REVIEW ARTICLE

Comparing the safety and effectiveness of various umbilical cord milking techniques and delayed cord clamping in full-term and preterm infants: A systematic review and meta-analysis

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Abstract

We compare the hematocrit, hemoglobin, need for transfusion, recurrent phototherapy, serum bilirubin level, and serum ferritin at different time frames for the umbilical cord milking (UCM) and delayed cord clamping (DCC) in both full-term and preterm infants. A comprehensive search through various databases aimed to compare UCM and DCC studies until May 2nd, 2023. Cochrane and NIH tools assessed RCTs and cohorts, respectively. Meta-analysis employed Review Manager 5.4 software, calculating MD and RR with 95% CIs for continuous and dichotomous data. We included 20 studies with a total of 5189 infants. Regarding preterm infants, hematocrit level showed no significant difference between intact Umbilical Cord Milking (iUCM) compared to DCC (MD = -0.24, 95% CI [-1.11, 0.64]). Moreover, Neonatal death incidence was significantly higher with the UCM technique in comparison to DCC (RR = 1.28, 95% CI [1.01 to 1.62]). Regarding term and late preterm infants, Hematocrit level showed no significant difference between the iUCM or cUCM techniques compared to DCC (MD = 0.21, 95% CI [-1.28 to 1.69]), (MD = 0.96, 95% CI [-1.02 to 2.95]), respectively. UCM led to a higher risk of neonatal death in preterm infants compared to DCC. However, the incidence of polycythemia was lower in the UCM group. Additionally, UCM was associated with higher rates of severe IVH events. Based on these findings, DCC may be preferred due to its lower incidence of severe IVH and neonatal death. *(Afr J Reprod Health 2023; 27 [11]: 99-125).*

Keywords: Preterm infant; full-term infant; umbilical cord milking; delayed cord clamping; meta-analysis

Résumé

Nous comparons l'hématocrite, l'hémoglobine, le besoin de transfusion, la photothérapie récurrente, le taux de bilirubine sérique et la ferritine sérique à différentes périodes pour la traite du cordon ombilical (UCM) et le clampage retardé du cordon (DCC) chez les nourrissons nés à terme et prématurés. Une recherche complète dans diverses bases de données visait à comparer les études UCM et DCC jusqu'au 2 mai 2023. Les outils Cochrane et NIH ont évalué les ECR et les cohortes, respectivement. La méta-analyse a utilisé le logiciel Review Manager 5.4, calculant le MD et le RR avec des IC à 95 % pour les données continues et dichotomiques. Nous avons inclus 20 études portant sur un total de 5 189 nourrissons. Concernant les nourrissons prématurés, le niveau d'hématocrite n'a montré aucune différence significative entre la traite du cordon ombilical intact (iUCM) et la DCC (DM = -0,24, IC à 95 % [-1,11, 0,64]). De plus, l'incidence des décès néonatals était significativement plus élevée avec la technique UCM qu'avec la technique DCC (RR = 1,28, IC à 95 % [1,01 à 1,62]). Concernant les nourrissons à terme et peu prématurés, le niveau d'hématocrite n'a montré aucune différence significative entre les techniques iUCM ou cUCM par rapport à la technique DCC (DM

= 0,21, IC à 95 % [-1,28 à 1,69]), (DM = 0,96, IC à 95 % [-1,02 à 2,95]), respectivement. L'UCM a entraîné un risque plus élevé de décès néonatal chez les nourrissons prématurés par rapport au DCC. Cependant, l'incidence de la polyglobulie était plus faible dans le groupe UCM. De plus, l'UCM était associée à des taux plus élevés d'événements IVH graves. Sur la base de ces résultats, le DCC peut être préféré en raison de sa plus faible incidence d'IVH grave et de décès néonatals. *(Afr J Reprod Health 2023; 27 [11]: 99-125).*

Mots-clés: Nourrisson prématuré ; nourrisson né à terme ; traite du cordon ombilical ; serrage retardé du cordon ; méta-analyse

Introduction

The umbilical cord serves as a vital lifeline connecting the fetus and the placenta forming a robust link between the fetal and maternal interface for overall fetal development especially for neuro-motor development[1]. Upon birth, the umbilical cord is severed, leaving behind a residual stump. This stump undergoes a process of desiccation and subsequent detachment, typically occurring within a timeframe of five days up to 15 days postpartum[2]. Cord clamping is an essential and time-sensitive procedure conducted immediately following childbirth, which involves the application of clamps to secure and sever the umbilical cord. Numerous prior studies have extensively explored the significance of cord clamping, encompassing its timing and methodology, concerning subsequent outcomes about the newborn[3,4].

Immediate Cord Clamping (ICC) refers to the practice of clamping and cutting the umbilical cord immediately after the baby is born, usually within the first 15 to 30 seconds. Traditionally, ICC has been a routine practice in many delivery settings in the past. DCC involves a deliberate delay in cutting the umbilical cord after the baby is born. The timing for DCC varies but generally involves waiting for a minimum of 30 to 60 seconds, or until cord pulsations cease. This delay permits the transfer of additional blood from the placenta to the baby and facilitates placental transfusion[5,6]. DCC has demonstrated favorable effects on the neurodevelopmental outcomes of full-term infants at both 12 months and four years of age[7,8]. Umbilical cord milking (UCM) is another method to facilitate the transfer of blood from the placenta to the newborn during the process of cord clamping. It involves manually squeezing of the umbilical cord toward the baby's abdomen or away from the placenta usually in a time frame from 20 to 30s before clamping and cutting the cord. Although the technique of milking may not be the safest option as in a previous study the infants were early pre-term and they had an increased risk of severe intraventricular hemorrhage[9], other numerous studies have suggested that inadequate iron levels, such as iron-deficiency anemia and without anemia, during early childhood and infancy can have detrimental and enduring effects on neurodevelopment[10].

There was a diversity of results between previous studies regarding the preferred technique. Therefore, our systematic review and meta-analysis aims to identify the optimal and safest technique for umbilical cord management in full-term infants, early preterm infants, and late preterm infants, considering both safety and effectiveness.

Methods

We performed this systematic review and meta-analysis depending on the recent updates of the PRISMA statement and Cochrane guidelines[11,12].

Literature search and data collection

Our research was conducted until the 2nd of May 2023 using the following databases: PubMed, Cochrane Library, Scopus, and Web of Science. Our research term was ("Infant*" OR "Newborn" OR "Neonate*" OR "Low Birth Weight" OR "Postmature" OR "Postmature Infant" OR "Premature" OR "Preterm" OR "Neonatal Prematurity" OR "Preterm Infants" OR "Premature Infant" OR "late preterm") AND ("umbilical cord milking" OR "delayed cord clamping" OR "Delayed Umbilical Cord" OR "Clamping Placental Transfusion" OR "Immediate Umbilical Cord Clamping" OR "Immediate Cord Clamping")

Studies selection and eligibility criteria

We included all relevant studies that met our criteria, regardless of their study design, including RCTs and cohort studies. The population of interest was both full-term infants and preterm infants. The interventions under investigation were DCC and UCM which were separated into two techniques

iUCM and cUCM, compared to any other technique. Our study assessed multiple outcomes, including hematocrit and hemoglobin levels within the first day of life, the occurrence of intraventricular hemorrhage (IVH), necrotizing enterocolitis, the need for inotropes and transfusions, neonatal death, polycythemia, retinopathy, severe IVH, serum bilirubin levels (at 24 to 48 hours), and serum ferritin levels at 6 to 8 weeks.

To ensure comprehensive coverage, we used the EndNote program to remove duplicate articles. Two separate reviewers conducted screening of titles and abstracts, as well as full-text evaluation, to assess the relevance of the studies. Furthermore, the references of the included studies were examined to ensure no relevant articles were missed. In case of any disagreements or conflicts, they were resolved by a third author.

Quality assessment

The Cochrane Risk of Bias tool (version 1) was used to evaluate our included RCTs[13]. This tool comprises several components: 1) identification of selection bias and other types of biases, 2) allocation of participants to different groups, 3) blinding of participants and investigators, 4) evaluation of outcomes and blinding in their assessment, and 5) randomization of the study population. The risk of bias is assessed as either high, low, or uncertain. Furthermore, for cohort studies, the NIH tool is used to evaluate their quality[14]. This assessment tool consisted of 12 questions that covered various aspects such as the justification for population and sample size, the research question, definition of the control group, inclusion criteria and case selection, event timing, blinding, and reporting of confounders. Then, the quality of the cohort studies based on the answers to the previous questions is classified into good, fair, or poor quality.

Data extraction

We extracted the data into Excel sheets contained the following items: 1) Summary characteristics including study ID, study arms, maternal age, gestational age, birth weight , gender, and mode of delivery, 2) Baseline data including site of study, study design, inclusion criteria, primary outcomes, and conclusion, and 3) Outcomes including hematocrit and hemoglobin levels within the first day of life, the occurrence of IVH (any grade) and necrotizing enterocolitis, the need for inotropes and transfusions, neonatal death, polycythemia, retinopathy, severe IVH (grade 3 and 4), serum bilirubin levels (at 24 to 48 hours), and serum ferritin levels at 6 to 8 weeks.

Data analysis

The statistical analysis was conducted using Review Manager (RevMan) v5.4. A significance level of p-value < 0.5 was considered as the threshold for statistical significance. Mean difference (MD) with a corresponding 95% confidence interval (95% CI) was calculated for continuous data, while risk ratios (RR) with a 95% CI were used for dichotomous data. Heterogeneity was assessed through the I-square test (I2) and chi-square test. If the p-value of the chi-square test was below 0.1 and the I2 value exceeded 50%, the data were considered heterogeneous. The fixed effect model was employed for analyzing homogeneous data, while the random effects model was utilized for analyzing heterogeneous data.

Results

Literature search and study selection

In accordance with our search strategy, a total of 1916 articles were identified after eliminating duplicate records. After evaluating the titles and abstracts, 46 studies were deemed eligible for full-text screening. Eventually, 20 studies fulfilled our inclusion criteria and were included in the quantitative analysis. These 20 articles provided statistical results that were utilized in our analysis. Figure 1

Study characteristics and quality

We included 18 RCTs[15-32], and two retrospective cohort studies[33,34], with a sample size of 5189 infants. The studies included in our analysis were conducted in multiple countries, demonstrating geographical diversity, such as Saudi-Arabia, USA, Italy, Thailand, Ireland, Egypt, the UK, and India. Our included studies had all types of delivery with various follow-up durations up to one year. Most of the included studies fairly distributed the intervention as the number of neonates who

