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Outcome of twin-twin transfusion syndrome according to the Quintero stage of the disease: a systematic review and meta-analysis

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Short title: Outcome of TTTS by stage of disease

Keywords: twin-twin transfusion syndrome; TTTS; Quintero staging system; twins; monochorionic twin pregnancy

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ABSTRACT

Objectives: To report the outcomes of twin-twin transfusion syndrome (TTTS) according to Quintero staging system.

Methods: Medline, Embase and Cinahl databases were searched for studies reporting outcomes of TTTS stratified by Quintero staging (I-V). The primary outcome was the survival rate according to TTTS stage. The secondary outcomes were gestational age at birth (weeks), preterm birth (PTB) <34, 32 and 28 weeks of gestation and neonatal morbidity. Outcomes were reported according to different management options (expectant, laser therapy or amnioreduction) for stage I, including only cases treated with laser therapy for stages II-IV and only those managed expectantly for stage V. Random-effect head-to-head meta-analyses were used to analyze the extracted data.

Results: Twenty-~~five~~ six studies (~~2477~~ 2699 twin pregnancies) were included. 610 (~~24~~22.6%) were diagnosed at Quintero stage I, ~~619~~ 692 (25.6%) at stage II, ~~1003~~ 1146 (~~40~~42.5%) at stage III, 24~~7~~1 (9.2~~7~~%) at stage IV and 4 (0.1~~2~~%) at stage V. Survival of at least one twin occurred in ~~456/522 (~~86.9% (95% CI 84.0-89.7; 456 cases) of~~)~~ pregnancies at stage I, ~~436/504 (~~85~~4.9~~% (95% CI 79.1-90.1; 514 cases))~~ at stage II, ~~709/864 (78.9~~80.6% (95% CI 75.7-85.1; 865 cases) ~~)~~at stage III, ~~154/187 (79.8~~82.8% (95% CI 73.6-90.4; 172 cases))~~ at stage IV and ~~1/3 (33~~54.6~~3~~% (95% CI 24.8-82.6; 5 cases))~~ at stage V. The rate of pregnancies with no survivor was ~~69/564 (~~11.8% (95% CI 8.4-15.8; 69 cases))~~ at stage I, ~~68/504 (~~15.~~1~~% (95% CI 9.9-20.9; 76 cases))~~ at stage II, ~~145/864 (20.1~~18.6% (95% CI 14.2-23.4; 165 cases))~~ at stage III, ~~33/187 (20.5~~17.2% (95% CI 9.6-26.4; 33 cases))~~ at stage IV and ~~2/3 (66~~45.4.~~7~~% (95% CI 17.4-75.2; 4 cases))~~ at stage V. Gestational age at birth was similar in stage I-III TTTS, and gradually decreases in stage IV and V. Overall, the incidence of PTB and neonatal morbidity increases as the severity of TTTS increases, but data on these two outcomes were limited by the small sample size of the included studies. When stratifying the analysis of stage I TTTS according to the type of intervention, perinatal survival of at least one twin was 84.9% (95% CI 70.4-95.1; 94~~/112 pregnancies~~ cases) in cases managed expectantly, 86.7% (95% CI 82.6-90.4; 249~~/285 pregnancies~~cases) in those undergoing laser therapy and 92.2% (85% CI 84.2-97.6; 56~~/60 pregnancie~~ cases) in those after amnioreduction, while double survival was 67.9% (95% CI 57.0-77.9; 73~~/108 pregnancie~~ cases), 69.7% (95% CI 61.6-77.1; 203~~/285 pregnancie~~ cases) and 80.8% (95% CI 62.0-94.2; 49~~/60 pregnancie~~ cases) in the three groups, respectively.

Conclusion: The overall survival in MCDA pregnancies affected by TTTS is higher at earlier Quintero stages (I-II), but perinatal survival rates are reasonable even at stage III and IV when treated with laser therapy. Gestational age at birth was similar in stage I-III TTTS, and gradually decreases in stage IV and V treated with laser. In pregnancies affected by stage I TTTS, amnioreduction was

associated with a slightly higher survival compared to laser therapy and expectant management, although these findings might only be confirmed by future head-to-head, randomized trials.

INTRODUCTION

Monochorionic (MC) twin pregnancies are at increased risk of perinatal mortality and morbidity compared to dichorionic (DC) gestations, mostly due to conditions arising from their peculiar placental vascular arrangement, such as twin-twin transfusion syndrome (TTTS), twin anemia-polycythemia (TAPS) and twin reverse arterial perfusion (TRAP) sequence.[1-11]

Although the pathophysiology of TTTS has not been fully elucidated yet, an unbalanced flow through the inter-twin vascular anastomoses are critical for the development of TTTS, leading to progressive hemodynamic derangements mainly consisting of cardiac overload of the recipient and chronic hypoperfusion and hypoxemia in the donor twin.[2,12]

TTTS is commonly graded according to the ultrasound staging system proposed by Quintero in 1999 and consisting in five progressive stages characterized by the presence of oligohydramnios/ polyhydramnios sequence (stage I), absent visualization of the donor's bladder (stage II), Doppler anomalies (stage III), fetal hydrops (stage IV) and eventually fetal demise of one or both twins (stage V).[13] While the majority of stage I TTTS remains stable or regress even without intervention,[14-15] fetoscopic laser ablation of placental anastomoses is the treatment of choice for stages II-IV TTTS.[2,16] Anyway, data on perinatal mortality and morbidity stratified by Quintero staging system in monochorionic twin pregnancies affected by TTTS are still scant.

More recently, another classification system mainly focused upon the echocardiographic features of the recipient twin, known as the CHOP (Children's Hospital of Philadelphia) score, has been proposed to correlate with the Quintero staging system and clinical outcome of MC twins affected by TTTS, although its actual prognostic value is still debated.[17-18]

In general, the overall survival rates of 50-70% can be expected after fetoscopic laser for the treatment of TTTS, with a 30-50% chance of overall perinatal death and 5-20% chance of long-term neurological impairment.[2] However, these figures referred to the overall population of MC twins affected by TTTS, while the occurrence of the different adverse outcome according to the individual stage of the disease has not been consistently reported yet.

The aim of this systematic review was to report the outcome of TTTS according to the Quintero stage of the disease.

METHODS

Protocol, information sources and literature search

This review was performed according to an a-priori designed protocol and recommended for systematic reviews and meta-analysis.[19-21] Medline and Embase databases were searched electronically on October 2019 utilizing combinations of the relevant medical subject heading (MeSH) terms, key words, and word variants for "twin-twin transfusion syndrome", "monochorionic pregnancies", "ultrasound" and "outcome". The search and selection criteria were restricted to English language. Reference lists of relevant articles and reviews were hand searched for additional reports. Prisma guidelines were followed.[22-24] The study was registered with the PROSPERO database (registration number: CRD42020150971).

Outcomes measures, study selection and data collection

The primary outcome was the survival rate, defined as:

- No survival: defined as death of both twins before birth
- Single survivor: defined as the survival to birth of only one twin
- Double survival: defined as survival to birth of both twins
- Survival of at least one twin

Secondary outcomes were:

- Gestational age at birth (expressed in weeks)
- Respiratory morbidity (including respiratory distress syndrome, transient tachypnoea of the new-born, continuous positive airway pressure for at least 24 hours, mechanical ventilation, need for supplemental oxygen, pulmonary hypertension or bronchopulmonary dysplasia)
- Neurological morbidity (including seizures, intra-ventricular haemorrhage and periventricular leukomalacia of any grade detected on ultrasound scan)
- Severe neurological morbidity (including seizures, intra-ventricular haemorrhage grade III and IV and periventricular leukomalacia grades II and III detected on ultrasound scan)
- Composite morbidity, defined as the occurrence of either of the morbidities
- Preterm birth (PTB) <34 weeks of gestation
- Preterm birth (PTB) <32 weeks of gestation
- Preterm birth (PTB) <28 weeks of gestation

All the explored outcomes were reported for monochorionic diamniotic (MCDA) twins according to the Quintero staging system of the disease,[13] defined as:

- Stage I: defined as the presence of oligohydramnios (maximum vertical pocket, MVP <2 cm) in the donor and polyhydramnios (MVP>8 cm) in the recipient twin.
- Stage II: defined as the non-visualization of fetal bladder in donor twin over 60 minutes of observation.
- Stage III: defined upon the presence of Doppler abnormalities (absent or reversed umbilical artery diastolic flow, reversed ductus venosus a-wave flow, pulsatile umbilical vein flow).
- Stage IV: defined as the presence of hydrops in one or both twins.
- Stage V: defined as the occurrence of fetal demise in one or both twins.

We aimed to explore the occurrence of mortality and morbidity in the overall populations of twins and in the donor and recipient twin separately.

For pregnancies affected by stage I, we reported all the explored outcomes according to different management options (expectant management, laser therapy and amnioreduction). The reason for this choice was based upon the fact that the optimal management for these pregnancies has still to be ascertained.[14] For stage II-IV TTTS, only studies reporting the outcome of pregnancies treated with laser were considered suitable for the inclusion in the current systematic review. Finally, for cases affected by stage V, we report the outcome only for those cases managed expectantly. Studies including higher order multiple gestations, those including monochorionic monoamniotic (MCMA) twin pregnancies, structural or chromosomal anomalies and those from which data the observed outcomes stratified by the stage of the disease could not be extrapolated were excluded. Studies published before 2000 were also excluded, as we considered that advances in prenatal imaging techniques, improvements in the diagnosis and treatment of TTTS make them less relevant. Only full text articles were considered eligible for the inclusion; case reports, conference abstracts and case series with fewer than 5 cases were excluded in order to avoid publication bias.

Two authors (DDM, ADA) reviewed all abstracts independently. Agreement regarding potential relevance was reached by consensus. Full text copies of those papers were obtained, and the same two reviewers independently extracted relevant data regarding study characteristics and pregnancy outcome. Inconsistencies were discussed by the reviewers and consensus reached or by discussion with a third author. If more than one study was published for the same cohort with identical endpoints, the report containing the most comprehensive information on the population was included to avoid overlapping populations.

Quality assessment, risk of bias and statistical analysis

Quality assessment of the included studies was performed using the Newcastle-Ottawa Scale (NOS) for cohort studies. According to NOS, each study is judged on three broad perspectives: the selection of the study groups; the comparability of the groups; and the ascertainment of the outcome of interest.[25] Assessment of the selection of a study includes the evaluation of the representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure and the demonstration that the outcome of interest was not present at start of study. Assessment of the comparability of the study includes the evaluation of the comparability of cohorts on the basis of the design or analysis. Finally, the ascertainment of the outcome of interest includes the evaluation of the type of the assessment of the outcome of interest, length and adequacy of follow-up. According to NOS a study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Random-effect meta-analyses of proportions were used to combine data. For the purpose of the analysis, the denominator was represented by the number of twins per each group for the computation of survivors and morbidity, while the number of pregnancies for the assessment of PTB and the presence of at least one and two survivors. Funnel plots displaying the outcome rate from individual studies versus their precision (1/standard error) were carried out with an exploratory aim. Tests for funnel plot asymmetry were not used when the total number of publications included for each outcome was less than ten. In this case, the power of the tests is too low to distinguish chance from real asymmetry.[26-27]

Between-study heterogeneity was explored using the I^2 statistic, which represents the percentage of between-study variation that is due to heterogeneity rather than chance. A value of 0% indicates no observed heterogeneity, whereas I^2 values of $\geq$50% indicate a substantial level of heterogeneity. All analyses were performed using StatsDirect Statistical Software (StatsDirect Ltd Cambridge, United Kingdom).

RESULTS

Study selection and characteristics

1455 articles were identified, 60 were assessed with respect to their eligibility for inclusion and ~~25~~ 26 studies[28-53~~2~~] were included in the systematic review (Table 1, Figure 1, Supplementary Table 1). These ~~25~~ 26 studies included 2699 ~~2477~~ MCDA twin pregnancies affected by TTTS. Gestational age at diagnosis of TTTS was reported only by ten studies.[28,30,32-33,~~37~~38-~~39~~8,410,~~46~~5,~~48~~7,~~52~~1] Out of the 2699 ~~2477~~ pregnancies affected by TTTS, 610 (22.6%) were diagnosed at Quintero stage I, 692 (25.6%) at stage II, 1146 (42.5%) at stage III, 247 (9.2%) at stage IV and 4 (0.1%) at stage V.~~610 (24.6%) were diagnosed at Quintero stage I, 619 (25%) at stage II, 1003 (40.5%) at stage III, 241 (9.7%) at stage IV and 4 (0.2%) at stage V.~~

Stage I TTTS were treated with laser therapy in 62.4% (285/457 pregnancies), amnioreduction in 13.1% (60/457 pregnancies) and expectant management in 24.5% (112/457 pregnancies) of cases, respectively.

The majority of stage II-IV TTTS were treated with laser therapy, except for one study[30] which evaluated the outcome of expectant management even at higher stages of the disease; three studies[~~40~~39,410,~~52~~1] in which TTTS was treated with amnioreduction and/or septostomy; one study[~~50~~49] in which both laser therapy and amnioreduction were performed for stage II-IV TTTS. In stage V TTTS, one study[30] evaluated the outcome of expectant management, while the other one[52] does not specify whether expectant management or amnioreduction and/or septostomy were performed.

The results of the quality assessment of the included studies using the NOS scale are presented in Table 2. Most of the included studies showed an overall good score regarding the selection and comparability of study groups, and for ascertainment of the outcome of interest. The main weaknesses of these studies were their retrospective design, small sample size and heterogeneity of outcomes observed. Furthermore, studies reporting information of morbidity were affected by the very small number of included cases and even smaller number of events, thus making it difficult to extrapolate objective evidence on the actual incidence of this outcome in the different stages of the disease.

Synthesis of the results

Stage I

Sixteen studies[28,29-31,33,~~35~~4,~~37~~6-~~40~~39,~~42~~1,~~46~~5,~~48~~7,~~51~~0-~~53~~2] reported information on stage I TTTS.

There was no survival of either twin in 11.8% of pregnancies affected by stage I TTTS (95% CI 8.4-15.8; 69/564), while one and two survivors were reported in 17.5% (95% CI 14.4-20.9; 95/560) and 70% (95% CI 65.4-74.4; 396/560) of cases, respectively. At least one twin survived in 86.9% of pregnancies (95% CI 84-89.7; 456/522) (Table 3; Figure 2).

Mean gestational age at delivery was 31.1 weeks (95% CI 29.9-32.2) (Table 4; Supplementary Figure S1a). PTB <34 and <32 weeks of gestation complicated 50% (95% CI 12.6-98.7; 1/2), and 27.1% (95% CI 13.9-42.8; 9/34) of pregnancies complicated by stage I TTTS, respectively, while there was no case of PTB <28 weeks of gestation among the included cases (Table 5).

