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BRIEF REPORT

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Role of age as eligibility criterion for ECMO in patients with ARDS: meta-regression analysis

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Abstract

Background Age as an eligibility criterion for V-V ECMO is widely debated and varies among healthcare institutions. We examined how age relates to mortality in patients undergoing V-V ECMO for ARDS.

Methods Systematic review and meta-regression of clinical studies published between 2015 and June 2024. Studies involving at least 6 ARDS patients treated with V-V ECMO, with specific data on ICU and/or hospital mortality and patient age were included. The search strategy was executed in PubMed, limited to English-language. COVID-19 and non-COVID-19 populations were analyzed separately. Meta-regressions of mortality outcomes on age were performed using gender, BMI, SAPS II, APACHE II, Charlson comorbidity index or SOFA as covariates.

Results In non-COVID ARDS, the meta-regression of 173 studies with 56,257 participants showed a significant positive association between mean age and ICU/hospital mortality. In COVID-19 ARDS, a significant relationship between mean age and ICU mortality, but not hospital mortality, was found in 103 studies with 21,255 participants. Sensitivity analyses confirmed these findings, highlighting a linear relationship between age and mortality in both groups. For each additional year of mean age, ICU mortality increased by 1.2% in non-COVID ARDS and 1.9% in COVID ARDS.

Conclusions The relationship between age and ICU mortality is linear and shows no inflection point. Consequently, no age cut-off can be recommended for determining patient eligibility for V-V ECMO.

Keywords V-V ECMO, ARDS, Age

Introduction

Acute Respiratory Distress Syndrome (ARDS) is a critical condition with a mortality rate exceeding 40% [1]. Despite being the recommended life-saving intervention when conventional treatments fail, standardized selection criteria for veno-venous extracorporeal membrane oxygenation (V-V ECMO) are still lacking. [2]. Although common clinical practice takes age into consideration as selection criteria for ECMO [3], the Extracorporeal Life Support Organization (ELSO) refrains from establishing a specific age threshold due to the variability in mortality rates and age cut-offs across predictive scoring systems and clinical trials [2].

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The lack of a specific age limit may be explained by the observation that mortality rates among older patients may range from less than 50% to over 80% [3, 4]. Additionally, a recent randomized clinical trial did not enforce an upper age limit for ECMO eligibility [5]. Furthermore, recent scoring systems incorporate different age thresholds to forecast survival among V-V ECMO patients [6].

Meta-regression analysis is a statistical technique that can be useful to explore sources of heterogeneity and to examine the relationship between study characteristics and the effect sizes reported in the included studies [7]. We conducted a systematic review and meta-regression analysis to describe the relationship between age and mortality in patients with ARDS treated with V-V ECMO.

Methods

This systematic review and meta-analysis of clinical studies was conducted in accordance with recent recommendations [8, 9]. We included studies that met the following criteria: (***a***) studies (observational, case series, and RCTs) had to include patients in whom ARDS was diagnosed according to the Berlin definition [10] and were treated with V-V ECMO; (***b***) studies had to enroll ≥ 6 patients; (***c***) studies had to report age and mortality [Intensive Care Unit (ICU) or hospital]. We conducted a literature search in the PubMed database including studies published between January 1st, 2015, and June 30th, 2024 (last access July 5th, 2024). The following search terms were used: "ECMO" OR "extracorporeal membrane oxygenation" OR "extracorporeal oxygenation". Articles were identified and assessed for eligibility independently by five of the authors (LB, MB, RdA, DN and ISZ). The database search was restricted to English language. The whole process was supervised by another author (TT), who was consulted also in cases of disagreement about eligibility. The methodological quality of the studies was independently assessed by two of the authors (LB and MB) using previously described methods (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools). In case of disagreement, a third author (TT) was consulted.

For articles reporting individual patients' data, mean age and median length of stay were computed. For articles that reported median age and range (min–max) or interquartile range (1st quartile – 3rd quartile), mean age was calculated using appropriate Wan's formula (see Additional methods, *online supplement*). Given the specific clinical characteristics and logistic challenges during the COVID-19 pandemic, the "conventional ARDS" and "COVID-19 ARDS" subgroups were examined separately. When papers reported information on subgroups "conventional ARDS" and "COVID-19 ARDS", each subgroup was included in the corresponding analysis.

