Review Article

Cognitive Deficits Following Intensive Care

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Summary

Background: Illnesses that necessitate intensive care can impair cognitive function severely over the long term, leaving patients less able to cope with the demands of everyday living and markedly lowering their quality of life. There has not yet been any comprehensive study of the cognitive sequelae of critical illness among non-surgical patients treated in intensive care. The purpose of this review is to present the available study findings on cognitive deficits in such patients, with particular attention to prevalence, types of deficit, clinical course, risk factors, prevention, and treatment.

Methods: This review is based on pertinent publications retrieved by a selective search in MEDLINE.

Results: The literature search yielded 3360 hits, among which there were 14 studies that met our inclusion criteria. 17–78% of patients had cognitive deficits after discharge from the intensive care unit; most had never had a cognitive deficit before. Cognitive impairment often persisted for up to several years after discharge (0.5 to 9 years) and tended to improve over time. The only definite risk factor is delirium.

Conclusion: Cognitive dysfunction is a common sequela of the treatment of non-surgical patients in intensive care units. It is a serious problem for the affected persons and an increasingly important socio-economic problem as well. The effective management of delirium is very important. General conclusions are hard to draw from the available data because of heterogeneous study designs, varying methods of measurement, and differences among patient cohorts. Further studies are needed so that study designs and clinical testing procedures can be standardized and effective measures for prevention and treatment can be identified.

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The term “post-intensive care syndrome” (PICS) refers to long-term functional impairment arising after treatment in an intensive care unit. The syndrome is characterized primarily by bodily impairment and by limitations of cognitive functional ability and mental health (1).

As a long-term phenomenon, PICS differs from delirium, an acute organic dysfunction of the brain that may be reversible once its cause has been eliminated. Cognitive deficits after critical illness have a negative effect on competence in everyday life and on the quality of life (2). The patient’s reintegration into the workplace, productivity at work, and financial income are particularly affected (3). The stress level on relatives caring for the patient is high (4). Further major socio-economic consequences of PICS include the costs of therapy, nursing care, and rehospitalizations (5–8).

The long-term effects of treatment in an intensive care unit on cognitive function have only recently become a major topic for research in intensive care medicine. Postoperative cognitive dysfunction (POCD) is a current focus of study [9–13], but cognitive deficits can also arise in patients treated in intensive care units who have not undergone surgery.

Reviews of this topic to date have concerned mixed cohorts containing both surgical and non-surgical patients. This review is focused on studies of cognitive deficits arising exclusively in patients who were treated in intensive care units without having undergone surgery. The primary objective is to determine the prevalence of cognitive deficits in such patients; the secondary objective is to gain an overview of the nature, course, and severity of the cognitive deficits, as well as of risk factors and measures for prevention and treatment.

The results are relevant to all persons who participate in the care of patients with cognitive dysfunction or with a severe illness necessitating intensive care. Intensive care physicians, nurses, and therapists can be sensitized to the long-term cognitive effects of the treatment they provide. They must be able to recognize risk factors and initiate preventive measures. If an affected patient presents with cognitive difficulties to a general practitioner’s office or other outpatient facility, a correct diagnosis will have to be made. Finally, knowledge about PICS can also help the patient’s relatives put the problem in the proper context so that they can give the patient optimal support (4).

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Method

Search strategy

We conducted a selective literature search in the MEDLINE/PubMed database for articles indexed up to and including 25 May 2019. The search strategy was based on several synonyms for “critical illness” and “cognitive dysfunction,” as follows: “(cognitive dysfunction OR cognitive impairment OR cognitive sequelae OR cognitive decline OR cognitive disability) AND (critical illness OR ICU OR intensive care).” Additionally, we carried out an analogous search in the reference lists of studies and reviews chosen by expert opinion.

Selection of studies

One of the authors (JK) screened all search hits by title and abstract in accordance with the inclusion and exclusion criteria. Two authors (JK, JVE) then selected studies meeting the inclusion criteria on the basis of the full texts.

The inclusion criteria were as follows:

- original studies on the prevalence of cognitive deficits in non-surgical patients treated in an intensive care unit, as determined by a standardized testing procedure
- publication in either English or German
- patients over 18 years old

Studies were excluded if the patient cohort included patients of the following types:

- postoperative/surgical patients
- patients whose indication for treatment was trauma
- patients with cardiac arrest and/or status post cardiopulmonary resuscitation
- patients with primary neurological disease.

Data extraction and analysis

Three of the authors (JK, JVE, FB) established the categories for data extraction by expert opinion and divided these categories into three sets; then each of these three authors extracted data from all studies in one set of categories and subsequently checked over the data extraction performed by the other two authors in the remaining categories.

Unclear points and controversial questions were discussed and settled by all authors by common agreement, with all authors participating on equal terms. We did not carry out a meta-analysis, as this would probably have been unhelpful in view of the heterogeneity of the study findings. Instead, we chose to represent the extracted data in descriptive terms.

Results

The literature search in the database yielded 3360 hits; further screening by titles and abstracts left 233 articles, whose full texts were then read for suitability. The analogous search in the reference lists yielded a single study on sepsis patients (14). A total of 14 studies were included in the analysis (*eFigure*).

