the ultrasound-measured UCA and the risk of sPTB.

Data Sources

We conducted and reported our study in terms of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist [15].

Search Strategy

Systematic literature was performed in PubMed, Web of Science, Scopus, and Google scholar from inception up to June 2020. We captured studies that have assessed the association between UCA and sPTB using both MeSH terms and any relevant keywords from databases: (“Uterocervical angle” OR “utero-cervical angle” OR “cervicouterine angle” OR “cervico-uterine angle” OR “uterine angle” OR “cervical angle”) AND (“preterm birth” OR “preterm labor” OR “preterm labour” OR “preterm delivery” OR “pre-term” OR “preterm” OR “early birth” OR “early delivery” OR “early labor” OR “early labour”). Our searches were performed in English language without date limitation. The reference lists of included studies were also manually checked to catch studies that were not captured by researchers in electronic literature searches.

Study Selection

In this study, articles that met the following inclusion criteria were included: study with an observational design conducted on human subjects in English language; evaluated the predictive role of UCA for sPTB; and indicated sufficient data to calculate mean difference with 95% confidence intervals (95% CI) for investigating UCA in patients with sPTB compared to the control subjects without sPTB. Afterward, both singleton and twin pregnancies were included in this review and subgroup’s analyses were also done to assess the UCA angle separately in each

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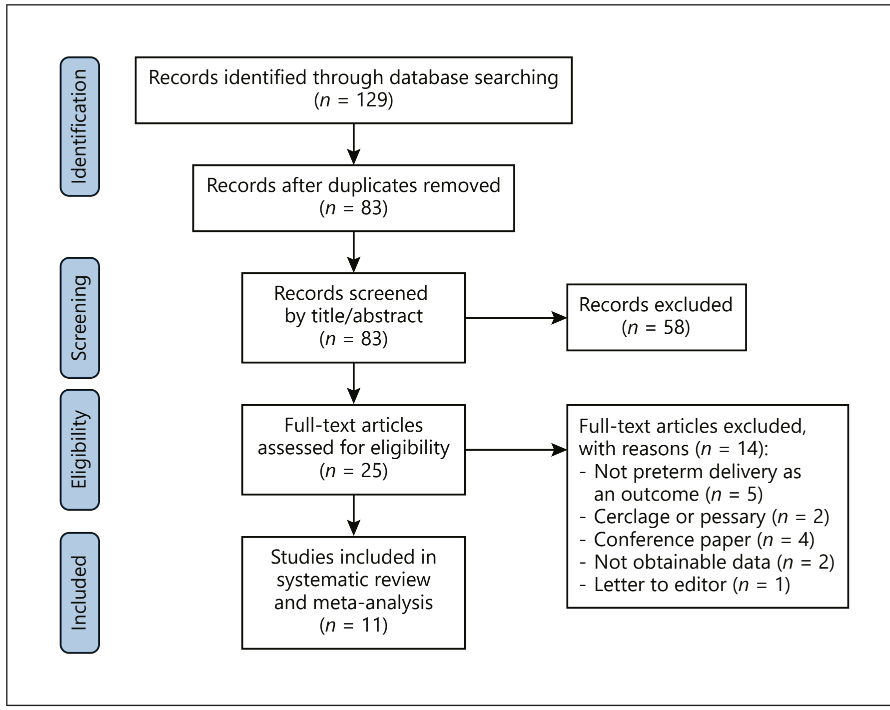

Fig. 1. PRISMA flowchart.

group. Also, some other records such as case report, case series, animal study, letter to editor, review study, abstracts without full text, and studies without a control group were excluded. Furthermore, studies reporting induced preterm delivery, women considered as high risk for sPTB (e.g., short cervix) as well as those studies indicating several mechanically induced changes in UCA (e.g., pessary insertion) were excluded.

Data Extraction and Outcome Measure

Data extraction from the included articles was performed by 2 independent authors (K.H. and N.A.) using the standard sheet form of Microsoft Excel®. Any discrepancies were resolved through censuses or discussion with a third author (M.K. or H.V.). The main outcome measure of this meta-analysis was the comparison between women with sPTB and those with term gestation in terms of UCA.

