

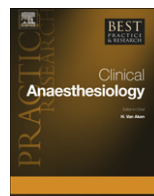


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Understanding terminology of delirium and long-term cognitive impairment in critically ill patients

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Delirium, an acute brain dysfunction, frequently affects intensive care unit (ICU) patients during the course of a critical illness. Besides the acute morbidities, ICU survivors often experience long-term sequelae in the form of cognitive impairment (LTICI-Cl). Though delirium and LTICI-Cl are associated with adverse outcomes, little is known on the terminology used to define these acute and chronic co-morbidities. The use of a correct terminology is a key factor to spread the knowledge on clinical conditions. Therefore, we first review the epidemiology, definition of delirium and its related terminology. Second, we report on the epidemiology of LTICI-Cl and compare its definition to other forms of cognitive impairments. In particular, we define mild cognitive impairment, dementia and finally postoperative cognitive dysfunction. Future research is needed to interpret the trajectories of LTICI-Cl, to differentiate it from neurodegenerative diseases and to provide a formal disease classification.

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Introduction

Every year an increasing number of patients are admitted to intensive care units (ICUs) for the management and treatment of a critical illness. The most recent statistics report that yearly, in the world between 13 and 20 million patients are mechanically ventilated, 15–19 million are admitted to an ICU for the treatment of sepsis and 1.1–5.5 million are treated for an acute lung injury.¹ The advancements in the medical treatments in the last years have led to a handful number of patients surviving a critical illness.² It has been progressively reported that these patients experience an acute and long-term morbidity in the form of cognitive, functional and emotional impairments along with diminished health-related quality of life.^{2,3}

Delirium is the most common form of acute brain dysfunction, which affects up to 80% of critically ill patients during an ICU stay, according to the severity of illness.^{4–6} The occurrence of delirium is also an independent predictor of adverse outcomes such as self-extubation and removal of catheters,⁷ longer hospital stay,^{8–10} increased cost,¹¹ higher 6-month and 1-year mortality^{12–15} and long-term cognitive impairment.^{16–20}

Indeed, cognitive impairment represents a conspicuous component of the long-term sequelae of ICU survivors.¹⁶ Different studies have analysed the presence of long-term cognitive impairment after a critical illness (LTCl-CI) at different time points showing neurocognitive impairments at 2 months,²¹ 3 months,^{22,23} 6 months,^{24,25} 9 months,²⁶ 1 year,^{22,23,27–29} 2 years³⁰ and 6 years^{31,32} after the hospitalisation for a critical illness. At 1 year, 46–70% of the patients show signs of LTCl-CI^{22,23,27–29} and, even more relevant, LTCl-CI is present in 25% of those who survive after 6 years.³¹

Among health-care providers, delirium and LTCl-CI are often unrecognised.²⁵ Hopkins et al.³⁰ showed that only 12% of the patients surviving a critical illness and admitted to rehabilitation were evaluated for the presence of cognitive impairments. The reason of this underdetection might be related to barriers in the terminology used to define these cognitive impairments.³³ We have previously reported that among 13 languages using the Romanic characters, only 54% use the term 'delirium' to indicate the disorder as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).³⁴ Even with LTCl-CI, there is still an uncertainty on how to define it in comparison to other cognitive impairment entities such as mild cognitive impairment (MCI), dementia and postoperative cognitive decline (POCD).

Here (1) we first review specific terminology of delirium, and then (2) we compare the definition of LTCl-CI with MCI, dementia and POCD.

Delirium terminology

Delirium is defined, accordingly to the DSM-IV-TR criteria,³⁴ as a clinical condition characterised by (1) a disturbance of consciousness with inattention, accompanied by (2) acute change in cognition (i.e., memory deficits, disorientation, language disturbances and perceptual disturbances) that is not better accounted for by a pre-existing, established or evolving dementia; (3) the disturbance develops over a short period of time (hours to days) with fluctuation over time; and (4) there is an evidence that the disturbance is caused by the direct physiological consequences of a general medical condition. The knowledge and the interest on delirium in critically ill patients have progressively increased over the course of the last few years.^{33,35} Nonetheless, there is still a lack of homogeneity in the use of terminology especially by physicians and health-care personnel who do not specialise in neuropsychiatric disciplines and for different background training and categorisation system. In a previous international survey,³³ we found that two terms are very consistently used when referring to acute brain dysfunction in critically ill patients: 100% of the selected languages use the term 'coma' or 'koma' to describe patients unresponsive to verbal and/or physical stimuli, and 100% use delirium tremens to define delirium due to alcohol withdrawal. Conversely, only 54% use the term delirium to indicate the disorder as defined by the DSM-IV.³⁴ Several years ago, Lipowski³⁶ called delirium "the Cinderella of American Psychiatry: taken for granted, ignored, and seldom studied." These findings underline the importance of providing further knowledge not just on the general definition of delirium but specifically on the terminology used in the research and clinical settings according to the time course, subtypes and sub-syndromal forms (Fig. 1).

