

BMJ Open Single assessment of delirium severity during postacute intensive care of chronically critically ill patients and its associated factors: post hoc analysis of a prospective cohort study in Germany

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ABSTRACT

Objectives To assess the delirium severity (DS), its risk factors and association with adverse patient outcomes in chronically critically ill (CCI) patients.

Design A prospective cohort study.

Setting A tertiary care hospital with postacute intensive care units (ICUs) in Germany.

Participants N=267 CCI patients with critical illness polyneuropathy and/or critical illness myopathy, aged 18–75 years, who had undergone elective tracheotomy for weaning failure.

Interventions None.

Measures *Primary outcomes:* DS was assessed using the Confusion Assessment Method for the Intensive Care Unit-7 delirium severity score, within 4 weeks (t1) after the transfer to a tertiary care hospital. In post hoc analyses, univariate linear regressions were employed, examining the relationship of DS with clinical, sociodemographic and psychological variables. *Secondary outcomes:* additionally, correlations of DS with fatigue (using the Multidimensional Fatigue Inventory-20), quality of life (using the Euro-Quality of Life) and institutionalisation/mortality at 3 (t2) and 6 (t3) months follow-up were computed.

Results Of the N=267 patients analysed, 9.4% showed severe or most severe delirium symptoms. 4.1% had a full-syndromal delirium. DS was significantly associated with the severity of illness ($p=0.016$, 95% CI -0.1 to -0.3), number of medical comorbidities ($p<0.001$, 95% CI $.1$ to $.3$) and sepsis ($p<0.001$, 95% CI $.3$ to 1.0). Patients with a higher DS at postacute ICU (t1), showed a higher mental fatigue at t2 ($p=0.008$, 95% CI $.13$ to $.37$) and an increased risk for institutionalisation/mortality ($p=0.043$, 95% CI 1.1 to 28.9 / $p=0.015$, 95% CI 1.5 to 43.2).

Conclusions Illness severity is positively associated with DS during postacute care in CCI patients. An adequate management of delirium is essential in order to mitigate functional and cognitive long-term sequelae following ICU.

Trial registration number DRKS00003386.

INTRODUCTION

Every 10th patient with protracted treatment in an intensive care unit (ICU), for example, because of sepsis with multiorgan

Strengths and limitations of this study

- We consecutively enrolled a quite homogeneous sample of long-term ventilated chronically critically ill (CCI) patients, using a straightforward timeline and applying a valid delirium assessment tool, the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU).
- For the first time, the CAM-ICU-7 delirium severity score, based on the CAM-ICU, was used and associated with sociodemographic, clinical and psychological risk factors as well as posthospital outcomes (fatigue, quality of life, institutionalisation/mortality) in CCI patients.
- The study was primarily designed to address post-traumatic stress disorder in CCI patients, therefore the study sample may be biased towards patients without delirium.
- The delirium assessment tool 'CAM-ICU' was not assessed at multiple time points, which could have led to a further underestimation of the delirium rate as well as delirium severity in CCI patients.

dysfunction, is prone to develop a clinical syndrome which is called chronic critical illness (CCI).^{1,2} Sepsis or other severe infections may precede CCI, leading to major dysfunctions of the central nervous system, non-focal encephalopathy and neurological long-term complications,^{3,4} among them critical illness polyneuropathy (CIP) or critical illness myopathy (CIM).^{2,5,6} These patients are exposed to prolonged mechanical ventilation and ICU lengths of stay, leading to an increased risk to develop significant sequelae, including delirium.^{7–10} Delirium refers to acute brain failures which usually manifest as acute or exacerbating deficits in global cognition, awareness, attention and/or executive functions. It develops quickly and fluctuates over the course of the

day.¹¹ Findings reveal a wide range of occurrence rates, varying across clinical contexts, admitting diagnoses and hospital departments.¹² The lowest rate could be proven for general hospital inpatients (eg, 20.7%¹³), the highest for older ICU patients (82%¹⁴), mechanically ventilated (81.7%¹⁵) and CCI patients (33.8% to 46.5%^{16 17}).