Three studies reported data on neonatal morbidity.[32,46,53] Composite morbidity was reported in 22.9% (95% CI 0.1-68.49; 44/188) twins affected by stage I TTTS, neurological and respiratory morbidity complicated 1.5% (95% CI 0.02-5.1; 2/148) and 19.1% (95% CI 11.3-29.1; 16/84) of twins after birth (Table 6).

When stratified the analysis according to the different management options - expectant, laser therapy or amnioreduction - the mean gestational age at diagnosis was 21.0, 21.4 and 23.5 weeks of gestation, respectively (Supplementary Table 2). No twin survived to birth in 15.1% (95% CI 4.9-29.6; 18/112) in those cases managed expectantly, in 13.2% (95% CI 9.6-17.4; 36/285) of those having laser treatment and in 7.8% (95% CI 2.5-15.8; 4/60) of those undergoing amnioreduction. Survival of at least one twin was reported in 84.9% (95% CI 70.4-95.1; 94/112) of cases managed expectantly, 86.7% (95% CI 82.6-90.4; 249/285) of those having laser therapy and in 92.2% (95% CI 84.2-97.6; 56/60) of those undergoing amnioreduction. Conversely, it was not possible to perform a comprehensive pooled data synthesis on the occurrence of morbidity according to different management options in view of the very small number of studies exploring this outcome (Table 7; Figure 3).

Stage II

~~Twelve~~ Fourteen studies[29,31,34-38,42,43,49,50,51,53] reported information on stage II TTTS.

There was no survival of either twin in 15.0% (95% CI 9.9-21.2; 68/504) of pregnancies, while one and two survivors were reported in 23.4% (95% CI 17.6-29.6; 109/504) and 61.9% (95% CI 51.6-69.9; 327/504) of cases, respectively. At least one survivor was reported in 84.9% (95% CI 78.8-90.1; 436/504) of pregnancies affected by TTTS and treated with laser therapy (Table 3; Figure 2).

Mean gestational age at treatment was 20.3, while mean gestational age at delivery was 31.4 weeks (29.5-33.3) (Table 4; Supplementary Table 3; Supplementary Figure S1b). PTB <34, <32 and 28 weeks of gestation occurred in 31.3% (95% CI 10.0-58.0; 4/12), 42.8% (95% CI 29.4-56.9; 20/47) and 17.6% (95% CI 1.6-45.3; 2/12) of pregnancies, respectively (Table 5).

Two studies reported data on neonatal morbidity.[43,53] Overall, composite morbidity affected 28.8% (95% CI 6.8-97.0; 39/124) of twins after birth. Neurological morbidity occurred in 5.2% (95% CI 0.3-15.4; 6/124), while respiratory morbidity in 70.4% (95% CI 56.4-82-0; 38/54) of twins (Table 6).

Stage III

~~Thirteen~~ Fifteen studies[29,31,34-38,42-45,49,50,51,53] ~~studies[29,31,34-37,41-44,48,50,52]~~ reported information on stage III TTTS.

No survival was observed in ~~20.1~~18.6% (95% CI 1~~5.0~~4.2-2~~8.5~~3.4; ~~145~~165/~~864~~1040) of twin pregnancies affected by stage III TTTS and treated with laser, while one and two survivors were reported in ~~36.8~~35.0% (95% CI ~~30.7~~29.3-4~~3.2~~0.8; ~~299~~341/1040/~~864~~) and ~~42.3~~45.4% (95% CI 3~~4.8~~8.2-~~49.9~~52.7; ~~420~~534/~~864~~1040) of cases, respectively. At least one survivor was reported in ~~78.9~~80.6% of pregnancies (95% CI 7~~3.3~~5.7-85~~4~~.1; ~~709~~865/~~864~~1040) (Table 3; Figure 2).

Mean gestational age at treatment was 20.2, while mean gestational age at delivery was 31.4 weeks (30.0-32.7) (Table 4; Supplementary Table 3; Supplementary Figure S1c), while PTB <34, <32 and <28 weeks of gestations complicated 37.3% (95% CI 5.2-78.0; 12/30), 53.3% (95% CI 36.1-70.2; 32/58) and 9.7% (95% CI 2.0-22.3; 3/30) of cases, respectively (Table 5).

Two studies reported data on neonatal morbidity.[~~43~~,~~32~~] Composite morbidity affected 29.3% (95% CI 18.6-91.8; 48/127) twins after stage III TTTS. Finally, neurological and respiratory morbidity were reported in 6.7% (95% CI 2.9-12.1; 8/127) and 64.8% (95% CI 52.5-75.8; 46/71) of twins after birth (Table 6).

Stage IV

Fifteen studies[29,31,34-38,42-45,49,50,51,53] ~~Thirteen studies[29,31,34-37,41-44,48,50,52]~~ reported data on stage IV TTTS.

There was no survival of either twin in ~~20.5~~17.2% of pregnancies (95% CI ~~11.6~~9.6-~~30.5~~26.4; 33/~~187~~205), while one and two survivors were reported in 2~~9.2~~7.7% (95% CI ~~23.0~~21.9-~~35.8~~33.9; ~~53~~55/~~187~~205) and ~~48.3~~53.7% (95% CI ~~34.6~~40.2-~~62.2~~66.8; ~~101~~117/~~187~~205) of cases, respectively. At least one survivor was reported in ~~79.8~~82.8% of pregnancies (95% CI ~~69.5~~73.6-~~88.4~~90.4; ~~154~~172/~~187~~205) (Table 3; Figure 2).

Mean gestational age at treatment was 21.4, while mean gestational age at delivery was 29.9 weeks (28.5-31.4) weeks (Table 4; Supplementary Table 3; Supplementary Figure S1d), while PTB <34 and <32 weeks of gestation was reported in 46.5% (95% CI 15.5-79.2; 3/7), 59.9% (95% CI 37.9-80.0; 11/18), while there was no pregnancy delivered <28 weeks (PP: 0, 95% CI 0-30.7; 0/7) (Table 5).

Two studies reported data on neonatal morbidity.[~~43~~,~~32~~] Composite neonatal morbidity complicated 24.1% (95% CI 0.02-71.8; 21/64) of twins after birth, while neurological and respiratory morbidity were reported in 5.9% (95% CI 1.6-13.0; 3/64), and 47.6% (95% CI 32.0-63.6; 20/42) of cases, respectively (Table 6).

Stage V

Outcome ascertainment of MC twin pregnancies affected by stage V TTTT was affected by the very small number of included cases (94 pregnancies) and even smaller number of events, with only two studies[30,52] reporting information of the outcomes observed in the present systematic review.

Death of the co-twin occurred in 66.745.4% of pregnancies (95% CI 9.417.4-75.299.2; 42/93), while the remaining twin survived in 33.354.6% (95% CI 240.8-8290.6; 51/93) of cases (Table 3; Figure 2).

Mean gestational age at delivery was 26.5 (24.4-28.5) weeks (Table 4; supplementary figure S1e), while there was no study reporting data on morbidity and on the incidence of PTB at different gestational age windows.

Sub-group analyses

It was not possible to perform a comprehensive pooled data synthesis on the incidence of mortality and morbidity in the donor and recipient twin separately and according to the gestational age at occurrence of the TTTS due to the very small number of included studies reporting these data.

DISCUSSION

Main findings

The findings from this systematic review show that the perinatal survival of twin pregnancies complicated by TTTS seems to be higher in the first stages (I and II) of the disease, although it remains high even in its later phases (stage III and IV). Conversely, the perinatal mortality is higher in stage V. ~~Survival of at least one twin occurred in 86.9% of cases at stage I, 84.9% at stage II, 78.9% at stage III, 79.8% at stage IV and 33.3% at stage V TTTS, while no survival of either twin was reported in 11.8%, 15.1%, 20.1%, 20.5% and 33.3% of cases, respectively.~~ Gestational age at birth was similar in stage I-III TTTS, and gradually decreases in stage IV and V. Overall, the incidence of PTB and neonatal morbidity increases as the severity of TTTS increases, but these data ~~on these two outcomes~~ were limited by the small sample size of the included studies.

When considering the different management options in pregnancies complicated by stage I TTTS (expectant management, laser therapy or amnioreduction) the perinatal survival of at least one twin was ~~84.9% in those managed expectantly, 86.7% in those undergoing laser therapy and 92.2% in those after amnioreduction~~similar, thus making it difficult to extrapolate a robust evidence on the optimal type of intervention when stage I TTTS is diagnosed ~~on ultrasound~~.

Strengths and limitations

The small number of cases in some of the included studies, their retrospective non-randomized design, lack of standardized criteria for the antenatal surveillance, management and timing of delivery of MCDA twin pregnancies complicated by TTTS represent the major limitations of this systematic review. Furthermore, some of the included studies reported data on the outcomes of stage II-IV TTTS treated with different management options - even though fetoscopic laser therapy is currently the gold standard for this subset of pregnancies – and it was not always possible to extrapolate information on cases treated with laser therapy only. It was not possible to draw any convincing evidence on stage V TTTS or on neonatal morbidity due to the negligible number of cases evaluated in this review. Another major limitation of the present review was the lack of stratification of the analysis according to the cardiovascular status of the affected twins, that~~.~~ p~~P~~revious studies have claimed as a potential ~~role of several fetal echocardiographic parameters in~~ predictor of~~ing~~ the outcome of ~~twin~~ pregnancies affected by TTTS, irrespective of the Quintero stage ~~of the disease~~. Unfortunately, the large majority of these studies did not report information according to TTTS different stages, thus making it impossible to integrate such information in the outcome ascertainment. Finally, we could not explore the effect of individual Doppler indices in affecting the outcome of twins undergoing laser as this information was not provided by the large majority of included studies.

Interpretation of findings and comparison with other published evidence

The findings from this study are in line with those reported in 2016 by Khalil et al[14] in terms of overall survival in Quintero stage I TTTS, but differ from the above-mentioned meta-analysis and a previous systematic review by Rossi and D'Addario[15] when stratifying outcomes according to the type of intervention. When focusing on higher Quintero stages treated with laser therapy, our results in terms of perinatal survival are concordant with those reported in the most recent and largest series[5~~43~~-5~~65~~] that showed a double survival rate ranging between 50-65% and that of at least one twin survival of 75-90% at stage II-IV. Likewise, our findings are also consistent with a recent systematic review reporting perinatal outcome of pregnancies affected by TTTS treated with laser therapy over the past 25 years, in which the double survival rate was 62%, while at least one survivor was reported in up to 88% in the subgroup analysis of studies published between 2011 and 2014.[5~~76~~]

Our results showed similar incidence of neonatal neurological morbidity at birth, compared with a previous meta-analysis by Rossi et al who reported an incidence of less than 10% and was comparable at Quintero stage II-IV, while it was lower at stage I.[5~~87~~]

Clinical and research implications

While laser therapy is considered the gold standard for stage II-IV TTTS,[2] the optimal management for Quintero stage I TTTS is still a matter of debate, as t~~. To date, t~~here are no published randomized controlled trials (RCT) exploring different management options~~. in stage I TTTS.~~

The findings from this review showed that, although perinatal survival of at least one twin was almost similar among the three management options, amnioreduction was associated with a slightly higher survival of both twins and lower chance of double fetal loss. These results should be interpreted with caution because the included studies were not designed to compare these strategies and were not powered for most of the observed outcomes. Amnioreduction is not exempt of ~~the~~ procedure-related complications, such as unintended septostomy, preterm premature rupture of membranes, abruption or infection~~,~~.[2] ~~Of note,~~and the rate of progression of stage I TTTS was reported to be 30% when amnioreduction was the first-line therapy, compared with none in ~~the~~ pregnancies treated with laser.[15] ~~In this scenario, f~~Further head-to-head RCTs are needed in order to elucidate the optimal management in pregnancies affected by stage I TTTS.

Fetoscopic selective laser ablation of anastomotic vessels followed by equatorial dichorionization (the Solomon technique) is currently recommended as the best available approach to treat stage II-IV TTTS between 16 and 26 weeks of gestation.[2] Our review showed that the overall survival was higher at earlier Quintero stages (I-II), ~~but~~ and the perinatal survival rates were still satisfying even at stage III and IV~~., particularly when considering at least one survivor.~~

In the present study, respiratory and neurological morbidities were intuitively lower at stage I TTTS (any management), while increased at stage II-IV (treated with laser), with respiratory morbidity affecting the majority of twins and neurological morbidity impairing up to 9% of newborns. The etiology of cerebral morbidity is still uncertain, as neurodevelopmental outcome was shown to be similar in monochorionic twins treated with laser therapy ~~for TTTS~~ and dichorionic control subjects, thus leading to the hypothesis that neurological impairment could rather represent a detrimental effect which is inherent in prematurity.[5~~98~~]

Conclusion

The overall survival in MCDA pregnancies complicated by TTTS is higher at earlier Quintero stages (I-II) than stage III and IV. Gestational age at birth was similar in stage I-III TTTS, and gradually decreases in stage IV and V.

Further ~~large randomized trials~~RCTs and long-term follow up studies are needed in order to elucidate the optimal ~~type of~~ management of pregnancies affected by stage I TTTS and to quantify the risk of neurological disability according to the severity of ~~the~~ disease.

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Table 1. General characteristics of the included studies.

