Understanding the "Extra-Corporeal Membrane Oxygenation Gap" in Veno-Arterial Configuration for Adult Patients: Timing and Causes of Death. Defining the Veno-Arterial Extracorporeal Membrane Oxygenation Gap

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Abstract

Background

Timing and causes of hospital mortality in adult patients undergoing veno-arterial extracorporeal membrane oxygenation (V-A ECMO) have been poorly described. Aim of the current review was to investigate the timing and causes of death of adult patients treated with V-A ECMO, and subsequently define the “V-A ECMO gap”, which represents the patients who are successfully weaned of ECMO but eventually die during hospital stay.

Methods

A systematic search was performed using electronic MEDLINE and EMBASE databases through PubMed. Studies reporting on adult V-A ECMO patients from January 1993 to October 2018 were screened. Timing, rates and causes of in-hospital mortality were analyzed.

Results

Sixty studies with 9,181 patients were included in this systematic review. Overall mortality was 37.6% during V-A ECMO support (reported by 60 studies) and 28.9% (57 studies) after weaning. Finally, 32.6% were discharged from hospital (60 studies). Most common causes of death on ECMO were multiple organ failure (MOF, 49.8%), followed by cardiac failure (20.6%) and neurological causes (15.7%). Most common causes of death after weaning were MOF (55.3%), followed by neurological complications (12.6%), persistent heart failure (10.7%) and pulmonary infections (6.8%).

Conclusions

More than one-third of adult V-A ECMO patients die during ECMO therapy. Additionally, almost one half of successfully weaned patients still decease during hospital stay, defining the “V-A ECMO gap”. Underreporting and lack of uniformity in reporting of important parameters remains problematic in ECMO research. Future studies should uniformly define
timing and causes of death in V-A ECMO patients to better understand the effectiveness and complications of this therapy. Systematic review registration PROSPERO 2019 number CRD42019130815

BACKGROUND

For several decades, Extracorporeal Membrane Oxygenation (ECMO) has been used to support patients in the presence of acute refractory heart and/or lung dysfunction [1]. In case of cardiogenic shock or cardiac arrest, the veno-arterial (V-A) configuration is used to support the cardio-circulatory system.

The use of ECMO has been gaining popularity over the last years. According to the Extracorporeal Life Support Organization (ELSO), there have been more than 26,000 ECMO cases in adult patients in more than 290 centers worldwide [2]. Recent reports have shown an exponential trend of ECMO use for adult respiratory compromise (veno-venous, [V-V] ECMO), increasing from 100 cases a year between 1996–2007 to more than 800 cases a year in the 2009–2012 period. This was mainly due to the H1N1 influenza pandemic in 2009 [3]. However, use of adult V-A ECMO has also increased over the past years, particularly in the post-cardiotomy setting [4, 5].

In-hospital mortality among V-A ECMO patients remains high. Previous reviews reported up to 50%-70% in-hospital mortality among adult patients [6, 7]. Furthermore, despite the knowledge and skills that ECMO teams have gained during the last years regarding this technology, mortality rates have not declined [8]. These findings might reflect the severity of illness, complexity of patient profile, or the older age of ECMO patients when compared to previous experiences [9]. Moreover, in-hospital ECMO mortality has not been comprehensively described until now. In particular, there are scarce data on the timing of death (i.e. during or after ECMO support) as well as on the main causes of death in this setting. Causes of death and complications on-ECMO are described relatively well, but in-
hospital mortality rate and cause of death in this setting are poorly reported and not well understood. We defined this observation and patient group as the “V-A ECMO gap”, which describes the quote of patients with unfavorable in-hospital outcome despite successful ECMO weaning. Even more complicating, it remains difficult to compare different studies to each other and to conduct systematic reviews and meta-analyses of separate trials as terminology, indications and outcomes are reported without uniformity. Therefore, the present systematic review investigated the timing and causes of death during the hospital stay in adult patients treated with V-A ECMO. Furthermore, it made an attempt to give insight into reporting, underreporting, uniformity of reporting and quality of reporting of indications and outcomes in adult V-A ECMO studies.

