UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

FACULDADE DE MEDICINA

PROGRAMA DE PÓS-GRADUAÇÃO EM MEDICINA: CIÊNCIAS MÉDICAS

TESE DE DOUTORADO

AVALIAÇÃO DE CONCEITOS, SOBREVIDA E CAPACIDADE FUNCIONAL EM PACIENTES CRÍTICOS CRÔNICOS

Diego Silva Leite Nunes

ORIENTADORA

Profa. Dra. Silva Regina Rios Vieira, M.D, PhD

Porto Alegre

2019

TESE DE DOUTORADO

AVALIAÇÃO DE CONCEITOS, SOBREVIDA E CAPACIDADE FUNCIONAL EM PACIENTES CRÍTICOS CRÔNICOS

Diego Silva Leite Nunes

Orientador: Prof[a]. Dr[a]. Silvia Regina Rios Vieira

Tese apresentada como requisito parcial para obtenção do título de Doutor em Medicina: Ciência Médicas, da Universidade Federal do Rio Grande do Sul, Programa de pós-graduação em Medicina: Ciências médicas.

Porto Alegre

2019

CIP - Catalogação na Publicação

SILVA LEITE NUNES, DIEGO
AVALIAÇÃO DE CONCEITOS, SOBREVIDA E CAPACIDADE FUNCIONAL EM PACIENTES CRÍTICOS CRÔNICOS / DIEGO SILVA LEITE NUNES. -- 2019.
82 f.
Orientador: SILVIA REGINA RIOS VIEIRA.

Tese (Doutorado) -- Universidade Federal do Rio Grande do Sul, Faculdade de Medicina, Programa de Pós-Graduação em Medicina: Ciências Médicas, Porto Alegre, BR-RS, 2019.

1. cuidados críticos. 2. doença crônica. 3. unidades de terapia intensiva. 4. respiração artificial. I. REGINA RIOS VIEIRA, SILVIA, orient. II. Título.

Elaborada pelo Sistema de Geração Automática de Ficha Catalográfica da UFRGS com os dados fornecidos pelo(a) autor(a).

AGRADECIMENTOS

Agradeço à Professora Silvia Vieira pela orientação, atenção e dedicação.

Agradeço à Dra. Roselaine Pinheiro pela prestatividade e pela extrema ajuda na coleta dos dados e orientação.

Agradeço ao Dr. Cassiano pela prestatividade, viabilizando a execução deste estudo.

Agradeço aos amigos pelos momentos de descontração e por compreenderem a ausência na fase final desta jornada.

Agradeço ao meu irmão Gustavo pela ajuda na fase de edição.

Agradeço a minha mãe que me ensinou a persistir e nunca desistir de ir em busca daquilo que faz sentido na minha vida.

Agradeço à minha maior parceira nessa aventura, minha esposa Oellen Stuani Franzosi, pela paciência e notável ajuda.

Enfim, agradeço a vida por ter me concedido saúde e tempo para concluir este projeto e, acima de tudo, agradeço a Deus.

RESUMO

Introdução: O desenvolvimento da medicina intensiva e a introdução de pacotes de cuidados baseados em evidências têm contribuído para o suporte das falências orgânicas e para o aumento da sobrevida de pacientes críticos, que no passado morreriam por disfunção múltipla orgânica. Concomitantemente, observamos o crescimento da população de pacientes com estado inflamatório persistente e dependente de cuidados intensivos por longos períodos. A doença crítica crônica (DCC) é marcada por piores desfechos hospitalares e funcionais, alto custo e piores desfechos a longo prazo após a alta da unidade de terapia intensiva (UTI). Durante muitos anos, a DCC vem sendo definida pela dependência do suporte ventilatório prolongado: (1) ≥14 dias de ventilação mecânica (VM), (2) ≥21 dias de VM, (3) necessidade de traqueostomia por VM prolongada. Entretanto, recentemente uma nova definição foi desenvolvida com a proposta de ser mais sensível para identificar os pacientes com DCC entre população de pacientes críticos. A nova definição consiste em (4) ≥8 dias de UTI mais uma das seguintes condições: traqueostomia, VM ≥96horas, sepse, lesões graves de pele, acidente vascular encefálico ou traumatismo craniano.

Objetivos: Esta tese está constituída por dois estudos. **Estudo 1:** No primeiro estudo, o objetivo foi avaliar as quatro definições de DCC mais usadas na literatura, incluindo a nova definição recentemente desenvolvida, quanto à capacidade de identificar a população de pacientes críticos crônicos nas internações da UTI. Ainda, no mesmo protocolo de pesquisa, a definição mais atual foi usada para selecionar uma amostra de pacientes com DCC e avaliar a sobrevida e a capacidade funcional em 12 meses após a alta da UTI. **Estudo 2:** O segundo estudo teve o objetivo de caracterizar a epidemiologia da DCC na população de pacientes atendida pelo sistema público de saúde no Brasil.

