Journal of Critical Care 53 (2019) 120–124

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Differences in 90-day mortality of delirium subtypes in the intensive care unit: A retrospective cohort study

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ARTICLE INFO

Keywords:
Delirium
ICU
Critical care
Mortality
Subtypes

ABSTRACT

Introduction: Many intensive care unit (ICU) patients suffer from delirium which is associated with deleterious short-term and long-term effects, including mortality. We determined the association between different delirium subtypes and 90-day mortality.
Materials and methods: Retrospective cohort study in ICU patients admitted in 2015–2017. Delirium, including its subtypes, was determined using the confusion assessment method-ICU (CAM-ICU) and Richmond agitation sedation scale (RASS). Exclusion criteria were insufficient assessments and persistent coma. Cox-regression analysis was used to determine associations of delirium subtypes with 90-day mortality, including relevant covariates (APACHE-IV, length of ICU stay and mechanical ventilation).
Results: 7362 ICU patients were eligible of whom 6323 (86%) were included. Delirium occurred in 1600 (25%) patients (stratified for delirium subtype: $N = 571$–36% mixed, $N = 485$–30% rapidly reversible, $N = 433$–27% hypoactive, $N = 111$–7% hyperactive). The crude hazard ratio (HR) for overall prevalent delirium with 90-day mortality was 2.84 (95%CI: 2.32–3.49), and the adjusted HR 1.29 (95%CI: 1.01–1.65). The adjusted HR for 90-day mortality was 1.57 (95%CI: 1.51–2.14) for the mixed subtype, 1.40 (95%CI: 0.71–2.73) for hyperactive, 1.31 (95%CI: 0.93–1.84) for hypoactive and 0.95 (95%CI: 0.64–1.42) for rapidly reversible delirium.
Conclusion: After adjusting for covariates, including competing risk factors, only the mixed delirium subtype was significantly associated with 90-day mortality.

1. Introduction

Delirium is an acute disturbance in cognition, attention and consciousness which cannot be explained by a preexisting or evolving neurocognitive disorder [1]. Approximately one third of intensive care unit (ICU) patients develop delirium [2], which is strongly associated with adverse outcomes as prolonged hospital length of stay [3,4], as well as long-term cognitive impairment after ICU discharge [5,6]. However, inconsistent results regarding the association of delirium occurrence and mortality are found [7].

Current delirium assessment in the ICU is usually performed by ICU nurses using either the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) [8] or the Intensive Care Delirium Screening Checklist (ICDSC) [9], as recommended by the current Society of Critical Care Medicine delirium guideline [7]. Based on the results of these assessment tools, combined with patients' level of arousal (most frequently defined using the Richmond Agitation Sedation Scale (RASS)) [10], several subtypes of delirium can be recognized, and are depending on patients' level of consciousness, or agitation [11]. The hypoactive subtype displays reduced levels of consciousness, motor activity and/or lethargy with RASS scores ≤0. The hyperactive subtype displays restlessness, agitation and sometimes aggression (RASS scores >0), while the mixed subtype has alternating periods of hypo- and hyperactivity [11,12]. Recently, the 'rapidly reversible' delirium subtype was defined as a separate entity, which abates quickly after cessation of sedation with a RASS score ≤ −1, and appears not to affect clinical outcomes [13].

Identification of the different delirium subtypes may be of importance, as these subtypes may prognosticate different outcomes [13,14]. However, current evidence is still limited, and the need for more data related to the attributable risk of delirium and its subtypes on mortality and other outcomes is recognized in the current Society

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https://doi.org/10.1016/j.jcrc.2019.06.007
0883-9441/

of Critical Care Medicine delirium guideline and multinational, inter professional research agenda [7,15].

Therefore, we aimed to investigate to what extent different delirium subtypes relate to mortality of ICU patients and other delirium-related outcomes.

2. Material and methods

2.1. Design, patients, and delirium measurement

A retrospective observational cohort study was conducted in ICU adults consecutively admitted to the 35 bed ICU between January 1st 2015 and December 31st 2017 of a university hospital. The study obtained ethical approval by the MREC region Arnhem-Nijmegen (2019–5430) which waived the need for informed consent.

