



Factors associated with a persistent delirium in the intensive care unit: A retrospective cohort study

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ABSTRACT

Purpose: To explore differences between ICU patients with persistent delirium (PD), non-persistent delirium (NPD) and no delirium (ND), and to determine factors associated with PD.

Materials and methods: Retrospective cohort study including all ICU adults admitted for ≥ 12 h (January 2015–February 2020), assessable for delirium and followed during their entire hospitalization. PD was defined as ≥ 14 days of delirium. Factors associated with PD were determined using multivariable logistic regression analysis.

Results: Out of 10,295 patients, 3138 (30.5%) had delirium, and 284 (2.8%) had PD. As compared to NPD ($n = 2854$, 27.7%) and ND ($n = 7157$, 69.5%), PD patients were older, sicker, more physically restrained, longer comatose and mechanically ventilated, had a longer ICU and hospital stay, more ICU readmissions and a higher mortality rate.

Factors associated with PD were age (adjusted odds ratio [aOR] 1.03; 95% confidence interval [CI] 1.02–1.04); emergency surgical (aOR 1.84; 95%CI 1.26–2.68) and medical (aOR 1.57; 95%CI 1.12–2.21) referral, mean Sequential Organ Failure Assessment (SOFA) score before delirium onset (aOR 1.18; 95%CI 1.13–1.24) and use of physical restraints (aOR 5.02; 95%CI 3.09–8.15).

Conclusions: Patients with persistent delirium differ in several characteristics and had worse short-term outcomes. Physical restraints were the most strongly associated with PD.

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1. Introduction

Delirium is a clinical expression of acute encephalopathy [1–4], and presents as an acute disturbance in consciousness, attention and cognition, which may fluctuate over the day. It is a common disorder, affecting many hospitalized patients, with an increased occurrence in critical illness. The incidence and prevalence rates of delirium in the intensive care unit (ICU) population, on average 29% and 40% (the latter reaching

up to as high as 80% in mechanically ventilated patients), respectively [2,4–7], are challenged by aging and the increasing number of patients with multiple comorbidities.

ICU delirium has increasingly been recognized and associated with detrimental outcomes, including prolonged duration of mechanical ventilation, prolonged ICU and hospital stay and long-term cognitive impairment [3,8–11]. Many risk factors associated with the onset of ICU delirium have been recognized, including pre-existing cognitive dysfunction, age, severity of illness, mechanical ventilation, use of benzodiazepines and drug abuse [2,5,12–14].

The median duration of ICU delirium is 2–3 days [15,16], but it can persist for weeks or even months; in rare cases, it never resolves [17]. In general, persistent delirium can be regarded as an episode of delirium that persists for a longer period of time, irrespective of treatment of underlying conditions. The 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) defines persistent delirium as a period of delirium which lasts for weeks or months [18]. It is unclear how patients with persistent delirium differ from those with delirium

Abbreviation list: aOR, adjusted Odds Ratio; APACHE IV, Acute Physiology And Chronic Health Evaluation IV; CAM-ICU, Confusion Assessment Method for the ICU; DOS, Delirium Observation Screening; DSM-5, Diagnostic and Statistical Manual of Mental Disorders; ICU, Intensive Care Unit; IQR, Interquartile Range; ND, No Delirium; NPD, Non-Persistent Delirium; PD, Persistent Delirium; RASS, Richmond Agitation Sedation Scale; SD, Standard Deviation; SOFA, Sequential Organ Failure Assessment.

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of a shorter duration and, moreover, which factors play a role in persistence of delirium. The only studies concerning persistent delirium have used different definitions and cut-off points (ranging from >1 week up to >6 months), mostly excluded ICU patients or did not focus on outcome [19–21].

Since delirium duration is associated with worse short and long-term outcomes [9,10,22], it may serve as a surrogate measure for delirium severity. Therefore, it is plausible that the impaired outcomes that are associated with delirium are due to patients with persistent delirium, while outcome is not or less impaired in delirium with shorter duration.

