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Prediction of chronic critical illness in a general intensive care unit☆

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ABSTRACT

Objective: To assess the incidence, costs, and mortality associated with chronic critical illness (CCI), and to identify clinical predictors of CCI in a general intensive care unit.
Methods: This was a prospective observational cohort study. All patients receiving supportive treatment for over 20 days were considered chronically critically ill and eligible for the study. After applying the exclusion criteria, 453 patients were analyzed.
Results: There was an 11% incidence of CCI. Total length of hospital stay, costs, and mortality were significantly higher among patients with CCI. Mechanical ventilation, sepsis, Glasgow score <15, inadequate calorie intake, and higher body mass index were independent predictors for CCI in the multivariate logistic regression model.
Conclusions: CCI affects a distinctive population in intensive care units with higher mortality, costs, and prolonged hospitalization. Factors identifiable at the time of admission or during the first week in the intensive care unit can be used to predict CCI.

Predição de doença crítica crônica em uma unidade geral de cuidados intensivos

Palavras-chave:
Doença crítica
Ventilação mecânica prolongada
Controle de custos
Mortalidade hospitalar

RESUMO

Objetivo: Avaliar a incidência, custos e mortalidade relacionados a doença crítica crônica (DCC) e identificar seus preditores clínicos em uma unidade de terapia intensiva geral.
Métodos: Trata-se de uma coorte observacional prospectiva. Todos pacientes que recebiam tratamento de suporte por mais de 20 dias eram considerados doentes críticos crônicos. Permaneceram 453 pacientes após a aplicação dos critérios de exclusão.
Resultados: A incidência de DCC foi de 11%. Permanência hospitalar, custos e mortalidade foram significativamente maiores na população com DCC. Ventilação mecânica, sepse,

☆ Study conducted at Hospital Mãe de Deus, Porto Alegre, RS, Brazil.
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Glasgow escore < 15, inadequada ingestão calórica e elevado índice de massa corporal foram preditores independentes para DCC em um modelo multivariado de regressão logística.
Conclusão: DCC abrange uma distinta população nas unidades de terapia intensiva apresentando maiores mortalidade, custos e permanência hospitalar. Alguns fatores presentes na admissão ou durante a primeira semana na unidade de terapia intensiva podem ser usados como preditores de DCC.

Introduction

Chronic critical illness (CCI) is defined by a prolonged dependence on life support. Transition from acute to chronic phase is often difficult to perceive in critically ill patients. One of the most common parameters used to define CCI is the need for prolonged mechanical ventilation (MV) or for tracheotomy.[1–5] Thus, CCI may be understood as an inadvertent outcome of technological advances used in the intensive care unit (ICU). In this scenario, patients survive an acute incident but still require prolonged life-support,[2,6] leading to a population with different pathophysiological characteristics from those of an acute ICU patient. Neuroendocrine,[7,8] metabolic,[9–11] and neuromuscular[12,13] adaptations are reported with an incidence of 5% to 20%.[6,14–16] This population is also characterized by increased in-hospital and post-hospital mortality,[14,17–22] elevated costs,[22,23] and significant dependence on social assistance, with frequent re-hospitalizations, home care, or institutionalization.[14,17,20] The annual *per capita* cost of these patients ranges from US$200,000 to US$500,000, representing a potential public health problem.[2,22,23] The purpose of this study was to assess the incidence, costs, and mortality associated with CCI, and to identify early predictors of CCI in a general ICU.

Material and methods

Study design

A prospective cohort study was conducted at the ICU of Hospital Mãe de Deus, a general private hospital located in Southern Brazil, with 32 beds occupied by medical and surgical patients. The inclusion criteria were all patients admitted in ICU (from June 1 to November 30, 2008), with the intention of comparing critically ill with chronic critically ill patients. The exclusion criteria were patients under the age of 18 years (9 patients), length of stay under 48 hours in the unit (172 patients), and patients with do not resuscitate orders (3 patients). Three missing cases were excluded. Four hundred and fifty-three patients were effectively followed-up.

This study was approved by the Institutional Review Board of Hospital Mãe de Deus, and registered in the Brazilian National System of Research and Ethics, under protocol number 0067.0.111.000-07.

Definitions and outcomes

Patients were classified as critically ill or chronically critically ill. The latter were defined as patients who remained in the ICU for over 20 days due to the need of mechanical ventilation or hemodynamic support. The main endpoints of the study were length of stay, hospital costs, and mortality.