Diagnoses on admission and patient population

The diagnoses on admission to the intensive care unit included the following: acute respiratory distress syndrome (ARDS), 9 studies; sepsis, 3 studies; chronic obstructive pulmonary disease (COPD), one study. A further study concerned a mixed patient population with ARDS, septic shock, or cardiogenic shock (15). The mean age of the patients in the studies ranged from 31 to 76.7 years (14, 16). The sex distribution was the same across studies. In 13 studies, patients were artificially ventilated. The APACHE-II scores (a measure of the severity of disease) ranged from 18.1 to 23.5 (2, 17–20).

Epidemiology

17–78% of patients discharged from an intensive care unit sustained long-term cognitive deficits (*Table 1*). Baseline data on cognitive performance ability were only obtained in a single study. Among survivors of severe sepsis, 6.1% had already had relevant cognitive deficits before admission to the intensive care unit; after discharge, 16.7% did (14).

In two studies, demographically matched control groups were used; in one of them, the matched controls were not hospitalized, while, in the other, they were hospitalized, but not treated in an intensive care unit (14, 21). Iwashyna et al. showed that treatment in an intensive care unit for sepsis increased the frequency of moderate to severe cognitive dysfunction compared to the control group (14). Ambrosino et al. compared the prevalence of cognitive deficits in patients with exacerbated COPD with their prevalence in the control group: the resulting figures were 39% vs. 3% on discharge, 8% vs. 5% at 3 months, and 17% vs. 5% at 6 months [21]).

In seven studies, patients were tested at multiple time points (*Table 1, Figure*) (2, 15, 20–24). A trend toward improvement compared to the condition on discharge was seen within the first year, but 17–63% of the patients were still cognitively impaired on their last follow-up 0.25 to 2 years after discharge. These studies yielded no data on the prevalence of the different degrees of severity of cognitive dysfunction.

Risk factors and treatment approaches

Hopkins et al. described a correlation between the duration of hypoxemia (oxygen saturation <90%) and the severity of cognitive deficits at the time of discharge in patients who were hospitalized in intensive care units because of adult respiratory distress syndrome (ARDS) (2, 17). Hyperglycemia (maximal blood glucose >153.5 mg/dL), hypoglycemia (mean blood glucose <108 mg/dL), and highly variable blood glucose values were likewise associated with a higher probability of the development of long-term cognitive deficits. The duration of treatment in the intensive care unit was relevant as well (19).

Multiple studies have concerned potential therapeutic approaches during intensive care, e.g., dietary regimens (restricted vs. full) (23) or statin

TABLE 1

Original articles on the prevalence of cognitive deficits after intensive care (patients with a non-surgical admitting diagnosis)

First author, year	Admitting diagnosis	Age	Sex (male/female, %)	Duration of intensive care (days)	Artificial ventilation (frequency in% or duration in days)	Delirium (frequency in% or duration in days)	Duration of follow-up / latest time point of testing (weeks)	Percentage of patients with cognitive deficits at various times of testing	Percentage of patients with cognitive deficits on latest test
Ambrosino 2002 (21)	COPD	68 (SD, 7)	70/30	n.d.	100%	n.d.	26	disch.: 39%; 3 M: 8%; 6 M: 17%	17%
Calsavara 2018 (22)	sepsis	49 (SD, 15.2)	42/58	6 (R, 4–13)	60.6%	n.d.	52	1 d after disch.: 36.4%; 1 Y: 18.7%	18.7%
Gilmore 2015 (20)	sepsis	60 (IQR, 52–74)	49/51	17 (IQR, 9–24)	92.9%	n.d.	52	disch.: 86%; 6 M: 57%; 1 Y: 63%	62.5%
Holzgraebe 2017 (16)	ARDS	31	71/29	n.d.	100%	n.d.	156	n.d.	16.6%
Hopkins 1999 (17)	ARDS	45.5 (R, 16–78)	45/55	29.2 (SD, 18.8)	100%; 28.6 d (SD, 19.5)	n.d.	52	n.d.	78%
Hopkins 2004 (18)	ARDS	46 (SD, 16)	46/54	34 (SD, 20)	100%; 28 d (SD, 19)	n.d.	52	n.d.	45.5%
Hopkins 2005 (2)	ARDS	46 (SD, 16)	46/54	34 (SD, 20)	100%; 28 d (SD, 19)	n.d.	104	disch.: 69.7%; 1 Y: 45.5%; 2 Y: 47%	47%
Hopkins 2010 (19)	ARDS	46 (SD, 16)	46/54	34 (SD, 20)	100%; 28 d (SD, 19)	n.d.	52	n.d.	45.5%
Iwashyna 2010 (14)	sepsis	76.7 (SD, 9.5)	43/57	n.d.	28.4%	n.d.	47	n.d.	16.7%
Needham 2013 (23)	ARDS	47 (SD, 14)	50/50	14.6 (SD, 11.6)	11.4 d (SD, 9.9)	90%	52	6 M: 36%; 1 Y: 25%	25%
Needham 2016 (24)	ARDS	52 (SD, 14)	47/53	12 (SD, 7)	100%	72%	52	6 M: 37%; 1 Y: 29%	29%
Rothenhäusler 2001 (26)	ARDS	41.5 (SD, 14.7)	52/48	43.7 (R, 8–235; SD, 42.8)	100%; 32.3 d (SD, 21.1)	n.d.	333	n.d.	23.9%
von Bahr 2018 (25)	ARDS	39 (IQR, 24–52)	63/37	n.d.	31 d (IQR, 15–45)	n.d.	468	n.d.	21.4%
Wilson 2018 (15)	ARDS, sepsis, cardiogenic shock	59 (IQR, 49–67)	48/52	n.d.	n.d.	n.d.	52	3 M: 37%; 12 M: 52%	52%