With respect to the an adequate delirium assessment in the ICU setting, the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) has turned out to be a rapid, valid and reliable instrument for use by non-psychiatric clinicians.^{18 19} However, in order to gain more insight into the clinical course and the underlying mechanistic relationships of delirium, the assessment of delirium severity (DS) seems to be more appropriate.²⁰ The measurement of symptom severity may help to detect clinically important syndromes that fall on a continuum between no symptoms and a diagnosis of delirium. This would be of prognostic relevance regarding clinical outcomes.^{21 22}

However, the validity of a CAM-based scoring system has been proven in former studies within general hospital²⁰ and ICU,²³ but not in CCI patients. Likewise, risk factors (eg, PRE-DELIRIC model: age, infection, severity of illness, use of sedatives) have been mainly studied for critically ill but not CCI patients.^{24–27} The assessment of a valid delirium severity score (DSS) and its predictors is of utmost importance, since delirium displays a major risk factor for the development of long-term cognitive and functional disabilities, months to years after ICU treatment.^{7 16 28} As already shown, predominantly for acutely ill patients, delirium could lead to deficiencies in patients rehabilitation outcomes. For instance, it may increase the risk for persistent ventilator dependence, longer stays in ICU, nursing home residence, the progression of former disorders (eg, dementia) as well as higher rehospitalisation and mortality rates.^{15 20 23 28–30} In particular, delirium within CCI might cause the development of functional and cognitive limitations, even >3years surviving severe sepsis.^{7–9} As a consequence, these patients may require rehospitalisation, institutionalisation, an increased amount of informal caregiving and thus, leading to higher emotional burdens. The latter maybe associated with the evolvement of psychiatric morbidity, such as depression and fatigue, leading to a diminished health-related quality of life, both in patients and their spouses.^{31–33} However, the association of delirium with psychological disorders has not been investigated, in particular after long-term ICU treatment in CCI patients.

The aims of the present study are: first, to assess the occurrence and severity of delirium in CCI patients during their treatment in a postacute ICU. Second, to examine the association of DS with clinical, sociodemographic and psychological risk factors. Third, to investigate whether DS is associated with patient-reported outcomes after hospitalisation, such as fatigue and health-related quality of life. Fourth, to outline whether DS can predict mortality and institutionalisation at follow-up. Findings may further

help to efficiently target preventive therapies at high-risk patients.

METHODS

Study design

We conducted a post hoc analysis of a prospective, longitudinal cohort study, originally designed to examine the frequency of acute stress disorder and post-traumatic stress disorder in CCI patients at three measurement points.³⁴ First, CCI patients were investigated according to a delirium/DS within 4 weeks following the transfer from acute-care ICU to a centre for weaning from long-term mechanical ventilation (t1), referred to as postacute ICU. Second, fatigue, health-related quality of life and patient status (dead, institutionalised vs discharged home) were assessed at follow-up via telephone, 3 (t2) and 6 (t3) months post-transfer. Further details on the study design are published elsewhere.³⁴

Patient and public involvement

Patients were not involved in the study design or in the conduct of the study. Representatives of the intensive care sector were involved in both the design and the implementation of the study results. Laymen reports of the present prospective cohort study are publicly available in German.

Participants

Between January 2011 and February 2013, we consecutively enrolled a quite homogeneous sample of CCI patients who were transferred from adult ICUs (medical, surgical, cardiac, neurosurgical) to a large tertiary care hospital with postacute ICUs for weaning from long-term mechanical ventilation. All patients, included in the present study, had undergone elective tracheotomy for weaning failure.

We consecutively enrolled patients who fulfilled the following inclusion criteria: presence of a diagnosis of critical illness polyneuropathy (CIP, International Classification of Diseases (ICD)-10: G62.80) or critical illness myopathy (CIM, ICD-10: G72.80) with or without sepsis, age between 18 and 75 years, a minimum length of ICU stay of 6 days, mechanical ventilation, sufficient German language skills, informed consent for study participation and presence of a delirium assessment using the CAM-ICU.^{18 35}

We excluded patients who refused study participation, who were transferred to another hospital or died before recruitment, showed insufficient German language skills, were sensorily impaired (eg, deaf-mute), persistently intubated and/or comatose, had a diagnosis of dementia (ICD-10 F00-F03), rapidly terminal disease states or an infaust prognosis (eg, malignancy). A flow chart of the recruitment process is shown in [figure 1](#). In the present post hoc analysis, slight differences to the recruitment numbers of the original study³⁴ are mainly due to the inclusion of patients with a delirium or positive CAM-ICU assessment.