Meta-regression results for mortality vs. age were reported using the b-regression coefficient. Gender, body mass index (BMI), standardized severity scores at admission [simplified acute physiology score (SAPS II) or acute physiology and chronic health evaluation (APACHE II), sequential organ failure assessment (SOFA) and Charlson comorbidity index] were used as covariates. Severity scores were standardized by dividing the mean by the standard deviation. Sensitivity analyses were performed taking into considerations: (a) the quality of studies; (b) the studies reporting only mean age; (c) the possible non-linear relationship between age and outcomes.

The Stata command "metaprop" was used to perform meta-analyses of proportions and to estimate statistical heterogeneity between studies. A random-effects model using the Der Simonian and Laird method (14) was used to estimate mortality using proportions and 95% confidence intervals (95% CI) and to produce forest plots. Meta-regression was used to investigate whether heterogeneity between studies could be explained by one or more study characteristics [11]. The significance level was set at $p < 0.05$. All statistical analyses were performed using Stata version 15 (StataCorp, 2017. Stata statistical software: Release 15. College Station, TX). Additional methods are presented in the *online supplement*.

Results

Figure E1 *(online supplement)* presents the results of the search and reasons for exclusion. The 261 eligible studies included 77,512 participants. Individual studies with the variables of interest are presented in Table E1 (non-COVID) and Table E2 (COVID). Fifteen studies were included in both tables because they reported information on subgroups of non-COVID and COVID patients.

Non-COVID ARDS

We included 173 studies with a total of 56,257 participants (2 RCTs, 2 case series and 169 observational). ICU mortality was reported in 51 studies (29%); in-hospital mortality was reported in 137 studies (79%). Mean age was available for 82 studies, while 91 studies reported the median and inter-quartile range (Table E1, *online supplement*). *In studies reporting ICU mortality*, mean age ranged between 29 and 73 years, and rate of death between 16 and 100%; heterogeneity (I^2) amounted to 93%. A positive significant association was found between mean age and ICU mortality (b = 0.012; SE(b): 0.003; $p = 0.001$) (Fig. 1, panel A and Table E3, *online supplement*). Variability in mean age explained part of the existing heterogeneity (residual heterogeneity $I^2 = 58\%$ and $R^2 = 27\%$). Multiple meta-regressions showed that the association between age and outcome remained significant after adjusting for all other covariates, except for

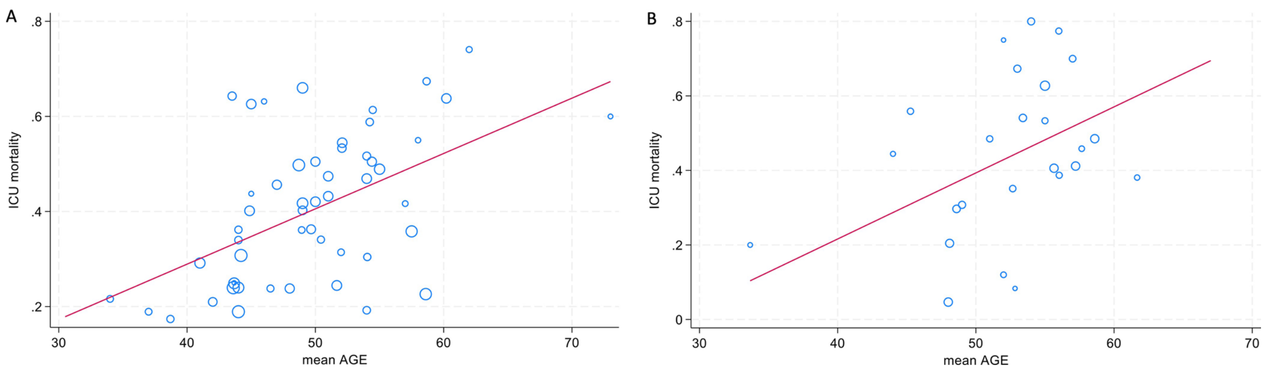

Fig. 1 Meta-regression of ICU mortality on mean age reported by authors or estimated using Wan's formula when only median and IQR was reported in studies including non-COVID-19 patients (panel A) and COVID-19 patients (panel B). Each study is represented by a circle sized according to the study weight. The red line represents the linear regression estimate

models adjusted for BMI that included only 12 studies and 2252 participants (Table E3).

