The Impact of Right Ventricular Dysfunction on the Mortality in Patients with Acute Respiratory Distress Syndrome: A Systematic Review and Meta-Analysis.

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Abstract

Background: Previous studies have found various incidences of right ventricular dysfunction (RVD) and its association with clinical outcome. In this systematic review and meta-analysis, we aimed to investigate the impact of the presence of RVD on mortality in patients with ARDS.

Method: We searched Medline, Embase, and the Cochrane Central Register of Controlled Trials for studies investigating the association between RVD and mortality. Two authors independently evaluated whether studies meet eligibility criteria and extracted the selected patients' and studies' characteristics and outcomes. The primary outcome was the association between mortality and the presence of RVD in patients with ARDS.

Results: We included 9 studies (N = 1,861 patients) in this meta-analysis. RVD was present in 21.0% (391/1,861). In the pooled meta-analysis, the presence of RVD in patients with ARDS was associated with significantly higher overall mortality (OR: 1.45, 95%CI: 1.13-1.86, p-value = 0.003, I^2 = 0%), as well as short-term mortality (OR: 1.48, 95%CI: 1.14-1.93, p-value = 0.003, I^2 = 0%).

Conclusion: In this systematic review and meta-analysis including 1,861 patients with ARDS, the presence of RVD was significantly associated with increased overall and short-term mortality.

Trial registration: The protocol was registered at PROSPERO (CRD42020206521).

Background

Despite advances in the management of ARDS including lung-protective ventilation, prone positioning, and neuromuscular blockade, the mortality still remains alarmingly high, with a recent meta-analysis reporting a mortality of 30–40%.[1] There is evolving evidence that right ventricular dysfunction (RVD) with associated hemodynamic compromise might be a significant factor associated with higher mortality in ARDS.[2]

The etiology of RVD in patients with ARDS is complex and is driven primarily by an increase in pulmonary vascular resistance due to ongoing inflammation, hypoxemia driven vasoconstriction, micro-thrombi formation, and vascular remodeling.[3] The thin-walled right ventricle with a low contractile reserve is ill-adapted for an abrupt increase in afterload, and this leads to acute cor-pulmonale in these patients. RVD is further exacerbated with the use of positive pressure ventilation in patients with ARDS due to increased RV afterload from increased intrathoracic pressure.[4]

Historically, pulmonary artery catheters were used to evaluate right heart function in ARDS patients, however, contemporary intensive care units (ICU) rarely use pulmonary artery catheters in routine practice.[5] The widespread usage of critical care echocardiography in recent times has renewed interest in better understanding not only the prognostic role of RVD in mortality associated with ARDS but also the factors associated with RVD.[2] Previous studies have reported a wide range of the prevalence of RVD in ARDS. Also, most of these studies had small sample sizes and varying methodologies which led to discordant results. In this systematic review and meta-analysis, we aim to pool these studies to better understand the prevalence of RVD and to report on the mortality in patients with ARDS who develop RVD.

Methods

Data Sources and Search Strategy

This study complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement,[6, 7] and the Meta-Analyses of Observational Studies in Epidemiology proposals.[8] Our protocol was registered at PROSPERO (CRD42020206521).

A comprehensive search of Medline, Embase, and Cochrane Central Register of Controlled Trials was conducted with the search strategy detailed in **Supplementary Table 1.** The search period was limited from 1990 to 2020. Our search was updated on August 28, 2020. We stored citations and removed duplicates using EndNote (Thomson Reuters, Toronto, Ontario, Canada). Two reviewers (R.S. and S.D.) independently reviewed the titles and abstracts obtained by the search and selected those that fit the inclusion criteria. We then retrieved these articles, independently read the full-text, and evaluated whether the articles fit our inclusion criteria on Covidence (https://www.covidence.org).

When there were disagreements between the two reviewers, it was discussed with the third reviewer (S.V.)
in detail to reach a consensus. Two authors (R.S. and S.D.) independently extracted the following data from the eligible studies: year of publication, country, number of participants, mean/median age, sex, the definition of RVD, cause of ARDS, the mortality, and inclusion and exclusion criteria.

