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Differences in long-term outcomes between ICU patients with persistent delirium, non-persistent delirium and no delirium: A longitudinal cohort study

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ABSTRACT

Purpose: Determine differences in physical, mental and cognitive outcomes 1-year post-ICU between patients with persistent delirium (PD), non-persistent delirium (NPD) and no delirium (ND).
Materials and methods: A longitudinal cohort study was performed in adult ICU patients of two hospitals admitted between July 2016–February 2020. Questionnaires on physical, mental and cognitive health, frailty and QoL were completed regarding patients' pre-ICU health status and 1-year post-ICU. Delirium data were from patients' total hospital stay. Patients were divided in PD (≥14 days delirium), NPD (<14 days delirium) or ND patients.
Results: 2400 patients completed both questionnaires, of whom 529 (22.0%) patients developed delirium; 35 (6.6%) patients had PD and 494 (93.4%) had NPD. Patients with delirium (PD or NPD) had worse outcomes in all domains compared to ND patients. Compared to NPD, more PD patients were frail (34.3% vs. 14.6%, $p = 0.006$) and fatigued (85.7% vs. 61.1%, $p = 0.012$). After adjustment, PD was significantly associated with long-term cognitive impairment only (aOR 3.90; 95%CI 1.31–11.63).
Conclusions: Patients with PD had a higher likelihood to develop cognitive impairment 1-year post-ICU compared to NPD or ND. Patients with PD and NPD were more likely to experience impairment on all health domains (i.e. physical, mental and cognitive), compared to ND patients.

1. Introduction

Delirium is an acute neuropsychiatric syndrome occurring as a consequence of a medical condition and is characterized by a disturbance in consciousness and cognition, with a fluctuating course and developing mostly in vulnerable patients (e.g., the elderly, critically ill patients) [1-3]. It is a form of acute encephalopathy, involving a rapidly developing pathobiological process in the brain which leads to changes from baseline cognitive status [4]. Delirium is a common occurring syndrome in the intensive care unit (ICU), with prevalence rates of over 50% in mechanically ventilated patients [1,5,6].

The median duration of ICU delirium is two to three days [7,8], but persisting delirium, defined by the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-V) as an episode of delirium which lasts for weeks or months, has also been reported [2,7]. Several risk factors for persisting delirium have been identified, e.g., advanced age,

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; CAM-ICU, Confusion Assessment Method for the ICU; CFQ, Cognitive Failure Questionnaire; CFS, Clinical Frailty Scale; CIS-8, Checklist Individual Strength; DOS, delirium observation screening; DSM-V, Diagnostic and Statistical Manual of Mental Disorders, 5th edition; EQ-5D-5L, EuroQol 5 dimensional 5-level; HADS, Hospital Anxiety and Depression Scale; IES-R, revised Impact of Event Scale; QoL, quality of life; LOS, length of stay; ND, no delirium; NPD, non-persistent delirium; PD, persistent delirium; PICS, Post-Intensive Care Syndrome; PTSD, post-traumatic stress disorder; RASS, Richmond Agitation Sedation Scale.

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use of high dosages of opioids or benzodiazepines, use of physical restraints, and longer duration of coma and mechanical ventilation [9,10].

ICU delirium in general is associated with poorer short-term and long-term outcomes, including cognitive impairment and reduced quality of life (QoL) [3,11-13]. ICU patients with persistent delirium (PD), defined as ≥14 delirium days, had a longer ICU and hospital stay and a higher mortality rate [10]. However, only limited research on long-term outcomes has been performed in patients with persisting delirium, where definitions varied and different cut-off points for PD (ranging from one week up to several months) were used. Most studies either excluded ICU patients or did not focus on long-term outcomes [9,14,15].

The aim of the present study was to determine differences in physical, mental and cognitive outcomes, frailty and quality of life 1-year post-ICU between patients with persistent delirium (PD), non-persistent delirium (NPD) and no delirium (ND).

2. Materials and methods

2.1. Study design and patients

This was a sub-study of the MONITOR-IC study (www.clinicaltrials.gov: NCT03246334) [16], an ongoing multicentre prospective cohort study measuring long-term outcomes of ICU survivors. The MONITOR-IC study was approved by the medical ethics committee of the Radboud University Medical Center (Radboudumc), CMO region Arnhem-Nijmegen, The Netherlands (IRB approval and registration number 2016–2724). Each participant or their legal representative provided written informed consent.

The present study includes all patients admitted to the ICUs of a university hospital (Radboudumc) and a non-university hospital (Jeroen Bosch Hospital) in the Netherlands that consented to follow-up. Inclusion of participants in the Radboudumc took place from inception of the MONITOR-IC study in July 2016 till February 2020, and in the Jeroen Bosch Hospital between October 2018 and February 2020. Patients aged <18 years, admitted to the ICU <12 h, or patients who could not be assessed for delirium (e.g., due to language problems or a persistent comatose condition) were excluded.

2.2. Delirium measurement and definitions

Assessment of delirium was performed from hospital admission to discharge. Presence of delirium during ICU stay was assessed three times daily by well-trained ICU nurses using the Confusion Assessment Method for the ICU (CAM-ICU) [17,18], including assessment of the level of arousal using the Richmond Agitation Sedation Scale (RASS) [19-21]. Patients with a RASS score of −4 or − 5 were considered comatose. Likewise, delirium during ward stay was assessed three times daily by means of the Delirium Observation Screening (DOS) scale [22]. Patients were considered delirious if they scored either CAM-ICU or DOS positive at least once on that day or were treated with antipsychotics (haloperidol or quetiapine) for no other reason than delirium. Delirium duration was calculated by summing all days with positive delirium assessments, while excluding non-delirium and comatose days in between. For example, a patient could either have positive delirium assessments on day 1 till 5 or on day 1, 3, 4, 8 and 9, which would both result in a delirium duration of 5 days. PD was defined as a total delirium duration of 14 days or more, which is in consonance with the definition of PD according to the DSM-V criteria [2,10]. Delirium duration shorter than 14 days was considered NPD and patients without delirium days were allocated to the ND group.

