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REVIEW ARTICLE

Extracorporeal membrane oxygenation in patients with hematologic malignancies: a systematic review and meta-analysis

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Abstract

Hematological malignancies (HM) have been, until recently, viewed as contraindications to extracorporeal membrane oxygenation (ECMO) due to bleeding and infectious complications. However, conflicting literature regarding whether ECMO should be used for patients with HM still exists. We conducted a random effects meta-analysis to investigate the outcomes of patients with HM on ECMO. We searched Medline, Embase, Scopus, and Cochrane through 10 October 2021. Risk of bias and certainty of evidence were assessed using the JBI checklists and GRADE approach respectively. Thirteen observational studies (422 patients with HM, 9778 controls without HM) were included. The pooled in-hospital mortality for patients with HM and those with hematopoietic stem cell transplants for HM indications needing ECMO were 79.1% (95%CI: 70.2–86.9%) and 87.7% (95%CI: 80.4–93.8%), respectively. Subgroup analyses found that mortality was higher in adults than children (85.1% vs 67.9%, $p_{interaction} = 0.003$), and in Asia compared to North America and Europe (93.8% vs 69.6%, $p_{interaction} < 0.001$). Pooled ECMO duration was 10.0 days (95%CI: 7.5–12.5); pooled ICU and hospital lengths of stay were 19.8 days (95%CI: 12.4–27.3) and 43.9 days (95%CI: 29.4–58.4) respectively. Age (regression coefficient [*B*]: 0.008, 95%CI: 0.003–0.014), proportion of males (*B*: 1.799, 95%CI: 0.079–3.519), and ECMO duration (*B*: −0.022, 95%CI: −0.043 to −0.001) were significantly associated with higher mortality. In-hospital mortality of patients with HM who needed ECMO was 79.1%, with better outcomes in children, and in North America and Europe. ECMO should not be regarded as routine support therapy in these patients but can be carefully considered on a case-by-case basis.

Keywords Extracorporeal membrane oxygenation · Hematologic neoplasm · Mortality · Systematic review · Meta-analysis

Introduction

Extracorporeal membrane oxygenation (ECMO) is a form of mechanical cardiopulmonary bypass to support patients in the intensive care unit (ICU) with severe cardiac or respiratory failure. Veno-arterial (VA) ECMO provides hemodynamic support and veno-venous (VV) ECMO offers respiratory support [1]. Outcomes following ECMO vary considerably depending on the age of the patient, underlying disease, indication for ECMO, and cannulation strategy. [2, 3] Offering ECMO to patients with hematological malignancies (HM) is associated with higher risk of adverse events.

Patients with underlying HM are prone to infections due to their underlying disease process or chemotherapy [4]. In these patients, acute respiratory failure is a life-threatening complication which warrants admission to the ICU [5, 6]. Despite recent advances in treatment modalities, almost half of them end up requiring invasive ventilation and have

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substantial mortality rates [7, 8]. Also, the use of ECMO in these patients has been associated with increased complications, such as bleeding and nosocomial infections [4].

Despite some studies evaluating the use of ECMO in patients with HM, [9] conflicting reports have been published thus far [7, 10, 11]. A recent review concluded that while there was an increasingly favorable prognosis among HM patients requiring ECMO over time, a more systematic approach was needed to quantify their findings [7]. To address the lack of conclusive evidence, we conducted a systematic review and meta-analysis to analyze the outcomes of patients with HM on ECMO, focusing on in-hospital mortality.

Methods

Search strategy and selection criteria

This review was registered with PROSPERO (CRD42021232647) and was conducted in adherence with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [12]. We searched Medline, Embase, Cochrane, and Scopus databases from 1st January 1990 to 10th October 2021 using the following keywords and their variations: "extracorporeal membrane oxygenation" and "hematologic malignancies" (Supplementary Table 1). We assessed all the relevant studies, and their citation lists to identify articles for inclusion. Studies reporting on at least 5 adult or pediatric patients with HM requiring ECMO were included. We excluded any non-human studies, case reports, and articles that did not report in-hospital mortality. We also excluded reviews of Extracorporeal Life Support Organization (ELSO) registry data to minimize the risk of patient duplication. In the case of overlapping patient data across two or more studies, we included the larger study.

Data collection

Data were collected using a prespecified data extraction form, and covered study characteristics, patient demographics, pre-ECMO and ECMO characteristics, mortality outcomes, and other relevant clinical outcomes.

Risk of bias assessment

We used the appropriate Joanna Briggs Institute (JBI) critical appraisal checklists to assess the eligibility of studies. The possibility of publication bias was assessed using Egger's test and visual inspection of the funnel plot. We performed a sensitivity analysis by excluding studies with comparatively higher risks of bias (JBI score < 8). The screening of articles, data collection, and risk of bias assessment were conducted independently by three reviewers (RRL, JJLS, SM), and any conflicts were resolved by a fourth reviewer (KR).

Statistical analysis

Statistical analyses were performed on R 4.0.2 using the meta (v4.17–0) and dmetar (v0.0.9000) packages. For continuous characteristics of studies, we generated the means and standard deviations from the information presented in each study as per Wan et al. [13] and pooled the means via meta-analysis. The primary aim of our study was to estimate the pooled in-hospital mortality among patients with HM who received ECMO. Secondary aims included the pooled risk ratio (RR) of mortality when compared to controls without HM supported on ECMO, the pooled mean of duration of ECMO support, ICU length of stay, and hospital length of stay for patients with HM. Due to the sparseness of data on the complications of ECMO, we aggregated each complication across studies and identified the most frequently reported complication and its corresponding percentage where the denominator was the total of reported complications.

