Complications and mortality of venovenous extracorporeal membrane oxygenation in the treatment of neonatal respiratory failure: a systematic review and meta-analysis

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Research article

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Abstract

Background: Extracorporeal membrane oxygenation (ECMO) has been increasingly used for severe neonatal respiratory failure refractory to conventional treatments. To systematically evaluate the complications and mortality of venovenous ECMO in the treatment of neonatal respiratory failure, we performed a systematic review and meta-analysis of all the related studies.

Methods: PubMed, Embase, and Cochrane Library were searched. The retrieval period was from the establishment of the database to February 2019. Two investigators independently screened articles according to the inclusion and exclusion criteria. The quality of article was assessed by the Newcastle-Ottawa scale (NOS). The meta-analysis was performed by Stata 15.0 software.

Results: Four observational studies were included, with a total of 347 newborns. The overall mortality at hospital charge was 12% (5% - 18%) with a heterogeneity of I2 = 73.8% (p = 0.01). Two studies reported mortality during ECMO and after decannulation, with 10% (0.8% -19.2%) and 6.1% (2.6% - 9.6%) respectively. The most common complications associated with venovenous ECMO were: pneumothorax (20.6%), hypertension (20.4%), cannula dysfunction (20.2%), seizure (14.9%), renal failure requiring hemofiltration (14.7%), infectious complications (10.3%), thrombi (7.4%), intracranial hemorrhage or infarction (6.6%), hemolysis (5.3%), cannula site bleeding (4.4%), gastrointestinal bleeding (3.7%), oxygenator failure (2.8%), other bleeding events (2.8%), brain death (1.9%), and myocardial stun (0.9%).

Conclusion: The overall mortality at discharge of venovenous ECMO in the treatment of neonatal respiratory failure was 12%. Although complications are frequent, the survival rate during hospitalization is still high. Further larger samples and higher quality of randomized controlled trials (RCT) are needed to clarify the efficacy and safety of this technique in the treatment of neonatal respiratory failure.

Background

Severe neonatal respiratory failure is associated with substantial mortality [1–2]. Despite the great development of mechanical management and some other conventional therapies, mortality is still high, and prognosis of neonates with extremely low oxygenation is especially poor [3]. And some complications such as ventilator-induced lung injury caused by mechanical ventilation may also affect the prognosis in return [4].

Extracorporeal membrane oxygenation (ECMO), also knows as extracorporeal life support (ECLS), is an important method for the treatment of neonatal respiratory failure refractory to high-frequency ventilation (HFV), pulmonary surfactant replacement, nitric oxide (NO) inhalation, and other conventional treatments [5–7].

During ECMO, blood is withdrawn from patient's body into a membrane oxygenator (artificial lung), where carbon dioxide is removed and oxygen is added. After heated to appropriate temperature, the oxygenated blood is then returned to a major vein or artery [8]. Nowadays, ECMO is used to treat various reversible neonatal diseases, the most common diagnoses aresuch as meconium aspiration syndrome (MAS), neonatal persistent pulmonary hypertension (PPHN), and, congenital diaphragmatic hernia (CDH), sepsis/pneumonia, respiratory distress syndrome (RDS), and so on [6,9]. Along with the development of new therapies such as high-frequency oscillatory ventilation (HFOV), exogenous surfactant therapy, and inhaled nitric oxide (iNO), fewer patients with MAS, PPHN and RDS are supported by ECMO [8–10]. Even so, the survival rate of neonates with MAS has been sustained highest, approximately 94%. The survival rates of neonates with RDS and PPHN come to the next, with 84% and 77%, respectively. Whereas patients with CDH had the worst survival in this cohort of patients, approximately 51% [6]. Conversely, increasing numbers of patients with CDH and other complex primary diagnoses are supported by ECMO during the last years, which means there exists a more critically ill situation needing increasingly complicated and lengthy ECMO runs in this group of patients. It provides temporary

cardiopulmonary support by replacing the cardiac and/or pulmonary function, which allows patients to win the time to recover. Compared to other age groups, the survival rate for neonatal extracorporeal membrane oxygenation is the highest [10]. There are two primary modes of ECMO for neonates: venoarterial extracorporeal membrane oxygenation (VA ECMO), the oxygenated blood returns to the arterial circulation, typically into the aorta; and venovenous extracorporeal membrane oxygenation (VV ECMO), the oxygenated blood returns to the venous system, typically into the right atrium [11]. Although VA ECMO is widely used in neonatal respiratory failure [6], it requires the ligation of the right carotid artery, thus risk the thrombi in the circuit [12]. While VV ECMO spares the carotid artery, filters any thrombi through pulmonary bed, receives highly oxygenated blood for the pulmonary circulation, and shortens the cannulation time [12]. These advantages make it more popular for neonatal respiratory failure over the years.

Since the extracorporeal Life Support Organization (ELSO) was built in 1989, until January 2019, more than 112,231 patients around the world have received ECMO, including 31,591 newborns who have received ECMO for respiratory diseases [1113]. The application of VV ECMO increased gradually in recent years. The withdrawal rate during hospitalization was 87%, and the survival rate at discharge was 73% in this group [13]. The ELSO database also showed a higher use rate of VA ECMO (73%) compared to VV ECMO (27%) for neonatal respiratory support [14]. However, the application of VV ECMO increased gradually in recent years, and the overall survival rate of VV ECMO was higher than that of VA ECMO [14].

There are many clinical studies on VV ECMO in the treatment of neonatal respiratory failure worldwide, most of them were registered in the ELSO database. However, for the unselected centers, a systematic review and meta-analysis about the complications and mortality associated with VV ECMO is still lacking. In this study, we aimedbut a systematic review and meta-analysis in this field is still lacking. The aim of this study is to evaluate the incidence of complications and in-hospital mortality of VV ECMO in the treatment of neonatal respiratory failure for these unselected patients.

Methods

Literature search

We conducted a systematic review and meta-analysis in accordance with Meta-analysis of Observational Studies in Epidemiology (MOOSE) and the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [1315–1416]. Pubmed, Embase, and Cochrane library were searched systematically for articles reporting on VV ECMO in the treatment of neonatal respiratory failure. The retrieval period was from the establishment of the database to February 2019. We used Mesh terms with the following search strategies: (“extracorporeal membrane oxygenation” OR “Oxygenators, membrane”) AND (“Adult respiratory distress syndrome” OR “Respiratory insufficiency”) AND “infant, newborn”. Language was restricted to English only. We also searched references of included articles to identify additional studies. Two investigators reviewed the citations independently.

Selection criteria

The title and abstract of citations were screened initially and full text was reviewed with the following inclusion criteria: (a) randomized and quasi-randomized controlled trials or observational studies; (b) Neonates with respiratory failure; (c) receiving VV ECMO, if VV ECMO and VA ECMO mixed, only studies reporting on independent outcomes for each mode were included, or the percentage of VA ECMO usage rate in the study was less than 10%, which produced negligible effect on the statistical analysis. (d) reporting on complications and mortality during hospitalization. (e) neonates more than 50. Articles thatwhich met all the inclusion criteria were included. Exclusion criteria including: (a) Case report, review, conference abstract, animal experiment, systematic review, meta-analysis and so on; (b) duplicated studies; (c) studies registered in ELSO database; (d) less than 50 patients; (e) studies without available outcomes of interest. The corresponding authors were contacted to request additional data.