2.3. Demographics and outcome measures

Patient demographics and clinical variables (e.g. pre-admission comorbidity, admission type, severity of illness (Acute Physiology and Chronic Health Evaluation [APACHE]-IV score) and ICU and hospital length of stay (LOS) were obtained from the medical health record. Data on delirium duration were collected retrospectively from the patients' records.

Baseline and 1-year post-ICU health measures were assessed using validated patient reported questionnaires in the different health domains (i.e. physical, mental and cognitive domain), frailty and QoL. The paper-based or online questionnaires were filled out by patients, or, in case they were unable to do so, their relatives. Elective ICU patients received the baseline questionnaire at the preoperative outpatient clinic, while emergently admitted patients (or their proxies) received the questionnaire early after ICU admission, thus rating their health status retrospectively.

2.4. Physical health

Fatigue was assessed by using the Checklist Individual Strength (CIS-8), including eight questions with a 7-point rating scale. The total score ranges from 8 to 56, where fatigue is indicated by a score of 27 or higher [23].

New physical problems, subsequent to ICU admission, (e.g. pain, muscle weakness, shortness of breath) were measured using a 30-item questionnaire with a 4-point Likert scale [24]. Answers were dichotomized into 'no problems' (no or mild problems) or 'problems' (moderate or severe problems).

2.5. Mental health

Symptoms of anxiety and depression were measured with the Hospital Anxiety and Depression Scale (HADS), which includes an anxiety (HADS-A) and a depression subscale (HADS-D), both consisting of seven items with a 4-point Likert scale resulting in a total score ranging from 0 to 21 for each subscale. A score of 8 or higher on the HADS-A or HADS-D indicates symptoms of anxiety or depression, respectively [25].

Post-traumatic stress disorder (PTSD) symptoms were assessed using the revised Impact of Event Scale (IES-R). This scale includes 22 questions and scoring on each item ranges from 0 to 4. PTSD symptoms were considered present when the mean score on all items was 1.6 or higher [26,27].

2.6. Cognitive health

Cognitive functioning was assessed using the abbreviated Cognitive Failure Questionnaire (CFQ), consisting of 14 questions with answer scores ranging from 0 to 4 [28]. This questionnaire covers cognitive functioning in daily life, such as memory and perception. Scores were transformed to a 0–100 range and a total of >43 points was considered as cognitive impairment [29,30]. The CFQ was added to the MONITOR-IC questionnaires in January 2017 and was evaluated for all patients admitted after.

2.7. Frailty and quality of life

Frailty was assessed with the Clinical Frailty Scale (CFS) [31]. This is a one-item scale on which a score of 1 indicates a very fit person, and a score of 9 indicates a terminally ill person. Results were dichotomized into 'frail' (score 5–9) and 'non-frail' (score 1–4) [32].

Quality of life was assessed using the EuroQol 5 dimensional 5-level (EQ-5D-5L) questionnaire [33], which covers five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), with five levels of response (no problems, slight problems, moderate problems, severe problems, extreme problems/unable to). A health state index value was calculated from individual health profiles using the Dutch standard reference value set [34]. Health state index values range from −0.446 (worse than death) to 1 (the value of full health).

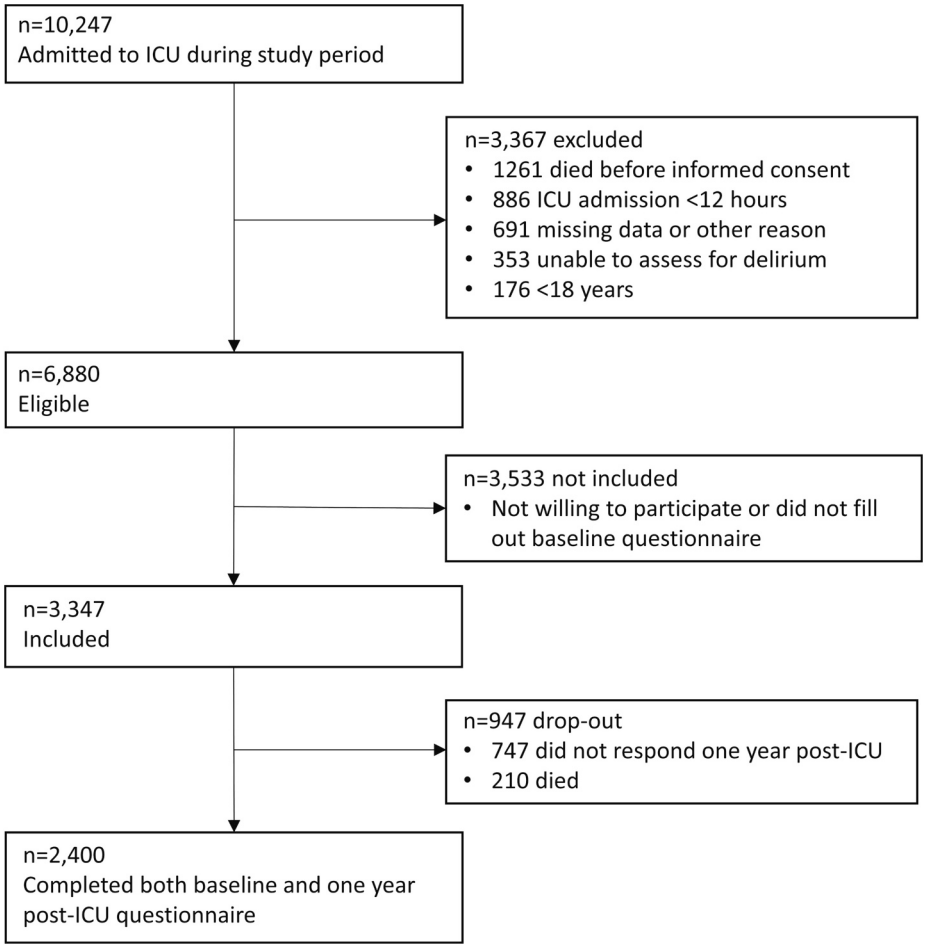

Fig. 1. Flow chart.