Author	Year	Country	Study design	Period considered	GA at diagnosis*	GA at treatment*	Outcomes observed	Pregnancies (n)
Washburn[28]	2018	USA	Retrospective	2006-2016	20.8 (3.7)	No treatment	GA at birth, mortality	30
Barbosa[29]	2018	Brazil	Prospective	2012-2016	NR	20.7 (2.9)	GA at birth, PTB, mortality	24
Duryea[30]	2016	USA	Retrospective	1997-2013	24 (17-21)	No treatment	GA at birth, mortality	20
Chang[31]	2016	China	Retrospective	2005-2014	NR	20.6 (2.7)	GA at birth, mortality	100
Hinch[32]	2016	Australia	Retrospective	2007-2013	20.7 (19-23.1)	NR	GA at birth, mortality, morbidity	28
Emery[33]	2016	USA	Retrospective	2005-2014	21.5 (2.7)	NR	GA at birth, mortality	124
Eschbach[34]	2016	The Netherlands	Retrospective	2007-2013	NR	19.7 (17.9-22.2)	GA at birth, mortality	
Has[35]	2014	Turkey	Retrospective	2006-2013	NR	21 (16-26)	GA at birth, mortality	85
Ruano[36]	2013	Spain-USA-Brazil	Retrospective	2010-2012	NR	20 (15.4-26)	Mortality	102
Swiatkowska-Freund[37]	2012	Poland	Prospective	2005-2010	NR	20 (16-26)	Mortality	94
Chmait[38]	2011	USA	Prospective	2002-2010	20.6 (2.4)	NR	GA at birth, mortality	682
Bebbington[39]	2010	USA	Retrospective	2005-2006	20.9 (0.4)	No treatment	GA at birth, mortality	42
Fichera[40]	2010	Italy	Retrospective	1999-2006	NR	21.4 (19.3-24.5)	Mortality	34
Korpraphong[41]	2010	Thailand	Retrospective	2000-2009	22.9 (15-32)	No treatment	Mortality	25
Meriki[42]	2010	Australia	Retrospective	2003-2008	NR	20 (16-25)	Mortality	79
Morris[43]	2010	United Kingdom	Prospective	2004-2009	NR	20.2 (18-22)	GA at birth, mortality	164
Cincotta[44]	2009	Australia	Prospective	2002-2007	NR	21 (18-28)	GA at birth, mortality, morbidity	100
Ruano[45]	2009	Brazil	Prospective	2006-2008	NR	22 (19-26)	GA at birth, mortality	19
Wagner[46]	2009	The Netherlands	Retrospective	2000-2007	21	21.2 (2.6)	GA at birth, mortality	50
Middeldorp[47]	2007	Belgium-The Netherlands	Prospective	2000-2004	NR	20 (16-26)	GA at birth, mortality	100
O'Donoghue[48]	2007	United Kingdom	Retrospective	2000-2006	21.3 (15.4-31.5)	No treatment	GA at birth, mortality	46
Sepulveda[49]	2007	Chile	Prospective	2003-2006	NR	21 (17-25)	GA at birth, PTB, mortality	33
Gray[50]	2006	Australia	Retrospective	1994-2003	NR	20 (19-22)	Mortality	58
Huber[51]	2006	Germany	Prospective	1999-2003	NR	20.7 (15.9-25.3)	GA at birth, mortality	200
Duncombe[52]	2004	Australia	Prospective	1992-2002	22.1 (19.7-25.4)	NR	GA at birth, mortality	69
Quintero[53]	2003	USA	Prospective	NR	NR	21.1	PTB, mortality, morbidity	173

GA, gestational age; NR, not reported; PTB, preterm birth; *: data reported as mean (standard deviations) or median (range).

Table 2. Quality assessment of the included studies according to Newcastle-Ottawa Scale (NOS) for cohort studies; a study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Author	Year	Selection	Comparability	Outcome
Washburn[28]	2018	★★★	★	★★
Barbosa[29]	2018	★★★	★	★★
Duryea[30]	2016	★★★	★	★★
Chang[31]	2016	★★★	★	★★
Hinch[32]	2016	★★★	★	★★
Emery[33]	2016	★★★	★	★★
Eschbach[34]	2016	★★★	★	★★
Has[35]	2014	★★★	★	★★
Ruano[36]	2013	★★★	★	★★
Swiatkowska-Freund[37]	2012	★★★	★	★★
Chmait[38]	2011	★★★	★	★★
Bebbington[39]	2010	★★★	★	★★
Fichera[40]	2010	★★★	★	★★
Korpraphong[41]	2010	★★★	★	★★
Meriki[42]	2010	★★★	★	★★
Morris[43]	2010	★★★	★	★★
Cincotta[44]	2009	★★★	★	★★
Ruano[45]	2009	★★★	★	★★
Wagner[46]	2009	★★★	★	★★
Middeldorp[47]	2007	★★★	★	★★
O'Donoghue[48]	2007	★★★	★	★★
Sepulveda[49]	2007	★★★	★	★★
Gray[50]	2006	★★★	★	★★
Huber[51]	2006	★★★	★	★★
Duncombe[52]	2004	★★★	★	★★
Quintero[53]	2003	★★★	★	★★

Table 3. Pooled proportions for single and double survival in MCDA twin pregnancies affected by TTTS according to the stage of the disease. (95% confidence intervals, CI, between parentheses).

Outcome	Studies (n)	Fetuses (n/N)	Raw proportions (95% CI)	I^2 (%)	Pooled Proportions (95% CI)
	Stage I				
No survivor	16	69/564	11.3 (8.8-14.1)	36.1	11.8 (8.4-15.8)
One survivor	15	95/560	16.9 (14.0-20.3)	3.6	17.5 (14.4-20.9)
At least one survivor	15	456/522	87.4 (84.2-90.1)	0.3	86.9 (84.0-89.7)
Two survivors	15	396/560	70.7 (66.8-74.5)	18.4	70.0 (65.4-74.4)
	Stage II				
No survivor~~No survivor~~	14~~12~~	76/590~~68/504~~	12.9 (10.4-15.8)~~13.5 (10.6-16.8)~~	65.4~~61.2~~	15.0 (9.9-20.9)~~15.1 (9.8-21.2)~~
One survivor~~One survivor~~	14~~12~~	123/590~~109/504~~	20.6 (17.8-24.3)~~21.6 (18.1-25.5)~~	43.5~~49.3~~	22.4 (17.6-27.7)~~23.4 (17.8-29.6)~~
At least one survivor~~At least one survivor~~	14~~12~~	514/590~~436/504~~	87.1 (84.2-89.6)~~86.5 (83.2-89.4)~~	65.4~~61.2~~	85.0 (79.1-90.1)~~84.9 (78.8-90.2)~~
Two survivors~~Two survivors~~	14~~12~~	391/590~~327/504~~	54.1 (50.0-58.1)~~64.9 (60.5-69.0)~~	74~~72.8~~	66.4 (52.6-69.9)~~60.9 (51.6-69.9)~~
	Stage III~~Stage III~~				
No survivor~~No survivor~~	15~~13~~	165/1040~~145/864~~	15.9 (13.8-18.2)~~16.8 (14.3-19.4)~~	65.8~~68.3~~	18.6 (14.2-23.4)~~20.1 (15.0-25.8)~~
One survivor~~One survivor~~	15~~13~~	341/1040~~299/864~~	32.8 (30.0-35.7)~~34.6 (31.4-37.9)~~	66.9~~65.3~~	35.0 (29.3-40.8)~~36.8 (30.7-43.2)~~
At least one survivor~~At least one survivor~~	15~~13~~	865/1040~~709/864~~	83.2 (80.8-85.3)~~82.1 (79.3-84.6)~~	66~~67.2~~	80.6 (75.7-85.1)~~78.9 (73.3-84.1)~~
Two survivors~~Two survivors~~	15~~13~~	534/1040~~420/864~~	51.4 (48.3-54.4)~~48.6 (45.2-52.0)~~	78.4~~75.5~~	45.4 (38.2-52.7)~~42.3 (34.8-49.9)~~
	Stage IV~~Stage IV~~				
No survivor~~No survivor~~	15~~13~~	33/205~~33/187~~	16.1 (11.7-21.8)~~17.6 (12.5-23.4)~~	56.3~~55.8~~	17.2 (9.6-26.4)~~20.5 (11.6-30.5)~~
One survivor~~One survivor~~	15~~13~~	55/205~~53/187~~	26.9 (21.2-33.9)~~28.3 (22.0-35.4)~~	0~~0~~	27.7 (21.9-33.9)~~29.2 (23.0-35.8)~~
At least one survivor~~At least one survivor~~	15~~13~~	172/205~~154/187~~	83.9 (78.6-88.3)~~82.4 (76.1-87.5)~~	56.3~~55.8~~	82.8 (73.6-90.4)~~79.8 (69.5-88.4)~~
Two survivors~~Two survivors~~	15~~13~~	117/205~~101/187~~	57.1 (50.2-63.7)~~54.0 (46.6-61.3)~~	70.2~~68.6~~	53.7 (40.2-66.8)~~48.3 (34.6-62.2)~~
	Stage V~~Stage V~~				
No survivor~~No survivor~~	2*~~1~~	4/92~~/3~~	44.4 (18.0-73.3)~~66.7 (9.4-99.2)~~	0-	45.4 (17.4-75.2)-
One survivor~~One survivor~~	2*~~1~~	5/91~~/3~~	55.6 (26.7-81.1)~~33.3 (0.8-90.6)~~	0-	54.6 (24.8-82.6)-

*one study[30] evaluated the outcome of expectant management, while the other one[52] does not specify whether expectant management or amnioreduction and/or septostomy were performed.

Table 4. Mean gestational age at birth in MCDA twin pregnancies affected by TTTS, according to the stage of the disease. Weighted means were obtained combining data from individual studies to perform meta-analyses of single-group continuous data. For the sake of completeness, raw means were also reported. (CI = Confidence Interval).

Disease stage	Studies (n)	Fetuses (Total sample)	Raw mean (95% CI)	Weighted mean (95% CI)	I^2 (%)
Stage I	13	527	30.9 (28.9-32.9)	31.1 (29.9-32.2)	87.4
Stage II	11	437	31.4 (29.9-32.9)	31.4 (29.5-33.3)	91.7
Stage III	12	750	31.3 (30.0-32.7)	31.4 (30.0-32.7)	87.2
Stage IV	12	170	30.1 (28.5-31.8)	29.9 (28.5-31.4)	47.3
Stage V	2	4	26.7 (22.2-31.1)	26.5 (24.4-28.5)	0

Table 5. Pooled proportions for morbidity in MCDA twins affected by TTTS according to the stage of the disease. (95% confidence intervals, CI, between parentheses).

Outcome	Studies (n)	Fetuses (n/N)	Raw proportions (95% CI)	I^2 (%)	Pooled Proportions (95% CI)
Stage I					
PTB <34 weeks	1	1/2	50.0 (12.6-98.7)	-	-
PTB <32 weeks	2	9/34	26.5 (12.9-44.4)	0	27.1 (13.9-42.8)
PTB <28 weeks	1	0/2	0.0 (0-84.2)	-	-
Stage II					
PTB <34 weeks	2	4/12	33.3 (9.9-65.1)	72.3	31.3 (10.0-58.0)
PTB <32 weeks	3	20/47	42.6 (28.3-57.8)	0	42.8 (29.4-56.9)
PTB <28 weeks	2	2/12	16.7 (2.1-48.4)	17.7	17.6 (1.6-45.3)
Stage III					
PTB <34 weeks	2	12/30	40.0 (22.7-59.4)	82.6	37.3 (5.2-78.0)
PTB <32 weeks	3	32/58	55.2 (41.5-68.3)	44.3	53.3 (36,1-70.2)
PTB <28 weeks	2	3/30	10.0 (2.1-26.5)	68.1	9.7 (2.0-22.3)
Stage IV					
PTB <34 weeks	2	3/7	42.9 (9.9-81.6)	73.8	46.5 (15.5-79.2)
PTB <32 weeks	3	11/18	61.1 (35.7-82.7)	0	59.9 (37.9-80.0)
PTB <28 weeks	2	0/7	0.0 (0-41.0)	0	0.0 (0-30.7)
Stage V					
PTB <34 weeks	-	-	-	-	-
PTB <32 weeks	-	-	-	-	-
PTB <28 weeks	-	-	-	-	-

Table 6. Pooled proportions for morbidity in MCDA twins affected by TTTS according to the stage of the disease. (95% confidence intervals, CI, between parentheses).

Outcome	Studies (n)	Fetuses (n/N)	Raw proportions (95% CI)	I^2 (%)	Pooled Proportions (95% CI)
Stage I					
Composite morbidity	3	44/188	23.4 (17.6-30.19)	97.7	22.9 (0.1-68.49)
Neurological morbidity (overall)	2	2/148	1.4 (1.6-4.8)	42.8	1.5 (0.02-5.1)
Severe neurological morbidity	2	2/84	2.4 (0.2-8.3)	-	-
Respiratory morbidity	1	16/84	19.1 (11.3-29.1)	-	-
Stage II					
Composite morbidity	2	39/124	31.5 (23.4-40.4)	98.9	28.8 (6.8-97.0)
Neurological morbidity (overall)	2	6/124	4.8 (1.8-10.2)	74.2	5.2 (0.3-15.4)
Severe neurological morbidity	1	5/54	9.3 (3.1-20.3)	-	-
Respiratory morbidity	1	38/54	70.4 (56.4-82.0)	-	-
Stage III					
Composite morbidity	2	48/127	37.8 (29.3-46.8)	98.5	29.3 (18.6-91.8)
Neurological morbidity (overall)	2	8/127	6.3 (2.8-12.0)	12.3	6.7 (2.9-12.1)
Severe neurological morbidity	1	6/71	8.5 (3.2-17.5)	-	-
Respiratory morbidity	1	46/71	64.8 (52.5-75.8)	-	-
Stage IV					
Composite morbidity	2	21/64	32.8 (21.6-45.7)	93.4	24.1 (0.02-71.8)
Neurological morbidity (overall)	2	3/64	4.7 (1.0-13.1)	0	5.9 (1.6-13.0)
Severe neurological morbidity	1	2/42	7.1 (1.5-19.5)	-	-
Respiratory morbidity	1	20/42	47.6 (32.0-63.6)	-	-
Admission to NICU					
Stage V					
Composite morbidity	-	-	-	-	-
Neurological morbidity (overall)	-	-	-	-	-
Severe neurological morbidity	-	-	-	-	-
Respiratory morbidity	-	-	-	-	-

Table 7. Pooled proportions for single and double survival in MCDA twin pregnancies affected by stage I TTTS according to different management options (expectant, laser and amnioreduction). (95% confidence intervals, CI, between parentheses).

Outcome	Studies (n)	Fetuses (n/N)	Raw proportions (95% CI)	I^2 (%)	Pooled Proportions (95% CI)
	Stage I (expectant)				
No survivor	4	18/112	16.1 (9.8-24.2)	67	15.1 (4.9-29.6)
One survivor	3	18/108	16.7 (10.2-25.1)	0	17.5 (11.0-25.1)
At least one survivor	4	94/112	83.9 (75.8-90.2)	67	84.9 (70.4-95.1)
Two survivors	3	73/108	67.6 (57.9-76.3)	29.4	67.9 (57.0-77.9)
	Stage I (laser therapy)				
No survivor	10	36/285	12.6 (9.0-17.1)	0	13.2 (9.6-17.4)
One survivor	10	46/285	16.1 (12.1-20.9)	0	16.7 (12.6-21.2)
At least one survivor	10	249/285	87.4 (82.9-91.0)	0	86.7 (82.6-90.4)
Two survivors	10	203/285	71.2 (65.6-76.4)	37.9	69.7 (61.6-77.1)
	Stage I (amnioreduction)				
No survivor	3	4/60	6.7 (1.8-16.2)	0	7.8 (2.5-15.8)
One survivor	3	7/60	11.7 (4.8-22.6)	62.1	12.9 (2.5-30.1)
At least one survivor	3	56/60	93.3 (83.8-98.2)	0	92.2 (84.2-97.6)~~59~~
Two survivors	3	49/60	81.7 (69.6-90.5)	61.7	80.8 (62.0-94.2)

Figure legend

Figure 1. Systematic review flowchart

Figure 2. Stage I-V TTTS survival rate bar chart

Figure 3. Stage I TTTS survival rate according to different management options bar chart

Outcome of twin-twin transfusion syndrome according to the Quintero stage of the disease: a systematic review and meta-analysis

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ABSTRACT

Objectives: To report the outcomes of twin-twin transfusion syndrome (TTTS) according to Quintero staging system.

