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NEONATAL FACTORS MATERNAL FACTORS AND INVASIVE PROCEDURES ASSOCIATED WITH LATE NEONATAL SEPSIS IN THE PERIOD 2011-2020 SYSTEMATIC REVIEW AND META-ANALYSIS.

FACTORES NEONATALES, MATERNOS Y PROCEDIMIENTOS INVASIVOS ASOCIADOS A SEPSIS NEONATAL TARDÍA EN EL PERIODO 2011-202.0 REVISIÓN SISTEMÁTICA Y METAANÁLISIS

Allison Poquioma Hernandez[1,a], Walter Mosquera Saira[1,a], María Loo Valverde[2,b], Luis Roldán-Arbieto[2,3], Víctor Vera Ponce[2,b], Jhony A. De La Cruz-Vargas[2,b]

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ABSTRACT

Objective: To review, evaluate and synthesize available literature on neonatal and maternal factors and invasive procedures associated with late neonatal sepsis during the last ten years. **Methods:** The databases used for the bibliographic search were: Pubmed/Medline, LILACS, SciELO, and Google Scholar. Analytical studies investigating risk factors for late neonatal sepsis by stages (title, abstract and full text) were selected. The risk of bias was assessed using the Newcastle Ottawa Scale. Heterogeneity was set, and a random-effects meta-analysis was performed for the following risk factors: gender, gestational age, birth weight, Apgar score at five min, premature rupture of membranes, route of delivery, use of a central venous catheter, and ventilation. Mechanics. The effect was measured with an odds ratio. The certainty of the evidence was determined using the GRADE methodology. The protocol was registered in PROSPERO. **Results:** Eight studies from 633 records were collected. Heterogeneity was high. Three male studies OR: 1.97(0.26-14.59) p=0.03; I2 =80%, prematurity two studies OR: 2.48 (1.13-5.45); p=0.04; I2 =72%, use of central venous catheter four studies – OR: 3.83 (1.07 – 13.71) p<0.01; I2 =89% and mechanical ventilation four studies OR: 2.83 (1.42 – 5.68); p<0.01; I2 =86%) were independent factors for the development of late neonatal sepsis. Studies had the lowest comparability assessment score when the risk of bias was applied. The results had low certainty of evidence. **Conclusion:** Male sex, prematurity, use of a central venous catheter, and mechanical ventilation are risk factors for late sepsis.

Keywords: Neonatal Sepsis; Risk factors; Infant, Newborn; Systematic Review. (Source: MeSH NLM)

RESUMEN

Objetivo: El presente trabajo se realizó con la intención de Revisar, evaluar y sintetizar literatura disponible sobre factores neonatales, maternos y procedimientos invasivos realizados en el neonato asociados a sepsis neonatal tardía durante los últimos diez años. **Métodos:** Las bases de datos utilizadas para la búsqueda bibliográfica fueron: Pubmed/Medline, LILACS, SciELO y Google Scholar Se seleccionaron estudios analíticos sobre investigación de factores de riesgo para sepsis neonatal tardía por etapas (título, resumen y texto completo). El riesgo de sesgo se evaluó con la Escala Newcastle Otawa. Se evaluó la heterogeneidad y se realizó un metaanálisis de efectos aleatorios para los siguientes factores de riesgo: sexo, edad gestacional, peso al nacer, Apgar a los cinco min, ruptura prematura de membranas, vía de parto, uso de catéter venoso central y ventilación mecánica. El efecto se midió con odds ratio. La certeza de la evidencia se determinó utilizando la metodología GRADE. El protocolo se registró en PROSPERO. **Resultados:** Se recopilaron ocho estudios de 633 registros. La heterogeneidad fue alta. tres estudios sexo masculino OR: 1,97(0,26-14,59) p=0.03; I2 =80%, prematuridad dos estudios OR: 2,48 (1,13-5.45); p=0.04; I2 =72%, uso de catéter venoso central cuatro estudios – OR: 3,83 (1,07 – 13,71) p<0.01; I2 =89% y ventilación mecánica cuatro estudios OR: 2,83 (1,42 – 5,68); p<0.01; I2 =86%) fueron factores independientes para el desarrollo de sepsis neonatal tardía. Los estudios tuvieron la puntuación más baja en evaluación de comparabilidad al aplicarse el riesgo de sesgo. Los resultados tuvieron certeza baja de evidencia. **Conclusión:** Sexo masculino, prematuridad, uso de catéter venoso central y ventilación mecánica son factores de riesgo para sepsis tardía.