2.8. Statistical analysis

Patients who did not complete both baseline and one-year questionnaires were excluded from the analyses. Possible selection bias was assessed by comparing differences in several characteristics between responders and non-responders (i.e., participants who filled out baseline questionnaires but did not complete one-year questionnaires). Missing data in the patient reported questionnaires were extrapolated using the half rule or, for the IES-R, replaced with the individual mean. This last method was only applied when 75% of the items on the questionnaire were completed.

Demographics, baseline and one-year outcome data were examined using descriptive statistics. Categorical variables were reported as proportions and continuous variables were reported as either means with standard deviation (SD) or medians with interquartile range (IQR), depending on the distribution of the data. Differences between the groups were tested using Chi-squared test, Fisher's exact test, independent *t*-test, Mann-Whitney *U* test, one-way ANOVA or Kruskal Wallis test, as appropriate. Different cut off points for delirium duration (1–6, 7–13 or ≥ 14 days) were used to perform sensitivity analyses [10].

Differences in long-term outcomes between the PD, NPD and ND group were determined by comparing both 1-year post-ICU prevalence scores of the patient reported outcome measures as well as by subtracting baseline outcome scores from the 1-year post-ICU scores. To examine associations of PD, NPD and ND with long-term outcomes in the physical, mental and cognitive domains, the patient reported outcomes were first dichotomized using the prespecified cut-off values and subsequently aggregated into a physical (including fatigue and new physical problems), mental (including anxiety, depression, and PTSD symptoms) and cognitive (cognitive impairment) composite score. An abnormal composite score was defined as ≥1 abnormal separate patient reported outcome (e.g., a patient with anxiety symptoms but no depression or PTSD symptoms was considered to have an abnormal mental composite score). Univariable and multivariable logistic regression analyses were performed for PD and NPD groups, with the ND group as reference. Baseline measures for fatigue, anxiety, depression and cognitive functioning were entered as covariables in the multivariable model along with the predetermined variables gender, age, pre-admission comorbidity, admission type, APACHE-IV score, hospital LOS, duration of mechanical ventilation and use of physical restraints [35]. Due to multicollinearity with the variable duration of mechanical ventilation, ICU LOS was excluded from the model. A two-sided *P*-value <0.05 was considered statistically significant. All data were analyzed using IBM SPSS Statistics version 25.0.

3. Results

From a total of 10,247 admitted patients, 6880 patients (67.1%) were eligible. Main exclusion reasons were an ICU admission <12 h (n = 886, 8.9%) and death before informed consent (n = 1261, 12.3%). Of all eligible patients, 3347 (48.6%) patients were included, of whom 2400 patients (71.7%) survived at least one year and completed both questionnaires (Fig. 1). Data on missing values are demonstrated in Supplemental Table 1. A comparative analysis between responders and non-responders is shown in Supplemental Table 2.

In total, 529 patients (22.0%) developed delirium, of which 35 (6.6%) patients had PD and 494 (93.4%) patients had NPD. In 15.9% of the delirium cases, delirium was diagnosed based only on the use of

Table 1
Demographics and baseline characteristics.