The following variables were assessed and registered for each patient: presence of prior chronic disease (chronic pulmonary obstructive disease; cardiac insufficiency; ischemic heart disease; renal disease; neuromuscular dysfunction [patients with major functional limitations such as secondary sequelae of stroke, paraplegia, quadriplegia, primary myopathy, degenerative diseases of the central nervous system determinants of muscle dysfunction]; severe psychiatric disorder [severe bipolar disorder, major depression, illicit drug use, schizophrenia]; dementia [significant cognitive disabilities registered or documented in the medical record, associated with degenerative diseases of the central nervous system or sequelae of stroke]; and diabetes), body mass index (BMI), systemic inflammatory response syndrome (SIRS, defined as two or more of the following: body temperature less than 36 °C or greater than 38 °C; heart rate greater than 90 beats per minute; tachypnea, with greater than 20 breaths per minute or, an arterial partial pressure of carbon dioxide less than 32 mmHg; white blood cell count less than 4,000 cells/mm^3 or greater than 12,000 cells/mm^3; the presence of greater than 10% immature neutrophils), sepsis (two SIRS criteria associated with proven or very probable infection), organ dysfunction in the ICU, acute physiology and chronic health evaluation II (APACHE II) score, sequential organ failure assessment (SOFA) score, laboratory tests, nutritional intake, and admission diagnosis. Readmission to the ICU was defined as a new admission occurring after 24 hours following discharge. The occurrence of any accident or unfavorable event in the ICU was also monitored; these were called adverse events and included urinary tract infection, catheter, probe or drain loss, and procedure-related complications. Inadequate nutritional intake was defined as a protein-calorie intake of less than 60% of that required, without a medical justification (such as interruption of feeding for procedures or transportation). Patients were considered hyperglycemic whenever at least half of the capillary or venous glucose measurements of the day reached more than 180 mg%. Body mass index (BMI) was calculated based on measured weight and height.

The following variables were collected and monitored (monitored daily, when appropriate): patient's name, age, gender, diagnosis at ICU admission, pre-ICU length of hospitalization, previous chronic disease, BMI, readmission after ICU discharge, surgery, APACHE II score, SOFA score, capillary glucose, sepsis, MV, hemodialysis, corticotherapy, use of intravenous insulin, need for vasopressor and/or inotropic agents, blood or blood products transfusions, laboratory results, enteral and/or parenteral nutrition (and caloric intake), intravenous sedation, cardiopulmonary resuscitation, pressure

ulcer, adverse events (accidental loss of probes or drain tubes and accidental extubation), do not resuscitate order, ICU and hospital length of stay, hospital approved costs, and survival or death.

Statistical analysis

Descriptive statistics (mean, standard deviation, absolute and relative frequencies) were calculated. Odds ratios (OR) and 95% confidence interval (95% CI) were calculated to estimate the magnitude of associations. Student's *t*-test for two independent samples and the chi-squared test were used to assess mean differences between groups. Assumptions of homogeneity of variance and normality were examined prior to testing (and a parametric or nonparametric test was chosen). A logistic regression model was constructed to determine predictors of CCI. A p-value of less than 0.05 was considered as significant. All variables that were predictive ($p < 0.20$) in the univariate analysis were entered into the logistic regression model. In the multivariate procedure, $p < 0.05$ was considered as the level of significance. The final model was constructed with a backward method following Wald's criterion and applying the "1 to 10" rule. Model adjustment and calibration were respectively evaluated with receiver operating characteristic (ROC) curve and Hosmer-Lemeshow goodness-of-fit test, respectively. Statistical analysis was performed with the Statistical Package for Social Sciences (SPSS) version 16 software.

Results

Table 1 summarizes the presentation and outcome of critically ill and chronically critically ill patients. The incidence of CCI was 11%, or 50 out of the 453 patients studied. Of these, 42 (84%) cases were due to prolonged mechanical ventilation, and eight (16%) were due to the need for intensive monitoring or inotropic and/or vasopressor infusion. There was no difference between the two groups regarding previous disease, except for higher incidence of prior neuromuscular disease in the CCI group (OR = 4.21, 95% CI: 1.63-10.9, $p = 0.003$).

