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# Management and outcomes in critically ill nonagenarian versus octogenarian patients

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## Abstract

**Background:** Intensive care unit (ICU) patients age 90 years or older represent a growing subgroup and place a huge financial burden on health care resources despite the benefit being unclear. This leads to ethical problems. The present investigation assessed the differences in outcome between nonagenarian and octogenarian ICU patients.

**Methods:** We included 7900 acutely admitted older critically ill patients from two large, multinational studies. The primary outcome was 30-day-mortality, and the secondary outcome was ICU-mortality. Baseline characteristics consisted of frailty assessed by the Clinical Frailty Scale (CFS), ICU-management, and outcomes were compared between octogenarian (80–89.9 years) and nonagenarian ( $\geq 90$  years) patients. We used multilevel logistic regression to evaluate differences between octogenarians and nonagenarians.

**Results:** The nonagenarians were 10% of the entire cohort. They experienced a higher percentage of frailty (58% vs 42%;  $p < 0.001$ ), but lower SOFA scores at admission ( $6 \pm 5$  vs.  $7 \pm 6$ ;  $p < 0.001$ ). ICU-management strategies were different. Octogenarians required higher rates of organ support and nonagenarians received higher rates of life-sustaining treatment limitations (40% vs. 33%;  $p < 0.001$ ). ICU mortality was comparable (27% vs. 27%;  $p = 0.973$ ) but a higher 30-day-mortality (45% vs. 40%;  $p = 0.029$ ) was seen in the nonagenarians. After multivariable adjustment nonagenarians had no significantly increased risk for 30-day-mortality (aOR 1.25 (95% CI 0.90–1.74;  $p = 0.19$ )).

**Conclusion:** After adjustment for confounders, nonagenarians demonstrated no higher 30-day mortality than octogenarian patients. In this study, being age 90 years or more is no particular risk factor for an adverse outcome. This should be considered— together with illness severity and pre-existing functional capacity - to effectively guide triage decisions.

**Trial registration:** NCT03134807 and NCT03370692.

**Keywords:** Octogenarians, Nonagenarians, Frailty, Intensive care medicine, Outcome

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## Introduction

The proportion of older patients has increased significantly over time. In 2030, there will be more than 30 million people over the age of 90 (nonagenarians) in 35 industrialised countries [1]. Consequently, health care providers nowadays perform medical procedures on very old patients (from surgery to oncological therapies), which were previously considered unfeasible because of age or age-related deterioration in physical and mental performance [2]. Similarly, the rate of older patients ( $\geq 80$  years) in intensive care units (ICU) is increasing [3–6]. Today, older patients utilise a disproportionate amount of health care resources compared to their relative proportion of the total population [3, 7].

In particular, the extent to which “old age” per se is a risk factor and the extent to which different groups of old patients differ from one another regarding the prognosis is the subject of continuing debate. Older patients suffer worse outcomes than younger patients undergoing intensive care [8, 9], but some studies failed to establish age as an independent predictor of mortality in older ICU patients [10, 11]. However, most prognostic studies demonstrated an almost linear relationship between chronological age and mortality after the age of 40 [12]. In this respect, patients ageing 80 years and more represent a particular challenge to intensive care medicine [13, 14]. Still, there are no large studies that further differentiate this group of very old ICU patients and it is unclear if being a nonagenarian is a risk factor for adverse outcomes. We hypothesize that critically ill nonagenarians have an elevated 30-day mortality compared to octogenarians. To address this hypothesis, we performed a retrospective cohort study comprised of two large, multinational prospective observational cohorts [13–15]. This post-hoc analysis combined data from the VIP-1 and VIP-2 studies to compare octo- and nonagenarians regarding 30-day mortality (primary outcome) and ICU mortality (secondary outcome), the distribution of risk factors, and the intensive care management [13–15].

## Methods

### Study subjects

The very old intensive care patients (VIP) studies, VIP1 and VIP2, were prospective, multi-centre studies, registered on ClinicalTrials.gov (ID: NTC03134807, NCT03370692). Both studies included very old intensive care patients (VIPs), defined as patients admitted to an ICU and aged 80 years or older. The main results from these studies have been published previously [13, 14, 16, 17]. In summary, for both studies, each participating ICU could include either consecutive patients admitted over a six-month period or the first 20 consecutive patients fulfilling the inclusion criteria (all patients aged 80 years or older). The data collection for VIP1 took place between October 2016 and

February 2017 and between May 2018 to May 2019 for VIP2. Both studies used similar inclusion criteria as described elsewhere [13]. Informed consent was obtained from study participants. Local ethical committees might have waived the need of informed consent.