Data extraction and quality assessment

Two investigators (JX and LZ) performed data extraction independently, disagreements were settled by a third investigator (LB). The inclusion and exclusion criteria were strictly followed in the process of literature screening. The following data were collected: demographic data of patients, features of included studies, procedural details and equipment informations of ECMO including maximum cannula size, pump type, oxygenator type, cannula type and so on. The main outcomes of interest included mortality during ECMO or at discharge and incidence of complications. We used the NOS to evaluate the quality of the included studies [1517].

Statistic analysis

We used Stata15.0 software for statistic analysis to quantitatively synthesize the mortality rate and complication rate during hospitalization. The results were presented as a summary point estimate (in %) with 95% confidential intervalinternal (CI). The heterogeneity between the studies was analyzed by the chi-square test, and was quantitatively determined by I^2. The published guidelines quantify heterogeneityvalues as three levels: low (I^2 = 25%–49%), moderate (I^2 = 50%–74%), and high (I^2 ≥75%) [1618]. A random-effects model using DerSimonian and Laird method for variance estimator was performed to report results. Statistic significance was set at a P less than 0.05 (two- tailed).

Results

Study selection

1263 studies (564 in Pubmed, 665 in Embase, 34 in Cochrane library) were initially reviewed and 4 studies were finally included with a total of 347 patients [1719–2022] (Fig. 1). We excluded the studies registered in the ELSO database to avoid overlapping with studies from the original centerre. All the included studies were single center or multicenter observational studies, which were implemented in Europe or the United States and published in English. NOS was used to perform quality assessment since all the studies were non-RCTs. Two studies got 6 stars [1719,2022], and two studies got 8 stars [1820,1921], which demonstrated a high quality for each study.

Study Characteristics

Demographic data of patients, features of included studies, Procedural details and equipment informations of ECMO are presented respectively in Table1, Table2, and Table3. Three3 single center retrospective studies and one multicenter retrospective study were found. Two studies were performed 20 years ago, when polymethylpenthene hollow fiber membranes technology wasere not available. All included studies reported complications and mortality of VV ECMO in the treatment of severe neonatal respiratory failure. Underlying diseases leading to respiratory failure were variable, most often included meconium aspiration syndrome and persistent pulmonary hypertension. Three studies included only VV ECMO patients, while the remaining study included patients in combination withof VV ECMO and VA ECMO. Outcomes were not reported independently in this study, but the proportion of patients received solely VV ECMO was more the 90%.

Mortality to hospital discharge ranged from 6% to 21%, and pooled mortality at hospital discharge was 12% (5% - 18%) with a heterogeneity of I^2 = 73.8% (p = 0.01) (Fig. 2). Two studies reported mortality during ECMO and after decannulation, with 10% (0.8% –19.2%) and 6.1% (2.6% - 9.6%) respectively. Complications occurred during hospitalization including pneumothorax (20.6%), hypertension (20.4%), cannula dysfunction (20.2%), seizure (14.9%), renal failure requiring hemofiltration (14.7%), infectious complications (10.3%), thrombi (7.4%), intracranial hemorrhage or infarction (6.6%), hemolysis (5.3%), cannula site bleeding (4.4%), gastrointestinal bleeding (3.7%), oxygenator failure (2.8%), other bleeding events (2.8%), brain death (1.9%), and myocardial stun (0.9%) (Table 4).

Subgroup analysis

Racial group, publication year, maximum cannula size, and age at the beginning of ECMO might be sources of heterogeneity between studies. So we performed subgroup analysis from these four aspects (Fig. 3, Fig. 4, Fig. 5, Fig. 6). The results showed that maximum cannula size and age at the beginning of ECMO were sources of heterogeneity between studies, while racial group and publication year were not sources of heterogeneity between studies. BesidesIn addition, the heterogeneity between studies might also originate in disease severity, ECMO equipment type, medical center's level, the experience of the medical staff who operatesing ECMO, and some other factors.

Because the included studies are fewer, we didn't perform meta-regression analysis and publication bias.

Discussion

Our study showed that the survival rate of neonates with respiratory failure after receiving VV ECMO treatment was as high as 88% at hospital discharge, even higher than that (73%) of neonates with respiratory failure treated by ECMO according to ELSO registry report in January 2019 [1113]. The reason might be that the data of ELSO come from the mixed population of VA ECMO and VV ECMO, and the patients who received VA ECMO mostly had hemodynamic instability and needed cardiac support, thus reduce the survival rate. According to the ELSO database, the survival rate of VA ECMO in the treatment of neonatal respiratory failure between 2012 and 2017 was 70%, while that of VV ECMO was 80% [1214].

Our results also showed that among the included studies, the mortality rate of patients in the Kkugdman et al's [1820] study was lowest, while that in the Chevalier et al's [2022] study was highest,. which was consistent with the ELSO database record. According to the ELSO database, neonates with MAS have the highest survival rate, with PPHN and CDH coming up next [6]. On one hand, neonates with MAS enrolled in the Kkugdman et al's study might have more stable respiratory status, plus some new treatment modalities (NO, HFV, surfactant) were used and the ECMO team was more experienced during this time, thus improve the survival rate. On another hand, in the Chevalier et al's study, cannula applied on neonates was small, which means this group of neonates were small, and at that time ECMO equipment was not advanced, team of VV ECMO was not so experienced, these factors might result in the relatively high mortality of this study.

Since a double-lumen catheter was designed in 1989, VV ECMO was increasingly used in neonatal respiratory failure, and ligation of the carotid artery was avoided [2123–2224]. Over the years, many studies have reported the benefits of VV ECMO for neonatal respiratory failure. Roberts et al [2325] in a single center study compared double-lumen venovenous extracorporeal membrane oxygenation with cephalic draining cannula (VVDL+V ECMO) with data as collected in the ELSO database, with survival rate of 89.1% and 68.7%, respectively. They concluded that VVDL+V approach was associated with improved survival and lower rates of complication as compared with the ELSO database. Fukuda et al [2426] also compared VA with VV access in the cerebral circulation of newborn infants during extracorporeal membrane oxygenation, the results showed that neonates with severe pulmonary failure can be effectively supported by VV ECMO. In addition to stable hemodynamics of the brain compared with VA ECMO, it has advantages in myocardial and pulmonary vascular oxygenation, resulting in favorable cerebral hemodynamics. Moreover, many studies have showed that VV ECMO compared favorably to VA ECMO for cardiovascular support [2527–2628]. Several other previous studies have also showed that VV ECMO was associated to lower rates of neurologic complications as compared with VA ECMO [213,2729–2830]. Some potential advantages of VV ECMO over VA ECMO might explain the results. During VV ECMO, ligation of arteries was avoided, pulmonary circulation and coronary artery perfusion were maintained well, thus left ventricular afterload was reduced.