METHODS

Search strategy

Potentially eligible studies were identified by searching the electronic MEDLINE and EMBASE databases through PubMed and Ovid, respectively. No unpublished data were obtained. The authors adhered to the PRISMA guidelines for reporting in systematic reviews and meta-analyses [10]. The following search criteria were used: Adult, Veno-arterial, Extracorporeal Life Support, Extra-Corporeal Membrane Oxygenation, ECMO, ECLS, V-A ECMO. All studies that reported on ECMO as a form of Mechanical Circulatory Support (MCS) in veno-arterial configuration in adult patients were identified in the study selection. Additionally, reference lists of the pre-screened studies were manually checked for additional eligible studies. Original studies from January 1993 to October 2018 were reviewed in order to include more modern ECMO technology. Furthermore, the study was registered in PROSPERO (registration number CRD42019130815)[11].

Study criteria
Due to the emergent nature of the condition and the lack of randomized data, all observational studies and case series comprising > 10 patients were considered for inclusion. Non-English studies and studies conducted in animal models or in paediatric cohorts were excluded. Studies with circulatory support other than V-A ECMO (V-V ECMO, combined ECMO modes, combination of ECMO and ventricular assist devices) were excluded as well. In case several MCS devices (i.e. left-ventricular or biventricular assist devices) were included in one study, results were included only if the V-A ECMO group was analysed separately. When multiple publications of the same research group were identified, the publication reporting on the largest cohort was used, if eligible. Studies including less than 10 patients, duplicates, editorials, commentaries, letters to editor, opinion articles, reviews or meeting abstracts were also excluded. Sample-size cutoffs were chosen pre-hoc in an attempt to limit the risks of imprecision and publication bias. Meta-analysis was intentionally not performed given the expected heterogeneity and low quality of the studies.

Finally, studies that did not report on at least on-ECMO mortality and discharge rate were excluded from analysis as they could not provide valuable information regarding the ECMO-gap.

Data extraction

The following key information was extracted from each publication by two independent reviewers: year of publication, mortality on ECMO, weaning rate, in-hospital mortality, number of discharged patients, cause of death on ECMO, cause of death after weaning and in-hospital complications.

End-point definition

The primary outcome is the reported mortality rate on-ECMO and mortality rate after
weaning during the ECMO-related hospitalization. These findings are then used to define
the V-A ECMO gap as follows: The difference between the rate of patients who were
successfully weaned from ECMO and the rate of patients who were finally discharged at
the end of the ECMO-related hospital admittance (i.e. the in-hospital mortality rate after
successful weaning). Secondary outcomes are, if available, causes of death either on-
ECMO or after weaning, rate of hospital discharge and complications of ECMO. Studies that
included causes of death on-ECMO and after weaning were analyzed separately.

Data synthesis

Data synthesis was performed by two researchers with extensive expertise in statistics
and epidemiology. Given the large number of patients expected to be included, the
potentially low quality of the studies and an expected number of missing patient data,
aggregate patient data was used. A freely available software package (RevMan v5.3,
Cochrane Collaboration, Oxford, UK) was used for data synthesis. Discrepancies were
resolved between two researchers by consultation of the principal investigator.

RESULTS

Included studies

The pre-defined literature search generated 12,436 studies. (Fig. 1). Sixty duplicates were
removed, after which 11,871 studies were excluded based on title, abstract and keywords.
Then, after careful full-text review, 415 studies were excluded for reasons specified in
Fig. 1 (PRISMA flow-chart). Eventually, 90 articles were included in our analysis. The
selected articles provided a total number of 12,569 adult patients. The number of patients
per article varied from 10 to 5,263. However, only 60/90 studies report on at least on-
ECMO mortality and discharge rate. These 30 studies were excluded from analysis as they
do not provide any valuable information on the ECMO-gap (See additional file 1). The 60
analyzed studies comprised 9,181 patients (Table 1).

Table 1
Full articles data including author, year, patient number, on-ECMO and after weaning mortality rate and discharge rate.