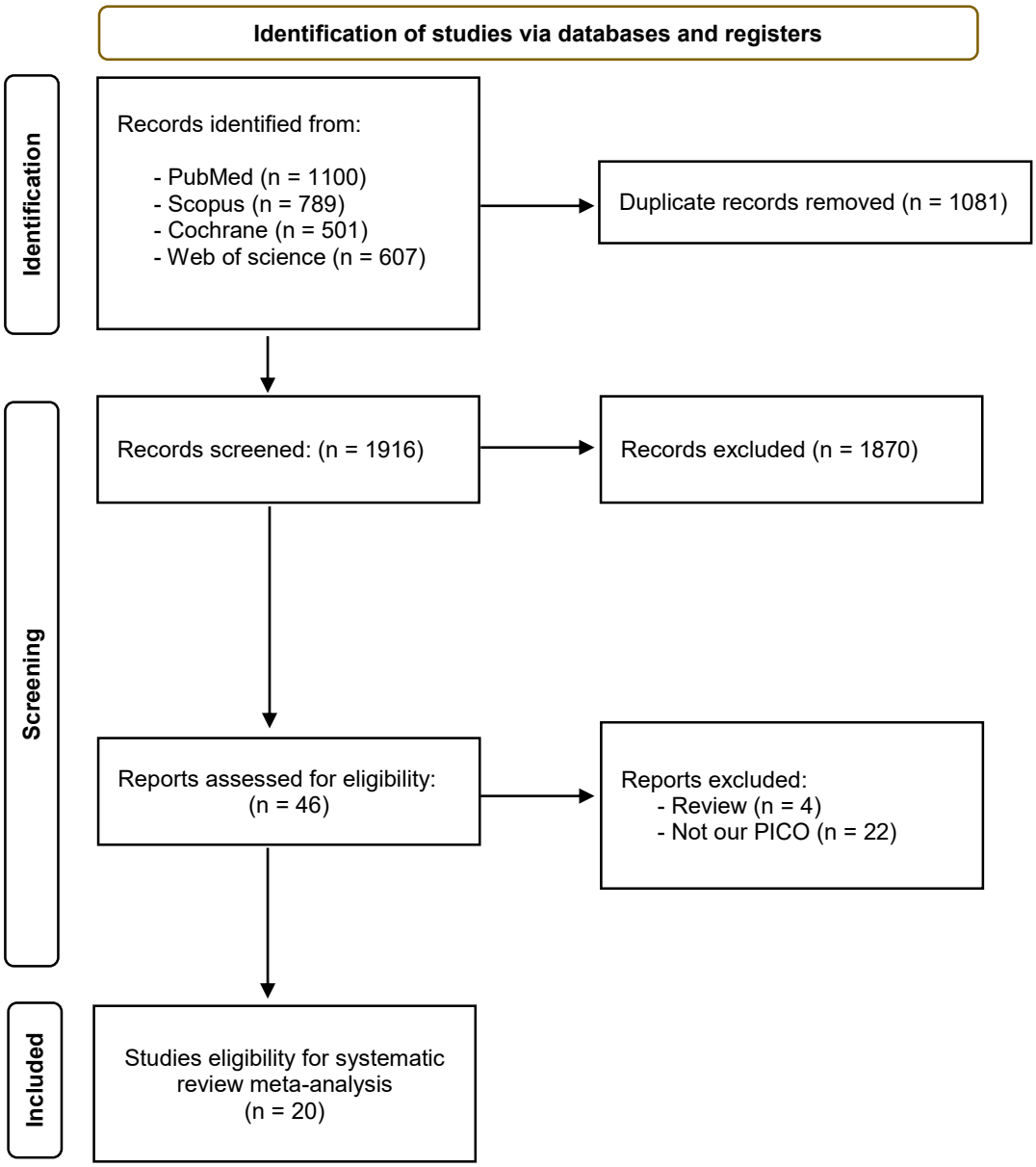


Figure1: PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only

underwent UCM and DCC are almost the same, with nine studies have total preterm population while ten studies have total population of full-term infants, in addition to Balaji *et al*. that had population of both preterm and full-term infants. Supplementary Table 1 contains the detailed summary and baseline characteristics of the included studies. Regarding their quality, the included RCTs had a moderate risk of bias, Figure 2. While for the cohort studies, they were of fair quality, and the detailed evaluation is presented in Supplementary Table 2.

Outcomes

1. Preterm infants:

A. Primary outcomes

Hematocrit level (at 24 to 48 hours)

Four studies mentioned the hematocrit level value at a time frame from 24 hours to 48 hours, all the included studies used intact Umbilical Cord Milking (iUCM) compared to DCC, and our included studies showed no significance between the two techniques. As pooled MD and 95% CI =

Supplementary Table 1: Summary and baseline characteristics of the included studies

N	Study ID	Study arms, n (%)	Site	Study design	Maternal age, (mean ± SD) y	Gestational age, (mean ± SD) weeks	Neonatal status	Birth weight, (mean ± SD) g	Male, n (%)	Follow up duration (months)	Mode of delivery, n (%)	Medical disorders, n (%)	Antenatal steroids, n (%)	Inclusion criteria	Primary endpoints	Conclusion
1	**Atia et.al 2022**	**UCM**, 100 (50%)	Kingdom of Saudi-Arabia	RCT(NCT03147846)	30.8 ± 7.1	a. 24< 28, 10(10%) b. 28< 32, 32(32%) c. 32< 35, 58(58%)	Preterm	1,573 ± 534	63 (63%)	Up to 12	1. Vaginal, 21 (21%) 2. Cesarean before labor onset, 36 (36%) 3. Cesarean after labor onset, 43 (43%)	1. DM, 3(3%) 2. HTN disorders, 4 (4%) 3. SCD, 1(1%)	-	1. Individuals with a singleton pregnancy 2. Admitted with preterm labor 3. between 24weeks and 34weeks gestation	1. First draw hemoglobin 2. First draw hematocrit 3. Need for respiratory assistance 4. Need for inotropes	"UCM facilitated a rapid transfer of placental blood equivalent to that of DCC for premature neonates. However, it resulted in increased rates of interventions and morbidities, especially in extremely preterm neonates"
		DCC,100 (50%)			28.8 ± 6.6	a. 24< 28, 5(5%) b. 28< 32, 20(20%) c. 32< 35, 75(75%)		1,781 ± 483	60 (60%)		1. Vaginal, 56 (56%) 2. Cesarean before labor onset, 13 (13%) 3. Cesarean after labor onset, 31 (31%)	1. DM, 4(4%) 2. HTN disorders, 2(2%) 3. SCD, 1(1%)				
2	**Kumbhat et.al 2021**	**UCM**, 432 (23.55%)	USA	Retrospective cohort study	28.8 ± 5.7	26.5 ± 1.7	Preterm	880.5 ± 247.9	216 (50.1%)	-	Cesarean delivery, 320 (74.1%%)	-	416 (96.3%)	1. Infants born between 22 and 28 weeks of gestation 2. In NRN centers from January 1, 2016, to December 31, 2018	Mortality or severe IVH	"This analysis of extremely preterm infants suggests that delayed cord clamping is the preferred practice for placental transfusion, as umbilical cord milking exposure was associated with an increase in the adverse outcome of severe IVH"
		DCC, 1402 (76.45%)			28.4 ± 6.1	26.4 ± 1.7		873.1 ± 247.2	700 (49.9%)		Cesarean delivery, 843 (60.1%)		1359 (97.1%)			
3	**Consonni et.al 2020**	**eUCC**, 53 (23.78%)	Italy	Retrospective cohort study	33.84 ± 6.33	≥37.0 weeks	Term	< 10th centile, 0	-	Up to six	In labor CS, 32 (60.3%)	-	-	1. From July 2017 to Dec 2017 2. All singleton term pregnancies that underwent CS	1. Neonatal Hct 2. Total bilirubin	"In term CS, neonatal Hct is significantly higher when the CS is performed in labor or with UCM. In elective CS, UCM could be a valid option to favor placental transfusion"
		dUCC, 137(61.43 %)			34.13 ± 5.39			< 10th centile, 9(6.5%)			In labor CS, 53 (38.6%)					
		UCM, 33 (14.79%)			32.5 ± 4.8			< 10th centile, 2(6%)			In labor CS, 15 (45.4%)					

4	**Panburana et.al 2020**	UCM, 84 (50%)	Thailand	RCT	29 ± 6	39.1 ± 1	Term	3,122 ± 331.8	37 (44.1%)	Up to 12	1. Vaginal delivery, 49 (58.3%) 2. Cesarean delivery, 35 (41.7%)	1. DM 22(26.2%) 2. Chronic HTN or PIH, 1(1.2%) 3. Hyperthyroidism, 1(1.2%)	-	1. From June 2017 to March 2018 2. Living singleton term pregnancies	1. Mean of hemoglobin levels 2. Adverse neonatal and maternal outcomes	"Both I-UCM and DCC revealed a comparable effect on hematologic status without deleterious effects on neonatal and maternal outcomes at the age of 48–72 hours in term neonates"
		DCC, 84 (50%)			29.2 ± 6.1	39.1 ± 1		3,155 ± 344.2	38 (45.2%)		1. Vaginal delivery, 50 (59.5%) 2. Cesarean delivery, 34 (40.5%)	1. DM, 20(23.8%) 2. Chronic HTN or PIH, 4(4.8%) 3. Hyperthyroidism, 1(1.2%)				
5	**Sura et.al 2021**	**UCM**, 140 (50%)	Kenya	RCT	27.2 ± 5.8	a. 28to<32weeks, 32(22.9%) b. 32to<37weeks, 108(77.1%)	Preterm	2,028.8 ± 526.2	71 (50.7%)	NR	Cesarean, 59 (41.2%)	-	-	1. Mother-baby pairs between 28to<37 weeksgestational age 2. Gestational age was confirmed by use of last menstrual period	1. Mean of hemoglobin levels 2. Mean of Hematocrit levels 3. Safety and adverse events	"UCM compared to DCC for preterm neonates resulted in similar outcomes for neonatalhaemoglobin,haematocrit ,anaemia and maternal primary PPH and a lower proportion of neonatal polycythemia and clinical jaundice.UCM offers a comparable method of placental transfusion compared to DCC and maybe considered as an alternative to DCC in preterm neonates at 28to<37weeks'gestation"
		DCC, 140 (50%)			27.7 ± 5.9	a. 28to<32weeks, 39(27.9%) b. 32to<37weeks, 101(72.1%)		2,013.6 ± 579.3	65 (46.4%)		Cesarean, 49 (35%)					
6	**Bichkar et.al 2019**	**UCM**, 25 (51.02%)	India	RCT	29 ± 4	30 ± 2	Preterm	1,315 ± 274	13 (52%)	-	cesarean delivery, 49 (100%)	1. PIH, 6(24%) 2. Diabetes, 2(8%)	21 (84%)	1. Pregnant women of <32-week gestation 2. Undergoing cesarean section delivery 3. Newborns with the gestational	1. Mean of hemoglobin levels 2. Mean of Hematocrit levels 3. Safety and adverse events	"UCM significantly improved respiratory and hemodynamic stability in preterm infants <32 weeks' gestation without associated complications"
		DCC, 24 (48.98%)			28 ± 3	30 ± 2		1,272 ± 269	14 (58.3%)			1. PIH, 5(20.8%) 2. Diabetes, 2(8.3%)	16 (66.66%)			

														age of 26–31weeks		
7	**Finn et.al 2019**	**ICC**,12(27.27%)	Ireland	RCT(ISRCTN92719670)	-	28.23 ± 4.03	Preterm	1,149.33 ± 719.52	-	-	-	-	-	1. Infants born at <32 weeks of gestation 2. Between December 2015 and September 2016	1. Severe IVH 2. Need for phototherapy 3. Need for inotropes 4. Safety and adverse events	"There were no differences in cerebral EEG activity and cerebral oxygenation values between cord management strategies at 6 and 12 hours"
		DCC, 14 (31.81%)				28 ± 2.63		1,015 ± 708.42								
		UCM, 18 (40.9%)				27.9 ± 3.14		1,058.33 ± 679.77								
8	**Katheria et.al 2019**	**UCM**, 236 (49.79%)	Multicenter mainly USA	RCT(NCT03019367)	30.4 ± 5.7	28.4 ± 2.4	Preterm	-	123 (52%)	Up to 36	Cesarean delivery, 180 (76%)	1. DM, 27(11%) 2. Chorioamnionitis, 67(28%) 3. PIH, 80(34%)	211 (89%)	1. Pregnant women less than 32 weeks' gestation 2. Ultrasonographic criteria were identified and recruited from the labor and delivery floor or perinatal special care unit at each site	1. Severe IVH 2. Need for phototherapy 3. Need for inotropes 4. Safety and adverse events	"In this post hoc analysis of a prematurely terminated randomized clinical trial of umbilical cord milking vs delayed umbilical cord clamping among preterm infants born at less than 32 weeks' gestation, there was no statistically significant difference in the rate of a composite outcome of death or severe intraventricular hemorrhage, but there was a statistically significantly higher rate of severe intraventricular hemorrhage in the umbilical cord milking group. The early study termination and resulting post hoc nature of the analyses preclude definitive conclusions"
		DCC, 238 (50.21%)			29.9 ± 5.6	28.4 ± 2.5			132 (55%)		Cesarean delivery, 159 (67%)	1. DM, 45(19%) 2. Chorioamnionitis, 84(35%) 3. PIH, 55(23%)	209 (88%)			

