BRIEF REPORT

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Critically Ill Older Adults' Representation in Intervention Trials: A Systematic Review

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OBJECTIVES: Older adults may be under-represented in critical care research, and results may not apply to this specific population. Our primary objective was to evaluate the prevalence of inclusion of older adults across critical care trials focused on common ICU conditions or interventions. Our secondary objective was to evaluate whether older age was used as a stratification variable for randomization or outcome analysis.

DESIGN, SETTING AND SUBJECTS: We performed a systematic review of previously published systematic reviews of randomized controlled trials (RCTs) in critical care. We searched PubMed, Ovid, CENTRAL, and Cochrane from 2009 to 2022. Systematic reviews of any interventions across five topics: acute respiratory distress syndrome (ARDS), sepsis/shock, nutrition, sedation, and mobilization were eligible.

MAIN RESULTS: We identified 216 systematic reviews and included a total of 253 RCTs and 113,090 patients. We extracted baseline characteristics and the reported proportion of older adults. We assessed whether any upper age limit was an exclusion criterion for trials, whether age was used for stratification during randomization or data analysis, and if age-specific subgroup analysis was present. The most prevalent topic was sepsis (78 trials, 31%), followed by nutrition (62 trials, 25%), ARDS (39 trials, 15%), mobilization (38 trials, 15%), and sedation (36 trials, 14%). Eighteen trials (7%) had exclusion criteria based on older age. Age distribution with information on older adults prevalence was given in six trials (2%). Age was considered in the analysis of ten trials (5%) using analytic methods to evaluate the outcome stratified by age.

CONCLUSIONS: In this systematic review, the proportion of older critically ill patients is undetermined, and it is unclear how age is or is not an effect modifier or to what extent the results are valid for older adult groups. Reporting age is important to guide clinicians in personalizing care. These results highlight the importance of incorporating older critically ill patients in future trials to ensure the results are generalizable to this growing population.

KEYWORDS: critical illness; humans; older adults; systematic review

OBJECTIVES

Currently, older adult patients 65 years old and above represent 40–50% of the ICU population (1). Octogenarians represent the fastest-expanding subgroup in the critical care population (2). Given the age-related changes in physiology, pharmacodynamics, and pharmacokinetics and higher propensity for poor outcomes, the inclusion of older adults in clinical trials and age consideration in analysis are necessary to inform their response to treatment more accurately. Clinical trial results in younger populations may or may not be generalizable to older adults. The frequency and the level at which older adults are included in critical care trials and the frequency of age-stratified analysis are unknown.

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KEY POINTS

Question: What is the prevalence of inclusion of older adults across critical care trials focused on common ICU conditions or interventions?

Findings: In this systematic review, of 253 randomized controlled trials, six trials (2%) provided information on older adults' prevalence, and only ten trials (5%) performed subgroup analysis based on older age.

Meaning: The proportion of older critically ill patients captured in critical care trials is undetermined. Available data to estimate how age is or is not an effect modifier or to what extent the results are valid for older adult groups are sparse. This population should be included in future critical care trials to ensure generalizable results.

We aimed to evaluate the representation of older adults in critical care trials and the applicability of the results to this specific population. The primary objective was to report the prevalence and inclusion of older adults across critical care trials focused on common ICU conditions. Our secondary objective was to evaluate whether older age was used as a stratification variable for randomization or outcome analysis.

DATA SOURCES

We performed a systematic review of PubMed, Ovid, CENTRAL, and Cochrane using key terms and medical subject headings terms (**eMethods**, http://links.lww.com/CCX/B361) from 2009 to December 2022. As previously published, we used a systematic review of systematic reviews' method (3–5). We included previously published systematic reviews of randomized controlled trials (RCTs) in critical care focused on prespecified ICU topics selected given their relevance to older adults: acute respiratory distress syndrome (ARDS), sepsis/shock, nutrition, sedation (trials focused on sedation, delirium, and sleep), and mobilization.

STUDY SELECTION

We excluded systematic reviews, including observational or noninterventional studies focused on surgical ICU patients such as trauma, burn, and cardiac surgery patients or on a specific disease (e.g., severe pancreatitis). From these systematic reviews, we extracted all trials to include in our analysis. Four paired independent authors (M.-F.F., M.B., C.D., R.C.) performed every step of the review (titles, abstracts, and articles). We resolved discrepancies by consensus with a third author (M.-F.F. or H.T.W.).