Measures

Socioeconomic characteristics (eg, age, family status, education) and medical history (eg, history of harmful

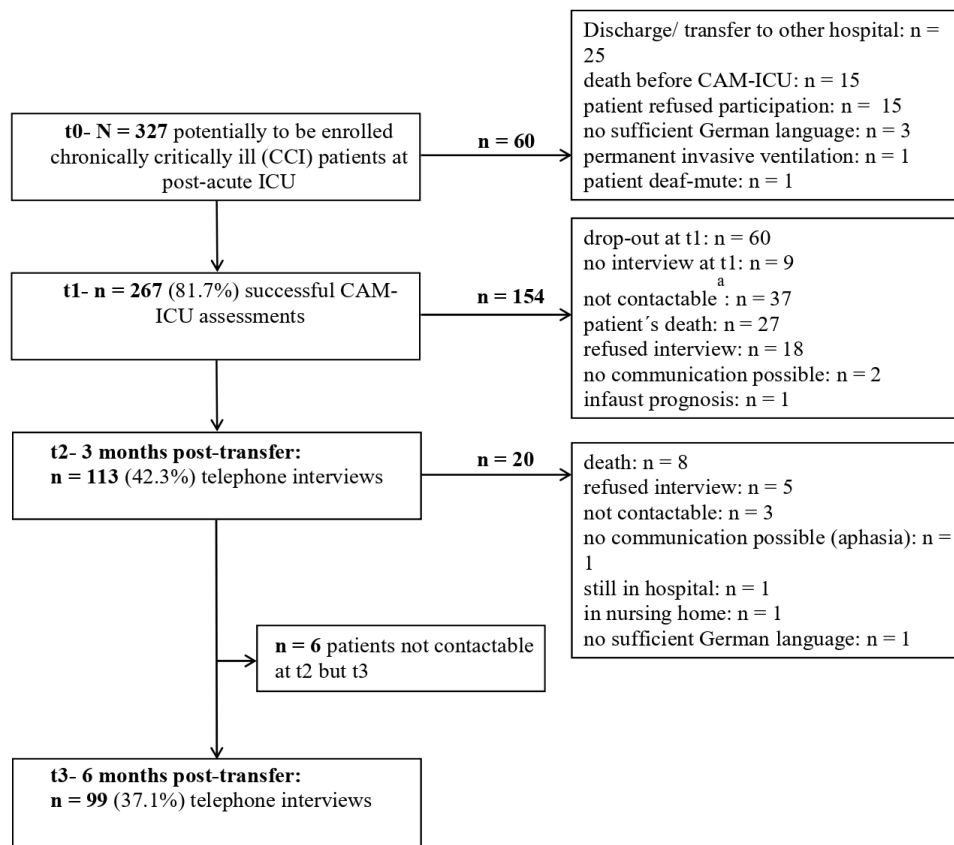


Figure 1 Flow chart displaying the number of potentially to be enrolled chronically critically ill (CCI) patients, the actual number of enrolled patients at t1 (within 4 weeks after transfer to postacute ICU), at t2 (3 months follow-up) and at t3 (6 months follow-up). CAM-ICU, Confusion Assessment Method for the Intensive Care Unit. a: Unknown reason: n=22, still in hospital: n=12, in nursing home: n=3.

alcohol consumption/anxiety or affective disorders, diagnosis of sepsis, number of sepsis episodes, severity of sepsis, site of infection, length of mechanical ventilation from the time of endotracheal intubation to successful unassisted breathing, length of ICU stay, number of medical comorbidities, presence of an organic brain syndrome: ICD-10 F07.9, medication, eg, exposure to antipsychotics, analgetics or sedatives) were extracted from patient record forms at t1. The patients' functional status was assessed by a trained study nurse, using the Barthel index. The Barthel index measures performance in activities of daily living in 11 domains (eg, faecal incontinence, urinary incontinence, help with grooming/toilet use), with values ranging between 0 and 100. A higher value is associated with a better degree of independence from caregivers. Additionally, the early rehabilitation Barthel index was assessed with seven domains (intensive care supervision, tracheostomy tube management and supervision, intermittent or continuous mechanical ventilation, confusion, behavioural disturbances, severe impairment of communication and dysphagia), with a minimum value of -325 and a maximum value of 0.³⁶ Both Barthel scales were summed up, yielding scores between -325 and 100. Interrater reliability is very high ($r=0.95$). Test-retest reliability is good as well ($r=0.89$).³⁷

CAM-ICU: the CAM-ICU¹⁸ was applied at t1, within 4 weeks following the transfer from acute-care ICU. It can be used for the non-verbal assessment of a delirium, which is appropriate for mechanically ventilated patients. For this purpose, four domains are evaluated, including (1) an acute onset or fluctuations in the course of mental status, using the Richmond Agitation Sedation Scale (RASS)³⁸ at t1; (2) inattention, using the Attention Screening Examination; (3) disorganised thinking, using four simple questions and (4) alteration in the level of consciousness, again using the RASS. The RASS is a 10-level scale ranging from '-5' unarousable to '+4' combative, and shows excellent reliability and acceptable validity in ventilated adult ICU patients. A patient was determined to be delirious if he/she manifested features 1 and 2, plus either feature 3 or 4. In order to assess DS, we applied a 7-point rating scale (0-7), derived from the CAM-ICU and RASS assessments. Each symptom of delirium is evaluated as described in detail by Khan *et al*²³ (acute onset and altered level of consciousness: absent (0) or present (1); inattention/disorganised thinking: absent (0), mild (1) and marked (2)). The CAM-ICU-7 DSS is categorised as 0-2 (no delirium), 3-5 (mild to moderate severity) and 6-7 (severe delirium).