An overall survival of 88% was seen in the 347 neonates, higher than that of other age groups treated with VV perfusion according to the ELSO database. In addition to the baseline characteristics, many other factors could explain it. Firstly, the development of perinatology, such as intrapartum antimicrobial prophylaxis for Group B Strep (GBS)-colonized

women, has greatly decreased the incidence of invasive early-onset GBS disease, contributing to the less severe status of the neonates [29]. Secondly, as patients with MAS, RDS and PPHN have a good response to supplemental therapies such as pulmonary surfactant and iNO, their recovery process has been accelerated accordingly. For neonatal ECMO, the most common diagnoses are congenital diaphragmatic hernia (CDH), meconium aspiration syndrome (MAS), and persistent pulmonary hypertension (PPHN), accounting for almost 75% of all neonatal respiratory ECMO cases [12]. Whilst for pediatric ECMO and adult ECMO, the most common diagnoses are pneumonia and ARDS [6]. However, the above studies of neonatal ECMO were performed in the pre-ARDS era, in which ARDS was usually considered as neonatal RDS, and surfactant was therefore used repeatedly. So far no studies have shown the beneficial effects of surfactant for adult and pediatric ARDS. This might explain the lower survival rate of pediatric and adult ECMO for respiratory failure. In 2017, the international ARDS collaborative group provided the first consensus definition for neonatal ARDS [30]. Actually, ARDS and RDS are two significant different diseases with different reactions to surfactant, and they should be therefore diagnosed and compared independently. Importantly, mortality rate is also associated with other factors like annual hospital ECMO volume for neonates and adults but not for pediatric cases [31].

In our study,However, a significant number of system-related complications, including mechanical complications, bleeding, pneumothorax, hypertension, seizure, renal failure, hemorrhage and so on, still occurred on patients during hospitalization, which had a deep impact on survival and long-term outcomes. According to ELSO registry data, the most common complication that occurred during ECLS for neonates with respiratory failure is mechanical complication, including clots in the ECMO circuit (oxygenator, bladder, hemofilter, or other)[6], which is consistent with our study results. Bleeding and clots complications are multifactorial, and the rates of that during ECMO have increased since 2000. This trend can not be solely explained by the evolution of anticoagulation management strategies. Since some reports showed that ACT range of 180–220 was used by the majority of ECMO centers from 1996 to 2002, and this was unchanged until 2008 [32–34]. Both patients and circuit related factors might be the relative causes, such as the underlying patient pathophysiology could increase the risk of hemorrhage. Even though there exists a lack of research and evidence of an ideal test of anticoagulation for patients, continuous unfractionated heparin and close monitoring of anticoagulation are still required to reduce the risk of thrombosis and hemorrhage [35]. In our study, the rates of Neurologic complications such as intracranial hemorrhage/infarction and seizure are high as well, with 6.6% and 14.9% respectively. When analyzing the ELSO registry report in 2016, neonates with ECMO have the highest rate of neurologic complications, with an IVH incidence of around 7.6% [6]. Various pre-existing factors like low birth weight, acidosis, hypoxia, hypotension, and organ failure have been found to be associated with neurologic injury. Besides, some ECMO factors such as modality of ECMO used, hemorrhage, seizures, and development of new organ failure increase the risk of CNS injuries furtherly [36]. So an understanding of risk factors associated with neonates undergoing ECMO and knowing how to deal with these factors are important to reduce complications. There exist some other complications as well, wWhether all these complications are definitely due to inadequate technology and equipment of ECMO, a lack of supportive care, or simply a critical condition that might be secondary to the underlying disease in the newborn remains unclear. However, along with evolving indications for ECMO, the monitoring technology and supportive therapies have dramatically changed during these years, especially when newer double lumen VV cannulas for respiratory failure have been introduced, the outcomes of patients have improved greatly. Further attempts, such as by improving the equipment of ECMO, or increasing the use of supportive treatments like vasoactive agents, are needed to determine whether such events can be reduced.

In this study, to minimize potential bias of observational study, we established inclusion and exclusion criteria strictly to provide accurate prevalence and incidence estimation, and we limited the minimum sample size of each study to 50 to reduce publication bias. Moreover, we excluded the studies published in the ELSO database to avoid data duplication and reduce selection bias, because only the selected medical centers had the chance to register in the ELSO database, which increased selection bias. InBy this way, detailed VV ECMO data of other medical centers other than the ELSO database were collected in this meta-analysis.

Limitations

There are some limitations in our study. Firstly, all the studies were non-RCT studies, which increased the risk of bias. Statistic quality of systematic review and meta-analysis is best assessed by RCTs. As to trials of VV ECMO in the treatment of neonatal respiratory failure, randomization would be possible if a group of patients were selected, all with no big difference in cardiac function, and then treated with either VA access or VV access. However, a pure randomized study is rare, whereas accuracy studies are relatively common and provide most of the available evidence [37]. AndSo the results of theseour studiesy should bewere interpreted cautiously. Secondly, only studies written in English were included in this meta-analysis, lacking data of other racial groups such as Asian might cause language bias. Thirdly, less than 10 studies were included, and publication bias and meta regression analysis were not performed, which might pose a potential risk of publication bias. Fourthly, the number of included studies was small and there was moderate heterogeneity among the studies. Fifthly, Some data in the original study could not be obtained, such as pump type, membrane type, and so on, and the baseline standards of each study might be inconsistent, many potential factors might play a role in our analysis. Lastly, the inclusion criteria might also result in the omission of potentially important studies, such as case reports and small sample studies. However, small sample studies might be affected by publications bias, historical bias, selective reporting, and other methodological deficiencies, which increase the risk of bias.

Conclusions

The results of this study showed that although VV ECMO treatment for neonatal respiratory failure might lead to some complications including pneumothorax, hypertension, cannula dysfunction, seizure, renal failure and so on, the survival rate during hospitalization is still high. Larger samples and higher quality of randomized controlled studies are needed to provide a more reliable basis for the application of VV ECMO in neonates with respiratory failure.

Abbreviations

CDH: congenital diaphragmatic hernia; CI: confidential internal; DL: double-lumen; ECLS: extracorporeal life support; ELSO: extracorporeal life support organization; HFV: high-frequency ventilation; MOOSE: meta-analysis of observational studies in epidemiology; MAS: meconium aspiration syndrome; NOS: Newcastle-Ottawa Scale; NO: nitric oxide; PPHN: persistent pulmonary hypertension; RDS: respiratory distress syndrome; PRISMA: preferred reporting items for systematic review and meta-analysis; RCT: randomized controlled trials; VV ECMO: venovenous extracorporeal membrane oxygenation; VA ECMO: venoarterial extracorporeal membrane oxygenation

Declarations

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Availability of data and materials

The data supporting our findings can be found by contacting with us

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Authors 'contributions

LB conceptualized and designed the study, revised the initial manuscript and approved the final manuscript as submitted. JX and LZ conducted literature search and data analysis; JXwrote the initial manuscript and approved the final manuscript as submitted. All the authors read and approved the final manuscript.