Therefore, the aim of the present study was to explore differences in patient-, delirium- and outcome related characteristics between ICU patients with persistent delirium, non-persistent delirium and no delirium. Secondly, we aimed to determine demographic and precipitating factors associated with persistent delirium, and outcome factors associated with delirium duration.

2. Materials and methods

2.1. Study design and participants

An exploratory retrospective cohort study was conducted including all consecutive ICU patients admitted to the Radboud University Medical Center between January 2015 and February 2020. Patients were followed throughout their entire hospital stay, including ward stay before and after ICU admission. Patients aged <18 years, patients with an ICU admission <12 h, persistent comatose patients, and patients who could not be assessed for delirium (due to language problems or other reasons that preclude delirium assessment, such as deafness) were excluded from analysis. The regional Medical Ethical Committee approved the study and waived the need for informed consent (CMO number 2020–6845).

2.2. Delirium assessment and definitions

Data on delirium assessments were obtained from hospital admission to discharge. Delirium and level of arousal during ICU admission were assessed every eight hours by well-trained ICU nurses [23] using the Confusion Assessment Method for the ICU (CAM-ICU) [24,25] and the Richmond Agitation Sedation Scale (RASS) [26], respectively. Patients with a RASS score of –4 or –5 were defined as comatose. Similarly, delirium on the ward was assessed every eight hours using the validated Delirium Observation Screening (DOS) scale [27]. Patients who were either CAM-ICU or DOS positive or were treated with antipsychotics (i.e., haloperidol or quetiapine) for reason of delirium, were defined as delirious. The last positive delirium assessment or last administered antipsychotic for reason of delirium, was considered as the end of delirium. Delirium duration was calculated by summing the days with delirium from the first until the last positive delirium assessment or administered antipsychotic, with non-delirium and comatose days in between excluded from the summation. For example, a patient could either have positive delirium assessments on day 1, 2, 4, and 5 or on day 1, 3, 4 and 9, which would both result in a delirium duration of 4 days. In an international digital ICU delirium expert meeting, consisting of five delirium experts from four different medical centers, consensus was achieved to define persistent delirium as a total delirium duration of ≥ 14 days, which is in consonance with the minimum period of time one could consider as a persistent delirium according to the DSM-5 criteria (where persistent delirium is defined as an episode of delirium which lasts for weeks or months) [18]. To reduce immortal time bias, patients with a delirium duration between 7 and 14 days who died during admission and were delirious in at least one of the three days prior to death ($n = 39$), were assigned to the persistent delirium group.

The cohort was divided into three groups, based on the presence and duration of delirium: persistent delirium (PD) with ≥ 14 delirium days, non-persistent delirium (NPD) with <14 delirium days, and no delirium (ND), defined as patients who were never CAM-ICU or DOS positive, and were not treated with antipsychotics as part of delirium treatment.

2.3. Variables and outcome measures

Demographic variables were gender, age, body mass index, pre-admission use of psychoactive medication, comorbidity, admission type, Acute Physiology and Chronic Health Evaluation IV (APACHE) score (range 0–286) [28] and daily Sequential Organ Failure Assessment (SOFA) scores (range 0–24) during ICU admission [29]. Delirium related data were delirium duration, physical restraint use and psychiatric consultations for reason of delirium or a history of a psychiatric disorder (the latter available from January 2016). Data regarding dosages of anesthetics/sedatives (clonidine, dexmedetomidine, esketamine and propofol), benzodiazepines (lorazepam, midazolam, oxazepam), opioids (morphine, remifentanyl and sufentanil), and antipsychotics (haloperidol or quetiapine) were gathered both prior to and after delirium onset to determine differences between the PD and NPD group.

Outcome related data were total days spent in the ICU, total comatose days, total days of mechanical ventilation, duration of hospital stay (including ICU days), ICU readmissions during hospital stay, in-hospital death and 90-days and 1-year mortality.

