Propensity-Adjusted Comparison of Mortality of Elderly Versus Very Elderly Ventilated Patients

Bernhard Wernly, Raphael Romano Bruno, Fernando Frutos-Vivar, Oscar Peñuelas, Richard Rezar, Konstantinos Raymondos, Alfonso Muriel, Bin Du, Arnaud W Thille, Fernando Ríos, Marco González, Lorenzo del-Sorbo, Maria del Carmen Marín, Bruno Valle Pinheiro, Marco Antonio Soares, Nicolas Nin, Salvatore M Maggiore, Andrew Bersten, Malte Kelm, Pravin Amin, Nahit Cakar, Gee Young Suh, Fekri Abroug, Manuel Jibaja, Dimitros Matamis, Amine Ali Zeggwagh, Yuda Sutherasan, Bertrand Guidet, Dylan W De Lange, Michael Beil, Sigal Svri, Vernon van Heerden, Hans Flaatten, Antonio Anzueto, Venet Osmani, Andrés Esteban, and Christian Jung

BACKGROUND: The growing proportion of elderly intensive care patients constitutes a public health challenge. The benefit of critical care in these patients remains unclear. We compared outcomes in elderly versus very elderly subjects receiving mechanical ventilation. METHODS: In total, 5,557 mechanically ventilated subjects were included in our post hoc retrospective analysis, a subgroup of the VENTILA study. We divided the cohort into 2 subgroups on the basis of age: very elderly subjects (age ≥ 80 y; *n* = 1,430), and elderly subjects (age 65–79 y; *n* = 4,127). A propensity score on being very elderly was calculated. Evaluation of associations with 28-d mortality was done with logistic regression analysis. RESULTS: Very elderly subjects were clinically sicker as expressed by higher SAPS II scores (53 ± 18 vs 50 ± 18, *P* < .001), and their rates of plateau pressure < 30 cm H_2O were higher, whereas other parameters did not differ. The 28-d mortality was higher in very elderly subjects (42% vs 34%, *P* < .001) and remained unchanged after propensity score adjustment (adjusted odds ratio 1.31 [95% CI 1.16–1.49], *P* < .001). CONCLUSIONS: Age was an independent and unchangeable risk factor for death in mechanically ventilated subjects. However, survival rates of very elderly subjects were > 50%. Denial of critical care based solely on age is not justified. (ClinicalTrials.gov registration NCT02731898.) *Key words: critically ill; elderly subjects; ICU; risk stratification; risk scores; mechanical ventilation.* [Respir Care 2021;66(5):814–821.

Introduction

Due to significant demographic changes in the last decades, patients > 80 y old represent a growing proportion of ICU admissions. These very elderly intensive care patients suffer from proportionally more comorbidities, exhibit higher mortality rates, and require increasingly invasive therapy regimens.[1-3] These changes will undoubtedly challenge future but also current health care resources, as it can already be observed in the COVID-19 pandemic.[4]

Mechanical ventilation is one of the most substantial and effective interventions in critical care medicine. In

Drs Wernly and Rezar are affiliated with the Clinic of Internal Medicine II, Department of Cardiology, Paracelsus Medical University of Salzburg, Salzburg, Austria. Drs Bruno, Kelm, and Jung are affiliated with the Division of Cardiology, Pulmonology and Vascular Medicine, Medical Faculty, University of Düsseldorf, Düsseldorf, Germany. Drs Frutos-Vivar, Muriel, and Esteban are affiliated with the Hospital Universitario de Getafe & Centro de Investigación en Red de Enfermedades Respiratorias, Getafe, Spain. Drs Peñuelas and Raymondos are affiliated with the Medizinische Hochschule, Hannover, Germany. Dr Muriel is affiliated with the Unidad de Bioestadística, Clinica Hospital Ramón y Cajal, Instituto Ramón y Cajal de Investigaciones Sanitarias & Centro de Investigación en Red de Opidemiología y Salud Pública, Madrid, Spain. Dr Du is affiliated with the Peking Union Medical College Hospital, Beijing, People's Republic

addition to its undeniable efficacy, it may also be associated with impaired hemodynamics, ventilator-induced lung injury, and ventilator-associated pneumonia. Furthermore, it also causes high treatment costs and in most of the cases a prolonged stay on intensive care wards. Noninvasive ventilation, thoughtful management of sedatives with daily wake-up trials, and new weaning strategies contribute to improved outcomes in mechanically ventilated subjects.[5-7] Protective ventilation strategies have been developed and proved beneficial in randomized trials.[8-10]