Methods: Medline, Embase and Cinahl databases were searched for studies reporting outcomes of TTTS stratified by Quintero staging (I-V). The primary outcome was the survival rate according to TTTS stage. The secondary outcomes were gestational age at birth (weeks), preterm birth (PTB) <34, 32 and 28 weeks of gestation and neonatal morbidity. Outcomes were reported according to different management options (expectant, laser therapy or amnioreduction) for stage I, including only cases treated with laser therapy for stages II-IV and only those managed expectantly for stage V. Random-effect head-to-head meta-analyses were used to analyze the extracted data.

Results: Twenty-six studies (2699 twin pregnancies) were included. 610 (22.6%) were diagnosed at Quintero stage I, 692 (25.6%) at stage II, 1146 (42.5%) at stage III, 247 (9.2%) at stage IV and 4 (0.1%) at stage V. Survival of at least one twin occurred in 86.9% (95% CI 84.0-89.7; 456 cases) of pregnancies at stage I, 85% (95% CI 79.1-90.1; 514 cases) at stage II, 80.6% (95% CI 75.7-85.1; 865 cases) at stage III, 82.8% (95% CI 73.6-90.4; 172 cases) at stage IV and 54.6% (95% CI 24.8-82.6; 5 cases) at stage V. The rate of pregnancies with no survivor was 11.8% (95% CI 8.4-15.8; 69 cases) at stage I, 15% (95% CI 9.9-20.9; 76 cases) at stage II, 18.6% (95% CI 14.2-23.4; 165 cases) at stage III, 17.2% (95% CI 9.6-26.4; 33 cases) at stage IV and 45.4% (95% CI 17.4-75.2; 4 cases) at stage V. Gestational age at birth was similar in stage I-III TTTS, and gradually decreases in stage IV and V. Overall, the incidence of PTB and neonatal morbidity increases as the severity of TTTS increases, but data on these two outcomes were limited by the small sample size of the included studies. When stratifying the analysis of stage I TTTS according to the type of intervention, perinatal survival of at least one twin was 84.9% (95% CI 70.4-95.1; 94 cases) in cases managed expectantly, 86.7% (95% CI 82.6-90.4; 249 cases) in those undergoing laser therapy and 92.2% (85% CI 84.2-97.6; 56 cases) in those after amnioreduction, while double survival was 67.9% (95% CI 57.0-77.9; 73 cases), 69.7% (95% CI 61.6-77.1; 203 cases) and 80.8% (95% CI 62.0-94.2; 49 cases) in the three groups, respectively.

Conclusion: The overall survival in MCDA pregnancies affected by TTTS is higher at earlier Quintero stages (I-II), but perinatal survival rates are reasonable even at stage III and IV when treated with laser therapy. Gestational age at birth was similar in stage I-III TTTS, and gradually decreases in stage IV and V treated with laser. In pregnancies affected by stage I TTTS, amnioreduction was associated with a slightly higher survival compared to laser therapy and expectant management, although these findings might only be confirmed by future head-to-head, randomized trials.

INTRODUCTION

Monochorionic (MC) twin pregnancies are at increased risk of perinatal mortality and morbidity compared to dichorionic (DC) gestations, mostly due to conditions arising from their peculiar placental vascular arrangement, such as twin-twin transfusion syndrome (TTTS), twin anemia-polycythemia (TAPS) and twin reverse arterial perfusion (TRAP) sequence.[1-11]

Although the pathophysiology of TTTS has not been fully elucidated yet, an unbalanced flow through the inter-twin vascular anastomoses are critical for the development of TTTS, leading to progressive hemodynamic derangements mainly consisting of cardiac overload of the recipient and chronic hypoperfusion and hypoxemia in the donor twin.[2,12]

TTTS is commonly graded according to the ultrasound staging system proposed by Quintero in 1999 and consisting in five progressive stages characterized by the presence of oligohydramnios/ polyhydramnios sequence (stage I), absent visualization of the donor's bladder (stage II), Doppler anomalies (stage III), fetal hydrops (stage IV) and eventually fetal demise of one or both twins (stage V).[13] While the majority of stage I TTTS remains stable or regress even without intervention,[14-15] fetoscopic laser ablation of placental anastomoses is the treatment of choice for stages II-IV TTTS.[2,16] Anyway, data on perinatal mortality and morbidity stratified by Quintero staging system in monochorionic twin pregnancies affected by TTTS are still scant.

More recently, another classification system mainly focused upon the echocardiographic features of the recipient twin, known as the CHOP (Children's Hospital of Philadelphia) score, has been proposed to correlate with the Quintero staging system and clinical outcome of MC twins affected by TTTS, although its actual prognostic value is still debated.[17-18]

In general, the overall survival rates of 50-70% can be expected after fetoscopic laser for the treatment of TTTS, with a 30-50% chance of overall perinatal death and 5-20% chance of long-term neurological impairment.[2] However, these figures referred to the overall population of MC twins affected by TTTS, while the occurrence of the different adverse outcome according to the individual stage of the disease has not been consistently reported yet.

The aim of this systematic review was to report the outcome of TTTS according to the Quintero stage of the disease.

METHODS

Protocol, information sources and literature search

This review was performed according to an a-priori designed protocol and recommended for systematic reviews and meta-analysis.[19-21] Medline and Embase databases were searched electronically on October 2019 utilizing combinations of the relevant medical subject heading (MeSH) terms, key words, and word variants for "twin-twin transfusion syndrome", "monochorionic pregnancies", "ultrasound" and "outcome". The search and selection criteria were restricted to English language. Reference lists of relevant articles and reviews were hand searched for additional reports. Prisma guidelines were followed.[22-24] The study was registered with the PROSPERO database (registration number: CRD42020150971).

Outcomes measures, study selection and data collection

The primary outcome was the survival rate, defined as:

- No survival: defined as death of both twins before birth
- Single survivor: defined as the survival to birth of only one twin
- Double survival: defined as survival to birth of both twins
- Survival of at least one twin

Secondary outcomes were:

- Gestational age at birth (expressed in weeks)
- Respiratory morbidity (including respiratory distress syndrome, transient tachypnoea of the new-born, continuous positive airway pressure for at least 24 hours, mechanical ventilation, need for supplemental oxygen, pulmonary hypertension or bronchopulmonary dysplasia)
- Neurological morbidity (including seizures, intra-ventricular haemorrhage and periventricular leukomalacia of any grade detected on ultrasound scan)
- Severe neurological morbidity (including seizures, intra-ventricular haemorrhage grade III and IV and periventricular leukomalacia grades II and III detected on ultrasound scan)
- Composite morbidity, defined as the occurrence of either of the morbidities
- Preterm birth (PTB) <34 weeks of gestation
- Preterm birth (PTB) <32 weeks of gestation
- Preterm birth (PTB) <28 weeks of gestation

All the explored outcomes were reported for monochorionic diamniotic (MCDA) twins according to the Quintero staging system of the disease,[13] defined as:

- Stage I: defined as the presence of oligohydramnios (maximum vertical pocket, MVP <2 cm) in the donor and polyhydramnios (MVP>8 cm) in the recipient twin.
- Stage II: defined as the non-visualization of fetal bladder in donor twin over 60 minutes of observation.
- Stage III: defined upon the presence of Doppler abnormalities (absent or reversed umbilical artery diastolic flow, reversed ductus venosus a-wave flow, pulsatile umbilical vein flow).
- Stage IV: defined as the presence of hydrops in one or both twins.
- Stage V: defined as the occurrence of fetal demise in one or both twins.

We aimed to explore the occurrence of mortality and morbidity in the overall populations of twins and in the donor and recipient twin separately.

For pregnancies affected by stage I, we reported all the explored outcomes according to different management options (expectant management, laser therapy and amnioreduction). The reason for this choice was based upon the fact that the optimal management for these pregnancies has still to be ascertained.[14] For stage II-IV TTTS, only studies reporting the outcome of pregnancies treated with laser were considered suitable for the inclusion in the current systematic review. Finally, for cases affected by stage V, we report the outcome only for those cases managed expectantly. Studies including higher order multiple gestations, those including monochorionic monoamniotic (MCMA) twin pregnancies, structural or chromosomal anomalies and those from which data the observed outcomes stratified by the stage of the disease could not be extrapolated were excluded. Studies published before 2000 were also excluded, as we considered that advances in prenatal imaging techniques, improvements in the diagnosis and treatment of TTTS make them less relevant. Only full text articles were considered eligible for the inclusion; case reports, conference abstracts and case series with fewer than 5 cases were excluded in order to avoid publication bias.

Two authors (DDM, ADA) reviewed all abstracts independently. Agreement regarding potential relevance was reached by consensus. Full text copies of those papers were obtained, and the same two reviewers independently extracted relevant data regarding study characteristics and pregnancy outcome. Inconsistencies were discussed by the reviewers and consensus reached or by discussion with a third author. If more than one study was published for the same cohort with identical endpoints, the report containing the most comprehensive information on the population was included to avoid overlapping populations.

Quality assessment, risk of bias and statistical analysis

Quality assessment of the included studies was performed using the Newcastle-Ottawa Scale (NOS) for cohort studies. According to NOS, each study is judged on three broad perspectives: the selection of the study groups; the comparability of the groups; and the ascertainment of the outcome of interest.[25] Assessment of the selection of a study includes the evaluation of the representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure and the demonstration that the outcome of interest was not present at start of study. Assessment of the comparability of the study includes the evaluation of the comparability of cohorts on the basis of the design or analysis. Finally, the ascertainment of the outcome of interest includes the evaluation of the type of the assessment of the outcome of interest, length and adequacy of follow-up. According to NOS a study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Random-effect meta-analyses of proportions were used to combine data. For the purpose of the analysis, the denominator was represented by the number of twins per each group for the computation of survivors and morbidity, while the number of pregnancies for the assessment of PTB and the presence of at least one and two survivors. Funnel plots displaying the outcome rate from individual studies versus their precision (1/standard error) were carried out with an exploratory aim. Tests for funnel plot asymmetry were not used when the total number of publications included for each outcome was less than ten. In this case, the power of the tests is too low to distinguish chance from real asymmetry.[26-27]

Between-study heterogeneity was explored using the I^2 statistic, which represents the percentage of between-study variation that is due to heterogeneity rather than chance. A value of 0% indicates no observed heterogeneity, whereas I^2 values of $\geq$50% indicate a substantial level of heterogeneity. All analyses were performed using StatsDirect Statistical Software (StatsDirect Ltd Cambridge, United Kingdom).

RESULTS

Study selection and characteristics

1455 articles were identified, 60 were assessed with respect to their eligibility for inclusion and 26 studies[28-53] were included in the systematic review (Table 1, Figure 1, Supplementary Table 1).

These 26 studies included 2699 MCDA twin pregnancies affected by TTTS. Gestational age at diagnosis of TTTS was reported only by ten studies.[28,30,32-33,38-39,41,46,48,52] Out of the 2699 pregnancies affected by TTTS, 610 (22.6%) were diagnosed at Quintero stage I, 692 (25.6%) at stage II, 1146 (42.5%) at stage III, 247 (9.2%) at stage IV and 4 (0.1%) at stage V.

Stage I TTTS were treated with laser therapy in 62.4% (285/457 pregnancies), amnioreduction in 13.1% (60/457 pregnancies) and expectant management in 24.5% (112/457 pregnancies) of cases, respectively.

The majority of stage II-IV TTTS were treated with laser therapy, except for one study[30] which evaluated the outcome of expectant management even at higher stages of the disease; three studies[40,41,52] in which TTTS was treated with amnioreduction and/or septostomy; one study[50] in which both laser therapy and amnioreduction were performed for stage II-IV TTTS. In stage V TTTS, one study[30] evaluated the outcome of expectant management, while the other one[52] does not specify whether expectant management or amnioreduction and/or septostomy were performed.

The results of the quality assessment of the included studies using the NOS scale are presented in Table 2. Most of the included studies showed an overall good score regarding the selection and comparability of study groups, and for ascertainment of the outcome of interest. The main weaknesses of these studies were their retrospective design, small sample size and heterogeneity of outcomes observed. Furthermore, studies reporting information of morbidity were affected by the very small number of included cases and even smaller number of events, thus making it difficult to extrapolate objective evidence on the actual incidence of this outcome in the different stages of the disease.

Synthesis of the results

Stage I

Sixteen studies[28,29-31,33,35,37-40,42,46,48,51-53] reported information on stage I TTTS.

There was no survival of either twin in 11.8% of pregnancies affected by stage I TTTS (95% CI 8.4-15.8; 69/564), while one and two survivors were reported in 17.5% (95% CI 14.4-20.9; 95/560) and 70% (95% CI 65.4-74.4; 396/560) of cases, respectively. At least one twin survived in 86.9% of pregnancies (95% CI 84-89.7; 456/522) (Table 3; Figure 2).

Mean gestational age at delivery was 31.1 weeks (95% CI 29.9-32.2) (Table 4; Supplementary Figure S1a). PTB <34 and <32 weeks of gestation complicated 50% (95% CI 12.6-98.7; 1/2), and 27.1%

(95% CI 13.9-42.8; 9/34) of pregnancies complicated by stage I TTTS, respectively, while there was no case of PTB <28 weeks of gestation among the included cases (Table 5).

Three studies reported data on neonatal morbidity.[32,46,53] Composite morbidity was reported in 22.9% (95% CI 0.1-68.49; 44/188) twins affected by stage I TTTS, neurological and respiratory morbidity complicated 1.5% (95% CI 0.02-5.1; 2/148) and 19.1% (95% CI 11.3-29.1; 16/84) of twins after birth (Table 6).

When stratified the analysis according to the different management options - expectant, laser therapy or amnioreduction - the mean gestational age at diagnosis was 21.0, 21.4 and 23.5 weeks of gestation, respectively (Supplementary Table 2). No twin survived to birth in 15.1% (95% CI 4.9-29.6; 18/112) in those cases managed expectantly, in 13.2% (95% CI 9.6-17.4; 36/285) of those having laser treatment and in 7.8% (95% CI 2.5-15.8; 4/60) of those undergoing amnioreduction. Survival of at least one twin was reported in 84.9% (95% CI 70.4-95.1; 94/112) of cases managed expectantly, 86.7% (95% CI 82.6-90.4; 249/285) of those having laser therapy and in 92.2% (95% CI 84.2-97.6; 56/60) of those undergoing amnioreduction. Conversely, it was not possible to perform a comprehensive pooled data synthesis on the occurrence of morbidity according to different management options in view of the very small number of studies exploring this outcome (Table 7; Figure 3).

Stage II

Fourteen studies[29,31,34-38,42-44,49,50,51,53] reported information on stage II TTTS.