Ethics approval and consent to participate

Our study was approved by the Institutional Review Board, Children's Hhospital of Chongqing Medical University, China.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Eriksen V, Nielsen LH, Klokker M, Greisen G. Follow-up of 5- to 11-year-old children treated for persistent pulmonary hypertension of the newborn. Acta Paediatr. 2009;98(2):304-309.
2. Walsh-Sukys MC, Bauer RE, Cornell DJ, Friedman HG, Stork EK, Hack M. Severe respiratory failure in neonates: mortality and morbidity rates and neurodevelopmental outcomes.J Pediatr. 1994;125(1):104-110.
3. Steinhorn RH. Treatment of hypoxemic respiratory failure in neonates: past, present and future. J Perinatol. 2016 Jun;36 Suppl 2:S1-2.
4. Kevin I Wheeler, Naomi McCallion, Colin J Morley, Peter G Davis, Claus Klingenberg. Volume-targeted versus pressure-limited ventilation in neonates. Cochrane Database Syst Rev. 2017 Oct; 2017(10): CD003666.
5. Frenckner B. Extracorporeal membrane oxygenation: a breakthrough for respiratory failure. J Intern Med. 2015; 278(6): 586–598.
6. Thiagarajan RR, Barbaro RP, Rycus PT, Mcmullan DM, Conrad SA, Fortenberry JD, et al. Extracorporeal Life Support Organization Registry International Report 2016. ASAIO J.2017 Jan/Feb;63(1):60-67.
7. Gattinoni L, Pesenti A, Mascheroni D, Marcolin R, Fumagalli R, Rossi F, et al. Low-frequency positive-pressure ventilation with extracorporeal CO2 removal in severe acute respiratory failure. JAMA 1986, 256:881–886.
8. Hintz S, Suttner D, Sheehan A, Rhine W, Van Meurs K. Decreased use of neonatal extracorporeal membrane oxygenation (ECMO): how new treatment modalities have affected ECMO utilization. Pediatrics. 2000;106:1339–1343.
9. Christou H, Van Marter LJ, Wessel DL, Allred EN, Kane JW, Thompson JE, et al. Inhaled nitric oxide reduces the need for extracorporeal membrane oxygenation in infants with persistent pulmonary hypertension of the newborn. Crit Care Med. 2000;28:3722–3727.
10. Barrington K, Finer N, Pennaforte T, Altit G. Nitric oxide for respiratory failure in infants born at or near term. Cochrane Database Syst Rev. 2017;1:CD000399.
11. Extracorporeal Life Support Organization. ECLS Registry Report. 2019. http://www.elso.org/Registry/Statistics/InternationalSummary.aspx. Accessed Jan 2019.
12. Mahmood B, Newton D, Pallotto EK. Current trends in neonatal ECMO. Semin Perinatol. 2018;42:80-88.

13. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000;283:2008-12.
14. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analysis of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009;339:b2700.
15. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010; 25: 603-5.
16. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta analysis. Stat Med.2002;21:1539-1558.
17. Speggiorin S, Robinson S G, Harvey C, Westrope C, Faulkner GM, Kirkland P, et al. Experience with the Avalon bicaval double-lumen veno-venous cannula for neonatal respiratory ECMO. Perfusion. 2015; 30:250-254.
18. Kugelman A, Gangitano E, Taschuk R, Garza R, Riskin A, McEvoy C, et al. Extracorporeal membrane oxygenation in infants with meconium aspiration syndrome: A decade of experience with venovenous ECMO. Journal of Pediatric Surgery. 2005; 40:1082-1089.
19. Knight GR, Dudell GG, Evans ML, Grimm PS. A comparison of venovenous and venoarterial extracorporeal membrane oxygenation in the treatment of neonatal respiratory failure. Crit Care Med. 1996; 24:1678-83.
20. Chevalier J Y, Couprie C, Larroquet, M, Renolleau S, Durandy Y, Costil J, et al. Venovenous single lumen cannula extracorporeal lung support in neonates. A five year experience. ASAIO Journal. 1993; 39: M654-M658.
21. Anderson HL III, Otsu T, Chapman RA, Barlett RH. Venovenous extracorporeal life support in neonates using a double lumen catheter. ASAIO Trans. 1989;35:650-653.
22. Otsu T, Merz SI, Hultquist KA, Attorri RJ, Anderson HL 3rd, Scheffler DE, et al. Laboratory evaluation of a double lumen catheter for venovenous neonatal ECMO. ASAIO Trans. 1989;35:647-650.
23. Roberts J, Keene S, Heard M, McCracken C, Gauthier TW. Successful primary use of VVDL+V ECMO with cephalic drain in neonatal respiratory failure. J Perinatol.2016;36:126-31.
24. Fukuda S, Aoyama M, Yamada Y, Saltoh N, Honjoh T, Hasegawa T, et al. Comparison of venoarterial versus venovenous access in the cerebral circulation of newborns undergoing extracorporeal membrane oxygenation. Pediatr Surg Int. 1999;15:78-84.
25. Cornish JD , Heiss KF , Clark RH, Strieper MJ, Boecler B, Kesser K. Efficacy of venovenous extracorporeal membrane oxygenation for neonates with respiratory and circulatory compromise. J Pediatr. 1993; 122: 105- 109.
26. Roberts N, Westrope C, Pooboni SK, Mulla H, Peek GJ, Sosnowski AW, et al. Venovenous extracorporeal membrane oxygenation for respiratory failure in inotrope dependent neonates . ASAIO Journal. 2003; 49: 568-571.
27. Dimmitt RA, Moss RL, Rhine WD, Benitz WE, Henry MC, Vanmeurs KP. Venoarterial versus venovenous extracorporeal membrane oxygenation in congenital diaphragmatic hernia: the Extracorporeal Life Support Organization Registry, 1990–1999. J Pediatr Surg. 2001; 36: 1199–1204.
28. Guner YS, Khemani RG, Qureshi FG, Wee CP, Austin MT, Dorey F et al. Outcome analysis of neonates with congenital diaphragmatic hernia treated with venovenous vs venoarterial extracorporeal membrane oxygenation. J Pediatr Surg. 2009; 44: 1691–1701.
29. Schrag S, Verani J. Intrapartum antibiotic prophylaxis for the prevention of perinatal group B streptococcal disease: experience in the United States and implications for a potential group B streptococcal vaccine. Vaccine. 2013;31(suppl 4):D20–D26.
30. De Luca D, van Kaam AH, Tingay DG, Courtney SE, Danhaive O, Carnielli VP, et al. The Montreux definition of neonatal ARDS: biological and clinical background behind the description of a new entity. Lancet Respir Med 2017;5:657-666.