Inclusion And Exclusion Criteria

We included interventional and observational studies that focused on the association between RVD and the mortality in patients (≥ 18 years old) with ARDS. Studies assessing RV structure and function with either transthoracic or transesophageal echocardiography (TTE or TEE), or pulmonary artery catheterization were included. ARDS was diagnosed based on either American European consensus conference[9] or Berlin definition.[10] We excluded studies where a 2 X 2 table between RV function and mortality cannot be constructed, conference proceedings (due to high risk of bias), and studies from non-English literature. If studies had duplication of data, and the same data was published at different time points, we chose the most relevant study as the representative sample for this meta-analysis.

The primary outcome for this study was the overall reported mortality defined as either the intensive care unit (ICU) mortality, in-hospital mortality, or mortality within 90 days. We also performed the pooled analysis for short-term mortality (ICU-mortality, in-hospital mortality, or mortality ≤ 30 days) and long-term

mortality (> 30 days), as well as the pooled analysis for adjusted odds ratio for the mortality.

Statistical analysis

The pooled odds ratios (ORs) and 95% confidence intervals (CI) were calculated using the random effect (DerSimonian- Laird) method.[11] Q statistic test, as well as I^2 statistic with 95% CI, were used to assess heterogeneity. For Q statistic, substantial heterogeneity was defined as $p < 0.05$. The I^2 statistic ranges from 0 to 100% ($I^2 < 25\%$: low heterogeneity, $I^2 = 25–50\%$: moderate heterogeneity, and $I^2 > 50\%$: substantial heterogeneity).[12]

To assess publication bias, we created the funnel plots and tested the symmetry of the funnel plots using Egger's regression test.[13]

Statistical analysis was performed using Comprehensive Meta-analysis version 3 software (Biostat Inc, Eaglewood, MJ, USA) and Review Manager (RevMan) 5.4.1 software (Cochrane Information Management System).

Assessment Of The Risk Of Bias

The risks of bias were independently evaluated by two authors (R.S. and S.D.) and verified by another author (S.V.). If there were disagreements, a discussion with the research team was held to reach a consensus. We assessed the study quality of each article using the quality of the study using a modified version of the Newcastle-Ottawa quality assessment scale.[14]

Results

Search results

Our search strategy identified 2,307 articles. After removing the duplicates and clearly irrelevant studies, full texts of 103 studies were assessed for eligibility. Fourteen studies reported the outcomes of interest for RVD in patients with ARDS.[15–28] Nine studies with a total of 1,861 patients were included for the final analysis as shown in Fig. 1.[16, 19–21, 23, 24, 26–28]

Baseline Characteristics

All articles were published between 2009 and 2018. Six studies were conducted in Europe,[16, 19–21, 23, 28] one in the United States, [27] and two in Asia, [24] [26]. Five were prospective observational studies,[20, 21, 24, 26, 28] two were retrospective studies,[16, 19] and two were the post-hoc analysis of a previously conducted randomized controlled trial.[23, 27] (Table 1**)** Inclusion and exclusion criteria for the studies are shown in **Supplementary Table 2**. The risk of bias for the included studies was evaluated using a modified version of the Newcastle-Ottawa Scale, as shown in Table 3.

Table 1
Characteristics of each study.

Authors	Country	Sample size	Setting	Study period	Definition of ARDS	Definition of RVD	Mortality
Osman / 2009	France	145	Multi-center, post-hoc analysis of RCT.	January 1999 – June 2001	American-European consensus conference	(1) MPAP > 25 mmHg, (2) CVP > PAOP, and (3) SVI < 30 mL/m^2, based on PAC.	28-day
Bull / 2010	United States	367	Post-hoc analysis of multicenter randomized controlled trial	June 2000 – Oct 2005	American-European consensus conference	CVP > PAOP	60-day
Fichet 2012	France	50	Single-center, prospective	Not reported	American-European consensus conference	TAPSE < 12mm or St < 11.5cm/sec	ICU
Legras / 2015	France	166	Multi-center, prospective	November 2009 -June 2012	American-European consensus conference	RVEDA/LVEDA ratio > 0.6 associated with systolic paradoxical ventricular septal motion by TTE or TEE.	28-day
Lazzeri / 2016	Italy	74	Single-center, retrospective	October 2009 – December 2013	Berlin definition. All included patients underwent VV-ECMO.	RVEDA/LVEDA ratio > 0.6 by TTE or TEE.	ICU
Mekonstso Dessap / 2016	France	752	Multi-center, prospective	1994– 2012	Berlin definition (Although the study was initiated begore 2011, all met the Berlin definition.)	RVEDA/LVEDA ratio > 0.6 associated with septal dyskinesia by TEE.	In-hospital
See / 2017	Singapore	234	Single-center, prospective	September 2012 – May 2014	Berlin definition	RVEDA/LVEDA ratio ≥ 1 by TTE.	In-hospital
Bonizzoli / 2018	Italy	28	Single-center, retrospective	January 2016 – June 2017	Berlin definition	RV strain free wall < 20%.	ICU
Zeiton / 2018	Egypt	45	Single-center, prospective	June 2016 – December 2016	Berlin definition	RVEDA/LVEDA ratio > 0.6 associated with septal dyskinesia by TTE.	28-day