Palabras clave: Sepsis Neonatal; Factores de Riesgo; Recién Nacido; Revisión Sistemática.(Fuente: DeCS BIREME)

[1] Ricardo Palma University. Lima Peru.
[2] Biomedical Sciences Research Institute (INICIB), Ricardo Palma University, Lima, Peru
[3] Escuela de Postgrado en Gestión Pública, Universidad Tecnológica del Perú, Lima, Perú
[a] Surgeon
[b] Doctor (a)
[c] Magister

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INTRODUCTION

Sepsis is the second leading cause of neonatal mortality, after prematurity. Most perinatal mortality occurs in the neonatal period [1]. Likewise, two-thirds of neonatal mortality occurs in the first week of life. Globally, the death rate from sepsis is 2,202 per 100,000 live births[1]. In Peru, the national neonatal mortality rate was ten per 100,000 live births in 2017 [2]. Sepsis generates a morbidity burden with short- and long-term complications, especially at the neurological level, such as cerebral palsy, delayed psychomotor development, and also prolongs hospital stay and increases hospital costs[1].

Neonatal sepsis is an infection characterized by bacteremia and is classified according to the time of onset into early and late sepsis [3,4]. The most frequent cut-off points are at 72 hours and seven days of life. There is currently no global consensus to define the cut-off point[1,5,6].

Early sepsis is associated with maternal infections such as urinary tract infection (UTI) and chorioamnionitis that are transmitted to the newborn through the birth canal [7,8]. While late sepsis is associated with medical care, it is even considered a nosocomial infection and a major complication in neonatal intensive care units (NICU)[1,9]. The incidence of late sepsis differs in infants of certain gestational ages, birth weight, and sex, and is associated with invasive procedures such as endotracheal intubation, total parenteral nutrition, venous catheter, necrotizing enterocolitis, among others.

Early-onset sepsis is associated with group B Streptococci [10]. The pathogens associated with late sepsis vary according to the distribution of each intensive care unit. Therefore, each NICU should study the profile of the pathogens specific to each hospital. Research on the incidence, risk factors, and distribution of pathogens is scarce in Peru.

Applying a risk factor-based approach to guide management decisions is one of the highly effective approaches to reducing neonatal sepsis mortality in high-income countries. It is recommended that in settings with limited resources and a high neonatal mortality rate, a combination of risk factors and clinical signs should serve as a guide for intrapartum and neonatal management. To reduce the burden of disease, it is essential to identify potential risk factors, followed by effective preventive or infection control measures.

For the above reasons, we have the objective of reviewing, evaluating and synthesizing the literature on the risk factors most frequently associated with the development of late neonatal sepsis through a systematic review-type study and subsequent meta-analysis. To our knowledge, this is the first systematic review and meta-analysis addressing risk factors for the development of late neonatal sepsis. Evidence from reviews of risk factors for late sepsis from this study will be used for the development of prevention strategies.

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METHODS

Study design type and area

This systematic review and meta-analysis have been reported according to the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) guideline.

Information sources and search strategy

An exhaustive literature search was performed in PubMed, SciELO, LILACS, and Google Scholar for studies published in the last ten years (2011-2020). A comprehensive search strategy was developed that included all possible risk factors for late neonatal sepsis according to the literature review based on MeSH terms and words from the title and abstract involving the following keywords: “late-onset sepsis”, “late onset septicemia”, “late onset bacteremia”, “late onset blood infection”, “infant”, “newborn”, “neonate”, “neonatology”, “risk”, “risk factors”, “risk factor”, “ causality” and “odds ratio”. Search terms within the domain were combined with 'OR' and cross-domain terms with 'AND'. A specific database filter was applied to limit the search to 'last ten years (2011-2020).

No language filter was applied. A search strategy was first developed for PubMed and later adapted for the other databases.

Study

selection Two authors independently selected studies using three-stage eligibility criteria: title, abstract, and full text. EndNote TM X8 software (Clarivate Analytics, Thomson Reuters, New York) to eliminate duplicates and store the studies for full-text reading. The study selection process was synthesized and outlined using a PRISMA flow diagram in the Shiny web application (https://estech.shinyapps.io/prisma_flowdiagram/) which shows the number of studies included and excluded in each phase of the study selection.

ELIGIBILITY

Criteria Inclusion criteria:

-Studies evaluating the risk of one or more neonatal factors, maternal factors or invasive procedures to develop late neonatal sepsis.

-Analytical studies that report a comparison of two groups: one with late neonatal sepsis and the other without sepsis.

-Studies that define late neonatal sepsis as that which occurs from 72h of life or more to 28 days of life.

-Studies that define cases of sepsis using laboratory criteria (eg culture, hematological parameters)

-Studies were published between 2010 and 2020.