DATA EXTRACTION

Each trial underwent review and data extraction in duplicate. From full texts, we extracted baseline characteristics, including sample size, critical care condition being studied, year of publication, single vs. multicentered, study location, intervention, and outcomes. First, we looked for the reported proportion of older adults defined as age above 65. Because of the lack of data, we could not calculate the proportion of studies including older adults and the proportion of older adults included in each study. Therefore, we calculated the proportion of RCTs with upper age cutoffs as exclusion criteria. We also calculated the proportion of trials with a mean age above 65 years to estimate older adults' inclusion. We standardized each RCTs age-central tendency measure and reported it in means. We estimated the mean (when unavailable) from the median and range based on a previously suggested formula (6). Second, we evaluated whether the authors used age for stratification during randomization or data analysis. We looked for age-specific subgroup analysis or age as covariable for regression analysis for the primary study outcome and any mortality outcomes within the reported outcomes (whether primary or secondary). Finally, we also identified whether authors considered age when reporting adverse events. The risk of bias in included trials was assessed by paired authors using the version 2 of the cochrane risk-of-bias tool for RCTs. Discrepancies were resolved by consensus with a third author (M.-F.F., H.T.W.).

It was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (7). We also used the synthesis without meta-analysis in systematic reviews: reporting guideline (8). We registered the protocol study on PROSPERO (CRD42020158318).

DATA SYNTHESIS

Study Characteristics and Trial Characteristics

Our search yielded 12,709 titles. We identified 216 systematic reviews, which included a total of 253 RCTs (113,090 patients) that met all inclusion criteria (**Fig. 1**; and **eTable 1**, http://links.lww.com/CCX/B361). Sepsis was the most prevalent topic with 78 (31%) RCTs, followed by nutrition (62 RCTs [25%]), ARDS (38 RCTs [15%]), mobilization (38 RCTs [15%]), and sedation (36 RCTs [14%]) (**Table 1**). One hundred twenty-six RCTs (50%) were multicentered trials with a median sample size of 111 participants (interquartile range [IQR], 57–308). Mortality was included as the primary or secondary outcome across 209 RCTs (83%).

The estimated risk of bias was low for 116 RCTs (46%), with some concerns across 91 RCTs (36%) and a high risk of bias for 45 RCTs (18%). For the ten RCTs reporting results with age consideration, the risk of bias was low for eight RCTs (80%; **eTable 4**, http://links.lww.com/CCX/B361).

Representation of Older Adults

Mean age was 61 years old (IQR, 56–65 yr old) (67 yr old [66–69 yr old] for sepsis RCTs, 56 yr old [52–59 yr old] for ARDS RCTs, 62 yr old [59–67 yr old] for sedation RCTs, 61 yr old [55–66 yr old] for nutrition RCTs, and 58 yr old [56–63 yr old] for mobility RCTs). The proportion of older adults within each study was reported in six of 253 RCTs (2%). Eighteen RCTs (7%) had exclusion criteria that included age restrictions for older patients. The exclusion criteria were older than 60–65 years for two RCTs (9, 10), older than 70–75 years for three RCTs (11–13), and older than 80–90 years for 13 RCTs (14–26; **eTable 2**, http://links.lww.com/CCX/B361). Two delirium (included in sedation topic) RCTs included exclusively patients 60 years old and above (27, 28). The proportion of RCTs with a mean or median age of 65 years old and above was higher in RCTs about sepsis (42%) compared with sedation (34%), nutrition (25%), ARDS (13%), and mobilization (13%). The distribution of age did not change through the years (B = 0.09; 95% CI, –0.068 to –0.418; $p = 0.157$).