31. Barbaro RP, Odetola FO, Kidwell KM, Paden ML, Bartlett RH, Davis MM, et al. Association of Hospital-Level Volume of Extracorporeal Membrane Oxygenation Cases and Mortality. Analysis of the Extracorporeal Life Support Organization Registry. Am J Respir Crit Care Med.2015;191:894-901.
32. Lawson DS, Walczak R, Lawson AF, Shearer IR, Ing R, Schulman S, et al. North American extracorporeal membrane devices: 2002 survey results. J Extra Corpor Technol. 2004;36:16–21.
33. Graves D, Chernin J, Kurusz M, Zwischenberger J. Anticoagulation practices during neonatal extracorporeal membrane oxygenation: survey results. Perfusion. 1996;11:461–6.
34. Lawson D, Lawson A, Walczak R, McRobb C, McDermott P, Shearer IR, et al. North American neonatal extracorporeal membrane oxygenation (ECMO) devices and team roles: 2008 survey results of Extracorporeal Life Support Organization (ELSO) centers. J Extra Corpor Technol. 2008;40:166–174.
35. Barton R, Ignjatovic V, Monagle P. Anticoagulation during ECMO in neonatal and paediatric patients. Thromb Res.2019;173:172-177.
36. Mehta A, Ibsen LM. Neurologic complications and neurodevelopmental outcome with extracorporeal life support. World J Crit Care Med. 2013;2:40–47.
37. Chandler J, Cumpston M, Thomas J, Higgins JPT, Deeks JJ, Clarke MJ. Chapter I: Introduction. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated August 2019). Cochrane, 2019. http://training.cochrane.org/handbook. Accessed Aug 2019.

Tables

Table 1. Demographic data of patients in included studies

Study	Number of patients	Included disease	Gestational Age (weeks)	Weight（Kg）	PaO2 (mmHg)	Oxygenation index	Age (days)
Speggiorin et al	72	Mixed	40	3.4	41.2	50	43.2
Kugelman et al	114	MAS	40.3±0.1	3.48±0.05	35.8±1.0	60±3	23
Knight et al	54	Mixed	39.6±0.3	3.595±0.072	38±2	NA	19±2
Chevalier et al	102	Mixed	38.1±2.2	3.054±0.62	49.5	46	71±94

MAS, Meconium aspiration syndrome; PaO2, Partial pressure of oxygen; NA, Not available.

Table 2. Features of included studies and quality assessment

Study	Year	Country	Design	Primary outcome	NOS score
Speggiorin et al	2015	Single center, UK	Retrospective study	Mortality and complications	6
Kugelman et al	2005	Single center, USA	Retrospective cohort study	Mortality and complications	8
Knight et al	1996	Multicenter, USA	Retrospective cohort study	Mortality and complications	8
Chevalier et al	1993	Multicenter, France	Retrospective study	Mortality and complications	6

NOS, Newcastle-Ottawa quality assessment scale.

Table 3. Procedural details and equipment information of ECMO

Study	VV ECMO (%)	VA ECMO (%)	VV ECMO convert to VA ECMO	ECMO duration (hours)	Site of insertion	Maximum cannula size	Oxygenator type	Cannula type	Pump type
Speggiorin et al	100%	0	0	90.5	Right internal jugular vein	16Fr	Polymethylpentene hollow fiber membrane	Double-lumen venous cannula	Ccentrifugal pump
Kugelman et al	100%	0	2	88.5	Right internal jugular vein	14Fr	NA	Double-lumen venous cannula	NA
Knight et al	100%	0	0	114±9	Right internal jugular vein	14Fr	NA	Double-lumen venous cannula	NA
Chevalier et al	95.3%	4.7%	5	117.8±84	Right internal jugular vein	10Fr	NA	Double-lumen venous cannula	Non-occlusive roller pump

Table 4. Outcomes and the incidence of complications of VV ECMO in the treatment of neonatal respiratory failure

Outcome	Number of studies reporting outcome	summary point estimate (CI 95%)
Hospital mortality		
Pooled mortality	4 (347)	12% (5%-18%)
Mortality during ECMO	2 (179)	10% (0.8%- 19.2%)
Mortality after decannulation	2 (179)	6.1% (2.6%- 9.6%)
Medical complications		
Gastrointestinal bleeding	1 (107)	3.7% (0.1%- 7.3%)
Intracranial hemorrage/infarction	3 (293)	6.6% (3.7%- 9.4%)
Cannula site bleeding	2 (179)	4.4% (-1.8%- 10.6%)
Hemolysis	1 (114)	5.3% (1.2%- 9.4%)
Other bleeding events	1 (107)	2.8% (-0.3%- 5.9%)
Seizure	2 (161)	14.9% (9.4%- 20.4%)
Brain death	1 (107)	1.9% (-0.7%- 4.4%)
Pneumothorax	1 (107)	20.6% (12.9%- 28.2%)
Hypertension	1 (54)	20.4% (9.6%- 31.1%)
Myocardiac stun	1 (114)	0.9% (-0.8%- 2.6%)
Renal failure needing hemofiltration	3 (275)	14.7% (5.9%- 23.5%)
Infectious complications	1 (107)	10.3% (4.5%- 16%)
Thrombi	1 (54)	7.4% (0.4%- 14.4%)
Mechanical complications		
Oxygenator failure	1 (72)	2.8% (-1.0%- 6.6%)
Cannula failure	2 (126)	20.2% (-4.2%- 44.7%)

VV ECMO, Veno-venous extracorporeal membrane oxygenation.