Criteria of exclusion

-Studies not available in their complete version

-Case reports, letters to the author or narrative reviews, and systematic reviews

-Studies that do not have a database

-Studies with unclear diagnostic criteria or that use clinical criteria exclusively

-Studies that evaluate early neonatal sepsis or in general.

Data extraction

The data was recorded in a data collection form and later digitized in a Microsoft Excel 2016 data sheet (Microsoft, Washington). For the qualitative analysis, the extraction domains included: title, author, year of publication, study period, country of execution, design, case definition, the definition of late neonatal sepsis, risk factors, and results. Dichotomous raw data for events and non-events, where available, were extracted and converted to OR.

Assessment of the Risk of bias and Certainty of the evidence

The Newcastle-Ottawa Scale (NOS) for observational studies was used to assess the quality of case-control studies and cohort studies. The NOS evaluates three categories of a given study: selection, comparability, and exposure/outcome. These are scored individually and counted up to a possible total of nine points. NOS is classified as follows: ≥ seven for low and < seven for high risk. Risk of bias plots were used to illustrate quality assessment using Review Manager (RevMan) version 5.4.1 software. (The Cochrane Collaboration, 2020).

To assess the certainty of the evidence in this study, the GRADE methodology was used through the GRADE pro online application (https://gradepro.org/), which reports the certainty of the evidence in a summary table. The GRADE methodology assesses four aspects: risk of bias, inconsistency, indirect evidence, and imprecision.

Quantitative analysis

For the statistical analysis, a random-effects meta-analysis was performed in the STATA MP v. program. 14.0 (Stata Corp LP, College Station, Texas, USA) to measure the association between risk factors and late neonatal sepsis. The effect size was measured by Odds ratio. (OR). All variables were dichotomous. The adjusted odds ratio was calculated to minimize confounding bias. The confidence interval was 95% and the value $p<0.05$. Statistical heterogeneity was assessed and reported using Cochran's Q statistic, I2, and Tau2. I2 from 25 to 50% was considered low, 50-75% moderate, and ≥75% high heterogeneity. The results of the meta-analysis were shown with Forest plot type diagrams. Tables were provided for the characteristics of the included studies and for the results of the quality

assessment. Publication bias should be developed if and only if there are at least ten studies in the meta-analysis using Funnel Plot diagrams, which is why publication bias is not assessed in this study.

RESULTS

Characteristics of included studies

A total of 633 studies were found. eight duplicates were removed and 625 titles were reviewed. Of these, 574 titles were excluded and 51 abstracts were screened.

Of these, 35 full-text registries were examined and 8 studies met the inclusion criteria for this review. The reasons for the exclusion of 27 full-text records were: no study of risk factors, another type of sepsis, absence of risk factors studied, and lack of data. The study selection process is illustrated in Figure 1.