In this post-hoc analysis of these two studies, all patients admitted acutely (non-electively) with complete data on age, gender, clinical frailty score (CFS), sequential organ failure assessment (SOFA) score, and ICU mortality were included. For this study, the elective patients included in VIP1 were excluded as their outcomes differ significantly compared with those admitted acutely, as previously shown [18]. The primary endpoint of this study was ICU-mortality, and the secondary endpoint was 30-day-mortality.

### Scales, scores, and limitations in life-sustaining therapy

The SOFA score was recorded on admission; it could be calculated manually or using an online calculator. Frailty was assessed by the clinical frailty scale (CFS). The CFS distinguishes nine classes of frailty from very fit (CFS 1) to terminally ill (CFS 9). The respective visual and simple description for this assessment tool was used with permission [19–21].

The Katz Activities of Daily Living (Katz ADL) scale is a widely used graded instrument to assess disability in chronically ill or older patients. It evaluates six primary and psychosocial functions: bathing, dressing, going to the toilet, transferring, feeding, and continence. The patient receives 1 point for every independent and 0 for every dependent activity (6 = independent patient, 0 = very dependent patient). For the patients in the VIP2 trial, disability was defined by Katz ADL score  $\leq 4$ .

For cognitive decline, VIP2 utilised the Short form of Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE). IQCODE is a questionnaire, completed by carers, with 16 questions about cognitive decline over the past 10 years. For each question, 1 to 5 points can be assigned. An average of 3 points per question is considered “normal”. A cumulative IQCODE of  $\geq 3.5$  is regarded as “cognitive decline” [19–21].

The burden of co-morbidity was assessed using the co-morbidity and polypharmacy score (CPS) [22]. The CPS calculates the total number of chronic diagnoses and drugs taken. Standard ICU procedures were also documented.

In addition, limitations of therapy, such as withholding or withdrawing treatment, were recorded. Withholding life-sustaining therapy (e.g. mechanical ventilation, renal replacement therapy, cardiopulmonary resuscitation) was defined as not performing a measure that was indicated; withdrawing was defined as stopping any kind of life-sustaining therapy. All these decisions were at the discretion of the treating physicians and documented

according to international recommendations. VIP2 recorded the exact date of treatment limitation, but VIP1 did not give specific details. Thus, the present analysis used withholding or withdrawing treatment as binary information at any time during the ICU-stay.

### Statistical analysis

Post-hoc power calculations using the 7110 octogenarians and 790 nonagenarians, primary outcome event rates of 40% versus 45%, and an alpha of 0.05, the power of the study to detect differences in 30-day mortality is 77%. Continuous data points are expressed as median  $\pm$  interquartile range. Differences between independent groups were calculated using the Mann Whitney U-test. Categorical data are expressed as numbers (percentage). The chi-square test was applied to calculate differences between groups. Sensitivity analysis, analysing only patients with SOFA scores below the 75th percentile SOFA score of 10 (i.e. all patients with  $\text{SOFA} < 10$ ) was performed. Univariable and multivariable logistic regression analysis was performed to assess associations with treatment limitations and mortality. Odds ratios (OR) and adjusted odds ratios (aOR) with respective 95% confidence intervals (CI) were calculated. Two sequential random effects, multilevel logistic regression models were used to evaluate the impact of being a nonagenarian on ICU- and 30-days- mortality. All patients with valid data on ICU-mortality were included. First, a baseline model with being nonagenarian as a fixed effect and ICU as random effect (model-1) was fitted. Second, to model-1, patient characteristics (SOFA, CFS, sex) (model-2) were added to the model. Adjusted odds ratios (aOR) with respective 95% confidence intervals (CI) were calculated. Sensitivity analysis, analysing only patients with and without any treatment limitation was performed. All tests were two-sided, and a  $p$ -value of  $< 0.05$  was considered statistically significant. SPSS version 23.0 (IBM, USA) and MedCalc Statistical Software version 19.1.3 (MedCalc Software bv, Ostend, Belgium; <https://www.medcalc.org>; 2019) were used for all statistical analyses.

## Results

### Study population

This study included 7900 patients. 10% of the patients were nonagenarians. Table 1 displays the baseline characteristics of nonagenarians versus octogenarians. Nonagenarians were predominantly female (57% versus 46%,  $p < 0.001$ ), evidenced higher rates of frailty (58% vs 42%;  $p < 0.001$ ), disability (44% vs. 26%;  $p < 0.001$ ) and cognitive decline (50% vs. 31%;  $p < 0.001$ ) but lower SOFA scores at admission ( $6 \pm 5$  vs.  $7 \pm 6$ ;  $p < 0.001$ ). Specific ICU-treatment strategies were used, with octogenarians receiving higher rates of organ support (renal replacement therapy, mechanical ventilation, vasoactive

drugs), while for nonagenarians there were higher rates of treatment limitation (40% vs. 33%;  $p < 0.001$ ; Table 1). After discharge from the ICU, most patients had a treatment limitation; 1053 octogenarians (55% of all octogenarians leaving the ICU alive) and 182 (85%) nonagenarians left the ICU with treatment limitations in place.