Figures

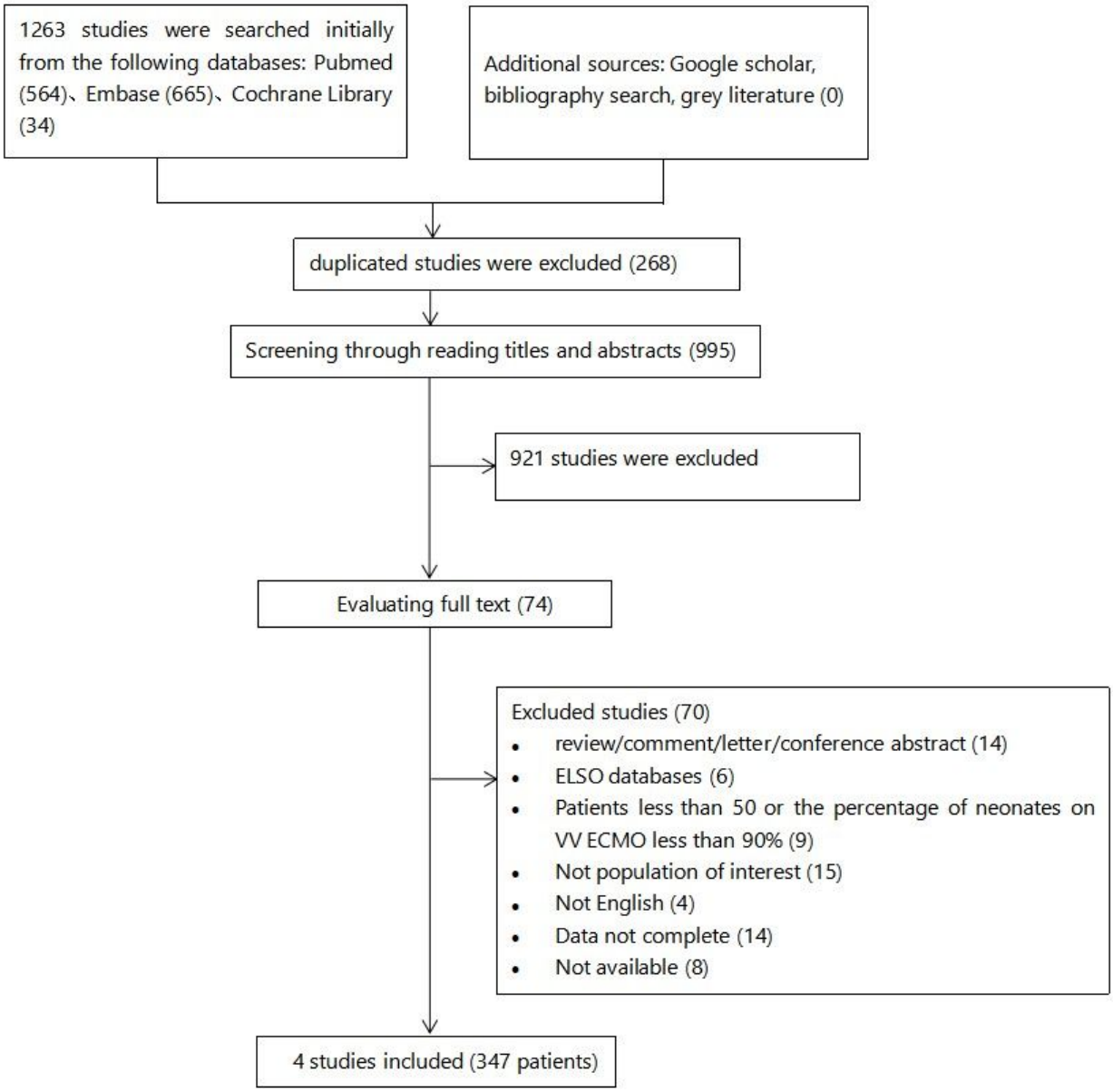

Figure 1

Flowchart of study screening for the systematic review and meta-analysis

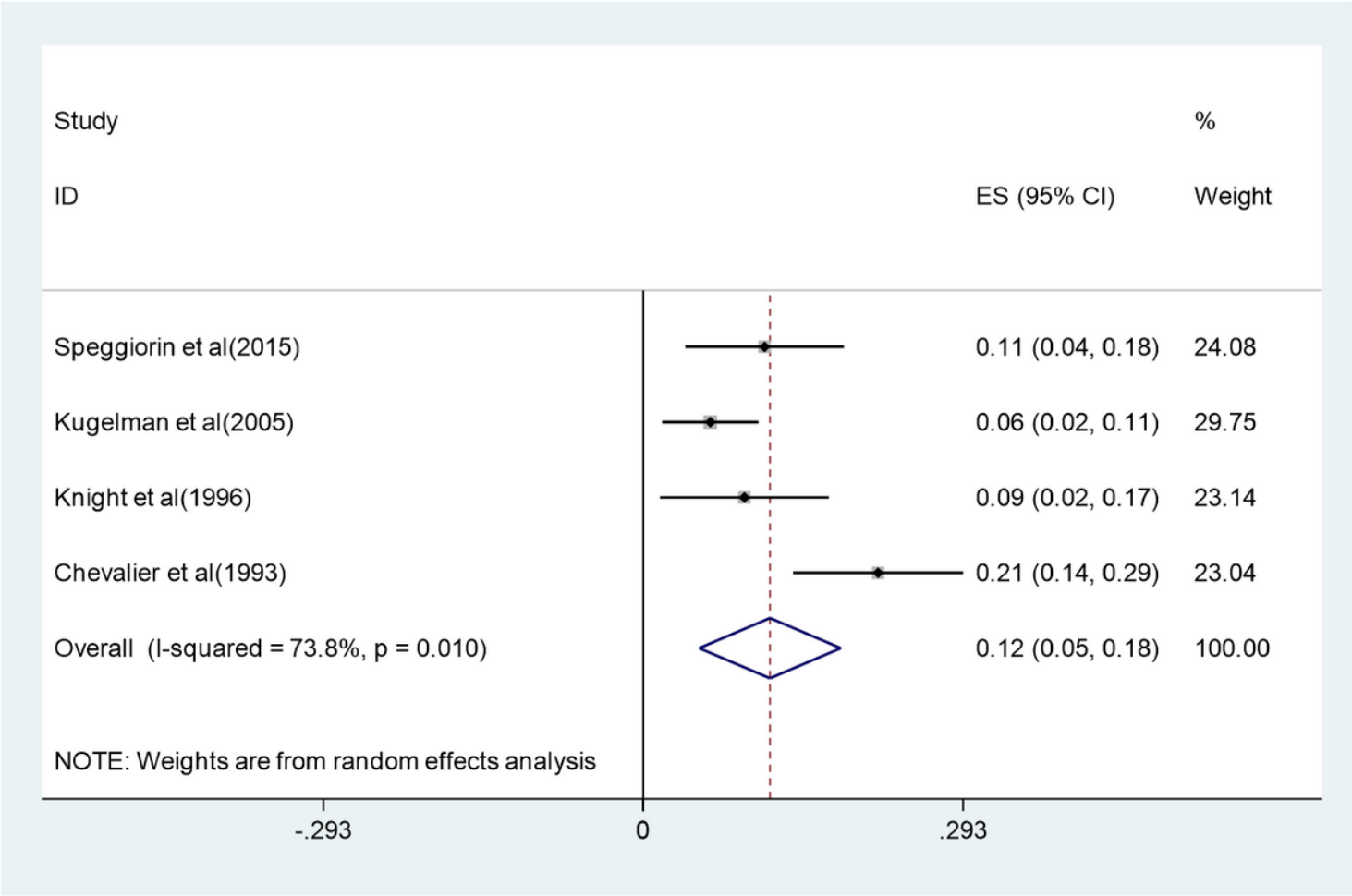

Figure 2

Forest plot of pooled mortality during hospitalization