9	**Shirk et.al 2019**	**UCM**, 100 (49.02%)	USA	RCT	28 ± 7.52	23 to 34	Preterm	1,620 ± 587	-	-	1. Spontaneous vaginal, 43 (21.1%) 2. Operative vaginal, 3 (1.5%) 3. Cesarean, 54 (54%)	1. DM, 14(14.1%) 2. Chronic HTN, 17(17%) 3. Preeclampsia, 37(37%) 4. FGR, 18(18%)	-	1. From April 18, 2014, through June 5, 2018 2. Patients with singleton pregnancies 3. Admitted to the hospital with expected preterm delivery	1. Occurrences of transfusion 2. Safety and adverse events	"This study demonstrates that milking the umbilical cord may be an acceptable alternative to delayed cord clamping because there were similar effects on neonatal hematocrit concentrations and the need for neonatal transfusions and no increased risk for complications or neonatal morbidity. The present data support the concept that milking of the umbilical cord may offer an efficient and timely method of providing increased blood volume to the infant"
		DCC, 104 (50.98%)			27.33 ± 7.52			1,579 ± 576			1. Spontaneous vaginal, 53 (26%) 2. Operative vaginal, 0 (0) 3. Cesarean, 51 (49%)	1. DM, 7(6.8%) 2. Chronic HTN, 10(9.7%) 3. Preeclampsia, 29(28.2%) 4. FGR, 12(11.7%)				
10	**Vashistha et.al 2019**	**UCM**, 100 (50%)	India	RCT	29.38 ± 7.228	>36 weeks	Term	-	-	-	cesarean delivery, 200 (100%)	-	-	1. From April 2018 to March 2019 in Saraswathi Institute, India 2. Term newborn babies born at >36 weeks 3. Either delivered vaginally or by caesarean section	1. Hemoglobin values at 6 weeks 2. Serum ferritin levels at 6 weeks	"A total of 200 subjects in term newborn babies born at >36 weeks either by vaginally or by caesarean section at our hospital who were residing within 5km radius of SIMS hospital, neonates allocated to milking group had higher hemoglobin values at 6 weeks as compared with delayed clamping group, indicating an increased amount of placental blood transfer in Umbilical cord milking group. Both the groups in our study achieved higher mean hemoglobin at 30
		DCC, 100 (50%)														

																minutes and 48 hours"
11	**Alzaree et.al 2018**	**UCM,** 125 (50%) **DCC,** 125 (50%)	Egypt	RCT	26.2 ± 4.4 25.6 ± 3.2	38.99 ± 0.96 38.93 ± 0.90	Term	-	-	Up to 12	Vaginal, 250 (100%)	-	-	250 pregnant women starting from ≥ 37 weeks' gestational age	Hemoglobin values at 6 weeks	"Umbilical cord blood milking after its clamping improves some important hematological parameters for newborns, especially in countries with high incidence of anemias in newborns and children"
12	**El-kotb et.al 2017**	**UCM**, 150 (50%) **DCC**, 150 (50%)	Egypt	RCT	22.4 ± 1.78 22.42 ± 1.67	38.6.6 ± 0.67 38.8 ± 0.5	Term	-	66 (44%) 70 (46.7%)	Up to 12	cesarean, 300 (100%)	-	-	1. Pregnant females admitted for elective cesarean section 2. At Ain Shams University Maternity Hospital 3. Completed 37 weeks of gestation confirmed by dates and third trimesteric ultrasound	1. Hemoglobin values at 6 weeks 2. Need for transfusion 3. Safety and adverse events	"For the first time in term babies, our study demonstrated that both UCM and DCC have comparable benefits in improving hematological status at 6 weeks without affecting producing any noteworthy significant adverse neonatal outcomes in initial 6weeks of life. As DCC has already been formulated as standard of care in all deliveries by American Academy of Pediatrics, UCM can be recommended in all deliveries in which DCC is not feasible or not practiced for any reason. UCM can be used in term neonates as a routine or in conditions where DCC is not feasible. In cases when the neonate

																requires resuscitation then UCM can be done by the neonatal team attending the baby at delivery"
13	**Piyadigama et.al 2017**	**UCM**, 33 (55%)	Sri Lanka	RCT	31.1 ± 4.6	-	Term	2989 ± 295.4	17 (51.5%)	Up to six	-	-	-	1. All pregnant mothers assigned for elective CD at term 2. From 1st of February to 31st March 2015	1. Mean Hemoglobin values 2. Mean total bilirubin levels 3. Birth APGAR of 1min and 5min	"Neonatal and maternal outcomes are not better with UCM than with DCC during elective CD"
		DCC, 27 (45%)			29.3 ± 6.6			2,869 ± 233.4	12 (44.4%)							
14	**Agrawal et.al 2016**	**UCM**, 83 (51.55%)	India	RCT	-	38.3 ± 1.2	Term	2,700 ± 300	44 (53%)	Up to 12	Vaginal, 53 (63.8%)	-	-	1. Between August 2013 to August 2014 2. Full-term newborns with a gestational age of 37–41 weeks	1. Mean Hemoglobin values 2. Mean Serum ferritin levels	"Term-born Indian infants who had DCC at 60–90 seconds or UCM showed no significant differences in ferritin and hemoglobin levels and growth parameters at 12 months of age"
		DCC, 78 (48.45%)				38.2 ± 1.2		2,700 ± 400	48 (61%)		Vaginal, 46 (58.9%)					
15	**Jaiswal et.al 2015**	**UCM**,100 (50%)	India	RCT	-	38.3 ± 1.1	Term	2,760 ± 300	58 (58%)	Up to 12	Vaginal delivery, 57 (57%)	-	-	1. Term newborn babies born at >36 weeks 2. Either by vaginally or by caesarean section 3. Mothers gave consent for blood sampling	1. Mean Hemoglobin values 2. Mean Serum ferritin levels	"In term neonates, the DCC and UCM had comparable effect on hematological parameters at 6 weeks of life"
		DCC, 100 (50%)				38.3 ± 1.12		2,751 ± 390	56 (56%)		Vaginal delivery, 60 (60%)					
16	**Katheria et.al 2015**	**UCM**, 75 (48.7%)	USA	RCT	31 ± 5	28 ± 2	Preterm	1,255 ± 413	29 (38.67 %)	-	Caserean, 154 (100%)	1. DM, 11(14.67%) 2. CA, 20(26.67%) 3. PIH, 22(29.33%)	-	1. Pregnant at 32 weeks' gestation 2. Recruited from the	1. Mean Birth Hemoglobin values 2. Mean Serum ferritin	"This is the first randomized controlled trial demonstrating higher systemic blood flow with UCM in

		DCC,79(51.3%)			30 ± 6	28 ± 2		1,132 ± 392	31 (39.24 %)			1. DM, 15(18.99%) 2. CA, 20(25.32%) 3. PIH, 25(31.65%)		labor and delivery and antepartum floors	levels 3. Safety and adverse events	preterm neonates compared with DCC. UCM may be a more efficient technique to improve blood volume in premature infants delivered by CD"
17	**Yadav et.al 2015**	**UCM**, 100 (33.33%)	India	RCT	-	38.5 ± 0.9	Term	2,860 ± 280	60 (60%)	Up to 6 weeks	Vaginal, 60 (60%)	-	-	1. Neonates enrolled were born at or beyond 37 weeks of gestation 2. Delivered by either vaginal or lower segment cesarean section	Serum ferritin level at 6 weeks	"Delayed cord clamping with milking the cut cord improved iron stores at 6 weeks of age in term infants, then either of the two interventions alone"
		DCC, 100 (33.33%)				38.4 ± 0.9		2,790 ± 310	52 (52%)		Vaginal, 59 (59%)					
		DCM, 100 (33.33%)				38.2 ± 0.9		2,740 ± 290	55 (55%)		Vaginal, 60 (60%)					
18	**Rabe et.al 2011**	**UCM**, 27 (46.55%)	UK	RCT	30.8 ± 6.3	29.5 2.7	Preterm	1,235 ± 468	11 (40.74 %)		Cesarean, 21 (78%)	1. DM, 4(14.81%) 2. HTN, 3(11.11%)	14 (52%)	1. Preterm neonates between 24and 32weeks of gestation 2. Antenatal informed consent could be obtained	1. Mean Hemoglob in values 2. Need for transfusio n 3. Safety and adverse events	"Milking the cord four times achieved a similar amount of placento-fetal blood transfusion compared with delaying clamping the cord for 30 seconds"
		DCC, 31 (53.45%)			29.1 ± 5.6	29.2 2.3		1,263 ± 428	17 (54.83 %)		Cesarean, 18 (58%)	1. DM, 1(3.22%) 2. HTN, 1(3.22%)	24 (77%)			
19	**Balaji et.al 2014**	**UCM,** 47 (48.96%)	India	RCT	25.6 ± 4.2	Term 38.7 ±1.5	Preterm and Term	2,951.3 ± 497.5	24 (51%)	At least Two	1. Vaginal, 16 (34%) 2. LSCS, 31 (66%)	-	-	1. All neonates >=34 weeks of gestation 2. Delivered either by LSCS or Vaginal delivery	Level of hemoglob in at 2 months of age	Umbilical cord milking is as effective as delaying the umbilical cord clamping in achieving higher hemoglobin levels at two months of age in late preterm and term infants delivered both by caesarean section and vaginal route
		DCC, 49 (51.04%)			25.5 ± 4.1	Term 38.5 ±1.5		3,058.4 ± 483.5)	23 (47%)		1. Vaginal, 19 (38.8%) 2. LSCS, 30 (61.2%)					
20	**Singh et.al 2018**	**UCM**, 28 (41.18%)	India	RCT	-	38.2 ± 1.01	Term	3,100 ± 380	18 (64.29 %)	-	1. Vaginal, 4 (14.29%) 2. LSCS, 24 (85.71%)	-	-	1. All neonates more than 37 weeks	1. Hemoglob in values at first	"Both the interventions i.e Delayed cord clamping

		DCC, 23 (33.82%)				37.6 ± 0.78		3,300 ± 360	11 (47.83 %)		1. Vaginal, 1 (4.34%)			2. Born either by vaginal route or through LSCS 3. Whose parents gave consent for blood sampling at birth and after 72 hours of age	day and 72 hours 2. Mean Hematocrit levels	performed alone or in combination with umbilical cord milking had comparable effect on hematological status in term neonates"
		Both, 17 (25%)				37.7 ± 0.77		3,300 ± 430	6 (35.29 %)		1. Vaginal, 2 (11.76%) 2. LSCS, 15 (88.24%)					

Supplementary Table 2: NIH Quality Assessment Tool for Observational Cohort Studies

ID	**NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies**														
	1. Was the research question or objective in this paper clearly stated?	**2. Were eligibility/selection criteria for the study population prespecified and clearly described?**	**3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?**	**4. Were all eligible participants that met the prespecified entry criteria enrolled?**	**5. Was the sample size sufficiently large to provide confidence in the findings?**	**6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?**	**7. Was the time frame sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?**	**8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (eg, categories of exposure, or exposure measured as continuous variable)?**	**9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?**	**10. Was the exposure(s) assessed more than once over time?**	**11. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?**	**12. Were the people assessing the outcomes blinded to the participants' exposures/interventions?**	**13. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?**	**14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?**	**t**
	Yes / No / Not reported (NR) or cannot determine (CD) or not applicable (NA)	**Yes / No / Not reported (NR) or cannot determine (CD) or not applicable (NA)**	**Yes / No / Not reported (NR) or cannot determine (CD) or not applicable (NA)**	**Yes / No / Not reported (NR) or cannot determine (CD) or not applicable (NA)**	**Yes / No / Not reported (NR) or cannot determine (CD) or not applicable (NA)**	**Yes / No / Not reported (NR) or cannot determine (CD) or not applicable (NA)**	**Yes / No / Not reported (NR) or cannot determine (CD) or not applicable (NA)**	**Yes / No / Not reported (NR) or cannot determine (CD) or not applicable (NA)**	**Yes / No / Not reported (NR) or cannot determine (CD) or not applicable (NA)**	**Yes / No / Not reported (NR) or cannot determine (CD) or not applicable (NA)**	**Yes / No / Not reported (NR) or cannot determine (CD) or not applicable (NA)**	**Yes / No / Not reported (NR) or cannot determine (CD) or not applicable (NA)**	**Yes / No / Not reported (NR) or cannot determine (CD) or not applicable (NA)**	**Yes / No / Not reported (NR) or cannot determine (CD) or not applicable (NA)**	
Kumbhat et.al 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	NR	NR	Yes	NR	Yes	Yes	**1**
Consonni et.al 2020	Yes	Yes	Yes	Yes	NR	Yes	Yes	NA	NR	NR	Yes	NR	Yes	Yes	**9**

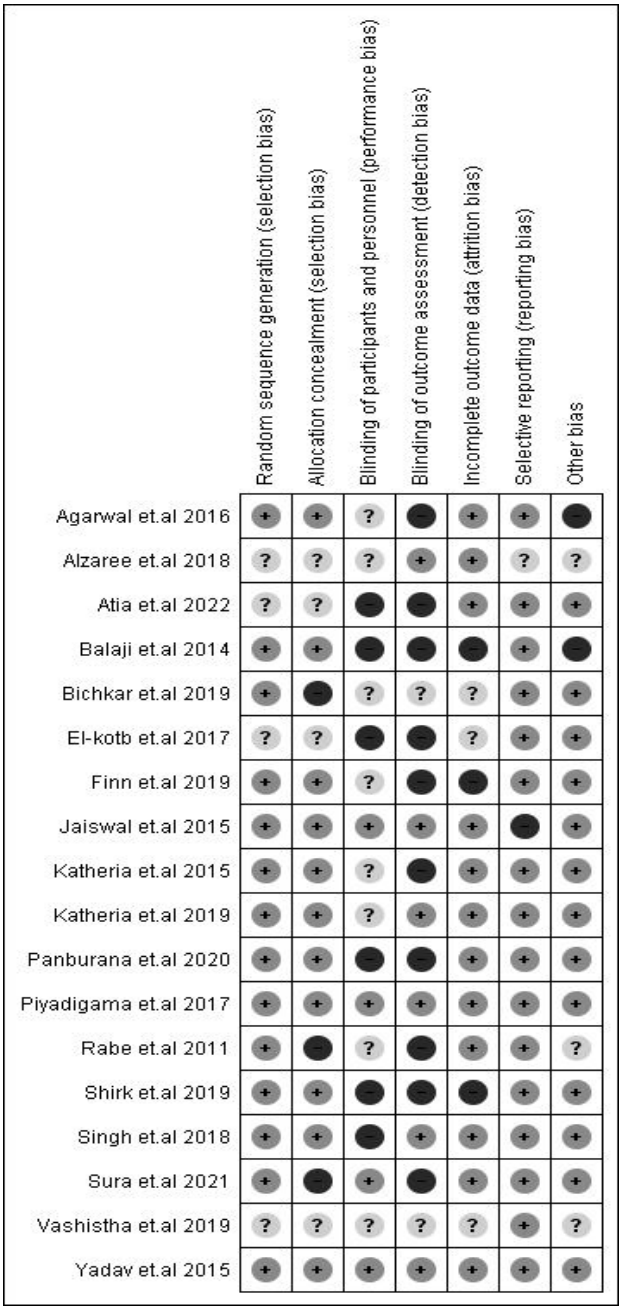


Figure 2: Risk of bias graph summary for RCTs

(-0.24 [-1.11, 0.64], p =0.6), the results were homogenous (P=0.66), and (I2 =0%). Figure 3