Characteristics	Total ($N = 2400$)		Persistent delirium (PD) ($n = 35$)		Non-persistent delirium (NPD) ($n = 494$)		No delirium (ND) ($n = 1871$)	
Patient characteristics								
Male sex, *n* (%)	1651	(68.8)	20	(57.1)	335	(67.8)	1296	(69.3)
Age (years), mean (± SD)	63.3	± 12.5	69.7	± 8.9[b,c]	63.7	± 12.9	63.1	± 12.5
Pre-admission comorbidity, n (%)	1835	(76.5)	21	(60.0)	329	(66.6)	1485	(79.4)[a,b*]
Cardiovascular	1282	(53.4)	12	(34.3)	211	(42.7)	1059	(56.6)[a,b*]
Respiratory	259	(10.8)	5	(14.3)	68	(13.8)[c]	186	(9.9)
Malignancy/impaired immunity	450	(18.8)	5	(14.3)	83	(16.8)	362	(19.3)
Diabetes mellitus	288	(12.0)	5	(14.3)	59	(11.9)	224	(12.0)
Pre-ICU health status								
Physical health								
Fatigue, *n* (%)	1456	(60.7)	22	(62.9)	300	(60.7)	1134	(60.6)
Mental health								
Anxiety symptoms, n (%)	570	(23.8)	10	(28.5)	140	(28.3)[c]	420	(22.4)
Depression symptoms, n (%)	515	(21.5)	3	(8.6)	124	(25.1)	388	(20.7)
Cognitive health								
Abnormal cognitive functioning, n (%)	109	(4.5)	0	(0)	27	(5.5)	82	(4.4)
Quality of life								
Frail, *n* (%)	245	(10.2)	3	(8.6)	59	(11.9)	183	(9.8)
EQ-5D-5L index value, median [IQR]	0.81	[0.65–0.89]	0.79	[0.70–0.89]	0.81	[0.60–0.89]	0.82	[0.66–0.89]
ICU characteristics								
Urgent admission, *n* (%)	819	(34.1)	28	(80.0)[b,c*]	285	(57.7)[c*]	506	(27.0)
Planned admission, *n* (%)	1581	(65.9)	7	(20)	209	(42.3)[a]	1365	(73.0)[a*,b*]
Elective cardiac surgery, *n* (%)	1158	(48.3)	7	(20)	162	(32.8)	989	(52.9)[a*,b*]
APACHE IV score, mean (± SD)	54.2	± 19.4	78.5	± 28.3[b*,c*]	63.7	± 23.1[c*]	51.3	± 16.9
Delirium duration (days), median [IQR]	0	[0–0]	20	[15–24][b,c*]	2	[1–4][c*]	n.a.	
Ward delirium days	0	[0–0]	6	[0–13][b*,c*]	0	[0–1][c*]	n.a.	
ICU delirium days	0	[0–0]	14	[8–21][b*,c*]	1	[1–3][c*]	n.a.	
Mechanically ventilated, *n* (%)	1783	(74.3)	35	(100)[b,c*]	442	(89.5)[c*]	1306	(69.8)
Mechanical ventilation days, median [IQR]	1	[0–2]	16	[8–26][b*,c*]	2	[1–8][c*]	1	[0–2]
Physical restraints, *n* (%)	934	(38.9)	32	(91.4)[b,c*]	322	(65.2)[c*]	580	(31.0)
ICU LOS, median [IQR]	2	[2-3]	23	[17–29][b*,c*]	4	[2−10][c*]	2	[2-2]
Hospital LOS, median [IQR]	10	[7-15]	41	[30–55][b*,c*]	15	[10–27][c*]	9	[7-13]

Abbreviation definitions: APACHE IV = Acute Physiology and Chronic Health Evaluation IV; EQ-5D-5L = EuroQol 5-dimensional 5-level; ICU=Intensive Care Unit; IQR = interquartile range; LOS = length of stay; SD = standard deviation.
[a] Significantly higher than persistent delirium; [b]Significantly higher than non-persistent delirium; [c]Significantly higher than no delirium; *$P < 0.001$. All significance values were adjusted by the Bonferroni correction for multiple testing.

antipsychotics and not on positive CAM-ICU/DOS scores. This occurred only in the NPD group, the median number of delirium days of these patients was 1 day [IQR 1–2].

3.1. Differences between PD, NPD and ND groups for patient and ICU characteristics

Patients with PD were significantly older than NPD and ND patients (mean age, 69.7, 63.7 ($p = 0.02$) and 63.1 years ($p < 0.01$), respectively), were more often urgently admitted to the ICU (80%, 57.7% ($p = 0.03$) and 27% ($p < 0.001$), respectively), had higher mean APACHE IV scores (78.5, 63.7 and 51.3, both $p < 0.001$), were more frequently physically restrained and had a longer duration of mechanical ventilation, ICU and hospital LOS (Table 1). Except for anxiety symptoms, which were more frequent in NPD patients compared to ND patients (28.3% versus 22.4%, $p = 0.015$), no significant differences were found in baseline reported health measures between the three groups (Table 1).

Sensitivity analyses with different cut-off points regarding delirium duration are shown in Supplemental Table 3.

3.2. Long-term patient reported outcomes

As compared to ND patients, patients with delirium (both PD and

Table 2
Long-term patient reported outcomes on separate health domains.

Domains	Total (N = 2400)		Persistent delirium (PD) (n = 35)		Non-persistent delirium (NPD) (n = 494)		No delirium (ND) (n = 1871)	
Physical health								
Fatigue, *n* (%)	1247	(51.9)	30	(85.7)[b,c*]	302	(61.1)[c*]	915	(48.9)
New physical complaints, median [IQR]	1	[0–3]	3	[1–5][c]	2	[0–4.25][c*]	1	[0–3]
Mental health								
Anxiety symptoms, *n* (%)	467	(19.5)	13	(37.1)[c]	135	(27.3)[c*]	319	(17.0)
Depression symptoms, *n* (%)	503	(21.0)	15	(42.9)[c]	142	(28.7)[c*]	346	(18.5)
PTSD symptoms, *n* (%)	120	(5.0)	1	(2.9)	34	(6.9)	85	(4.5)
Cognitive health								
Abnormal cognitive functioning, *n* (%)	223	(9.3)	7	(20.0)[c]	62	(12.6)[c]	154	(8.2)
Quality of life								
Frail, *n* (%)	223	(9.3)	12	(34.3)[b,c*]	72	(14.6)[c*]	139	(7.4)
EQ-5D-5L index value, median [IQR]	0.85	[0.73–1.00]	0.72	[0.59–0.85]	0.79	[0.65–0.89]	0.85	[0.74–1.00][a*,b*]

Abbreviation definitions: EQ-5D-5L = EuroQol 5-dimensional 5-level; IQR = interquartile range; PTSD = post-traumatic stress disorder.
[a] Significantly higher than persistent delirium; [b] Significantly higher than non-persistent delirium; [c] Significantly higher than no delirium; *$P < 0.001$. All significance values were adjusted by the Bonferroni correction for multiple testing.