Overview of the terminology of delirium		
<p align="center">Overall definition of delirium: A clinical condition characterized by (1) a disturbance of consciousness with inattention, accompanied by (2) acute change in cognition (i.e., memory deficits, disorientation, language disturbances and perceptual disturbances) that is not better accounted for by a pre-existing, established or evolving dementia; (3) the disturbance develops over a short period of time (hours to days) with fluctuation over time; (4) there is evidence that the disturbance is caused by the direct physiological consequences of a general medical condition.</p>		
Terminology according to time course	Motoric subtypes classification	Additional definitions
<ul style="list-style-type: none"> - <u>Prevalent delirium</u> Delirium is detected at the time of admission to a clinical setting - <u>Incident delirium</u> delirium newly occurs during the course of a stay in a clinical setting - <u>Persistent delirium</u> delirium symptoms persist over the course of time 	<ul style="list-style-type: none"> - <u>Hyperactive delirium</u> is characterized by increased psycho-motor activity with agitated behavior - <u>Hypoactive delirium or "quiet" delirium</u> is characterized by reduced psycho-motor behavior and lethargy - <u>Mixed delirium</u> alternates unpredictably between a hyperactive and a hypoactive manifestation 	<ul style="list-style-type: none"> - <u>Subsyndromal delirium</u> a condition in which patients have one or more symptoms that never progress to a full diagnosis of delirium as described by the DSM-IV-TR criteria - <u>Delirium superimposed on dementia</u> when delirium occurs in patients with a pre-existing dementia

Fig. 1. Overview of the terminology of delirium.

Delirium terminology and time course

Delirium can be defined according to the time of presentation as prevalent, incident and persistent (Fig. 1). Delirium is defined as 'prevalent' when it is detected at the time of admission to a clinical setting. Conversely, delirium can be defined as 'incident' if it newly occurs during the course of a stay in a clinical setting. Finally, delirium can be named 'persistent' when delirium symptoms persist over the course of time. In the past, delirium was considered as a transitory syndrome. Several studies^{37–40} in non-ICU setting have shown that delirium symptoms can persist up to 1 month after the first diagnosis.⁴¹ Pisani et al.,¹² analysing the effect of delirium on mortality, reported the persistence of delirium up to 10 days after the first diagnosis in ICU patients.

Motoric subtypes definition

Delirium has been traditionally classified in non-ICU settings^{42–44} according to the psychomotor behaviour into subtypes as hyperactive, hypoactive delirium and mixed delirium^{42,45} (Fig. 1). 'Hyperactive delirium' is characterised by increased psycho-motor activity with agitated behaviour. 'Hypoactive' or 'quiet' 'delirium' is characterised by reduced psycho-motor behaviour and lethargy. Mixed delirium alternates unpredictably between a hyperactive and a hypoactive manifestation. In the ICU setting, the motoric subtypes of delirium have been defined with the use of the confusion assessment method for the ICU (CAM-ICU)^{4,6} along with the Richmond Agitation and Sedation Scale (RASS).^{46,47} The CAM-ICU is a screening tool for the detection of delirium in critically ill patients. The CAM-ICU presents a two-step approach. Level of consciousness (arousal) is first evaluated with the RASS,^{46,47} a 10-point scale ranging from –5 (no response to voice or physical evaluation) to +4 (overtly combative, violent and immediate danger for staff), with a score of 0 denoting a calm and alert patient. Patients who are comatose (RASS –5 or –4) cannot be assessed for delirium. Patients with a RASS score