We anticipated significant inter-study heterogeneity given the different intervention thresholds and subsequent management of patients with HM on ECMO. As such, random effects meta-analyses (DerSimonian and Laird) [14] were conducted. To pool the proportions across studies, the Freeman-Tukey double arcsine transformation was used [15]. For continuous outcomes, pooled means and mean differences are presented. For each pooled estimate, their respective 95% confidence intervals (CIs) are reported. For the study specific proportions, 95% CIs were computed using the Clopper-Pearson method [16].

Subgroup analyses for the primary aim of our study were conducted with continuity correction to include studies with zero events. Categorical variables included were age (adults vs children as defined by each study) and geographical region (Asia vs North America and Europe). A separate post hoc subgroup analysis looking at the mortality of those receiving hematopoietic stem cell transplants (HSCT) for HM indications, and comparing mortality between neutropenic versus non-neutropenic patients with HM was conducted as well. Univariable study-level meta-regression was conducted when the covariates were continuous and there were at least 6 studies to explore potential sources of heterogeneity or prognostically relevant study-level covariates [17].

We used the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach to assess the inter-study heterogeneity for our primary and secondary aims [18, 19] This helps to define the quality of the evidence in terms of the confidence that the estimated effect is similar to the true effect.

Table 1 Demographics and outcomes of patients in the included studies[#]

Study	Centre	Groups	No. of patients	Patient Characteristics*	Pre-ECMO and ECMO characteristics	Hematological malignancies	Outcomes
Cho 2019	*Asan Medical Center, South Korea*	HM	23	44 (29-51) years 15 males 10 HSCT 9 Chemo	SAPS II: 58.0 (51.0-68.5) SOFA: 14.0 (13.0-17.0) P/F: 63.0 (49.5-107.5) 9 VV-ECMO 14 VA-ECMO 15 RRT Plt: 64.0 (47.0-86.0) ×10^3/μL	6 AML, 2CML, 1 CML+AML, 4 MM, 3 MDS, 5 lymphoma	21 HM non-survivors 7 HSCT non-survivors 9 ECMO weaning success ECMO duration: 104.7 (37.1-221.2) hrs ICU LOS: 10.0 (6-15.5) days
Choi 2016	*Seoul Saint Mary's Hospital, South Korea*	HM	22	47.4±11.8 years 16 Males 22 ARDS 13 HSCT 6 Chemo	SOFA: 12.7±3.5 P/F: 62.0 (50.9-76.1) PaCO2: 63.08±21.18 pH: 7.25±0.13 VV ECMO: 19 VA ECMO: 3 RRT: 9 Plt: 78.6±80.8 ×10^3/μL	14 AML, 4 ALL, 2 HL, 1 MM, 1 MDS	21 HM non-survivors 13 HSCT non-survivors 2 ECMO weaning success ECMO duration: 162.0 (60.25-251.25) hrs
		Non-HM	44	58.7±19.8 years 31 Males 44 ARDS 0 Chemo	SOFA: 10.9±3.6 P/F: 64.5 (49.6-73.6) PaCO2: 50.11±25.35 pH: 7.00±0.13 VV ECMO: 39 VA ECMO: 5 RRT: 27 Plt: 154.4±89.0 ×10^3/μL	NA	32 non-survivors 14 ECMO weaning success ECMO duration: 217.5 (112.75-322) hrs
Coleman 2020	*Pediatric Health Information System, USA*	HM	151	31 HSCT	NR	101 leukemia, 19 lymphoma	103 HM non-survivors 25 HSCT non-survivors ECMO duration: 194.3±339.1 hrs Hospital LOS: 38.7±39.0 days
		Non-HM	9043	NR	NR	NA	NR
Cortina 2018	*Medical University of Innsbruck, Austria*	HM	9	14.0 [1.0-18.0] years 8 Chemo	P/F: 47.0 [32.0-67.0] VV ECMO: 9 VA ECMO: 2 RRT: 3 Plt: 35.0 [19.0-106.0] ×10^3/μL	5 ALL, 3 AML, 1 JMML	5 HM non-survivors 5 ECMO weaning success ECMO duration: 14.0 [2.0-24.0] days
Maue 2019	*Riley Children's hospital, USA*	HM	7	5.6 (1.1-12.7) years 4 males BMI 28.9 (24.0-33.6) 7 HSCT	P/F: 34.0 (17.0-35.0) pH: 7.14 (7.07-7.18) VV ECMO: 4 VA ECMO: 3 RRT: 6 Plt: 52.0 (43.0-153.0) ×10^3/μL	NR	6 HM and HSCT non-survivors 2 ECMO weaning success ECMO duration: 7.0 (1.0-8.0) days Hospital LOS: 14.0 (7.0-50.0) days
		Non-HM	31	7.9 (3.6-12.6) years 12 males BMI 27.8 (23.1-30.2)	P/F: 34.0 (22.0-43.0) pH: 7.09 (7.00-7.23) VV ECMO: 9 VA ECMO: 22 RRT: 16 Plt: 175.0 (98.0-295.0) ×10^3/μL	NA	21 non-survivors 24 ECMO weaning success ECMO duration: 8.0 (4.0-13.0) days Hospital LOS: 39.0 (14.0-77.0) days
Na 2019	*16 tertiary or university-affiliated hospitals in South Korea*	HM	18	61.0 (56.0-70.0) years 29 males 18 ARDS	NR	NR	18 HM non-survivors 3 ECMO weaning success ECMO duration: 7.1 (0.8-25.4) days
		Non-HM	443	63.0 (55.0-77.0) years 33 males 443 ARDS	NR	NA	265 non-survivors 254 ECMO weaning success
Park 2021	*Samsung Medical Center, South Korea*	HM	30	47.0±15.2 years 19 males BMI: 22.7±2.9 7 HSCT	SAPS II: 50.6±15 SOFA: 12.5±3.4 PaO2: 71.0 (54.8-82.9) mmHg pH: 7.10±0.20 VV ECMO: 14 VA ECMO: 16 RRT: 18 Plt: 41.5 ×10^3/μL	14 AML/CML, 9 NHL, 7 MM	26 HM non-survivors 6 HSCT non-survivors 12 ECMO weaning success ICU LOS: 19.6±16.6 days Hospital LOS: 48.6±72.4 days