### Survival analysis in the total cohort

The overall ICU mortality was 27% ( $N = 2134$  of 7900 patients), the 30-day-mortality was 39% ( $N = 3080$  of 7555 patients). Compared to the octogenarians the nonagenarians had a similar ICU mortality (27% vs. 27%;  $p = 0.973$ ), but a higher 30-day-mortality (45% vs. 40%;  $p = 0.029$ , Fig. 1). Nonagenarians showed a significantly longer length of ICU-stay (84 h versus 54 h,  $p < 0.001$ ).

### Comparison of nonagenarians versus octogenarians in the multilevel logistic regression models

After the adjustment for the ICU cluster as a random effect (model-1), nonagenarians had an increased risk for withholding life-sustaining therapy (aOR 1.54 (95% CI 1.22–1.94;  $p < 0.001$ )), but not for withdrawal (aOR 1.03 (95% CI 0.77–1.39;  $p = 0.82$ )). Nonagenarians received significantly less mechanical ventilation, renal replacement therapy and vasoactive drugs. There was no difference between both age groups regarding the use of mechanical ventilation, vasopressors, and ICU-mortality, but an increased risk for 30-day-mortality (aOR 1.39 (95% CI 1.13–1.72);  $p = 0.002$ ). After adding patient-specific confounders (model-2), nonagenarians demonstrated no significant risks compared to octogenarians (Table 2)

## Discussion

This study examines the largest multi-centre prospectively recruited group of intensive care patients of 90 years and older published to date. Nonagenarians differ in their baseline risk distribution, management, and clinical outcomes from octogenarians. Nonagenarians had higher rates of frailty, cognitive impairment, and disability. However, when compared with octogenarians, nonagenarians had a lower illness severity and required less organ support. After adjustment for relevant confounders, the 30-day mortality did not differ between both groups.

Our results are in line with other studies looking at older ICU patients: Fuchs et al. evaluated a cohort of more than 7000 surgical and medical ICU patients and found age, especially above 75 years, to be an independent risk factor for mortality [9, 23]. In a large retrospective analysis of 1,807,531 patients admitted to an ICU between 1997 and 2016, Jones et al. reported increased

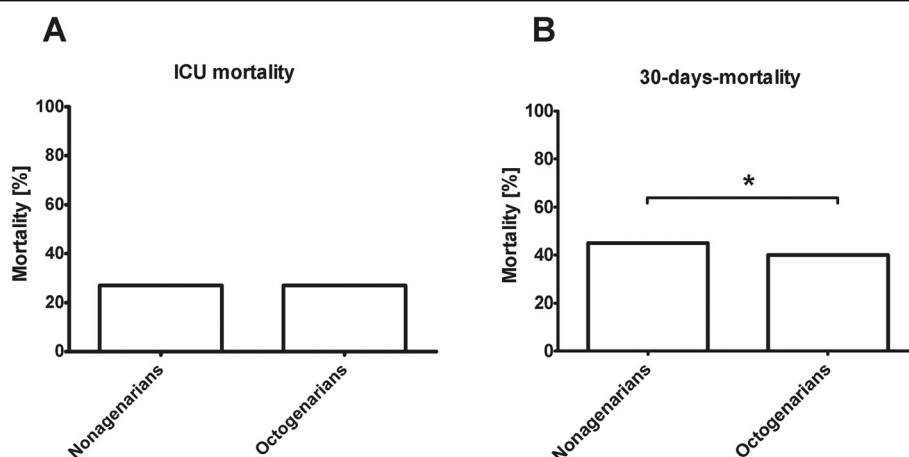
**Table 1** Baseline characteristics in the total cohort, nonagenarians versus octogenarians