Among patients with CCI, 38 had a tracheotomy (76%), performed on average 16.8 ± 8.1 days after admission. There was no difference between groups regarding the development of renal dysfunction, hepatic dysfunction, thrombocytopenia, days of fasting, and need for parenteral nutrition. Pressure ulcers occurred more frequently among patients with CCI (51.9%) than in the non-CCI group (6%) ($p < 0.001$), and were more often observed after the first ten days in the ICU. The SOFA score varied significantly between groups; however, the daily variation of the score was not significant between CCI and non-CCI patients. The total cost of chronically critically ill patients was US$ 9,174,852.00 (50 patients), while the cost for critically ill patients was US$ 13,408,495.00 (403 patients). Table 1 shows the mean *per capita* cost for the two groups.

Among the 50 patients with CCI, 29 died during hospitalization (58%). Regarding previous chronic morbidities, only dementia was significantly associated with death in this population (seven patients with dementia died, 100%, $p = 0.009$). These patients were not palliative, and treatment was not considered futile by the medical staff. Table 2 presents data for survivor and non-survivor patients with CCI. Age, need for neurosurgery, APACHE II score, and sepsis were significantly different between groups. Total hospital stay and costs did not differ between survivors and non-survivors.

Fig. 1 shows daily records of mean SOFA in critically ill patients, grouped according to survival status, and chronically critically ill patients. A significant difference emerged among these three populations on day six (panel A). No differences were found in SOFA scores between chronically critically ill patients who survived and those who did not survive (panel B).

A logistic regression was performed with CCI status as the dependent variable. Based on the results of the bivariate analyses (Table 1), variables were selected for the logistic regression model if they were significantly associated with the outcome at a p-value of < 0.20. The final model included the following variables: abnormal BMI, MV in the first four days, sepsis in the first four days, abnormal Glasgow score, and inadequate caloric intake (for at least three days during the first week in the ICU). A ROC curve was constructed to assess the predictive accuracy of the model. The Hosmer and Lemeshow goodness-of-fit test showed that the model adequately fit the data ($p = 0.788$), with a good discriminative capacity (area under ROC curve = 0.803). The inclusion of prior neuromuscular disease in combination with any four of the five predictive parameters increased the specificity, but decreased the sensitivity of the model.

Discussion

The main goal of this study was to identify the incidence and the clinical characteristics of CCI in a general ICU, and to identify early predictors of this condition. This population has been defined by different criteria,[1,2,5,6,24,25] generally involving dependence on mechanical ventilation.[4,25] A chronically critically ill patient is a patient who depends on any ICU support while staying in the ICU for an extended period. CCI was mostly defined by prolonged MV (84%), showing an incidence of 11%, which is similar to that found in other studies.[6,14–16] No differences were found regarding gender or age of patients who progressed to CCI compared to acute patients; nevertheless, older age, sepsis, and higher APACHE II scores were associated with increased mortality in the CCI group, as shown in Table 2. There was no association between previous chronic disease and CCI, with the exception of neuromuscular disease (such as paraplegia, muscular atrophy, neurodegenerative disease, or sequelae of stroke). This exception is not surprising, since it involves the muscular system, which is at the core of CCI. Neuromuscular dysfunction plays an important role in the pathogenesis of muscle fatigue, a prevalent issue in chronically critically ill patients.[12]

Tracheotomy was highly prevalent in this sample, and reflects the difficulty in weaning these patients from MV. Higher scores on APACHE II, a predictor of mortality, or on SOFA, an index of severity, generally indicate more seriously ill patients and were associated with an increased risk of developing a CCI (Table 1). Neurosurgery was more frequent in the CCI group. Possibly for this reason, an abnormal

Table 1 – Baseline characteristics and outcome of chronically critically ill (CCI) and critically ill (CI) patients.