ARDS, adult respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; d, days; disch., discharge; ICU, intensive care unit; IQR, interquartile range; n.d., no data; M, months; R, range; SD, standard deviation; Y, years

FIGURE

Overview of risk factors, pathophysiology, affected cognitive domains, types of course, sequelae, and approaches to the prevention and treatment of cognitive deficits arising in non-surgical patients after treatment in an intensive care unit (e9).

administration (24). These treatments have not been found to lower the incidence of cognitive dysfunction.

Study design

Most of the included studies were prospective studies carried out in single centers (*eTable 1*). The studies were performed over a 28-year period from 1985 to 2013. The periods of follow-up ranged from 0.5 to 9 years (21, 25). The most commonly used time point for testing was one year after discharge from intensive care.

Four studies employed time points for testing that were two years or more after the discharge from intensive care (2, 16, 25, 26); one of these studies had a prospective design (2). In six of the 14 studies (42.9%), patients were included in the study upon admission to the intensive care unit. In the remaining 8 studies, patients were included either upon discharge or at their first follow-up.

Patients who were already cognitively impaired before undergoing intensive care were excluded from five studies. Reported in-hospital mortality varied widely, from 10.9% (24) to 43.9% (20), even after correction for censored patients, i.e., those who declined or were lost to further follow-up (*Table 2*).

Testing procedures used, and affected cognitive domains

A wide variety of testing procedures were used to study a similarly wide variety of cognitive domains, and varying definitions of cognitive dysfunction were applied in different studies (*eTable 1*, *Figure*). Four

studies (28.6%) exclusively used cognitive screening instruments (e.g., the MMSE), questionnaires, or structured interviews (e.g., TICS, IQCODE). Ten studies (71.4%) employed more extensive neuropsychological testing batteries. There was no correlation between the type of cognitive testing used (screening vs. neuropsychological test battery) and the reported prevalence of cognitive impairment after intensive care.

Multiple cognitive domains were tested in all studies. The most commonly tested domains were memory, executive function, perception, attention, motor function, and speech comprehension. Deficits commonly affected multiple domains, with variation in the domains that were affected.

Discussion

These findings show that cognitive deficits are common in persons who have undergone treatment in intensive care units (without surgery). 17–78% of the patients were cognitively impaired after intensive care; in general, the impairments were new, they were most severe immediately after discharge, and they lasted a long time (at least 0.5 to 9 years).

The patients in this study did not differ to any significant extent from patients in other studies with mixed cohorts (both surgical and non-surgical patients) with respect to the prevalence and course of cognitive dysfunction (27–40, e1–e7) (*eTable 3*, *eTable 4*). Cognitive impairment increases after intensive care, compared either to baseline or to a control group, in mixed patient cohorts just as in exclusively non-surgical ones (31, 32, 34, 39). Cognitive

TABLE 2

Selected original articles: information on the number of included patients, mortality, loss to follow-up, and the number of patients evaluated at the time point of follow-up