Hemoglobin level (Within the 1st day of life)
Eight studies mentioned the hemoglobin level value at a time frame within the 1st day of life. Seven included studies used the iUCM technique compared to DCC (the pooled MD = -0.02, 95% CI [-0.40 to 0.35], P = 0.9), with a sub-group of cut umbilical cord milking (cUCM) which contained only one paper (the pooled MD = 0.40, 95% CI [-0.23 to 1.03], P = 0.22). Our included papers showed no significance between the two techniques. As total pooled MD and 95% CI = (0.04 [-0.29, 0.38], p =0.80), the results were homogenous (P=0.09), and (I2 =43%). The subgroup test was non-significant (P=0.26). Figure 4. We excluded katheria et. Al. 2015 to solve heterogeneity and the obtained results with six studies remained insignificant (MD = -0.13, 95% CI [-0.48 to 0.22], *P-value* = 0.48). Supplementary Figure 1

B. Secondary outcomes

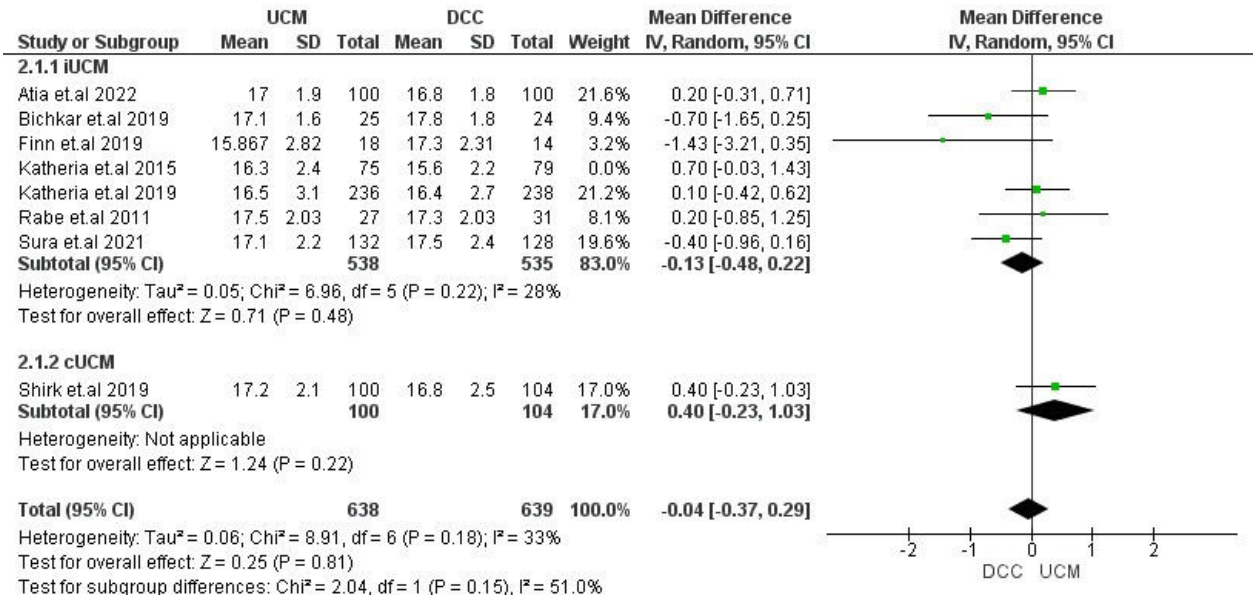
Neonatal death
Neonatal death was reported in six studies. UCM was associated with a significantly higher incidence in comparison to DCC (RR = 1.28, 95% CI [1.01 to 1.62], P = 0.04). Figure 5

Polycythemia
Polycythemia was reported in five studies. iUCM was associated with a lower incidence of polycythemia compared to DCC (RR = 0.54, 95% CI [0.32 to 0.90], P = 0.02). Supplementary Figures 2

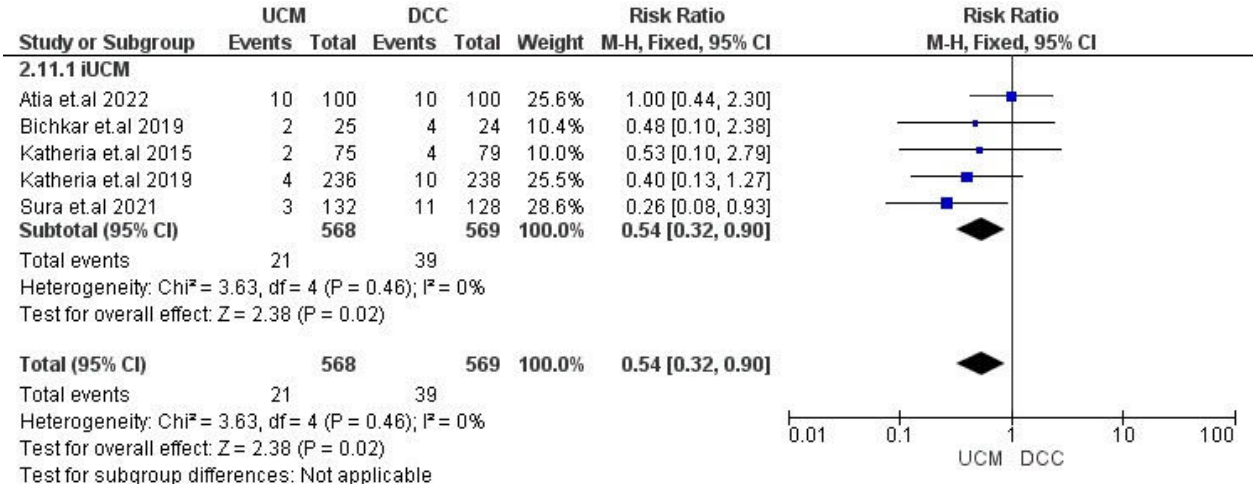
Severe IVH (grade 3 and 4)
Severe IVH was reported also in five studies. iUCM was associated with a higher incidence compared to DCC (RR = 2.03, 95% CI [1.10 to 3.76], P = 0.02). Supplementary Figures 3

IVH (any grade) and
IVH was reported in six studies; five of the included studies used the iUCM technique while the last one didn't mention the technique used for UCM, the pooled results were non-significant (RR = 1.02, 95% CI [0.66 to 1.59], *P-value* = 0.92). Supplementary Figures 4.

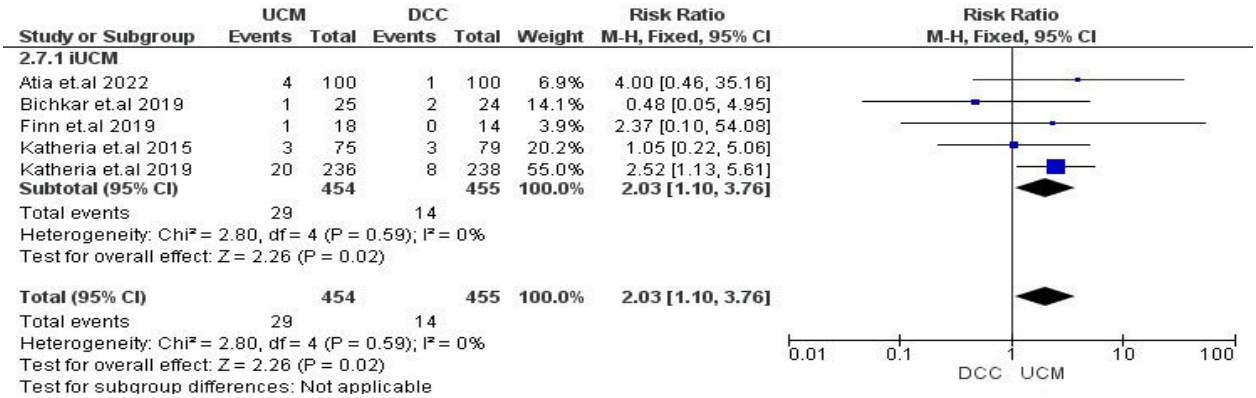
Necrotizing enterocolitis
Necrotizing enterocolitis was reported in six studies; five studies used the iUCM technique while the last one didn't mention the exact technique. The pooled results were non-significant (RR = 1.02, 95% CI [0.66 to 1.59], *P-value* = 0.92), and (RR = 1.03, 95% CI [0.75 to 1.40], *P-value* = 0.87) respectively. Supplementary Figures 4 and 5, respectively.