| Author                      | Year | Patient nr. (ECMO) | On ECMO mortality | Weaning rate | % | discharge rate | % |
|-----------------------------|------|--------------------|-------------------|--------------|---|----------------|---|
| Acker [35]                  | 2001 | 37                 | 10                | 27           |   | 27             |   |
| Ariyarnam [36]              | 2014 | 14                 | 7                 | 50           | 7 | 50             | 3 |
| Aso [37]                    | 2016 | 5263              | 1823              | 34.6         | 3389 | 64.3          | 1994 | 37.9 | 1395 | 26.5 |
| Aziz* [12]                  | 2010 | 10                 | 4                 | 40           | 6  | 60             | 0  |
| Bednarczyk [38]             | 2014 | 32                 | 7                 | 21.9         | 18 | 56.3           | 3  |
| Beurther et [39]            | 2013 | 87                 | 48                | 55.1         | 39 | 44.8           | 7  |
| Borges Lima [40]            | 2015 | 11                 | 2                 | 18.1         | 9  | 81.8           | 2  |
| Bouabdellaouzi* [13]        | 2017 | 10                 | 5                 | 50           | 5  | 50             | 0  |
| Chen* [14]                  | 2005 | 15                 | 1                 | 6.6          | 14 | 93.3           | 3  |
| Chou [41]                   | 2010 | 40                 | 11                | 27.5         | 29 | 72.5           | 8  |
| Chung [42]                  | 2012 | 134                | 66                | 49.3         | 68 | 50.7           | 11 |
| Demondon* [15]              | 2013 | 77                 | 40                | 52           | 19 | 24.7           | 4  |
| Den Uil* [16]               | 2017 | 132                | 46                | 34.8         | 86 | 65.1           | 19 |
| Dini* [17]                  | 2015 | 14                 | 6                 | 42.8         | 8  | 57.1           | 0  |
| Esper [43]                  | 2015 | 18                 | 3                 | 16.6         | 15 | 83.3           | 3  |
| Fiser [44]                  | 2001 | 51                 | 35                | 68           | 16 | 31             | 8  |
| George [45]                 | 2018 | 32                 | 11                | 34.4         | 21 | 65.6           | 4  |
| Guenther* [18]              | 2013 | 41                 | 15                | 37           | 26 | 63             | 6  |
| Hei [46]                    | 2010 | 68                 | 16                | 23.5         | 52 | 67.4           | 9  |
| Hsu* [19]                   | 2010 | 51                 | 24                | 47           | 27 | 53             | 10 |
| Kagawa [47]                 | 2010 | 77                 | 40                | 51.9         | 37 | 48             | 19 |
| Kara [48]                   | 2016 | 24                 | 9                 | 37.5         | 15 | 62.5           | 0  |
| Kim GS* [49]                | 2017 | 61                 | 34                | 55.7         | 27 | 44.3           | 8  |
| Kim DW [50]                 | 2018 | 38                 | 17                | 44.7         | 21 | 55.3           | 1  |
| Kim H* [20]                 | 2012 | 27                 | 5                 | 18.5         | 22 | 81.5           | 6  |
| Ko* [21]                    | 2002 | 76                 | 30                | 39.4         | 46 | 60.5           | 22 |
| Kosinski* [22]              | 2018 | 29                 | 11                | 37.9         | 18 | 62             | 2  |
| Lazzara [51]                | 1993 | 11                 | 3                 | 27.2         | 8  | 73             | 2  |
| Lee SN [52]                 | 2017 | 95                 | 40                | 42.1         | 55 | 57.9           | 25 |
| Loforte [53]                | 2014 | 228                | 84                | 36.8         | 107| 46.9           | 22 |
| Study     | Year | Number | On-ECMO Mortality Rate | Weaning Mortality Rate | Total Mortality Rate |
|-----------|------|--------|------------------------|------------------------|---------------------|
| Luyt [54] | 2012 | 41     | 34.1%                  | 23%                    | 34%                 |
| Mikus [55] | 2013 | 14     | 7%                     | 50%                    | 22%                 |
| Mirabel [56] | 2011 | 35     | 13%                    | 22%                    | 0%                  |
| Muehrcke [57] | 1996 | 23     | 10%                    | 43.5%                  | 49.5%               |
| Pasrija [30] | 2018 | 56     | 1%                     | 1.8%                   | 2.8%                |
| Pokersnik [58] | 2012 | 49     | 22%                    | 44.9%                  | 45.1%               |
| Rastan [59] | 2010 | 517    | 190%                   | 36.7%                  | 39.7%               |
| Rubino [60] | 2017 | 101    | 43%                    | 42.6%                  | 50%                 |
| Sakamoto [62] | 2012 | 98     | 44%                    | 44.9%                  | 55.1%               |
| Sangalli [63] | 2016 | 16     | 10%                    | 10%                    | 10%                 |
| Saxena [64] | 2015 | 45     | 21%                    | 46.7%                  | 65%                 |
| Shinn [65] | 2009 | 92     | 33%                    | 35.9%                  | 59%                 |
| Slottosch [66] | 2013 | 77     | 92%                    | 37.6%                  | 48%                 |
| Smedira [67] | 2001 | 202    | 83%                    | 41%                    | 71%                 |
| Smith* [23] | 2001 | 17     | 6%                     | 35.2%                  | 65%                 |
| Stub* [24] | 2015 | 24     | 11%                    | 45.8%                  | 13%                 |
| Takayama [68] | 2015 | 101    | 40%                    | 39.6%                  | 24%                 |
| Tanaka [7] | 2016 | 84     | 34%                    | 40%                    | 50%                 |
| Tarzian [69] | 2015 | 64     | 9%                     | 14%                    | na                  |
| Tsai [70] | 2017 | 105    | 31%                    | 30%                    | 74%                 |
| Unosawa* [25] | 2013 | 47     | 18%                    | 24.3%                  | 29%                 |
| van den Brink [71] | 2017 | 12     | 4%                     | 33.3%                  | 8%                  |
| Wang S* [26] | 1996 | 18     | 9%                     | 50%                    | 9%                  |
| Wang J* [27] | 2013 | 87     | 36%                    | 41%                    | 51%                 |
| Wong [72] | 2017 | 103    | 49%                    | 47.6%                  | 54%                 |
| Wu [73] | 2010 | 110    | 43%                    | 40%                    | 67%                 |
| Yeh [74] | 2018 | 99     | 71%                    | 71.7%                  | 28%                 |
| Zhang [75] | 2006 | 32     | 18%                    | 56.2%                  | 14%                 |
| Zhao [76] | 2015 | 24     | 8%                     | 33.3%                  | 16%                 |
| n = 60 | Total | 9181  | 3448                   | 37.5%                  | 35492               |