RV: right ventricle / right ventricular

RVD: right ventricular dysfunction

TAPSE: tricuspid annular plane systolic excursion

St: peak systolic velocity at the tricuspid valve

ACP: acute cor pulmonale

VV-ECMO: veno-venous extracorporeal membrane oxygenation

MPAP: mean pulmonary artery pressure

TTE: transthoracic echocardiography

TEE: transesophageal echocardiography

RCT: randomized controlled trial

PAC: pulmonary artery catheter

MPAP: mean pulmonary artery occlusion pressure

CVP: central venous pressure

PAOP: pulmonary artery occlusion pressure

SVI: stroke volume index

Table 2
The characteristics of included patients.

Authors		Age	Male (%)	Fluid in 24 hours (ml)	Vasopressors	Mechanical ventilation	P/F ratio	PEEP (cmH_2O)	Plateau pressure (cmH_2O)	Compliance (mL/cmH_2O)	LV function	S
Osman /2009	RVD/ACP (+)	64 (13)	35.7 % (5/14)	—	78.6 % (11/14)	100 % (14/14)	115 (26)	6 (4)	28 (6)	23 (5)	SVI: 23 (3) (mL/m^2)	5
	RVD/ACP (-)	60 (16)	70.2 % (92/131)	—	76.3 % (100/131)	100 % (131/131)	98 (35)	7 (4)	25 (6)	32 (10)	SVI: 36 (12) (mL/m^2)	5
Bull / 2010	RVD/ACP (+)	50 †	55.2% †† (262/475)	—	36.4% †† (173/475)	100% (44/44)	160 †	9.3 †	26.2 †	—	Survived: CI: 4.5 (1.4)	A II
	RVD/ACP (-)			—		100% (323/323)				—	Died: CI; 4.4 (1.6)	
Fichet / 2012	RVD/ACP (+)	60 (42–72)	67.9% (19/28)	4000 (3000–6000)	53% (8/15)	100% (28/28)	100 (82–117)	10 (8–11)	28 (26–30)	—	49.5 (36–62)	5 5
	RVD/ACP (-)	51 (37–65)	50.0 % (9/18)	4000 (2000–6000)	45% (16/35)	100% (18/18)	122 (86–150)	8 (8–10)	24 (20–28)	—	63 (55–66)	4 6
Legras / 2015	RVD/ACP (+)	56 (15)	—	—	50.0 % (18/36) *	100 % (36/36) *	112 (91 = 154)	10 (8–14) **	—	—	CI: 2.9 (2.6–3.4) ** ($L/min/m^2$)	4
	RVD/ACP (-)	—	—	—	47.7 % (62/130) *	100 % (130/130) *	114 (72–145)	11 (8–12) **	—	—	CI: 3.2 (2.6-4.0) ** ($L/min/m^2$)	
Lazzeri / 2018	RVD/ACP (+)	57 (14)	70.6 % (12/17)	—	64.7 % (11/17)	100 % (17/17)	—	—	—	—	—	4
	RVD/ACP (-)	60 (13)	75.4 % (43/57)	—	45.6 % (26/57)	100 % (57/57)	—	—	—	—	—	

*: The numbers were described for patients with only ACP or without ACP and PFO (Patients with only PFO or with PFO and ACP were excluded).

**: The value was reported as median with interquartile range.

***: The summation of each number did not fit the reported total number.

†: The standard deviation could not be calculated

††: The numbers and percentages are per total population included in the study but not all patients were evaluated for RVD/ACP. Therefore, the total numbers actually analyzed number of patients.