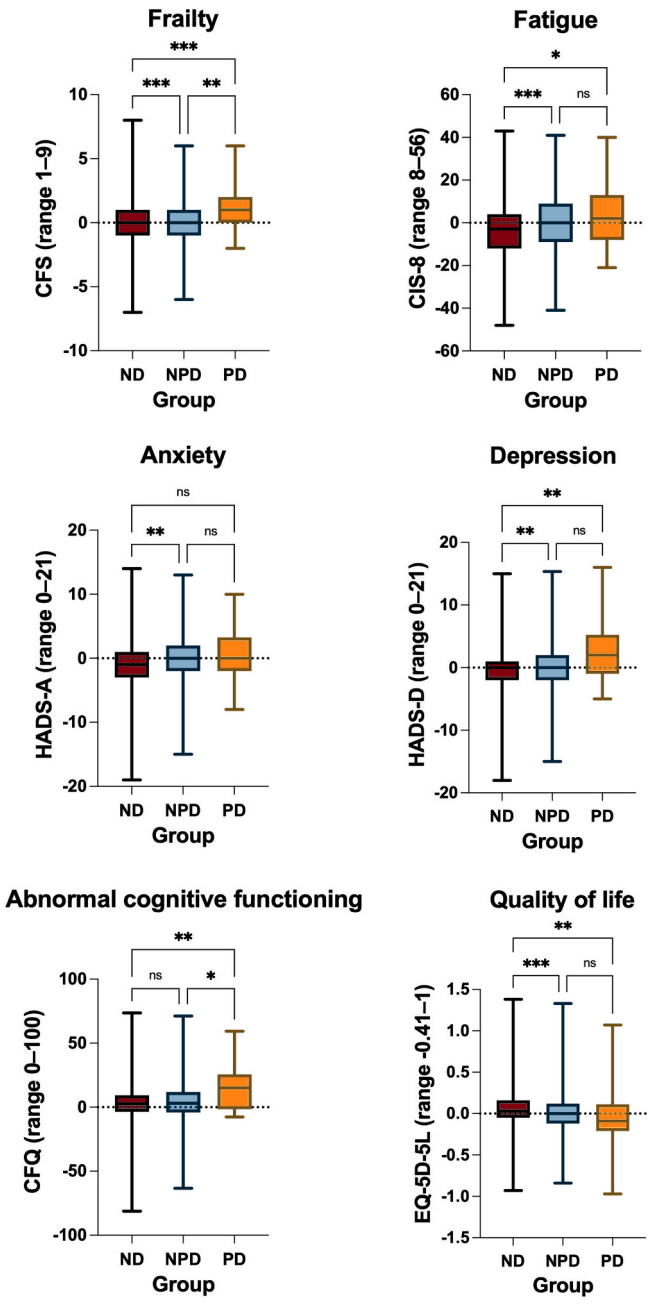

Fig. 2. Time differences in patient reported outcomes from baseline to 1-year post-ICU.
Abbreviations: CFS = Clinical Frailty Scale; CIS-8 = Checklist Individual Strength; HADS = Hospital Anxiety and Depression Scale; CFQ = Cognitive Failure Questionnaire; EQ-5D-5L = EuroQol 5-dimensional 5-level; ND = no delirium; NPD = non-persistent delirium; PD = persistent delirium.
*** $p < 0.001$
** $p < 0.01$.
* $p < 0.05$.
ns = not significant.

NPD) had worse 1-year outcomes on all separate health domains. Patients with delirium were more likely to experience fatigue (85.7% and 61.1% vs. 48.9%, both $p < 0.001$), to have anxiety (37.1% and 27.3% vs. 17.0%, $p = 0.006$ and $p < 0.001$, respectively) and depression symptoms (42.9% and 28.7% vs. 18.5%, $p = 0.001$ and $p < 0.001$, respectively) and reported significantly more cognitive impairment (20% and 12.6% vs. 8.2%, $p = 0.02$ and $p = 0.004$, respectively) and a lower quality of life (median EQ-5D-5L index value, 0.72 and 0.79 vs. 0.85, both $p < 0.001$). No differences in occurrence of PTSD symptoms were found. Compared to NPD, PD patients were more likely to be frail (34.3% vs. 14.6%, $p = 0.006$) and fatigued (85.7% vs. 61.1%, $p = 0.012$) (Table 2).

Differences in patient reported outcomes between baseline and 1-year post-ICU are shown in Fig. 2 and Supplemental Table 4. Compared to the NPD group, as well as the ND group, PD patients had a greater increase in frailty (median difference, [IQR]; 1 [0–2] vs. 0 [−1–1], $p = 0.002$ and 0 [−1–1], $p < 0.001$, respectively) and cognitive impairment (median difference, [IQR]; 15.1 [−1.6–25.6] vs. 3.1 [−4.1–11.9], $p = 0.02$ and 2.6 [−3.6–9.4], $p = 0.007$, respectively) after one year (Supplemental Table 4).

3.3. Associations of PD and NPD with long-term outcomes

In the unadjusted model, both PD and NPD were significantly associated with physical, mental and cognitive impairment (Supplemental Table 5). After adjusting for predetermined covariables, PD was significantly associated only with cognitive impairment in the long term (adjusted odds ratio (aOR) 3.90; 95%CI 1.31–11.63) (Table 3).

4. Discussion

This multicentre cohort study showed that patients with delirium (PD and NPD) had worse outcomes in the physical, mental and cognitive health domain, and reported a lower quality of life one year after ICU admission compared to patients without delirium. Patients with PD were more likely to experience frailty and fatigue compared to NPD or ND patients. After correction for predetermined covariables, PD only remained significantly associated with cognitive impairment in the long-term.

This is the first study that used delirium data of patients' complete hospital stay, including the ICU and studied different duration groups of delirium and its relation with 1-year outcome, including Post-Intensive Care Syndrome (PICS), frailty and quality of life.