First author, year	Number of patients included in study	Number and percentage of patients who died in intensive care	Number and percentage of patients (with respect to overall patient group) who underwent cognitive assessment on follow-up	Number and percentage of patients (with respect to overall patient group) who were censored	Total intra- and post-hospital mortality of uncensored patients (number and percentage)
Ambrosino 2002 (21)	63	n.d. (inclusion after intensive care)* ¹	6 M: 36 (57.2)	6 M: 17 (27)	6 M: 10 (21.7)
Calsavara 2018 (22)	33	n.d. (inclusion after intensive care)* ¹	1 Y: 16 (48.4)	6 (18.1)	8 (29.6)
Gilmore 2015 (20)	98	43 (43.9)	1 Y: 16 (16.3)	18 (18.4)	63 (78.8)
Holzgraefe 2017 (16)	13	n.d. (inclusion after intensive care)* ¹	3 Y: 7 (53.8)	4 (30.8)	2 (22.2)
Hopkins 1999 (17)	106	39 (36.8)	1 Y: 55 (51.9)	9 (8.5)	42 (43.3)
Hopkins 2004 (18)	74	n.d. (inclusion after intensive care)* ¹	1 Y: 66 (89.2)	5 (7.6)	3 (4.3)
Hopkins 2005 (2)	120	42 (41.2)	1 Y: 66 (55); 2 Y: 62 (51.7)	1 Y: 8 (6.7); 2 Y: 10 (8.3)	1 Y: 45 (40.2); 2 Y: 47 (42.7)
Hopkins 2010 (19)	74	n.d. (inclusion after intensive care)* ¹	1 Y: 66 (89.2)	5 (7.6)	3 (4.3)
Iwashyna 2010 (14)	1194	n.d.* ²	1 Y: 516 (43.2)	1 Y: 32 (2.7)	862 (74.2)
Needham 2013 (23)	349	70 (20.1)	6 M: 163 (46.7); 1 Y: 149 (42.7)	6 M: 94 (26.9); 1 Y: 111 (31.8)	6 M: 92 (36.1); 1 Y: 100 (42.0)
Needham 2016 (24)	329	36 (10.9)	6 M: 130 (39.5); 1 Y: 148 (45)	6 M: 134 (40.7); 1 Y: 115 (35.0)	3 M: 60 (30.8); 6 M: 65 (30.4)
Rothenhäusler 2001 (26)	192	73 (38.0)	6 Y: 46 (24.0)	56 (29.2)	90 (66.2)
Von Bahr 2018 (25)	38	n.d. (inclusion after intensive care)* ¹	9 Y: 28 (73.7)	10 (26.3)	0 (0)
Wilson 2018 (15)	195	n.d. (inclusion after intensive care)* ¹	1 Y: 153 (78.5)	46 (23.6)	0 (0)

*¹Patients included in study at the end of intensive care or afterward. Intrahospital mortality of original cohort not reported.

*²Patients included in study at the beginning of intensive care. Intrahospital mortality not reported.

Censored = lost to follow-up or declined further participation in study (dropped out of study). M, months; n.d., no data; Y, years.

impairment in mixed patient cohorts is usually mild or moderate (27, 28, 30, 32, 36, 38, e1). In studies with exclusively non-surgically treated patients, the prevalence of individual grades of cognitive impairment was not reported.

As an illustration, the prospective BRAIN-ICU cohort study revealed, in a mixed patient population with 18% surgical patients, an increase in the prevalence of cognitive impairment from 6% at baseline to 40% (for a test result 1.5 standard deviations [SD] below the reference mean, comparable to the effect of moderate traumatic brain injury) and 26% (for a test result 2 SD below the reference mean, comparable to mild Alzheimer dementia) three months after discharge. The corresponding figures at one year were 34% and 24% (e1).

This is a problem of considerable socioeconomic importance, as persons with cognitive deficits often face

long-lasting impairments in everyday competence and in the quality of life.

Pathogenesis

Neuroradiological and neuropathological studies have provided evidence of diffuse brain damage. There are global and local patterns of atrophy, as well as cortical and subcortical lesions, particularly in the corpus callosum, the hippocampus, and the basal ganglia (7, e8, e9). Delirium has also been linked to abnormalities of brain structure. It may be that the pathogenetic mechanism of acute brain dysfunction goes on to produce chronic structural changes that impair cognition over the long term (e10).

This pathogenetic mechanism seems to be of a multifactorial nature, with contributory roles played by metabolic factors (such as hyper- and hypoglycemia), hemodynamic factors (such as hypotension and

BOX

The management of delirium

- **Prophylaxis**
 - for patients at high risk: low-dose haloperidol
 - avoidance of oversedation
 - stimulating measures in the daytime: mobilization and reorientation (with visual aids, hearing aids, communication, and daylight)
 - sleep-promoting measures at night: reduction of light and noise, availability of earplugs and blindfold sleep masks
- **Non-pharmacological treatment**
 - early mobilization, physio- and ergotherapy
 - cognitive stimulation
 - improvement of environmental factors (noise reduction, light adjustment)
 - avoidance of social deprivation
- **Treatment with drugs**
 - in low doses: haloperidol, risperidone, olanzapine, or quetiapine
 - continuous administration of alpha-2-agonists

Excerpted from the German S3 guideline on analgesia, sedation, and delirium management in intensive care medicine (e21)

hypoxemia), inflammation, and toxic influences (from sedative, analgesic, and anticholinergic drugs, among others) (7, 19, 33, 40, e3, e8, e9, e11–e13). Some of these factors may generate and sustain a systemic inflammatory reaction. It is thought that neuro-inflammatory processes induced by spreading of the inflammatory reaction across the blood-brain barrier cause neuronal injury (e12).

Risk factors for cognitive deficits after intensive care

Delirium is the best-studied risk factor for long-term cognitive deficits after intensive care, in both non-surgical and mixed surgical/non-surgical patient cohorts. Denke et al. showed an association between the duration of delirium and impaired cognitive ability in a cohort of ARDS patients (e14). Similarly, the BRAIN-ICU study revealed that a longer duration of delirium was independently associated with poorer cognitive test results at 3 and 12 months in a mixed patient cohort (e1).

It has not yet been conclusively determined whether old age is an independent risk factor (8). The patient cohorts in the studies considered in this review all contained patients of all age groups, but no age-dependent increase was found in the prevalence of cognitive deficits after intensive care. Nor was age found to have a significant effect in the BRAIN-ICU study (e1). The results of other studies with mixed patient cohorts appear to support the hypothesis of a higher risk at older ages, but long-term cognitive deficits can clearly arise in patients of any age, including children (e15–e17).