Authors		Age	Male (%)	Fluid in 24 hours (ml)	Vasopressors	Mechanical ventilation	P/F ratio	PEEP (cmH_2O)	Plateau pressure (cmH_2O)	Compliance (mL/cmH_2O)	LV function	S
Mekontso Dessap / 2016	RVD/ACP (+)	57 (16)	63.4 % (104/164)	—	68.,9 % (113/164)	100 % (164/164)	106 (40)	8 (4)	26 (5)	28 (11)	—	5
	RVD/ACP (-)	58 (17)	68.5 % (403/588)	—	66.2 % (389/588)	100 % (588/588)	118 (42)	8 (4)	24 (4)	32 (12)	—	5
See / 2017	RVD/ACP (+)	65 (13)	65.2 % (43/66)	—	33.3 % (22/66)	89.4 % (59/66)	169 (63)	7 (3)	21 (5)	34 (18)	LVEF < 40% (10/66)	A II
	RVD/ACP (-)	62 (15)	61.3 % (103/168)	—	32.7 % (55/168)	88.1 % (148/168)	172 (69)	6 (3)	21 (2)	29 (12)	LVEF < 40% (28/168)	A II
Bonizzoli / 2018	RVD/ACP (+)	58 †	53.3 % (16/30)	—	—	100% (3/3)	107 †	12.7 †	—	—	54.9% †	4
	RVD/ACP (-)			—	—	100% (25/25)			—	—		
Zeitoun / 2018	RVD/ACP (+)	39 (14)	39.0 % (3/10)		100% (10/10)	100 % (10/10)	77 (13)	14 (1)	40 (7)	—	—	-
	RVD/ACP	49	48.6%	—	74.3 %	100 %	151	11 (2)	32 (10)	—	—	-

*: The numbers were described for patients with only ACP or without ACP and PFO (Patients with only PFO or with PFO and ACP were excluded).

**: The value was reported as median with interquartile range.

***: The summation of each number did not fit the reported total number.

†: The standard deviation could not be calculated

††: The numbers and percentages are per total population included in the study but not all patients were evaluated for RVD/ACP. Therefore, the total numbers actually analyzed number of patients.

Authors	(-)	Age (15)	Male (%) (17/35)	Fluid in 24 hours (ml)	Vasopressors (26/35)	Mechanical ventilation (35/35)	P/F ratio (61)	PEEP (cmH_2O)	Plateau pressure (cmH_2O)	Compliance (mL/cmH_2O)	LV function	S
*: The numbers were described for patients with only ACP or without ACP and PFO (Patients with only PFO or with PFO and ACP were excluded).												
**: The value was reported as median with interquartile range.												
***: The summation of each number did not fit the reported total number.												
†: The standard deviation could not be calculated												
††: The numbers and percentages are per total population included in the study but not all patients were evaluated for RVD/ACP. Therefore, the total numbers actually analyzed number of patients.												

Table 3
Newcastle-Ottawa Scale assessment of pooled studies.

Study	Selection				Comparability	Outcomes			Total
	Representativeness of exposed cohort	Selection of nonexposed cohort	Ascertainment of exposure	Outcome not present at the start of the study		Assessment of outcomes	Length of follow-up	Adequacy of follow-up	
Osman / 2009	*	*	*	*	— †	*	*	*	7
Bull / 2010	*	*	*	*	—	*	*	*	7
Fichet / 2012	*	*	*	*	—	*	*	*	7
Legras / 2015	*	*	*	*	—	*	*	*	7
Lazzeri / 2016	*	*	*	*	—	*	*	*	7
Mekontso Dessap / 2016	*	*	*	*	**	*	*	*	9
See / 2017	*	*	*	*	**	*	*	*	9
Bonizzoli / 2018	*	*	*	*	—	*	*	*	7
Zeiton / 2018	*	*	*	*	—	*	*	*	7
†: Although multivariate analysis was performed, it was not for 28-day mortality (it was for 90-day mortality).									

The mean/median age of included patients ranged from 41 to 62, and 44.4–73% were males. Mean/median Simplified Acute Physiology Score II score ranged from 43–50 (patients with RVD: 47–55, patients without RVD: 43–54). In included population, 98.5% (1,834/1,861), and 55.3% (1,030/1,861) received mechanical ventilation, and vasopressors, respectively. Eight of nine studies reported mean/median positive end-expiratory pressure (PEEP) level (range: 7 to 12.7 cmH_2O) and P/F ratio (range: 99–171) when patients were evaluated for RVD. Plateau pressure was reported in 6 studies and it ranged from 21 to 33.6 cmH_2O. (Table 2) The definition of RVD used in each study is reported in Table 1.