Table 1 (continued)

		Non-HM	68	60.5±11.4 years 52 males BMI: 23.8±3.2	SAPS II: 48.4±18.2 SOFA: 10.1±3.8 PaO2: 81 (62-143) mmHg pH: 7.20±0.20 VV ECMO: 24 VA ECMO: 44 RRT: 31 Plt: 145.0 ×10^3/μL	NA	42 non-survivors 34 ECMO weaning success ICU LOS: 22.0±23.6 days Hospital LOS: 50.9±58.3 days
Potratz 2021	*University Children's Hospital Münste, Germany*	HM	17	10.2±6.1 years 11 males 6 HSCT 3 ARDS 4 Chemo	pH: <7.1 VV ECMO: 11 VA ECMO: 6 RRT: 7	9 ALL, 1 MDS, 4 AML, 2 LBL (NHL), 1 HL	11 HM non-survivors 5 HSCT non-survivors 8 ECMO weaning success ECMO duration: 14.29±12.52 days
		Non-HM	3	7.83±7.15 years 1 male 3 HSCT	pH: <7.1 VV ECMO: 2 VA ECMO: 1 RRT: 1	NA	2 non-survivors ECMO duration: 27.33±15.69 days
Ranta 2021	Swedish Registry	HM	12	5.2±5.1 years 26 males 0 HSCT	VV ECMO: 4 VA ECMO: 4	7 ALL, 2 AML, 1 mixed phenotype acute leukemia, 1 mature B-cell leukemia, 1 NHL	6 HM non-survivors 7 ECMO weaning success ECMO duration: 15.0 [1.0-72.0] days ICU LOS: 20.8±19.0 days
Schmidt 2018	*10 ICUs in seven countries*	HM	62	14 HSCT	NR	15 AML/ALL/MDS, 38 NHL/HL/MM, 9 CML/others	47 HM non-survivors 13 HSCT non-survivors
		Non-HM	141	NR	NR	NA	96 non-survivors
Stecher 2018	*Internal ICU of the University Hospital of the Ludwig-*	HM	20	9 HSCT 20 ARDS 4 Chemo	SAPS II: 66.5±14.5 VV ECMO: 20 VA ECMO: 0	NR	16 HM non-survivors 9 HSCT non-survivors ECMO duration: 11.7±8.7 days
	Maximilians University Munich, Germany	Non-HM	5	5 ARDS	SAPS II: 70.6±14.4 VV ECMO: 5 VA ECMO: 0	NA	4 non-survivors ECMO duration: 10.6±6.8 days
Wohlfarth 2014	*Medical University of Vienna, General Hospital*	HM	14	32.0 (22.0-51.0) years 8 males 5 HSCT 14 ARDS 9 Chemo	SAPS II: 51.0 (42.0-65.0) SOFA: 12.0 (11.0-13.0) P/F: 60.0 (53.0-65.0) PaCO2: 49.0 (43.0-59.0) mmHg pH: 7.29 (7.23-7.37) VV ECMO: 11 VA ECMO: 3 RRT: 5 Inotropes: 14 Plt: 35.0 (26.0-51.0) ×10^3/μL	10 NHL, 2 HL, 1 AML, 1 MM	7 HM non-survivors 4 HSCT non-survivors ECMO duration: 8.5 (4.0-16.0) days ICU LOS: 22.0 (14.0-42.0) days Hospital LOS: 56.0 (44.0-101.0) days
Wohlfarth 2017	*ICUs in 12 European tertiary care centers (Austria, Germany, France, and Belgium).*	HM	37	37.0 (26.0–49.0) years 20 males 37 HSCT 37 ARDS	SAPS II: 56.0 (42.0-67.0) P/F: 69.0 (52.0-83.0) PaCO2: 57.0 (47.0-71.0) mmHg pH: 7.29 (7.18-7.37) VV ECMO: 37 VA ECMO: 0 RRT: 19 Plt: 34.0 (14.0–49.0) ×10^3/μL	22 Acute leukemia, 5 lymphoma, 3 MDS	30 HM and HSCT non-survivors 11 ECMO weaning success ECMO duration: 15.0 (8.0-23.0) days ICU LOS: 28.0 (14.0-33.0) days

[#]Characteristics relevant to the column and reported by the study are presented. Studies with no information on the characteristics are presented as NR (not reported). Characteristics not relevant to non-HM patients are presented as NA (not applicable)

[*]Data represented as mean ± standard deviation, median (interquartile range), or median [range]

Abbreviations: AML: acute myeloid leukemia; ALL: Acute lymphoblastic leukemia; ARDS: acute respiratory distress syndrome; Chemo: Chemotherapy; CML: chronic myeloid leukemia; ECMO: extracorporeal membrane oxygenation; HL: Hodgkin's lymphoma; HM: Hematological malignancies; HSCT: Hematopoietic stem cell transplant; ICU: intensive care unit; JMML: Juvenile myelomonocytic leukemia; LBL: lymphoblastic lymphoma; LOS: length of stay; MDS: myelodysplastic syndrome; MM: Multiple myeloma; NA: Not applicable; NHL: Non-Hodgkin's lymphoma; NR: Not reported; P/F: PaO_2/FiO_2; Plt: Platelets ($\times 10^3/\mu L$); RRT: Renal replacement therapy; SAPS II: Simplified Acute Physiology Score II; SOFA: Sequential Organ Failure Assessment; VA-ECMO: Venoarterial ECMO; VV-ECMO: Venovenous ECMO