Other risk factors, including hypo- and hyperglycemia, have been confirmed in studies with mixed

patient cohorts (e18). As for hypoxemia, the evidence is mixed (e11). The severity of illness, as measured by the APACHE-II score, seems to play a lesser role (e9). In summary, the current state of the evidence is weak. Only delirium can now be considered a clearly established risk factor.

The prevention of cognitive dysfunction after intensive care

The effective prevention and treatment of delirium might, therefore, be essential for the prevention of long-term deficits. Delirium in intensive care is the target of treatment strategies such as the so-called ABCDEF bundle (e19, e20), and it counts as one of ten quality indicators in intensive care medicine (e21, e22) (Box). Further recommendations include early mobilization, physiotherapy, and other early rehabilitative measures, as well as music therapy, the creation of individual rehabilitation plans, and the keeping of an intensive-care diary (e9, e13, e17, e23–e25).

Approaches to treatment

There have been hardly any studies of specific treatments to date (e26). The RETURN study showed that a focused, multidisciplinary rehabilitation program consisting of cognitive stimulation, physiotherapy, and ergotherapy improved the cognitive ability of the intervention group compared to a control group that underwent non-protocol-based rehabilitation (e27).

Other types of combined therapy with intensified cognitive components are also promising, but only a few have been evaluated to date (e7, e8, e28, e29). It seems advisable to start specific treatment as early as possible, even while the patient is still in the intensive care unit (e26, e30, e31).

Clinical implications

Although many aspects remain unclear, a number of recommendations can already be made for clinical practice (e9):

- Non-pharmacological treatment approaches play the most important role in the prevention and treatment of cognitive impairment.
- Structured, multimodal, and quality-indicator-oriented therapeutic concepts are helpful for the provision of patient-specific treatment and for the minimization of risk factors.
- The effective management of delirium is very important.
- Patients should be followed over the long term in outpatient and inpatient structures with special interdisciplinary competence.
- All professionals who care for the affected patients and their relatives in a variety of contexts should provide information about the long-term risk of cognitive impairment after intensive care, thereby increasing understanding among the persons concerned and helping them achieve their objectives and priorities.

Limitations

We systematically searched only one database, and we limited the analysis to publications in English or German. The wide variation in prevalence figures can be attributed in part to the heterogeneity of patient cohorts, the non-uniform testing procedures, and the differing time points of evaluation (e9, e12). In view of these differences, no meta-analysis could be performed.

Many of the studies provided less than full information. In most of them, no baseline data were obtained on the patients' cognitive status before the initiation of intensive care; these studies are thus uninformative with respect to a central question, namely, whether the observed cognitive deficits arose de novo or as a worsening of pre-existing deficits. Half of the studies provided no data on mortality in the intensive care unit. Case numbers were often low, and patients were often enrolled in the studies only after their discharge from intensive care. This late time point of patient inclusion, along with the high rates of loss to follow-up in some of the studies, may have resulted in a selection bias favoring patients with greater-than-average willingness and ability to participate in the studies. A bias of this kind would make it difficult to validly answer the question whether risk-factor modification during intensive care might improve the clinical outcome.

Overview

The marked heterogeneity among studies with regard to testing procedures and defining criteria makes it difficult to assess the prevalence (and various other aspects) of cognitive impairment after illnesses that necessitate intensive care. It is, therefore, very important that the evaluation of cognitive function should be standardized by the use of consensus-approved measurement instruments, along with the simultaneous acquisition of data on relevant covariables, such as sedation and pain scores.

In future studies, baseline data should be recorded, the clinical course during treatment in intensive care—including delirium, if it arises—should be precisely characterized, and losses to follow-up should be minimized. More prospective, multicenter, interdisciplinary research projects are needed to give us robust information about this long-term dimension of intensive care medicine. In particular, the risk factors should be better characterized, and opportunities for intervention should be identified (e9, e11).

Conflict of interest statement

Dr. Borchers has received reimbursement of travel expenses from Forum für medizinische Fortbildung FomF GmbH and from Asklepios Klinik St. Georg, as well as lecture honoraria from Charité Healthcare Services GmbH, Forum für medizinische Fortbildung FomF GmbH, and Klinikum Ernst von Bergmann GmbH.

Dr. Weiss has served as a paid consultant for Orion Pharma Ltd. and has received lecture honoraria from Orion Pharma Ltd. and Dr. F. Köhler Chemie GmbH.

Prof. Spies has received payment for carrying out research and clinical studies from Ardis Pharmaceutical Inc., B. Braun Melsungen AG, Drägerwerk AG & Co. KGaA, Grünenthal GmbH, Infectopharm GmbH, Sedana Medical Ltd., and Sintetica GmbH.

The remaining authors state that they have no conflict of interest.