Consequently, these measures are increasingly applied in practice and associated with improved outcomes.[11,12] It is, however, unknown whether and to what extent these changes in practice and outcomes apply to very elderly intensive care patients, as elderly patients are known to show delayed and less effective responses to acute pathophysiological stressors, forming the basis of today's well-known concept of frailty.[3]

The VENTILA study is a prospective, international, multicenter, single-cohort study.[13] We hypothesized that age is an independent predictor of an adverse outcome in mechanically ventilated patients, irrespective of applied ventilation regimens in an international registry of mechanically ventilated subjects.[12,14] This study aimed to evaluate crude and adjusted mortality rates in elderly subjects on mechanical ventilation.

QUICK LOOK

Current knowledge

In critically ill but very elderly patients, the benefit of endotracheal intubation and invasive mechanical ventilation is unknown. The decision to provide mechanical ventilation to elderly patients is primarily decided on a case to case basis.

What this paper contributes to our knowledge

Age was an independent and unchangeable risk factor for death in mechanically ventilated subjects. However, survival rates in very elderly subjects were $>$ 50%. Denial of critical care based solely on age is not justified.

Methods

Study Subjects

We retrospectively evaluated a subgroup from the VENTILA study from 2004, 2010, and 2016. The VENTILA study evaluated subjects on mechanical ventilation to assess outcomes and trends over time. The study was approved by the research ethics committee at each participating center, and the need for informed consent was waived. In brief, baseline characteristics including age, sex, and severity at admission estimated by the Simplified Acute Physiology Score (SAPS II), which ranges from 0 (lower severity) to 163 (higher severity), was prospectively collected. In addition, variables related to management of ventilator settings,

of China. Dr Thille is affiliated with the University Hospital of Poitiers, Poitiers, France. Dr Ríos is affiliated with the Hospital Nacional Alejandro Posadas, Buenos Aires, Argentina. Dr González is affiliated with the Clínica Medellín & Universidad Pontificia Bolivariana, Medellín, Colombia. Dr del-Sorbo is affiliated with the Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Ontario, Canada. Dr Marín is affiliated with the Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado, Hospital Regional 1 de Octubre, México City, México. Dr Pinheiro is affiliated with the Pulmonary Research Laboratory, Federal University of Juiz de Fora, Juiz de Fora, Brazil. Dr Soares is affiliated with the Hospital Universitario Sao Jose, Belo Horizonte, Brazil. Dr Nin is affiliated with the Hospital Universitario de Montevideo, Montevideo, Uruguay. Dr Maggiore is affiliated with the Università degli Studi G. d'Annunzio Chieti e Pescara, Chieti, Italy. Dr Bersten is affiliated with the Department of Critical Care Medicine, Flinders University, Adelaide, South Australia, Australia. Dr Amin is affiliated with the Bombay Hospital Institute of Medical Sciences, Mumbai, India. Dr Cakar is affiliated with the Istanbul Faculty of Medicine, Istanbul, Turkey. Dr Suh is affiliated with the Center for Clinical Epidemiology, Samsung Medical Center, Seoul, Republic of Korea. Dr Abroug is affiliated with the Hospital Fattouma Bourguina, Monastir, Tunisia. Dr Jibaja is affiliated with the Hospital de Especialidades Eugenio Espejo, Quito, Ecuador. Dr Matamis is affiliated with the Papageorgiou Hospital, Thessaloniki, Greece. Dr Zeggwagh is affiliated with the Centre Hospitalier Universitarie, Ibn Sina - Mohammed V University, Rabat, Morocco. Dr Sutherasan is affiliated with the Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand. Dr Guidet is affiliated with the Hôpitaux de Paris, Hôpital Saint-Antoine, service de réanimation médicale, Sorbonne Universités, Paris, France. Dr De Lange is affiliated with the Department of Intensive Care Medicine, University Medical Center, University Utrecht, Utrecht, The Netherlands. Drs Beil, Svri, and van Heerden are affiliated with the Medical Intensive Care Unit, Hadassah University Hospital, Jerusalem, Israel. Dr Flaatten is affiliated with the Department of Anesthesia and Intensive Care, Haukeland University Hospital, Bergen, Norway. Dr Anzueto is affiliated with the South Texas Veterans Health Care System and University of Texas Health Science Center, San Antonio, Texas. Dr Osmani is affiliated with the Fondazione Bruno Kessler Research Institute, Trento, Italy.