	Results		p-value
	CCI (50)	CI (403)	
General characteristics			
Age (years)	68 (± 18.4)	66.1 (± 17.2)	0.484
Male gender	21 (42%)	214 (53%)	0.138
Pre-ICU days	11.4 (± 30.8)	4.5 (± 10.9)	0.120
ICU total days	40.8 (± 24.2)	8.7 (± 18.0)	< 0.001
ICU re-admission	5 (10%)	31 (7.7%)	0.577
Surgery	21 (42%)	151 (37.5%)	0.533
Neurosurgery	9 (18%)	33 (8.2%)	0.036
Pressure ulcers	26 (48.1%)	28 (6.9%)	< 0.001
Adverse event[a]	2 (4%)	9 (2.2%)	0.271
Scores			
BMI (kg/m^2)	25.2 (± 4.8)	22.3 (± 10.6)	0.002
BMI (kg/m^2) ≥ 26	33 (67.3%)	160 (40%)	< 0.001
APACHE II score	18.4 (± 6.1)	15.3 (± 6.9)	0.004
APACHE II predicted mortality	26.8%	16.7%	< 0.001
SOFA score on day one	4.7 (± 2.7)	2.5 (± 2.8)	< 0.001
Clinical scenarios			
Hyperglycemia[b] on day one	10 (23.8%)	65 (15.8%)	0.184
Hyperglycemia[b] in the first 96 h	4 (8%)	21 (5.2%)	0.505
Sepsis on day one	11 (26.2%)	56 (13.6%)	0.029
Sepsis in the first 96 h	10 (23.8%)	43 (10.5%)	0.020
Glasgow < 15 on day one	26 (61.9%)	118 (28.7%)	< 0.001
Glasgow < 15 in the first 96 h	25 (59.5%)	87 (21.1%)	< 0.001
Delirium[c]	3 (7.1%)	38 (9.2%)	1.000
CPR day one to day eight	3 (7.1%)	8 (2.0%)	0.073
Therapies			
Blood (packed red blood cell units)	3.8 (± 4.9)	0.6 (± 1.6)	< 0.001
MV on day one	34 (68%)	101 (25.1%)	< 0.001
MV in the first 96 h	25 (50%)	50 (12.4%)	< 0.001
Vasopressor/inotropic on day one	16 (32%)	80 (19.9%)	0.047
Vasopressor/inotropic in the first 96 h	6 (12%)	39 (9.7%)	0.376
Intravenous sedation on day one	21 (42%)	51 (12.7%)	< 0.001
Intravenous sedation in the first 96 h	11 (22%)	24 (6.0%)	0.001
Corticosteroid on day one	6 (12%)	50 (12.4%)	0.934
Corticosteroid in the first 96 h	6 (12%)	37 (9.2%)	0.453
Parenteral nutrition	4 (8%)	6 (5.1%)	0.486
Inadequate caloric intake[d]	7 (14%)	8 (2%)	< 0.001
Outcomes			
Hospital stay in days	86.5 (± 76.7)	24.7 (± 33.4)	< 0.001
Cost[e]	183.4 (± 158.7)	33.2 (± 35.7)	< 0.001
ICU mortality	16 (32%)	47 (11.8%)	< 0.001
Hospital mortality	28 (56%)	67 (16.6%)	< 0.001

Data presented as mean ± standard deviation and absolute and relative frequencies.
CCI, chronic critical illness; CI, critical illness; ICU, intensive care unit; BMI, body mass index (kg/m^2); APACHE II, Acute Physiology and Chronic Health Evaluation II; APACHE II mortality, calculation of mortality prediction for the score; SOFA, sequential organ failure assessment; PN, parenteral nutrition; Glasgow, neurological evaluation score; MV, mechanical ventilation; CPR, cardiopulmonary resuscitation.

[a] adverse event: urinary tract infection, loss of catheter, probe or drain, accidents related to procedures;
[b] blood glucose > 180 mg%;
[c] temporary disorder of the mental faculties with excitement, mental confusion, disorientation and/or hallucination;
[d] three or more days in the first week with less than 60% of caloric intake relative to predicted need, and absence of gastric or intestinal dysfunction;
[e] mean *per capita* cost in thousands of US$.

Glasgow score was strongly associated with CCI. It should be kept in mind that the sicker the patient, the greater the chance of developing complications such as CCI. Thus, neurological disorders and sepsis, which represent common etiologies of severe illness, especially when concomitant, were significantly associated with CCI.

Myopathy in critically ill patients has become a subject of considerable interest in recent studies. It is related to immobility, inflammation, prolonged sedation, and MV,[26–29] all of which are involved in CCI. Patients affected by CCI often are not able to maintain sufficient nutritional intake. In the present study, daily nutritional intake was considered

Table 2 – Clinical differences between survivor and non-survivor chronically critically ill patients.