Key messages

- 17 to 78% of non-surgical patients treated in intensive care units suffer from cognitive deficits that may impair their competence for everyday living and lessen their quality of life.
- Cognitive deficits often arise de novo after treatment in an intensive care unit and can be caused by a variety of non-surgical illnesses that necessitate intensive care.
- The prevalence of cognitive deficits is highest in the first few months after discharge and lower thereafter; in some cases, however, the deficit can persist for years.
- The pathophysiology, risk factors, and potential treatments of such deficits are manifold and, as yet, inadequately studied. The only definitively established risk factor is delirium.
- The effective management of delirium is of central importance for the prevention of long-term cognitive deficits.

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Cognitive Deficits Following Intensive Care

by Joel Kohler, Friedrich Borchers, Matthias Endres, Björn Weiss, Claudia Spies, and Julius Valentin Emmrich

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eTABLE 1

Neuropsychological tests used, diagnostic criteria for the presence of cognitive dysfunction, information provided on whether there was a control group and on the educational level of the patients studied, study design, and study implementation

First author, year	Country	Study design	Study period	Patient inclusion before or at the start of intensive care or after its termination	Pre-existing cognitive deficit as a criterion of exclusion	Test procedure(s) used	Definition of cognitive dysfunction	Control group	Information on educational level (n = years of schooling)
Ambrosino 2002 (21)	Italy	pr., mo.	01.1996–12.1998	after termination	n.d.	MMSE	<24/30	yes	n.d.
Calsavara 2018 (22)	Brazil	pr., mo.	n.d.	at start	n.d.	CERAD battery: Verbal fluency, BNT, MMSE; WL Learning, WL Recall, WL Recognition Discriminability; TMT: A & B	TMT A: >300 sec.	no	7 (IQR, 4–8)
Gilmore 2015 (20)	USA	pr., mo.	11.2009–02.2011	before start	n.d.	Telephone interview for cognitive status (TICS-m)	≤ 31 points on score adjusted for educational level	no	n.d.
Holzgärd 2017 (16)	Sweden	re., mo.	10.2012–07.2013	after termination	n.d.	WAIS-IV; RAVLT; ROCF; WMS: LM I & II	global cognition score <reference mean	no	12.1
Hopkins 1999 (17)	USA	pr., mo.	02.1994–07.1998	after termination	n.d.	WAIS-R; WMS-R; RAVLT; ROCF; TMT: A & B	<reference mean in at least one domain (memory/attention/concentration) measured by WMS-R	no	12.8
Hopkins 2004 (18)	USA	pr., mo.	02.1994–12.1999	after termination	yes	WAIS-R; WMS-R; RAVLT; ROCF; TMT: A & B, VFT	two test scores 1.5 SD or one test score 2 SD below reference mean	no	13 (SD, 2.3)
Hopkins 2005 (2)	USA	pr., mo.	02.1994–12.1999	after termination	yes	WAIS-R; WMS-R; RAVLT; ROCF; TMT: A & B, VFT	two test scores 1.5 SD or one test score 2 SD below reference mean	no	13 (SD, 2.3)
Hopkins 2010 (19)	USA	pr., mo.	02.1994–12.1999	after termination	yes	WAIS-R; WMS-R; RAVLT; ROCF; TMT: A & B, VFT	two test scores 1.5 SD or one test score 2 SD below reference mean	no	13 (SD, 2.3)
Iwashyna 2010 (14)	USA	pr., mu.	1998–2005	before start	no	adapted TICS; IQCODE	adapted TICS: max. 35 points, CD: <11; IQCODE: no CD: assessment as good to excellent, CD: assessment as adequate or poor	yes	n.d.

First author, year	Country	Study design	Study period	Patient inclusion before or at the start of intensive care or after its termination	Pre-existing cognitive deficit as a criterion of exclusion	Test procedure(s) used	Definition of cognitive dysfunction	Control group	Information on educational level (n = years of schooling)
Needham 2013 (23)	USA	pr., mu.	07.2008–05.2012	at start	yes	HSCT; COWAT; WAIS-III: LM I & II; Similarities Score, DS	two test scores 1.5 SD or one test score 2 SD below reference mean	no	n.d.
Needham 2016 (24)	USA	pr., mu.	03.2010–09.2013	at start	yes	HSCT; VFT; WAIS: Similarities, DS, LM I & II	two test scores 1.5 SD or one test score 2 SD below reference mean	no	13
Rothenhäusler 2001 (26)	Germany	re., mo.	01.1985–01.1995	after termination	n.d.	SKT (short cognitive performance test for assessing deficits of memory and attention)	score >4/27	no	n.d.
Von Bahr 2018 (25)	Sweden	re., mo.	01.1995–07.2009	after termination	n.d.	WAIS; RAVLT; ROCF; Free and Cued Selective and Reminding test; WMS; Delis–Kaplan Executive Function System	1 SD below reference mean	no	11.6 (SD, 3.5)
Wilson 2018 (15)	USA	pr., mu.	03.2007–05.2010	after termination	no	Ruff-TUD, COWAT, Brief-I	1.5 SD below reference mean	no	12 (IQR, 12–14)