Every eight hours shift, well-trained ICU nurses assessed patients for delirium using the CAM-ICU and the Richmond Agitation Sedation Scale (RASS) [10]. Demographic, outcome characteristics, and delirium assessments were documented in the electronic health record. Monthly, delirium assessment compliance and delirium prevalence numbers were monitored. ICU patients were divided into five subgroups: non-delirious (patients without any positive CAM-ICU assessment during the ICU stay), rapidly reversible delirium (patients with one positive CAM-ICU and a RASS score ≤ −1), hyperactive delirium (≥1 positive CAM-ICU with solely RASS score > 0), hypoactive delirium (≥2 positive CAM-ICU assessments with RASS scores ≤0) or mixed delirium (positive CAM-ICU assessments with RASS scores −3 to +4). Patients with sustained coma (RASS -4/−5) during their entire ICU stay or patients with missing over two-thirds of the expected delirium assessments (based on the number of full shifts admitted) were excluded.

In accordance with the hospital ICU delirium protocol, patients with delirium were treated with haloperidol 2–3 times daily; hypoactive delirium 0.5–1 mg, mixed subtype delirium 1–2 mg, and hyperactive delirium with 2–5 mg of haloperidol. Haloperidol treatment was terminated when patients became CAM-ICU negative for >24 h. Administration of medication was documented, including the cumulative dosage of haloperidol in the electronic health record (EPIC, Verona, Wisconsin, United States of America).

2.2. Outcome measures

Primary outcome was the association between delirium subtypes and 90-day all-cause mortality, adjusted for relevant covariates. Secondary outcomes were delirium duration, duration of mechanical ventilation, cumulative dose of haloperidol during ICU admission and ICU and hospital length of stay (LOS).

2.3. Statistical analyses

Demographic data were collected and reported using descriptive statistics. Continuous variables were reported as either mean (SD) or median (first and third inter quartile range [IQR]) and differences between groups were tested using a one-way ANOVA or Kruskal-Wallis H test, depending on their distribution.

Cox proportional hazard regression analysis was used for survival analysis over 90-days period of time, including the delirium subtypes and adjusted for the covariates APACHE-IV [16] score, need for mechanical ventilation and length of stay in the ICU [7,13]. The latter covariate also served as a competing risk factor which was entered as continuous variable in the regression analysis. Statistical significance was defined as a p-value <.05. Data were analyzed using SPSS version 25.0.

3. Results

From January 2015 till January 2018 a total of 7362 patients were admitted to the ICU. Of them, 1039 (14%) patients were excluded from analysis, 608 (8%) since less than two-thirds of the expected delirium assessments were performed, 303 (4%) as they received haloperidol without any positive CAM ICU score (and could therefore not be assigned to a delirium subtype), and 128 (2%) because of persistent coma during their entire ICU stay, making a delirium diagnosis impossible. Finally, 6323 (86%) patients were included with a mean (±SD) age of 61(±16) years and the majority ($n = 3633$, 58%) of patients were admitted after planned surgical procedures. The median APACHE-IV score was 56 [IQR 43–71], the APACHE-IV predicted probability of death was median 6% [IQR 2–16], which both varied widely between the five delirium subgroups. The delirium prevalence rate was 25% ($n = 1600$). The mixed subtype occurred in 571 (36%), the rapidly reversible subtype in 485 (30%), the hypoactive subtype in 433 (27%), and the hyperactive subtype in 111 (7%) of patients with delirium (Table 1, Fig. 1, Supplemental Fig. 1).

3.1. Primary outcome

Of the total group of 6323 included patients, 366 (6%) died within 90 days after ICU admission. Within subgroups, significant differences

Table 1
Demographic and outcome measures.