In studies reporting in-hospital mortality, mean age ranged between 29 and 73 years, and rate of death between 0 and 100%; heterogeneity amounted to 92%. Meta-regression showed a positive significant association between patients' mean age and in-hospital mortality ($b = 0.008$; SE(b): 0.002; $p < 0.001$) (Fig. 2, panel A and Table E3, *online supplement*). Variability in age explained part of the existing heterogeneity (residual heterogeneity $I^2 = 60\%$). In this case, the association between age and outcome remained significant after adjusting for all the other covariates (Table E3).

COVID-19 ARDS

We included 103 studies conducted between 2020 and 2024 with a total of 21,255 participants (1 RCT, 5 case series and 97 observational). Mean age was available for 45 studies, while 58 studies reported the median and inter-quartile range (Table E2, *online supplement*). ICU mortality was reported in 26 studies (25%), while in-hospital mortality was reported in 89 studies (86%) (Table E2, *online supplement*); mean age ranged between 34 and 67 years. *In studies reporting ICU mortality*, rate of death ranged between 5 and 80% with I^2 equal to 91%. *In studies reporting in-hospital mortality*, mortality ranged between 17 and 75% and I^2 was 82.8%. No significant association was found between mean patients age and in-hospital mortality (Fig. 2, panel B and Table E4, *online supplement*). Vice versa, meta-regression showed a significant relationship between patients' mean age and ICU mortality ($b = 0.018$; SE(b): 0.008; $p = 0.040$) (Fig. 1, panel B and Table E4, *online supplement*). The association between age and outcome remained significant, after adjusting for selected covariates, except when adjusting for severity. This latter model included only 4 studies and 138 participants (Table E4).

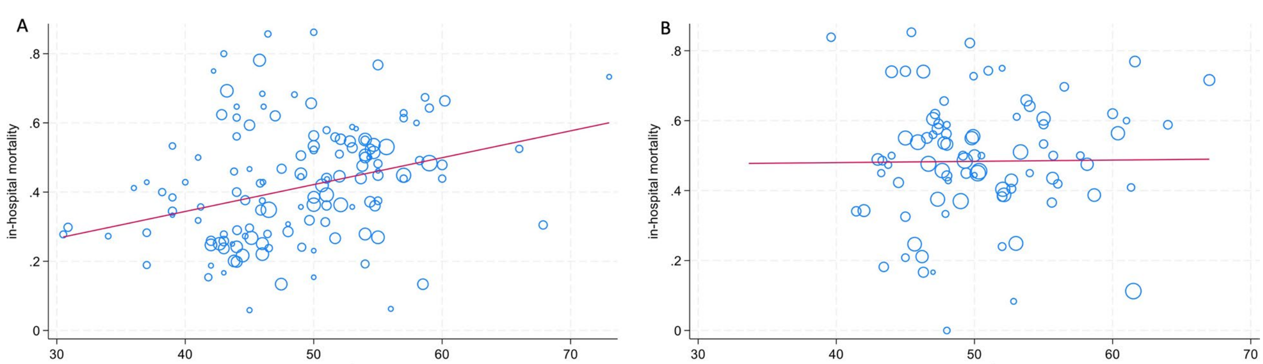

Fig. 2 Meta-regression of in-hospital mortality on mean age reported by authors or estimated using Wan's formula when only median and IQR was reported in studies including non-COVID-19 patients (panel A) and COVID-19 patients (panel B). Each study is represented by a circle sized according to the study weight. The red line represents the linear regression estimate

Sensitivity analyses

Results of the sensitivity analyses based on good and fair-quality studies (quality assessment process is summarized in Tables E5a-b-c and E6a-b-c, *online supplement*) confirmed the findings in non-COVID and COVID patients (Tables E7 and E8 and Figure E2, *online supplement*); sensitivity analyses based on studies reporting only mean age showed that only the relationship between in-hospital mortality and age in non-COVID population remained significant (Tables E7 and E8 and Figure E3, panel C, *online supplement*); lastly, analyses exploring the possible non-linear relationship between age and outcomes confirmed that the relationships between ICU mortality and in-hospital mortality with age in the two groups were not accounted for by higher-order (quadratic or cubic) functions (TableS E7 and E8).

