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Survival of patients with acute pulmonary embolism treated with venoarterial extracorporeal membrane oxygenation: A systematic review and meta-analysis

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ABSTRACT

Background: To examine whether venoarterial extracorporeal membrane oxygenation (VA-ECMO) improves survival of patients with acute pulmonary embolism (PE).
Methods: Following the PRISMA guidelines, a systematic search was conducted up to August 2019 of the databases: PubMed/MEDLINE, EMBASE and Cochrane. All studies reporting the survival of adult patients with acute PE treated with VA-ECMO and including four patients or more were included. Exclusion criteria were: correspondences, reviews and studies in absence of a full text, written in other languages than English or Dutch, or dating before 1980. Short-term (hospital or 30-day) survival data were pooled and presented with relative risks (RR) and 95% confidence intervals (95% CI). Also, the following predefined factors were evaluated for their association with survival in VA-ECMO treated patients: age > 60 years, male sex, pre-ECMO cardiac arrest, surgical embolectomy, catheter directed therapy, systemic thrombolysis, and VA-ECMO as single therapy.
Results: A total of 29 observational studies were included ($N = 1947$ patients: VA-ECMO $N = 1138$ and control $N = 809$). There was no difference in short-term survival between VA-ECMO treated patients and control patients (RR 0.91, 95% CI 0.71–1.16). In acute PE patients undergoing VA-ECMO, age > 60 years was associated with lower survival (RR 0.72, 95% CI 0.52–0.99), surgical embolectomy was associated with higher survival (RR 1.96, 95% CI 1.39–2.76) and pre-ECMO cardiac arrest showed a trend toward lower survival (RR 0.88, 95% CI 0.77–1.01). The other evaluated factors were not associated with a difference in survival.
Conclusions: At present, there is insufficient evidence that VA-ECMO treatment improves short-term survival of acute PE patients. Low quality evidence suggest that VA-ECMO patients aged ≤60 years or who received SE have higher survival rates. Considering the limited evidence derived from the present data, this study emphasizes the need for prospective studies.
Protocol registration: PROSPERO CRD42019120370.

1. Introduction

Massive pulmonary embolism (PE) is associated with poor survival. The obstructive shock caused by massive PE can result in end-organ failure and cardiac arrest [1,2]. Venoarterial Extracorporeal Membrane Oxygenation (VA-ECMO) is increasingly used as a treatment strategy in hemodynamically compromised patients with acute PE. VA-ECMO restores the circulation and unloads the right ventricle by bypassing the

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pulmonary circulation. While circulation is restored, the PE can resolve or be removed. So, in case of acute PE, VA-ECMO may be used as bridge to recovery or bridge to treatment.

Although VA-ECMO enables haemodynamic stability and restores tissue perfusion, it is unknown if this high-risk therapy will lead to higher survival rates in acute PE patients. In addition, it is not clear which patients would benefit the most and for which patients this highly invasive therapy with major complication rate would not be a suitable treatment option.

In an attempt to investigate whether VA-ECMO treatment is beneficial and if there are any factors associated with clinical outcome, we performed a systematic review and meta-analysis on the current available evidence. The aim of this study is to examine whether VA-ECMO treatment is associated with an improved survival in acute PE patients and to explore factors that may be associated with survival.

2. Materials and methods

This study is performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [3]. It is listed in the PROSPERO register with registration number CRD42019120370.

2.1. Study eligibility criteria

To qualify for inclusion studies had to include adults (≥ 18 years) with acute PE of any aetiology who received VA-ECMO treatment. We also included studies that only contained a subgroup of acute PE patients with VA-ECMO. A control group (defined as acute PE patients without VA-ECMO treatment) was not necessary to qualify for inclusion. Studies were only included if they reported the primary outcome (short-term survival) for PE patients that received VA-ECMO. Any type of study (e.g., randomized trial, observational cohort, case-control, case-series) containing four patients or more was included. Exclusion criteria were studies that only involved patients with cardiac arrest or shock due to other aetiologies than PE. Further, correspondences, reviews and studies in absence of a full text, written in other languages than English or Dutch or dating before 1980 were also excluded.

2.2. Search

A medical information specialist conducted a systematic search of the following databases: PubMed/MEDLINE (OVID), EMBASE (OVID) and the Cochrane Central Register of Controlled Trials (CENTRAL) up to 5 August 2019. The full search is available in the Additional file Appendix 1. In summary, we integrated various search terms containing 'extracorporeal life support' combined with 'pulmonary embolism' applying the Boolean operator 'AND' using medical subject headings (Mesh) and free terms. Synonyms were added to the search: 'Extracorporeal membrane oxygenation' or 'ECMO' or 'ECLS' combined with 'pulmonary thromboembolism' using the Boolean operator 'OR' to screen on various synonyms.