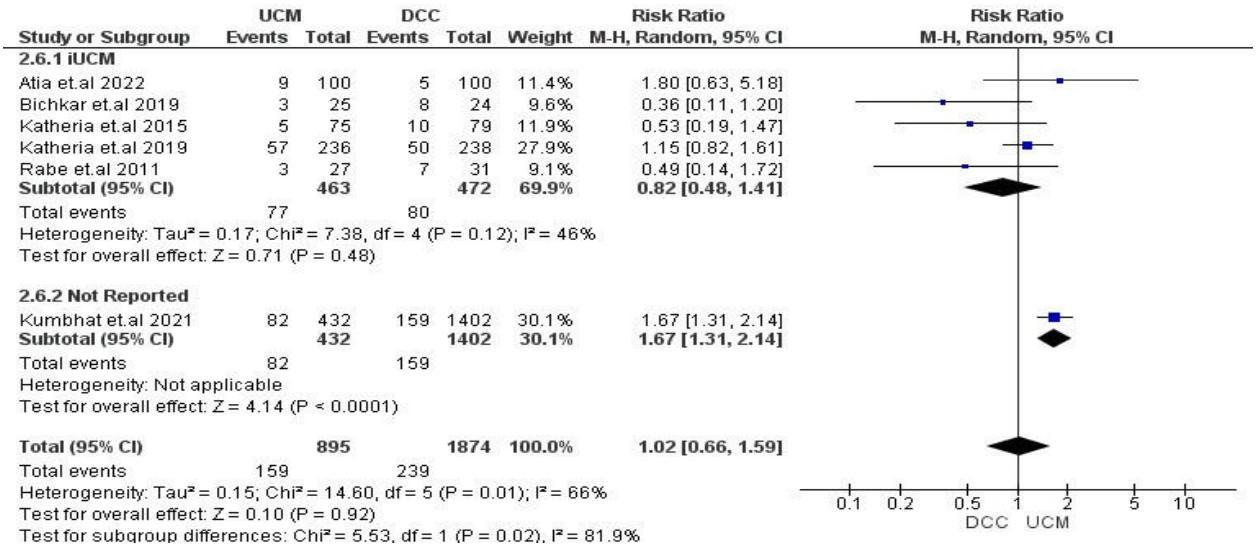
Supplementary Figure 1



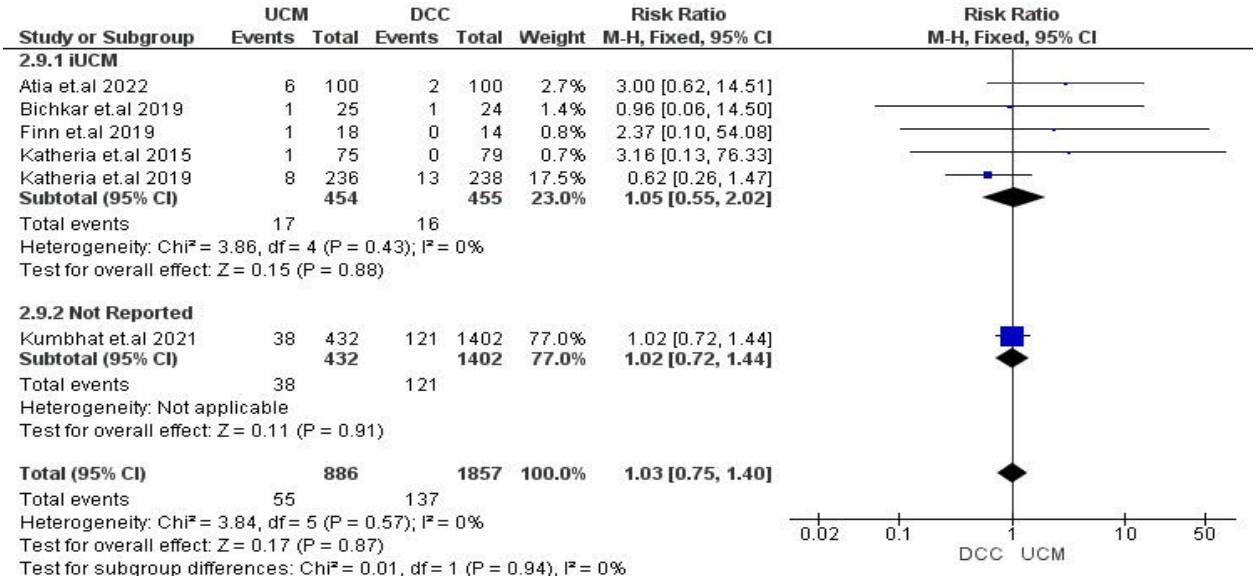
Supplementary Figure 2



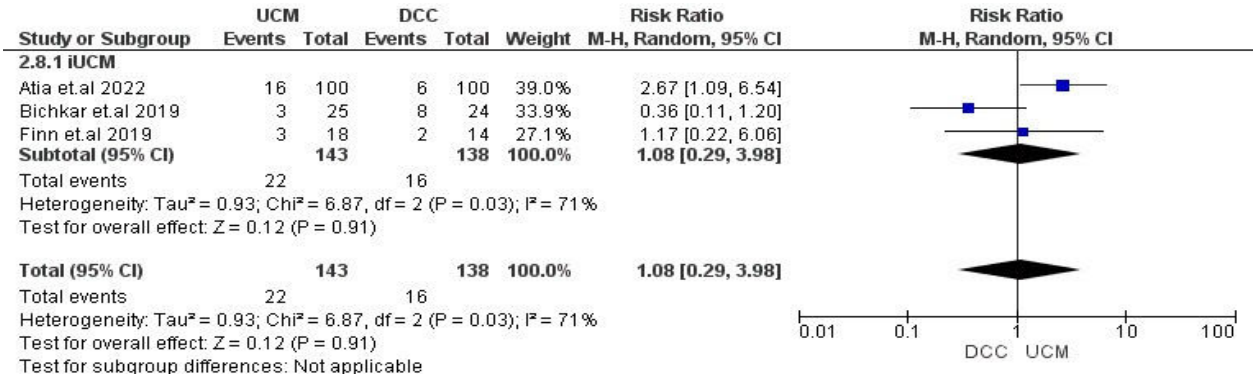
Supplementary Figure 3



Supplementary Figure 4



Supplementary Figure 5



Supplementary Figure 6

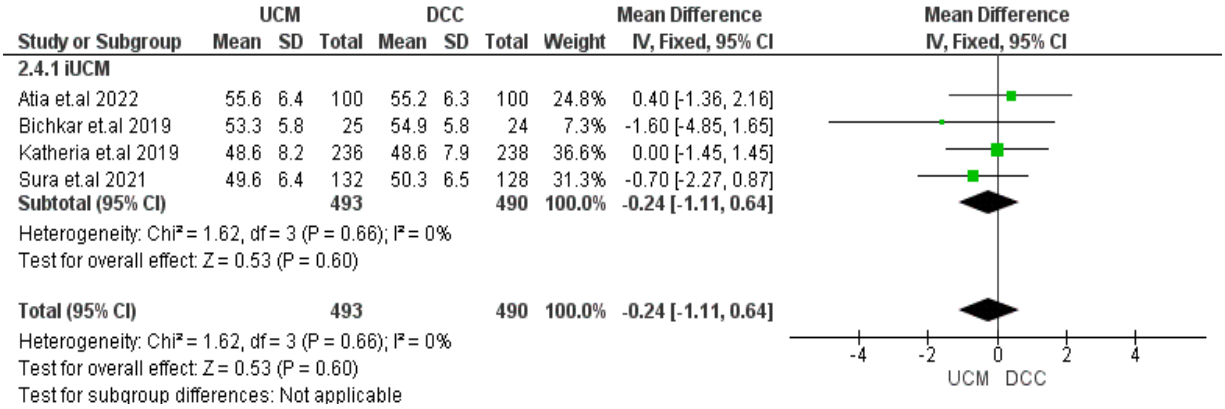


Figure 3: Forest plot of hematocrit level (at 24 to 48 hours) for preterm infants

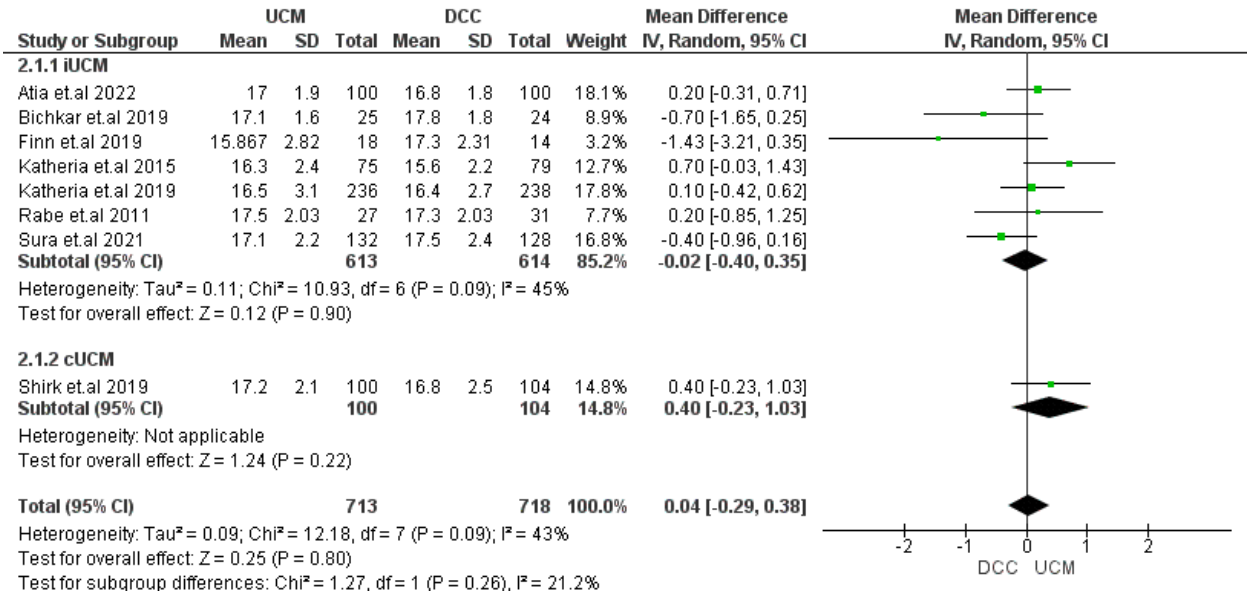


Figure 4: Forest plot of hemoglobin level (within the 1st day of life) for preterm infants

The need for inotropes

The need for inotropes was reported in three studies that used the iUCM technique with no significant difference between both techniques (RR = 1.08, 95% CI [0.29 to 3.98], P = 0.91). Pooled results were heterogenous, and we solved the heterogeneity by removing Atia et. Al 2022 and the pooled results remained insignificant (RR = 0.56, 95% CI [0.18 to 1.73], P-value = 0.32). Supplementary Figures 6 and 8

Need for transfusion

Need for transfusion is another adverse event that had no significant incidence between the iUCM and DCC (RR = 1.12, 95% CI [0.70 to 1.77], P-value = 0.64). Pooled results were heterogenous, and we solved the heterogeneity by removing Atia et. Al 2022 and the pooled results remained insignificant (RR = 0.89, 95% CI [0.68 to 1.16], *P-value* = 0.38). Supplementary Figures 7 and 9

Retinopathy

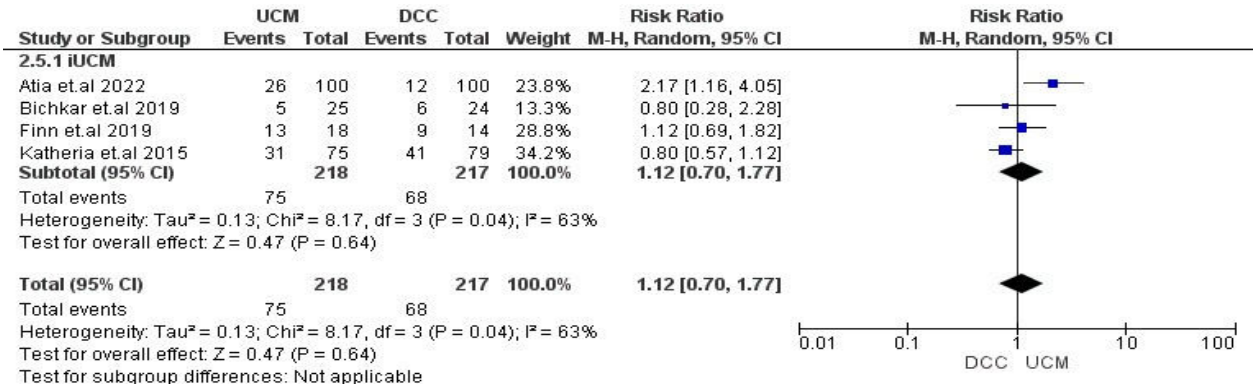
Retinopathy was mentioned in four studies with no significant incidence between the two comparator groups (RR = 0.66, 95% CI [0.37 to 1.19], P = 0.17). Supplementary Figure 10

2. Term or late preterm:

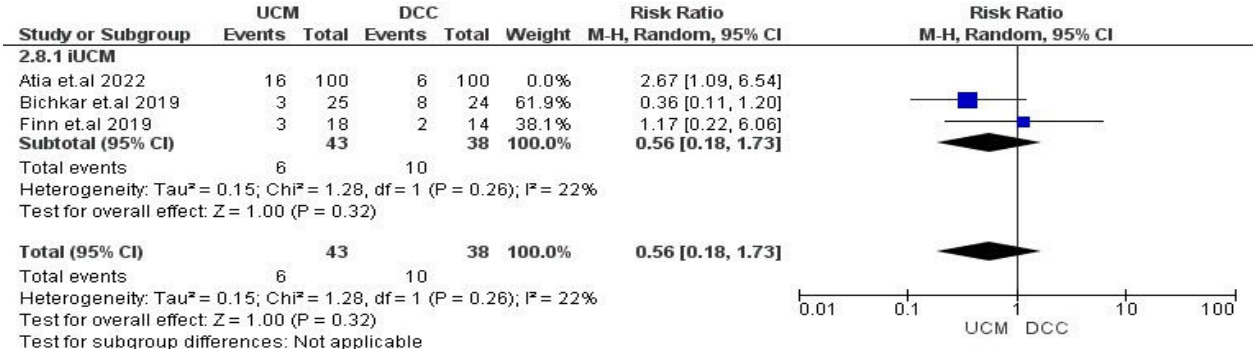
A. Primary outcomes

Hematocrit level (At 24 to 48 hours)

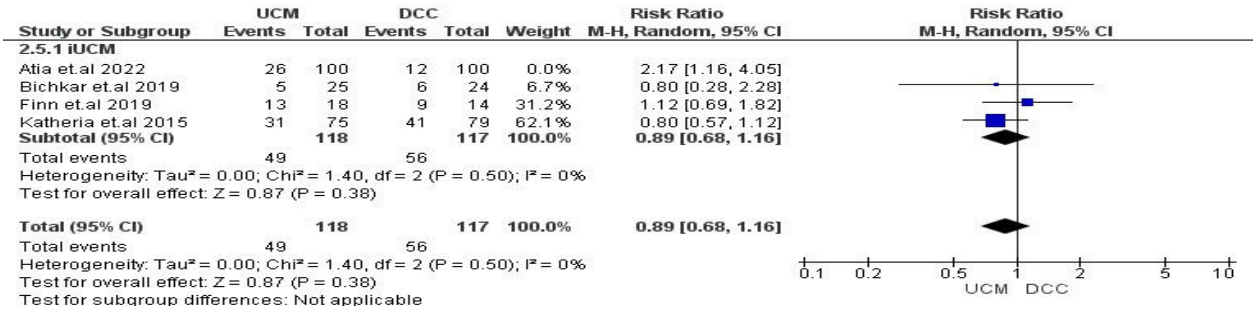
Six studies mentioned the Hematocrit level at a time from 24 to 48 hours. The included studies that used



