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SYSTEMATIC REVIEW

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Understanding the "extracorporeal membrane oxygenation gap" in veno-arterial configuration for adult patients: Timing and causes of death

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Abstract

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 supported 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. 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 December 2020 were screened. The studies included in this review were studies that reported more than 10 adult, human patients, and no mechanical circulatory support other than V-A ECMO. Information extracted from each study included mainly mortality and causes of death on ECMO and after weaning. Complications and discharge rates were also extracted. Sixty studies with 9181 patients were included for analysis in this systematic review. Overall mortality was 38.0% (95% confidence intervals [CIs] 34.2%-41.9%) during V-A ECMO support (reported by 60 studies) and 15.3% (95% CI 11.1%-19.5%, reported by 57 studies) after weaning. Finally, 44.0% of patients (95% CI 39.8-52.2) were discharged from hospital (reported by 60 studies). Most common causes of death on ECMO were multiple organ failure, followed by cardiac failure and neurological causes. More than one-third of V-A ECMO patients die during ECMO support. Additionally, many 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 support.

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KEYWORDS
cause of death, complications, extracorporeal life support, extracorporeal membrane oxygenation, mortality, temporary mechanical circulatory support

1 | INTRODUCTION

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 61.000 ECMO cases in adult patients in more than 450 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 and 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] and the COVID-19 pandemic in 2020. However, use of adult V-A ECMO has also increased over the past years, particularly in the postcardiotomy 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] Despite the knowledge and skills that ECMO teams have gained during the last years regarding this technology, mortality rates have not declined,[8] which might reflect the severity of illness, complexity of patient profile, or the older age of ECMO patients when compared with previous experiences.[9] Moreover, in-hospital ECMO mortality has not been comprehensively described until now. In particular, data are limited on the timing of death (ie, 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-hospital, but after weaning, 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.

Still, 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 aims to investigate the timing and causes of death during the hospital stay in adult patients supported with V-A ECMO. Furthermore, it will make 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.

2 | METHODS AND MATERIALS

2.1 | Protocol

A predefined protocol was registered in PROSPERO (CRD42019130815).[10] This systematic review was written in accordance with the Preferred Reporting in Systematic Reviews and Meta-analyses (PRISMA) statement.[11]

2.2 | Search strategy

Potentially eligible studies were identified by searching the electronic MEDLINE and EMBASE databases through PubMed and Ovid, respectively. (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 V-A configuration in adult patients were identified in the study selection. Additionally, reference lists of the prescreened studies were manually checked for additional eligible studies. Original studies from January 1993 to December 2020 were reviewed in order to include more modern ECMO technology.

2.3 | 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 pediatric 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 (ie, 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. 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.

2.4 | Data extraction

The following key information was extracted from each publication: 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.

2.5 | 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 (ie, 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.

2.6 | 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, heterogeneity of results was expected, and these should be interpreted with caution. Still, to illustrate the mortality rates on- and after ECMO, these rates were reported per study with corresponding 95% confidence intervals (95% CIs). All studies were assigned a certain weight, based on their sample size and distribution of data. Eventually, these rates were also pooled and presented in the same fashion. The results of I^2 test for heterogeneity were also reported in which a result of >50%, in conjunction with a P value <.10 was considered significant. Complications and causes of death were reported as ranges. A freely available software package (OpenMetaAnalyst, http://www.cebm.brown.edu/openmeta) was used for data synthesis.

3 | RESULTS

3.1 | Included studies

The predefined literature search generated 12 436 studies (Figure 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 Figure 1 (PRISMA flowchart). Eventually, 91 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 5263. However, only 60/91 studies reported on at least on-ECMO mortality and discharge rate. These 31 studies were excluded from analysis as they do not provide any valuable information on the ECMO-gap (Table S1). The 60 analyzed studies comprised 9181 patients (Table 1).