Subsequently, the following data were extracted: the first author's name, year of publication, study design, study setting, participants' characteristics (case and control groups), singleton or twin population, number and age of the patients in sPTB group and control subjects, mean (SD) of UCA in case and control groups, type of ultrasound (transvaginal and transperineal), and pregnancy trimester at ultrasound.

Quality Assessment

In this study, Newcastle-Ottawa Scale was used to assess the quality of eligible studies. Accordingly, this quality assessment tool mainly evaluates the 3 aspects of "participant selection, comparability of study groups, and assessment of outcome or exposure." Regarding this tool, a study with an Newcastle-Ottawa Scale score above 7 is considered as high quality [16].

Statistical Analysis

The overall pooled effect size was calculated by weighted mean differences (WMDs). In addition, the Cochran (Q) statistic and I^2 test were applied to assess heterogeneity between the included studies. A Q test of $p < 0.1$ and $I^2 \geq 50\%$ was considered to have a significant heterogeneity across the included studies. Sensitivity analyses were conducted to assess the influence of one by one study on the overall pooled SMDs after the exclusion of each study using the leave-one-out method. Finally, subgroup analyses (including number of fetuses [singleton and twin], study country [USA, Spain, and others], study design [cohort, case control, and others], preterm birth cutoff [37 weeks and <37 weeks], type of ultrasound [TVS and TPS] and quality scores [high and low]), and meta-regression method (based on publication year and total sample size) were used to identify the source of heterogeneity accord-

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Table 1. Characteristics of included studies assessing the association between UCA and preterm delivery

Authors	Publication year	Country	Sample size (case/control)	Study design	Type of ultrasound	Ultrasound at trimester	Mean age in cases	Singleton/twin	Cutoff preterm delivery	NOS quality
Bafali et al. [17]	2018	Turkey	32/50	Prospective empirical	TVS	2nd trimester	25.88±4.67	Singleton	37	Low
Benito Vielba et al. [18]	2020	Spain	6/171	Retrospective cohort	TVS	2nd trimester	34.17±6.21	Twin	28	High
Dziadosz et al. [19]	2016	USA	84/888	Retrospective cohort	TVS	2nd trimester	33±5	Singleton	37	High
Farràs Llobet et al. [13]	2018	Spain	34/241	Retrospective case control	TVS	2nd trimester	30.3±6.5	Singleton	34	High
Farràs Llobet et al. [20]	2020	Spain	17/1,358	Prospective cohort	TVS	2nd trimester	33.1 (30.0–37.2)*	Singleton	34	High
Knight et al. [21]	2017	USA	116/143	Retrospective cohort	TVS	2nd trimester	29.42±5.83	Twin	36	High
Lynch et al. [22]	2019	USA	49/65	Retrospective cohort	TVS	2nd trimester	28±5	Twin	37	High
Sawaddisan et al. [12]	2020	Thailand	31/325	Prospective cohort	TVS	2nd trimester	34.5 (29–36.8)*	Singleton	37	High
Sepúlveda-Martínez et al. [14]	2016	Chile	93/225	Prospective case control	TVS	2nd trimester	29.8 (22.7–34.9)*	Singleton	34	High
Shi et al. [23]	2018	China	84/980	Prospective case control#	TPS	2nd trimester	28.7±4.9	Singleton	37	Low
Sur et al. [24]	2017	India	18/51	Prospective observational	TVS	2nd trimester	nr	Singleton	37	Low

UCA, uterocervical angle; NOS, Newcastle-Ottawa Scale; nr, not reported; TVS, transvaginal sonography; TPS, transperineal sonography. * Median [interquartile range]. # Indirectly conceived from methods.