Multidimensional Fatigue Inventory-20 (MFI-20): the MFI-20^{39 40} is a 20-item self-report measurement of fatigue severity. It covers the five dimensions ‘general fatigue’, ‘physical fatigue’, ‘mental fatigue’, ‘reduced motivation’ and ‘reduced activity’. Items are summed up to a simple total score, with a minimum value of 4 (absence of fatigue) and a maximum value of 20 for each subscale. A total fatigue score is calculated as the sum of the subscale scores (range 20–100). Higher scores indicate higher levels of fatigue. For the present study, particularly the subscale ‘mental fatigue’ was considered, assessing, for example, the extent of difficulties in concentration, as well as sustaining performance in mental tasks, that might result in transient decline in cognitive performance. The MFI-20 was applied via telephone at 3 (t2) and 6 months (t3) following discharge from acute-care ICU. Validity has been shown for different populations, for example, patients with cancer, army recruits, patients with chronic fatigue syndrome and CCI patients.^{33 39} Internal consistency has been reported to be good for the general, physical and mental fatigue dimensions (Cronbach’s $\alpha=0.84$), and adequate for the subscales reduced activity and reduced motivation (Cronbach’s $\alpha >0.65$).³⁹

Euro-Quality of Life (EQ-5D-3L): quality of life was assessed with the questionnaire EQ-5D-3L⁴¹ at t2 and t3. The EQ-5D-3L measures health-related quality of life on five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), which are evaluated within three severity levels (no problems, some or moderate problems, extreme problems or unable). A single one-dimensional index value is generated based on a simple sum score according to Hinz *et al.*⁴²

Statistical analysis

Normal distribution was ascertained by Kolmogorov-Smirnov test. In case of normally distributed data, arithmetic means and standard deviations (SD), otherwise data medians and interquartile ranges (IQR) are reported. For categorical variables, absolute and relative frequencies are presented. Mann-Whitney U test or t-test was used to compare medians or means of outcome variables between followed up and dropped out patients. Fisher’s exact test or χ^2 test was run, in case of nominal outcome data. The association of the CAM-ICU-7 DSS with clinical (eg, sepsis, length of mechanical ventilation/ICU stay, severity of medical illness/Barthel index, number of medical comorbidities, medication), sociodemographic (eg, age, gender, family/education status) and psychological variables was analysed using univariate linear regressions. The choice of these variables was mainly driven by research on risk factors for intensive care delirium (see the systematic review by Van Rompaey *et al.*²⁴). We had to adapt our choice of potential predictors to the availability of information on these data in the patient records, mainly because the present study was originally designed to assess the frequency of stress-related disorders in CCI patients.³⁴ Since there was only a low percentage of cases with a delirium (see ‘Results’ section), we did not

calculate logistic regression analyses. Exploratory, the CAM-ICU-7 DSS was correlated with the subscales of the MFI-20, the health-related quality of life as assessed with the EQ-5D-3L and the status (dead, institutionalised vs discharged home) after hospital discharge at t2 and t3, using Spearman’s rank correlation coefficients. Additionally, the CAM-ICU-7 DSS was entered in a multinomial logistic regression analysis, controlling for covariates as partially suggested by Khan *et al.*²³ (age, gender, length of ICU/mechanical ventilation, number of comorbidities, sepsis, education/family status). Both the CAM-ICU-7 DSS and MFI-20 subscale mental fatigue were correlated with the length of mechanical ventilation/length of ICU stay, using Spearman’s rank correlations. For all analyses, a significance level of $\alpha=0.05$ (two-sided) and z standardised values were applied. All data were analysed using SPSS V.26.0.0.0 (SPSS, Chicago, Illinois, USA).