There was no survival of either twin in 15.0% (95% CI 9.9-20.9; 76/590) of pregnancies, while one and two survivors were reported in 22.4% (95% CI 17.6-27.7; 123/590) and 66.4% (95% CI 52.6-69.9; 391/590) of cases, respectively. At least one survivor was reported in 85.0% (95% CI 79.1-90.1; 514/590) of pregnancies affected by TTTS and treated with laser therapy (Table 3; Figure 2).

Mean gestational age at treatment was 20.3, while mean gestational age at delivery was 31.4 weeks (29.5-33.3) (Table 4; Supplementary Table 3; Supplementary Figure S1b). PTB <34, <32 and 28 weeks of gestation occurred in 31.3% (95% CI 10.0-58.0; 4/12), 42.8% (95% CI 29.4-56.9; 20/47) and 17.6% (95% CI 1.6-45.3; 2/12) of pregnancies, respectively (Table 5).

Two studies reported data on neonatal morbidity.[44,53] Overall, composite morbidity affected 28.8% (95% CI 6.8-97.0; 39/124) of twins after birth. Neurological morbidity occurred in 5.2% (95% CI 0.3-15.4; 6/124), while respiratory morbidity in 70.4% (95% CI 56.4-82-0; 38/54) of twins (Table 6).

Stage III

Fifteen studies[29,31,34-38,42-45,49,50,51,53] reported information on stage III TTTS.

No survival was observed in 18.6% (95% CI 14.2-23.4; 165/1040) of twin pregnancies affected by stage III TTTS and treated with laser, while one and two survivors were reported in 35.0% (95% CI 29.3-40.8; 341/1040) and 45.4% (95% CI 38.2-52.7; 534/1040) of cases, respectively. At least one survivor was reported in 80.6% of pregnancies (95% CI 75.7-85.1; 865/1040) (Table 3; Figure 2).
Mean gestational age at treatment was 20.2, while mean gestational age at delivery was 31.4 weeks (30.0-32.7) (Table 4; Supplementary Table 3; Supplementary Figure S1c), while PTB <34, <32 and <28 weeks of gestations complicated 37.3% (95% CI 5.2-78.0; 12/30), 53.3% (95% CI 36.1-70.2; 32/58) and 9.7% (95% CI 2.0-22.3; 3/30) of cases, respectively (Table 5).
Two studies reported data on neonatal morbidity.[44,53] Composite morbidity affected 29.3% (95% CI 18.6-91.8; 48/127) twins after stage III TTTS. Finally, neurological and respiratory morbidity were reported in 6.7% (95% CI 2.9-12.1; 8/127) and 64.8% (95% CI 52.5-75.8; 46/71) of twins after birth (Table 6).

Stage IV

Fifteen studies[29,31,34-38,42-45,49,50,51,53] reported data on stage IV TTTS.
There was no survival of either twin in 17.2% of pregnancies (95% CI 9.6-26.4; 33/205), while one and two survivors were reported in 27.7% (95% CI 21.9-33.9; 55/205) and 53.7% (95% CI 40.2-66.8; 117/205) of cases, respectively. At least one survivor was reported in 82.8% of pregnancies (95% CI 73.6-90.4; 172/205) (Table 3; Figure 2).
Mean gestational age at treatment was 21.4, while mean gestational age at delivery was 29.9 weeks (28.5-31.4) weeks (Table 4; Supplementary Table 3; Supplementary Figure S1d), while PTB <34 and <32 weeks of gestation was reported in 46.5% (95% CI 15.5-79.2; 3/7), 59.9% (95% CI 37.9-80.0; 11/18), while there was no pregnancy delivered <28 weeks (PP: 0, 95% CI 0-30.7; 0/7) (Table 5).
Two studies reported data on neonatal morbidity.[44,53] Composite neonatal morbidity complicated 24.1% (95% CI 0.02-71.8; 21/64) of twins after birth, while neurological and respiratory morbidity were reported in 5.9% (95% CI 1.6-13.0; 3/64), and 47.6% (95% CI 32.0-63.6; 20/42) of cases, respectively (Table 6).

Stage V

Outcome ascertainment of MC twin pregnancies affected by stage V TTTT was affected by the very small number of included cases (9 pregnancies) and even smaller number of events, with only two studies[30,52] reporting information of the outcomes observed in the present systematic review.
Death of the co-twin occurred in 45.4% of pregnancies (95% CI 17.4-75.2; 4/9), while the remaining twin survived in 54.6% (95% CI 24.8-82.6; 5/9) of cases (Table 3; Figure 2).

Mean gestational age at delivery was 26.5 (24.4-28.5) weeks (Table 4; supplementary figure S1e), while there was no study reporting data on morbidity and on the incidence of PTB at different gestational age windows.

Sub-group analyses

It was not possible to perform a comprehensive pooled data synthesis on the incidence of mortality and morbidity in the donor and recipient twin separately and according to the gestational age at occurrence of the TTTS due to the very small number of included studies reporting these data.

DISCUSSION

Main findings

The findings from this systematic review show that the perinatal survival of twin pregnancies complicated by TTTS seems to be higher in the first stages (I and II) of the disease, although it remains high even in its later phases (stage III and IV). Conversely, the perinatal mortality is higher in stage V. Gestational age at birth was similar in stage I-III TTTS, and gradually decreases in stage IV and V. Overall, the incidence of PTB and neonatal morbidity increases as the severity of TTTS increases, but these data were limited by the small sample size of the included studies.

When considering the different management options in pregnancies complicated by stage I TTTS (expectant management, laser therapy or amnioreduction) the perinatal survival of at least one twin was similar, thus making it difficult to extrapolate a robust evidence on the optimal type of intervention when stage I TTTS is diagnosed.

Strengths and limitations

The small number of cases in some of the included studies, their retrospective non-randomized design, lack of standardized criteria for the antenatal surveillance, management and timing of delivery of MCDA twin pregnancies complicated by TTTS represent the major limitations of this systematic review. Furthermore, some of the included studies reported data on the outcomes of stage II-IV TTTS treated with different management options - even though fetoscopic laser therapy is currently the gold standard for this subset of pregnancies – and it was not always possible to extrapolate information on cases treated with laser therapy only. It was not possible to draw any convincing evidence on stage V TTTS or on neonatal morbidity due to the negligible number of cases evaluated in this review. Another major limitation of the present review was the lack of stratification of the analysis according to the cardiovascular status of the affected twins, that previous studies have claimed as a potential predictor of the outcome of pregnancies affected by TTTS, irrespective of the Quintero stage. Unfortunately, the large majority of these studies did not report information according to TTTS different stages, thus making it impossible to integrate such information in the outcome ascertainment. Finally, we could not explore the effect of individual Doppler indices in affecting the outcome of twins undergoing laser as this information was not provided by the large majority of included studies.

Interpretation of findings and comparison with other published evidence

The findings from this study are in line with those reported in 2016 by Khalil et al[14] in terms of overall survival in Quintero stage I TTTS, but differ from the above-mentioned meta-analysis and a previous systematic review by Rossi and D'Addario[15] when stratifying outcomes according to the type of

intervention. When focusing on higher Quintero stages treated with laser therapy, our results in terms of perinatal survival are concordant with those reported in the most recent and largest series[54-56] that showed a double survival rate ranging between 50-65% and that of at least one twin survival of 75-90% at stage II-IV. Likewise, our findings are also consistent with a recent systematic review reporting perinatal outcome of pregnancies affected by TTTS treated with laser therapy over the past 25 years, in which the double survival rate was 62%, while at least one survivor was reported in up to 88% in the subgroup analysis of studies published between 2011 and 2014.[57]

Our results showed similar incidence of neonatal neurological morbidity at birth, compared with a previous meta-analysis by Rossi et al who reported an incidence of less than 10% and was comparable at Quintero stage II-IV, while it was lower at stage I.[58]

Clinical and research implications

While laser therapy is considered the gold standard for stage II-IV TTTS,[2] the optimal management for Quintero stage I TTTS is still a matter of debate, as there are no published randomized controlled trials (RCT) exploring different management options.

The findings from this review showed that, although perinatal survival of at least one twin was almost similar among the three management options, amnioreduction was associated with a slightly higher survival of both twins and lower chance of double fetal loss. These results should be interpreted with caution because the included studies were not designed to compare these strategies and were not powered for most of the observed outcomes. Amnioreduction is not exempt of procedure-related complications, such as unintended septostomy, preterm premature rupture of membranes, abruption or infection,[2] and the rate of progression of stage I TTTS was reported to be 30% when amnioreduction was the first-line therapy, compared with none in pregnancies treated with laser.[15] Further head-to-head RCTs are needed in order to elucidate the optimal management in pregnancies affected by stage I TTTS.

Fetoscopic selective laser ablation of anastomotic vessels followed by equatorial dichorionization (the Solomon technique) is currently recommended as the best available approach to treat stage II-IV TTTS between 16 and 26 weeks of gestation.[2] Our review showed that the overall survival was higher at earlier Quintero stages (I-II), and the perinatal survival rates were still satisfying even at stage III and IV.

In the present study, respiratory and neurological morbidities were intuitively lower at stage I TTTS (any management), while increased at stage II-IV (treated with laser), with respiratory morbidity affecting the majority of twins and neurological morbidity impairing up to 9% of newborns. The etiology of cerebral morbidity is still uncertain, as neurodevelopmental outcome was shown to be

similar in monochorionic twins treated with laser therapy and dichorionic control subjects, thus leading to the hypothesis that neurological impairment could rather represent a detrimental effect which is inherent in prematurity.[59]

Conclusion

The overall survival in MCDA pregnancies complicated by TTTS is higher at earlier Quintero stages (I-II) than stage III and IV. Gestational age at birth was similar in stage I-III TTTS, and gradually decreases in stage IV and V.

Further RCTs and long-term follow up studies are needed in order to elucidate the optimal management of pregnancies affected by stage I TTTS and to quantify the risk of neurological disability according to the severity of disease.

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Table 1. General characteristics of the included studies.

Author	Year	Country	Study design	Period considered	GA at diagnosis*	GA at treatment*	Outcomes observed	Pregnancies (n)
Washburn[28]	2018	USA	Retrospective	2006-2016	20.8 (3.7)	No treatment	GA at birth, mortality	30
Barbosa[29]	2018	Brazil	Prospective	2012-2016	NR	20.7 (2.9)	GA at birth, PTB, mortality	24
Duryea[30]	2016	USA	Retrospective	1997-2013	24 (17-21)	No treatment	GA at birth, mortality	20
Chang[31]	2016	China	Retrospective	2005-2014	NR	20.6 (2.7)	GA at birth, mortality	100
Hinch[32]	2016	Australia	Retrospective	2007-2013	20.7 (19-23.1)	NR	GA at birth, mortality, morbidity	28
Emery[33]	2016	USA	Retrospective	2005-2014	21.5 (2.7)	NR	GA at birth, mortality	124
Eschbach[34]	2016	The Netherlands	Retrospective	2007-2013	NR	19.7 (17.9-22.2)	GA at birth, mortality	
Has[35]	2014	Turkey	Retrospective	2006-2013	NR	21 (16-26)	GA at birth, mortality	85
Ruano[36]	2013	Spain-USA-Brazil	Retrospective	2010-2012	NR	20 (15.4-26)	Mortality	102
Swiatkowska-Freund[37]	2012	Poland	Prospective	2005-2010	NR	20 (16-26)	Mortality	94
Chmait[38]	2011	USA	Prospective	2002-2010	20.6 (2.4)	NR	GA at birth, mortality	682
Bebbington[39]	2010	USA	Retrospective	2005-2006	20.9 (0.4)	No treatment	GA at birth, mortality	42
Fichera[40]	2010	Italy	Retrospective	1999-2006	NR	21.4 (19.3-24.5)	Mortality	34
Korpraphong[41]	2010	Thailand	Retrospective	2000-2009	22.9 (15-32)	No treatment	Mortality	25
Meriki[42]	2010	Australia	Retrospective	2003-2008	NR	20 (16-25)	Mortality	79
Morris[43]	2010	United Kingdom	Prospective	2004-2009	NR	20.2 (18-22)	GA at birth, mortality	164
Cincotta[44]	2009	Australia	Prospective	2002-2007	NR	21 (18-28)	GA at birth, mortality, morbidity	100
Ruano[45]	2009	Brazil	Prospective	2006-2008	NR	22 (19-26)	GA at birth, mortality	19
Wagner[46]	2009	The Netherlands	Retrospective	2000-2007	21	21.2 (2.6)	GA at birth, mortality	50
Middeldorp[47]	2007	Belgium-The Netherlands	Prospective	2000-2004	NR	20 (16-26)	GA at birth, mortality	100
O'Donoghue[48]	2007	United Kingdom	Retrospective	2000-2006	21.3 (15.4-31.5)	No treatment	GA at birth, mortality	46
Sepulveda[49]	2007	Chile	Prospective	2003-2006	NR	21 (17-25)	GA at birth, PTB, mortality	33
Gray[50]	2006	Australia	Retrospective	1994-2003	NR	20 (19-22)	Mortality	58
Huber[51]	2006	Germany	Prospective	1999-2003	NR	20.7 (15.9-25.3)	GA at birth, mortality	200
Duncombe[52]	2004	Australia	Prospective	1992-2002	22.1 (19.7-25.4)	NR	GA at birth, mortality	69
Quintero[53]	2003	USA	Prospective	NR	NR	21.1	PTB, mortality, morbidity	173

GA, gestational age; NR, not reported; PTB, preterm birth; *: data reported as mean (standard deviations) or median (range).

Table 2. Quality assessment of the included studies according to Newcastle-Ottawa Scale (NOS) for cohort studies; a study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Author	Year	Selection	Comparability	Outcome
Washburn[28]	2018	★★★	★	★★
Barbosa[29]	2018	★★★	★	★★
Duryea[30]	2016	★★★	★	★★
Chang[31]	2016	★★★	★	★★
Hinch[32]	2016	★★★	★	★★
Emery[33]	2016	★★★	★	★★
Eschbach[34]	2016	★★★	★	★★
Has[35]	2014	★★★	★	★★
Ruano[36]	2013	★★★	★	★★
Swiatkowska-Freund[37]	2012	★★★	★	★★
Chmait[38]	2011	★★★	★	★★
Bebbington[39]	2010	★★★	★	★★
Fichera[40]	2010	★★★	★	★★
Korpraphong[41]	2010	★★★	★	★★
Meriki[42]	2010	★★★	★	★★
Morris[43]	2010	★★★	★	★★
Cincotta[44]	2009	★★★	★	★★
Ruano[45]	2009	★★★	★	★★
Wagner[46]	2009	★★★	★	★★
Middeldorp[47]	2007	★★★	★	★★
O'Donoghue[48]	2007	★★★	★	★★
Sepulveda[49]	2007	★★★	★	★★
Gray[50]	2006	★★★	★	★★
Huber[51]	2006	★★★	★	★★
Duncombe[52]	2004	★★★	★	★★
Quintero[53]	2003	★★★	★	★★

Table 3. Pooled proportions for single and double survival in MCDA twin pregnancies affected by TTTS according to the stage of the disease. (95% confidence intervals, CI, between parentheses).