	CCI		p-value
	Survivors (21)	Non-survivors (29)	
Age (years)	58.2 (±16.3)	75.2 (±15.8)	0.001
Male gender	12 (57.1%)	11 (37.9%)	0.179
Pre-ICU days	6.3 (±19.1)	23.5 (±43.8)	0.068
Surgery	15 (71.4%)	10 (34.5%)	0.059
Neurosurgery	8 (38.1%)	4 (13.8%)	0.047
BMI (kg/m^2)	26.1(±5.2)	26.3 (±4.8)	0.885
APACHE II score	15.5 (±5.3)	20.6 (±7.0)	0.007
SOFA score on day one	3.6 (±2.8)	5.0 (±2.7)	0.099
SOFA score on day two	4.1 (±3.0)	4.7 (±3.0)	0.448
SOFA score on day three	3.8 (±2.9)	4.5 (±2.7)	0.444
SOFA score on day seven	4. (±2.8)	3.7 (±2.9)	0.704
Hyperglycemia[a] on day one	2 (9.5%)	9 (31%)	0.073
Hyperglycemia[a] in the first 96 h	1 (4.8%)	7 (24.1%)	0.117
Sepsis on day one	1 (4.8%)	13 (44.8%)	0.002
Sepsis in the first 96 h	1 (4.8%)	11 (37.9%)	0.007
Glasgow score < 15 on day one	13 (61.9%)	19 (65.5%)	0.793
Glasgow score < 15 in the first 96 h	13 (61.9%)	17 (58.6%)	0.815
Glasgow score < 10 on day one	5 (23.8%)	7 (24.1%)	0.979
CPR day one to day eight	2 (9.5%)	1 (3.4%)	0.565
Blood[b]	3.7 (±4.3)	2.2 (±3.1)	0.136
VP-IT on day one	3 (14.3%)	12 (41.4%)	0.039
VP-IT in the first 96 h	2 (9.5%)	5 (17.2%)	0.684
IV sedation on day one	11 (52.4%)	10 (34.5%)	0.206
IV sedation in the first 96 h	6 (28.6%)	7 (24.1%)	0.724
Hospital stay in days	108.4 (±85.6)	107.6 (±111.5)	0.978
Cost[c]	204.7 (±187.5)	166.8 (±133.1)	0.409

Data presented as mean ± standard deviation and absolute and relative frequencies.
CCI, chronic critical illness; ICU, intensive care unit; BMI, body mass index (kg/m^2); CPR, cardiopulmonary resuscitation; VP-IT, vasopressor and/or inotropic infusion; IV, intravenous.
[a] blood glucose > 180 mg%;
[b] packed red blood cell units;
[c] mean *per capita* cost in thousands of US$.

insufficient when patients received less than 60% of the planned goal. There is much speculation concerning the link between malnutrition and poor healing of pressure ulcers[30] and muscle fatigue.[31] A relatively higher supplementation of essential (as compared to branched-chain amino acids) has been shown to decrease proteolysis in patients with myopathy.[32] That practice is not regularly implemented at Hospital Mãe de Deus, where muscle weakness and fatigue are

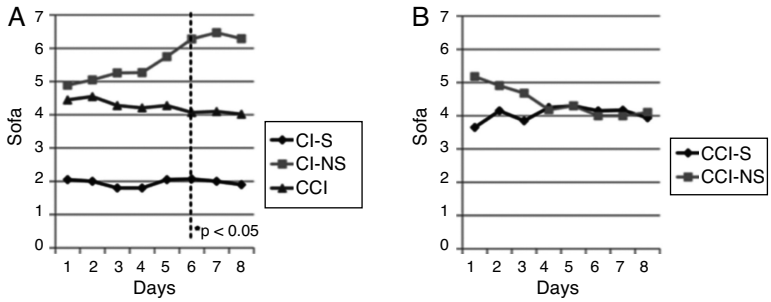

Fig. 1 – (Panel A) – Daily records of the total SOFA score between patients with CCI and non-CCI survivors (CI-S) and non-survivors (CI-NS). Note that the average cumulative change in the SOFA score in the CCI population over eight days is insignificant (less than one point). When daily SOFA modification (evaluation of cumulative improvement or worsening related to organ dysfunction) were compared among groups, no significant difference was found. The means were compared by ANOVA, a = 5%. (Panel B) – Daily records of the SOFA score between the patients with CCI survivors (CCI-S) and non-survivors (CCI-NS). There was no significant difference in the total SOFA scores from day one to day eight between groups. *the dashed line shows the period in which the three groups differ significantly, in terms of absolute value of the SOFA score.
CCI, chronic critically ill; CI-S, critically ill survivor; CI-NS, critically ill non-survivor.

frequently observed. Inadvertently reduced caloric intake is associated with CCI (Table 1), and protocols to ensure adequate nutrition to critically ill patients should be instituted.