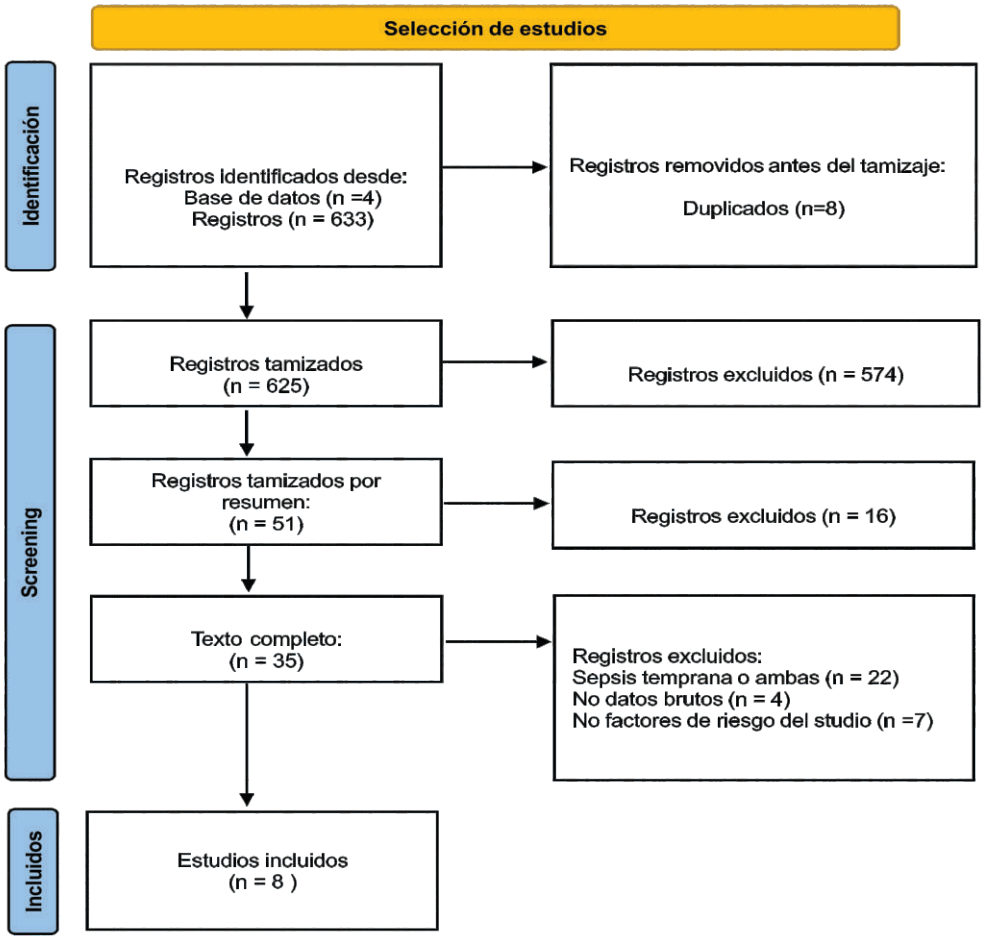

Figure N°1. Diagrama de flujo PRISMA mostrando la selección de estudios incluidos en el análisis cuantitativo (metaanálisis)

Fuente: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Homann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi:10.1136/bmj.n71

Regarding the design, of the eight studies, six were cases and controls, one retrospective cohort, and oneprospective cohort. Six studies were done in term infants and two in preterm infants. All studies were carried out in the Neonatal Intensive Care Unit. According to the definition of sepsis, two studies defined it as that which appears after seven days, four studies took 72h as the cut-off point, and one did not specify. Likewise, there were variations in the guidelines used to diagnose neonatal sepsis: eight studies required positive cultures to confirm neonatal sepsis, and one applied clinical criteria. A summary of the characteristics of the included studies can be seen in Table N°1.

Tabla N°1. Características de los estudios incluidos.

No	*Título*	*Diseño*	*Autor*	*Objetivo*	*País*	*Período*	*Pacientes*
1	Risk factors of late -onset neonatal sepsis in Taiwan: A matched case-control study	Casos y Controles	Kung2016	Identificar factores de riesgo para SNT	Taiwán	2003 - 2006	Neonatos en UCI
2	Risk Factors for Late -Onset Sepsis in Preterm Infants: A Multicenter Case -Control Study	Casos y Controles	El Manouni2019	Identificar factores de riesgo para SNT	Países bajos y Bélgica	2014-2017	Neonatos prematuros en UCI
3	Risk factors and etiology of neonatal sepsis after hospital delivery: A case -control study in a tertiary care hospital of Rajshahi, Bangladesh.	Casos y Controles	Rafi2020	Identificar factores de riesgo para SNT	Bangladesh	2019	Neonatos en UCI
4	Association between birth route and late -onset sepsis in very preterm neonates	Cohorte Retrospectiva	Olivier2016	Identificar asociacion entre vía de parto y SNT	Canadá	2010 - 2014	Neonatos prematuros en UCI
5	Late onset sepsis in newborn babies: epidemiology and effect of a bundle to prevent central line associated bloodstream infections in the neonatal intensive care unit	Cohorte Retrospectiva	Resende2015	Evaluar el efecto de la implementacion de medidas basadas en la evidencia en la SNT	Brazil	2010 - 2012	Neonatos en UCI
6	Risk factors and lethality of laboratory-confirmed bloodstream infection caused by non -skin contaminant pathogens in neonates	Casos y Controles	Romanelli2013	Identificar factores de riesgo para SNT	Brazil	2008 - 2012	Neonatos en UCI
7	Nosocomial infections (late onset sepsis) in the Neonatal Intensive Care Unit (NICU)	Casos y Controles	Joseph2012	Identificar factores de riesgo para SNT	Singapur	2005 - 2007	Neonatos con muy bajo peso al nacer en UCI
8	Late-onset neonatal sepsis, risk factors and interventions: an analysis of recurrent outbreaks of Serratia marcescens, 2006e2011	Casos y Controles	Samuelsson2014	Identificar factores de riesgo para SNT	Sweden	2006 - 2011	Neonatos en UCI