Drs Wernly and Bruno are co-first authors.

Supplementary material related to this paper is available at http://www.rcjournal.com.

The authors have disclosed no conflicts of interest.

Correspondence: Christian Jung MD PhD, Division of Cardiology, Pulmonology and Vascular Medicine, University Duesseldorf, Moorenstraße 5, 40225 Duesseldorf, Germany. E-mail: christian.jung@med.uni-duesseldorf.de.

DOI: 10.4187/respcare.08547

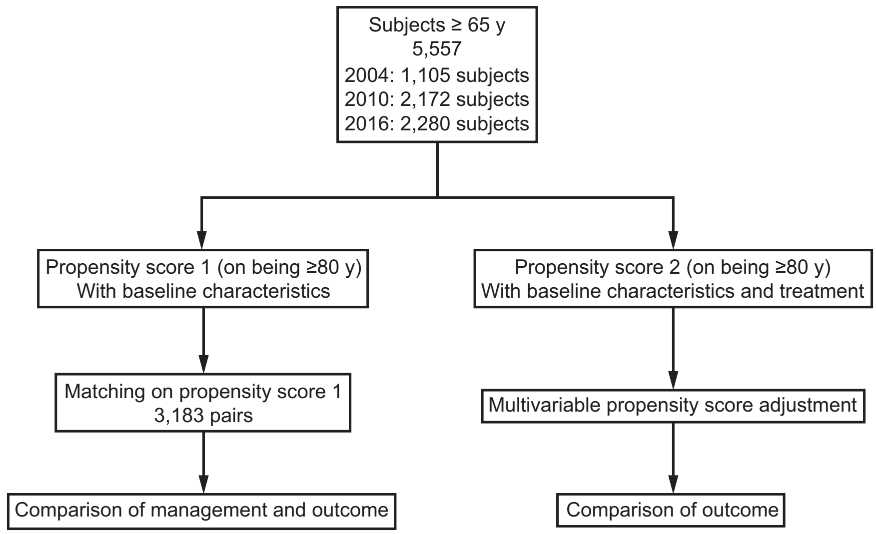

Fig. 1. Flow chart.

sedation, daily gas exchange, neuromuscular blockers, and complications such as ARDS, sepsis, or ventilator-associated pneumonia were registered. Organ function (ie, cardiovascular, renal, hepatic, hematologic) was assessed according to the Sequential Organ Failure Assessment (SOFA) score. Organ failure was defined as a SOFA subscore > 2 for the organ in question. Subject data were collected for the duration of ventilation or until day 28. Subjects were followed until their discharge from the hospital. In the event of discharge from the hospital before day 28 after starting mechanical ventilation, the status on this day was registered. The present substudy included all subjects age ≥ 65 y with complete data on age, country, the main indication for ventilation, SAPS II score, creatinine, and pH (n = 5,557 subjects) from the VENTILA study cohort (Fig. 1). Subjects ≥ 80 y were considered to be very elderly intensive care subjects (n = 1,430) based on previous studies, whereas the remaining subjects were considered elderly (n = 4,127).[1,3] The primary end point was mortality up to day 28. The secondary end points were the decision to withdraw treatment, duration of the mechanical ventilation, and tracheostomy. Initial SAPS II score was calculated by the treating physician within 24 h after admission as previously reported.[15]