RESULTS

Baseline characteristics

Of N=327 potentially eligible CCI patients, a subsample of n=267 (81.7%) patients could be successfully evaluated using the CAM-ICU (see figure 1, flow chart). About three-quarter of the patients were male (72.3%). One-third of the sample (31.8%) was older than 65 years, with a median age of 61.6 years (range 25.6–71.9 years). More than half of the patients (58.8%) reported at least 10 years of education (table 1). Median length of ICU stay was 73 days and length of mechanical ventilation 53 days. Nearly three-quarter (70.4%) of the total sample had an anamnesis of sepsis, mostly located at the respiratory tract. Most patients suffered from an acute respiratory insufficiency (80.1%). One-third had a hypertension (55.4%), left heart failure (33.7%), atrial fibrillation (35.2%) or coronary heart disease (30.0%) (see online supplemental table S1). More than half of the patients (50.9%) had >10 medical comorbidities. Those patients who could not be enrolled (drop outs at t0 or t1) were more severely ill than the patients enrolled in the present study (for further information, see table 1, online supplemental table S2).

Frequency of delirium and delirium severity score

Inter-rater reliability (without the RASS score) for the CAM-ICU assessment in the present study was calculated, with an intraclass correlation coefficient (ICC) of 0.66 that lies within the range reported for different patients samples (ICC=0.64–0.82)³⁸; 4.1% (n=11) of the enrolled sample fulfilled the criteria for a delirium according to the CAM-ICU assessment at t1. The median RASS score corresponded to an alert state of attention (median=0, IQR=0–0). According to the classification of the CAM-ICU-7 DSS (median=0, IQR=0–0), 79% (n=211) of the patients had no delirium, 11.6% (n=31) had a mild to moderate and 9.4% (n=25) had a severe form.

Risk factors associated with DSS

As significant risk factors for more severe delirium symptoms at time of recruitment (t1), mostly clinical variables

Table 1 Baseline demographic and clinical characteristics of the cohort of n=267 chronically critically ill patients who have been assessed using the CAM-ICU and were compared with dropped out patients at t0

Characteristic	Cohort n=267	Drop outs (t0) n=60	U/ χ^2	P value
Age, yrs median (IQR)	61.6 (55.9–66.6)	60.5 (53.7–65.4)	7490.500	0.432 (U)†
Gender, n (%)				
Male	193 (72.3)	44 (73.3)		
Female	74 (27.7)	16 (26.7)	0.027	0.869 (χ^2)‡
Family status, n (%)§				
Single	28 (10.7)	7 (13.7)		
Married/Cohabited	179 (68.3)	38 (74.5)		
Divorced/Living apart	42 (16.0)	5 (9.8)		
Widowed	13 (5.0)	1 (2.0)	2.550	0.466 (χ^2)‡
Education, n (%)¶				
<10 years	96 (41.2)	10 (43.5)		
≥10 years	137 (58.8)	13 (56.5)	0.045	0.833 (χ^2)‡
ICU stay, days median (IQR)	73.0 (52.0–105.0)	71.0 (46.3–123.0)	7939.000	0.915 (U)†
Mechanical ventilation, days median (IQR)	53.0 (33.0–77.0)	56.5 (36.8–93.8)	7425.000	0.377 (U)†
ICU stay in acute-care ICU, days median (IQR)	35.0 (25.0–54.0)	42.5 (27.0–75.0)	6656.500	0.041* (U)†
Mechanical ventilation in acute-care ICU, days median (IQR)	31.0 (19.0–46.0)	36.5 (25.0–69.0)	5992.500	0.002** (U)†
Sepsis, n (%)				
No sepsis	79 (29.6)	12 (20.0)		
Sepsis	107 (40.1)	20 (33.3)		
Severe sepsis or septic shock	81 (30.3)	28 (46.7)	6.111	0.047* (χ^2)‡
Site of infection, n (%)				
Respiratory**	140 (52.4)			
Urinary/Genitals**	25 (9.4)			
Abdominal**	20 (7.5)			
Bones/Soft tissue**	13 (4.9)			
Wound infection**	6 (2.2)			
Heart**	5 (1.9)			
Multiple**	28 (10.5)			
Others**††	23 (8.6)			
Unknown	21 (7.9)			
Barthel index, median (IQR)				

Continued

Table 1 Continued

Characteristic	Cohort n=267	Drop outs (t0) n=60	U/ χ^2	P value
At admission at postacute ICU	-200.0 (-225.0--140.0)	-200.0 (-225.0--138.8)	7283.000	0.264 (U)†
At discharge from postacute ICU, median (IQR)	-60.0 (-140.0-0.0)	-157.5 (-225.0--35.0)	4797.000	<0.001*** (U)†
At discharge from rehabilitation hospital, median (IQR)	40.0 (-50.0-75.0)	-147.5 (-225.0-38.8)	4225.000	<0.001*** (U)†
MFI subscales, t2/t3 median (IQR)				
General fatigue	12.0 (9.0-15.0)/12.0 (9.0-14.0)			
Physical fatigue	13.0 (11.0-16.0)/13.0 (11.0-16.0)			
Reduced motivation	9.0 (6.0-11.0)/8.0 (6.0-11.0)			
Reduced activity	12.0 (9.0-16.5)/13.0 (10.0-16.0)			
Mental fatigue	8.0 (4.0-11.0)/8.0 (5.0-11.0)			
EQ-5D-3L, t2/t3 median (IQR)	70.0 (55.0-80.0)/70.0 (50.0-80.0)			

* $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$.