Tabla N°1. Características de los estudios incluidos *(continuación).*

No	*Título*	*Factores de riesgo*	*Método diagnóstico*	*Definición de SNT*	*Resultados*
1	Risk factors of late -onset neonatal sepsis in Taiwan: A matched case-control study	Maternos: RPM P. invasivos: CVC, VM, NPT	Cultivo	> 7d	NPT (OR 6.07 IC 95% 1.14 -32.32, p=0.034)
2	Risk Factors for Late -Onset Sepsis in Preterm Infants: A Multicenter Case -Control Study	Neonatales: sexo. Maternos: RPM, tipo de parto P. invasivos: CVC, VM, NPT	Cultivo	> 72 h	NPT (OR 1.29 IC 95% 1.07 -1.55, p=0.006)
3	Risk factors and etiology of neonatal sepsis after hospital delivery: A case -control study in a tertiary care hospital of Rajshahi, Bangladesh.	Neonatales: edad, peso, apgar, sexo. Maternos: RPM, tipo d e parto, ITU	Cultivo	> 72 h	ITU (OR 5.48 IC95% 1.58 -18.99, p<0.05). Sexo masculino (OR 0.33 IC95% 0.13 -0.88, p<0.05)
4	Association between birth route and late-onset sepsis in very preterm neonates	Maternos: tipo de parto	Cultivo	> 48 h	No asociacion de SNT con via de parto.
5	Late onset sepsis in newborn babies: epidemiology and effect of a bundle to prevent central line associated bloodstream infecti ons in the neonatal intensive care unit	Neonatales: edad, peso, apgar. P. invasivos: CVC, VM, NPT	Clínica	> 7 d	Prematuridad (OR 1.83 IC95% 1.03 -3.26, p=0.04), Peso <1500 g (OR 2.70 IC95% 1.16-3.74, p=0.01), CVC (OR 5.10 IC95% 2.32-11.26, p<0.001), VM (OR 2.72 IC95% 1.65-2.42, p<0.001)
6	Risk factors and lethality of laboratory -confirmed bloodstream infection caused by non -skin contaminant pathogens in neonates	Neonatales: edad, peso, apgar. Maternos: RPM. P. invasivos: CVC, VM, NPT	Cultivo	No especifica	CVC (OR 8.99, p=0,047)
7	Nosocomial infections (late onset sepsis) in the Neonatal Intensive Care Unit (NICU)	P. invasivos: CVC, VM, NPT, tubo toracico	Cultivo	> 72 h	CVC (p=0.02), VM (p=0.001)
8	Late-onset neonatal sepsis, risk factors and interventions: an analysis of recurrent outbreaks of Serratia marcescens, 2006e2011	Neonatales: edad (continua), peso (continua). Maternos: RPM. P. invasivos: CVC (continua), VM (continua)	Cultivo	> 72 h	Edad gestacional (OR 0.94 IC95% 0.93 -0.96), p<0.001), peso al nacer (OR 0.17 IC95% 0.089-0.317, p<0.001), CVC (OR 2.6 IC95% 1.7-2.0, p<0.001), VM (OR 1.6 IC95% 1.2-2.0, p<0.001)

Risk Factors

Four neonatal factors, two maternal factors, and twoinvasive procedures associated with late neonatal sepsis were studied. The most frequently described risk factors are premature rupture of the membranes, use of a central venous catheter, and the need for mechanical ventilation (four studies each). A meta-analysis was performed for a total of eight factors. The details of the factors included in the meta-analysis have been provided in Table N°2.

Table 2. Factores de riesgo incluidos en el metaanálisis para sepsis neonatal tardía.

Factores de riesgo	Comparación	n
Factores neonatales		
Sexo	Masculino, Femenino	3
Edad gestacional	<37 semanas, >37 semanas	2
Peso al nacer	<2500 g, >2500 g	3
Apgar 5'	<7, =7	2
Factores maternos		
Ruptura prematura de membranas	Si, No	4
Tipo de parto	Vaginal, Cesárea	2
Procedimientos invasivos		
Ventilación mecánica	Si, No	4
Catéter venoso central	Si, No	4

For neonatal factors, a meta-analysis was performed for four risk factors (Figure N°2) of which, male sex (3 studies – OR: 1.97 (0.26-14.59); p=0.03; I2 =80%), and prematurity (two studies – OR: 2.48 (1.13-5.45); p=0.04; I2 =72%), significantly increased the odds of late neonatal sepsis.

Factors that increased the probability of late neonatal sepsis but were not significant in the meta-analysis were low birth weight (three studies – OR: 2.50 (1.20-5.18); p=0.14; I2 =53%) and low Apgar at 5' (2 studies – OR: 1.47 (1.01-2.13); p=0.32; I^2=18%).