3.2 | Mortality rates, weaning, and discharge

On-ECMO mortality was reported by all 60 studies (n = 9181 patients). Overall, on-ECMO mortality rate was 38.0% (95% CI 34.2%-41.9%) (Table 1) ranging from 6.6% to 68.0%. After weaning, mortality rate was reported by 57 studies (n = 8814 patients). In-hospital mortality rate after weaning was 15.3% (95% CI 11.1%-19.5%), which represents the *ECMO Gap*. For both mortality rates, significant heterogeneity was noted (I^2 > 95%, P < .001). A minority of patients could not be weaned and received another form of MCS or transplantation. Weaning rate was reported by 59 studies (n = 9117 patients) and was reported to be 57.0% (95% CI 53.3%-60.7%). Eventually, 44.0% (95% CI 39.8%-52.2%) of patients were discharged home. Again, similar heterogeneity was noted (P < .001).

3.3 | Causes of death

Of the 60 articles, only 16 specifically reported in detail on cause of death on-ECMO and after ECMO weaning.[12-27] In these studies, 675 adult patients were included, of which 37.5% (95% CI 31.2%-43.9%) died on-ECMO (Table 1) and 60.3% (95% CI 51.2-69.4) were weaned successfully. A small percentage was not weaned but received a form of permanent MCS or transplant, of which some patients were discharged.

After analyzing the 16 papers, we found that the most common causes of death on ECMO (Table 2) were multiple organ failure (MOF, ranging from 27% to 100%), followed by cardiac failure (ranging from 15% to 80%), neurological causes (ranging from 3% to 50%), and bleeding (ranging from 8% to 20%). Although MOF was the most common cause of