On the sixth day, the daily SOFA score showed a difference between CCI and non-CCI patients (Fig. 1A). However, the SOFA score was not able to differentiate survivors and non-survivors among chronically critically ill patients (Fig. 1B). According to these data, APACHE II and SOFA scores, routinely used in many ICUs, could predict the likelihood of a lengthy stay in the ICU. Honarmand et al.[33] demonstrated that the SOFA score on days zero, two, and four predicted the need for MV in surgical patients, but not the amount of time on ventilatory support. The fact that the SOFA score performed better in the present study could be related to differences in the studied samples. In the present study, the cumulative mean SOFA score did not change significantly during the first days in chronically critically ill patients (variation of less than one point, Fig. 1). This indicates that, in terms of organ dysfunction, neither worsening nor significant improvement was observed over a week, suggesting that the early therapy offered to these patients should be readjusted. Thus, it could be argued that the initial presentation is sufficient to determine chronicity, but insufficient to cause death. With time these conditions take their toll, which explains the late mortality observed (Table 1).

APACHE II was used to predict hospital and ICU mortality rates. The observed and predicted ICU mortality rates of critically ill patients were respectively 12.1% and 16.7% (standardized mortality rate [SMR] 0.72, 95% CI: 0.54-0.95, $p = 0.0173$). For patients with CCI, there was no increased mortality in the ICU, contrary to the initial expectations. The observed and predicted ICU mortality rates were 30.9% and 26.8%, respectively (SMR = 1.15, 95% CI: 0.64-1.92, $p = 0.5917$). Regarding hospital mortality, we found, respectively, an observed and predicted hospital mortality of chronically critically ill patients of 52.4% and 26.8% (SMR = 2, 95% CI: 1.3-2.9, $p < 0.001$), and for critical patients, of 17.8% and 16.7% (SMR = 1.07, 95% CI: 0.8-1.3, $p = 0.543$). Thus, CCI could be potentially associated with increased mortality. The present population of chronically critically ill patients appears similar to that of Estenssoro et al.,[16] with a higher mortality rate occurring later, suggesting that the effects of humoral, hormonal, and neurological changes may extend over a long period of time, including the period after hospitalization, which has been described by others.[2,9,14,19]

CCI patients accounted for 11% of the total population studied, and consumed 40.6% of the resources (Table 1). The average cost per day for one CCI patient was US$ 2,121.00, compared to US$ 1,347.00 for critical patients. The data suggest that differentiating the management of ICU patients (early recognition of the potential for chronic course, improvement in motor rehabilitation processes, and adequacy of nutritional support), reducing the incidence of CCI by 1%, and the mean hospitalization for CCI patients by 10% could save US$ 1,971,342.00 per year. The amount saved could be reinvested in hiring human resources to implement protocols for this population, to avoid ventilator-associated pneumonia, to prevent sepsis, and for nutritional support, weaning from MV, and mobilization.

For the logistic regression, all data were used in different sets (grouping four or five parameters). Clinically relevant parameters, earliest altered data, and statistical significance were always given priority in the model. Thus, it was possible to detect five variables that taken together predicted early CCI: abnormal BMI, MV (first four days), sepsis (first four days), abnormal Glasgow score (first four days), and inadequate nutrition in the first week. Other compositions of five variables, entering "previous neuromuscular disease" in the multivariate model, were also significant, albeit with slightly lower sensitivity and higher specificity. These variables should be evaluated in larger, multicenter studies, to analyze their reproducibility and accuracy in predicting CCI. Moreover, these parameters should be the focus of different treatment protocols to uncover strategies that could potentially reduce the incidence of CCI, improve outcomes, and reduce costs.

The present study has some limitations. Patients with CCI who survived were not followed-up to monitor the outcome over a long period after hospital discharge. Sleep or psychiatric disorders were not assessed in this protocol, which could have an impact on the course and outcome of CCI. Patient's distress and family burden were also not studied. Finally, this study was only conducted at a single center.

Conclusions

The present data show the complex, serious, and fragile nature of chronically critically ill patients. Early identification of these patients is crucial in order to apply a more appropriate therapy, which requires improving the understanding and care of these patients. Abnormal BMI, MV, sepsis, abnormal Glasgow score, and inadequate nutrition in the first week are common and early predictors. Among patients who became CCI, older age and sepsis at admission were associated with increased mortality. Future studies should address the impact of multidisciplinary management in maintaining patient stability through individualized ventilatory support, differentiated nutritional support, mobilization, and muscle strengthening.

Conflicts of interest

The authors declare no conflicts of interest.

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