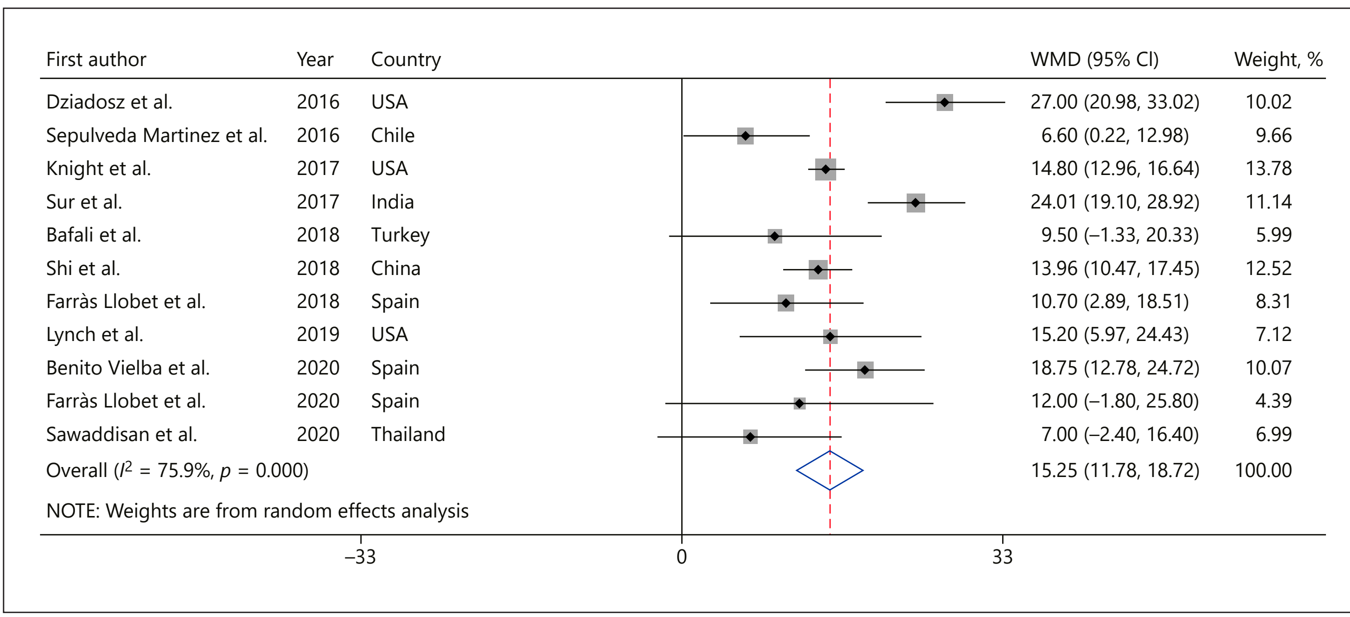

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Fig. 2. Meta-analysis of UCA for sPTB. sPTB, spontaneous preterm birth; WMD, weighted mean difference; CI, confidence interval.

ing to the suspected potential variables. Moreover, Begg's rank correlation and Egger's regression tests were used to verify the evidence of publication bias. In this study, all data analyses were performed using the STATA version 12.0 (Stata Corp., College Station, TX, USA) software package.

Results

Study Selection Process and Characteristics

The literature search identified 129 records. After eliminating duplicates, 83 studies remained, and of these, 25 full-text articles retrieved to assess their eligibility in terms of the inclusion criteria. After reviewing the full

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Table 2. Subgroup analyses for association between UCA and preterm delivery

Subgroups	UCA		
	studies, n	pooled WMD (95% CI)	heterogeneity (I^2%, p value[a])
Singleton/twin			
Singleton	8	14.43 (8.79, 20.06)	82.4, <0.001
Twin	3	15.14 (13.42, 16.87)	0.0, 0.464
Study design			
Cohort	6	16.62 (11.58, 21.66)	73.7, 0.002
Case control	3	11.05 (6.37, 15.72)	50.8, 0.131
Other(s)	2	17.59 (3.47, 31.72)	82.5, 0.017
Study country			
USA	3	18.98 (10.59, 27.37)	86.2, 0.001
Spain	3	14.88 (9.18, 20.57)	29.4, 0.242
Other(s)	5	12.82 (6.13, 19.52)	83.1, <0.001
Quality status			
High	8	14.53 (10.14, 18.92)	74.6, <0.001
Low	3	16.56 (8.43, 24.70)	84.1, 0.002
Preterm delivery cutoff			
37 weeks	6	16.85 (10.71, 22.98)	81.7, <0.001
<37 weeks	5	13.19 (9.26, 17.12)	55.2, 0.063
Type of ultrasound			
TVS	10	15.29 (11.16, 19.43)	77.9, <0.001
TPS	1	13.96 (10.47, 17.45)	na

WMD, weighted mean difference; TVS, transvaginal sonography; TPS, transperineal sonography; na, not applicable; UCA, uterocervical angle; CI, confidence interval. [a] p for heterogeneity.