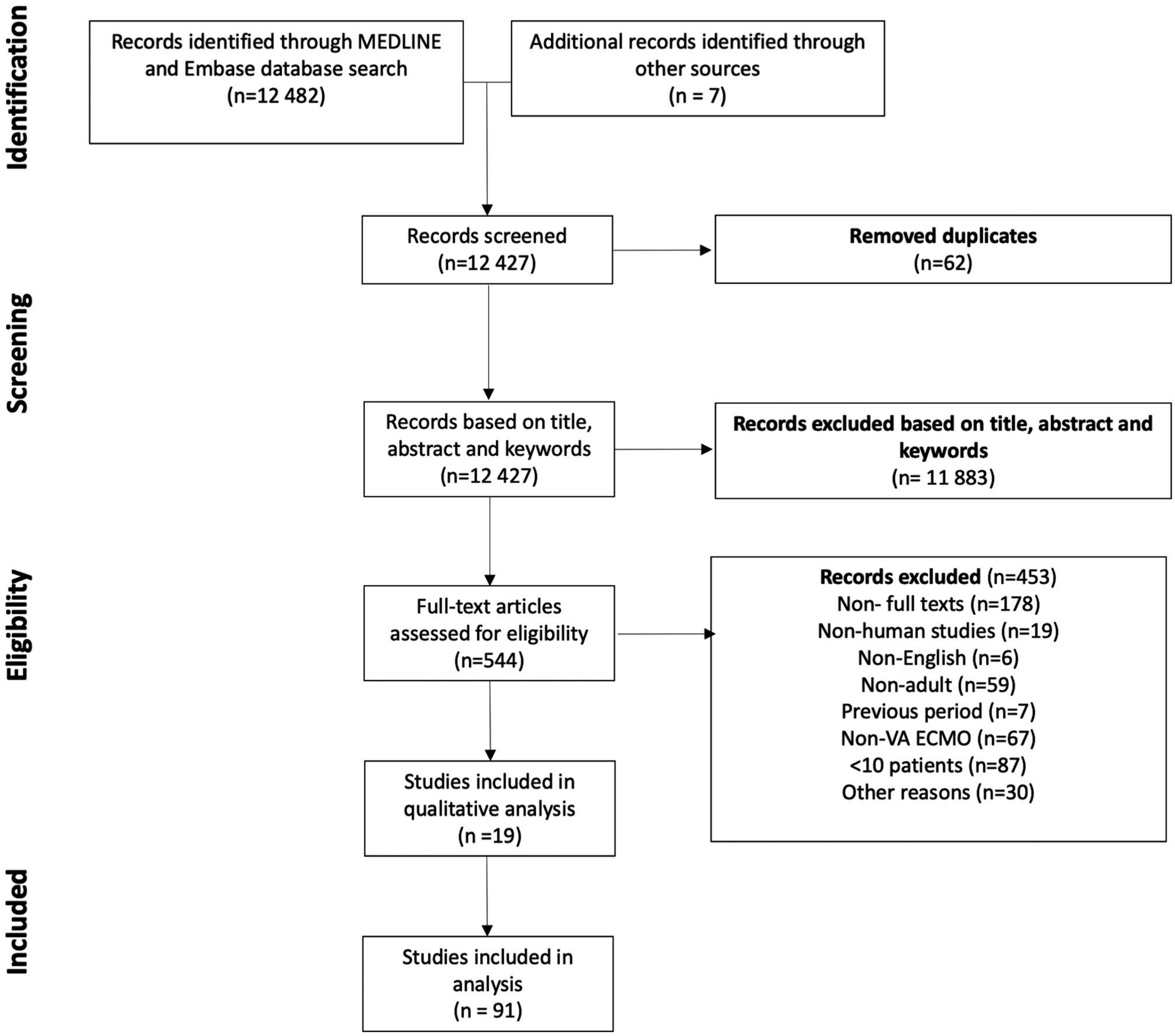

FIGURE 1 Study selection procedure shown in a PRISMA flow diagram. V-A ECMO, veno-arterial extracorporeal membrane oxygenation

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 (Table 2). The most common causes of in-hospital death after ECMO weaning were MOF (ranging from 33% to 100%) followed by neurological causes, cardiac failure, and pneumonia (Table 2).

3.4 | Complications in V-A ECMO

The cost-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[12-19,21,23-25,30] and presented in Table 3.

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 (ie, 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 decease after weaning of ECMO, in hospital. We defined this discrepancy as the "V-A ECMO-gap." From our view, an underreporting, either in terms of uniformity or quality about ECMO-related fatal events, came clearly out. Indeed, only two thirds of selected papers provided information about timing of deaths and related causes.

TABLE 1 Study characteristics and ECMO outcomes, including on-ECMO mortality, weaning rate, and after weaning mortality rate and discharge rate