2.3. Study selection

Two reviewers (M.K. and L.M.) independently screened all titles and abstracts. After selecting articles for full text screening, they discussed any disagreements regarding inclusion or exclusion. Next, these selected papers were independently screened (by M.K. and L.M.) in full text and if they met the selection criteria, they were included for data extraction. Disagreements concerning inclusion or exclusion for this review were discussed and when needed a third reviewer (A.V.) was consulted. All of the disagreements regarding eligibility were resolved.

2.4. Definitions

The primary outcome was short-term survival, defined as hospital or 30-day survival. Long-term survival was defined as ≥3-month survival. Favourable neurological outcome was defined as a cerebral performance category (CPC) score of 1–2. As secondary outcome, factors were evaluated for their association with survival in patients treated with VA-ECMO. The following pre-defined factors were evaluated: age > 60 years, male sex, cardiac arrest occurring pre ECMO initiation or during ECMO initiation (i.e., extracorporeal cardiopulmonary resuscitation, ECPR), surgical embolectomy, catheter directed therapy (i.e., thrombectomy or thrombolysis, CDT), systemic thrombolysis and VA-ECMO as single therapy.

2.5. Data extraction

Two reviewers (M.K. and L.M.) extracted the data independently, using a pre-defined standardized data extraction form. Extracted data were compared and in case of discrepancies the original articles were checked. The pre-defined data extraction included: study characteristics (e.g., author and study design), number of PE patients (categorized in VA-ECMO and control), patient demographics (e.g., age and sex), baseline characteristics (e.g., predisposing factors and extracorporeal cardiopulmonary resuscitation, ECPR), treatment characteristics (e.g., systemic thrombolysis and surgical embolectomy), clinical course (e.g., complications) and clinical outcomes (e.g., survival and neurological outcome). We classified study design as descriptive study or cohort study as described by Grimes et al. [4]

For the meta-analyses on factors associated with outcome, data were collected from studies that reported individual patient outcomes of patients treated with VA-ECMO (survivors and non-survivors). In case data were missing regarding the evaluated factors, we attempted to obtain this information by contacting the first author.

2.6. Quality assessment

The quality of the individual studies and the certainty of evidence were assessed by two independent reviewers (M.K. and L.M.). The overall quality / certainty of evidence was rated using the GRADE's approach. [5] All included studies had an observational design and were therefore evaluated using the Newcastle-Ottawa Scale (NOS) for the individual quality assessment of non-randomized studies [6]. The NOS is a 'star-rating system' divided in to three sections: the selection of the study groups (max. 4 stars); the comparability of the groups (max. 2 stars); and the ascertainment of respectively, either the exposure or outcome of interest for case-control or cohort studies (max. 3 stars). The NOS scoring system is classified as: poor quality 0–3 stars; fair quality 4–6 stars, good quality 7–9 stars. Discrepancies were resolved by discussion.

2.7. Statistical analysis

First, we narratively described study, patient, clinical characteristics, and outcomes for each included study. Studies were categorized as VA-ECMO with control or, only VA-ECMO patients without a control group. Continuous variables were reported using mean and standard deviation (SD) or median and 25–75% quartiles (IQR) where applicable. Categorical variables were reported using numbers and percentages.

Second, for the meta-analysis involving all controlled studies, association with survival was evaluated by calculating the pooled risk ratio (RR) with 95% confidence interval (95% CI). The RRs were compared using the random-effects model and the DerSimonian and Laird method. Because of the presence of multiple zero cells, a value of 0.5 was added to each cell. Forest plots were provided for our primary outcome (short-term survival) and secondary outcome (factors evaluated for their association with survival in patients treated with VA-ECMO).

Third, in a pre-defined additional analysis we divided patients in three subgroups: [1] Patients with obstructive shock before ECMO placement; [2] Patients who experienced a cardiac arrest before or during ECMO placement; [3] these cardiac arrest patients were further divided in patients with ROSC before or during ECMO placement and patients without ROSC during ECMO placement (i.e., ECPR) patients. A loss of output and/or pulsatility during ECMO treatment was not taken into account in these subgroups. To estimate summary effects sizes, we used a single column meta-analysis technique. We synthesized a weighted average proportion (effect size) by using a random effects model. Due to the small sample size and some extreme proportions, we used a double-arcsin transformation on the data. The forest plot data were back transformed to proportions. With this analysis we attempted to decrease the heterogeneity between studies.

For these meta-analyses, heterogeneity was assessed using I^2 and Tau^2 statistics. In accordance with the Cochrane handbook, an I^2 of more than 40% was classified as substantial heterogeneity. [7] Egger regression tests and funnel plots were provided to assess publication bias. A sensitivity analysis was performed to check if outlying studies influenced our results. In the factors that contained outliers, additional analysis with exclusion of these studies was performed. A two-sided *p*-value of ≤0.05 was considered statistically significant, except for Egger regression test in which a two-sided p-value of ≤0.10 was considered statistically significant. We performed all analyses using the Meta package in R studio, version 3.6.0.