2.4. Statistical analysis

Descriptive analyses were conducted to examine demographic-, delirium-, medication- and outcome related characteristics between the groups. Depending on the data distribution, continuous variables were reported as either mean with standard deviation (SD) or median with first and third interquartile range [IQR]. Categorical variables were reported as proportions. Differences between the groups were analyzed using Chi-squared test for categorical variables, and independent *t*-test, Mann-Whitney *U* test, one-way ANOVA or Kruskal Wallis test for continuous variables, depending on the number of groups and data distribution. Sensitivity analyses using different cut-off points for delirium duration (1–4 days, 5–9 days, 10–13 days and ≥ 14 days of delirium) were conducted.

Univariable and multivariable logistic regression analyses were used to determine associations between demographic and precipitating variables and persistent delirium, with the NPD group as reference. Use of physical restraints, mean SOFA score before delirium onset and daily medication dosages before delirium onset were considered as precipitating variables. Data on mean SOFA score before delirium onset for patients who had delirium before ICU admission were imputed with the mean from either the PD or NPD group. Variables for the multivariable model were included based on either a *P*-value <.20 in univariable logistic regression analysis, a statistically significant difference between PD and NPD or expert opinion. Pearson's and Spearman's correlation coefficients, for continuous and categorical variables, respectively, were analyzed in conjunction with Variance Inflation Factors (VIF) to ensure no multicollinearity (defined as a correlation coefficient > 0.6 or a VIF >5) among the variables was present. For this reason, the variable duration of physical restraint use was dichotomized.

To determine associations between delirium duration and outcomes, multivariable logistic regression analyses were performed on the outcome variables extended duration of mechanical ventilation, extended duration of hospital stay and in-hospital mortality, adjusted for the covariates gender, age, pre-admission comorbidity, admission type, mean SOFA score during ICU admission and days spent in ICU. Duration of mechanical ventilation and duration of hospital stay were dichotomized, using the highest quartile (2 and 17 days, respectively) as an extended duration of that variable. Again, no multicollinearity was observed between the variables.

Statistical significance was defined as a P -value $< .05$. All data were analyzed using IBM SPSS Statistics version 25.0.

3. Results

A total of 12,144 ICU patients were eligible, of whom 10,295 (84.8%) were included for analysis. Reasons for exclusion were an ICU stay < 12 h ($n = 1136$, 9.4%), patients who were unable to be assessed for delirium ($n = 453$, 3.7%), age < 18 years ($n = 226$, 1.9%), or missing delirium or ICU data ($n = 34$, 0.3%) (Fig. 1). The overall mean (\pm SD) age of the cohort was 61.9 (± 15.1) years, the majority ($n = 6538$, 63.5%) was male, most (70.1%, $n = 7216$) were surgical patients, and the mean (\pm SD) APACHE IV score was 67.6 (± 22.9) (Table 1). The overall delirium prevalence rate was 30.5% ($n = 3138$), of which 284 patients (9.1%) had a persistent delirium, and 2854 (90.9%) had a non-persistent delirium.

3.1. Differences between PD, NPD and ND patients

As compared to NPD and ND, PD patients were significantly older, more severely ill, were physically restrained for longer, needed more psychiatric consultations, had more coma days, more days on the mechanical ventilator, a longer ICU and hospital stay, more ICU readmissions and a higher in-hospital-, 90-days- and 1-year mortality rate (Table 1). Sensitivity analyses with different cut-off points for delirium duration are shown in Supplementary Table 1. Further details on psychoactive medication use, comorbidities and medical admission subgroups are provided in Supplementary Table 2.

Furthermore, prior to delirium onset, PD patients received, on average, a significantly higher daily dose of esketamine, propofol, midazolam, oxazepam and sufentanil as compared to NPD patients (Supplementary Table 3), and also received significantly more sedatives, benzodiazepines, opioids and anti-psychotics after the onset of delirium (Supplementary Table 4).