of -3 or greater (-2 to $+4$) can be assessed by the CAM-ICU. The CAM-ICU comprises four features. To be diagnosed as delirious, one needs to have a RASS score of -3 or higher (-2 to $+4$), with an acute change or fluctuation in mental status (Feature 1), accompanied by inattention (Feature 2), and either altered level of consciousness (Feature 3) or disorganised thinking (Feature 4). A patient is defined as having 'hyperactive delirium' if the CAM-ICU screening is positive for the presence of delirium and the RASS score is above 0; 'hypoactive delirium' is identified when the CAM-ICU screening is positive for delirium and the RASS score is between -1 and -3 . It is an interesting reporting that the prevalence of hypoactive delirium in critically ill patients ranges from 43.5% to 67%,^{48–50} while the pure hyperactive and mixed ranges from 0% to 1.6%, and from 6% to 54.9%, respectively.^{48–50}

Additional definitions

'Subsyndromal delirium (SSD)' is defined as a condition in which patients have one or more symptoms that never progress to a full diagnosis of delirium as described by the DSM-IV-TR criteria. For instance, a patient can have an acute change in mental status and disorganised thinking but does not show signs of inattention. It has been mainly described in non-ICU settings.^{51–54} Nonetheless, Ouimet and colleagues⁵⁵ defined the presence of sub-syndromal delirium using the intensive care delirium checklist (ICDSC) in an ICU population.⁵ The ICDSC score ranges from 0 to 8, with a score of 4 or higher indicating the presence of delirium. SSD was identified in 33.3% of a cohort of ICU patients using an ICDSC cut-off score of 1–3. It has been showed that ICU patients who have sub-syndromal delirium experience worse outcomes than those who have no delirium at all, confirming previous reports^{51,54} of graded severity of brain dysfunction from normal to sub-syndromal to delirium.

Finally, when delirium is identified in patients with pre-existing dementia, it is named 'delirium superimposed on dementia (DSD)'.⁵⁶ DSD has been specifically studied outside the ICU, and Fick and colleagues described a prevalence of DSD in a systematic review of the literature ranging from 50% to 89%.⁵⁷

Cognitive impairment terminology

ICU survivors often suffer significant long-term sequelae in the form of cognitive impairment.¹⁶ Though there has been an increasing interest on the LTICI-CI, it remains unclear how to best define it, as it is a less specific syndrome (as currently understood) than other diagnostic entities such as MCI, dementia and POCD. We report in detail the definitions, which have been used to describe these clinical entities trying to bring clarity to clinicians in their daily practise.

Long-term cognitive impairment after a critical illness

Jackson et al.⁵⁸ have recently underlined that in the context of ICU survivors, two terms are often used in synonymous fashion – cognitive impairment and cognitive dysfunction; though it is unclear whether these terms always refer to the same clinical entity. In general, it may be more appropriate to use the term 'cognitive impairment' instead of 'cognitive dysfunction' given the fact that the neuropsychological changes found following a critical illness tend to persist and reflect deficits of a magnitude that are, indeed, functionally impairing.

The neurocognitive impairments of the patients with LTICI-CI are heterogeneous and most frequently involve memory, executive function and attention and are often similar to those experienced by individuals suffering from conditions such as a mild traumatic brain injury (MTBI) or MCI.^{25,59} These neurocognitive impairments represent a major burden for family and caregivers since they affect the abilities of ICU survivors to return to work, reduce life satisfaction and increased medical costs.³¹ To date, there is still a lack of consensus on how to define LTICI-CI especially in comparison to other forms of cognitive impairments, though broad agreement exists that a uniform definition would be helpful.⁶⁰ Patients have been tested²⁵ with neuropsychological batteries, which assess different cognitive domains: mental status, psychomotor speed, verbal fluency, working memory, verbal memory, visual memory and visuo-construction. Though definitions vary, they have tended to be quite restrictive (e.g., difficult to reach), as using such definitions ensure that subjects defined as 'impaired' are truly

impaired and not false positives. One such definition (from a battery of nine tests) identifies impairment as either two neuropsychological test scores at least two standard deviation (S.D.) below the norm-referenced mean or three scores that are at least 1.5 S.D. below the norm-referenced mean.²⁵

While definitions of impairment are sometimes developed by researchers and applied externally to test batteries (as described above), in other instances definitions of impairment or dysfunction are 'built into' existing neuropsychological batteries. Such is the case with the repeatable battery for the assessment of neuropsychological status (RBANS),⁶¹ a 'stand alone' tool for the evaluation of cognitive functioning widely employed in the assessment of elderly and medically ill patients,^{62,63} and as a 'stand alone' battery, it differs from those commonly used in research which often are comprised of individuals tests of specific domains culled from a range of sources. The RBANS generates 'index scores' based on subtest raw scores, which are interpreted based on the following classification system: 69 and below – extremely low, 70–79 – borderline, 80–89 – low average, 90–109 – average, 110–119 – high average, 120–129 – superior and 130 and above – very superior. The RBANS assesses immediate and delayed memory, attention and concentration, visual spatial construction and language. The tests and scoring system are described in Table 1.