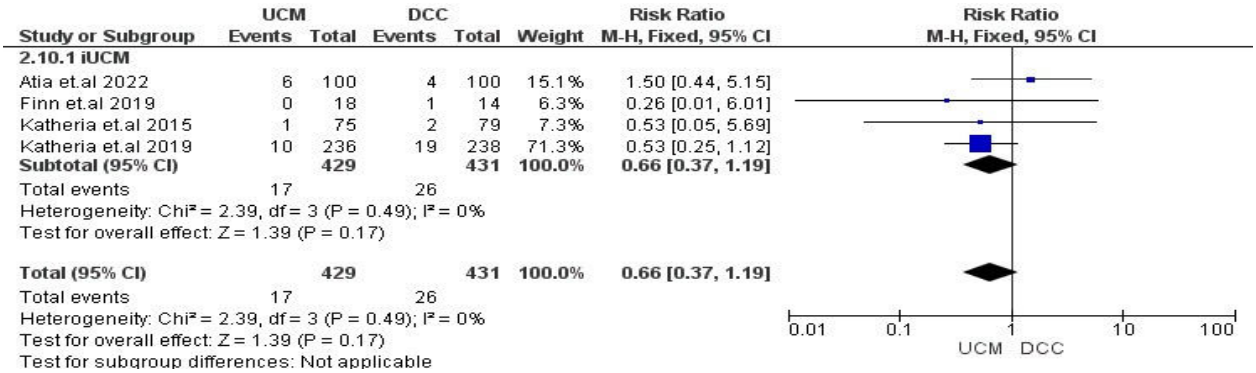
Supplementary Figure 7



Supplementary Figure 8



Supplementary Figure 9



Supplementary Figure 10

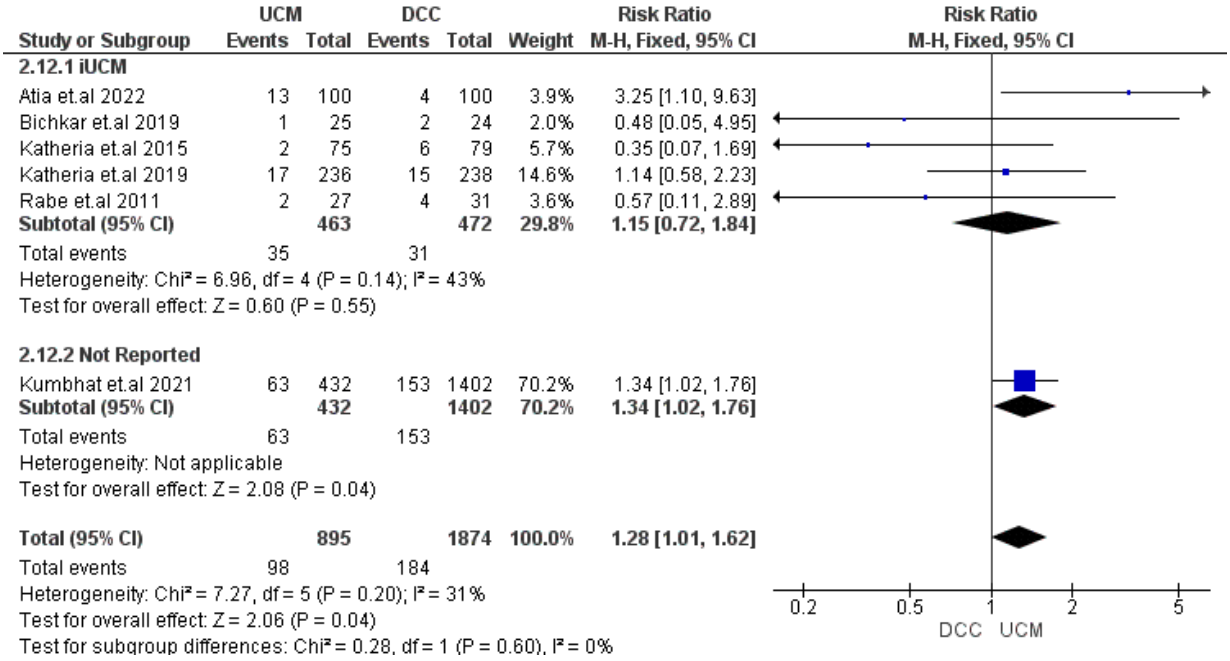


Figure 5: Forest plot of the incidence of neonatal death for preterm infants

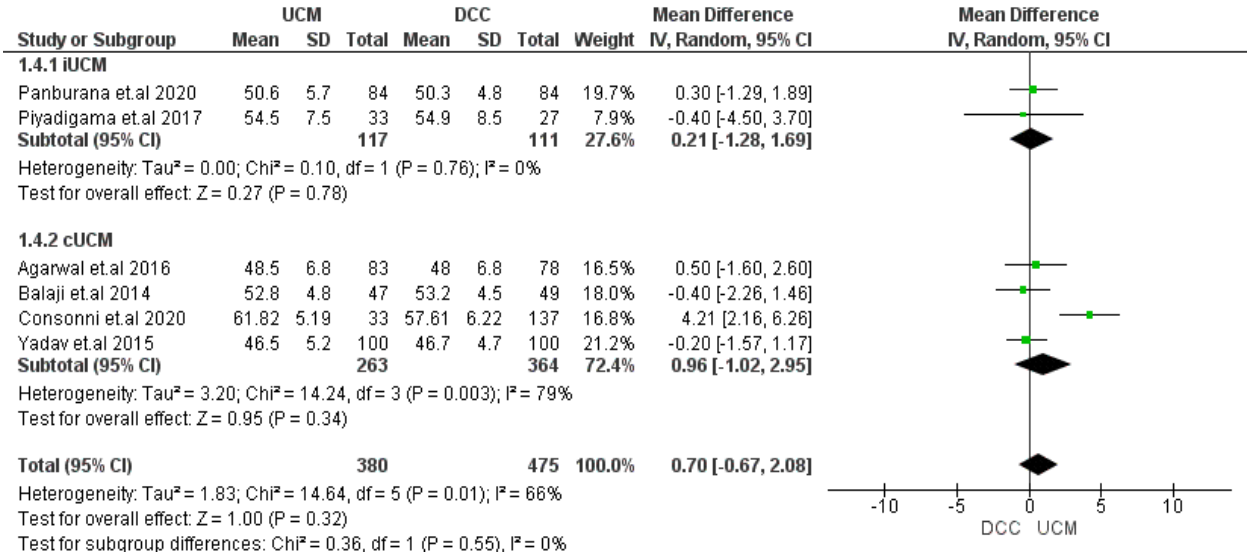


Figure 6: Forest plot of hematocrit level (At 24 to 48 hours) for term or late preterm infants

the iUCM technique compared to DCC were two, with no difference between both techniques (MD = 0.21, 95% CI [-1.28 to 1.69], P = 0.78). Also, four studies compared cUCM to DCC with no difference (MD = 0.96, 95% CI [-1.02 to 2.95], P = 0.34). The pooled MD and 95% CI for both subgroups were (0.70 [-0.67, 2.08], p =0.32). Figure 6. The test for subgroup difference was non-significant (P=0.55). Also, the results were heterogeneous (P=0.003, I2=79%) in the second subgroup. We excluded Consonni et. al 2020 to solve heterogeneity and the obtained results with three studies remained insignificant (MD = -0.10, 95% CI [-1.08 to 0.88], *P-value* = 0.84) Supplementary Figure 11

Hemoglobin level (Within the 1st day of life)

Six studies mentioned the hemoglobin level value within the 1st day of life. Three included studies compared iUCM to DCC and showed no significant difference (MD = -0.19, 95% CI [-0.66 to 0.28],

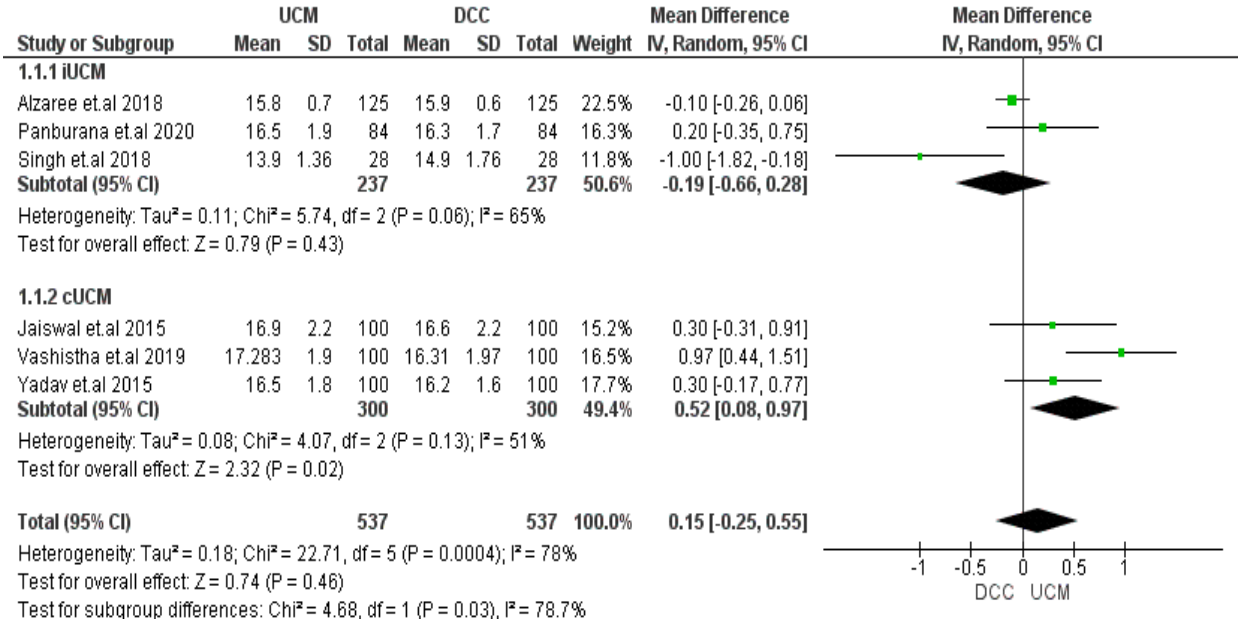


Figure 7: Forest plot of hemoglobin level (Within the 1st day of life) for term or late preterm infants

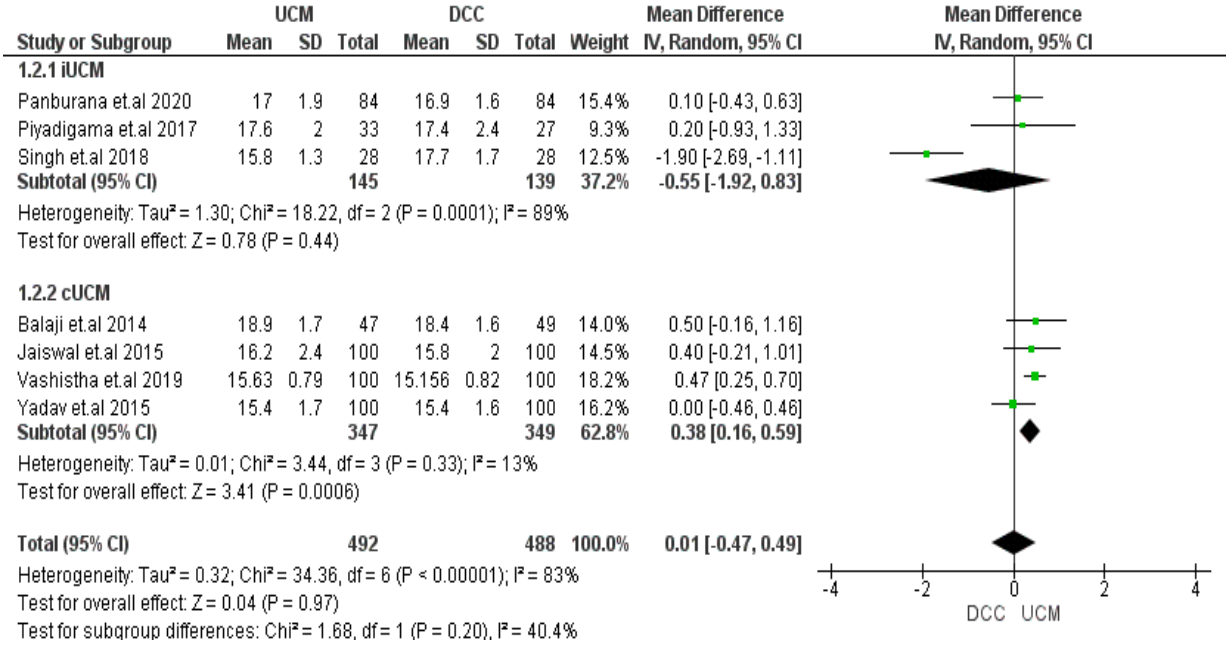
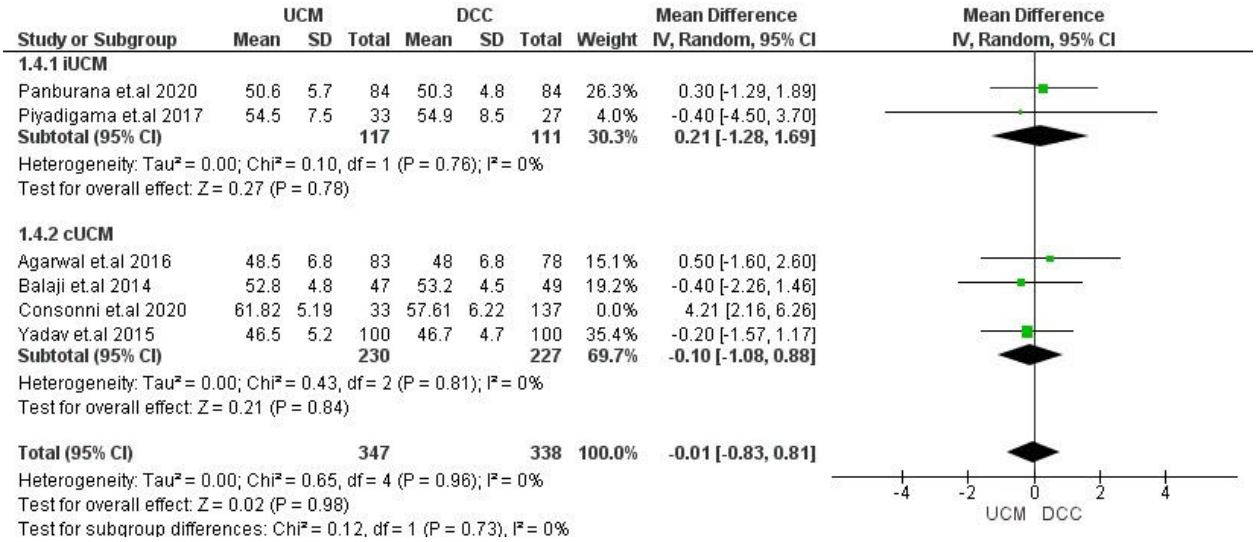