In many studies, adjustment for age, level of education, and/or premorbid intelligence level (IQ) was mentioned in the Methods section, and other publications were cited for a description of the main study cohort. CD, cognitive dysfunction; ICU, intensive care unit; IQR, interquartile range; mo., monocentric (single-center) study; mu., multicenter study; n.d., no data; pr., prospective; re., retrospective; SD, standard deviation. For abbreviations of test procedures, see e Table 2.

eTABLE 2

Table of abbreviations for the test procedures mentioned in eTable 1

Abbreviation	Test
Brief-I	Behavior Rating Inventory of Executive Function Initiation
BNT	Boston Naming Test
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
COWAT	Controlled Oral Word Association Test
DS	Digit Span
HSCT	Hayling Sentence Completing Test
IQCODE	Informant Questionnaire on Cognitive Decline in the Elderly
LM	Logical Memory
MMSE	Mini Mental State Examination
RAVLT	Rey Auditory Verbal Learning Test
ROCF	Rey-Osterrieth Complex Figure
Ruff-TUD	Ruff-Total Unique Design
TICS	Telephone Interview for Cognitive Status
TMT	Trail Making Test
VFT	Verbal Fluency Test
WAIS	Wechsler Adult Intelligence Scale
WMS	Wechsler Memory Scale
WL	Word List

eTABLE 3

Original articles on the prevalence of cognitive deficits after intensive care: studies with mixed patient populations (surgical and non-surgical admitting diagnoses)

First author, year	Country	Study design	Study period	Admitting diagnosis	Patient inclusion before or at the start of intensive care or after its termination	Patients who underwent cognitive assessment on follow-up (number and percentage of total)	Age (R, IQR, SD)	Sex (male/female, %)	Pre-existing cognitive deficit as a criterion of exclusion	Duration of intensive care (days)	Artificial ventilation (percentage of patients or number of days)	Delirium (percentage of patients or number of days)	Percentage of patients with cognitive deficits at various times of testing
Cronberg 2009 (27)	Sweden	pr., mu.	09.2002–10.2005	cardiac arrest	at start	43 (22.9)	62.4 (R, 18–85)	79/21	n.d.	n.d.	100%	n.d.	n.d.
Cronberg 2015 (28)	multi-national	pr., mu.	11.2010–01.2013	cardiac arrest	at start	455 (48.5)	59 (SD, 12.7)	84/16	n.d.	n.d.	100%	n.d.	n.d.
Daly 2009 (29)	USA	re., mo.	k. A.	mixed (N)	after termination	257 (76.9)	60.9 (SD, 16.5)	44/56	n.d.	n.d.	100%; 11.9 d (SD, 10.9)	n.d.	n.d.
de Azevedo 2017 (30)	Brazil	pr., mo.	03.2014–02.2015	mixed (S, N)	at start	413 (57.0)	57 (IQR, 46–72)	51/49	yes	10 (IQR, 5–19)	13.4%; 3 d (IQR, 1.2–6.7)	13.3%	n.d.
Ehlenbach 2010 (31)	USA	pr., mu.	1994–2007	mixed (T)	before start	41 (100)	75.4	56/44	yes	n.d.	n.d.	n.d.	n.d.
Girard 2010 (32)	USA	pr., mo.	10.2003–03.2006	mixed (N)	before start	3 M: 76 (40.6); 1 Y: 52 (27.8)	61 (IQR, 47–71)	52/48	no	n.d.	100%; 2–10 d (IQR)	84%	3 M: 79%; 1 Y: 71%
Jackson 2003 (33)	USA	pr., mo.	2.2000–5.2001	mixed	at start	34 (12.4)	53.2 (SD, 15.3)	52/47	yes	10 (IQR, 8–13)	6 d (IQR, 4–12)	4.5 d	n.d.
Jackson 2010 (34)	USA	pr., mo.	10.2003–03.2006	mixed (N)	at start	3 M: 80 (44.4); 1 Y: 63 (35.0)	68 (IQR, 56–76)	49/51	no	n.d.	100%	n.d.	3 M: 91%; 1 Y: 70%
Jones 2006 (35)	UK	pr., mo.	03.2003–11.2004	mixed (T)	after termination	1 W: 30 (100); 2 M: 16 (53.3)	54 (R, 18–78)	57/43	n.d.	14 (R, 6–45)	100%	28%	in ICU: 100%; 1 week: 86%; 2 M: 50%
Lijia 2015 (36)	multi-national	pr., mu.	06.2011–09.2013	cardiac arrest	after termination	287 (44.0)	60 (IQR, 52–68)	89/11	n.d.	n.d.	100%	n.d.	n.d.
Mikkelsen 2012 (37)	USA	pr., mu.	06.2000–09.2006	mixed (T)	after termination	102 (47.9)	49 (IQR, 40–58)	43/57	n.d.	10 (IQR, 7–16)	100%; 6 d (IQR, 4–9)	n.d.	n.d.
Mitchell 2018 (38)	Australia	pr., mo.	11.2011–12.2014	mixed (S, T)	after termination	3 M: 88 (59.5); 6 M: 79 (53.4)	57 (IQR, 43–65)	69/31	n.d.	4.3 (IQR, 2.1–7.9)	100%	19%	3 M: 41%; 6 M: 24%
Nelson 2006 (39)	USA	pr., mo.	09.2003–01.2005	mixed (S, N)	at start	3 M: 75 (37.1); 6 M: 60 (29.7)	72 (R, 21–99)	58/42	no	16 (IQR, 11–22)	100%	27.7%	3 M: 77%; 6 M: 71%
Nunes 2003 (40)	Portugal	cs., mo.	04.1997–12.2000	cardiac arrest	after termination	11 (100)	51 (R, 23–79)	82/18	n.d.	3.5	100%	n.d.	n.d.