An important question is whether LTICI-CI reflects patterns associated with neurodegenerative diseases such as Alzheimer's disease (AD)⁶⁴ or, alternatively, whether cognitive impairment after critical illness is static. The typical AD pattern at the beginning of the disease is characterised primarily though not exclusively by memory impairment and with cognitive deficits, which worsen progressively over time involving other cognitive domains (e.g., executive functions and language). By contrast, patients with LTICI-CI have diffuse neurocognitive deficits with a pattern, particularly among younger subjects, which appears to stabilise around 12–24 months after hospital discharge.⁵⁹ As such, it appears that the cognitive impairment occurring in many ICU survivors is not neurodegenerative, though there may be substantial exceptions to this rule, including large numbers of individuals with mild subclinical decrements who transition more rapidly into dementia than would otherwise be the case. The majority of the studies evaluating LTICI-CI have excluded patients with pre-existing cognitive impairments.^{17,28,32,59} In the next sections, we report specific criteria for the diagnosis of MCI and dementia.

MCI and dementia

To provide a clear insight of the terminology of dementia, it is important to first define MCI and dementia, and then provide specific knowledge on the most common type of dementia (i.e., AD).

MCI is 'generally used to refer to a transitional zone between normal cognitive function and clinically probable AD'. MCI is a clinical condition defined by the presence of the following criteria^{65–67}: (1) the person is neither normal nor demented (does not meet DSM-IV criteria for a dementia syndrome); (2) there is evidence of cognitive deterioration shown by either objectively measured decline over time and/or subjective report of decline by self and/or informant in conjunction with objective cognitive deficits; (3) the activities of daily living (i.e., taking medication, use of telephone, managing money, transportation, shopping and housework) are preserved, and complex instrumental functions are either intact or minimally impaired. MCI is further classified into four different subtypes according to specific neurocognitive deficits assessed through neuropsychological testing, though controversy exists about the stability of these more narrow constructs: (1) MCI amnesic: when only memory impairment is detected; (2) MCI multidomain amnesic: no memory impairment and multiple impairments in other neuropsychological domains (e.g., language and visuospatial); (3) MCI multidomain non-amnesic: more than one neuropsychological domain is impaired and the memory is normal; and (4) MCI single non-memory: one single neuropsychological domain is impaired and there is no memory impairment. Scores on cognitive tests for individuals with MCI are typically 1.5 S.D. below the mean for their age- and education-matched data, though MCI is a clinical diagnosis and no fixed cut-off criteria exist. A European longitudinal study reported an incidence rate per 1000 person years between 11.4 for amnesic MCI and 33.8 for other types of cognitive impairment no dementia.⁶⁸ A 12% progression rate yearly from MCI to dementia is reported.⁶⁹

Dementia criteria and specifically AD criteria have been recently updated.^{67,70} The prevalence of dementia increases dramatically with ageing. In fact, dementia affects 5–8% of individuals over the age of 65, 15–20% over the age of 75 years and 25–50% of the individuals older than 85 years. AD represents

Table 1

Definitions of cognitive impairments.