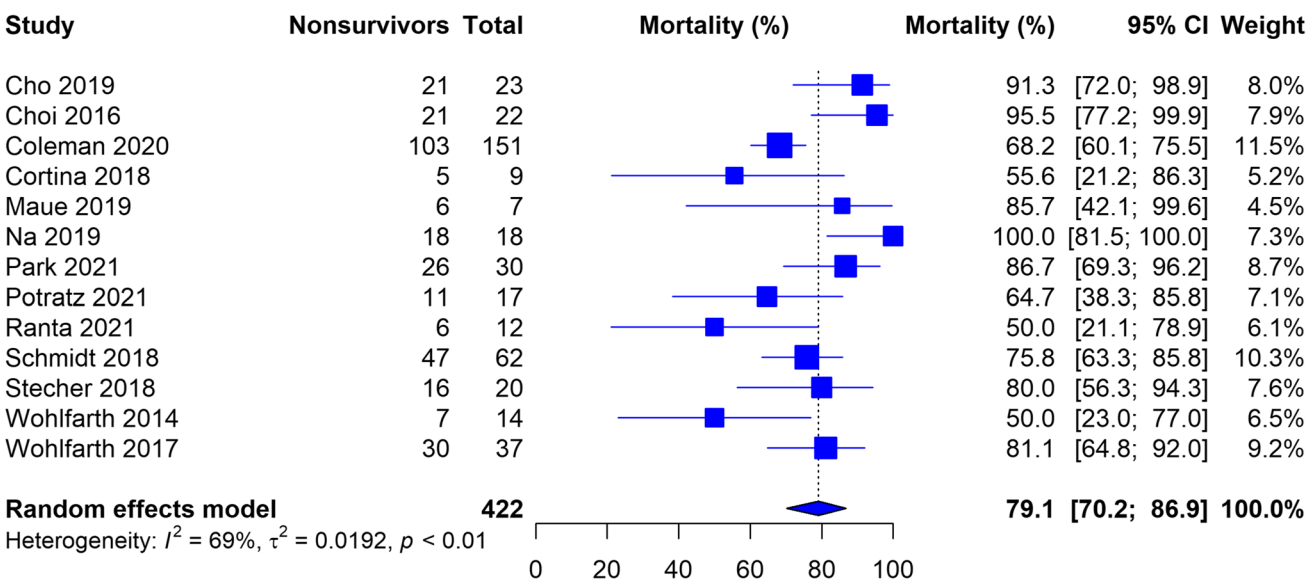


Fig. 1 Pooled in-hospital mortality of patients with hematological malignancies on extracorporeal membrane oxygenation

Results

Of 814 references, we assessed 56 full-text articles after initial screening. A total of 13 studies reporting on 422 patients with HM and 9778 controls without HM requiring ECMO were included in this analysis (Supplementary Fig. 1) [4, 11, 20–30].

Assessment of study quality

Based on the JBI critical appraisal checklist for case series, the studies included for this review were of high quality, with 8 studies scoring a minimum of 9/10 (Supplementary Table 2). A summary of the assessment of certainty using the GRADE approach is presented in Table 3.

Characteristics of patients

Table 1 reports the characteristics of the included studies. Four studies (93 patients with HM) were from Asia, 2 studies were from North America (158 patients with HM), 6 studies were from Europe (109 patients with HM), and 1 multi-continental study was conducted (62 patients with HM). The pooled mean age of patients with HM supported by ECMO was 26.7 years (95%CI: 15.0–38.5). The majority of the patients were male (61.3%, 95%CI: 53.3–68.8%), with severe acute respiratory distress syndrome (ARDS) (PaO_2/FiO_2 [P/F] ratio: 56.7, 95%CI: 46.8–66.6) and organ dysfunction (Sequential Organ Failure Assessment score: 12.5, 95%CI: 11.1–13.9; Simplified Acute Physiology Score II: 56.9, 95%CI: 51.2–62.6). VV ECMO was the predominant cannulation strategy utilized (79.9%, 95%CI: 58.6–91.8%), while the remaining patients were cannulated on VA ECMO. The most common HM was leukemia (65.3%, 95%CI: 45.6–80.8%), followed by lymphoma (18.8%, 95%CI: 9.8–33.2%), multiple myeloma (2.4%, 95%CI: 0.5–10.9%), and myelodysplastic syndrome (1.6%, 95%CI: 0.3–7.2%). 35.8% (95%CI: 21.5–53.2%) of patients with HM were on chemotherapy, while 46.1% (95%CI: 19.9–74.7%) received HSCT for HM indications. For patients with HM, the pooled mean platelet count was $50.9 \times 10^3/\mu L$ (95%CI: 37.0–64.7) and pooled mean leukocyte count was $7.0 \times 10^3/\mu L$ (95%CI: 4.3–9.7) prior to ECMO. Among the patients without HM, these were $158.1 \times 10^3/\mu L$ (95%CI: 139.9–176.2) and $12.6 \times 10^3/\mu L$ (95%CI: 9.4–15.7) respectively. 41.5% (95%CI: 30.6–53.2%) of patients with HM were neutropenic, defined as an absolute neutrophil count $< 0.5 \times 10^3/\mu L$ by the studies. 50.8% (95%CI: 42.33–59.2%) of patients with HM received renal replacement therapy compared to 51.8% (95%CI: 43.6–59.8%) of patients without HM.