To date, studies have not been able to identify clearly which patients are more at risk for developing cognitive impairment [1,3,8,11-13,36-39]. Nonetheless, one study demonstrated that elevated serum levels of amyloid-β were found in delirious patients and were correlated with cognitive impairment, and so delirium might represent an early stage of dementia [40]. However, these findings only suggest a correlation between the two factors, without implying a causal relationship. As shown in the present study, not only the occurrence, but also duration of delirium is associated with development of cognitive impairment. These findings are consistent with other literature on delirium, where longer duration of delirium was found to be associated with more cognitive dysfunction [3,11,13,37,41].

After an ICU stay for critical illness, many ICU survivors experience physical, mental and cognitive health problems known as the Post-Intensive Care Syndrome (PICS) [42], which may last long beyond hospitalization and highly impacts daily functioning and quality of life. Although PICS has increasingly gained recognition in recent years, the impact of ICU delirium on PICS has not yet been investigated. Previous literature has shown pre-ICU health status to be strongly associated with health problems in the long term after an ICU stay [24,43-45]. The present study provides new insights into the association between duration of delirium with the different domains of PICS and quality of life in the long-term. All used questionnaires are well validated for its use in the specific domain. This could issue a possible interaction, as it is possible that patients that are somewhat cognitively impaired, also experience a degree of depression as a result of this. However, the core set of instruments advises to use symptom specific questionnaires and an overall quality of life questionnaire to determine patients' functioning [46]. Therefore, we measured all these concepts with validated questionnaires, accepting some degree of overlap.

The remarkably large proportion of pre-admission comorbidity in the ND group compared to the NPD and PD group can be explained by

Table 3
Associations of persistent and non-persistent delirium with long-term outcomes in a multivariable logistic regression model.

Variables	Physical composite score *Fatigue or ≥2 new physical complaints*		Mental composite score *Anxiety, depression, or PTSD symptoms*		Cognitive impairment	
	aOR (95%CI)	*P*-value	aOR (95%CI)	*P*-value	aOR (95%CI)	*P*-value
No delirium	Ref.	n.a.	Ref.	n.a.	Ref.	n.a.
Non-persistent delirium	1.27 (0.96–1.69)	0.10	1.20 (0.90–1.60)	0.21	1.24 (0.80–1.93)	0.33
Persistent delirium	2.28 (0.59–8.75)	0.23	0.68 (0.26–1.79)	0.44	3.90 (1.31–11.63)	0.015
Male sex	0.65 (0.52–0.81)	<0.001	0.86 (0.68–1.07)	0.18	0.97 (0.69–1.37)	0.86
Age (years)	1.01 (1.00–1.02	0.004	1.02 (1.01–1.03)	<0.001	0.98 (0.97–1.00)	0.01
Pre-admission comorbidity	1.04 (0.78–1.39)	0.80	0.81 (0.60–1.09)	0.16	0.57 (0.37–0.87)	0.01
BL fatigue	3.66 (2.95–4.53)	<0.001	1.67 (1.30–2.13)	<0.001	1.42 (0.94–2.13)	0.10
BL anxiety or depression	1.62 (1.30–2.02)	<0.001	5.54 (4.41–6.96)	<0.001	2.37 (1.65–3.41)	<0.001
BL cognitive impairment	2.04 (1.19–3.49)	0.01	2.18 (1.39–3.43)	0.001	8.86 (5.58–14.07)	<0.001
Urgent admission	1.98 (1.50–2.62)	<0.001	2.05 (1.54–2.74)	<0.001	1.57 (1.02–2.41)	0.04
APACHE IV score	1.00 (0.99–1.00)	0.10	1.00 (0.99–1.01)	0.66	1.01 (1.00–1.02)	0.21
Mechanical ventilation days	1.02 (0.98–1.05)	0.37	1.01 (0.98–1.03)	0.70	0.99 (0.96–1.03)	0.65
Use of physical restraints	1.19 (0.96–1.48)	0.11	1.17 (0.93–1.48)	0.18	0.98 (0.68–1.42)	0.93
Hospital LOS	1.02 (1.00–1.02)	0.01	1.01 (1.00–1.02)	0.18	1.00 (0.98–1.02)	0.80

Abbreviation definitions: aOR = adjusted Odds Ratio; APACHE IV = Acute Physiology and Chronic Health Evaluation IV; BL = baseline; CI = confidence interval; LOS = length of stay; PTSD = post-traumatic stress disorder.

the large number of cardiac surgery patients in this group. However, since nearly 15% (169 of 1158 patients) of the cardiac surgery patients developed delirium, we chose not to exclude this group from the analyses.

This study has some limitations. First, the design of the MONITOR-IC study might have introduced some bias. Patients filled out the baseline questionnaires retrospectively, which might have induced recall bias. However, the patients' pre-admission health status was evaluated as shortly as possible after admission and, if possible, with help of proxies. Moreover, electively admitted patients answered the baseline questionnaires prospectively. Second, a group of 947 patients was identified as non-responder. As shown in Supplemental table 1, significantly worse baseline values on multiple levels (demographics, admission type, ICU data) were found in non-responders compared to responders. This might have resulted in underestimation of the long-term outcomes since pre-ICU health status is known to be a strong predictor for long-term outcome [35]. Furthermore, patients that did not participate in the MONITOR-IC study were not included in the analyses of the present study, which might have introduced some selection bias. Also, in the Netherlands, it is not common to admit patients with severe cognitive impairment to the ICU, only patients with mild cognitive impairment are admitted to the ICU. Third, relatively many participants had missing data regarding abnormal cognitive functioning, because the CFQ was added to the questionnaires in 2017, six months after the start of inclusion of the MONITOR-IC study. This could have influenced the results of the regression analyses. Fourth, data on delirium assessments were collected retrospectively, in contrast to the design of the MONITOR-IC study. Delirium duration was calculated as the cumulative number of delirium days, and since comatose days and days without a registered positive CAM-ICU or DOS score were considered as non-delirium days, this might have caused underreporting of delirium duration (e.g., not reported three times daily in the patients' file). Previous literature has shown that delirium is often underdiagnosed or underreported in general wards [47-50]. However, in both participating centers, delirium screening is well-implemented and is a great point of interest in both care and research. Furthermore, in this study we included ward data, which provides a complete view on ICU delirium. Fifth, possible treatment of mental problems could have affected the results on long-term outcomes. However, information on mental treatment was not collected in any of the groups. Therefore, we can only speculate that mental treatment may have affected our results.