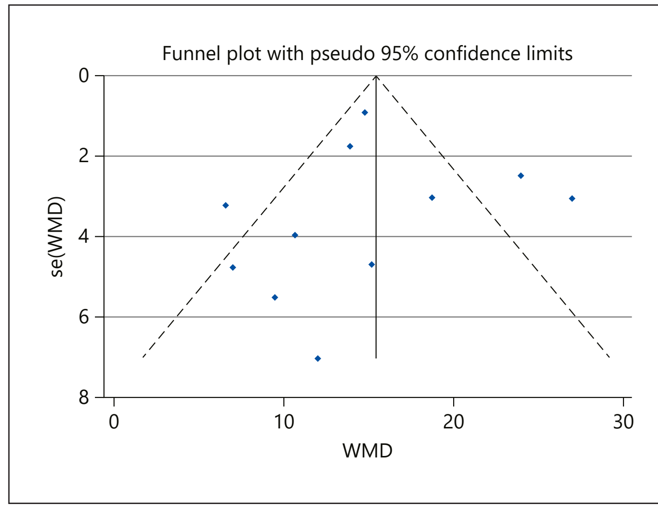

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Fig. 3. Funnel plot. WMD, weighted mean difference.

text of these studies, 14 more studies were also excluded, and 11 studies remained as the basis for this meta-analysis (Fig. 1).

Eleven studies all conducted on the second trimester UCA as well as its association with sPTB were included in this study [12–14, 17–24], with a total of 5,061 patients (4,511 Singleton and 550 twin). Of these studies, 6 were prospective [12, 14, 17, 20, 23, 24] and 5 were retrospective studies [13, 18, 19, 21, 22]. Except one study [23], all UCA measurements were performed transvaginally in other studies. Notable, all these studies were published between 2016 and 2020, and 3 studies were conducted in the USA [19, 21, 22], 3 in Spain [13, 18, 20], one in Turkey [17], one in China [23], one in Chile [14], one in Thailand [12], and one in India [24]. The characteristics of these eleven included articles with more details are shown in Table 1.

Main Outcomes

The forest plot for UCA values in women with sPTB and controls is presented in Figure 2. The pooled results with random-effects model reveal that UCA values were significantly higher in the pregnancies complicated by sPTB (WMD = 15.25, 95% CI: 11.78–18.72, $p < 0.001$; $I^2 = 75.9\%$, $p < 0.001$) compared to the control group. Moreover, the same significant results were observed for singleton (WMD = 14.43, 95% CI: 8.79–20.06, $p < 0.001$; $I^2 = 82.4\%$, $p < 0.001$), and twin pregnancies (WMD = 15.14, 95% CI: 13.42–16.87, $p < 0.001$; $I^2 = 0.0\%$, $p = 0.464$).

Due to the existence of a significant heterogeneity ($I^2 = 75.9\%$, $p < 0.001$), subgroup analyses were conducted based on the potential suspected variables as follows: number of fetuses, study country, study design, quality status, sPTB cutoff, and type of ultrasound (Table 2). Also, all the Pooled WMD results were statistically significant after subgroup analyses; however, heterogeneity has significantly decreased among those studies conducted on twin gestations, designed as case-controls, conducted in Spain, and defined sPTB as <37 weeks (Table 2).

Afterward, publication year and sample size were investigated as potential contributor's variables using meta-regression method. The findings of meta-regression analysis showed that there was no significant influence of total sample size (Coefficient = 0.002, $p = 0.739$) and publication year (Coefficient = −1.23, $p = 0.429$) in the included studies on the association between UCA and sPTB. Moreover, sensitivity analysis indicated that the pooled WMD was not significantly changed when each study was excluded.