Primary aim

Of 13 observational studies (422 patients), the pooled in-hospital mortality for patients with HM needing ECMO was 79.1% (95%CI: 70.2–86.9%, high certainty, Fig. 1), with the absence of asymmetry in the funnel plot indicating a low probability for publication bias ($p_{egger} = 0.51$, Supplementary Fig. 2). Sensitivity analysis excluding 2 studies [4, 23] with a JBI score of < 8 did not significantly change the pooled estimate (79.4%, 95%CI: 69.6–87.8%).

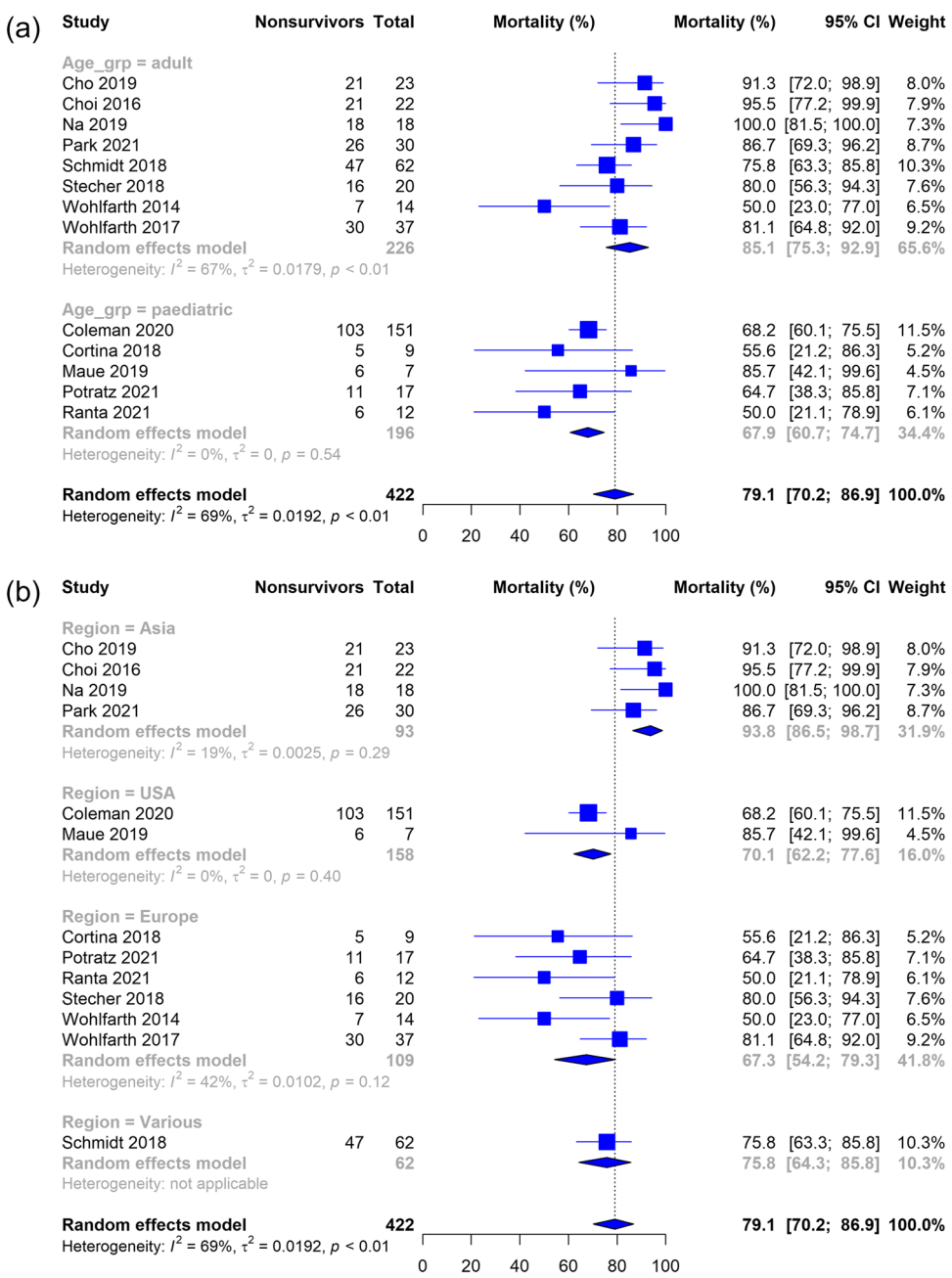
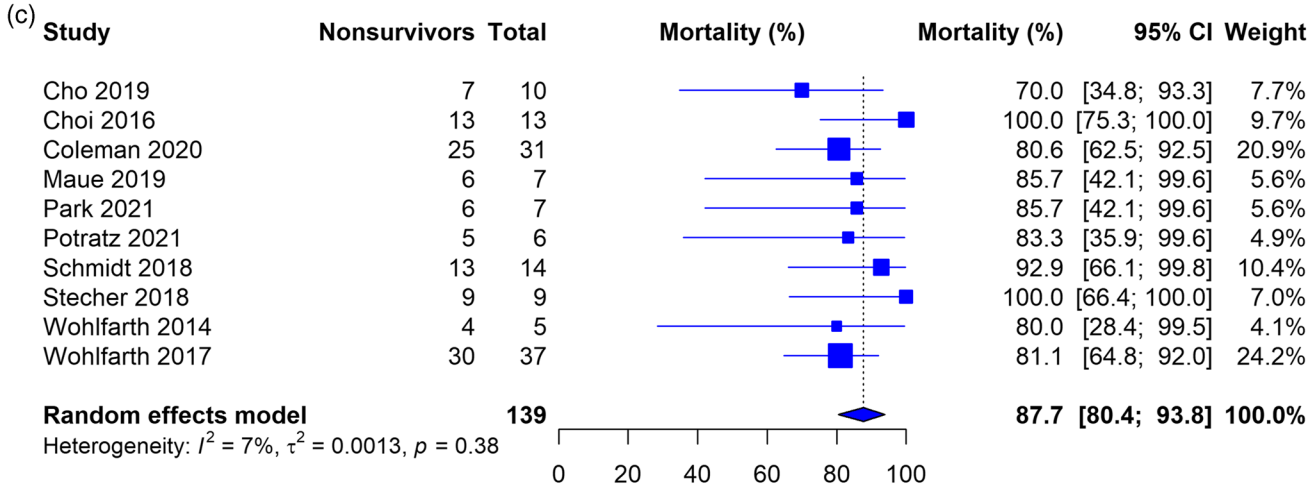