Author	Year	Total number of patients	On-ECMO mortality (n)	%	95% CI	Weaning rate (n)	%	95% CI	Mortality after weaning (n)	%	95% CI	Discharge rate (n)	%	95% CI
Acker[35]	2001	37	10	27.0	12.7-41.3	27	73.0	58.7-87.3	1	2.7	0-7.9	26	70.3	55.5-85.0
Ariyaratnam[36]	2014	14	7	50.0	23.8-76.2	7	50.0	23.8-76.2	3	21.4	0-42.9	2	14.3	0-32.6
Aso[37]	2016	5263	1823	34.6	33.4-35.9	3389	64.4	63.1-65.7	1994	37.9	36.6-39.2	1395	26.5	25.3-27.7
Aziz[a12]	2010	10	4	40.0	9.6-70.4	6	60.0	29.6-90.4	0	0	0-16.9	6	60.0	29.6-90.4
Bednarczyk[38]	2014	32	7	21.9	7.6-36.2	18	56.2	39.1-73.4	3	9.4	0-19.5	15	46.9	29.6-64.2
Beurtheret[39]	2013	87	48	55.2	44.7-65.6	39	44.8	34.4-55.3	7	8.0	2.3-13.8	32	36.8	26.6-46.9
Borges Lima[40]	2015	11	2	18.2	0-41.0	9	81.8	59.0-100.0	2	18.2	0-41.0	7	63.6	35.2-92.1
Bouabdallaoui[a13]	2017	10	5	50.0	19.0-81.0	5	50.0	19.0-81.0	0	0	0-16.9	5	50.0	19.0-81.0
Chen[a14]	2005	15	1	6.7	0-19.3	14	93.3	80.7-100.0	3	20.0	0-40.2	11	73.3	51.0-95.7
Chou[41]	2010	40	11	27.5	13.7-41.3	29	72.5	58.7-86.3	8	20.0	7.6-32.4	21	52.5	37.0-68.0
Chung[42]	2012	134	66	49.3	40.8-57.7	68	50.7	42.3-59.2	11	8.2	3.6-12.9	57	42.5	34.2-50.9
Demondion[a15]	2013	77	40	51.9	40.8-63.1	19	24.7	15.0-34.3	4	5.2	0.2-10.2	30	39.0	28.1-49.9
Den Uil[a16]	2017	132	46	34.8	26.7-43.0	86	65.2	57.0-73.3	19	14.4	8.4-20.4	67	50.8	42.2-59.3
Dini[a17]	2015	14	6	42.9	16.9-68.8	8	57.1	31.2-83.1	0	0	0-12.3	8	57.1	31.2-83.1
Esper[43]	2015	18	3	16.7	0-33.9	15	83.3	66.1-100.0	3	16.7	0-33.9	12	66.7	44.9-88.4
Fiser[44]	2001	51	35	68.6	55.9-81.4	16	31.4	18.6-44.1	8	15.7	5.7-25.7	8	15.7	5.7-25.7
George[45]	2018	32	11	34.4	17.9-50.8	21	65.6	49.2-82.1	4	12.5	1.0-24.0	17	53.1	35.8-70.4
Guenther[a18]	2013	41	15	36.6	21.8-51.3	26	63.4	48.7-78.2	6	14.6	3.8-25.5	20	48.8	33.5-64.1
Hei[46]	2010	68	16	23.5	13.4-33.6	52	76.5	66.4-86.6	9	13.2	5.2-21.3	43	63.2	51.8-74.7
Hsu[a19]	2010	51	24	47.1	33.4-60.8	27	52.9	39.2-66.6	10	19.6	8.7-30.5	17	33.3	20.4-46.3
Kagawa[47]	2010	77	40	51.9	40.8-63.1	37	48.1	36.9-59.2	19	24.6	15.0-34.3	18	23.4	13.9-23.8
Kara[48]	2016	24	9	37.5	18.1-56.9	15	62.5	43.1-81.9	0	0	0-7.5	15	62.5	43.1-81.9
Kim GS[49]	2017	61	34	55.7	43.3-68.2	27	44.3	31.8-56.7	8	13.1	4.6-21.6	16	26.2	15.2-37.3
Kim DW[50]	2018	38	17	44.7	28.9-60.5	21	55.3	39.5-71.1	1	2.6	0-7.7	20	52.6	36.8-68.5
Kim H[a20]	2012	27	5	18.5	3.9-33.2	22	81.5	66.8-96.1	6	22.2	6.5-37.9	16	59.3	40.7-77.8
Ko[a21]	2002	76	30	39.4	28.5-50.5	46	60.5	49.5-71.5	22	28.9	18.8-39.1	20	26.3	16.4-36.2
Kosinski[a22]	2018	29	11	37.9	20.3-55.6	18	62.1	44.4-79.7	2	6.9	0-16.1	16	55.2	37.1-73.3
Lazzara[51]	1993	11	3	27.3	1.0-53.6	8	72.7	46.4-99.0	2	18.2	0-41.0	6	54.5	25.1-84.0
Lee SN[52]	2017	95	40	42.1	32.2-52.0	55	57.9	48.0-67.8	25	26.3	17.5-35.2	30	31.6	22.2-40.9
Loforte[53]	2014	228	84	36.8	30.6-43.1	107	46.9	40.5-53.4	22	9.6	5.8-13.5	122	53.5	47.0-60.0
Luyt[54]	2012	41	14	34.1	19.6-48.7	23	56.1	40.9-71.3	5	12.2	2.2-22.2	18	43.9	28.7-59.1

(Continues)

TABLE 1 (Continued)