5. Conclusions

One year after ICU admission, patients with delirium (PD and NPD) were more likely to experience impairment on all health domains (i.e. physical, mental and cognitive) and QoL, as compared to ND patients. Furthermore, PD patients were more likely to be frail and fatigued, compared to NPD or ND patients. After adjusting for relevant covariables, PD remained significantly associated only with experienced cognitive impairment in the long term. The present study is the first to provide insight into long-term outcomes on multiple health domains of patients who developed delirium (PD or NPD) or no delirium during their ICU stay. This study suggests that besides presence, also duration of delirium may play an important role in the development of cognitive impairment. These findings support the general view that stresses the importance of prevention, early recognition and management of ICU delirium.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2023.154277.

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Differences in long-term outcomes between ICU patients with persistent, non-persistent and no delirium: A longitudinal cohort study

Supplementals

Supplemental table 1. Missing values of patient reported outcomes

	Total (n=2400)		Persistent delirium (PD) (n=35)		Non-persistent delirium (NPD) (n=494)		No delirium (ND) (n=1871)	
	T0, *n (%)*	**T3, *n (%)***	**T0, *n (%)***	**T3, *n (%)***	**T0, *n (%)***	**T3, *n (%)***	**T0, *n (%)***	**T3, *n (%)***
Physical health *n* (%)								
Fatigue	18 (0.8)	14 (0.6)	0 (0)	0 (0)	6 (1)	2 (0.4)	12 (0.6)	8 (0.4)
New physical complaints median	-	0 (0)	-	0 (0)	-	0 (0)	-	0 (0)
Mental health, *n* (%)								
Anxiety symptoms	10 (0.4)	6 (0.3)	1 (3)	0 (0)	4 (0.8)	1 (0.2)	5 (0.3)	5 (0.3)
Depression symptoms	8 (0.3)	7 (0.3)	1 (3)	0 (0)	3 (0.6)	2 (0.4)	4 (0.2)	5 (0.3)
PTSD symptoms	-	34 (1)	-	1 (3)	-	13 (3)	-	20 (1)
Cognitive health, *n* (%)								
Abnormal cognitive functioning	321 (13)	144 (6)	6 (17)	4 (11)	88 (18)	40 (8)	227 (12)	100 (5)
Quality of life, *n* (%)								
Frail	12 (0.5)	8 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)	12 (0.6)	8 (0.4)
EQ-5D-5L index value	39 (2)	32 (1)	0 (0)	1 (3)	11 (31)	9 (2)	28 (1.5)	22 (1)

Abbreviation definitions: *T0 = pre-admission, T3 = 1-year post-ICU*
EQ-5D-5L= EuroQol 5-dimensional 5-level; IQR=interquartile range; PTSD=post-traumatic stress disorder.

Supplemental table 2. Comparison of demographics and baseline characteristics between responders and non-responders

	Responders (n=2400)	Non-responders (n=947)	*P*-value
Male sex, *n* (%)	1651 (68.8)	587 (62.0)	<0.001
Age (years), mean (± SD)	63.3 ± 12.5	61.5 ± 15.0	0.001
Pre-admission comorbidity, n (%)	1835 (76.5)	737 (77.8)	0.40
Physical health			
Fatigue, *n* (%)	1456 (60.7)	648 (68.4)	<0.001
Mental health			
Anxiety symptoms, *n* (%)	570 (23.8)	303 (32.0)	<0.001
Depression symptoms, *n* (%)	515 (21.5)	309 (32.6)	<0.001
Cognitive health			
Abnormal cognitive functioning, *n* (%)	109 (4.5)	63 (6.7)	0.003
Quality of life			
Frail, *n* (%)	245 (10.2)	158 (16.7)	<0.001
EQ-5D-5L index value, median [IQR] **ICU characteristics**	0.81 [0.65-0.89]	0.77 [0.51-0.88]	<0.001
Urgent admission, *n* (%)	819 (34.1)	360 (38.0)	0.03
Planned admission, *n* (%)	1581 (65.9)	587 (62.0)	0.03
Elective cardiac surgery, *n* (%)	1158 (48.3)	353 (37.3)	<0.001
APACHE IV score, mean (± SD)	54.2 ± 19.4	54.4 ± 22.8	0.82
Delirium, *n* (%)	529 (22.0)	273 (28.8)	<0.001
Delirium duration (days), median [IQR] Ward delirium days	0 [0-0]	0 [0-1]	<0.001
ICU delirium days	0 [0-0]	0 [0-0]	0.01
Mechanically ventilated, *n* (%)	0 [0-0]	0 [0-1]	<0.001
Mechanical ventilation days, median [IQR]	1783 (74.3)	662 (69.9)	0.01
Physical restraints, *n* (%)	1 [0-2]	1 [0-2]	0.55
ICU LOS, median [IQR]	934 (38.9)	445 (47.0)	<0.001
Hospital LOS, median [IQR]	2 [2-3]	2 [2-4]	<0.001
Died within 1 year, *n* (%)	10 [7-15]	11 [7-17]	0.003
	0 (0)	210 (22.2)	<0.001