Fig. 2 Subgroup analysis of **a** age (adult vs pediatric), **b** geographical region (Asia vs North America and Europe), and **c** patients with hematopoietic stem cell transplant

Subgroup analysis

Based on subgroup analysis, studies reporting on adult patients had a significantly higher mortality (8 studies, 226 patients, 85.1%, 95%CI: 75.3–92.9%) compared to those reporting on pediatric patients (5 studies, 196 patients, 67.9%, 95%CI: 60.7–74.7%, $p_{\text{interaction}} = 0.003$, Fig. 2a). Similarly, studies reporting from centers in Asia (4 studies, 93 patients, 93.8%, 95%CI: 86.5–98.7%) had a higher mortality rate when compared to studies reporting from centers in North America and Europe (8 studies, 267 patients, 69.6%, 95%CI: 61.3–77.4%, $p_{\text{interaction}} < 0.001$, Fig 2b). The multi-continental study by Schmidt et al. reported a mortality rate of 75.8% (95%CI: 64.3–85.8%) [28]. The subgroup of patients who received HSCT for HM indications had a relatively higher in-hospital mortality of 87.7% (95%CI: 80.4–93.8%, Fig 2c) compared to the pooled mortality for all patients with HM. There was no significant difference in mortality between neutropenic versus non-neutropenic patients with HM (RR 1.1, 95%CI: 0.4–3.2).

Fig. 2 (continued)



Meta-regression analyses

Univariable meta-regression found that the proportion of male patients (regression coefficient [*B*]: 1.799, 95%CI: 0.079–3.519, $p = 0.040$), mean age (*B*: 0.008, 95%CI: 0.003–0.014, $p = 0.005$), and mean ECMO duration (*B*: −0.022, 95%CI: −0.043 to −0.001, $p = 0.036$) had significant associations with in-hospital mortality (Fig. 3). Other factors such as mean P/F ratio and proportion of patients receiving HSCT and VV-ECMO were not significantly associated with in-hospital mortality (Table 2).

Secondary aims

Seven studies (176 patients with HM, 735 controls without HM) reported on the in-hospital mortality in patients with HM and without HM receiving ECMO support [4, 21, 24–26, 28, 29]. HM was not significantly associated with an increased risk of in-hospital mortality (RR: 1.28, 95%CI: 0.99–1.66, $p = 0.06$, very low certainty, Fig. 4).

The pooled duration of ECMO support was 10.0 days (95%CI: 7.5–12.5, 11 studies, moderate certainty); pooled ICU and hospital length of stay were 19.8 days (95%CI: 12.4–27.3, 5 studies, moderate certainty) and 43.9 days (95%CI: 29.4–58.4, 4 studies, moderate certainty), respectively (Supplementary Fig. 3). A total of 81 complications were reported among the 9 studies (171 patients) (Supplementary Table 3). Hemorrhagic (55.6%) complications were the most commonly reported among this patient cohort (Table 3).

Discussion

This review reported on the pooled in-hospital mortality in patients with HM who received ECMO. Patients were predominantly young adult males from North America and Europe with severe ARDS receiving VV-ECMO with a pooled in-hospital mortality of 79.1%. Additionally, we noted that increasing age, shorter ECMO duration, and male sex were significantly associated with higher mortality. Subgroup analysis found higher mortality in adults than children, in Asia compared to North America and Europe, and in patients who received hematopoietic stem cell transplant for HM indications (87.7%). Hemorrhagic (55.6%) complications were the most frequently reported among the studies in this review.

In a recent sub-analysis of The Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG SAFE) trial, immunocompromised patients with ARDS (20.8% of the patient cohort) suffered from significantly higher mortality rates (52.4%) compared to immunocompetent individuals (36.2%), irrespective of disease severity [31]. Similarly, another analysis from the same database found that active neoplasm, HM, and immunosuppression were independently associated with mortality [32] Azoulay et al. noted an in-hospital mortality of 64% in a cohort of 1004 patients with ARDS and underlying malignancies, of which 86% had HM [33]. Patients with allogeneic HSCT were also at increased risk of higher mortality if they developed hypoxemic respiratory failure [33]. Early admission to ICU was associated