	Not delirious	Rapidly reversible	Hyperactive	Hypoactive	Mixed
	$N = 4723$	$N = 485$	$N = 111$	$N = 433$	N = 571
Male/female, n (%)	2969/1754 (63/37)	293/192 (60/40)[a]	85/26 (77/23)[a]	224/209 (52/48)[a]	392/179 (69/31)[a]
Age, mean (sd)	61 ± 16	64±15[a]	63 ± 16	64±13[a]	66±13[a]
APACHE IV score	52 [40–66]	61 [48–74][a]	65 [53–82][a]	76 [56–93][a]	75 [60–91][a]
APACHE IV mortality probability (%)	4 [2−10]	8 [3−20][a]	13 [5–27][a]	25 [11–50][a]	24 [11–46][a]
Urgent admission, n (%)	2765 (40)	253 (52)[a]	63 [57][a]	333 (77)[a]	406 (71)[a]
Admission type					
Planned surgical	3123 (66)	250 (52)[a]	46 (41)[a]	88 (20)[a]	126 (22)[a]
Medical	1179 (25)	162 (33)[a]	45 (41)[a]	249 (58)[a]	327 (57)[a]
Acute surgery	421 (9)	73 (15)[a]	20 (18)[a]	96 (22)[a]	118 (21)[a]
Duration mechanical ventilation (days)	1 [0–2]	2 [1–2][a]	2 [1–3][a]	3 [1−10][a]	7 [2–15][a]
Delirium duration (days)	–	1 [1–1][b]	1 [1–1][b]	2 [2–4][b]	5 [3−10][b]
Haloperidol dose during ICU stay (mg)	–	2 [1–5][b]	2 [1–6][b]	7 [3–15][b]	17 [7–31][b]
LOS ICU	1 [1–1]	1 [1–3][a]	2 [1–4][a]	4 [2−12][a]	9 [4–20][a]
LOS hospital	8 [5–13]	11 [6–19][a]	11 [7–20][a]	20 [10–40][a]	11 [7–20][a]
Died in the ICU, n (%)	119 (3)	12 (3)	4 (4)	36 (8)[a]	51 (9)[a]
Died in 90 days, n (%)	188 (4)	29 (6)	9 (8)	55 (13)[a]	85 (15)[a]

Data are presented as median [IQR], unless mentioned otherwise.
[a] Statistically significantly different ($p < .05$) from non delirious.
[b] Statistically significantly different ($p < .05$) from other delirium subgroups.

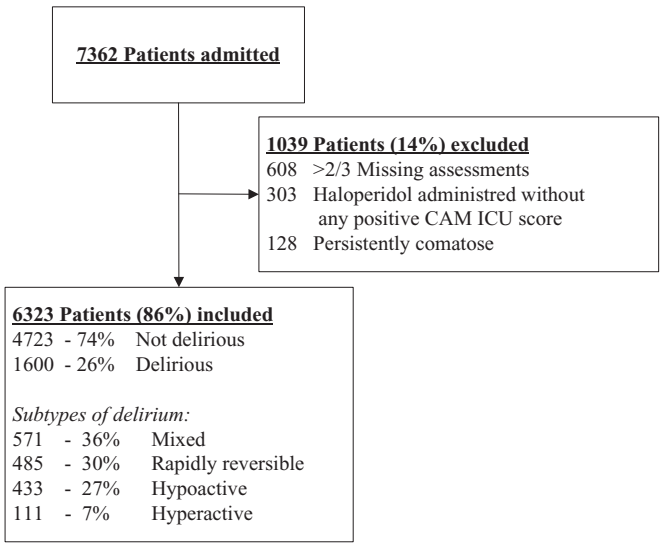

Fig. 1. Flow chart of included patients.

were found in 90-days mortality, varying from 4% in non-delirious patients to 15% in the mixed delirium subtype (Table 1, Supplemental Fig. 2).

The crude hazard ratio (HR) for prevalent ICU delirium with 90-day mortality was 2.84 (95%CI: 2.32–3.49) and the adjusted HR was 1.29 (95%CI: 1.01–1.65). Regarding the ICU delirium subtypes, the mixed subtype was significantly associated with increased 90-day mortality (adjusted HR 1.57 (95%CI: 1.51–2.14)). The adjusted HR for the hyperactive subtype was 1.40 (95%CI 0.71–2.73), for the hypoactive subtype this was 1.31 (95%CI 0.93–1.84) and for the rapidly reversible subtype 0.95 (95%CI: 0.64–1.42) (Fig. 2, Supplemental fig. 3).