Abbreviation definitions: *APACHE IV=Acute Physiology and Chronic Health Evaluation IV; EQ-5D-5L= EuroQol 5-dimensional 5-level; ICU=Intensive Care Unit; IQR=interquartile range; LOS=length of stay; SD=standard deviation.*

Supplemental table 3. Sensitivity analysis with different cut-off points for delirium duration on baseline values

	1-6 days (n=428)	7-13 days (n=66)	>= 14 days (n=35)	*P*-value
Male sex, *n* (%)	294 (68.7)	41 (62.1)	20 (57.1)	0.25
Age (years), mean (± SD)	63.6 ± 13.1	64.5 ± 11.1	69.7 ± 8.9	0.02
Pre-admission comorbidity, n (%)	293 (68.5)	36 (54.5)	21 (60)	0.06
Physical health				
Fatigue, *n* (%)	259 (60.5)	41 (62.1)	22 (62.9)	0.95
Mental health				
Anxiety symptoms, *n* (%)	119 (27.8)	21 (31.8)	10 (29.4)	0.82
Depression symptoms, *n* (%)	105 (24.5)	19 (28.8)	3 (8.8)	0.07
Cognitive health				
Abnormal cognitive functioning, *n* (%) **Quality of life**	19 (4.4)	8 (12.1)	0 (0)	0.009
Frail, *n* (%)	50 (11.7)	9 (13.6)	3 (8.6)	0.75
EQ-5D-5L index value, median [IQR] **ICU characteristics**	0.81 [0.60-0.89]	0.81 [0.57-0.89]	0.79 [0.70-0.89]	0.99
Urgent admission, *n* (%)	234 (54.7)	51 (77.3)	28 (80)	<0.001
Planned admission, *n* (%)	194 (45.3)	15 (22.7)	7 (20)	<0.001
Elective cardiac surgery, *n* (%)	154 (36.0)	8 (12.1)	7 (20)	<0.001
APACHE IV score, mean (± SD)	62.8 ± 22.8	69.4 ± 23.9	78.5 ± 28.3	<0.001
Delirium duration (days), median	2 [1-3]	8 [8-11]	20 [15-24]	<0.001
[IQR] Ward delirium days	0 [0-1]	1 [0-4]	6 [0-13]	<0.001
ICU delirium days	1 [1-2]	7 [4-9]	14 [8-21]	<0.001
Mechanically ventilated, *n* (%)	377 (88.1)	65 (98.5)	35 (100)	0.004
Mechanical ventilation days, median	2 [1-6]	9 [5-15]	16 [8-26]	<0.001
[IQR] Physical restraints, *n* (%)	260 (60.7)	62 (93.9)	32 (91.4)	<0.001
ICU LOS, median [IQR]	3 [2-8]	14 [9-19]	23 [17-29]	<0.001
Hospital LOS, median [IQR]	14 [9-24]	29 [19-43]	41 [30-55]	<0.001

Abbreviation definitions: *APACHE IV=Acute Physiology and Chronic Health Evaluation IV; EQ-5D-5L= EuroQol 5-dimensional 5- level; ICU=Intensive Care Unit; IQR=interquartile range; LOS=length of stay; SD=standard deviation.*

Supplemental Table 4. Time differences in patient reported outcomes from baseline to 1-year post-ICU				
Change (Δ) in:	**Total (N=2400)**	**Persistent delirium (PD) (n=35)**	**Non-persistent delirium (NPD) (n=494)**	**No delirium (ND) (n=1871)**
Physical health				
Fatigue	-2 [-11 – 5]	2 [-8 – 13][c]	0 [-9 – 9][c*]	-3 [-12 – 4]
Mental health				
Anxiety symptoms	0 [-3 – 1]	0 [-2 – 3]	0 [-2 – 2][c]	-1 [-3 – 1]
Depression symptoms	0 [-2 – 2]	2 [-1 – 5][c]	0 [-2 – 2][c]	0 [-2 – 1]
Cognitive health				
Cognitive impairment	2.8 [-3.7 – 10.1]	15.1 [-1.6 – 25.6][b,c]	3.1 [-4.1 – 11.9]	2.6 [-3.6 – 9.4]
Quality of life				
Frailty[1]	0 [-1 – 1]	1 [0 – 2][b,c*]	0 [-1 – 1][c*]	0 [-1 – 1]
EQ-5D-5L index value	0.01 [-0.07 – 0.15]	-0.09 [-0.21 – 0.11][c]	0 [-0.12 – 0.12][c*]	0.03 [-0.05 – 0.16]

Abbreviation definitions: *EQ-5D-5L= EuroQol 5-dimensional 5-level; ICU=Intensive Care Unit; IQR=interquartile range.* Data are presented as median [IQR] differences.

[1]Positive values of frailty indicate more frailty

[a]Significantly higher than persistent delirium; [b]Significantly higher than non-persistent delirium; [c]Significantly higher than no delirium;[*]P<0.001. All values were adjusted by the Bonferroni correction for multiple testing.

Supplemental table 5. Univariate associations of persistent and non-persistent delirium with long-term outcomes						
	Physical composite score *Fatigue or >=2 new physical complaints*		**Mental composite score** *Anxiety, depression, or PTSD symptoms*		**Cognitive impairment**	
	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value
No delirium	Ref.		Ref.		Ref.	
Non-persistent delirium	1.79 (1.45-2.22)	<0.001	1.87 (1.52-2.28)	<0.001	1.66 (1.21-2.28)	0.002
Persistent delirium	7.86 (2.40-25.77)	0.001	2.38 (1.22-4.65)	0.011	3.06 (1.30-7.22)	0.011