3. Results

3.1. Study selection

A total of 913 unique articles were retrieved during our search. We assessed 91 articles full text for eligibility and included 29 articles for this review, of which 24 articles reported individual patient outcome data and were included in the meta-analysis [8-36]. All included studies had an observational design. The reasons for exclusion of the articles are listed in Fig. 1. Overall, a total number of 1947 acute PE patients were included in the studies. Of these patients, 1138 received VA-ECMO treatment and 809 patients did not receive VA-ECMO treatment (control group). In the studies which reported the predefined subgroups, 143 patients were reported as being in shock and 511 patients suffered a cardiac arrest, of whom 106 patients received ECPR. The criteria and indications for the decision to initiate VA-ECMO in the included studies are available in Additional file Table A.

3.2. Characteristics

Study characteristics are shown in Additional file Table B for the included studies. There were 20 descriptive studies and 9 retrospective cohort studies. Patient characteristics of acute PE patients treated with VA-ECMO and control patients are shown in the Additional file Table C. The clinical course of patients is shown in Table 1.

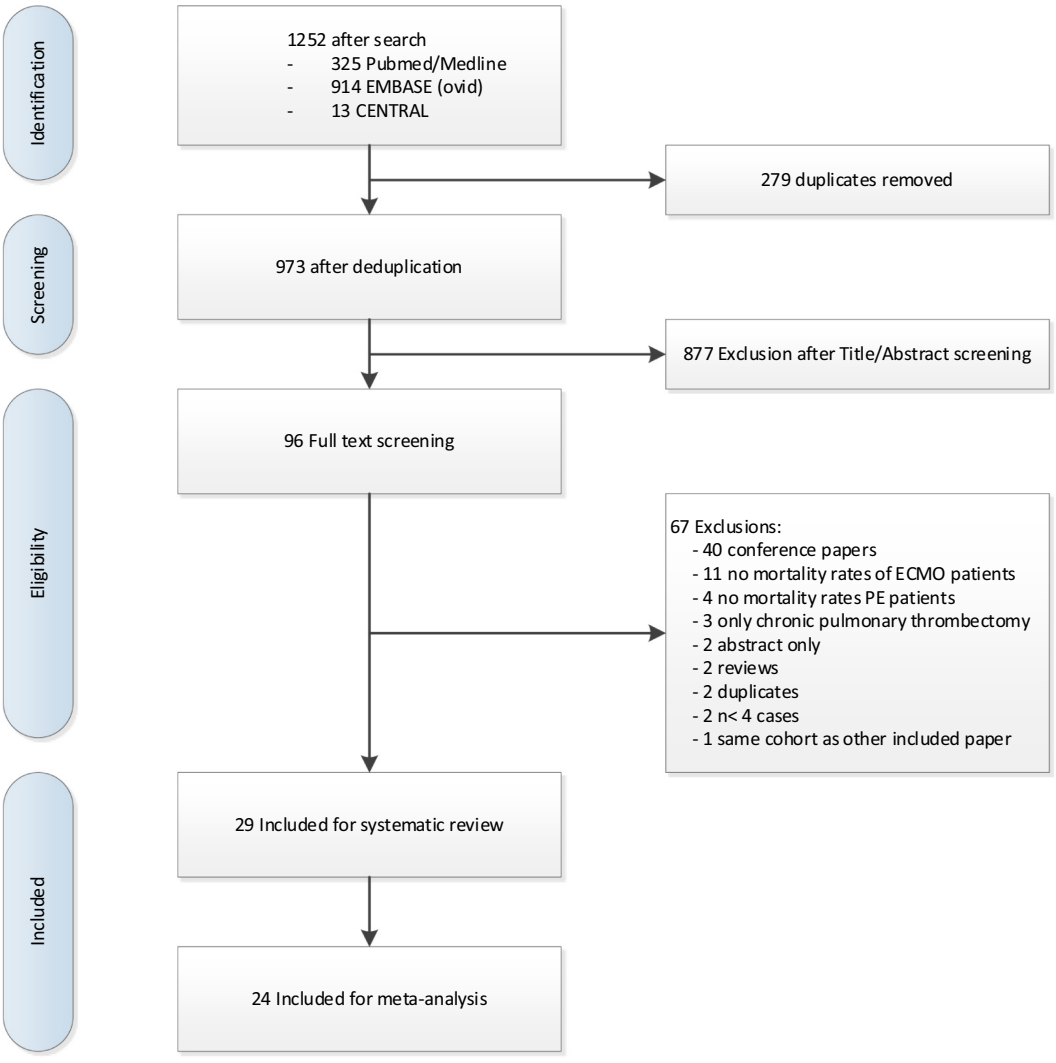

Fig. 1. Flowchart of study selection using PRISMA guidelines.

3.3. Complications

Twelve of the included studies reported complication rates. The classifications/definitions of complications were not reported (most studies) or heterogeneous among the studies. In the Additional file Table D the classification of complications of individual studies is reported. The incidence of complications differed widely, as shown in Table 1. Bleeding occurred in 8–100% of the patients, neurological complications (including neurological bleeding) in 8–76%, AKI/CVVH in 14–76%, and VA-ECMO problems in 5–66% of the patients.