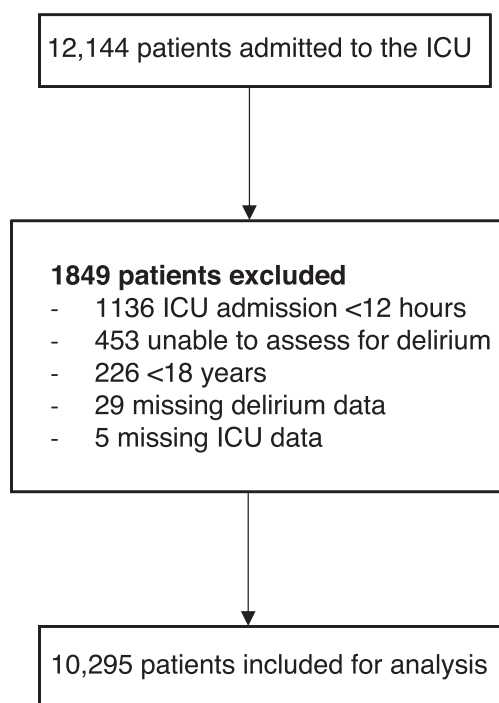


Fig. 1. Flowchart of patient inclusion.

3.2. Demographic and precipitating factors associated with persistent delirium

In the multivariable model, age (adjusted odds ratio (aOR) 1.03; 95% CI 1.02–1.04), emergency surgical (aOR 1.84 95%CI 1.26–2.68) and medical admission (aOR 1.57; 95%CI 1.12–2.21), mean SOFA score before delirium onset (aOR 1.18; 95%CI 1.13–1.24) and use of physical restraints (aOR 5.02; 95%CI 3.09–8.15) were significantly associated with PD (Table 2). The unadjusted associations are shown in Supplementary Table 5.

3.3. Outcomes associated with delirium duration

After adjusting for covariates, delirium duration was significantly associated with an extended duration of mechanical ventilation (aOR 1.04; 95%CI 1.01–1.07) and an extended hospital stay (aOR 1.23; 95% CI 1.19–1.27). Delirium duration was not associated with in-hospital mortality (Table 3).

4. Discussion

This large retrospective cohort study showed that ICU patients with persistent delirium differ in several patient characteristics and had worse short-term outcomes as compared to patients with non-persistent delirium and no delirium. Furthermore, in the multivariable model, factors associated significantly with persistent delirium were age, admission type, severity of illness and the overall use of physical restraints before and after onset of delirium.

These results are one of the first in this field of ICU delirium uncovering differences between persistent and non-persistent delirium, following patients during the entire hospital admission. Furthermore, the factors associated with PD in this study illustrate that these are not only risk factors for incident delirium, as previous research has shown [12–14], but similarly need to be considered as potential risk factors for persistent ICU delirium.

This study reflects earlier work which revealed that physical restraints are still frequently used in Dutch ICUs – especially in patients with delirium [30]. The strong association found between physical restraint use and persistent delirium, although it does not imply a causal relationship, contributes to the controversial role that physical restraints have on the outcomes of critically ill patients, and once more emphasizes the need for a more prudent and reserved approach to using physical restraints in the ICU. Importantly, the use of physical restraints could very likely maintain delirium duration, and minimization could therefore be helpful to reduce the delirium burden. Future studies should evaluate the differences in outcomes and adverse effects using pharmacological restraints instead of physical restraints in patients with delirium, for example using guideline recommended short acting sedative agents such as dexmedetomidine, which has been shown to increase ventilator-free hours and accelerate resolution of delirium in agitated patients [13,31,32].

Although the use of benzodiazepines is associated with delirium in critically ill adults [13,33–35], we could not confirm this for persistent delirium. Possibly, benzodiazepine use contributes to transitioning to delirium, but not in sustaining it. However, this hypothesis warrants further investigation.

There is only one other study that investigated persistent delirium in ICU patients [20], although this study only included older patients and defined PD as delirium that persisted upon discharge to the ward, hence impeding comparability with our findings. Nevertheless, our study found similar results regarding an association with age and PD.