Outcome	Studies (n)	Fetuses (n/N)	Raw proportions (95% CI)	I^2 (%)	Pooled Proportions (95% CI)
	Stage I				
No survivor	16	69/564	11.3 (8.8-14.1)	36.1	11.8 (8.4-15.8)
One survivor	15	95/560	16.9 (14.0-20.3)	3.6	17.5 (14.4-20.9)
At least one survivor	15	456/522	87.4 (84.2-90.1)	0.3	86.9 (84.0-89.7)
Two survivors	15	396/560	70.7 (66.8-74.5)	18.4	70.0 (65.4-74.4)
	Stage II				
No survivor	14	76/590	12.9 (10.4-15.8)	65.4	15.0 (9.9-20.9)
One survivor	14	123/590	20.6 (17.8-24.3)	43.5	22.4 (17.6-27.7)
At least one survivor	14	514/590	87.1 (84.2-89.6)	65.4	85.0 (79.1-90.1)
Two survivors	14	391/590	54.1 (50.0-58.1)	74	66.4 (52.6-69.9)
	Stage III				
No survivor	15	165/1040	15.9 (13.8-18.2)	65.8	18.6 (14.2-23.4)
One survivor	15	341/1040	32.8 (30.0-35.7)	66.9	35.0 (29.3-40.8)
At least one survivor	15	865/1040	83.2 (80.8-85.3)	66	80.6 (75.7-85.1)
Two survivors	15	534/1040	51.4 (48.3-54.4)	78.4	45.4 (38.2-52.7)
	Stage IV				
No survivor	15	33/205	16.1 (11.7-21.8)	56.3	17.2 (9.6-26.4)
One survivor	15	55/205	26.9 (21.2-33.9)	0	27.7 (21.9-33.9)
At least one survivor	15	172/205	83.9 (78.6-88.3)	56.3	82.8 (73.6-90.4)
Two survivors	15	117/205	57.1 (50.2-63.7)	70.2	53.7 (40.2-66.8)
	Stage V				
No survivor	2*	4/9	44.4 (18.0-73.3)	0	45.4 (17.4-75.2)
One survivor	2*	5/9	55.6 (26.7-81.1)	0	54.6 (24.8-82.6)

*one study[30] evaluated the outcome of expectant management, while the other one[52] does not specify whether expectant management or amnioreduction and/or septostomy were performed.

Table 4. Mean gestational age at birth in MCDA twin pregnancies affected by TTTS, according to the stage of the disease. Weighted means were obtained combining data from individual studies to perform meta-analyses of single-group continuous data. For the sake of completeness, raw means were also reported. (CI = Confidence Interval).

Disease stage	Studies (n)	Fetuses (Total sample)	Raw mean (95% CI)	Weighted mean (95% CI)	I^2 (%)
Stage I	13	527	30.9 (28.9-32.9)	31.1 (29.9-32.2)	87.4
Stage II	11	437	31.4 (29.9-32.9)	31.4 (29.5-33.3)	91.7
Stage III	12	750	31.3 (30.0-32.7)	31.4 (30.0-32.7)	87.2
Stage IV	12	170	30.1 (28.5-31.8)	29.9 (28.5-31.4)	47.3
Stage V	2	4	26.7 (22.2-31.1)	26.5 (24.4-28.5)	0

Table 5. Pooled proportions for morbidity in MCDA twins affected by TTTS according to the stage of the disease. (95% confidence intervals, CI, between parentheses).

Outcome	Studies (n)	Fetuses (n/N)	Raw proportions (95% CI)	I^2 (%)	Pooled Proportions (95% CI)
Stage I					
PTB <34 weeks	1	1/2	50.0 (12.6-98.7)	-	-
PTB <32 weeks	2	9/34	26.5 (12.9-44.4)	0	27.1 (13.9-42.8)
PTB <28 weeks	1	0/2	0.0 (0-84.2)	-	-
Stage II					
PTB <34 weeks	2	4/12	33.3 (9.9-65.1)	72.3	31.3 (10.0-58.0)
PTB <32 weeks	3	20/47	42.6 (28.3-57.8)	0	42.8 (29.4-56.9)
PTB <28 weeks	2	2/12	16.7 (2.1-48.4)	17.7	17.6 (1.6-45.3)
Stage III					
PTB <34 weeks	2	12/30	40.0 (22.7-59.4)	82.6	37.3 (5.2-78.0)
PTB <32 weeks	3	32/58	55.2 (41.5-68.3)	44.3	53.3 (36,1-70.2)
PTB <28 weeks	2	3/30	10.0 (2.1-26.5)	68.1	9.7 (2.0-22.3)
Stage IV					
PTB <34 weeks	2	3/7	42.9 (9.9-81.6)	73.8	46.5 (15.5-79.2)
PTB <32 weeks	3	11/18	61.1 (35.7-82.7)	0	59.9 (37.9-80.0)
PTB <28 weeks	2	0/7	0.0 (0-41.0)	0	0.0 (0-30.7)
Stage V					
PTB <34 weeks	-	-	-	-	-
PTB <32 weeks	-	-	-	-	-
PTB <28 weeks	-	-	-	-	-

Table 6. Pooled proportions for morbidity in MCDA twins affected by TTTS according to the stage of the disease. (95% confidence intervals, CI, between parentheses).

Outcome	Studies (n)	Fetuses (n/N)	Raw proportions (95% CI)	I^2 (%)	Pooled Proportions (95% CI)
Stage I					
Composite morbidity	3	44/188	23.4 (17.6-30.19)	97.7	22.9 (0.1-68.49)
Neurological morbidity (overall)	2	2/148	1.4 (1.6-4.8)	42.8	1.5 (0.02-5.1)
Severe neurological morbidity	2	2/84	2.4 (0.2-8.3)	-	-
Respiratory morbidity	1	16/84	19.1 (11.3-29.1)	-	-
Stage II					
Composite morbidity	2	39/124	31.5 (23.4-40.4)	98.9	28.8 (6.8-97.0)
Neurological morbidity (overall)	2	6/124	4.8 (1.8-10.2)	74.2	5.2 (0.3-15.4)
Severe neurological morbidity	1	5/54	9.3 (3.1-20.3)	-	-
Respiratory morbidity	1	38/54	70.4 (56.4-82.0)	-	-
Stage III					
Composite morbidity	2	48/127	37.8 (29.3-46.8)	98.5	29.3 (18.6-91.8)
Neurological morbidity (overall)	2	8/127	6.3 (2.8-12.0)	12.3	6.7 (2.9-12.1)
Severe neurological morbidity	1	6/71	8.5 (3.2-17.5)	-	-
Respiratory morbidity	1	46/71	64.8 (52.5-75.8)	-	-
Stage IV					
Composite morbidity	2	21/64	32.8 (21.6-45.7)	93.4	24.1 (0.02-71.8)
Neurological morbidity (overall)	2	3/64	4.7 (1.0-13.1)	0	5.9 (1.6-13.0)
Severe neurological morbidity	1	2/42	7.1 (1.5-19.5)	-	-
Respiratory morbidity	1	20/42	47.6 (32.0-63.6)	-	-
Admission to NICU					
Stage V					
Composite morbidity	-	-	-	-	-
Neurological morbidity (overall)	-	-	-	-	-
Severe neurological morbidity	-	-	-	-	-
Respiratory morbidity	-	-	-	-	-

Table 7. Pooled proportions for single and double survival in MCDA twin pregnancies affected by stage I TTTS according to different management options (expectant, laser and amnioreduction). (95% confidence intervals, CI, between parentheses).

Outcome	Studies (n)	Fetuses (n/N)	Raw proportions (95% CI)	I^2 (%)	Pooled Proportions (95% CI)
	Stage I (expectant)				
No survivor	4	18/112	16.1 (9.8-24.2)	67	15.1 (4.9-29.6)
One survivor	3	18/108	16.7 (10.2-25.1)	0	17.5 (11.0-25.1)
At least one survivor	4	94/112	83.9 (75.8-90.2)	67	84.9 (70.4-95.1)
Two survivors	3	73/108	67.6 (57.9-76.3)	29.4	67.9 (57.0-77.9)
	Stage I (laser therapy)				
No survivor	10	36/285	12.6 (9.0-17.1)	0	13.2 (9.6-17.4)
One survivor	10	46/285	16.1 (12.1-20.9)	0	16.7 (12.6-21.2)
At least one survivor	10	249/285	87.4 (82.9-91.0)	0	86.7 (82.6-90.4)
Two survivors	10	203/285	71.2 (65.6-76.4)	37.9	69.7 (61.6-77.1)
	Stage I (amnioreduction)				
No survivor	3	4/60	6.7 (1.8-16.2)	0	7.8 (2.5-15.8)
One survivor	3	7/60	11.7 (4.8-22.6)	62.1	12.9 (2.5-30.1)
At least one survivor	3	56/60	93.3 (83.8-98.2)	0	92.2 (84.2-97.6)
Two survivors	3	49/60	81.7 (69.6-90.5)	61.7	80.8 (62.0-94.2)

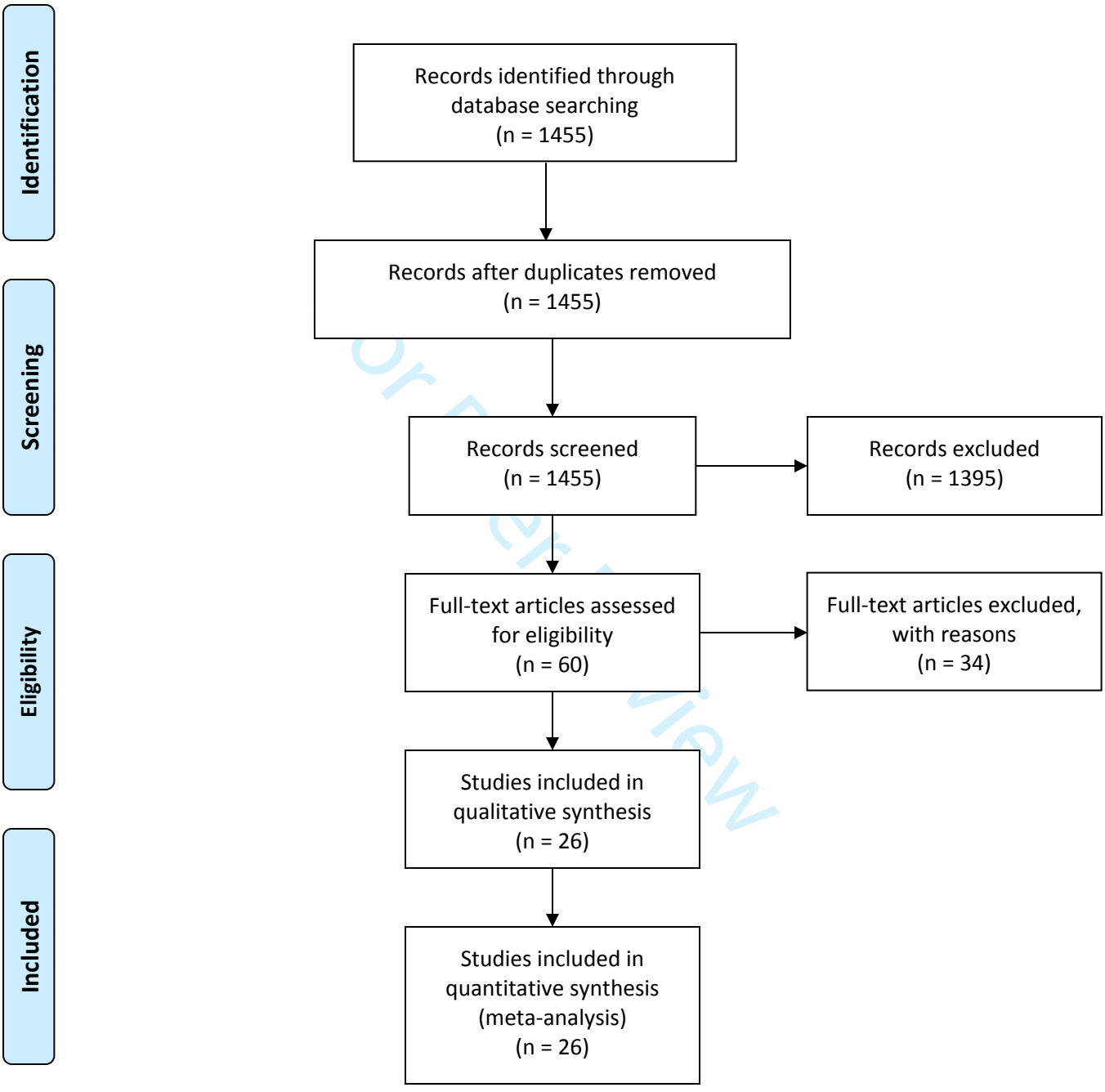
Figure legend

Figure 1. Systematic review flowchart

Figure 2. Stage I-V TTTS survival rate bar chart

Figure 3. Stage I TTTS survival rate according to different management options bar chart

PRISMA 2009 Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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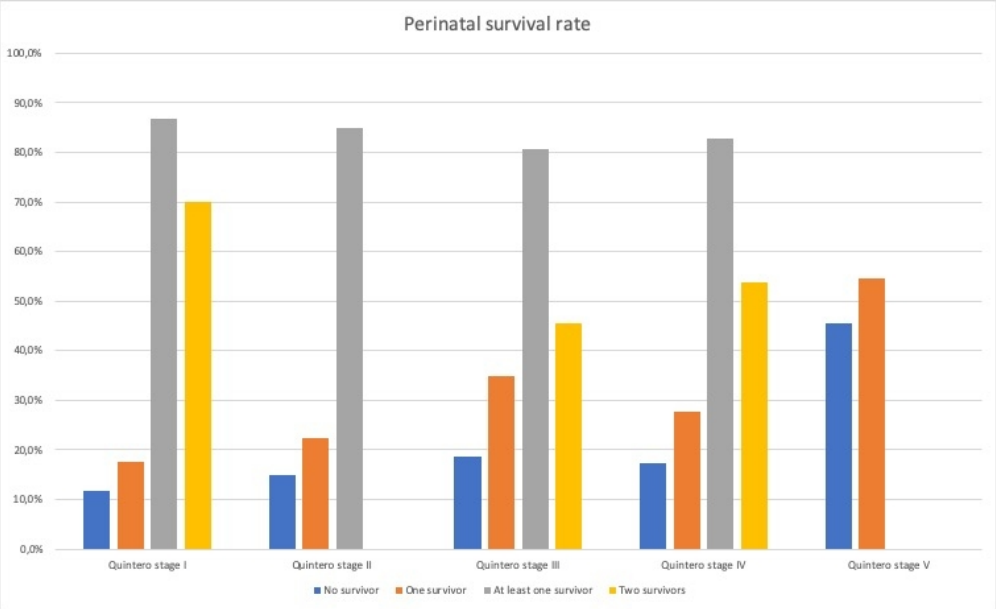