Discussion

Results of the present study indicate that in ARDS patients treated with V-V ECMO (both COVID and non-COVID), ICU mortality increases linearly with age without a clear age cut-off that would contraindicate V-V ECMO.

Age is a critical factor in determining eligibility for ECMO in severe ARDS due to its resource-intensive nature and associated risks. Nevertheless, while age is often factored into clinical decision-making as a criterion for ECMO selection [6], the existing data supporting a precise age threshold for V-V ECMO indication remain sparse and contradictory, precluding the establishment of a specific age cutoff [2]. In fact, although a recent study reported a non-linear age-mortality relationship in patients with ARDS [12], retrospective analyses have shown varying survival rates across different age groups [3], with some studies suggesting "acceptable" outcomes even in patients over 65 years of age [4]. Moreover, (*a*) a recent RCT has included older patients without observing significant differences in outcomes compared to younger cohorts [5]; (*b*) although age is included in mortality prediction scores for ECMO, variations exist in the age classes used [6, 13] and even very young patients receiving V-V ECMO exhibit age-related outcome differences [14]. Our meta-regression analysis showed a linear relationship between age and ICU/in-hospital mortality across COVID and non-COVID studies. These data confirm a very recent registry-based cohort study that demonstrated a linear relationship between age and in-hospital mortality and an increase in post-ECMO complications starting as early as 30 years of age [15].

Strengths of this study include its comprehensive search, robust methodology, and application of meta-regression to generate evidence from pooled data, that may represent a reasonable option to generate robust evidence from pooled data when the inherent sample heterogeneity may limit the design and conduct of clinical trials in the critical care settings [16]. Limitations include the predominance of observational studies and the limited number of studies including elderly patients, posing challenges in defining a clear age threshold. Moreover, although the utmost care has been taken in excluding papers presenting data from the same databases (i.e., duplications or overlaps), we cannot totally exclude the possibility that a small number of patients may be present as duplicates in more than one included study. Another limitation of this study is the lack of the a priori registration of the protocol in PROSPERO.

In 2022, more than 20% of the EU population aged 65 and over. In the United States, approximately 17% of the nation's population (more than 56 million) is aged 65 and older. Consequently, the number of elderly patients admitted to intensive care units (ICUs) is expected to increase [17]. Under these circumstances, data regarding the outcome of older patients treated with advanced forms of artificial support such as ECMO may optimize the care of these patients in terms of targeting resources to those patients who are most likely to benefit [18]. Severity of the acute condition and age-related decline of resilience to stress are the most relevant determinants of critically ill geriatric patients [19]. However, the aging process is characterized by substantial inter-individual heterogeneity of such decline. Some studies suggest that age alone should not be a criterion for refusing prolonged mechanical ventilation in patients over 70 [20].

Under these circumstances, the observed linear relationship between age and mortality in ARDS patients (both COVID and non-COVID) receiving V-V ECMO treatment confirms that, although age plays a significant role in determining outcomes, individual variations in resilience or frailty may complicate simple age-based criteria. Furthermore, short-term outcomes like ICU or hospital mortality do not provide a comprehensive picture. Future research should focus on the impact of age and frailty on long-term outcomes, including functional status and quality of life in ICU survivors.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-024-05074-z.

Additional file1 (DOCX 1515 KB)

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Author contributions
Concept and design: VMR, TT, PR. Data acquisition: RDS, MB, LB, RDA, DN, ISZ, IT, TT. Statistical analysis: RDS, PR. Data analysis and interpretation: RDS, PR, TT, VMR. Writing the first draft: TT, VMR, RDS, PR. Reviewing the manuscript for important intellectual content: LM, IT. Approval of manuscript final version: all authors.

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

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
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Competing interests
The authors declare no competing interests.

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