Author	Year	Total number of patients	On-ECMO mortality (n)	%	95% CI	Weaning rate (n)	%	95% CI	Mortality after weaning (n)	%	95% CI	Discharge rate (n)	%	95% CI
Mikus[55]	2013	14	7	50.0	23.8-76.2	6	42.9	16.9-68.8	1	7.1	0-20.6	6	42.9	16.9-68.8
Mirabel[56]	2011	35	13	37.1	21.1-53.2	22	62.9	46.8-78.9	1	2.9	0-8.4	21	60.0	53.8-76.2
Muehrcke[57]	1996	23	10	43.5	23.2-63.7	9	39.1	19.2-59.1	2	8.7	0-20.2	7	30.4	11.6-49.2
Pasrija[30]	2018	56	1	1.8	0-5.3	14	25.0	13.7-36.3	5	8.9	1.5-16.4	50	89.3	81.2-97.4
Pokersnik[58]	2012	49	22	44.9	31.0-58.8	27	55.1	41.2-69.0	11	22.4	10.8-34.1	16	32.7	19.5-45.8
Rastan[59]	2010	517	190	36.8	32.6-40.9	327	63.2	59.1-67.4	199	38.5	34.3-42.7	128	24.8	21.0-28.5
Rubino[60]	2017	101	43	42.6	32.9-52.2	58	57.4	47.8-67.1	24	23.8	15.5-32.1	34	33.7	24.4-42.9
Saito[61]	2007	91	34	37.4	27.4-47.3	56	61.5	51.5-71.5	17	18.7	10.7-26.7	40	44.0	33.8-54.2
Sakamoto[62]	2012	98	44	44.9	35.1-54.7	54	55.1	45.3-64.9	22	22.4	14.2-30.7	32	32.7	19.5-45.8
Sangalli[63]	2016	10	1	10.0	0-28.6	9	90.0	71.4-100.0	1	10.0	0-28.6	8	80.0	55.2-100.0
Saxena[64]	2015	45	21	46.7	32.1-61.2	24	53.3	38.8-67.9	13	28.9	15.6-42.1	11	24.4	11.9-37.0
Shinn[65]	2009	92	33	35.9	26.1-45.7	59	64.1	54.3-73.9	20	21.7	13.3-30.2	39	42.4	32.3-52.5
Slottosch[66]	2013	77	29	37.7	26.8-48.5	48	62.3	51.5-73.2	11	14.3	6.5-22.1	37	48.1	36.9-59.2
Smedira[67]	2001	202	83	41.1	34.3-47.9	71	35.1	28.6-41.7	NR	–	–	76	37.6	30.9-44.3
Smith[a23]	2001	17	6	35.3	12.6-58.0	11	64.7	42.0-84.5	4	23.5	3.4-43.7	7	41.2	17.8-64.6
Stub[a24]	2015	24	11	45.8	25.9-65.8	13	54.2	34.2-74.1	1	4.1	0-12.2	12	50.0	30.0-70.0
Takayama[68]	2015	101	40	39.6	30.1-49.1	24	23.8	15.5-32.1	NR	–	–	58	57.4	47.8-67.1
Tanaka[7]	2016	84	34	40.5	30.0-51.0	50	59.5	49.0-70.0	14	16.7	8.7-24.6	36	42.9	32.3-53.4
Tarzia[69]	2015	64	9	14.1	5.5-22.6	NR	–	–	NR	–	–	37	57.8	45.7-69.9
Tsai[70]	2017	105	31	29.5	20.8-38.2	74	70.5	61.8-79.2	19	18.1	10.7-25.5	55	52.4	42.8-61.9
Unosawa[a25]	2013	47	18	38.3	24.4-52.2	29	61.7	47.8-75.6	15	31.9	18.6-45.2	14	27.7	14.9-40.4
van den Brink[71]	2017	12	4	33.3	6.7-60.0	8	66.7	40.0-93.3	0	0	0-12.2	8	66.7	40.0-93.3
Wang S[a26]	1996	18	9	50.0	26.9-73.1	9	50.0	26.9-73.1	3	16.7	0-33.9	6	33.3	11.6-55.1
Wang J[a27]	2013	87	36	41.4	31.0-51.7	51	58.6	48.3-69.0	8	9.2	3.1-15.3	43	49.4	38.9-59.9
Wong[72]	2017	103	49	47.6	37.9-57.2	54	52.4	42.8-62.1	11	10.7	4.7-16.6	43	41.7	32.2-51.3
Wu[73]	2010	110	43	39.1	30.0-48.2	67	60.9	51.8-70.0	21	19.1	11.7-26.4	46	41.8	32.6-51.0
Yeh[74]	2018	99	71	71.7	62.8-80.6	28	28.3	19.4-37.2	15	15.2	8.1-22.2	13	13.1	6.5-19.8
Zhang[75]	2006	32	18	56.2	39.1-73.4	14	43.7	26.6-60.9	6	18.8	5.2-32.3	8	25.0	10.0-40.0
Zhao[76]	2015	24	8	33.3	14.5-52.2	16	66.7	47.8-85.5	8	33.3	14.5-52.2	8	33.3	14.5-52.2
n = 60	Total	9181	3385	38.0	34.2-41.9	5492	57.0	53.3-60.7	2659	15.3	11.1-19.5	2994	44.0	39.8-52.2

Abbreviations: CI, confidence interval; ECMO, extracorporeal membrane oxygenation; NR, not reported.