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Publication Bias

Scatters in the funnel plots for UCA were almost symmetrical graphically, which indicate the low evidence of potential publication bias (Fig. 3). Accordingly, these findings were statistically confirmed using Begg's and Egger's tests for meta-analysis, which showed no significant publication bias (P Begg's test = 0.586, P Egger's test = 0.908).

Discussion/Conclusion

To the best of our knowledge, this comprehensive report is the first meta-analysis to confirm that UCA is significantly wider among singleton and twin pregnancies complicated by sPTB. Also, it has the potential of being used as a useful predictive tool to identify those women who are at the risk of sPTB.

Although there are many complex mechanisms involved in sPTB, changes in cervical tissue and anatomy have been shown to play key roles in pathophysiology of labor [25]. A combination of pressures from adjacent organs, and more importantly from growing uterus, can affect the internal os and cervical function [8, 26]. In addition, the integrity and anatomy of cervix in a pregnant woman can be displayed by measuring CL and UCA [27]. In this regard, it can be said that an obtuse UCA is associated with a linear and direct force of gravid uterus, while an acute UCA is hypothesized to be accompanied with less direct force on the internal os, which can play a supportive role in maintaining cervical integrity as well as preventing dilatation.

According to abovementioned pathophysiologic correlations, UCA has been recently used to predict various obstetrics complications other than sPTB, such as success of induction of labor, differentiating false labor from the true one, and determining the mode of delivery [28–30]. Regarding the application of UCA for sPTB, a study by Sepúlveda-Martínez et al. [14] demonstrated that the UCA measurement is independent of CL, which has been surprisingly shown to have a higher detection rate in identifying the pregnancies at the risk of sPTB, compared to CL [20].

Since UCA is a relatively novel ultrasonographic marker in the field of obstetrics, so it is too early for it to reach a firm conclusion on UCA utilization in clinical settings. This is mainly due to the fact that most of these reports were designed as retrospective and non-randomized studies, which can lead to variant types of bias, especially selection bias.

Implications for Future Research/Practice

Although the results of this meta-analysis along with the findings of previous reports suggest UCA as a promising predictive measure for sPTB, the current data are not sufficient to propose a widespread use of UCA in the current clinical settings, accordingly, mainly due to having inadequate data to compare the predictive value, sensitivity, and specificity of UCA with the currently used screening methods like CL. Moreover, future well-designed prospective studies should focus on the determination of the optimum cutoff value for early diagnosis of the women who are at the risk of sPTB, while adjusting for potential confounders.

Strengths and Limitations

The limitations of this review are those related to the pooling of data in meta-analyses, including a relatively small number of eligible studies as well as a significant heterogeneity among the included studies. In order to minimize these biases, we only included those studies conducted on the low risk pregnant women and excluded those reporting short CL, pessary insertion or cerclage for study participants. Moreover, in this study, we explored the heterogeneity by conducting subgroup, meta-regression, and sensitivity analyses to minimize the effect of potential confounders. Notably, the strength of this meta-analysis lies in the fact that it is the first of its kind showing that, an obtuse UCA in ultrasound examination can increase the risk of sPTB.

In conclusion, the results of the current systematic review and meta-analysis demonstrate that ultrasound-measured UCA is significantly wider in singleton and twin pregnancies complicated by sPTB. In addition, this ultrasonographic marker has the potential of being used as a predictive tool for sPTB. We strongly suggest performing further studies using a more standardized approach, to diminish heterogeneity, as well as conducting some studies comparing the predictive value and accuracy of UCA with those of CL, to achieve a more reliable conclusion.

Statement of Ethics

The authors have no ethical conflicts to disclose. It is a systematic review and meta-analyses.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Funding Sources

Not applicable.

Author Contributions

K.H. was involved in study design, search in databases, quality assessment, study selection, data extraction, manuscript drafting, and critical discussion. M.K., N.A., and H.V. were involved in study design, quality assessment, data analysis, and critical discussion. M.B.V. contributed to quality assessment, data analysis, critical discussion, and manuscript drafting. A.S.M. and M.P.C. contributed to interpreting data, manuscript drafting, and revising manuscript. All authors read and approved the final manuscript.

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