Figure 8: Forest plot of hemoglobin level (At 48 to 72 hours) for term or late preterm infants

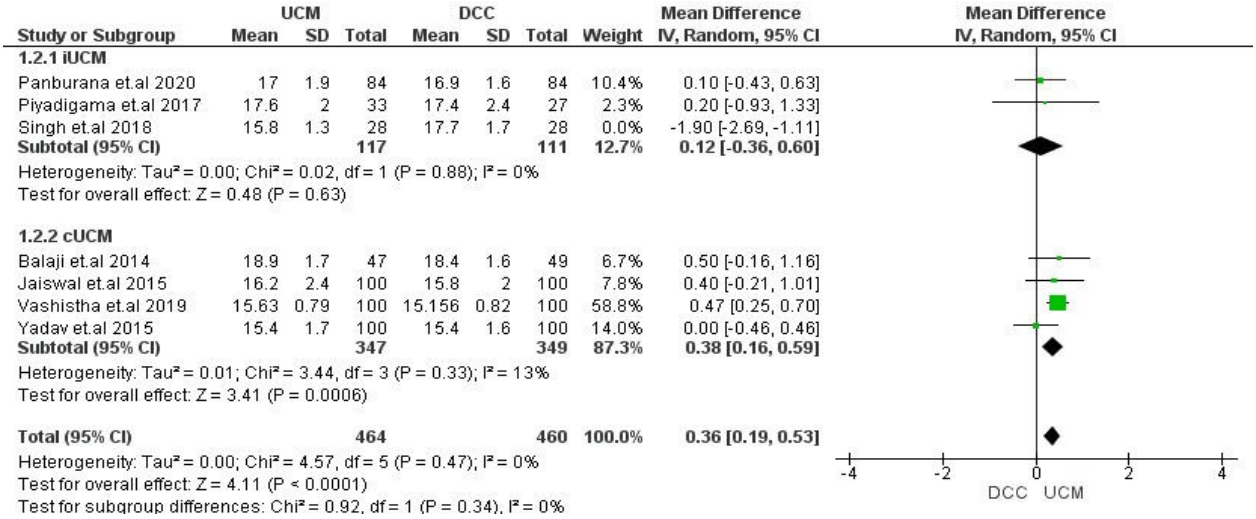
P-value = 0.43). Additionally, a subgroup of studies used cUCM showed a significant increase in hemoglobin level within the 1st day compared to DCC (MD = 0.52, 95% CI [0.08 to 0.97], *P-value* = 0.02). The pooled results were heterogeneous in the first subgroup (P=0.06, I2=65%). and the heterogeneity couldn't be solved. **Figure 7.** The test for subgroup difference was significant (P=0.03).

Hemoglobin level (At 48 to 72 hours)

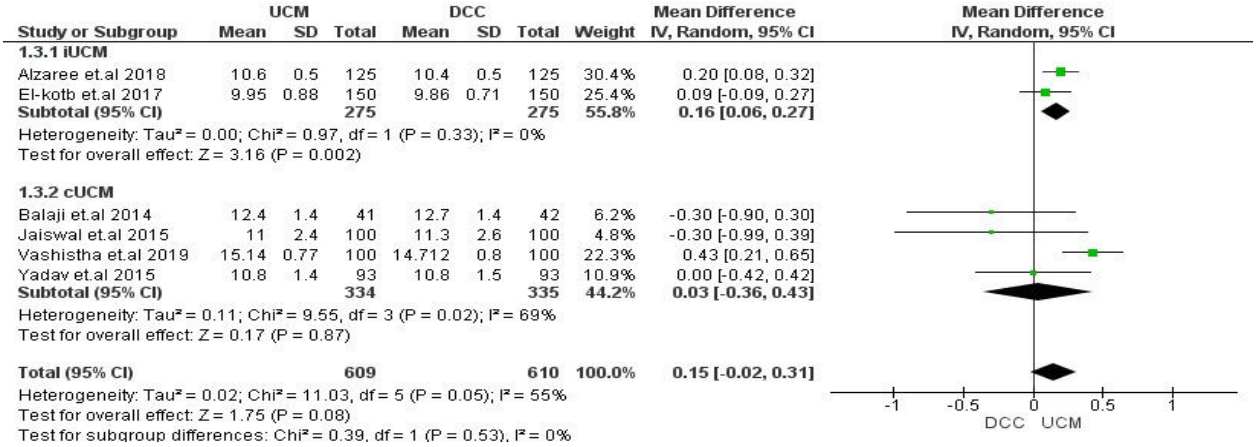
Seven studies mentioned the hemoglobin level value at a time frame of 48 to 72 hours. Three included studies compared iUCM to DCC and showed no significant difference (MD = -0.55, 95% CI [-1.92 to 0.83], *P-value* = 0.44). Also, a subgroup of cUCM which contained four papers showed a significant increase in hemoglobin level