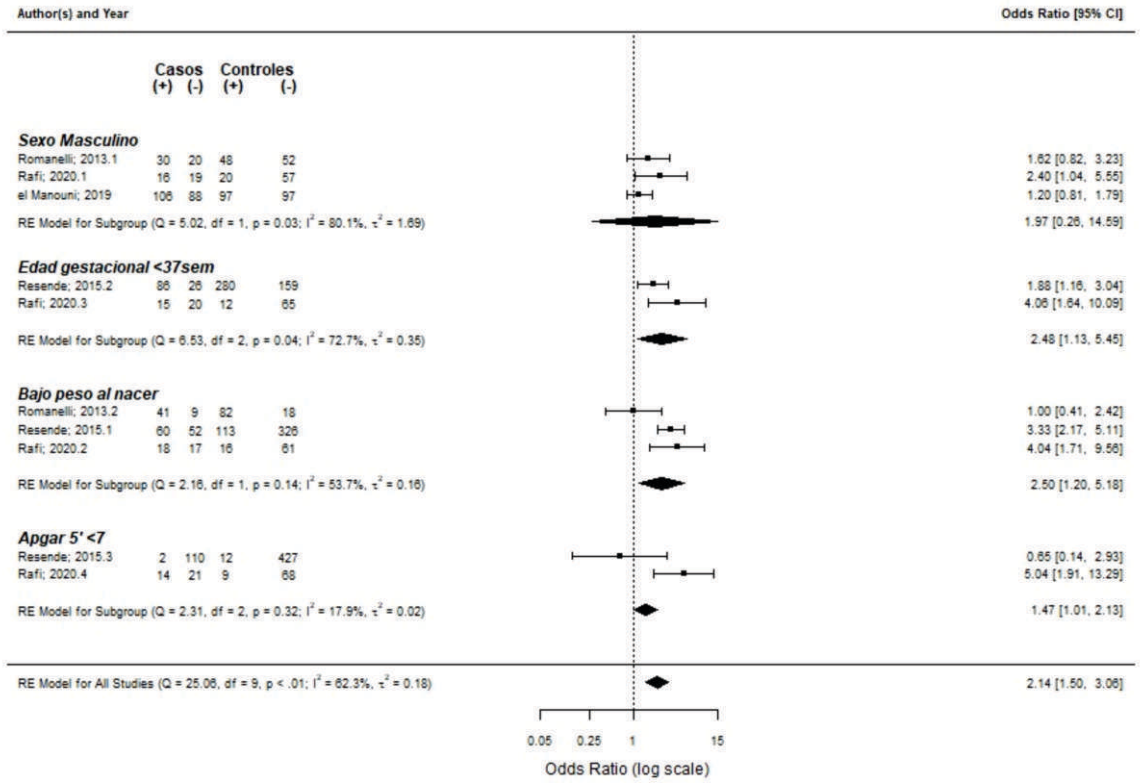

Figure N° 2. Forest plot showing a random-effects meta-analysis in male, preterm, low birth weight or depressed newborns at birth with and without late neonatal sepsis, respectively.

For maternal factors, a meta-analysis was performed for two factors. Premature rupture of membranes (four studies – OR: 1.04 (0.76 – 1.42); p=0.16; I2 =0%) increased the incidence of late neonatal sepsis. Vaginal delivery was not associated with late neonatal sepsis (three studies – OR: 0.94 (0.78 – 1.12); p=0.32; I2 =20%) (Figure N°3).