	nonagenarians <i>n</i> = 790	octogenarians <i>n</i> = 7110	<i>p</i> -value
Male sex <i>n</i> (%)	339 (43%)	3812 (54%)	< 0.001
Age			
median ( $\pm$ IQR)	91 (90–93)	83 (81–86)	< 0.001
Frailty Score - CFS			
median ( $\pm$ IQR)	5 (4–6)	4 (3–6)	< 0.001
Frailty (CFS > 4) <i>n</i> (%)	454 (58)	2962 (42)	< 0.001
ADL			
median ( $\pm$ IQR)	5 (3–6)	6 (4–6)	< 0.001
Disability (ADL $\leq$ 4)	151 (44)	805 (26)	< 0.001
IQCODE			
median ( $\pm$ IQR)	3.5 (3–4)	3.2 (3–4)	< 0.001
Cognitive Decline (IQCODE $\geq$ 3.5)	149 (50)	812 (31)	< 0.001
SOFA score	6 (4–9)	7 (4–10)	< 0.001
median ( $\pm$ IQR)			
ICU length of stay (hours)			
median ( $\pm$ IQR)	84 (24–117)	54 (37–186)	< 0.001
Treatment withdrawn and/or withheld (%)	312 (40)	2302 (33)	< 0.001
NIV <i>n</i> (%)	168 (21)	1794 (23)	0.03
Intubation <i>n</i> (%)	324 (41)	3685 (52)	< 0.001
Renal replacement therapy <i>n</i> (%)	33 (4)	816 (12)	< 0.001
Vasoactive drugs <i>n</i> (%)	414 (52)	4179 (59)	0.002
Admission diagnosis <i>n</i> (%)			< 0.001
Respiratory failure	155 (20)	1745 (23)	
Circulatory failure	136 (17)	968 (14)	
Combined circulatory & respiratory failure	104 (13)	825 (12)	
Sepsis	74 (9)	966 (14)	
Multitrauma w/o Head Injury	23 (3)	128 (2)	
Trauma with Head Injury	18 (2)	124 (2)	
Head Injury	29 (4)	166 (2)	
Intoxication	1 (< 1)	36 (< 1)	
Cerebral Injury (Non-Traumatic)	38 (5)	469 (7)	
Emergency Surgery	91 (12)	817 (12)	
Other	91 (12)	866 (12)	

CFS Clinical Frailty Scale, SOFA Sequential Organ Failure Assessment, ADL Activity of Daily Life measured with the Katz index, IQCODE Informant Questionnaire on Cognitive Decline in the Elderly, ICU Intensive Care Unit, NIV Non-Invasive Ventilation, SD Standard Deviation

mortality in patients older than 84 years, although they had a similar illness severity at ICU admission compared to younger patients [23]. Conversely, in a study evaluating 5882 patients after cardiac arrest, age alone was only a weak predictor of mortality [24]. In a recent study by Roedl et al., a survival rate of 46% with a good neurological outcome was reported for nonagenarians after cardiac arrest [11]. Recently, Druwé et al. performed a subgroup analysis on out-of-hospital cardiac arrests with

a special interest in the resuscitation attempts in octogenarians: Most physicians considered cardiopulmonary resuscitation to be appropriate even in older patients with poor outcome perspectives [25]. Furthermore, in another study by Becker et al., the ICU mortality of nonagenarians was low at 30% and, importantly, the one-year survival was 50%, indicating outcomes “better than expected” in nonagenarians [26]. Of note, the study by Becker et al. was a single-centre study, and the number



**Fig. 1** Comparison of 30-day and ICU-mortality. **A:** ICU-mortality [%], **B:** 30-day-mortality [%]. \* =  $p < 0.05$

of patients who received vasoactive drugs was lower when compared to the patients in our multi-centre study. Therefore, we propose the higher mortality rates reported in the present study may be more representative of a “real-world scenario”.

Demoule et al. performed a matched case-control study in 36 nonagenarians admitted to an ICU. They were matched according to sex with 72 controls: ICU admissions chosen from the 20- to 69-year age range. They found no differences in the reason for admission, but nonagenarians suffered significantly less from pre-existing co-morbidities. Advanced life-

support interventions were used equally. ICU and intra-hospital mortality, as well as the length of stay, did not differ significantly between nonagenarians and the control group [27]. Despite differences in the absolute length of stay, the trend of a shorter length of stay for older (nonagenarian) intensive care patients is consistent with previous studies [28].

Interestingly, being a nonagenarian was independently associated with the decision for withholding life-sustaining therapy, but not for withdrawing it. After adjustment for patient characteristics, nonagenarians evidenced no particular risk for treatment limitations

**Table 2** Associations of primary exposure (being nonagenarian) with mortality and management strategies in a multilevel logistic regression model