3.4. Quality assessment and certainty of evidence

According to the GRADE's approach, the certainty of the evidence was low, as all included studies had an observational design and the overall quality was fair to poor. Quality assessment of the individual studies measured by the NOS resulted in a fair quality score for 22 studies and a poor quality score for 7 studies (Additional file Table E).

3.5. Short-term survival

Meta-analysis showed no difference in short-term survival for VA-ECMO treated patients and control patients (RR 0.91, 95% CI 0.71–1.16) (Fig. 2). The average weighted short-term survival proportion of VA-ECMO treated acute PE patients was 0.81 (95% CI 0.59–0.97) in shock patients, 0.50 (95% CI 0.39–0.60) in cardiac arrest patients and 0.34 (95% CI 0.21–0.49) in ECPR patients (shown in Fig. 3). The individual study results on survival outcomes of VA-ECMO vs. control patients are summarised in Table 2. For the three VA-ECMO treated subgroups (i.e., shock, cardiac arrest, and ECPR) results are shown in Additional file Table F.

There was significant heterogeneity between the studies regarding short-term survival in shock patients and cardiac arrest patients. No significant risk of publication bias was found. Additional file Table G shows the assessment of heterogeneity and risk of publication bias for short-term survival of VA-ECMO vs. control patients and per subgroup. Additional file Appendix 2 shows the funnel and influence plot of short-term survival.

As mentioned, there were limited control groups available for the subgroup analysis. Only two studies reported VA-ECMO patients with a control group regarding survival outcomes in shock patients. Kjaergaard et al. [14] ($N = 38$) showed a survival rate of 81.8% in the control group and Takahashi et al. [16] ($N = 24$) showed a survival rate of 100% in the VA-ECMO treated group as well as the control group. For cardiac arrest three studies included a control group. Mandigers et al. [10] ($N = 68$) showed a survival rate of 31.8% in the VA-ECMO treated group and 10.9% in the control group. Kjaergaard et al. [14] (N = 38) showed a survival rate of 54.5% in the VA-ECMO treated group and 80% in the control group. Shiomi et al. [15] ($N = 31$) showed a survival rate of 100% in the VA-ECMO treated group and 50% in the control group.

3.6. Factors associated with survival in patients with VA-ECMO

Of the 24 studies included in the meta-analysis on patients treated with VA-ECMO, 12 studies ($n = 137$) reported the age of individual patients, 16 studies ($n = 239$) reported sex differences, 22 studies ($n = 330$) reported cardiac arrest, 17 studies ($n = 275$) reported surgical embolectomy, 11 studies ($n = 193$) reported CDT, 15 studies ($n = 225$) reported systemic thrombolysis and 14 studies ($n = 178$) reported VA-ECMO as single treatment.

Two factors were associated with a significant difference in survival (Additional file Table H). Age > 60 years was associated with lower chance of survival, compared with age ≤ 60 years (RR 0.72, 95% CI 0.52–0.99). Surgical embolectomy was associated with higher chance of survival, compared with patients who did not undergo surgical

Table 1a
Clinical course of massive pulmonary embolism patients treated with/without VA-ECMO. Studies including VA-ECMO and control patients.

	Study	Number of PE patients		Shock (n, %)		Cardiac arrest (n, %)		ECPR (n, %)	Reperfusion therapy (type, n, %)			Complications (type, n, %)				
		VA-ECMO	Control	VA-ECMO	Control	VA-ECMO	Control	VA-ECMO	*Surgical Embolectomy*	*CDT*	*Systemic thrombolysis*	*Bleeding*	*Neurological (incl bleeding)*	*Infection*	*AKI/CVVH*	*Other*
3	Bougouin	12	70			12 (100)	70 (100)									
8	Funakoshi	112	249			48 (43)	45 (18)		29 (26)		83 (74)					
13	Mandigers	22	46			22 (100)	46 (100)	22 (100)			19 (86)	13 (59)	2 (9)	5 (24)	7 (32)	
14	Meneveau	52	128	13 (25)	58 (45)	39 (75)	45 (35)	18 (35)	17 (33)		20 (38)	20 (39)	4 (8)	24 (46)	22 (42)	27 (52)
15	Minakawa	94	261													
16	Moon	14	9	2 (21)	1 (11)	11 (79)	8 (89)		1 (7)		1 (7)					
24	Kjaergaard	22	16	5 (23)	14 (88)	22 (100)	0 (0)	22 (100)	5 (23)	1 (5)	12 (55)	3 (14)	2 (9)			VA-ECMO problems 1 (5)
25	Shiomi	9	22													
26	Takahashi	16	8			11 (69)	0 (0)		16 (100)			3 (19)				

Table 1b
Studies including only VA-ECMO patients, without control group.