ECMO: Extracorporeal membrane oxygenation, NA: not available.
* indicates studies that report on causes of death.

**Mortality rates and survival**

On-ECMO mortality was reported by all 60 studies (n = 9,181). Overall On-ECMO mortality was 37.6% (n = 3,448) (Table 1) varying between 6.6–68.0%. After weaning mortality rate
was reported by 57 studies. In-hospital mortality rate after weaning was 28.9% (2,659/7,724 patients) which represents the ECMO Gap.

Weaning and discharge

Out of all reported patients, 59.8% (n = 5,492/9,117) were successfully weaned from ECMO, reported by 59/60 studies. A small percentage (2.6%) could not be weaned and received another form of MCS or transplantation. Finally, 32.6% was discharged from hospital (2,995/9,181 patients), which was reported by all 60 studies.

Causes of death

Of the 60 articles, only 16 specifically reported in detail on cause of death on-ECMO and after ECMO weaning [12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27]. In these studies, 675 adult patients were included, with 267 patients (39.6%) dying on ECMO (Table 2), and 390 patients (57.8%) weaned successfully. A small percentage was not weaned but received a form of permanent MCS or transplant, of which some patients were discharged. Of the weaned patients, 103 patients (26.4%) still died during hospital stay.

Survival to hospital discharge was 44.1% (n = 298) (See additional file 2).

| Table 2 Causes of death on-ECMO and after weaning. |
|-----------------------------------------------|
| On-ECMO cause of death | #  | %  | After weaning cause of death | #  | %  |
|------------------------|----|----|------------------------------|----|----|
| MOF                    | 133| 49.8| MOF                          | 57 | 55.3|
| Neurological           | 42 | 15.7| Neurological                 | 13 | 12.6|
| Sepsis                 | 6  | 2.3 | Sepsis                       | 5  | 4.9 |
| Cardiac Failure        | 55 | 20.6| Cardiac Failure              | 11 | 10.7|
| Bleeding               | 22 | 8.2 | Bleeding                     | 1  | 1.0 |
| Aortic dissection      | 1  | 0.4 | Pulmonary infection          | 7  | 6.8 |
| LV thrombosis          | 1  | 0.4 | Arrhythmia                   | 3  | 2.9 |
| ECMO dysfunction       | 3  | 1.1 | Sudden death                 | 4  | 3.9 |
| Family request         | 1  | 0.4 | Cardiac Rupture              | 2  | 1.9 |
| Arrhythmia             | 2  | 0.8 |                              |    |     |
| Graft Rejection        | 1  | 0.4 |                              |    |     |
|                        |    |    |                              | 267|     |

MOF: Multi-organ failure, LV: Left ventricle, ECMO: Extracorporeal membrane oxygenation

After analyzing the 16 papers, we found that the most common causes of death on ECMO (Table 2) were multiple organ failure (MOF, 49.8%), followed by cardiac failure (20.6%)
neurological causes (15.7%), and bleeding (8.7%). Although MOF was the most common cause of death in most papers, some authors, like Smith et al. [23] and Unosawa et al. [25], show that conditions such as persistent heart failure can also be a common cause of death in these patients (See additional file 2). The most common causes of in-hospital death after ECMO weaning were MOF (55.3%) followed by neurological causes (12.6%), cardiac failure (10.7%) and pulmonary infections (6.8%) (Table 2).