3.2. Secondary outcomes

Patients with delirium needed mechanical ventilation significantly longer and had a significantly longer ICU length of stay, compared to the non-delirious patients (Table 1). Patients with hypoactive or mixed subtype had significantly higher APACHE IV scores and predicted probabilities towards death during ICU admission compared to non delirious patients (Table 1). Furthermore, patients with a hypoactive or mixed subtype of delirium had significantly longer duration of the delirium, ICU and hospital length of stay, and the cumulative dose of haloperidol administered during their ICU stay was significantly higher compared to patients with rapidly reversible or hyperactive delirium (Table 1).

4. Discussion

In this retrospective cohort study including over 6000 ICU patients, overall prevalent ICU delirium and the mixed delirium subtype were statistically significant associated with increased 90-day mortality, even after adjustment for relevant covariates. The rapidly reversible delirium subtype seems to have similar outcome as non delirious patients. Furthermore, hypoactive and hyperactive delirium were not significantly associated with 90-day mortality.

The sample size of the cohort of over 6000 patients gave sufficient statistical power to determine the association of the different subtypes of delirium with mortality. It seems likely that the most frequently occurring mixed subtype of delirium is responsible for the small, but statistically significant, association we found for the overall prevalent ICU delirium with mortality. This is similar to other prevalent delirium studies [17-19] but with a lower association. Plausibly, the adjustment for the competing risk factor length of ICU stay may contribute to this lower association, since an increasing length of ICU stay also increases chances for mortality [20]. Only in one other study included length of ICU stay and severity of illness over time were used as competing risk factors, and this study found no association between prevalent delirium