		Number of PE patients	Shock (n, %)	Cardiac arrest (n, %)	ECPR (n, %)	Reperfusion therapy (type, n, %)				Complications (type, n, %)					
	Study	VA-ECMO	VA-ECMO	VA-ECMO	VA-ECMO	*Surgical Embolectomy*	*CDT*	*Systemic thrombolysis*	*Other*	*Bleeding*	*Neurological (incl bleeding)*	*Infection*	*AKI/CVVH*	*VA-ECMO problems*	*Other*
1	Al-Bawardy	13	13 (100)	13 (100)		4 (31)	3 (23)	8 (62)		7 (54)					2 (15)
2	Aso	353													
4	Corsi	17	2 (12)	15 (82)	7 (41)	2 (12)	2 (12)	8 (47)		15 (88)	4 (24)	2 (12)	13 (76)		2 (12)
5	de Chambrun	4	4 (100)	4 (100)	0 (0)										
6	Dennis	5		5 (100)	5 (100)										
7	Dolmatova	5	5 (100)	4 (80)		1 (20)	2 (40)	3 (60)			1 (20)				3 (60)
9	George	32		15 (47)		2 (6)	19 (59)	5 (16)		11 (34)					
10	Kawahito	7	1 (14)	5 (71)	5 (71)	3 (43)		7 (100)							
11	Maggio	19	11 (58)	10 (53)	8 (42)	4 (21)	7 (37)	6 (32)		14 (74)	5 (24)	5 (24)	5 (24)	3 (14)	15 (79)
12	Malekan	4	3 (75)							4 (100)					
17	Munakata	10	1 (10)	9 (90)		8 (80)	8 (80)	2 (20)		10 (100)		1 (10)			
18	Omar	4	3 (75)	2 (50)		2 (50)	2 (50)		RVAD 1 (25)						
19	Pasrija	20		5 (25)	2 (10)	11 (55)	1 (5)	7 (35)		2 (10)			4 (20)		1 (5)
20	Swol	5		5 (100)	5 (100)	2 (40)		3 (60)	Only VA ECMO 1 (20)	3 (60)	1 (20)			2 (40)	
21	Sakuma	7		5 (71)		1 (14)	1 (14)	6 (86)							
22	Hashiba	12		12 (100)	6 (50)		4 (33)	6 (50)		6 (50)					
23	Maj	6		6 (100)	6 (100)	1 (17)	2 (33)	2 (33)		2 (33)	1 (17)	1 (17)		1 (17)	3 (50)
27	Tayama	7	7 (100)	2 (29)		5 (71)		6 (86)		3 (43)					1 (14)
28	Ius	36		15 (42)		20 (56)		19 (53)		3 (8)	2 (6)		5 (14)		10 (28)
29	Elbadawi	219				45 (20.4)		54 (24.9)		59 (27)				144 (66)	

VA-ECMO = veno arterial extracorporeal membrane oxygenation, PE = pulmonary embolism, ECPR = extracorporeal cardiopulmonary resuscitation.
CDT = catheter directed thrombectomy/thrombolysis.
RVAD = right ventricular assist device, AKI = acute kidney injury, CVVH = continuous veno venous hemofiltration.

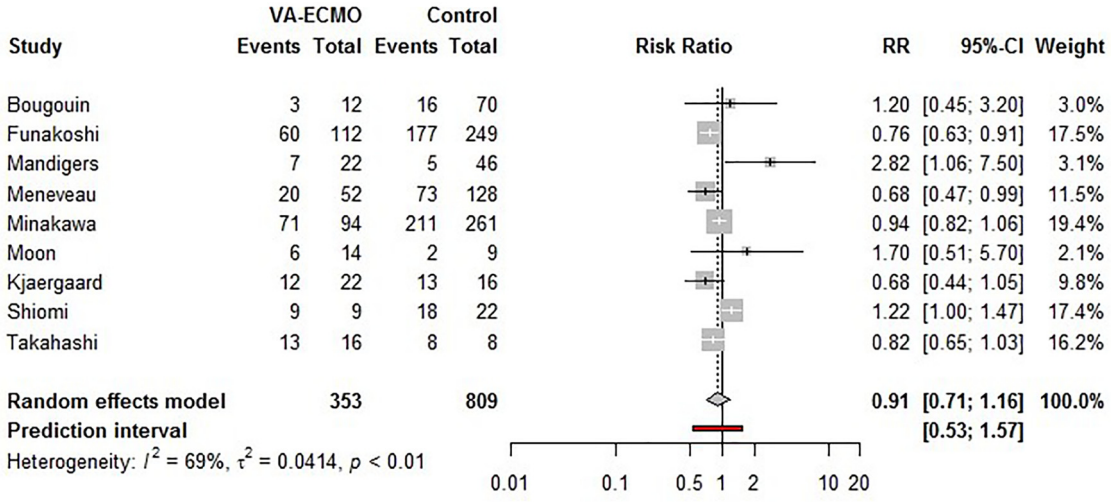

Fig. 2. Short-term survival of VA-ECMO and control patients.

emobolectomy (RR 1.96, 95%CI 1.39–2.76). Also, there was a trend toward a lower survival for patients who suffered a cardiac arrest prior to or during VA-ECMO placement, compared to patients without cardiac arrest (RR 0.88, 95% CI 0.77–1.01). Male sex, catheter directed therapy, systemic thrombolysis and ECMO as single treatment were not associated with a difference in survival. Forest plots of the evaluated factors are included in the Additional file Appendix 3: A-G.