Outcomes

RVD was present in 21.0% (391/1,861) of the cohort. In the pooled meta-analysis of 9 studies, the presence of RVD in patients with ARDS was associated with a significantly higher overall mortality (OR: 1.45, 95%CI: 1.13–1.86, p-value = 0.003, I^2 = 0%), as shown in Fig. 2. In subgroup analysis investigating short-term and long-term mortalities, the presence of RVD in patients with ARDS was associated with significantly higher short-term mortality (OR: 1.48, 95%CI: 1.14–1.93, p-value = 0.003, I^2 = 0%), while the association was not significant in long-term mortality (OR: 1.24, 95%CI: 0.66–2.33, p-value = 0.003, I^2 = 0%), as shown in **Supplementary Fig. 2**.

In the pooled analysis of 3 studies that investigated adjusted odds ratio of mortality, the presence of RVD was associated with a significantly higher mortality (OR: 1.95, 95%CI: 1.30–2.93, p-value = 0.001, I^2 = 0%), as shown in **Supplementary Fig. 2**. Although Lazzeri et al. reported OR for ICU-mortality using a stepwise regression analysis adjusting for TAPSE < 16mm, we did not include this study in the pooled analysis of studies investigated adjusted OR because this was not a multivariate analysis adjusting for risk factors of ICU-mortality.

We detected no evidence of publication bias when we assessed the funnel plots visually, as shown in **Supplementary Fig. 2**. We also statistically assessed publication bias using Egger's regression test and found no publication bias (p-value = 0.080).

Discussion

In this systematic review and meta-analysis, that included 1,861 patients with ARDS, RVD was present in 21.0% (391 patients) of the cohort. The presence of RVD in ARDS was associated with a significantly higher risk of overall and short-term mortality

This systematic review also highlights that RVD in literature was evaluated by different modalities and a multitude of definitions which might account for the wide range (9.5–89.5%) of reported prevalence of RVD in ARDS. The ideal modality for the recognition of RVD in critically ill patients remains inconclusive. The complex anatomy of RV and the challenges of image-acquirement in patients with.[29] However, in most ICUs expertise and access to TEE remains limited, constraining the widespread applicability of TEE as a modality of choice. In addition, as shown in our systematic review, various parameters used to define RVD adds to inconsistency in our understanding of RVD in ARDS. This variability arises from the lack of a standardized definition of RVD in critically ill patients, supporting the acute need for validated criteria for RVD in ARDS with various modalities to better understand the prevalence and impact of RVD in patients with ARDS.

In our study, we demonstrated that RVD in ARDS was associated with increased short-term and overall mortalities. Initial studies [16, 20, 21, 23, 27] were not conclusive in assessing the impact of RVD in ARDS owing to their limited sample size and heterogeneity of the study population.

The determinants of higher mortality with RVD in patients with ARDS remain poorly understood. Studies have identified driving pressure ≥ 18 cmH_2O, PaCO2 ≥ 48 cm_2O, and P/F ratio < 150 mmHg as independent factors associated with the development of RVD.[21] In some, the compromised right ventricle enters a vicious cycle of hemodynamic compromise from cor-pulmonale, deteriorating organ perfusion and failure culminating into death. The concern for higher mortality with RVD in ARDS has steered experts from the “Lung protective” to the “RV protective” approach in ARDS management. The management entails reducing lung stress by limiting plateau < 27 cm H_2O and driving pressure at < 18 cm H_2O. Prone position ventilation, an intervention with a mortality benefit in ARDS has also been shown to relieve RV enlargement and septal dyskinesia by reducing PVR.[30, 31] The use of pulmonary vasodilators or inotropic agents may also have a role in reducing PVR in RVD.[32] Veno-venous extracorporeal membranous oxygenation or extracorporeal carbon dioxide removal has been shown to unload the RV in patients with ARDS and RVD.[33] In addition, the extracorporeal management facilitates limiting injurious ventilator settings and correcting hypercapnia, factors know to worsen RVD. It still remains unclear if the integration of these interventions in a systematic fashion translates to improved clinical outcomes. A randomized controlled trial with well-defined criteria for the early diagnosis of RVD is warranted to evaluate the effectiveness of the RV-protective strategy.