Statistical Analysis

Continuous variables are expressed as median (interquartile range) and compared using the U test or mean ± SD and compared using analysis of variance. Categorical data are expressed as numbers (percentage). The chi-square test was applied to calculate differences between groups. Both univariable and multivariable logistic regression analysis was performed to predict binary outcomes (ie, treatment withdrawal, mortality, plateau pressure < 30 cm H_2O, driving pressure < 15 cm H_2O, tidal volume 6–8 mL/kg predicted body weight). Odds ratios and adjusted odds ratios with respective 95% CIs were calculated. Two propensity scores for very elderly intensive care subjects were calculated (Fig. 1). Propensity score 1 included the baseline variables: SAPS II score (per point), location (each country as dummy variable), admission diagnosis (each diagnosis as dummy variable), sex, weight, predicted body weight, height, creatinine, year of inclusion (each year as dummy variable). For the matched cohort, 1:1 propensity-score matching was obtained using "nearest neighbor" matching, and the maximum allowed distance was a change in propensity score 1 of 0.001. Propensity score 2 included all of the items in propensity score 1 plus pH, P_{aO_2}/F_{IO_2}, peak pressure, plateau pressure, PEEP, tidal volume per predicted body weight, P_{aCO_2}, and treatment withdrawal. A P value of < .05 was considered statistically significant. SPSS 22.0 (IBM, Armonk, New York) and MedCalc Statistical Software 19.1 (MedCalc Software, Ostend, Belgium) were used for statistical analysis.

Results

Study Cohort

In total, 5,557 mechanically ventilated subjects age ≥ 65 y were included in this post hoc retrospective analysis. There was a trend toward a higher proportion of very elderly subjects from the year 2004 (21%) to 2010 (24%) and 2016 (30%) (Fig. 2). The overall 28-d mortality was 36%, and there was a trend toward lower mortality over time in both elderly subjects and very elderly subjects (Fig. 3).

Age as a continuous variable was associated with higher odds of 28-d mortality (odds ratio 1.02 [95% CI 1.01–

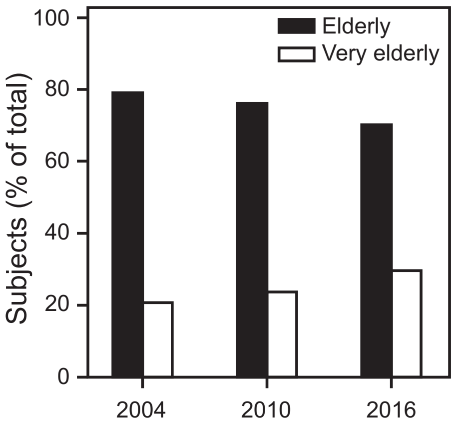

Fig. 2. There was a trend toward a higher proportion of very elderly intensive care subjects from the year 2004 (21%) to 2010 (24%) and 2016 (30%).

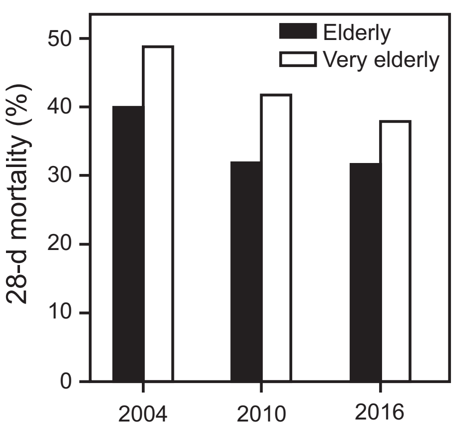

Fig. 3. The overall 28-d mortality was 36%, and there was a trend toward lower mortality over time (2004: 40% vs 49%; 2010: 32% vs 42%; 2016: 32% vs 38%) in both elderly intensive care subjects and very elderly intensive care subjects.

1.03], $P < .001$), even after correction for propensity score 1 (adjusted odds ratio 1.02 [95% CI 1.01–1.03], $P < .001$) and propensity score 2 (adjusted odds ratio 1.02 [95% CI 1.01–1.03], $P < .001$).

Very elderly intensive care subjects were clinically sicker as expressed by higher SAPS II score (53 ± 18 vs 50 ± 18, $P < .001$). Baseline characteristics of included subjects are shown in Table 1 (see the supplementary materials at http://www.rcjournal.com). The rates of plateau pressure < 30 cm H_2O were higher in very elderly intensive care subjects, whereas other parameters did not differ between very elderly and elderly intensive care subjects, both in univariable analysis and after adjustment for propensity score 1 (see Table 2). Rates of treatment withdrawal were 16% in the overall cohort and higher in very elderly subjects compared to elderly subjects (20% vs 15%, $P < .001$) and remained unchanged after adjustment for propensity score 1 (adjusted odds ratio 1.37 [95% CI 1.15–1.64], $P < .001$). The rates of development of ARDS were similar between very elderly and elderly intensive care subjects (Table 3).