Eighteen RCTs (7%) used age for

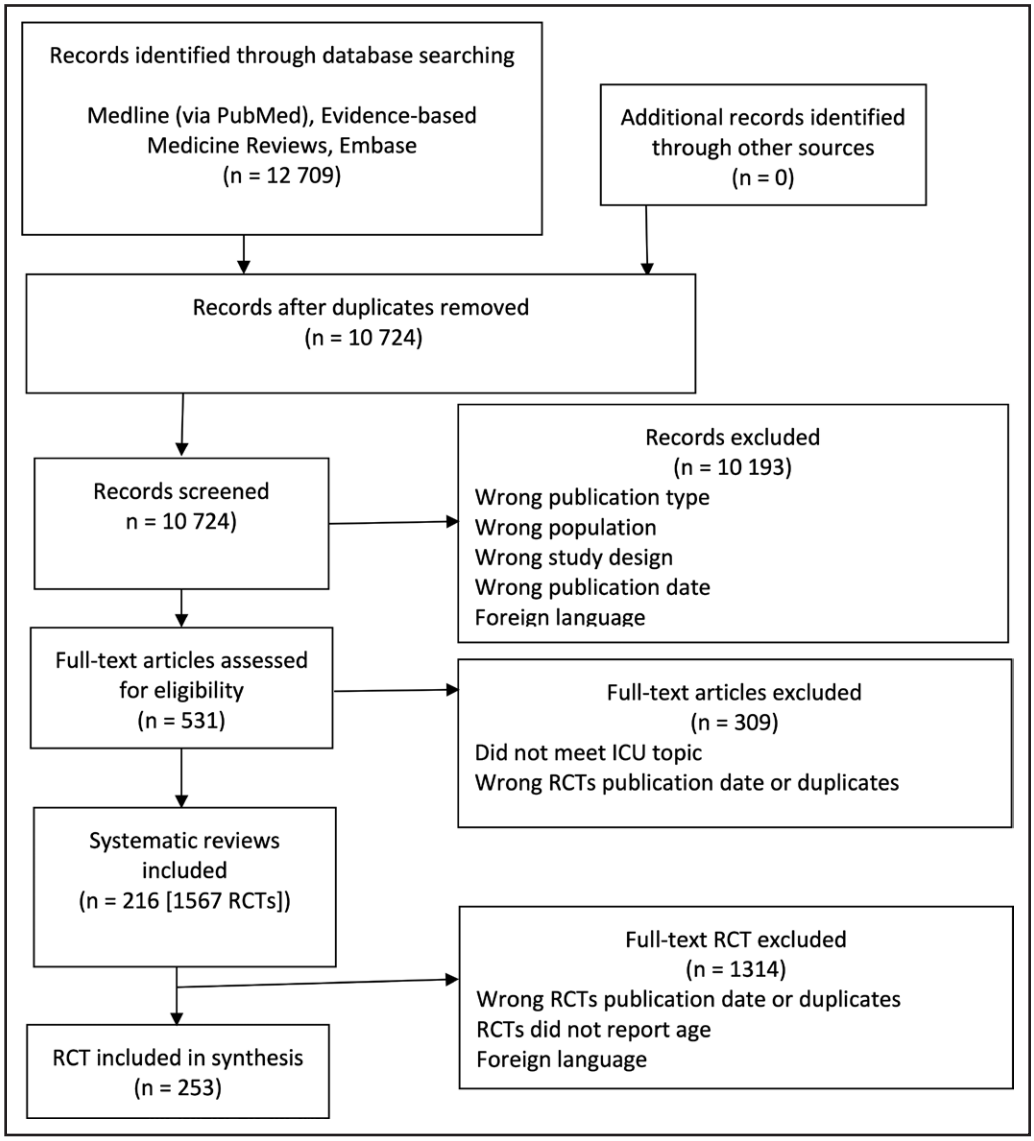

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram flow chart. RCT = randomized controlled trial.

TABLE 1.
Randomized Control Trials' Characteristics

Characteristics	*n* = 253
Number of centers involved, *n*/total *n* (%)	
Single centered	95/253 (38)
Multicenter	158/253 (62)
Population, *n*/total *n* (%)	
Medical	22/253 (9)
Mixed (medical and chirurgical)	146/253 (58)
Unspecified (but not exclusively chirurgical)	85/253 (33)
Sample size	
Median (IQR)	111 (58–309)
Range	16–15,786
Female participation	
Mean prevalence (SD)	0.40 (0.11)
Range	0.13–0.82
Critical care trial topic, *n*/total *n* (%)	
Nutrition	62/253 (25)
Mobilization	38/253 (15)
Sepsis	78/253 (31)
Acute respiratory distress syndrome	39/253 (15)
Sedation[a]	36/253 (14)
Age, yr, median (IQR)	
Nutrition	60 (54–65)
Mobilization	58 (56–61)
Sepsis	61 (61–66)
Acute respiratory distress syndrome	55 (52–59)
Sedation	62 (59–68)
Trials with a mean age above 65, *n*/total *n* (%)	71/253 (28)
Region, *n*/total *n* (%)	
Asia	54/242 (22)
North America	45/242 (19)
Latin America	19/242 (8)
Middle East and Africa	15/242 (6)
Europe	88/242 (36)
Oceania region	21/242 (9)
Outcomes, *n*/total *n* (%)	
Mortality	208/253 (82)
Primary outcome	73/208 (35)
Secondary outcome	135/208 (65)
Other primary outcomes	181/253 (72)

IQR= interquartile range.