[a]Studies that report on causes of death.

TABLE 2 Causes of death on-ECMO and after weaning

Author	Year	Cause of death on-ECMO (n, %)	Cause of death after weaning (n, %)
Aziz[12]	2010	MOF (2, 50%) Neurological (2, 50%)	–
Bouabdallaoui[13]	2017	MOF (4, 80%) Sepsis (1, 20%)	–
Chen[14]	2005	MOF (1, 100%)	MOF (2, 67%) Neurological (1, 33%)
Demondion[15]	2013	MOF (26, 65%) Cardiac failure (6, 15%) Bleeding (3, 8%) Sepsis (3, 8%) Aortic dissection (1, 3%) LV thrombosis (1, 3%)	MOF (2, 50%) Neurological (2, 50%)
Den Uil[16]	2017	MOF (17, 40%) Neurological (18, 39%) Cardiac failure (10, 22%) ECMO dysfunction (1, 2%)	MOF (12, 63%) Neurological (4, 21%) Cardiac failure (3, 16%)
Dini[17]	2015	MOF (4, 67%) Cerebral hemorrhage (2, 33%)	–
Guenther[18]	2013	MOF (9, 60%) Neurological (6, 40%)	MOF (5, 83%) Neurological (1, 17%)
Hsu[19]	2010	MOF (20, 83%) Neurological (2, 8%) Bleeding (2, 8%)	Cardiac failure (4, 40%) Pneumonia (6, 60%)
Kim H[20]	2012	Cardiac failure (4, 80%) Bleeding (1, 20%)	Cardiac failure (1, 17%) Sepsis (2, 33%) Arrhythmia (3, 50%)
Ko[21]	2002	MOF (16, 53%) Neurological (3, 10%) Circulatory shock (2, 7%) Bleeding (5, 17%) Arrhythmia (2, 7%) Graft rejection (1, 3%) Family request (1, 3%)	MOF (17, 81%) Neurological (1, 45%) Sudden death (4, 9%)
Kosinski[22]	2018	MOF (11, 100%)	MOF (2, 100%)
Smith[23]	2001	Neurological (2, 33%) Cardiac failure (4, 67%)	Neurological (2, 50%) Sepsis (2, 50%)
Stub[24]	2015	MOF (3, 27%) Neurological (4, 36%) Cerebral hemorrhage (2, 18%) Bleeding (2, 18%)	Cardiac failure (1, 100%)
Unosawa[25]	2013	MOF (5, 28%) Neurological (4, 22%) Cardiac failure (7, 39%) Bleeding (2, 11%)	MOF (8, 53%) Neurological (2, 13%) Cardiac failure (2, 13%) Cardiac rupture (2, 13%) Pneumonia (1, 7%)

(Continues)

TABLE 2 (Continued)

Author	Year	Cause of death on-ECMO (n, %)	Cause of death after weaning (n, %)
Wang S[26]	1996	MOF (5, 56%) Sepsis (2, 22%) Tube rupture (1, 11%) ECMO dysfunction (1, 11%)	MOF (1, 33%) Sepsis (1, 33%) Cerebral hemorrhage (1, 33%)
Wang J[27]	2013	MOF (10, 28%) Neurological (1, 3%) Cardiac failure (22, 61%) DIC (3, 8%)	MOF (8, 100%)

Abbreviations: DIC, disseminated intravascular coagulation; ECMO, extracorporeal membrane oxygenation; LV, left ventricle; MOF, multiorgan failure.