The 28-d mortality was higher in very elderly intensive care subjects (42% vs 34%, $P < .001$) and remained unchanged after correction for propensity score 1 (adjusted odds ratio 1.31 [95% CI 1.16–1.49, $P < .001$) and propensity score 2 (adjusted odds ratio 1.28 [95% CI 1.07–1.54], $P = .008$). In a sensitivity analysis including only subjects without treatment withdrawal, 28-d mortality was higher in very elderly intensive care subjects (odds ratio 1.42 [95% CI 1.21–1.67], $P < .001$). In a sensitivity analysis evaluating only subjects included in 2004 (odds ratio 1.42 [95% CI 1.07–1.90], $P = .02$), 2010 (odds ratio 1.62 [95% CI 1.32–1.98], $P < .001$), and 2016 (odds ratio 1.32 [95% CI 1.09–1.59], $P = .004$), mortality remained higher in very elderly intensive care subjects.

After propensity score 1 matching ($n = 1,378$ per group), baseline risk was evenly distributed (Table 4). Ventilation pressures did not differ between elderly and very elderly intensive care subjects. In the matched cohort, both rates of treatment withdrawal (19% vs 13%, $P < .001$) and 28-d mortality were higher in very elderly compared to elderly intensive care subjects (42% vs 36%, $P = .003$).

There was no difference regarding the duration of the mechanical ventilation for elderly intensive care subjects and very elderly intensive care subjects (6 ± 8 d vs 6 ± 7 d, respectively, $P = .15$). This observation persisted after propensity score 1 matching (6 ± 8 d vs 6 ± 7 d, respectively, $P = .97$). Elderly intensive care subjects received significantly more tracheostomies (16% vs 13%; odds ratio 0.79 [95% CI 0.66–0.95], $P = .01$). Very elderly intensive care subjects had a lower rate of tracheostomy both after matching propensity score 1 (16% vs 13%, $P = .02$) and after adjusting for propensity score 1 (adjusted odds ratio 0.82 [95% CI 0.68–0.98], $P = .03$).

Discussion

In this study, age > 80 y was independently associated with higher mortality in mechanically ventilated subjects in a mixed cohort of general intensive care subjects who were > 65 y old. This finding persisted after propensity score adjustment and in several sensitivity analyses. Given the increasing proportion of elderly patients and the indeterminate benefit of critical care measures in these patients, our data support the inclusion of age in triage decisions and treatment restriction after an ICU trial, as proposed previously.[16] However, survival rates in very elderly intensive care subjects were relatively high (> 50%), and denial of critical care based solely on chronological age does not seem justified.

Table 1. Comparison of Baseline Characteristics

	Elderly Subjects (n = 4,127)	Very Elderly Subjects (n = 1,430)	Total Cohort (n = 5,557)	P
Age, y	72 (4)	84 (4)	75 (7)	< .001
Body mass index, kg/m^2	27 (6)	25 (5)	26 (6)	< .001
SAPS II	50 (18)	53 (18)	51 (18)	< .001
Creatinine, mg/dL	1.67 (1.74)	1.69 (1.37)	1.68 (1.65)	.68
ICU length of stay, d	13 (14)	12 (15)	13 (14)	.18
Duration of mechanical ventilation, d	9 (9)	8 (10)	9 (9)	.21
pH				.52
Normal (7.35–7.45)	1,551 (38)	560 (39)	2,111 (38)	
Alkalosis (> 7.45)	563 (14)	196 (14)	759 (14)	
Acidosis (< 7.35)	2,013 (49)	674 (47)	2,687 (48)	
Plateau pressure, cm H_2O				.03
28–30	164 (7)	42 (5)	206 (7)	
< 28	1,985 (88)	732 (92)	2,717 (89)	
> 30	101 (5)	25 (3)	126 (4)	
Tidal volume by PBW, mL/kg				
6–8	1,591 (41)	578 (43)	2,169 (41)	
< 6	280 (7)	97 (7)	377 (7)	
> 8	2,031 (52)	680 (50)	2,711 (52)	
PEEP, cm H_2O				.002
6–8	1,153 (28)	419 (30)	1,572 (29)	
< 6	2,187 (54)	793 (57)	2,980 (55)	
> 8	713 (18)	189 (14)	902 (17)	
P_{aO_2}/F_{IO_2}				.24
> 200	2,110 (55)	719 (54)	2,829 (55)	
199–100	1,268 (33)	469 (35)	1,737 (34)	
< 100	475 (12)	148 (11)	623 (12)	
Driving pressure < 15 cm H_2O	1,377 (62)	491 (62)	1,868 (62)	.93