†P value from Mann-Whitney U test.

‡P value from χ^2 test.

§Cohort: n=5 missing values, drop outs: n=9 missing values.

¶Cohort: n=34 missing values, drop outs: n=37 missing values.

**Cohort: n=1 missing value.

††Cohort: n=1 aorta, n=1 brain, n=1 nose, n=2 intracardiac catheter, n=16 central venous catheter, n=2 port system.

EQ-5D-3L, Euro-Quality of Life; MFI, Multidimensional Fatigue Inventory.

Table 2 Univariate logistic regression using Enter as method for the identification of sociodemographic, clinical and psychological predictors of the CAM-ICU-7 delirium severity score during postacute intensive care in chronically critically ill (CCI) patients (n=267)

Univariate linear regression

	Beta (standardised)	95% CI	P value
Sociodemographic variables			
Age	0.056	-0.066 to 0.180	0.361
Gender	0.035	-0.194 to 0.353	0.566
Family status, no partnership vs partnership†	-0.003	-0.267 to 0.255	0.964
Education status <10 years vs ≥10 years‡	-0.091	-0.399 to 0.069	0.167
Clinical variables			
Number of sepsis episodes	0.114	-0.007 to 0.237	0.064
Sepsis in postacute ICU	0.231	0.313 to 0.962	<0.001***
Barthel index at admission in postacute ICU	-0.147	-0.271 to 0.028	0.016*
Number of medical comorbidities	0.221	0.105 to 0.344	<0.001***
Use of antipsychotic medication (in postacute ICU)	0.046	-0.191 to 0.423	0.459
Use of sedative medication (in postacute ICU)	-0.023	-0.311 to 0.210	0.702
Use of analgetic medication (in postacute ICU)	0.030	-0.204 to 0.341	0.622
Organic brain syndrome (in acute-care ICU)	0.268	0.307 to 0.780	<0.001***
Length of mechanical ventilation (in acute-care ICU)	0.008	-0.115 to 0.131	0.896
Length of ICU stay (in acute-care ICU)	0.086	-0.035 to 0.209	0.163
Psychological variables at (postacute) ICU			
History of depressive disorder	0.073	-0.113 to 0.454	0.236
History of harmful alcohol consumption	0.030	-0.223 to 0.368	0.629
History of anxiety disorder	-0.032	-0.531 to 0.310	0.604

Method of univariate logistic regression analysis: Enter.

*P≤0.05, ***p≤0.001.

†n=5 missing values.

‡n=34 missing values.

CAM-ICU, Confusion Assessment Method for the Intensive Care Unit.

could be identified, that is, sepsis in postacute ICU, the number of medical comorbidities, the degree of functional impairment as assessed by the Barthel index and a diagnosis of organic brain syndrome (table 2).

Association with fatigue, health-related quality of life, institutionalisation or death at follow-up

Cronbach's α for the MFI-20 was 0.91 (with a range of 0.50 for 'reduced motivation' and 0.86 for 'mental fatigue') at t2 and 0.93 (with a range of 0.64 for 'reduced motivation' and 0.84 for 'mental fatigue') at t3. A correlation analysis revealed a significantly positive, small-sized association between the CAM-ICU-7 DSS score at the time of recruitment (t1) and mental fatigue at t2 (Spearman's correlation=0.247, p=0.008, 95% CI 0.132 to 0.373), but not at t3 (Spearman's correlation=0.029, p=0.773, 95% CI -0.092 to 0.150, see online supplemental table S3).

In the present study, Cronbach's α for the health-related quality of life was 0.74 at t2 and 0.77 at t3. No significant associations could be shown for the CAM-ICU-7 DSS with the health-related quality of life.

A worse CAM-ICU DSS was associated with death or institutionalisation in a hospital/nursing home at t2 but not at t3 (t2: Spearman's correlation=0.318, p<0.001; t3: Spearman's correlation=0.140, p=0.125) (see online supplemental table S3).