First author, year	Country	Study design	Study period	Admitting diagnosis	Patient inclusion before or at the start of intensive care or after its termination	Patients who underwent cognitive assessment on follow-up (number and percentage of total)	Age	Sex (male/female, %)	Pre-existing cognitive deficit as a criterion of exclusion	Duration of intensive care (days)	Artificial ventilation (percentage of patients or number of days)	Delirium (percentage of patients or number of days)	Percentage of patients with cognitive deficits at various times of testing
Pandharipande 2013 (e1)	USA	pr., mu.	03.2007–05.2010	mixed (S, N)	at start	3 M: 448 (54.2); 6 M: 382 (46.2)	61 (IQR, 51–71)	50/50	no	n.d.	90%	75%	3 M: 40%; 1 Y: 34%
Sacanella 2011 (e2)	Spain	pr., mo.	k. A.	mixed	at start	112 (48.7)	73.4 (SD, 5.5)	57/43	yes	9.4 (SD, 10.2)	54%	n.d.	discharge: 15%; 1 Y: 10%
Sukantarat 2005 (e3)	UK	pr., mo.	04.2000–03.2003	mixed (S)	after termination	3 M: 51 (100); 6 M: 45 (88.2)	59.5 (R, 26–82)	43/57	n.d.	9 (R, 3–78)	3.5 d (R, 0–74)	n.d.	3 M: 55%; 9 M: 27%
Torgersen 2010 (e4)	Norway	cs., mu.	12.2005–03.2008	cardiac arrest	after termination	26 (30.2)	61.5 (R, 22–79)	88/12	yes	n.d.	n.d.	n.d.	n.d.
Torgersen 2011 (e5)	Norway	pr., mo.	01.2008–02.2009	mixed	after termination	3 M: 21 (38.2); 1 Y: 17 (30.9)	51.3 (R, 18–77; SD, 16.2)	65/45	yes	10.0 (R, 1–36; SD, 9.5)	6.9 d (R, 0–29.8; SD, 8.5)	n.d.	8.2 d: 64.3 %; 3 M: 11%; 1 Y: 10%
Woon 2012 (e6)	USA	pr., mu.	08.2007–12.2008	mixed (S, T)	after termination	53 (75.7)	54.4 (R, 21–85; SD, 17.3)	50/50	yes	15.4 (SD, 9.8)	100%; 8.8 d (SD, 6.4)	n.d.	n.d.
Zhao 2017 (e7)	China	pr., mo.	01.2013–09.2013	mixed (S, N)	after termination	299 (90.1)	51 (R, 21–78)	47/53	n.d.	28 (SD, 5.35)	n.d.	n.d.	3 d: 52%; 3 M: 82%

Mixed: mixed diagnoses on admission to intensive care unit. (S): including surgical/postoperative patients; (N): includes patients with primary neurological disease; (T): includes trauma patients. cs, cross-sectional; d, days; ICU, intensive care unit; IQR, interquartile range; M, months; mo., monocentric; mu., multicenter; n.d., no data; pr., prospective; R, range; re., retrospective; SD, standard deviation; Y, years

eTABELLE 4

Original articles on the prevalence of cognitive deficits after intensive care: studies with mixed patient populations (surgical and non-surgical admitting diagnoses) – supplement to eTable 3

First author, year	Duration of follow-up / latest time point of testing (weeks)	Number of patients included in the study	Percentage of patients with cognitive dysfunction on latest test
Cronberg 2009 (27)	31	94	93%
Cronberg 2015 (28)	26	939	17%
Daly 2009 (29)	9	334	26.8%
de Azevedo 2017 (30)	48	724	49.9%
Ehlenbach 2010 (31)	52	41	12.2%
Girard 2010 (32)	52	187	71.6%
Jackson 2003 (33)	26	275	32%
Jackson 2010 (34)	52	180	70%
Jones 2006 (35)	9	30	50%
Lilja 2015 (36)	26	652	51%
Mikkelsen 2012 (37)	52	213	55%
Mitchell 2018 (38)	26	148	24%
Nelson 2006 (39)	26	203	70.6%
Nunes 2003 (40)	93	11	45.4%
Pandharipande 2013 (e1)	52	826	34%
Sacanella 2011 (e2)	52	230	10%
Sukantarat 2005 (e3)	39	51	27%
Torgersen 2010 (e4)	89	86	52%
Torgersen 2011 (e5)	52	55	10%
Woon 2012 (e6)	26	70	57%
Zhao 2017 (e7)	13	332	82%