Figure 2

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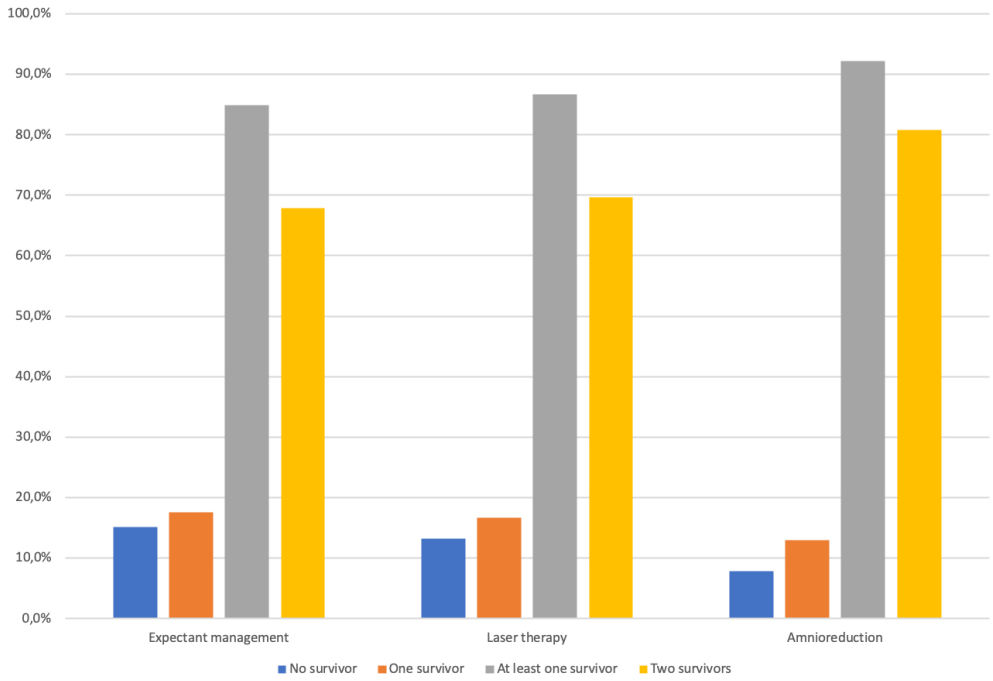


Stage I TTTS survival rate according to different management options bar chart

Supplementary Table 2. Excluded studies and reason for the exclusion.

Author	Year	Title	Reason for the exclusion
Groene	2019	TTTS with and without sIUGR prior to fetoscopic laser surgery: short and long term outcomes	Data stratified by Quintero stage only for the sIUGR+TTTS group
Korsakissok	2018	Mortality morbidity and 2-years neurodevelopmental prognosis of TTTS after fetoscopic laser therapy: a prospective 58 patients cohort study	No data on pregnancy outcome stratified by TTTS stage
Washburn	2018	Polyhydramnios affecting a recipient-like twin: risk of progression to TTTS and outcomes	No data useful for this review; overlapping risk with an included study (Wagner 2018)
Ortiz	2016	Chorioamniotic membrane separation after fetoscopy in monochorionic twin pregnancy: incidence and impact on perinatal outcome	No data on pregnancy outcomes stratified by TTTS stage
Snowise	2015	Donor Death After Selective Fetoscopic Laser Surgery for TTTS	The present studies reports the occurrence of donor and recipiente death according to TTTS stage; however, it was not possible to extrapolate information on the occurrence of recipient's death. Authors contacted, no reply
Lopriore	2014	Acute peripartum TTTS: incidence, risk factors, placental characteristics and neonatal outcome	Only patients with acute peripartum TTTS, chronic TTTS excluded
Barrea	2013	TTTS: perinatal outcome and recipient heart disease according to treatment strategy	No data on pregnancy outcomes stratified by TTTS stage
Bashat	2013	Outcome after fetoscopic selective laser ablation of placental anastomoses vs equatorial laser dichorionization for the treatment of TTTS	No data on pregnancy outcomes stratified by TTTS stage
Papanna	2012	Cerclage for cervical shortening at fetoscopic laser photocoagulation in TTTS	No data on pregnancy outcomes stratified by TTTS stage
Stirnemann	2012	Timing of delivery following selective laser photocoagulation for TTTS	No data on pregnancy outcomes stratified by TTTS stage
Halvorsen	2012	Survival and neonatal outcome after fetoscopic guided laser occlusion (FLOC) of TTTS in Sweden	No data on pregnancy outcomes stratified by TTTS stage
Rustico	2012	Fetal and maternal complications after selective FLS for TTTS: a single center experience	No data on pregnancy outcomes stratified by TTTS stage
Valsky	2012	Fetoscopic laser surgery for TTTS after 26 weeks of gestation	No data on pregnancy outcomes stratified by TTTS stage
Sundberg	2012	Invasive treatment in complicated monochorionic twin pregnancies: indications and outcome of 120 consecutively treated pregnancies	It is not possible to extrapolate data useful for this review
Cruz Martinez	2011	Incidence and clinical implications of early inadvertent septostomy after laser therapy for TTTS	No data on pregnancy outcomes stratified by TTTS stage
Papanna	2010	Chorioamnion Separation as a Risk for pPROM after Laser Therapy for TTTS	No data on pregnancy outcomes stratified by TTTS stage
Sago	2010	The outcome and prognostic factors of TTTS following fetoscopic laser surgery	Data stratified by stage I+II and III+IV TTTS
Yang	2010	Fetoscopic laser surgery for TTTS: local experience from Hong Kong	No data on pregnancy outcomes stratified by TTTS stage

Lopriore	2009	Risk factors for neurodevelopment impairment in TTTS treated with fetoscopic laser surgery	No data on pregnancy outcomes stratified by TTTS stage
Luks	2009	The pediatric surgeons' contribution to in utero treatment of TTTS	Data stratified by stage I+II and III+IV TTTS
Muratore	2009	Survival after laser surgery for TTTS: when are they out of the woods?	No useful data for this review
Habli	2008	The outcome of TTTScomplicated with placental insufficiency	No data on pregnancy outcomes stratified by TTTS stage
Ierullo	2007	Severe twin–twin transfusion syndrome: outcome after fetoscopic laser ablation of the placental vascular equator	No data on pregnancy outcomes stratified by TTTS stage
Michelfelder	2007	Early manifestations and spectrum of recipient twin cardiomyopathy in TTTS: relation to Quintero stage	No data useful for this review
Cavicchioni	2006	IUFD following laser treatment in TTTS	Only cases with IUFD of one or both twins
Lopriore	2005	Neonatal outcome in TTTS treated with fetoscopic laser occlusion of vascular anostomosis	No data on pregnancy outcomes stratified by TTTS stage
Lim	2005	Outcome of TTTS managed by a specialized clinic	Of the two cases which might have been potentially included, one had not information on any of the outcomes explored in the present review, while the other underwent TOP. Furthermore, all the other cases received interventions other than laser therapy
Dickinson	2004	The progression of disease stage in TTTS	Same study population of Duncombe 2003 (included)
Senat	2004	Endoscopic laser surgery versus serial amnioreduction for severe TTTS	No data on pregnancy outcomes stratified by TTTS stage
Tan	2004	Doppler for Artery–Artery Anastomosis and Stage-Independent Survival in TTTS	The included cases underwent multiple treatment options and It was not possible to extrapolate information on cases in stage I undergoing expectant management or intervention and those in stages II-III-IV and IV undergoing laser therapy
Taylor	2002	Validation of the Quintero Staging system for TTTS	It is not possible to extrapolate data useful for this review
Blaicher	2002	TTTS: an unsolved problem	No clear data on clinical management
Johnson	2001	Amnioreduction vs septostomy in TTTS	No data on pregnancy outcomes stratified by TTTS stage
Mari	2001	Perinatal morbidity and mortality rates in severe TTTS: Results of the International Amnioreduction Registry	No data on pregnancy outcomes stratified by TTTS stage
Berghella	2001	Natural history of TTTS	No data on pregnancy outcome stratified by TTTS stage

Supplementary Table 2. Mean gestational age at diagnosis in twin pregnancies affected by stage I TTTS, according to the type of approach to disease management. Weighted means were obtained combining data from individual studies to perform random-effect meta-analyses of single-group continuous data. For the sake of completeness, raw means were also reported.

Management	N. of studies (sample)	Raw mean (95% CI)	Weighted mean (95% CI)	I^2 (%)
Expectant management	4 (112)	21.6 (21.3-21.9)	21.0 (20.2-21.8)	32.5
Laser ablation	6 (246)	21.9 (21.7-22.0)	21.4 (21.1-21.7)	0.0
Amnioreduction	1 (30)	23.5 (22.4-24.5)	23.5 (22.5-24.5)	--

TTTS: Twin-to-twin transfusion syndrome; CI = Confidence Interval.

Supplementary Table 3. Mean gestational age at treatment in twin pregnancies affected by TTTS, according to the stage of the disease. Weighted means were obtained combining data from individual studies to perform random-effect meta-analyses of single-group continuous data. For the sake of completeness, raw means were also reported.

Disease stage	N. of studies (sample)	Raw mean (95% CI)	Weighted mean (95% CI)	I^2 (%)
Stage II	6 (367)	20.4 (20.3-20.5)	20.3 (19.7-20.8)	59.3
Stage III	7 (653)	20.6 (20.5-20.7)	20.2 (20.0-20.5)	0.0
Stage IV	7 (145)	21.7 (21.6-21.9)	21.4 (20.7-22.2)	35.7

N: number; TTTS: Twin-to-twin transfusion syndrome; CI = Confidence Interval.

Supplementary Table 4. Results of the multiple meta-regression models predicting the summary estimate of (a) mean gestational age at treatment; (b) mean gestational age at diagnosis in twin pregnancies affected by TTTS.

Variables included	**Regression coefficient**	**p**
Model 1: Mean gestational age at treatment		
Stage 2 TTTS (ref. cat.)	0	--
Stage 3 TTTS	0.229	0.9
Stage 4 TTTS	1.274	0.9
Model 2: Mean gestational age at diagnosis		
Approach to TTTS management	0.754	0.9
(expectant = 1; laser ablation = 2; amnioreduction = 3)		

TTTS: Twin-to-twin transfusion syndrome.

Figure S1a. Weighted mean gestational age at birth (weeks) in MCDA twin pregnancies affected by TTTS - Stage I.

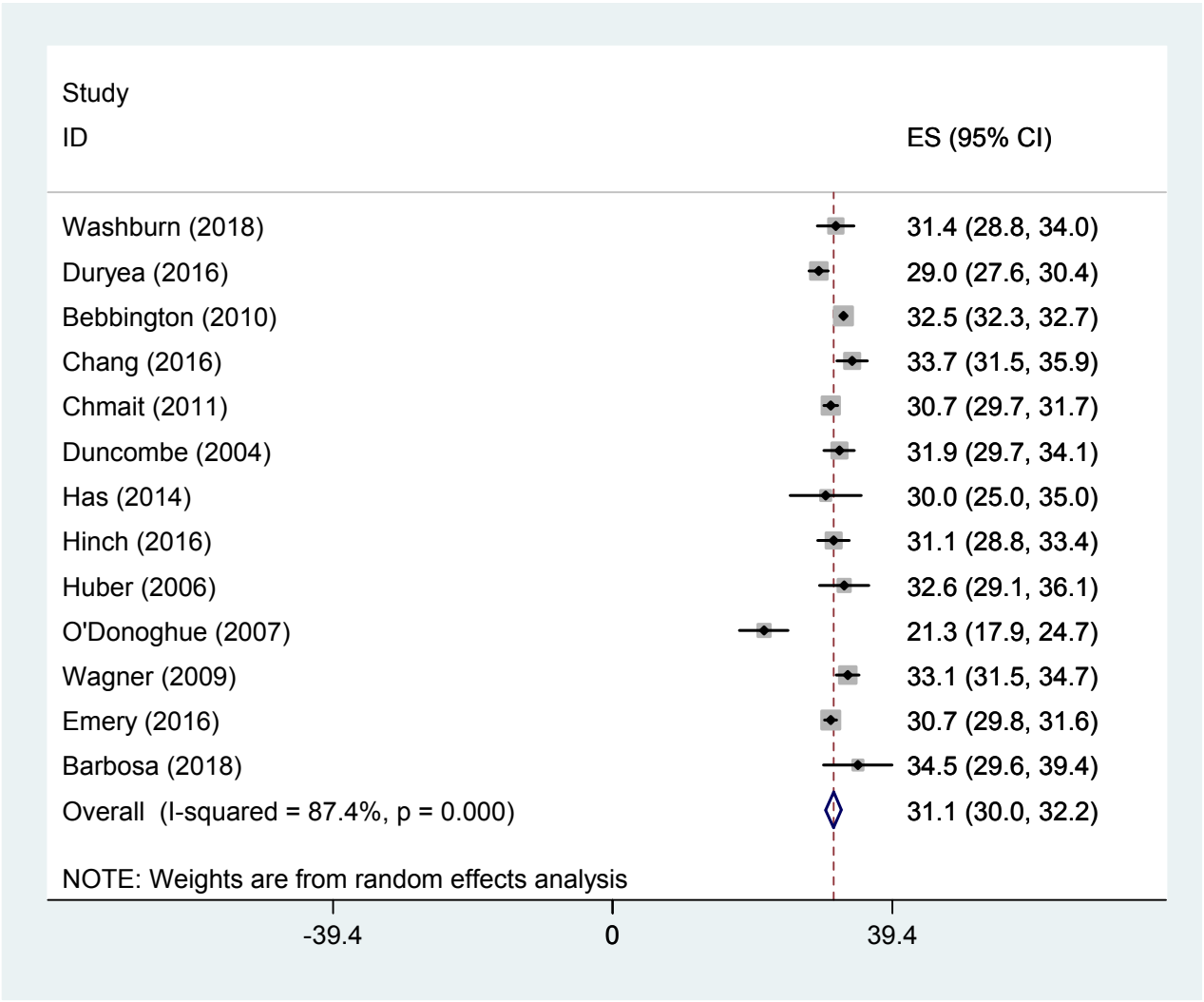


Figure S1b. Weighted mean gestational age at birth (weeks) in MCDA twin pregnancies affected by TTTS - Stage II.