In multinomial regression analyses, the CAM-ICU-7 DSS at postacute care (t1) could be identified as independent risk factor for both, institutionalisation and death, 3 months following ICU discharge (t2) (see table 3). At t2, an increase of the CAM-ICU-7 score by one point can increase the risk for being institutionalised rather than being discharged home by the factor 5.5, and the risk of dying by the factor 8.0. At t3, the increase of the CAM-ICU DSS was associated with a nearly five-times increased risk of dying (see online supplemental table S4).

DISCUSSION

In the present study, we investigated the frequency of delirium in CCI patients and found a lower rate of delirium than formerly reported in comparable patient

Table 3 Sociodemographic and clinical characteristics associated with the outcome (dead, institutionalised vs discharged home) at 3 months follow-up (t2)

Factors	Institutionalised at t2		Death at t2	
	Adjusted OR (95% CI)	P value in final model	Adjusted OR (95% CI)	P value in final model
Age	1.075 (0.675 to 1.714)	0.760	1.172 (0.647 to 2.122)	0.600
Gender	2.060 (0.687 to 6.180)	0.197	1.639 (0.507 to 5.303)	0.409
Family status	1.724 (0.686 to 4.332)	0.247	0.828 (0.263 to 2.612)	0.748
Barthel index at admission	0.705 (0.436 to 1.140)	0.153	1.225 (0.752 to 1.993)	0.415
CAM-ICU-7 delirium severity score	5.514 (1.054 to 28.853)	0.043*	8.035 (1.496 to 43.153)	0.015*
Length of mechanical ventilation	0.435 (0.179 to 1.059)	0.067	1.552 (0.474 to 5.075)	0.467
Length of ICU stay	3.878 (1.605 to 9.367)	0.003**	0.796 (0.217 to 2.918)	0.730
Number of sepsis episodes	0.951 (0.571 to 1.585)	0.848	1.716 (1.077 to 2.735)	0.023*
Number of comorbidities	0.843 (0.496 to 1.433)	0.529	1.608 (0.893 to 2.894)	0.113

*P≤0.05, **p≤0.01.

CAM-ICU, Confusion Assessment Method for the Intensive Care Unit.

populations.^{16 17} However, we only used one single assessment point in order to evaluate a diagnosis of delirium and DS, instead of using daily assessments over a longer period of time. Similarly, low rates of delirium have been reported in studies using a single assessment point^{43 44} (eg, 9.6% in elderly emergency department patients⁴³; 2.1% for community hospital patients⁴⁴). Above, our rate falls within a wide range of delirium incidences, as previously described for medical inpatients (eg, 3%–29%).⁴⁵

The severity of the medical illness, complication by sepsis, a diagnosis of organic brain syndrome and number of comorbidities, were associated with DS during postacute ICU in these patients. This has been already shown in a study by Hope *et al.*¹⁶ As underlying mechanism for the association of more medical than sociodemographic and psychological factors influencing the evolution of severe delirium symptoms, and a delirium as well, a shared pathophysiology comprising neuroinflammation, an aberrant stress response, neurotransmitter imbalances and neuronal network alterations are supposed.⁴⁶ Moreover, a combination of medications, traumatic stress, pain, inflammation, hypoxaemia and brain injury during the prolonged stay on ICU may contribute to more severe delirium symptoms and promote the development of psychiatric disorders.⁴⁷ Thus, appropriate pharmacological and non-pharmacological strategies are warranted in order to improve long-term neurocognitive outcomes and prevent the evolution of a delirium. These strategies include a cautious use of benzodiazepines, the use of either propofol or dexmedetomidine instead, the short-term use of haloperidol or an atypical antipsychotic in case of agitation or self-harm. Furthermore, an early physical mobilisation, the reduction of sleep deprivation, support with reorientation, application of adequate pain and agitation management protocols and the improvement of hearing as well as vision are essential.^{46 48} In line with this, future research should address the investigation

of potential modifiable and also iatrogenic risk factors, such as the reduction of sedation, treatment of hypoxia and of sepsis, in order to decrease worse outcomes in long-term cognitive functioning.⁴⁹

We could not find any association between the duration of mechanical ventilation, and DS at postacute ICU or the MFI-20 subscale ‘mental fatigue’ at follow-up (see online supplemental table S5). This is in line with findings by Girard *et al.*,²⁸ who also could not find any association. Furthermore, there is evidence that mechanical ventilation does not alter the risk of delirium occurrence.⁴⁸ However, mechanically ventilated patients, especially those with long-term ventilation, are prone to develop acute and long-term forms of cognitive impairments.^{15 50} In contrast, most studies confirmed that delirium or more severe delirium symptoms are rather causes than consequences for a longer hospital length of stay or length of mechanical ventilation, respectively.^{45 51 52} In line with this, we also did not find an association between the length of mechanical ventilation/length of ICU stay in acute-care hospital and DSS in the present study population. A further analysis confirmed a significantly positive association between the total length of mechanical ventilation/length of stay (summarising both acute-care and postacute care ICU stay) with the CAM-ICU-7 DSS (online supplemental table S5). The inconsistencies of evidence may be explained by differences in measurement methods. In order to assess the extent of cognitive dysfunctions, we used a simple screening score of the CAM-ICU and the subscale ‘mental fatigue’ of the MFI-20 questionnaire, instead of using more objective neuropsychological tests.⁴⁷