Data are presented as n (%).
SAPS = Simplified Acute Physiology Score
PBW = predicted body weight

Table 2. Logistic Regression Analysis of Parameters in Very Elderly Intensive Care Subjects

	Univariable Analysis		Multivariable Analysis	
	Odds Ratio (95% CI)	P	Adjusted Odds Ratio (95% CI)	P
Plateau pressure < 30 cm H_2O	1.62 (1.12–2.35)	.01	1.55 (1.06–2.27)	.02
Driving pressure <15 cm H_2O	1.01 (0.85–1.19)	.93	0.94 (0.79–1.11)	.45
Tidal volume 6–8 mL/kg PBW	1.08 (0.95–1.23)	.22	1.11 (0.98–1.26)	.11

PBW = predicted body weight

The mortality rate in this study assessing very elderly intensive care subjects on mechanical ventilation was high compared to other collectives assessing very elderly intensive care subjects.[1,17-19] However, subjects from this study group were older or sicker, as reflected by higher SAPS II scores. Further, in a previous study by Flaatten et al,[1] 23.8% of all subjects received no ICU-specific interventions. In the VENTILA cohort, however, all subjects were mechanically ventilated, and the necessity for ventilation was associated with higher mortality in all critically ill subjects. Very elderly intensive care subjects had a similar duration of invasive mechanical ventilation but were less likely to receive a tracheostomy. One reason for this difference could be the reluctance in these patients to take more invasive measures. In practice, tracheostomy is usually performed for prolonged ventilation, which may have been ruled out from the outset in very elderly subjects. However, this assumption is speculative because no data are available. This is particularly important because patients with prolonged ventilation can develop chronic critical illness, which can lead to shorter life expectancy and lower quality of life despite the primary survival of intensive care therapy.[20]

Very elderly mechanically ventilated intensive care subjects suffered higher mortality compared to elderly intensive care subjects. This association of age and very elderly intensive care subjects' status with mortality remained independent even after correction for parameters assessing the severity of disease and ventilation pressures. Also, in a sensitivity analysis after excluding all subjects with treatment restrictions, mortality in very elderly subjects was higher compared to elderly intensive care subjects. Therefore, age per se constitutes an important (and inevitable) risk factor for mortality in mechanically ventilated patients. Several factors, including decreased cardiac capacity and pulmonary compliance, as well as reduced overall physiological reserve in the elderly, could contribute to the worse outcomes in older mechanically ventilated individuals.[21] Unfortunately, no pulmonary compliance measurements were documented in the VENTILA study. Frailty is prevalent in geriatric patients and has been shown to predict outcomes reliably, especially in very elderly intensive care subjects.[1,19,22] However, in this study, no data about frailty were available, which is a significant limitation of our analysis.

Regardless of overall high mortality rates in very elderly intensive care subjects, and despite comparable disease severity (according to SAPS II score) in very elderly intensive

Table 3. Rates of Development of ARDS

ARDS	Elderly Subjects (n = 4,127)	Very Elderly Subjects (n = 1,430)	P
Day 1	320 (8)	101 (7)	.42
Day 2	275 (7)	84 (7)	.32
Day 3	231 (8)	64 (6)	.11
Day 4	184 (8)	58 (7)	.59
Day 5	161 (8)	43 (7)	.18
Day 6	137 (8)	38 (7)	.41
Day 7	119 (8)	28 (6)	.13

Data are presented as n (%).