Furthermore, we found that delirium duration, even after accounting for confounders such as length of ICU stay, was significantly associated with a prolonged duration of mechanical ventilation and an extended hospital stay, which is in line with earlier studies examining ICU delirium and short-term outcomes [3,10,13]. Previous work has

Table 1
Demographic, delirium and outcome data of all subgroups and the total cohort.

Male sex, n (%)	Persistent delirium (PD) (n = 284)		Non-persistent delirium (NPD) (n = 2854)		No delirium (ND) (n = 7157)		Total (N = 10,295)	
	194	(68.3)	1801	(63.1)	4543	(63.5)	6538	(63.5)
Age (years) ^d	67.2	±11.8 ^{bc*}	63.5	±14.8 ^{c*}	61.0	±15.1	61.9	±15.1
BMI (kg/m ²) ^d	26.3	±4.9	26.7	±4.9	26.8	±4.9	26.8	±4.9
Pre-admission use of psychoactive medication, n (%) ^{d,e}	24	(8.5) ^{c*}	188	(6.6) ^{c*}	186	(2.6)	398	(3.9)
Pre-admission comorbidity, n (%) ^{d,e}	183	(64.4)	1827	(64.0)	5482	(76.6) ^{a,b*}	7492	(72.8)
Admission type, n (%) ^{d,e}								
Medical	144	(50.7) ^{c*}	1255	(44.0) ^{c*}	1680	(23.5)	3079	(29.9)
Surgical	140	(49.3)	1599	(56.0)	5477	(76.5) ^{a,b*}	7216	(70.1)
Elective	57	(40.7)	1018	(63.7) ^{a*}	4744	(86.6) ^{a,b*}	5819	(80.6)
Emergency	83	(59.3) ^{b,c*}	581	(36.3) ^{c*}	733	(13.4)	1397	(19.4)
APACHE IV score ^f	86.7	±21.3 ^{bc*}	76.1	±23.2 ^{c*}	63.5	±21.5	67.6	±22.9
Peak SOFA score (all ICU admissions)	11.9	±3.3 ^{b,c*}	9.3	±3.5 ^{c*}	7.1	±3.3	7.8	±3.5
SOFA score ^f	6.9	±2.8 ^{bc*}	6.3	±2.6 ^{c*}	5.2	±2.6	5.5	±2.7
Before delirium onset	9.2	±2.9 ^{ba}	7.4	±3.0	n.a.		n.a.	
After delirium onset	5.5	±2.8 ^{ba}	6.2	±2.9	n.a.		n.a.	
Delirium duration (days)	18	[14–23] ^{ba}	2	[1–4]	n.a.		n.a.	
Ward delirium days	0	[0–6] ^{ba}	0	[0–0]	n.a.		n.a.	
ICU delirium days	15	[9–22] ^{ba}	2	[1–3]	n.a.		n.a.	
Physical restraints, n (%)	265	(93.3)	1991	(69.8)	2822	(39.4)	5078	(49.3)
Duration of physical restraint use (days)	24	[11–37] ^{b,c*}	2	[0–7] ^{c*}	0	[0–1]	0	[0–2]
Psychiatric consultations, n (%)	78	(27.5) ^{b,c*}	204	(7.1) ^{c*}	31	(0.4)	313	(3.0)
During ICU admission	57	(73.1) ^{bc*}	105	(51.5)	10	(32.3)	172	(55.0)
On ward before 1st ICU admission	7	(9.0)	20	(9.8)	4	(12.9)	31	(9.9)
On ward post ICU admission	14	(17.9)	79	(38.7) ^a	17	(54.8) ^{a*}	110	(35.1)
Days spent in ICU	27	[17–42] ^{b,c*}	4	[2–11] ^{c*}	2	[2–2]	2	[2–4]
Comatose days	1	[0–5] ^{b,c*}	1	[0–1] ^{c*}	0	[0–1]	0	[0–1]
Mechanically ventilated, n (%)	280	(98.6) ^{b,c*}	2443	(85.6) ^{c*}	4984	(69.6)	7707	(74.9)
Days on mechanical ventilator	22	[12–36] ^{b,c*}	3	[1–8] ^{c*}	1	[0–2]	1	[0–2]
Duration of hospital stay (days)	45	[29–67] ^{b,c*}	15	[9–26] ^{c*}	9	[6–13]	10	[7–17]
≥1 ICU readmission during hospital stay	77	(27.1) ^{b,c*}	341	(11.9) ^{c*}	208	(2.9)	626	(6.1)
In-hospital death, n (%)	90	(31.7) ^{b,c*}	323	(11.3) ^{c*}	400	(5.6)	813	(7.9)
90-days mortality, n (%)	102	(35.9) ^{b,c*}	477	(16.7) ^{c*}	611	(8.5)	1190	(11.6)
1-year mortality, n (%)	132	(46.5) ^{b,c*}	648	(22.7) ^{c*}	985	(13.8)	1765	(17.1)