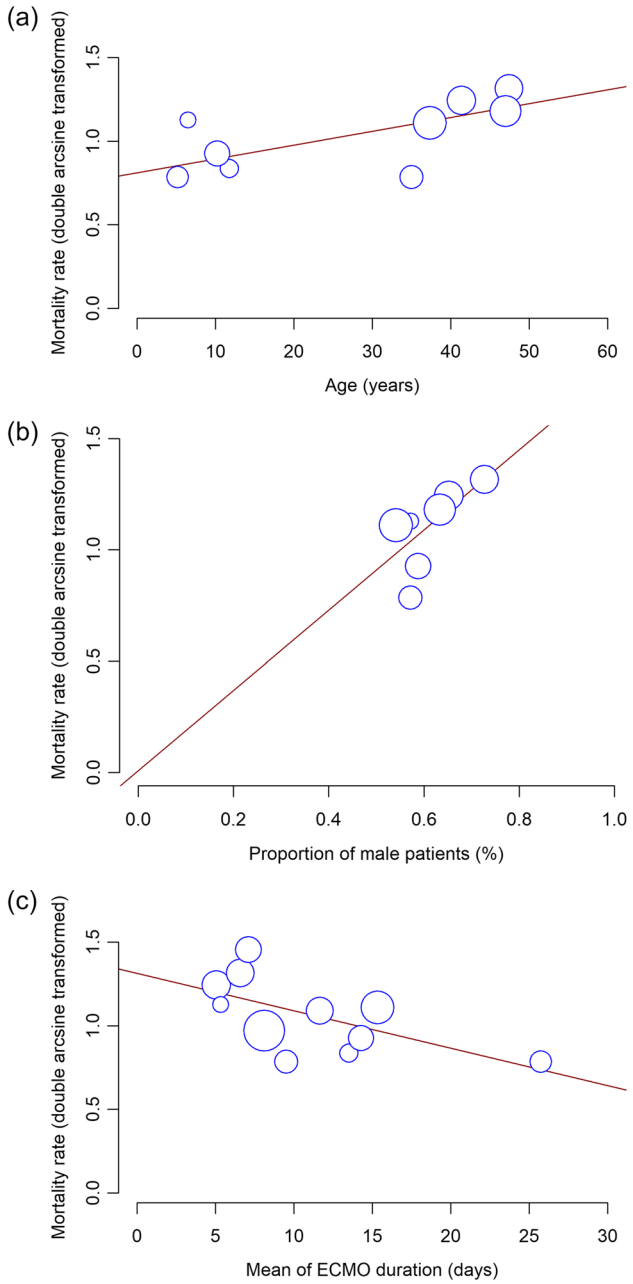


Fig. 3 Bubble plots for meta-regression of **a** mean of age, **b** proportion of male patients, and **c** mean of extracorporeal membrane oxygenation duration with in-hospital mortality

with improved outcomes [5]. A recent ELSO registry analysis of pediatric patients with HSCT requiring ECMO showed an overall in-hospital survival of 19%, although this had improved to 26% within the last decade ($p = 0.01$) [34]. Although the outcomes of patients with HM have shown considerable improvement due to advancements in therapeutic strategies in recent years, patients need to be carefully selected for resource intensive modalities like ECMO, given its high mortality and intense resource utilization [5, 35].

Patients with concomitant ARDS and HM have a relatively high mortality of 77% [36], and it has been well established that initiation of invasive ventilation accounted for poorer outcomes in this cohort [37]. Due to the complex underlying disease pathophysiology, the management of these patients using ECMO as a rescue therapy is more challenging, and they have more frequent complications such as bleeding and nosocomial infections while on ECMO [38]. Further evaluation of the safety of ECMO in spontaneously breathing patients with HM to prevent endotracheal intubation and ventilator associated pneumonia should be considered. While ELSO guidelines consider major pharmacological immunosuppression (absolute neutrophil count $< 0.4 \times 10^3/\mu L$) as a relative contraindication to ECMO, [39] recent ECMO cohorts nonetheless enrolled immunocompromised patients [40, 41]. In the ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial, 22% of the patients were immunocompromised with a 60-day mortality of 56% in the treatment group [42]. In contrast, we observed a pooled mortality of 79% in our cohort of patients with HM who received ECMO therapy.

The high mortality in our review could be attributed to the underlying disease process, high organ dysfunction scores, associated multi-organ failure (MOF), and nosocomial complications. Prior studies also observed poor survival patterns in patients with associated MOF in this cohort [5, 36]. We found that hemorrhagic complications were the most commonly reported complication among patients with HM, potentially attributable to the concomitant anticoagulation, thrombocytopenia and coagulation factor consumption by the ECMO circuit in addition to the underlying disease [42]. We observed that the cumulative mean platelet count in patients with HM was lower than that of patients without HM, possibly contributing to both increased bleeding episodes while on ECMO support and higher mortality. Review of existing transfusion thresholds to correct coagulopathy and thrombocytopenia in this group of high-risk patients should be considered, given the increased bleeding risk while on ECMO.

There are several limitations to our study. First, due to the resource-intensive nature of ECMO, particularly in this patient cohort, randomized controlled trials are logistically challenging. All the studies in our analysis

Table 2 Univariable meta-regression of patient, pre-ECMO and ECMO characteristics with in-hospital mortality

Covariate	Studies	Regression coefficient	LCI	UCI	*p*-value
Mean of age	9	0.008	0.003	0.014	**0.005**
Proportion of males	7	1.799	0.079	3.519	**0.040**
Mean of ECMO duration	11	−0.022	−0.043	−0.001	**0.036**
Proportion of patients with HSCT	11	0.233	−0.059	0.524	0.118
Mean of P/F ratio	6	0.005	−0.007	0.017	0.446
Proportion of patients on VV ECMO	10	0.166	−0.376	0.707	0.549

p-values < 0.05 are highlighted in bold

Abbreviations: ECMO = extracorporeal membrane oxygenation; HSCT = hematopoietic stem cell transplant; LCI = lower confidence interval; P/F = PaO_2/FiO_2; UCI = upper confidence interval; VV = veno-venous