Long-term cognitive impairment after critical illness (LTICI-CI)	<p>The presence of cognitive impairment is defined according to a neuropsychological battery (Repeatable Battery for the Assessment of Neuropsychological Status-RBANS).⁶¹</p> <p>The overall scores are age and education adjusted index scores, which rely on the following classification scheme:</p> <table border="0"> <thead> <tr> <th data-bbox="337 353 433 371">Index score</th> <th data-bbox="742 353 849 371">Classification</th> </tr> </thead> <tbody> <tr> <td data-bbox="337 374 458 393">130 and above</td> <td data-bbox="742 374 854 393">Very superior</td> </tr> <tr> <td data-bbox="337 396 413 414">120–129</td> <td data-bbox="742 396 811 414">Superior</td> </tr> <tr> <td data-bbox="337 418 413 436">110–119</td> <td data-bbox="742 418 849 436">High average</td> </tr> <tr> <td data-bbox="337 440 404 458">90–109</td> <td data-bbox="742 440 811 458">Average</td> </tr> <tr> <td data-bbox="337 462 404 480">80–89</td> <td data-bbox="742 462 845 480">Low average</td> </tr> <tr> <td data-bbox="337 484 391 502">70–79</td> <td data-bbox="742 484 824 502">Borderline</td> </tr> <tr> <td data-bbox="337 505 451 524">69 and below</td> <td data-bbox="742 505 861 524">Extremely low</td> </tr> </tbody> </table>	Index score	Classification	130 and above	Very superior	120–129	Superior	110–119	High average	90–109	Average	80–89	Low average	70–79	Borderline	69 and below	Extremely low
Index score	Classification																
130 and above	Very superior																
120–129	Superior																
110–119	High average																
90–109	Average																
80–89	Low average																
70–79	Borderline																
69 and below	Extremely low																
Mild cognitive impairment (MCI)	<p>MCI is a clinical condition defined by the presence of the following criteria^{65–67}:</p> <ol style="list-style-type: none"> 1) The person is neither normal nor demented (does not meet DSM-IV criteria for a dementia syndrome); 2) There is evidence of cognitive deterioration shown by either objectively measured decline (typically cognitive scores are 1–1.5 standard deviations below the mean for their age and education matched data) over time and/or subjective report of decline by self and/or informant in conjunction with objective cognitive deficits; 3) The activities of daily living (i.e. taking medications, use of telephone, managing money, transportation, shopping, housework) are preserved and complex instrumental functions are either intact or minimally impaired. 																
Dementia	<p>MCI classification according to neuropsychological tests</p> <ol style="list-style-type: none"> 1) MCI amnesic: when only memory impairment is detected 2) MCI multidomain amnesic: no memory impairment and multiple impairments in other neuropsychological domains (e.g., language and Visuospatial) 3) MCI multidomain non amnesic: more than one neuropsychological domain is impaired and the memory is normal; 4) MCI single non memory: one single neuropsychological domain is impaired and there is no memory impairment <p>Dementia can be diagnosed^{67,70} when there are cognitive or neuropsychiatric symptoms that</p> <ol style="list-style-type: none"> 1) Interfere with the ability to function at work or at usual activities; 2) and represent a decline from previous levels of functioning and performing; 3) and are not explained by delirium or major psychiatric disorder; 4) Cognitive impairment is detected and diagnosed through a combination of (a) history-taking from the patient and a knowledgeable informant and (b) an objective cognitive assessment, either a “bedside” mental status examination or neuropsychological testing. 5) The cognitive or behavioural impairment involves at least two of the following domains: a. Impaired ability to acquire and remember new information; b. Impaired reasoning and handling of complex tasks; c. Impaired visuospatial abilities; d. Impaired language functions; e. changes in personality and behaviour. 																
Postoperative cognitive dysfunction (POCD)	<p>Diagnosis of probable Alzheimer's Dementia⁷⁰</p> <ol style="list-style-type: none"> 1) Symptoms appear gradually over the course of months to years; 2) There is a clear-cut history of worsening of cognition by report or observation; 3) And the most common neurocognitive deficits are in one of the following categories: <ol style="list-style-type: none"> a. Amnesic presentation (impairment in learning and recall of recently learnt information); b. Nonamnesic presentations (language, visuospatial or executive functions deficits as detected through neurocognitive testing). 4) The diagnosis of probable AD dementia should not be made if there are prominent feature of a history of a recent stroke, Lewy bodies dementia or other dementia such as frontotemporal dementia. In the recent updates on the diagnosis of <p>POCD^{77,78} is defined in an individual when their reliable change index (RCI) score is less than -1.96 on ≥ 2 tests and/or their combined z score was less than -1.96. This classifies POCD on the basis of a substantial failure on ≥ 2 tests, or a more pervasive subtle decline across the neuropsychological test battery.</p>																

the most common type of dementia accounting for 50–75% of the cases of dementia. The last World Alzheimer Report estimated that there were 35.6 million people living with dementia worldwide in 2010, increasing to 65.7 million by 2030 and 115.4 million by 2050.⁷¹