There are limitations in this study. First, the sample sizes of the included studies were relatively small. However, the results of all included studies were quite consistent and the generalizability of this studies’ finding appears to be robust. Second, the definition and modality used to define RVD were not consistent and this might have affected the result of each study. In addition to inconsistent criteria, the limited information of loading conditions including PEEP, plateau pressure, and fluid balance made it challenging to assess RV function accurately. Future studies evaluating RVD in critically ill patients need to use validated criteria developed in concordance with existing ASE guidelines to ensure consistent reporting of prevalence and outcomes of RVD in this population. Third, only two studies investigated long-term mortality and the association between the presence of RVD and long-term mortality was not significant.[23, 27] In addition to a small number of included patients, this might be also because long-term mortality in patients with ARDS mainly depends on non-modifiable factors such as age or comorbidities while short-term outcome has improved with the development of therapeutic interventions.[34]

Conclusion

In this systematic review and meta-analysis including 1,861 patients with ARDS, the presence of RVD was significantly associated with increased overall and short-term mortality. This result implicates the importance of right ventricle assessments in patients with ARDS.

Abbreviations

list
RV
right ventricle / right ventricular
RVD
right ventricular dysfunction
ARDS
acute respiratory distress syndrome
ICU
intensive care unit
TTE
transthoracic echocardiography
TEE
transesophageal echocardiography
PRISMA
Preferred Reporting Items for Systematic Reviews and Meta-Analyses
OR
odds ratio
CIs

confidence intervals
PEEP
positive end-expiratory pressure
RVEDA
right ventricular end-diastolic area
LVEDA
left ventricular end-diastolic area
TAPSE
tricuspid annular plane systolic excursion
St
peak systolic velocity at the tricuspid valve
ACP
acute cor pulmonale
VV-ECMO
veno-venous extracorporeal membrane oxygenation
MPAP
mean pulmonary artery pressure
RCT
randomized controlled trial
PAC
pulmonary artery catheter

Declarations

Author's Contributions

R.S. and S.D. are equally responsible for the conception of the study design, data collection and analysis, interpretation of the analysis, writing of the draft, and critical revision of the manuscript. M.S, contributed substantially to data collection. W.C. contributed substantially to data analysis and interpretation. P.C., A.D. and S.V. supervised drafting and revision of the manuscript. All authors approved the submission of the final manuscript.

Conflicts of Interest

We declare no competing interests.

Data sharing statement

All data associated with this manuscript are included in the main text and supplementary materials.

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Ethics approval

The following systematic review and meta-analysis was registered in PROSPERO

Consent for publication

All authors consent to publication of manuscript and support material.