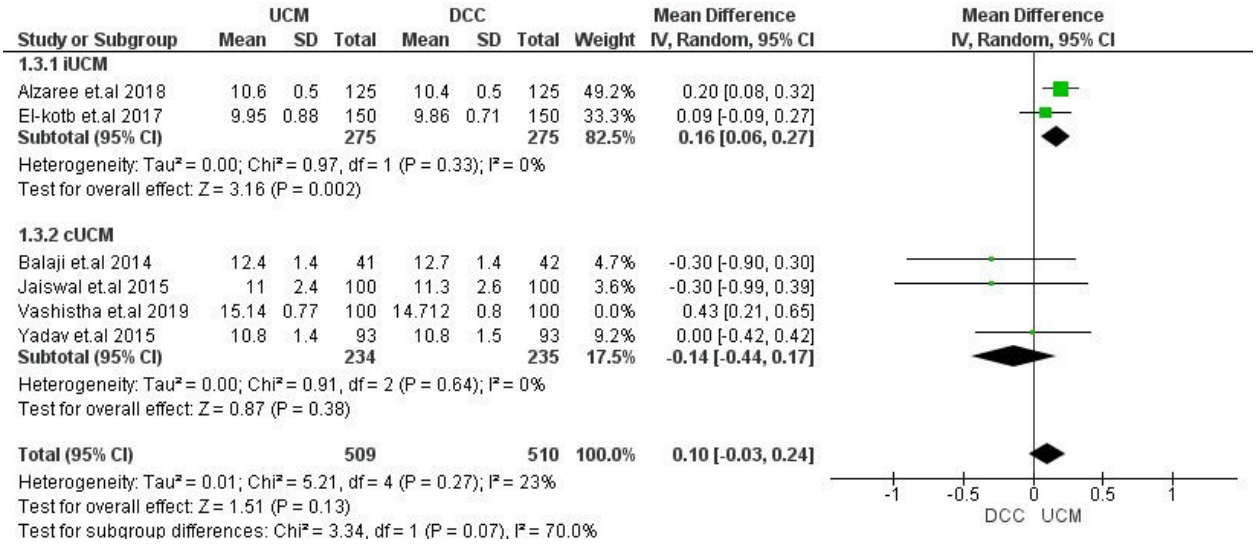
Supplementary Figure 11



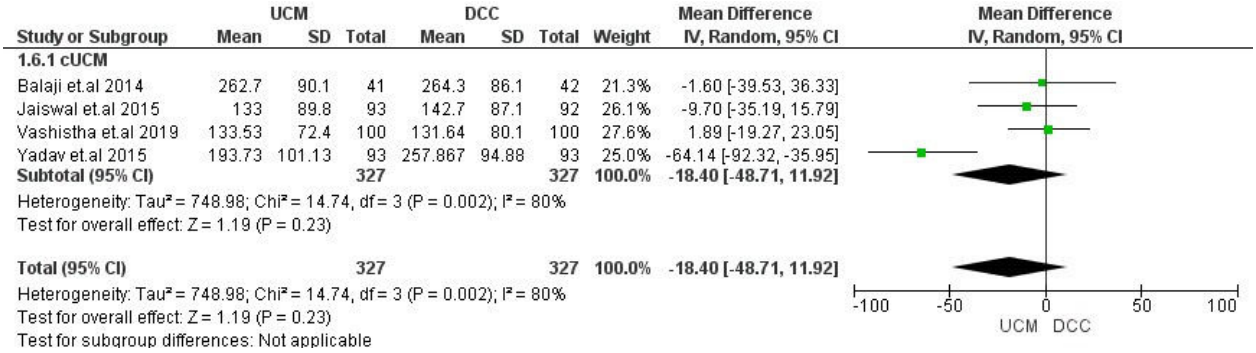
Supplementary Figure 12



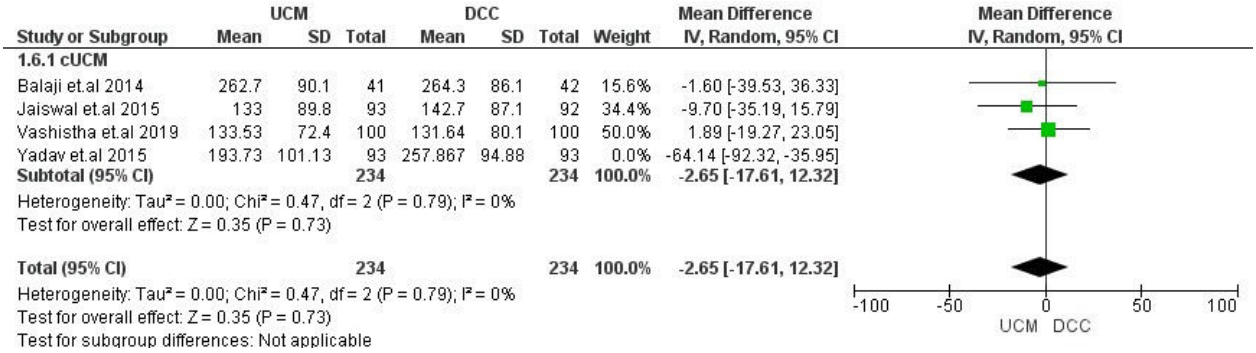
Supplementary Figure 13



Supplementary Figure 14



Supplementary Figure 15

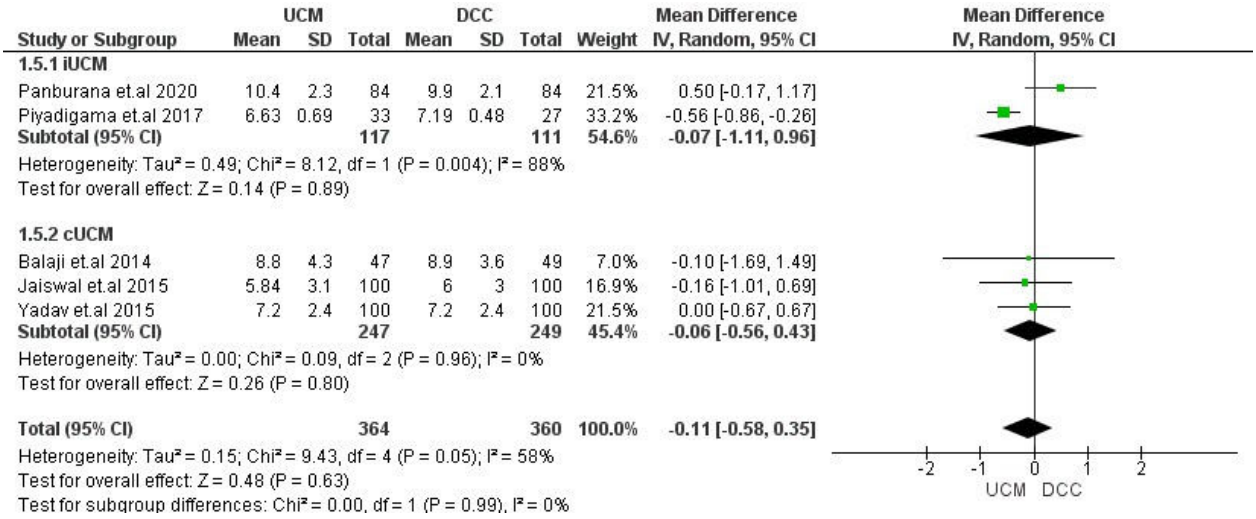


Supplementary Figure 16

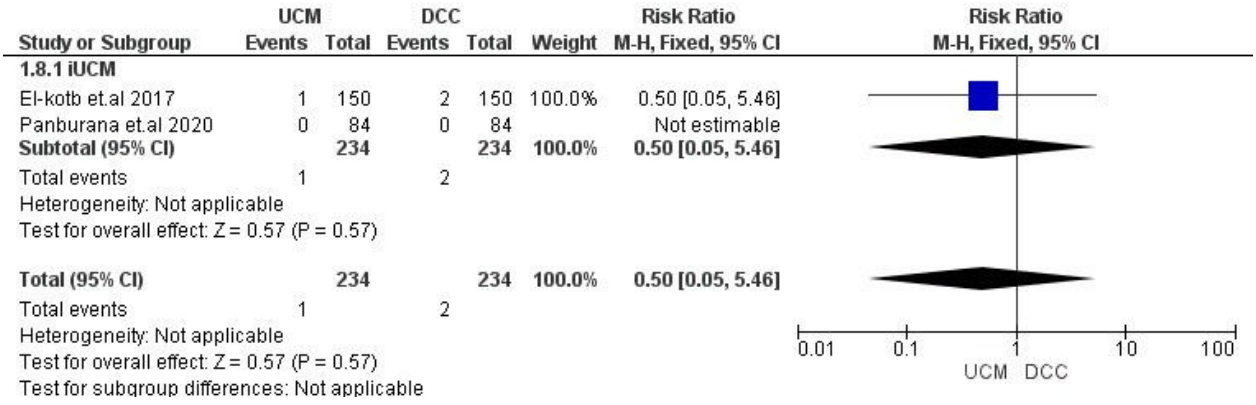
with cUCM (MD = 0.38, 95% CI [0.16 to 0.59], *P-value* = 0.0006). The results were heterogeneous in the first subgroup (P=0.0001), and (I2 =89%). **Figure 8.** We excluded Singh et. al 2018 to solve heterogeneity and the obtained results with two studies remained insignificant (MD = 0.12, 95% CI [-0.36 to 0.60], *P-value* = 0.63). Supplementary Figure 12. The test for subgroup difference was non-significant (P=0.20).

Hemoglobin level (At 6 to 8 weeks)

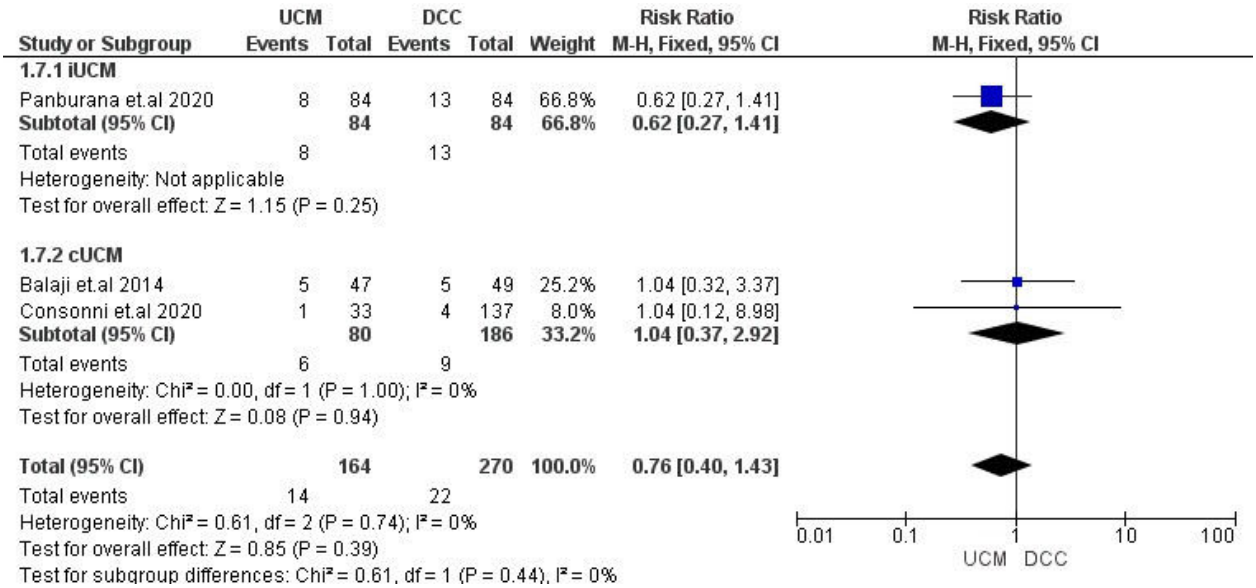
Six studies mentioned the hemoglobin level value in a time frame of 6 to 8 weeks. The included studies showed a significant increase in the HB with



Supplementary Figure 17



Supplementary Figure 18



Supplementary Figure 19

iUCM compared to DCC (MD = 0.16, 95% CI [0.06 to 0.27], P = 0.002). On the other hand, a subgroup of cUCM compared to DCC showed no significant difference between the two groups (the pooled MD = 0.03, 95% CI [-0.36 to 0.43], *P-value* = 0.87). The results were heterogeneous in the second subgroup (P=0.02, I2 =69%). Supplementary Figure 13. We excluded Vashistha et. al 2019 to solve heterogeneity and the results remained insignificant (MD = -0.14, 95% CI [-0.44 to 0.17], *P-value* = 0.38). Supplementary Figure 14. The test for subgroup difference was non-significant (P=0.53).

Serum ferritin level (at 6 to 8 weeks)

Four studies mentioned the serum ferritin level from 6 to 8 weeks. All included studies used cUCM compared to DCC and they showed no significant difference between the two groups (MD = -18.40, 95% CI [-48.71 to 11.92], *P-value* = 0.23). The results were heterogeneous as (P=0.002) and (I2 =80%). Supplementary Figure 15. We excluded Yadav et. al 2015 to solve heterogeneity and the results remained insignificant (MD = -2.65, 95% CI [-17.61 to 12.32], *P-value* = 0.73). Supplementary Figure 16

Serum bilirubin level (At 24 to 48 hours)

Five studies evaluated the serum bilirubin level value at a time frame of 24 to 48 hours. Two studies used iUCM compared to DCC technique and they found no significant difference (MD = -0.07, 95% CI [-1.11 to 0.96], P-value = 0.89). Also, three studies used cUCM compared to DCC with no significant difference (MD = -0.06, 95% CI [-0.56 to 0.43], *P-value* = 0.80). The pooled results in the first subgroup were heterogenous but the heterogeneity could not be resolved. The test for the subgroup was non-significant (P=0.99). Supplementary Figure 17

B. Secondary outcomes

The need for transfusion

The need for transfusion was mentioned in two studies that used the iUCM technique compared to DCC with no significant difference between two groups (RR = 0.50, 95% CI [0.05 to 5.46], P-value = 0.57). Supplementary Figure 18

Recurrent phototherapy

Recurrent phototherapy is another adverse event that had no significant incidence between the UCM and DCC whether iUCM or cUCM techniques were used with pooled results (RR = 0.76, 95% CI [0.40 to 1.43], *P-value* = 0.39) and the results were homogenous (p=0.74) (I2=0%). The subgroup difference test was non-significant (P=0.44). Supplementary Figure 19.

Discussion

In our study, a total of 18 RCTs and two retrospective cohort studies were included, encompassing a sample size of 5189 infants. Our study was divided into two main categories as we tested the safety and efficacy outcomes in preterm infants and full-term or late preterm infants. UCM was linked to more incidence of neonatal death in preterm infants compared with DCC. Also, the iUCM showed a significantly higher incidence in the occurrence of severe IVH compared to DCC. On the other hand, the incidence of polycythemia was significantly higher in the DCC group compared to the iUCM group. The iUCM technique showed superiority in the hemoglobin level at 6 to 8 weeks in full term infants compared to DCC, while the cUCM showed significance in the hemoglobin level in the first day of life and at 48 to 72 hours compared to DCC in full term infant. None of the remaining results showed any significant differences between the two techniques, whether in preterm or full-term infants. Furthermore, there was no association observed between the two techniques and any additional adverse events in either full-term or preterm infants. Additionally, the test of subgroup difference showed no significant difference between both techniques of UCM.

Previous studies and reviews mentioned the immediate cord clumping (ICC) as they compared it with DCC and UCM. Because of previous studies that showed both DCC and UCM are superior to ICC, few reviews focused on comparing DCC with UCM. They proved that DCC showed a significantly lower incidence of neonatal deaths and was associated with a lower incidence of major disabilities[35-37]. The previous meta-analysis compared the UCM and DCC found that UCM is suitable for the replacement of DCC[38].

Whether in preterm infants or full-term infants, our meta-analysis matched previous studies as there is no difference in the hemoglobin or hematocrit in the total results, although hemoglobin

results varied from cUCM to DCC in the first three days as the subgroup results showed that cUCM technique was more significantly higher in hemoglobin levels compared to DCC in full term infants.

Although UCM was proven to show superiority in improving the need for blood transfusion and be associated with lower incidence of overall IVH in a previous meta-analysis[39]. Our results are different from these results as UCM showed no superiority in the overall IVH in our analysis compared to DCC concerning preterm infants. On the other hand, UCM was associated with a higher incidence of the only severe IVH compared to DCC.

Previous studies support the evidence that UCM could improve the brain damage in the neonates with HIE as it provides the neonates with umbilical cord blood which is rich in stem cells that help in the improvement of brain injury[40,41]. Moreover, previous meta showed that UCM could be more beneficial compared to ICC in the intermediate and long-term outcomes although no difference in improvement in the early short-term clinical outcomes[42].

Our study possessed several strengths that enhance its credibility. Firstly, we included both preterm and full-term infants, allowing us to examine the outcomes in a broader population. Moreover, we conducted a separate analysis of the different techniques of umbilical cord milking (UCM), specifically distinguishing between intact-UCM and cut-UCM, thereby providing more comprehensive results. Furthermore, the majority of the studies included in our analysis are RCTs, which are known for their robust evidence. However, it is important to acknowledge the limitations of our study. Twelve of the RCTs included in our analysis were rated as low quality according to the risk of bias tool, indicating potential biases in their methodology. Additionally, one study by Kumbhat et al did not specify the specific UCM technique utilized, which limits the interpretation of their findings. Furthermore, there were variations in the timing of the DCC across the included? Metastudies, and most studies predominantly employed cUCM instead of iUCM, thereby limiting the ability to assess the efficacy and safety of iUCM.

Conclusions

In conclusion, our study provides valuable insights into the comparison of the UCM and DCC techniques in both preterm and full-term infants. We found that UCM was associated with a higher incidence of neonatal death in preterm infants compared to DCC, while the incidence of polycythemia was lower in the UCM group. On the other hand, UCM was associated with higher rates of severe IVH events. Importantly, there was no evidence of additional adverse events associated with either technique. Finally, DCC may still the preferred option over UCM due to the lower incidence of severe IVH and neonatal death. We recommend higher quality RCTs to investigate the safety and efficacy between DCC and UCM by comparing various timings in DCC with the two techniques of UCM to cover all the possibilities and integrate more precise data to find the best technique in full-term infants and preterm infants. Also, in-depth study of IVH is crucial.

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Conflict of interest

The authors declare no conflict of interest.

Availability of data

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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