Table 4. Comparison of Baseline Characteristics After 1:1 Propensity Score Matching

	Elderly Subjects (n = 4,127)	Very Elderly Subjects (n = 1,430)	P
Age, y	72 (4)	84 (4)	< .001
Body mass index, kg/m^2	26 (5)	26 (5)	.93
SAPS II	52 (18)	52 (18)	.94
Creatinine, mg/dL	1.72 (1.92)	1.69 (1.37)	.58
ICU length of stay, d	13 (15)	12 (15)	.31
Duration of mechanical ventilation, d	9 (9)	8 (10)	.62
pH			.46
Normal (7.35–7.45)	509 (37)	540 (39)	
Alkalosis (> 7.45)	200 (15)	188 (14)	
Acidosis (< 7.35)	669 (49)	650 (47)	
Plateau pressure, cm H_2O			.21
28–30	51 (7)	39 (5)	
< 28	664 (89)	711 (92)	
> 30	29 (4)	24 (3)	
Tidal volume by PBW, mL/kg			.16
6–8	516 (40)	564 (43)	
< 6	100 (8)	92 (7)	
> 8	691 (53)	650 (50)	
PEEP, cm H_2O			.16
6–8	391 (29)	403 (30)	
< 6	745 (55)	765 (57)	
> 8	219 (16)	183 (14)	
P_{aO_2}/F_{IO_2}, mm Hg			.27
> 200	704 (55)	697 (54)	
199–100	419 (33)	452 (35)	
< 100	157 (12)	137 (11)	
Driving pressure < 15 cm H_2O	471 (63)	476 (62)	.52

Data are presented as n (%).
SAPS = Simplified Acute Physiology Score
PBW = predicted body weight

care subjects in 2006 and 2016, mortality evidenced a 20% relative decrease from 2006 to 2016. Several factors likely contributed to these improved outcomes. First, general advances in intensive care medicine, improved aseptic procedures, and anti-infective treatment options, as well as new interventional techniques, were developed and implemented. Second, innovative treatment strategies such as early goal-directed therapy and lactate-guided treatment could have improved awareness for potential treatment targets and hence survival rates in some subjects.[23]

Interestingly, considering the decreasing mortality rates in very elderly intensive care subjects, the rates of treatment withdrawal also decreased from 2010 to 2016 (no data for 2006 are available). This trend could reflect a more restrictive admission policy on intensive care wards for very elderly intensive care patients. Clinical judgment and the understanding of the limited prognosis of very elderly intensive care patients in recent years might have contributed to this trend. Specifically, the structured assessment of frailty using clinical frailty scores and other measures has advanced the understanding of elderly patients considered for intensive care treatment.[1,19,22] However, the specific trends over time are beyond the scope of this manuscript.

Risk prediction in critically ill patients is essential to guide treatment and allocate critical care to those who can benefit. Several parameters to stratify patients, including the SAPS II score, are available to aid this process.[15,24] However, established risk scores and parameters were not explicitly evaluated for very elderly intensive care subjects.[25,26] Therefore, risk prediction and stratification in these patients represent a particular challenge.[27,28] An intensive care trial consisting of intensive care treatment for 24–72 h could help guide treatment and potential treatment restrictions.[29-32] After this initial timeframe, the very elderly intensive care patient could be "re-triaged" and new treatment goals identified based on risk parameters, a thorough assessment including frailty by geriatric specialists, and after open communication with relatives. Clear communication regarding informed consent with elderly critically ill patients and families of very elderly intensive care patients who have a limited chance of recovery and higher mortality after undergoing ventilation is essential when discussing pending intubation and before decisions on treatment escalation are made. For further treatment, specific geriatric rehabilitation could and should be planned from an early time point to help increase survival further and reduce long-term morbidity.[33] This study confirms the association between age and mortality in mechanically ventilated subjects.[34] However, not all hope is lost because mortality was $< 50\%$. Future research on how to detect very elderly intensive care patients in whom palliative care is more appropriate seems necessary because age alone might not be sufficient to risk-stratify critically ill subjects with respiratory failure.

Limitations

This subgroup analysis is retrospective. The registry involved many ICUs from around the world with different demographics and intensive care structures. Furthermore, survival in very elderly intensive care subjects was high at $> 50\%$. We have no information about frailty, which might play a greater role in outcomes for intensive care patients than chronologic age. Thus, we speculate that frailty may be the missing link between age and mortality.

Conclusions

Age was an independent and unchangeable risk factor for death in mechanically ventilated subjects. Ventilation duration did not differ, but very elderly intensive care subjects had significantly fewer tracheostomies. Denial of critical care should be not justified by age alone.

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