The present finding of a significant though small-sized positive association between DS at postacute ICU and mental fatigue at t2 but not t3 is in line with findings by Girard *et al.*,²⁸ showing that long-term cognitive performance can be predicted by the cognitive status

during ICU stay in survivors of CCI. Another study could show that mechanically ventilated patients who developed delirium during ICU stay were nine times more likely to be discharged with cognitive impairment than were those without delirium.¹⁵ However, our results should be interpreted cautiously since mental fatigue is rather a subjective measure of the perceived difficulty to sustain task performance. Future studies should therefore validate this subjective measure on more objective instruments such as the Repeatable Battery for the Assessment of Neuropsychological Status and Trail Making Test or a more comprehensive neuropsychological test battery.²⁸

In our present study, DS at post-ICU turned out to be an independent risk factor for being institutionalised or dead at follow-up. This is line with former findings in elderly medical inpatients,²¹ general hospital,²⁰ ICU patients²³ and mechanically ventilated patients.¹⁵ Nevertheless, the present results should be regarded as preliminary and need replication in further studies. Moreover, there was no significant association of the CAM-ICU-7 DSS with health-related quality of life after hospital discharge. This finding also needs replication in further studies.

Our findings should be critically evaluated considering the following methodological shortcomings. First, the present study is a post hoc analysis of a study primarily designed to assess post-traumatic stress disorder in CCI patients following prolonged treatment on ICU.³⁴ The assessment of the CAM-ICU was originally applied in order to ascertain that the patients are cognitively able to be interviewed according to assess an acute/post-traumatic stress disorder. Patients who were cognitively impaired, for instance, showing a positive screening of the CAM-ICU subscales 'attention' and 'disorganised thinking' or presented a delirium, were screened again after 1 week. In case the delirium or delirium symptoms persisted, the patients were excluded from further study participation. Thus, patients with more severe delirium symptoms or persistent delirium dropped out, leading to a selection bias—towards patients without a full or subsyndromal delirium manifestation or with only mild delirium symptoms.

Additionally, the CAM-ICU was not assessed at multiple time points (eg, daily, biweekly) during the ICU stay, but only twice at maximum. However, a single CAM-ICU assessment in patients who have a prolonged ICU stay provides a less reliable estimate of delirium frequency. Future studies should apply the CAM-ICU more often, for example, daily²⁸ or biweekly,¹⁶ in order to gain access to the number of days spent in delirium. The latter has been found to be an independent predictor of long-term survival.^{15 53 54}

Furthermore, we did not have any information regarding further relevant variables measured before the patients were transferred to the chronic care facility, including prehospital functional ability, pre-existing cognitive function or frailty. These variables display major

influencing factors for long-term brain dysfunctions. Future studies should therefore address for example, activities of daily living or a functional independence measure by interviewing a family member or surrogate. Moreover, future research should apply different tools in order to assess delirium and delirium symptom severity (eg, Delirium Rating Scale-Revised-98). This would allow to specify the convergent validity of the CAM-ICU-7 DSS.

Altogether, the present study underlines the urgency for ongoing clinical and research efforts to reduce cognitive and thus functional disability in older adults surviving serious medical illnesses^{55 56} and to provide appropriate multidisciplinary resources to facilitate both, physical and neuropsychological rehabilitation. Consequently, adequate delirium management strategies as well as early mobility and prevention programmes are needed in order to mitigate cognitive and physical long-term sequelae as well as high societal costs of chronic critical illness.²⁸

CONCLUSION

In conclusion, nearly every 10th CCI patient showed severe or most severe delirium symptoms. Primarily clinical factors have been identified to be associated with DS during the postacute ICU stay in these patients, including a diagnosis of sepsis, number of medical comorbidities and the extent of functional impairment. Most importantly, patients showing a higher DSS during their stay on the weaning ward, also suffered from more severe mental fatigue and had an increased risk for being institutionalised or dead at follow-up. Thus, a single assessment of a DS sum score during admission at postacute ICU can be used to assess the clinical course in CCI patients. Future research should focus on interventions designed to improve the management of delirium and severe delirium symptoms in CCI patients.

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