Assessment of the risk of publication bias showed no significant bias for the evaluated factors. Also, no significant heterogeneity was identified. The funnel plots are included in the Additional file Appendix 4: A-G and the influence plots are included in the Additional file Appendix 5: A-G. Sensitivity analyses of the results by exclusion of outlying studies did not result in a significant difference (Additional file Table I).

4. Discussion

In this systematic review and meta-analysis, we found insufficient evidence of short-term survival benefit for VA-ECMO treatment in acute PE patients. Furthermore, in acute PE patients who were treated with VA-ECMO, we found that age ≤ 60 years and treatment with surgical embolectomy were associated with improved survival.

A possible explanation why VA-ECMO treatment did not improve short-term survival in acute PE patients might be that patients who needed VA-ECMO treatment may be more severely ill and hemodynamically compromised than patients without VA-ECMO treatment. Furthermore, VA-ECMO treatment is associated with severe complications, which may counterbalance a possible benefit of treatment.

In the broad continuum of obstructive shock, acute PE resulting in a cardiac arrest is the most severe form of shock which probably justifies VA-ECMO treatment. Even in patients treated with ECPR, we found a short-term survival rate of 34%. This is higher than the survival rate of patients with cardiac arrest due to acute PE without VA-ECMO treatment ranging from 8.5–18.3% as reported in previous studies. [37,38]

In patients treated with VA-ECMO for acute PE, age ≤ 60 years and surgical embolectomy were associated with higher chance of survival. Furthermore, we found a trend ($p = 0.06$) toward lower survival in patients suffering a cardiac arrest before VA-ECMO treatment, compared to non-cardiac arrest patients. Most probably, this higher survival indicates that younger patients and patients who are in a condition good enough to undergo a surgical embolectomy, are the less ill patients with a higher a priori chance of survival. The trend toward lower survival in cardiac arrest patients could be explained by the severity of the illness as well as resuscitation difficulties, as conventional CPR is often insufficient in patients with massive PE due to a right ventricle outflow obstruction [39-41].

We performed a comprehensive systematic review evaluating survival in VA-ECMO treated and control acute PE patients. To our knowledge, this is the first meta-analysis to examine the survival for predefined subgroups and predictors for survival in acute PE patients with VA-ECMO treatment. A previous review published in 2015 evaluating the role of ECMO in acute PE included 78 patients treated with ECMO (11 case reports, 9 case series).[42] Although we included studies reporting on 4 patients or more, we were able to include 1138 patients treated with VA-ECMO in our review. The difference in sample size between our and the previous review highlights the fact that VA-ECMO is increasingly utilized as a treatment strategy in acute PE.

Despite the low evidence and lack of benefit of VA-ECMO treatment in the overall acute PE group, there may be a possible benefit in the subgroup of patients who suffered a (refractory) cardiac arrest. More research is needed to find out if VA-ECMO treatment could be beneficial. In severe shock patients as well as patients suffering (refractory) cardiac arrest it is important to perform prospective studies to compare VA-ECMO treated patients with non-VA-ECMO treated patients. Cardiac arrest with or without ROSC before ECMO placement are different entities which may have a very different prognosis. Unfortunately, most of the included articles did not differentiate between these subgroups or report separate outcome. Future studies should clearly differentiate between patients who had a cardiac arrest but gained ROSC before ECMO placement and patients with ECPR.

Additionally, the advantages or disadvantages of systemic thrombolysis in patients who are treated with VA-ECMO has to be investigated. Also, in order to adequately compare therapies and their outcome, studies should more clearly report the indication and timing of reperfusion therapies. For instance, the use of ECMO treatment prior to surgical intervention (and maintained during or removed after procedure) can have a different indication and outcome than ECMO treatment after surgical intervention.