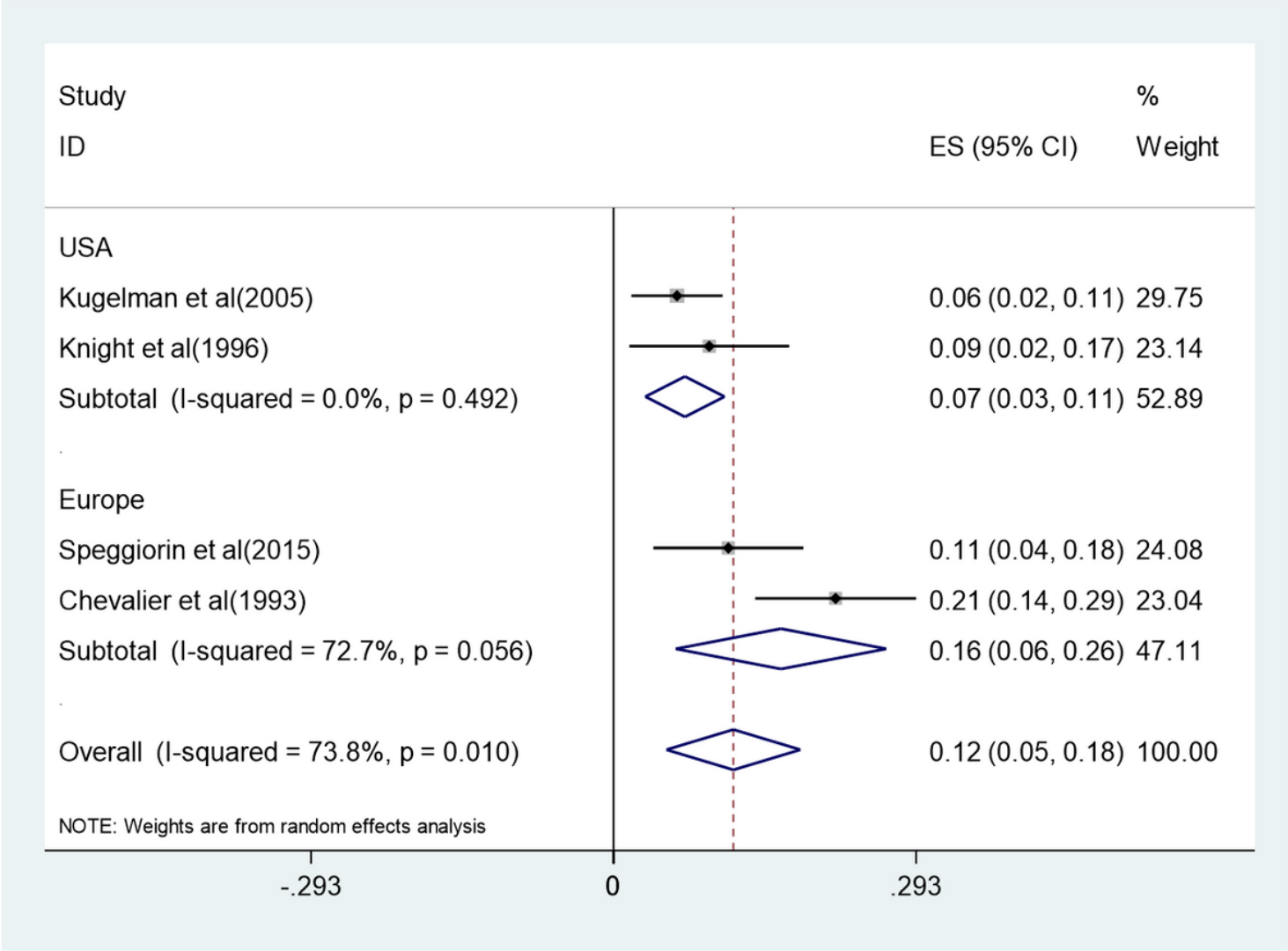

Figure 3

Forest plot of mortality across racial groups

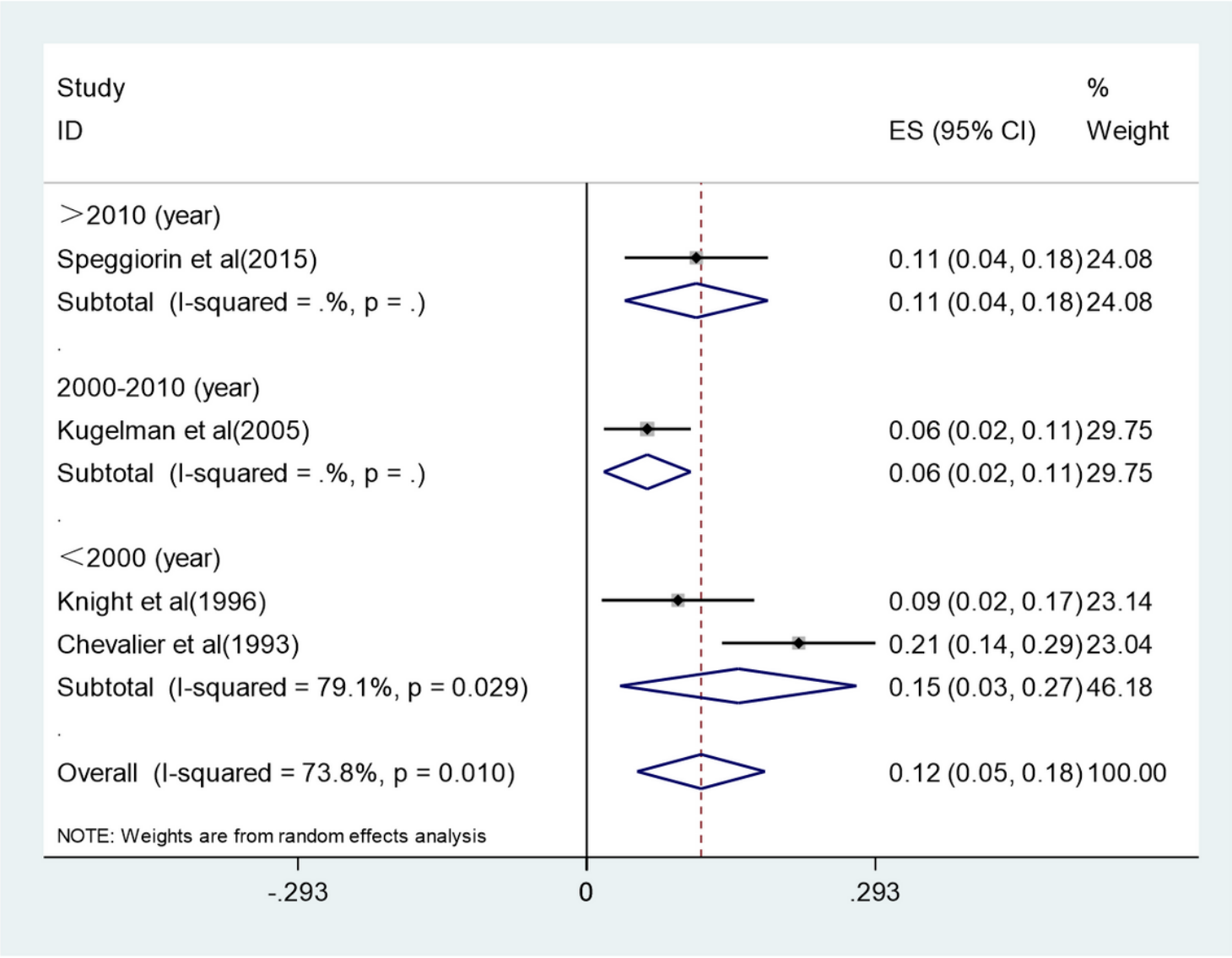

Figure 4

Forest plot of mortality from different publication years

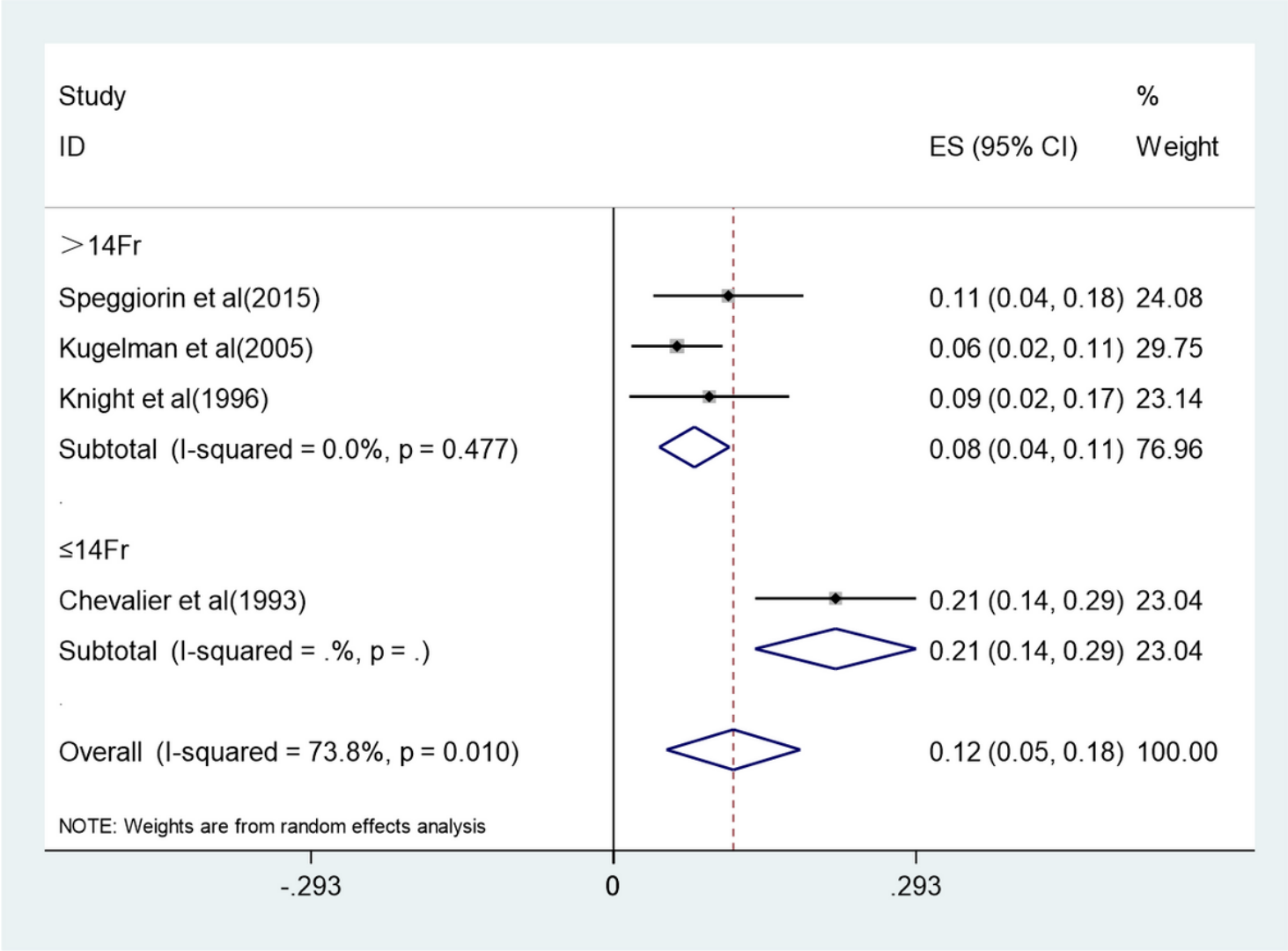

Figure 5