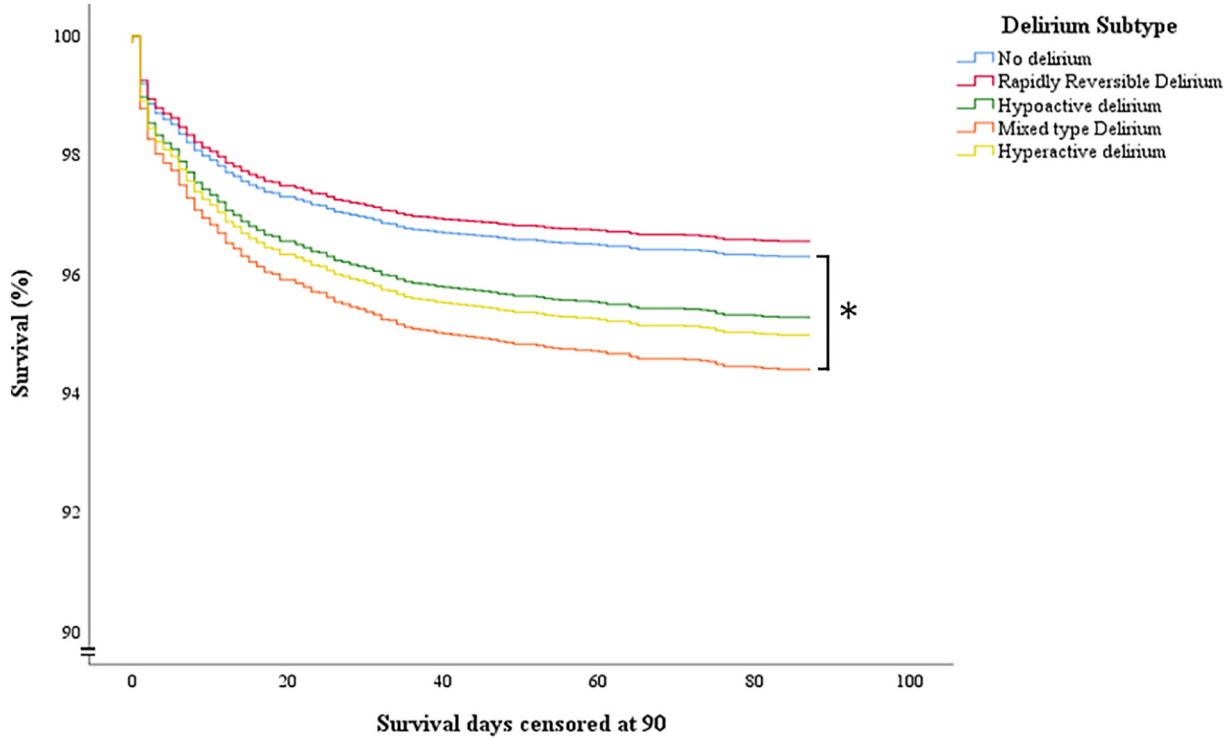

Fig. 2. Kaplan-Meier survival plot of subtypes of delirium and 90-day survival, adjusted for APACHE-IV score, need for mechanical ventilation and length of stay in the ICU.

and 30-days mortality [21]. Nevertheless, sensitivity analyses indicated that persistent delirium may still be associated with mortality at the long-term [21]. This may illustrate that severity of delirium, of which delirium duration is the most frequently used surrogate measure, is probably a more important factor than only prevalent delirium. Importantly, in this study [21] no subtypes of delirium were presented, while it is known that the delirium duration in the mixed delirium subtype is the longest [22].

Our large cohort data confirm the previous finding in 102 patients [13] that rapidly reversible delirium does not negatively influence patient outcomes. The lower prevalence in the hypoactive and hyperactive delirium subtypes, as well as the smaller difference in mortality compared to non-delirious patients, may have limited the association found with mortality due to a lack of statistical power. Inclusion of a larger cohort could have resolved this, but based on our results we expect this would require a multiple of the currently used cohort, which in our opinion limits the relevance to daily clinical practice.

Our study has limitations that need to be addressed. First, this was a retrospective cohort study of which we only analyzed data of patients in which we verified that at least two-third of the daily expected CAM-ICU assessments were performed enabling us to correctly stratify for the delirium subtypes. Although we cannot rule out that the drawbacks of a retrospective study may have biased our results, e.g. by excluding patients who could not be assigned to the delirium subtypes, we have ensured high-quality data, and thus the accuracy and validity of the outcomes found. Second, this was a single center study which may reduce the generalizability of the results, despite that the demographic measures of the included patients at baseline seem comparable with other studies [2,23]. Third, the delirium prevalence rate in this cohort was relatively low which could be explained by a relatively high proportion of elective surgical patients with lower delirium incidence rates [22]. Fourth, a small but still considerable proportion of 4% of admitted patients received haloperidol without any positive CAM-ICU assessment. The majority of these patients probably had a clinical diagnosis of delirium, but could not be reliably assigned to one of the subgroups, and were therefore subsequently excluded from our analysis. This may be because of instrumental performance limitations of the CAM-ICU assessment tool [7,24-27].

5. Conclusion

In this large retrospective cohort study, after adjusting for covariates the mixed delirium subtype was significantly associated with 90-day mortality. Other subtypes of delirium were not significantly associated with 90-day mortality, and the rapidly reversible subtype seems to have similar outcomes as non delirious patients.

Authors contributions

PR collected and merged all data, performed analysis, wrote en edited the final manuscript. KT and FS helped collecting data, and contributed in writing the final manuscript. PP helped analysing data, and contributed in writing the final manuscript. MB mentored the data collection performed analysis and mentored the writing of the final manuscript. All authors read and approved the final manuscript.

Authors information

PR is RN, CCRN, MSc and is nursing scientist and PhD-student. FS and KT are MD's and collected data during their graduation. PP is MD and PhD and professor of the department of experimental Intensive Care Medicine. MB is RN, CCRN and PhD and is assistant professor at the department of experimental Intensive Care Medicine.

Acknowledgements

We would like to thank the patients and staff of the department of Intensive Care Medicine of the Radboud University Medical Center whom contributed to this study by collecting and registering the required data in our hospital data system. Specific we want to thank Sjef van der Velde for his assistance gathering the required data from the hospitals data warehouse.

Declaration of interest

None.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2019.06.007.

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