The diagnosis of dementia is being revised and expanded.^{67,70} Presently, dementia can be diagnosed when there are cognitive or neuropsychiatric symptoms that (1) interfere with the ability to function at work or at usual activities; (2) represent a decline from previous levels of functioning and performing; (3) are not explained by delirium or major psychiatric disorder; (4) cognitive impairment is detected and diagnosed through a combination of (a) history taking from the patient and a knowledgeable informant and (b) an objective cognitive assessment, either a 'bedside' mental status examination or neuropsychological testing and (5) the cognitive or behavioural impairment involves at least two of the following domains: (a) impaired ability to acquire and remember new information; (b) impaired reasoning and handling of complex tasks; (c) impaired visuospatial abilities; (d) impaired language functions; and (e) changes in personality and behaviour.

Probable AD dementia is diagnosed when a patient meets criteria for dementia as described above and presents one of the following characteristics⁷⁰: (1) symptoms appear gradually over the course of months to years; (2) there is a clear-cut history of worsening of cognition by report or observation; and the most common neurocognitive deficits are in one of the following categories: (a) amnesic presentation (impairment in learning and recall of recently learnt information) and (b) non-amnesic presentations (language, visuospatial or executive functions deficits as detected through neurocognitive testing). The diagnosis of probable AD dementia should not be made if there are prominent features of a history of a recent stroke, Lewy bodies dementia or other dementia such as frontotemporal dementia. In the recent updates on the diagnosis of dementia, there have been thorough discussions on the role of biomarkers and neuroimaging. Nonetheless, in the context of this review, we report information mainly on terminology differences and therefore we refer the reader to the Recommendations of the National Institute on Ageing and the Alzheimer's Association workgroup⁷⁰ for further details on the clinical and research use of these additional investigations.

Postoperative cognitive dysfunction

POCD is common and it has been studied after cardiac and non-cardiac surgery. It is reported in up to 30–65% of the patients at hospital discharge and 20–40% after few months of surgery, though questions exist related to the extent to which it represents a newly developed condition or whether it reflects a process of change that commonly occurs in individuals with cardiovascular disease, for example, even in the absence of surgery.^{72,73} The definition of POCD is variable and controversial and POCD should be differentiated from delirium.⁷⁴ This distinction is possible through the use of neurocognitive tests. Several approaches have been taken to define POCD.^{74,75} Commonly used criteria include a 20% percentage change from a baseline evaluation in a pre-defined number of tests (usually two or more tests) or an absolute decline (>1 S.D.) from baseline scores in two or more neuro-psychological tests, though numerous other definitions have been employed as well. This approach, however, does not take into account the age-matched controls and, thus, the variability that could occur in healthy individuals over time.⁷⁶ A more recent approach relies upon statistically driven methods to assess 'real change' through formulae such as the reliable change index (RCI).^{77,78} The RCI can be mathematically calculated using published methodology.^{77,78}

Summary

ICU survivors often present acute and chronic cognitive co-morbidities in the form of delirium and long-term cognitive impairment (LTCI-CI), which are associated with adverse outcomes. Among health-care providers, delirium and LTCI-CI are often unrecognised.

The reason of this underdetection might be related to barriers in the terminology used to define these cognitive impairments. The use and knowledge of a correct terminology is a key factor to advance the management and to further develop research studies on these emergent health-care burdens in ICU survivors.

Practise points

- Delirium is the most common form of acute brain dysfunction in critically ill patients and it is often underdetected.
- Delirium is an independent predictor of longer hospital stay, increased hospital cost, higher 6-month and 1-year mortality and long-term cognitive impairment.
- Long-term cognitive impairment occurs in at least 5 out of 10 patients at 1 year after an acute critical illness and its presence is often underestimated.
- The reason for underdetection for acute and long-term brain dysfunction might indeed be related to barriers in the terminology used in these clinical entities.

Research agenda

- Further research is warranted to increase the knowledge of delirium and long-term cognitive impairment following a critical illness.
- Future research should provide a specific definition of LTCI-CI to differentiate from other forms of cognitive impairment such as MCI, AD and POCD.
- The clinical definition of the trajectories of LTCI-CI would allow to design protocols for the prevention and treatment of this increasing health-care burden.

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Potential conflict of interest

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