Forest plot of mortality with different maximum cannula sizes

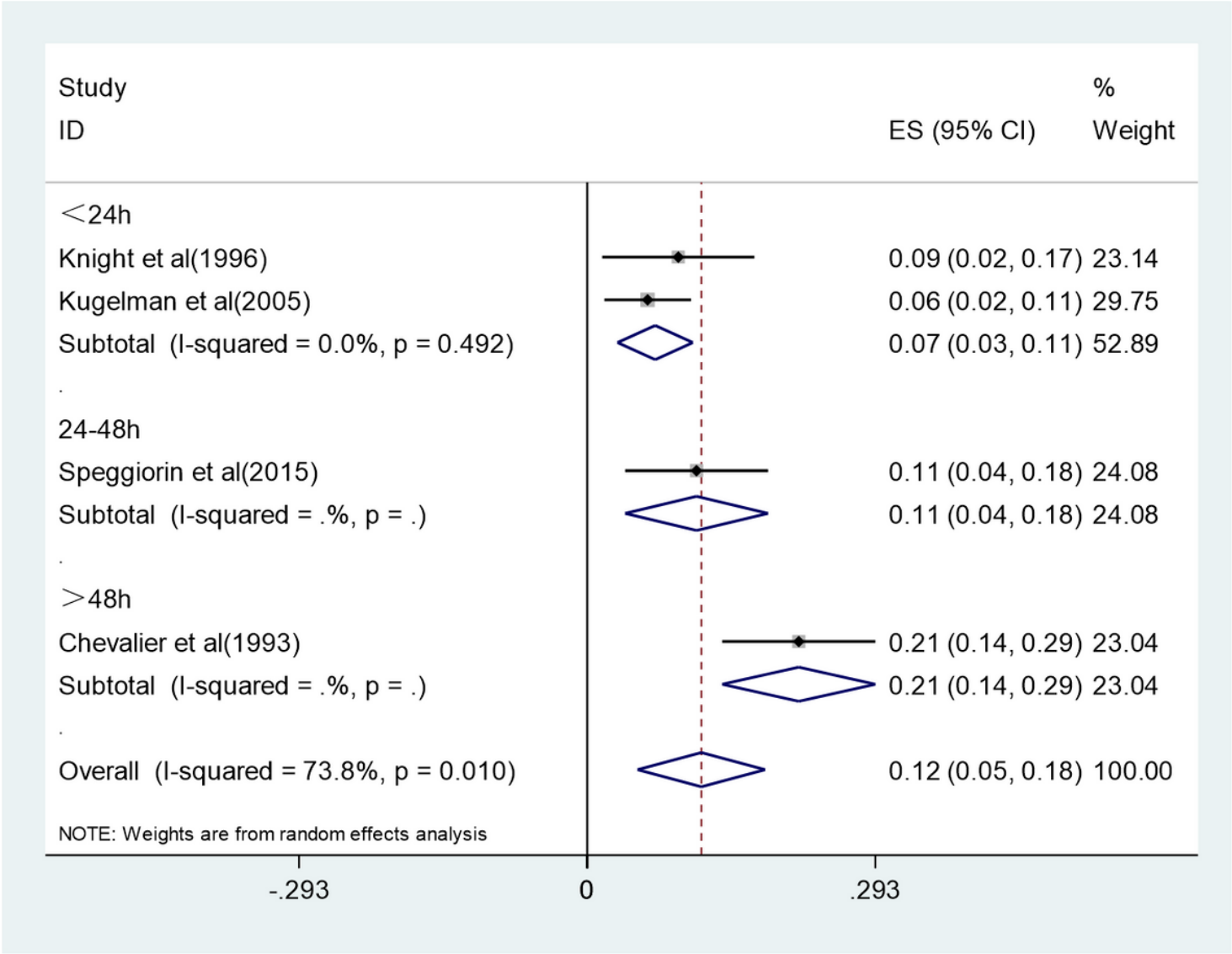

Figure 6

Forest plot of mortality at different ages at the beginning of ECMO

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PRISMA2009checklist.doc