	octogenarians	nonagenarians	p-value	model-1	model-2
Treatment withheld	27% (1945)	35% (279)	< 0.001	aOR 1.54 (95% CI 1.22–1.94; $p < 0.001$ )	aOR 0.95 (95% CI 0.67–1.36; $p = 0.79$ )
Treatment withdrawn	14% (1026)	13% (102)	0.24	aOR 1.03 (95% CI 0.77–1.39; $p = 0.82$ )	aOR 0.73 (95% CI 0.48–1.10; $p = 0.13$ )
NIV	25% (1794)	21% (168)	0.014	aOR 0.79 (95% CI 0.61–1.03; $p = 0.08$ )	aOR 0.85 (95% CI 0.59–1.22; $p = 0.36$ )
Mechanical Ventilation	52% (3685)	41% (324)	< 0.001	aOR 0.72 (95% CI 0.56–0.93; $p = 0.01$ )	aOR 1.26 (95% CI 0.85–1.87; $p = 0.26$ )
RRT	11% (816)	4% (33)	< 0.001	aOR 0.32 (95% CI 0.19–0.53; $p < 0.001$ )	aOR 0.55 (95% CI 0.28–1.08; $p = 0.08$ )
Vasoactive drugs	59% (4179)	52% (414)	< 0.001	aOR 0.74 (95% CI 0.58–0.95; $p = 0.017$ )	aOR 0.90 (95% CI 0.60–1.35; $p = 0.62$ )
30d Mortality	40% (2743)	44% (337)	0.029	aOR 1.39 (95% CI 1.13–1.72; $p = 0.002$ )	aOR 1.25 (95% CI 0.90–1.74; $p = 0.19$ )
ICU-Mortality	27% (1921)	27% (213)	0.97	aOR 1.10 (95% CI 0.87–1.40; $p = 0.43$ )	aOR 0.91 (95% CI 0.63–1.32; $p = 0.63$ )

NIV Non-Invasive Ventilation, RRT renal replacement therapy, ICU Intensive Care Unit, aOR Adjusted Odds Ratio, 95% CI 95% Confidence Interval

Model 1 - ICU cluster (the patient's individual ICU) as random effect

Model 2 - Model 1 plus patient level (SOFA, CFS, age, sex)



compared to octogenarians. These findings contradict the usual expectation that physicians in general tend to be more reluctant to provide organ support to nonagenarians compared to similarly sick octogenarians. In nonagenarians, ICU re-triage should be emphasised: after an initial intensive care treatment for up to 48 h, patients should be critically evaluated in cooperation with their family and/ or carers and discharged to a normal ward for best-supportive care if further intensive care seems unethical, unjustified, or unlikely to improve outcomes. However, modern intensive care medicine is not limited to life-sustaining measures. Even beyond invasive ventilation, renal replacement therapy or cardiopulmonary resuscitation, intensive care medicine can provide valuable treatment for the patient, which might be intensified palliative therapy. Based on our data, being a nonagenarian does not represent a particular risk factor for adverse outcomes. Application of ICU re-triage could help to reduce the economic burden of ICU care in very old patients, in addition to unethical intensive care and distress caused to health care providers.

Mortality was similar between octogenarians and nonagenarians at ICU discharge and after 30 days. The long-term outcomes of the VIP2 study are awaited and will answer the question of whether this effect remains stable further over time.

An important limitation is, that we have no information about pre-ICU triage decisions, although this might be an important factor for the differences in disease illness scores and frailty between nonagenarians and octogenarians. Furthermore, this study only provides detailed information up to ICU-discharge and there was a significant rise in mortality during the 30 days after ICU-discharge, but we do not have detailed data on decisions made and developments during this period. Another limitation is that no a priori sample size calculation was made to detect a difference in the mortality between nonagenarians and octogenarians. Our post-hoc power calculation shows that the present study is likely underpowered for the primary outcome, and thus the reporting results that are at a higher risk of false positive results. However, this was counterbalanced by using a multilevel model to adjust for relevant confounders.

## Conclusion

Nonagenarian ICU patients demonstrated higher rates of frailty but had less acute organ dysfunction than octogenarians. After adjustment for multiple relevant confounders, nonagenarians did not suffer from worse outcomes compared to octogenarian ICU patients. Rather than being a nonagenarian, the severity of illness, functional capacity – and of course the patients' will – should guide triage decisions.

## Acknowledgements

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**France**

CH Francois Mitterrand	Pau	Reanimation polyvalente	Antoine Romen
Hôpital Privé Claude Galien	Quincy sous Sénart	Polyvalente	Arnaud Galbois
Saint Antoine	Paris	Medecine Intensive Reanimation	Bertrand Guidet
Germon and Gauthier	Béthune	Médecine Intensive Réanimation	Christophe Vinsonneau
Hôpital Ambroise Paré	Boulogne Billancourt	Medecine Intensive Reanimation	Cyril Charron
CH Dr. Schaffner	Lens	Reanimation polyvalente	Didier Thevenin
Hopital Européen Georges Pompidou	Paris	Médecine Intensive Réanimation	Emmanuel Guerot
CHU de Besançon	Besançon	Département de Anesthésie Réanimation Chirurgicale	Guillaume Besch
Hôpital Cochin	Paris	Médecine Intensive Réanimation	Guillaume Savary
Victor Dupouy	Argenteuil	Service de Réanimation Polyvalente et USC	Hervé Mentec
Centre Hospitalier Général	Cambrai	Réanimation polyvalente	Jean-Luc Chagnon
Dieppe General Hospital	Dieppe	Médecine Intensive Réanimation	Jean-Philippe Rigaud
CHU Dijon Bourgogne	Dijon	Medecine intensive- Réanimation	Jean-Pierre Quenot
CH Bigorre	Tarbes	service de réanimation polyvalente	Jeremy Castanera
CH de Charleville-Mézières	Charleville-Mézières	Medecine Intensive Reanimation	Jérémy Rosman
CHU Amiens	Amiens	Reanimaiton medicale	Julien Maizel
Groupe Hospitalier Paris Saint Joseph	Paris	Réanimation polyvalente	Kelly Tiercelet
CHU de Besançon	Besancon	Réanimation Médicale	Lucie Vettoretti