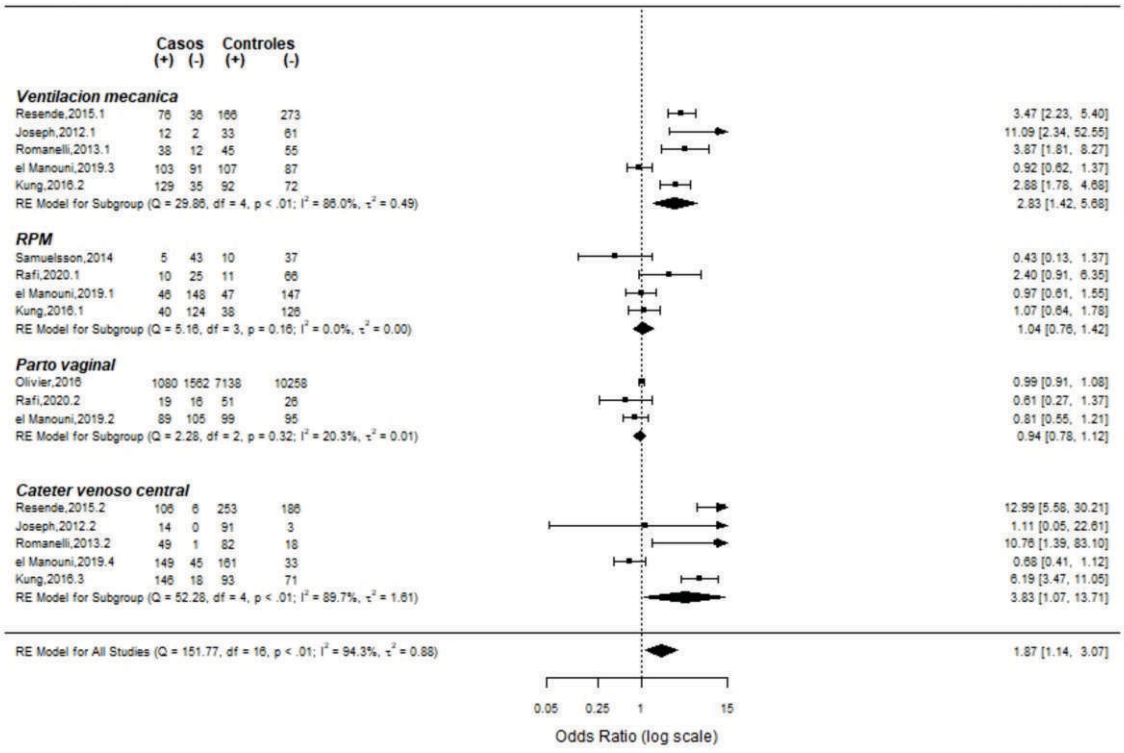

Figure N° 3. Forest plot showing a random-effects meta-analysis in newborns who require mechanical ventilation, vwho have a maternal history of PROM, who were born vaginally, or who have a central venous catheter, respectively, with and without late sepsis.

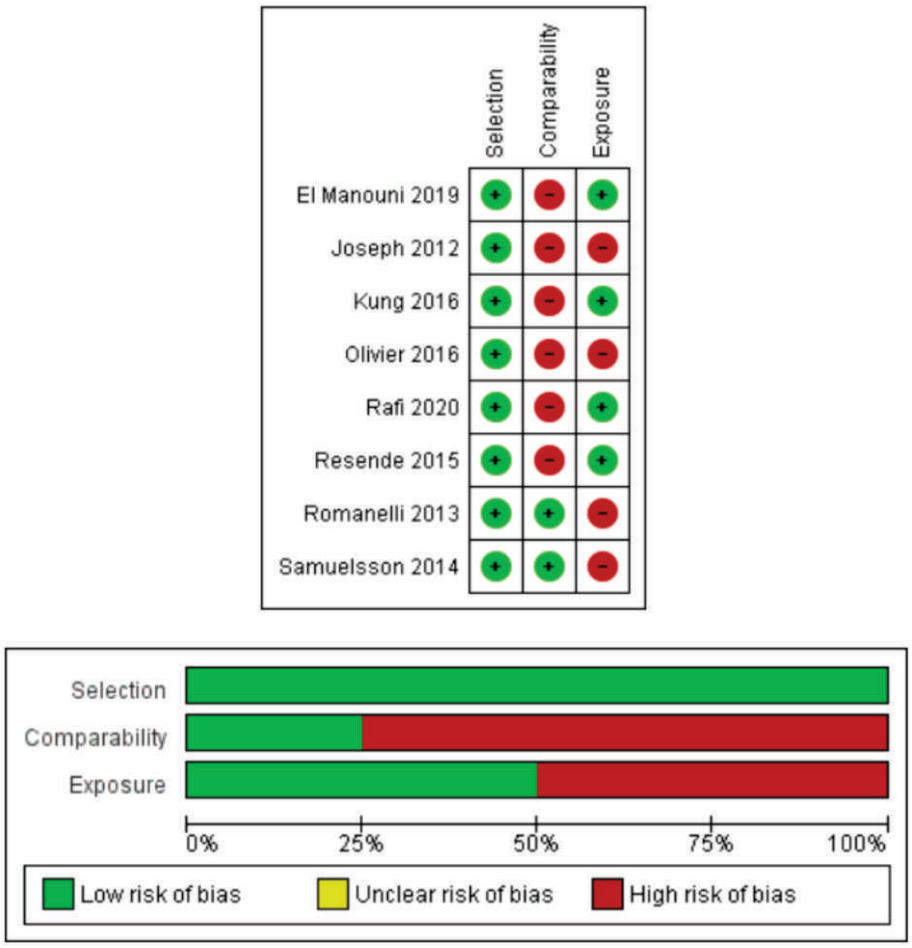

Figure 4. Gráfico mostrando el riesgo de sesgo.

Assessment of risk of bias

When performing a quality assessment using the NOS for cases and controls, four studies were rated good, two fair studies, and two poor studies). The category with the lowest rating was "comparability". None of the studies reported the use of a reporting checklist to describe their studies.