Data are presented as mean ± SD or median [IQR], except where stated. All significance values were adjusted by the Bonferroni correction for multiple testing.

^a Significantly higher than persistent delirium.

^b Significantly higher than non-persistent delirium.

^c Significantly higher than no delirium.

* P < .001.

^d Data from first ICU admission.

^e Further details on psychoactive medication, comorbidities and medical admission subgroups are given in Supplementary Table 2

^f Data from ICU admission in which delirium was first observed. Data were imputed with the mean of the PD or NPD group if delirium started on ward. Data from first ICU admission were used for ND group.

Table 2
Demographic and precipitating factors associated with persistent delirium^a.

Factor	Adjusted OR (95%CI)	P-value
Male sex	1.26 (0.96–1.65)	0.10
Age (years)	1.03 (1.02–1.04)	<0.001
Pre-admission use of psychoactive medication	1.37 (0.86–2.18)	0.19
Admission type		
Elective surgical	Ref.	
Emergency surgical	1.84 (1.26–2.68)	0.002
Medical	1.57 (1.12–2.21)	0.01
Mean SOFA score before delirium onset	1.18 (1.13–1.24)	<0.001
Use of physical restraints	5.02 (3.09–8.15)	<0.001
Daily medication dosage before delirium onset		
Clonidine (10 µg/kg)	1.08 (0.95–1.22)	0.23
Esketamine (mg/kg)	1.06 (0.91–1.24)	0.46
Propofol (10 mg/kg)	1.04 (0.96–1.12)	0.37
Midazolam (mg/kg)	1.02 (0.96–1.08)	0.58
Oxazepam (10 mg)	1.04 (0.81–1.32)	0.79
Morphine (mg)	0.98 (0.94–1.02)	0.23
Sufentanil (10 µg/kg)	1.05 (0.95–1.16)	0.36

^a NPD group was used as reference.

similarly established an association between delirium duration and long-term cognitive impairment [9], adding to the body of evidence suggesting that delirium duration is likely to be considered as a

significant indicator of delirium severity, affecting both short- and long-term outcomes. However, additional research, using the CAM-ICU-7 [36] or DRS-R-98 [37] as a validated measure for the ICU and ward, respectively, is needed to further examine the exact role of delirium duration as a marker for delirium severity.

This study has several limitations that need to be considered. First, this was a retrospective cohort study, which could have biased our results, since for instance information regarding pre-existing dementia was lacking. However, only few patients with dementia are admitted to the ICU in the Netherlands [38]. Furthermore, given the very large sample size and the fact that delirium is an area of permanent interest in our ICU since 2007 [23], we feel that the most relevant factors were included in this large cohort database, for which data are collected on a regular base.

Second, as clear criteria for defining persistent delirium are lacking, we were forced to define this entity ourselves and use a predetermined cut-off value of ≥14 days of delirium. Although this definition was deliberately chosen based on consensus of delirium experts and in conformity the DSM-5 criteria [18], this cut-off value could have attributed to the differences regarding duration related ICU outcome variables between the PD and NPD group. However, given the fact that delirium assessments were collected throughout the entire hospital stay, the attributable effect of the cut-off value on these differences was attenuated.