(Continued)

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Tenon	Paris	Service de Réanimation Médico Chirurgicale	Michel Djibré
Groupe Hospitalier Sud Ile de France	Melun	Département de médecine intensive	Nathalie Rolin
Clinique Du Millenaire	Montpellier	Reanimation Chirurgicale II et III	Philippe Burtin
Marne La Vallee	Jossigny	Reanimation Polyvalente	Pierre Garcon
CHU Lille	Lille	Critical Care Center	Saad Nseir
CHU de Caen	Caen	Service de Réanimation Médicale	Xavier Valette

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Klinikum rechts der Isar TU München	München	Toxikologische Intensivstation	Christian Rabe
University Hospital Ulm	Ulm	Anesthesiologic Intensive Care Department	Eberhard Barth
Katholisches Krankenhaus St. Johann Nepomuk	Erfurt	Klinik für Innere Medizin II/ Kardiologie und Internistische Intensivmedizin	Henning Ebel
Klinikum rechts der Isar, School of Medicine, Technical University of Munich	München	Intensivstation IS2/L2a	Kristina Fuest
Jena University Hospital, Department of Internal Medicine I	Jena	Internistische Intensivstation	Marcus Franz
West German Heart and Vascular Center Essen (WHGZ)	Essen	INTK	Michael Horacek
Universitätsmedizin der Johannes Gutenberg-Universität Mainz	Mainz	Anästhesie-Intensivstation	Michael Schuster
University Hospital Frankfurt	Frankfurt am Main	Department of Anaesthesiology, Intensive Care Medicine and Pain Therapy	Patrick Meybohm
University Hospital Düsseldorf	Düsseldorf	M1/2	Raphael Romano Bruno
Robert-Bosch-Krankenhaus	Stuttgart	1D	Sebastian Allgäuer
Heidelberg University Hospital	Heidelberg	Station 13 IOPIS	Simon Dubler



(Continued)

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University Hospital Leipzig	Leipzig	Department of Anesthesiology and Intensive Care Medicine	Stefan Schering
St Vincenz Hospital	Limburg/Lahn	Intensive care unit	Stephan Steiner
Hannover Medical School	Hannover	44	Thorben Dieck
Universitätsklinikum Knappschafts-Krankenhaus Bochum	Bochum	Operative IBA	Tim Rahmel
Universitätsklinikum Schleswig-Holstein	Lübeck	IKI 12a	Tobias Graf

**Greece**

Asklepieio Voulas	Athens	ICU	Anastasia Koutsikou
Xanthi General Hospital	Xanthi	Xanthi ICU	Aristeidis Vakalos
Sismanoglio - Amallia Fleming G. H	Marousi - Athens Attika	Sismanoglio	Bogdan Raitsiou
General Hospital Agios Pavlos	Thessaloniki	ICU Agios Pavlos	Elli Niki Flioni
General Hospital of Larissa	Larissa	General ICU	Evangelia Neou
Lamia General Hospital	Lamia	Lamia ICU	Fotios Tsimpoukas
University Hospital of Ioannina	Ioannina	Intensive Care Unit	Georgios Papathanakos
General Hospital of Athens Korgialeneio Mbenakeio Red Cross	Athens	ICU	Giorgos Marinakis
General Hospital of Eleusis Thriassio	Eleusis	ICU Latsio	Ioannis Koutsodimitropoulos
KONSTANTOPOULEION GEN. HOSPITAL	Athens	General ICU	Kounougeri Aikaterini
Sotiria Hospital	Athens	ICU 1st Department of Pulmonary Medicine Athens Medical School, National and Kapodistrian University of Athens	Nikoletta Rovina
General Hospital of Patra	Achaia	ICU	Stylliani Kourelea
G Gennimatas Hospital of Thessaloniki	Thessaloniki	ICU G GENNIMATAS	Polychronis Tasioudis
Agioi Anargiroi Hospital	Athens	General ICU	Vasiliios Zidianakis
Theagenio	Theassaloniki	Meth Theagenio	Vryza Konstantinia

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University General Hospital Ahepa	Thessaloniki	Metha	Zoi Aidoni
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**Ireland**