Certainty of the evidence

The GRADE methodology was used to assess the certainty of the evidence for this systematic review. We found that for all risk factors (neonatal, maternal, and invasive procedures), the evidence was of low certainty. This was mainly due to the risk of bias, inconsistency, and imprecision of the evidence.

DISCUSSION

This meta-analysis aimed to identify neonatal and maternal risk factors and invasive procedures performed on the newborn, such as central venous catheter placement, mechanical ventilation, parenteral nutrition, and chest tube, associated with the development of late neonatal sepsis described in medical literature for the last ten years. The study showed that male gender, prematurity, the use of a central venous catheter, and the need for mechanical ventilation significantly increased the odds of developing late neonatal sepsis. The results are consistent with other studies [11-15]. Knowing the risk factors would help in the prevention and early identification of late neonatal sepsis. There was variation in the case definitions as well as in the definition of late neonatal sepsis in the studies included in our review.

Similar variability has been found in the world literature on late neonatal sepsis. Most are defined as cases those neonates with symptoms and signs in addition to positive blood culture, and others are defined as cases those neonates with symptoms and signs and with laboratory tests without the need for a positive culture. Another difference between the studies was the cut-off point in time to define neonatal sepsis. Six studies define late sepsis as that which appears after 72 hours of life, which coincides with most antecedents. (11,16,17,18,) While two studies define it as that which appears after seven days to 28 days of life[11,16,17,18].

While two studies define it as that which appears after seven days to 28 days of life[9,19,20].

We found a higher incidence of sepsis among male neonates, possibly based on the 'male disadvantage hypothesis'. Regarding maternal factors, it was found that premature rupture of membranes increased the incidence of late neonatal sepsis, but it was not an independent risk factor, also described by other authors [10,19,17,20]. No association was found between the route of delivery and late neonatal sepsis as in other studies [21]. Male neonates are more sensitive to adverse perinatal and postnatal environmental conditions and are more likely to be born preterm and with lower birth weight, both of which increase the risk of neonatal sepsis [1]. Higher initial respiratory support required by male neonates may lead to worse outcomes[22,23-25].

Prematurity has also been implicated as a significant risk factor, as in other studies [7,9,26,27]. In this study, low birth weight and low Apgar at five' increased the incidence of late neonatal sepsis, although it was not an independent factor. This finding contrasts with some antecedents[16,17,28].

It is probably due to the low number of compared studies. Regarding maternal factors, it was found that premature rupture of membranes increased the incidence of late neonatal sepsis, but it was not an independent risk factor, as described by other authors [10,17,19,20]. No association was found between the route of delivery and late neonatal sepsis as in other studies[21].

As found in the medical literature and various studies, we identified that the use of invasive devices such as central venous catheters and endotracheal tubes are independent factors of late neonatal sepsis [16-18,29].

The present study presented some limitations. The limited number of studies available, as well as the type of studies included, correspond to cohorts and cases, and controls, which could increase the risk of bias. Likewise, we found high heterogeneity between the studies. As strengths, we have that the present study represents the first meta-analysis on factors associated with late neonatal sepsis, which highlights the need for further research on this topic. This work has followed the guide for systematic reviews PRISMA. and has been subjected to the GRADE evaluation. The level of evidence ranged from very low (four studies) to low (four studies).

CONCLUSIONS

In this systematic review of observational studies, it was found that male or premature newborns have a higher risk of developing late neonatal sepsis. Among the invasive procedures, we found that the use of a central venous catheter and the need for mechanical ventilation are independent factors of late neonatal sepsis.

No association was found between birth weight, low Apgar at five minutes, maternal history of premature rupture of membranes or vaginal delivery, and the development of late sepsis in newborns. There is a lack of evidence on the risk factors associated with late neonatal sepsis in Peru. Recognition of risk factors should help develop a preventive strategy against neonatal sepsis.

RECOMMENDATIONS

Efforts to reduce the neonatal mortality rate should focus on the management and prevention of prematurity, as well as paying special attention to male newborns because they are more vulnerable. It is recommended to optimize surveillance of nosocomial infections through management protocols for invasive procedures to reduce the incidence of neonatal sepsis. Solid research is required in the country of Peru in this regard to obtain updated statistics.

Author contributions: Allison Poquioma: data collection, study design, statistical interpretation, writing of the protocol and manuscript. Walter Mosquera: data collection. María Loo Valverde: study design, protocol review, manuscript review, Luis Roldán: statistical analysis, Víctor Vera: protocol review, supervision, Dr. Jhony De La Cruz: protocol review, manuscript review and supervision.

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Correspondence: *Allison Poquioma Hernandez.*
Address: *Av. Alfredo Benavides 5440, Santiago de Surco.*
Telephone number: *951209937*
E-mail: *apoquiomah@gmail.com*

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