Perfusion therapy with thrombolysis resulted in a reduction of adverse outcome (i.e. combined end-point of mortality and recurrent PE) in a population consisting mostly of high-risk PE patients with the presence of cardiogenic shock. [2] The risk of severe bleeding with this treatment is approximately 10%. However, if thrombolytic therapy is combined with ECMO there is an additional increased risk of bleeding (due to the need for vascular access) which should be taken into careful consideration. The use of ECMO alone as reperfusion method could offer an alternative, but is currently considered controversial. We speculate

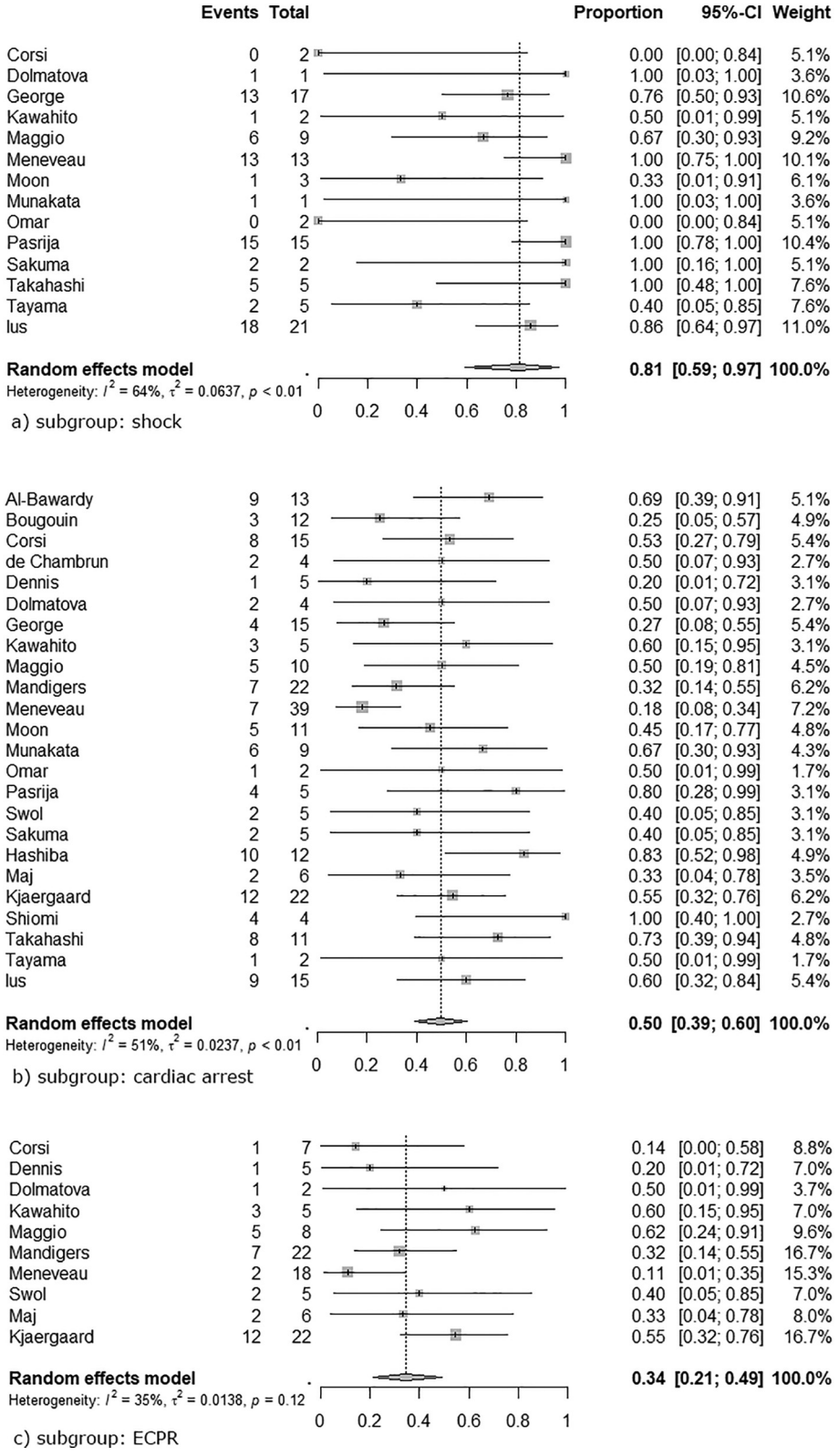

Fig. 3. Short-term survival of VA-ECMO patients per subgroup (shock, cardiac arrest and ECPR).

that in patients in whom ECMO treatment is deemed necessary a combination of ECMO and surgical intervention may be a better option than ECMO combined with thrombolysis. However, with the current data it is impossible to derive an evidence based recommendation regarding this subject.

4.1. Limitations

Only limited evidence can be derived from the present data due to the observational design of the included studies, only fair-poor quality of the individual studies, relatively small sample sizes and substantial

Table 2a
Survival outcomes of massive pulmonary embolism patients treated with/without VA-ECMO. Studies including VA-ECMO and control patients