Mater Misericordiae University Hospital	Dublin	Department of Critical Care Medicine	Brian Marsh
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University Hospital Galway	Galway	General ICU	Chris Read
St James's Hospital	Dublin	ICU	Ignacio Martin-Loeches

**Italy**

Arnas Ospedale Civico De Christina Benfratelli	Palermo	Terapia Intensiva Polivalente Con Trauma Center	Andrea Neville Cracchiolo
Istituto Ortopedico Rizzoli	Bologna	TIPO	Aristide Morigi
San Giuseppe	Empoli	Terapia Intensiva	Italo Calamai
Humanitas Research Hospital	Milan	General ICU	Stefania Brusa

**Libya**

Al-Zawia University Hospital	Al-Zawia	ICU	Ahmed Elhadi
Alkhums Hospital	Alkhums	ICU	Ahmed Tarek
Elkhadra Hospital	Tripoli	ICU	Ala Khaled
Abo Selim Trauma Hospital	Tripoli	ICU	Hazem Ahmed
Tripoli Medical Center	Tripoli	CCU	Wesal Ali Belkhair

**Netherland**

Medisch Spectrum Twente	Enschede	Intensive Care Center	Alexander D. Cornet
Erasmus Medical Center	Rotterdam	ICU adults	Diederik Gommers
UMC Utrecht	Utrecht	ICU departement	Dylan de Lange
Albert Schweitzer Ziekenhuis	Dordrecht	ICU asz	Eva van Boven
Isala Hospital	Zwolle	Intensive Care	Jasper Haringman
Diakonessenhuis Utrecht Haga Ziekenhuis	Utrecht The Hague	Intensive care ICU	Lenneke Haas

(Continued)

			Lettie van den Berg
Canisius Wilhelmina Ziekenhuis	Nijmegen	C38	Oscar Hoiting
Jeroen Bosch Ziekenhuis	Den Bosch	IC JBZ	Peter de Jager
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Zuyderland Medical Center	Heerlen	Zuyderland Heerlen	Tom Dormans
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**Norway**

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Sykehuset Telemark	Skien	Intensiv Skien	Bente Jannestad
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Ålesund hospital	Ålesund	Dept. Anesthesia and Intensive Care, Surgical ICU	Finn H. Andersen
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Namsos Sykehus	Namsos	Intensivavdeling	Jan Peter Jensen
Haukeland University Hospital	Bergen	Medisinsk intensiv og overvåkning (MIO)	Jørund Langørgen
Oslo University Hospital	Oslo	Intensive Care section Ullevaal	Kirsti Tøien
Stavanger University Hospital	Stavanger	Department of Intensive Care	Kristian Strand
Haugesund sjukehus	Haugesund	Intensivavdelingen	Michael Hahn
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**Poland**

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(Continued)

Szpital Wojewódzki w Bełchatowie	Bełchatów	Oddział Intensywnej Terapii	Aleksandra Biernacka
University Hospital in Zielona Góra	Zielona Góra	Clinical Department of Anesthesiology and Intensive Care	Bartosz Kudłinski
Regional Teaching Hospital	Bielsko-Biała	Department of Anaesthesiology and Intensive Care	Dariusz Maciejewski
St. John Grande Hospital	Kraków	Oddział Anestezjologii i Intensywnej Terapii	Dorota Studzińska
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Uniwersyteckie Centrum Kliniczne w Gdańsku	Gdańsk	Klinika Anestezjologii i Intensywnej Terapii	Jan Stefaniak
Pomeranian Medical University	Szczecin	Department of Anesthesiology and Intensive Care	Joanna Solec-Pastuszka
University Hospital in Cracow	Kraków	Anaesthesiology and Intensive Care Unit No.1	Joanna Zorska
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(Continued)

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Infant Jesus Teaching Hospital	Warsaw	I Department of Anaesthesiology and Intensive Care	Paweł Zatorski
Regional Hospital in Białystok	Białystok	Department of Anaesthesiology and Intensive Care	Piotr Galkin
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Saint Lucas Hospital, Kąnskie	Kąnskie	Intensive Care Department	Wojciech Gola

**Portugal.**

Centro Hospitalar do Porto	Oporto	Serviço de Cuidados Intensivos 1	Alexandre Fernandes Pinto
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Hospital São Francisco Xavier	Lisbon	Unidade Cuidados Intensivos Polivalente	Ana Rita Santos
Hospital da Luz	Lisboa	UCI Hospital da Luz	Cristina Sousa
Hospital de Viseu	Viseu	UCIP	Inês Barros
Hospital Professor Doutor Fernando Fonseca EPE	Amadora	Serviço de Medicina Intensiva SMI	Isabel Amorim Ferreira
Hospital Garcia de Orta - HGO	Almada	Serviço de Medicina Intensiva	Jacobo Bacariza Blanco
Hospital São Bernardo - CH Setúbal	Setúbal	Serviço de Cuidados Intensivos	João Teles Carvalho
Centro Hospitalar de Trás Montes e Alto Douro	Vila Real	Serviço de Medicina Intensiva	Jose Maia
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CHMT-Abrantes	Abrantes	SMI	Nuno Catorze