Table 3Associations of delirium duration with extended^a duration of mechanical ventilation, extended^a hospital stay and in-hospital mortality, adjusted for relevant covariates.

Factor	Extended duration of mechanical ventilation (≥2 days)		Extended hospital stay (≥17 days)		In-hospital mortality	
	Adjusted OR (95%CI)	P-value	Adjusted OR (95%CI)	P-value	Adjusted OR (95%CI)	P-value
Delirium duration (days)	1.04 (1.01–1.08)	0.01	1.23 (1.19–1.27)	<0.001	0.99 (0.98–1.01)	0.45
Male sex	1.38 (1.25–1.53)	<0.001	0.87 (0.78–0.97)	0.01	0.83 (0.70–0.99)	0.04
Age (years)	1.00 (1.00–1.00)	0.59	1.00 (0.99–1.00)	0.03	1.04 (1.04–1.05)	<0.001
Pre-admission comorbidity	1.33 (1.16–1.52)	<0.001	0.88 (0.77–1.00)	0.05	0.96 (0.80–1.14)	0.062
Admission type						
Elective surgical	Ref.		Ref.		Ref.	
Emergency surgical	1.45 (1.23–1.71)	<0.001	2.09 (1.77–2.47)	<0.001	7.58 (5.75–10.00)	<0.001
Medical	1.19 (1.04–1.37)	0.01	1.34 (1.17–1.54)	<0.001	11.60 (9.05–14.85)	<0.001
Mean SOFA score during ICU admission	1.36 (1.33–1.39)	<0.001	1.01 (0.99–1.03)	0.46	1.44 (1.40–1.49)	<0.001
Days spent in ICU	1.62 (1.56–1.68)	<0.001	1.21 (1.19–1.22)	<0.001	1.02 (1.02–1.03)	<0.001

^a The highest quartile of the variables were used as a cut-off value prior to dichotomization.

Third, assessments for delirium presence during ward stay were not always consistently performed, especially when patients did not show any signs of delirium. Moreover, non-delirium and comatose days in between were not included in the summation for delirium duration. This could have resulted in an underestimation of delirium duration in some cases. However, patients who have or had delirium who are discharged from the ICU to the ward, are protocolized to be assessed for delirium during ward stay, which may limit underdiagnosis.

Fourth, this was a single center study, which may diminish the generalizability of the results. However, given the sample size of over 10,000 patients, whom were assessed for delirium by well-trained nurses, using the guideline recommended CAM-ICU or DOS and given the demographic and delirium characteristics of our cohort, which seem to be in line with other studies [5,6,20], we believe this effect remains marginal.

The results of this study can help both physicians and nurses in daily practice to identify patients who could be at risk to develop a persistent ICU delirium. Moreover, the deleterious outcomes associated with delirium duration should, once more, urge every healthcare professional to take each and every measure available to prevent, and if necessary, recognize and treat ICU delirium [13,39]. Future research on persistent delirium is required to focus further on both risk factors (for example by analyzing real-time hemodynamical and ventilatory data using artificial intelligence techniques) and long-term outcomes as quality of life, mental problems (anxiety, depression, post-traumatic stress disorder) and cognitive impairment.

5. Conclusions

Patients with persistent delirium differ on several aspects from patients with non-persistent delirium or no delirium: they were older, more severely ill, and had worse short-term outcomes, including longer duration of coma and mechanical ventilation, a longer ICU and hospital stay, more ICU readmissions and a higher mortality rate. Multiple patient related factors showed associations with persistent delirium, of which the use of physical restraints was the most strongly associated.

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Declarations of interest

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Authors' contributions

RK and MvdBo contributed to study concept and design, RK merged all data, performed the analysis and drafted and edited the final manuscript. MvdBo supervised RK during the process. MvdBe, AS and MP contributed to critical revision of the manuscript. All authors read and approved the final manuscript.

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