		Short-term survival (n, %)			Long-term survival (n, %)			CPC 1/2 score of survivors		Causes of death	
	Study	Definition	VA-ECMO	Control	Definition	VA-ECMO	Control	VA-ECMO	Control	VA-ECMO	Control
3	Bougouin	hospital	3/12 (25.0)	16/70 (22.9)							
8	Funakoshi	30 day	60/112 (53.6)	177/249 (71.1)							
13	Mandigers	hospital	7/22 (31.8)	5/46 (10.9)				6/7 (86.0)	3/4 (75.0)	Neurologic n= 11 (50.0), hemodynamic n=2 (9.0), (multi)organ dysfunction syndrome n=2 (9.0)	Neurologic n=2 (4.3), hemodynamic n=39 (84.8)
14	Meneveau	30-day	20/52 (38.5)	73/128 (57.0)	90-day	18/52 (34.6)	68/128 (53.1)				
15	Minakawa	hospital/30-day	71/94 (75.5)	211/261 (80.8)							
16	Moon	hospital	6/14 (42.8)	2/9 (22.2)	90-day	6/14 (42.9)					
24	Kjaergaard	30 day	12/22 (54.5)	13/16 (81.3)	1 year	10/22 (45.5)	9/13 (69.2)			Hemodynamic n=3 (13.6)	Neurologic n=1 (6.3)
25	Shiomi	hospital	9/9 (100.0)	18/22 (81.8)							Neurologic n=2 (22.2), (multi) organ dysfunction syndrome n=1 (4.5)
26	Takahashi	30 day	13/16 (81.3)	8/8 (100.0)						Neurologic n=2 (12.5), (multi) organ dysfunction syndrome n=1 (6.25)	

heterogeneity between the studies regarding the primary outcome. Due to the observational nature of the studies there were discrepancies between ECMO and control patients which makes it difficult to interpret results. For example, the proportion of patients with cardiac arrest differed among ECMO and control patients in the studies performed by Funakoshi, Meneveau, Kjaergaard and Takahashi. Also, the indication for ECMO treatment differed among studies or was not reported.

Although we performed an extensive systematic review of the current available evidence regarding VA-ECMO treatment in acute PE, we applied study selection criteria (exclusion of studies published before the year 1980 and/or less than 4 patients and language restrictions [i.e., only English/Dutch]) which may limit our findings.

Another limitation is that we were unable to analyse the effect of complications in ECMO treated patients. ECMO is associated with

Table 2b
Studies including only VA-ECMO patients, without control group.

1	Al-Bawardy	30 day	9/13 (69.2)	1 year	6/13 (46.2)		
2	Aso	hospital	127/353 (36.0)				
4	Corsi	hospital	8/17 (47.1)	90 day	8/17 (47.1)		
5	de Chambrun	hospital	2/4 (50.0)			2/2 (100.0)	
6	Dennis	hospital	1/5 (20.0)			1/1 (100.0)	
7	Dolmatova	hospital	3/5 (60.0)				Neurologic n= 1 (20.0), hemodynamic n= 1 (20.0)
9	George	hospital	17/32 (53.1)				
10	Kawahito	hospital	4/7 (57.1)				Hemodynamic n=2 (28.6)
11	Maggio	hospital	11/19 (57.9)	1 year	11/19 (57.9)		Neurologic n=4 (21), hemodynamic n=1 (5.2), (multi) organ dysfunction syndrome n=1 (5.2)
12	Malekan	hospital	4/4 (100.0)				
17	Munakata	30-day	7/10 (70.0)				
18	Omar	hospital	1/4 (25.0)				(multi) organ dysfunction syndrome n=1 (25.0)
19	Pasrija	hospital	19/20 (95.0)	90-day	19/20 (95.0)	19/19 (100.0)	Neurologic n=1 (5.0)
20	Swol	hospital	2/5 (40.0)				Neurologic n=1 (20), hemodynamic n=2 (40.0)
21	Sakuma	hospital	4/7 (57.1)				
22	Hashiba	hospital	10/12 (83.3)			7/10 (70.0)	
23	Maj		2/6 (33.3)				
27	Tayama		3/7 (42.9)				Hemodynamic n=3 (42.9), (multi) organ dysfunction syndrome n=1 (14.3)
28	Ius	hospital	23/36 (63.9)				Neurologic n=7 (19.4), hemodynamic n=2 (5.6), (multi)organ dysfunction syndrome n=2 (5.6)
29	Elbadawi	hospital	84/219 (38.4)				
Total			***341/785 = 43.4%***				

VA-ECMO = veno arterial extracorporeal membrane oxygenation, CPC = cerebral performance category.

several major adverse events such as bleeding and this should be properly investigated. However, due to heterogeneity among the included studies or the absence of classification of complications this analysis could not be performed in this meta-analysis.

5. Conclusions

At present, there is insufficient evidence that VA-ECMO treatment improves survival of acute PE patients. Low quality evidence suggest that VA-ECMO patients aged ≤60 years or who received SE have higher short-term survival rates. Considering the limited evidence derived from the present data, this study emphasizes the need for prospective studies.

Ethics approval

Not applicable.

Consent for publication

Not applicable.

Data availability

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

Authors' contributions

MK and LM conducted the study, performed the analysis and wrote the manuscript. AV, JH, DM and CU were responsible for the design of the study and final version of the manuscript. DK contributed in the primary design and data collection. WR and JB contributed to the statistical design and analysis. All authors read and approved the final manuscript.

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Declaration of Competing Interest

The authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2021.03.006.

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