Complications on V-A ECMO

The risk-benefit ratio is a highly debated issue in ECMO research, especially in regard to complications and hospital stay. [28, 29]. In the current study, complications were analyzed in 13 articles reporting on complications [12, 13, 14, 15, 16, 17, 18, 19, 21, 23, 24, 25, 30]. These complications were divided into 10 groups. The most common complication was bleeding (34.6%), including cannulation site bleeding, visceral and intracranial bleedings. Also, 14.9% of complications were related to leg ischemia (Table 3). The complications specified per study are illustrated in additional file 3.

| Complication group           | Number of patients | %   |
|-----------------------------|--------------------|-----|
| Renal                       | 86                 | 15.1|
| Neurological                | 25                 | 4.3 |
| Bleeding                    | 170                | 29.8|
| Leg ischemia                | 73                 | 12.8|
| Respiratory                 | 84                 | 14.7|
| Sepsis                      | 13                 | 2.3 |
| Wound infection             | 11                 | 1.9 |
| Mechanical                  | 35                 | 6.1 |
| Incomplete sternal closure  | 35                 | 6.1 |
| Other                       | 2                  | 0.4 |

**DISCUSSION**

In-hospital mortality among V-A ECMO patients remains high. Despite the knowledge and skills that ECMO teams have gained during the last years regarding this technology, mortality rates have not declined. Furthermore, in-hospital ECMO mortality has not been comprehensively described until now. In particular, there are scarce data on the timing of
death (i.e. during or after ECMO support) as well as on the main causes of death in this setting. In our own experience, we observed a lot of patients to still dease after weaning of ECMO, in hospital. We defined this discrepancy as the ‘V-A ECMO-gap’.

In order to describe this ECMO gap, we conducted a systematic review of all studies reporting on V-A ECMO mortality and causes of death between January 1993 and October 2018. Additionally, we made an attempt to give insight into reporting, underreporting, uniformity of reporting and quality of reporting of indications and outcomes in adult V-A ECMO studies.

In this systematic review, initially 90 studies were included. However, merely 60/90 (66.7%) studies reported on on-ECMO mortality, weaning rate and discharge rate. This finding further defines the ECMO-gap in reporting on V-A ECMO outcomes.

Overall on-ECMO mortality was 37.5% and weaning rate was 59.8%. Still, it remains difficult to interpret the discharge rate in respect to the weaning rate for the patients that could not be weaned. In some cases, they underwent some modality of other MCS (or transplant) and are in several studies included in the overall patients discharged from hospital, as other papers only report non-transplanted (or non-MCS) discharged patients [14, 15].

As 59.8% of patients were successfully weaned from ECMO and 32.6% was discharged home, the ECMO gap therefore represents almost 30% of treated patients. This means, 45.5% of patients still die after being weaned successfully of ECMO therapy. We attempted to find an explanation for this finding by assessing differences in causes of death.

Many authors report on-ECMO and after weaning mortality rates, but most of them only provide partial details or do not provide causes of death. For example, Cheng et al. report survival to discharge as a cumulative rate, although, they did not specify whether death
occurred on-ECMO or after weaning [31]. This provides another example of underreporting in V-A ECMO research.

Only 16/60 studies reported on causes of death. Most common causes of death on-ECMO were MOF, cardiac failure, neurological causes and bleeding, while most common causes after weaning were MOF, cardiac failure, neurological causes and respiratory causes. A marked difference in cause of death between on-ECMO and after weaning mortality rate, is bleeding (8.2% vs 1.0%). Bleeding can be a result of systemic effects of cardiopulmonary bypass, causing platelet dysfunction and hemodilution of clotting factors. Combined with the administration of anticoagulation while on ECMO, reducing the risk of circuit clotting, intracranial bleeding is a highly feared and lethal on-ECMO complication [32].