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Figures

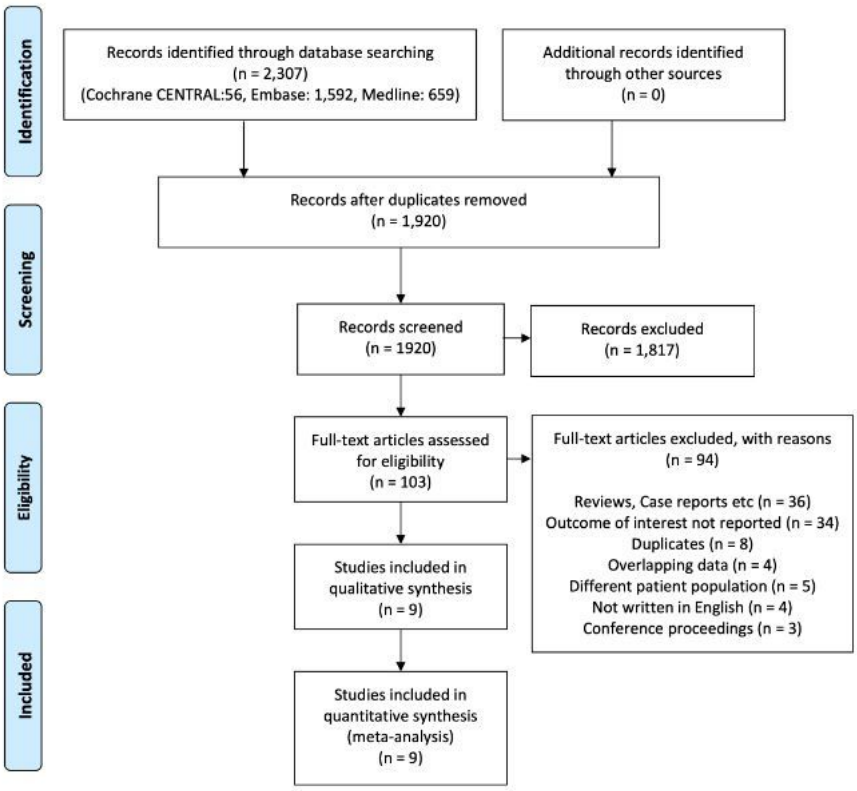

Figure 1

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) chart. Identification and selection of studies for inclusion.

Figure 2

The pooled analysis for the mortality

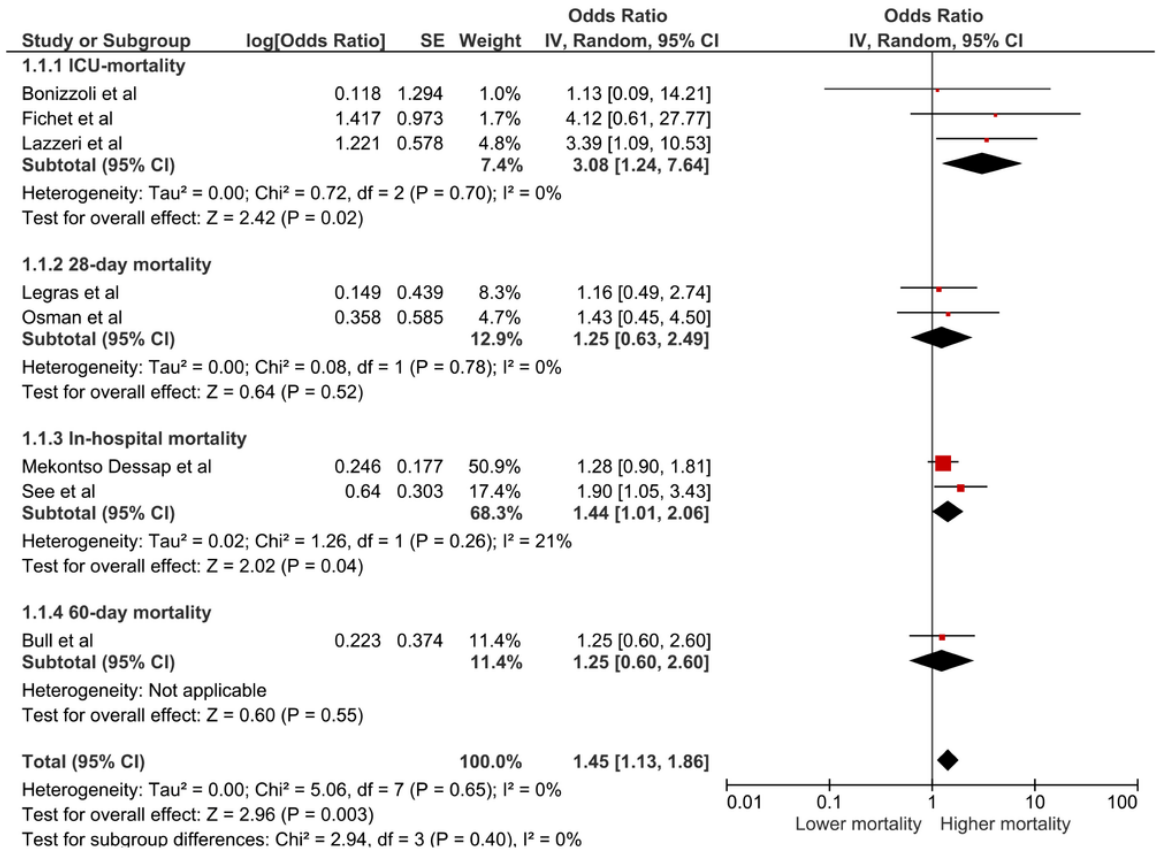

Figure 2

Forest plot of patients with right ventricular dysfunction versus those without: The pooled odds ratios of ICU-mortality, 28-day mortality, In-hospital mortality, 60-day mortality, and overall mortality are shown.

Supplementary Files

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