[a]Sedation refers to any studies that evaluated sedation, delirium, and sleep in the ICU.

Denominators that do not equal the sample sizes are due to missing data.

randomization or stratification. The age cutoff for randomization and stratification varied between 50 and 65 years old (29–37). In total, ten RCTs (4%) used analytic methods to evaluate the outcome stratified by age (four RCTs in sepsis [24, 38–40], two RCTs in ARDS [41, 42], one RCT in sedation [36], and three RCTs in nutrition [29, 33, 43]), which 1 (10%) (39) noted differences in outcome when stratified by age. Outcomes were mortality in nine of ten RCTs (24, 29, 33, 36, 38, 40–43) (primary for five; secondary for four; and **eTable 3**, http://links.lww.com/CCX/B361).

DISCUSSION

Our review of 253 RCTs found that older age was listed as an exclusion criterion in only 7% of RCTs reviewed. Furthermore, the proportion of older adults within studies was only reported in six trials through stratification, and most studies did not include age as a randomization or stratification variable nor included age in their analysis. Only two RCTs included exclusively older adults 60 years old and above. This limits our ability to draw conclusions about the association between the intervention and the outcome for older adults.

The underrepresentation of older adults has been explored using systematic reviews in other fields, such as cardiovascular diseases (44, 45), Alzheimer (46), and, more recently, COVID-19 (47) trials. Similarly, in those reviews, the proportion of older adults was not reported in most trials, with the mean and median age being the most available information on patients' overall age. The lack of data on the proportion of older adults in RCTs is particularly problematic for RCTs focusing on sedation, nutrition, and mobilization. Given their relevance to geriatric syndromes (physical, cognitive, and independence impairment, malnutrition, delirium [48–50]), a more complete description of patients' ages would help clinicians better assess the external validity and the applicability of these studies to the geriatric ICU population.

With only ten studies stratifying their analysis for age, the limited number of studies and patients preclude us from any conclusions on the efficacy of our therapies on older critically ill patients. Considering age as a continuous covariate in regression models can identify age as a relevant risk factor. Still, it does not inform on the strength of the association specifically with older adults (greater or less). We acknowledge that the need for a larger number of patients for sufficient statistical power is one important limitation associated with performing subgroup analyses. With more standardized reporting guidelines with a clear focus on the older adult population and the rise of large, adaptative, platform trials as well as multicenter, international collaborations could afford us the ability to delve deeper into this subgroup of patients when relevant.

Our study has some limitations. First, we excluded specific subgroups of the ICU population (trauma, burn, and cardiac surgery), so we cannot extrapolate our results to these fields. Second, we lacked access to more granular data, so we could not perform patient-level meta-analysis. Finally, we did not include the most recent COVID-19 pandemic studies, given our concern about their generalizability to non-COVID populations.

CONCLUSIONS

Age considerations are important factors to reflect on in future critical care RCTs. Whether age is an effect modifier, or to what extent the results of ICU RCTs are valid for older adult groups, are important aspects to clinicians in personalizing care. Future research should evaluate barriers to inclusion and recruitment and emphasize the importance of their inclusion and unique analytic considerations.

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Drs. Forget, Wang, and Munshi were involved in conceptualization. Dr. Wang and Mr. Coveney were involved in methodology. Drs. Carignan, Dessureault, Gravel, Bienvenue, Bouchard, Durivage, Forget, and Wang were involved in formal analysis and investigation. Drs. Forget and Wang were involved in writing–original draft preparation. Drs. Carignan, Dessureault, Gravel, Bienvenue, Bouchard, Durivage, Forget, Wang, and Munshi were involved in writing–review and editing. Drs. Wang and Munshi were involved in supervision. Drs. Forget and Wang had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Drs. Forget and Wang are both co-first authors.

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The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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