Multi-organ failure is a relatively common cause of death on-ECMO, especially in cases where V-A ECMO is initiated in a late phase and MOF is already irreversible. It seems counterintuitive that MOF is a similarly important, or even more important, cause of death on-ECMO compared to after weaning. We can speculate that this is due to a too early initiation of the weaning process. On-ECMO acute renal failure is an independent predictor for MOF after weaning [21]. Renal function on-ECMO is often assessed by serum creatinine levels rather than by urine volume. Urine volume is a more sensitive marker for acute renal failure than serum creatinine [33]. Subsequently, impaired renal function on-ECMO could be masked by use of diuretics, which are regularly used during the weaning process for correction of fluid overload. Finally, the increased rate of pneumonia as cause of death in the weaned group, can be related to the increased length of hospitalization and intubation time, which are obvious independent predictors for development hospital acquired pneumonias [34].

However, it should be noted that determining the exact primary cause of death is challenging, especially in the setting of ECMO, and it remains difficult to differentiate
between solitary organ failure and MOF. Still, the lack of reporting causes of death (as illustrated by the merely 16 studies describing these findings) together with the lack of reporting mortality rates of ECMO patients (as illustrated by the 30 initially excluded studies), makes comprehensive understanding of the "ECMO Gap" even more extensive and challenging.

Comparing the results in both Tables 1 and 2 reveals a slightly increased ECMO survival in the studies contained in Table 1 (studies overall), yet on the other hand, in-hospital mortality after weaning and discharge rate are improved in the studies contained in Table 2 (studies reporting on causes of death). We can only speculate on these findings, which might be explained by the fact that these well-reporting papers comprise single-center studies with high expertise and a wider range of patient inclusion for ECMO treatment (especially post-cardiotomy), which could lead to a slightly higher mortality rate on ECMO, but improved outcomes after weaning.

Limitations

A number of limitations should be recognized when considering this review. During the course of composing this review, a large number of papers dealing mainly with adult V-A ECMO have been assessed. The reports included, however, were quite heterogeneous, meaning that not all outcomes were reported in all papers, making it impossible to carry it out a true meta-analysis. Moreover, 30 of the studies which were included in the systematic review, had to be excluded from analysis as they did not report on the most essential outcomes, further defining the ECMO-gap in reporting on ECMO outcomes. Furthermore, due to language restrictions, not all studies could be reviewed. Additionally, it remains challenging to relate mortality to indication as there is no uniformity in reporting of indications and outcomes in ECMO research. However, it is believed that despite these potential issues the main ideas and results of the review are preserved as
the ECMO-gap is defined and a light is shed on the difference in reporting and underreporting of existing studies.

CONCLUSION

In-hospital mortality rate of adult V-A ECMO patients remains high. Detailed information about timing and causes of death is, however, not adequately reported in the literature. Identifying the timing and causes of death on-ECMO and after weaning, revealed a similar amount of ECMO patients to die on-ECMO as after weaning but still in hospital. Timing of death is related to different causes of death, of which bleeding on-ECMO is the most predominant one compared to after weaning mortality rate, while MOF remains the most important cause of death in both groups.

Underreporting and lack of uniformity in reporting of important parameters such as timing of death, causes of death and complications, remain problematic in ECMO research. Future studies should fully and uniformly define timing and causes of death in V-A ECMO patients to better understand the effectiveness and complications of this therapy.

LIST OF ABBREVIATIONS

ECMO extracorporeal membrane oxygenation
ELSO extracorporeal life support organization
MCS mechanical circulatory support
MOF multi-organ failure
PRISMA preferred reporting items for systematic reviews and meta-analyses
V-A veno-arterial
V-V veno-venous

DECLARATIONS

Ethics approval
Not applicable.

Consent for publication
Not applicable.

Availability of data and materials
Not applicable. The current systematic review does not contain any original data.

Competing interests
The authors declare that they have no competing interests.

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Authors contributions
MM and SH were responsible for the conception, design, acquisition, analysis, interpretation of the study and its results and drafting of the manuscript. AM was responsible for acquisition, analysis and interpretation. FST, AO, EN, DMJ, EB, PM, GR, TD, GB and JM were responsible for the conception, design and revision of the work. RL was responsible for conception, design, acquisition, analysis, interpretation of the study and its results and drafting of the manuscript and supervision.

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**ADDITIONAL FILES**

Additional file 1.docx, Studies excluded because of failure to report on ECMO-gap outcomes.

Additional file 2.docx, Specific causes of death on-ECMO and in-hospital after weaning specified per study.

Additional file 3.docx, Complications specified per study.

**Figures**
Figure 1

Study selection procedure shown in a PRISMA flow diagram. V-A ECMO: veno-arterial extracorporeal membrane oxygenation

Supplementary Files

This is a list of supplementary files associated with the primary manuscript. Click to
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Additional File 1.docx
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