**Russia.**

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**Spain.**

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Hospital General Universitario de Albacete	Albacete	UCI Polivalente	Angela Prado Mira
Hospital Clinic of Barcelona	Barcelona	Respiratory Intensive Care Unit	Catia Cilloniz
Hospital Universitario Río Hortega	Valladolid	UVI Polivalente y Coronaria	David Perez-Torres
Universitario La Paz	Madrid	Surgical ICU	Emilio Maseda
General Universitario de Castellón	Castellón	Servicio de Medicina Intensiva	Enver Rodríguez
Hospital Universitario Río Hortega	Valladolid	UVI Neurocríticos Trauma y Quemados	Estefania Prol-Silva
Hospital de Tortosa Verge de la Cinta	Tortosa	Servei de Medicina Intensiva	Gaspar Eixarch
Parc Taulí	Sabadell	Parc Taulí	Gemma Gomà
Clínico Universitario de Valencia	Valencia	Surgical Intensive Care Unit	Gerardo Aguilar
Hospital Universitario de Torrejón	Torrejón de Ardoz, Madrid	Intensive Care UNit	Gonzalo Navarro Velasco
Hospital General de Catalunya	Barcelona	HGC	Marián Irazábal Jaimes
Hospital Universitario Sagrado Corazon	Barcelona	Intensive Care Unit	Mercedes Ibarz Villamayor
Hospital reina Sofía	Murcia	Reina Sofía	Noemí Llamas Fernández
Complejo Hospitalario de Segovia	Segovia	ICU Segovia	Patricia Jimeno Cubero
Universitario de Getafe	Getafe	Intensive Care and Burn Unit	Sonia López-Cuenca
Germans Trias i Pujol Hospital	Badalona	General ICU	Teresa Tomasa
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**Sweden.**

Umeå University	Umeå	Department of Surgical and Perioperative Sciences, Anesthesiology and Intensive Care Medicine	Camilla Brorsson
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Sundsvall Hospital	Sundsvall	Sundsvall ICU	Henrik Westberg
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(Continued)

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Alingsås Lasarett	Alingsås	Intensivvårdsavdelningen	Joakim Sivik
Västervikssjukhus	Västervik	IVA Västervikssjukhus	Johan Berkus
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Linköping University Hospital	Linköping	Cardiothoracic Intensive Care Unit	Sten Walther

**Switzerland.**

Hopitaux Universitaires de Genève	Geneva	Adult Intensive Care Unit	Filippo Boroli
University of Bern Inselspital	Bern	Department of Intensive Care Medicine	Joerg C. Schefold
Fribourg Hospital	Fribourg	Intensive Care Unit	Leila Hergafi
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**Turkey.**

Ordu University Training and Research Hospital	Ordu	General ICU	Ismail Yildiz
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**Wales.**

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**Authors' contributions**

BW, RRB and CJ analysed the data and wrote the first draft of the manuscript. HF and BG and DL contributed to statistical analysis and improved the paper. MK and AB and AM and FA and AA and SF and MC and SC and LF and ML and JM and BM and RM SO and CO and BP and IS and WS and AV and XW and SL and CB and SW and JS and MJ and YN and ME JF and TZ gave guidance and improved the paper. All authors read and approved the final manuscript.

**Authors' information**

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**Availability of data and materials**

The anonymised data can be requested from the authors if required. The datasets analysed during the current study are not publicly available due to the different local institutional and/or licensing committees but are available from the corresponding author on reasonable request.

**Declarations****Ethics approval and consent to participate**

The primary competent ethics committee was the Ethics Committee of the University of Bergen, Norway. A study protocol was provided to participating centres. Every participating centre obtained ethics approval according to local legislation. A copy of the ethics approval was sent to the study coordinator before start of the study. Institutional research ethic board approval was obtained from each study site. This was a prerequisite for participation in the study. All methods were carried out in accordance with relevant guidelines and regulations. All experimental protocols were approved by the local institutional and/or licensing committees. Written informed consent was obtained of all included subjects, except for patients from VIP2 of sites where study inclusion was explicitly granted without written informed consent. The inclusion of deceased patients was strictly in accordance with the requirements of the local competent ethics committees. In most cases, the consent of the patient or the legal guardian was mandatory (see above). The studies conducted were observational studies. No examinations (e.g. blood sampling) or tissue sampling took place.

**Consent for publication**

The manuscript does not contain any individual person's data in any form.

**Competing interests**

The authors declare that they have no competing interests.

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