were observational, which introduces a risk of bias and potential confounding, particularly without any risk- or propensity-score adjustment methods. This is further exacerbated by the fact that the sample sizes were small and heterogeneous — the indications for ECMO varied across studies, and patient profiles and diagnoses were diverse as well. To account for this, we used the random effects model for meta-analysis and were able to identify some sources of heterogeneity through subgroup analysis and meta-regression. Nonetheless, the meta-regression analyses are limited by the small sample size and limited number of studies. Furthermore, it is also prone to type II errors and ecological fallacy [43]. Second, patients who received HSCT for HM indications were included in the mortality analysis for patients with HM on ECMO. This may lead to confounding because up until recently, ECMO for HSCT was regarded as futile with < 10% survival, while ECMO for carefully selected patients with HM was regarded as acceptable with a 30–40% survival. Third, some data were poorly reported such as the incidence of MOF or secondary infections, which might be prognostically significant in this cohort. In our analysis, we used surrogate markers (SOFA score, leukocyte counts) to estimate the likelihood of developing these complications, but such analyses are nonetheless indirect, and do not reflect the prevalence of these complications. Some studies also did not provide data for patients with and without HM separately or did not include patients without HM, making direct comparisons or meta-regression challenging.

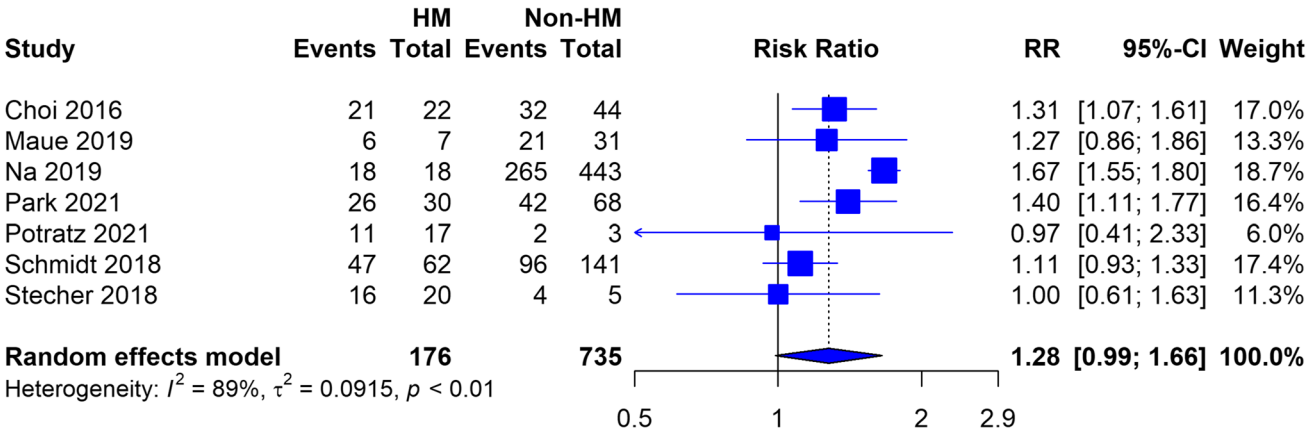


Fig. 4 Risk ratio of mortality comparing patients with and without hematological malignancies on extracorporeal membrane oxygenation

Table 3 Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) findings

№ of studies	Certainty assessment						Effect			Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of events	№ of individuals	Rate (95% CI)		
In-hospital mortality											
13	observational studies	not serious	not serious[a]	not serious	not serious	none	317	422	event rate 79.1% (70.2 to 86.9)	⊕⊕⊕⊕ High	CRITICAL
Duration of ECMO											
11	observational studies	not serious	serious[b]	not serious	not serious	none	-	330	mean 10.0 days (7.5 to 12.5)	⊕⊕⊕◯ Moderate	IMPORTANT
ICU length of stay											
5	observational studies	not serious	serious[b]	not serious	not serious	none	-	115	mean 19.8 days (12.4 to 27.3)	⊕⊕⊕◯ Moderate	IMPORTANT
Hospital length of stay											
4	observational studies	not serious	not serious	not serious	serious[c]	none	-	202	mean 43.9 days (29.4 to 58.4)	⊕⊕⊕◯ Moderate	IMPORTANT

Explanations
a. There was some heterogeneity (I^2=69%). Some of the 95% confidence intervals (CI) do not overlap, and point estimates are sparsely distributed. However, subgroup analysis and meta-regression analyses found significant factors that were associated with mortality, hence possibly accounting for the heterogeneity. As such, this was a borderline decision to not rate down for inconsistency.
b. There was substantial heterogeneity. Some of the 95% CIs do not overlap, and point estimates are sparsely distributed.
c. The 95% CI is very wide (29.4-58.4 days).

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[intervention]	[comparison]	Relative (95% CI)	Absolute (95% CI)		
Relative risk of mortality comparing patients with HM and without HM supported on ECMO												
7	observational studies	not serious	serious[a]	not serious	not serious	none	145/176 (82.4%)	462/735 (62.9%)	**RR 1.28** (0.99 to 1.66)	**176 more per 1,000** (from 6 fewer to 415 more)	⊕◯◯◯ Very low	NOT IMPORTANT

CI: confidence interval; **RR:** risk ratio

Explanations
a. There is considerable heterogeneity (I^2=89%). Some of the 95%CIs do not overlap, and point estimates are sparsely distributed.

Conclusion

Survival of patients with HM requiring ECMO are relatively poor when compared to other indications for ECMO. Patients at risk of worse outcomes include older age, male gender, and recipients of HSCT. Given the higher mortality of this cohort while on ECMO, extracorporeal therapy should be considered judiciously on a case-by-case basis for each patient. Future studies should focus on exploring the ideal time of initiation of ECMO and attempt to establish specific initiation criteria in these patients.

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Declarations

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent was not applicable since the manuscript does not contain any patient data.

Conflict of interest The authors declare no competing interests.

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