It is still challenging to explain this ECMO-gap. Many factors can be considered, such as a weaning process that was initiated in a too early phase, and ethical factors should be recognized. Deaths also occur after weaning of support due to recognition of futility by health workers in order to facilitate a more humanized healthcare or by family members.

Overall, on-ECMO mortality was 38.0%, and weaning rate was 60.3%. 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 nontransplanted (or non-MCS) discharged patients.[14,15]

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, whereas 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. 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]

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]

The lack of reporting causes of death together (as illustrated by the merely 16 studies describing these findings) 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 challenging.

4.1 | 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 difficult to interpret the results of a true meta-analysis. Therefore, as illustrated by the levels of heterogeneity, pooled rates should be interpreted with caution. 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.

It remains challenging to relate mortality to indication as there is no uniformity in reporting of indications and outcomes in ECMO research. Providing the certain causes of death is not always possible because autopsies are not routinely performed, for example, neurological complications and causes of death. 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.

TABLE 3 Complication rates

	Year	Complication	n	%
Aziz[12]	2010	Bleeding	1	10
		Hemolysis	1	10
		Renal failure	1	10
		Pneumonia	1	10
		Sepsis	1	10
Bouabdallaoui[13]	2017	Pulmonary edema	2	40
		Sepsis	1	20
		Bleeding	1	20
		Limb ischemia	1	20
Chen[14]	2005	Renal	4	26.6
		Neurological	3	20
		Respiratory	1	6.6
		Bleeding	3	20
Demondion[15]	2013	Pneumonia	40	51.3
		ARF	36	46.1
		Pulmonary edema	24	31.6
		Major bleeding	16	21.3
		Lower limb ischemia	7	9.2
		Wound infection	6	8
		Stroke	2	2.6
Den Uil[16]	2017	Bleeding	40	43.4
		Stroke	8	8.6
		Sepsis	11	11.9
		Limb ischemia	13	14.1
		Cannula change	20	21.7
Dini[17]	2015	Renal failure	7	100
Guenther[18]	2013	Cannula related	4	9.7
		Cannula site bleeding	2	4.8
		Cannula- wound healing	2	4.8
		Lower limb ischemia	5	12.1
		Pump thrombosis	1	2.4
Hsu[19]	2010	ARF	38	75
		Femoral bleeding	20	39
		Hematuria	17	33
		GI bleeding	13	25
		Pulmonary infection	11	22
		Compartment syndrome	5	9.8
		ARDS	5	9.8
		Limb ischemia	3	5.9
		Leg amputation	2	3.9
		Neurologic complication	3	5.9
		Catheter-related infection	3	5.9
		Pancreatitis	1	2
Ko[20]	2002	Neurological	9	11.8
		Lower limb reperfusion	20	26.3
		Toe cyanosis	10	13.1
		Fasciotomy	3	3.9
		Bleeding related	35	46
Pasrija[30]	2018	Sepsis	1	20
		Dysrhythmia	1	20
		Tracheostomy	3	60
Smith[23]	2001	Major bleeding	6	35
		Lower limb ischemia	4	23
Stub[24]	2015	Bleeding	16	69
		Cannula-related reintervention	10	38
Unosawa[25]	2012	Incomplete sternal closure	14	100

Abbreviations: ARDS, acute respiratory distress syndrome; ARF, acute renal failure; GI, gastrointestinal.

5 | CONCLUSION

In-hospital mortality rate of adult V-A ECMO patients is still high. The detailed information about timing and causes of death are, however, not adequately reported in the literature. Identifying the extent and causes of death on-ECMO and after weaning revealed many of ECMO patients to still die after weaning, in hospital. Timing of death is related to different causes of death, of which bleeding on-ECMO is the most predominant one compared with 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 remains 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 support.

CONFLICT OF INTEREST

The authors have no financial disclosure and conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

Study design: Makhoul, Heuts, Taccone, Obeid, Mirko, Broman, Malfertheiner, Meani, Raffa, Delnoij, Maessen, Bolotin, Lorusso
Data acquisition: Makhoul, Heuts, Mansouri, Lorusso
Data analysis: Makhoul, Heuts, Mansouri, Lorusso
Data interpretation: Makhoul, Heuts, Mansouri, Lorusso
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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

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