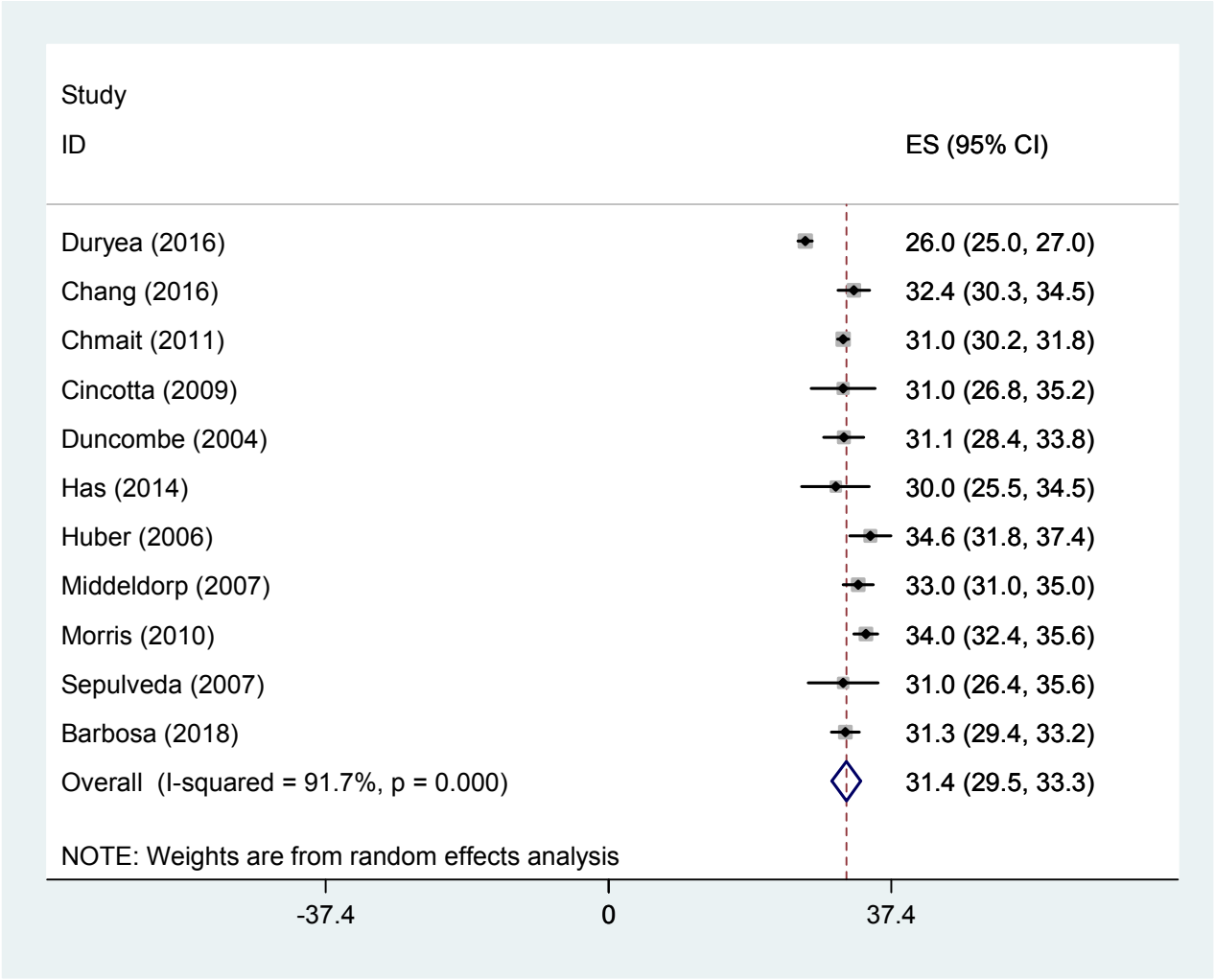


Figure S1c. Weighted mean gestational age at birth (weeks) in MCDA twin pregnancies affected by TTTS - Stage III.

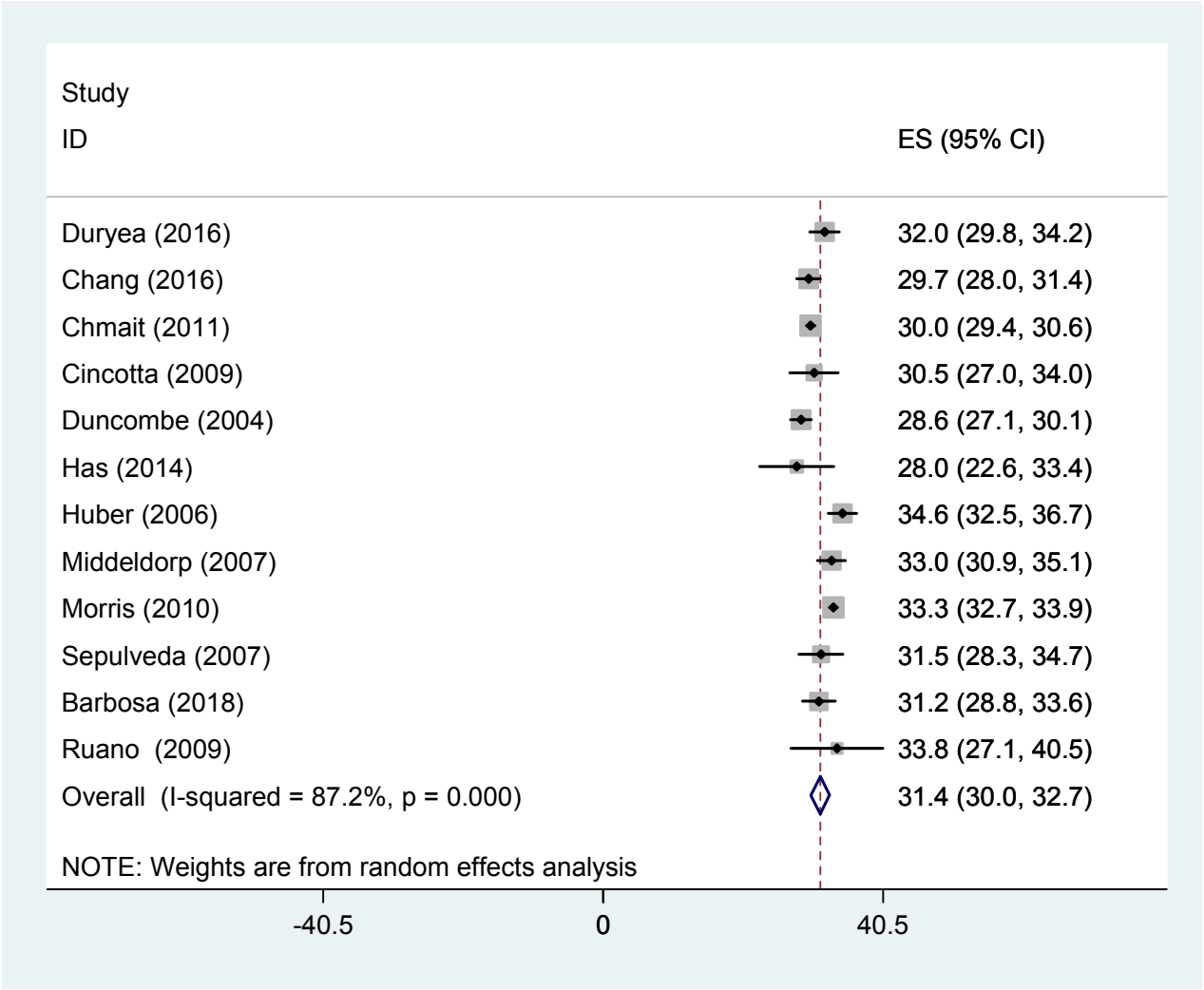


Figure S1d. Weighted mean gestational age at birth (weeks) in MCDA twin pregnancies affected by TTTS - Stage IV.

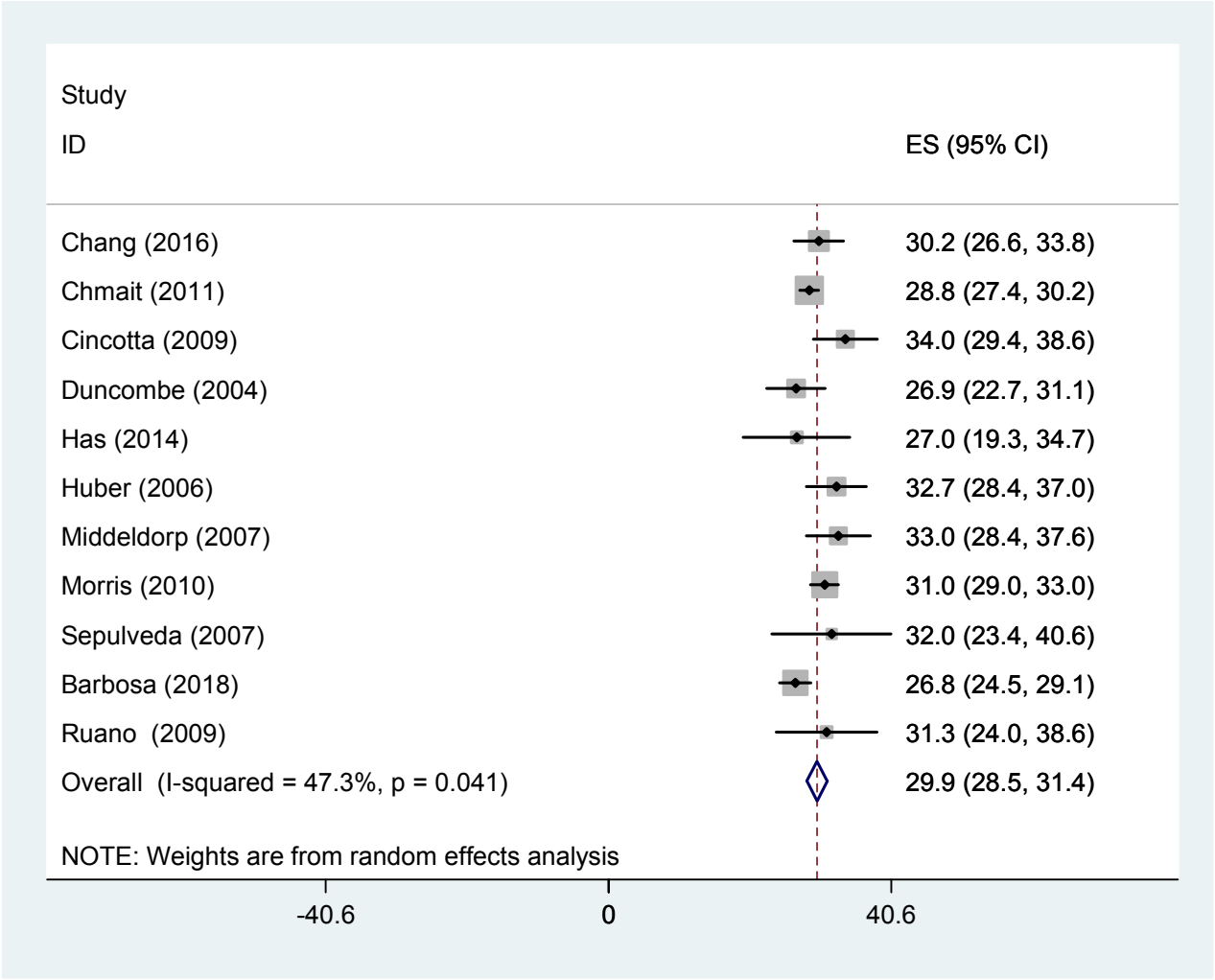
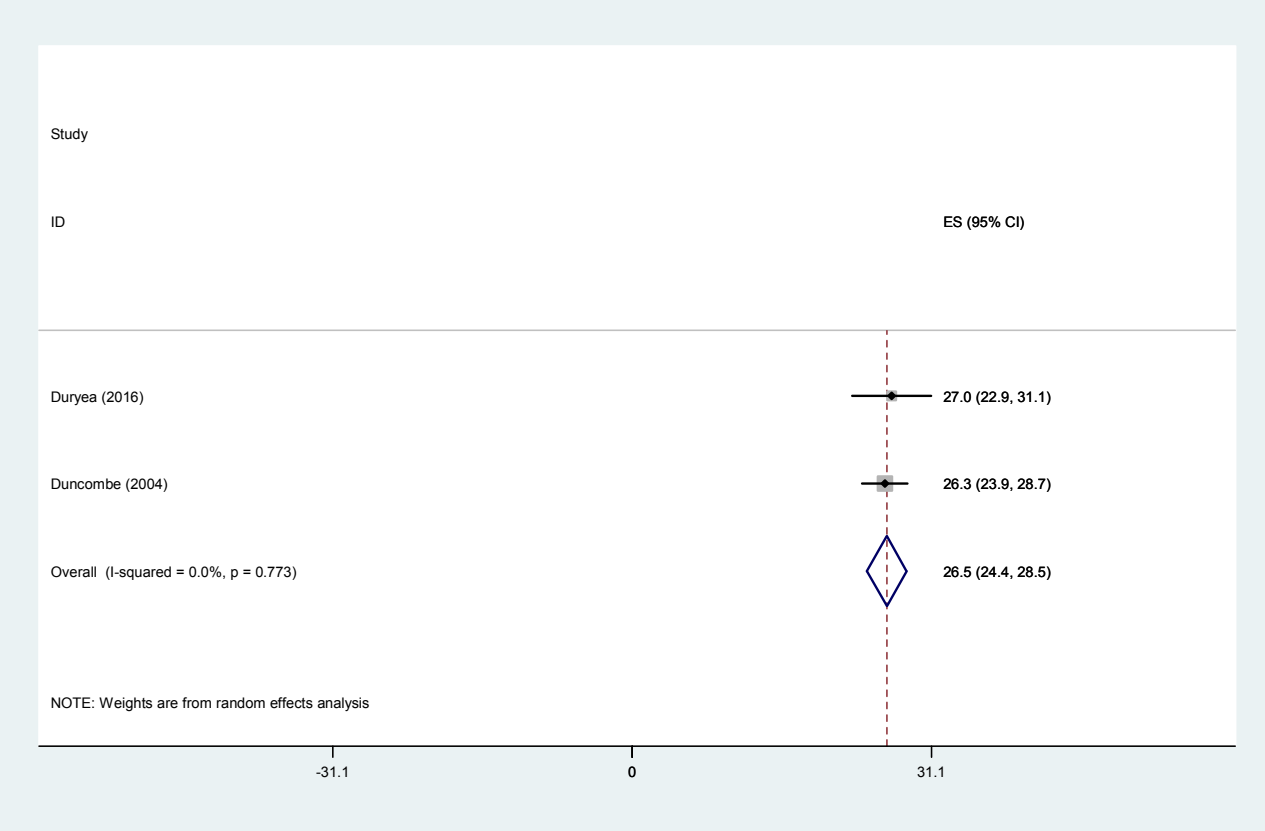


Figure S1e. Weighted mean gestational age at birth (weeks) in MCDA twin pregnancies affected by TTTS - Stage V.



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4-5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4-5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4-5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7-9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7-9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11-13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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