Materiais e métodos: Estudo 1: Estudo de coorte histórica com seleção de pacientes com as quatro definições mais relevantes de DCC usadas na literatura e avaliação de desfechos hospitalares e ad capacidade preditiva das definições para o desfecho mortalidade. Uma amostra de pacientes com DCC pela definição mais atual foi avaliada por 12 meses para medida da capacidade funcional e sobrevida. Os pacientes

foram selecionados em uma base de dados institucional de uma UTI de um hospital privado de alta complexidade. **Estudo 2:** Estudo de coorte histórica que avaliou uma base de dados do sistema público de saúde do Brasil. Todas internações com passagem pela UTI ocorridas no estado do Rio Grande do Sul foram incluídas. O critério mais atual de DCC foi usado para selecionar os pacientes crônicos e diferenciá-los do grupo de pacientes críticos agudos. Características clínicas, desfechos hospitalares, impacto financeiro e fatores de risco para desenvolver DCC foram avaliados.

Resultados e conclusões: Estudo 1: 146 internações com definição de DCC de ≥14 dias de ventilação mecânica (VM), 79 internações com ≥21 dias de VM, 89 internações com definição de DCC por necessidade de traqueostomia por VM prolongada e 494 internações com a definição mais atual de DCC (≥8 dias de UTI mais uma das seguintes condições: traqueostomia, VM ≥96horas, sepse, lesões graves de pele, acidente vascular encefálico ou traumatismo craniano) foram analisadas. As características entre as internações nos quatro grupos de definições de DCC foram semelhantes. Uma mortalidade discretamente menor nas definições de DCC por necessidade de traqueostomia e no critério atual comparada as definições de tempo de VM ≥14 e ≥21 dias (52.8%, 46% e 61%, 65.8%, respectivamente) foi verificada. A especificidade das definições em predizer mortalidade foi semelhante, porém a sensibilidade foi maior usando a definição mais atual (8.6%, 41.7% e 16.2%, 9.5%, respectivamente). Para atender ao segundo objetivo do estudo, 55 pacientes com o critério atual de DCC foram avaliados por 12 meses após a alta da UTI. A capacidade funcional entre três e seis meses após a alta foi significativamente menor comparada ao estado pré internação, tendendo a recuperação funcional em 12 meses. A sobrevida em 12 meses foi de 74.5%. O critério atual de DCC é mais sensível que os até então usados para predizer o principal desfecho desta condição, a mortalidade. Pacientes com DCC apresentam pior desfecho funcional entre três e seis meses após a alta da UTI, mas tendem a retomar a capacidade funcional basal até 12 meses após a alta. **Estudo 2:** 48.708 internações agudas e 8056 internações com critério de DCC foram incluídas. A prevalência de DCC foi de 16.5%. A mortalidade hospitalar foi maior no grupo de internações crônicas (20.5% e 31.7%, respectivamente) o valor médio por hospitalização também foi maior no grupo de críticos crônicos (R$ 4.157,25 maior

que as internações críticas agudas). Internações com origem via emergência (RR 1.67, IC95% 1.51 – 1.85), porte hospitalar médio (RR 1.28, IC95% 1.19 – 1.38), internações clínicas (RR 1.27, IC95% 1.20 – 1.34) e a presença de infecção (RR 5.75, IC95% 5.5 – 6.01) foram fatores de risco para DCC. As faixas etárias com ≥35 anos marcaram maior mortalidade nas internações com DCC em relação às internações críticas agudas. Este estudo confirma que é possível avaliar a epidemiologia da DCC na base de dados do sistema público de saúde brasileiro. Os dados avaliados mostram elevada prevalência de DCC bem como maior mortalidade e maior custo para o sistema de saúde comparada às internações críticas agudas. Infecção, internações clínicas, acesso hospitalar via emergência e internações em hospitais de médio porte foram fatores de risco para DCC.

Conclusão da tese: O conjunto dos dados desta tese mostra que o critério recentemente proposto para definir DCC é mais sensível que os anteriormente propostos para identificar o principal desfecho desta população - a mortalidade hospitalar. As características clínicas semelhantes entre os grupos de definições mostram que parece tratar-se dos mesmos pacientes em diferentes fases de evolução temporal da DCC. Os sobreviventes da internação na UTI sofrem declínio da capacidade funcional em até seis meses após a alta, mas tendem a recuperá-la em um ano. Mostramos que é possível avaliar a epidemiologia da DCC em bases de dados do sistema publico de saúde. Este é o primeiro estudo que utilizou a base de dados do sistema de saúde para apresentar a epidemiologia da doença crítica crônica no Brasil. A alta prevalência, com elevada mortalidade e custo maior ao sistema de saúde destacam esta condição como importante problema de saúde pública.

Palavras-chave: paciente crítico, respiração artificial, ventilação mecânica prolongada, traqueostomia, doença crítica crônica, paciente crítico crônico, sobrevida, mortalidade, capacidade física funcional, custos.

ABSTRACT

Introduction: The development of intensive medicine and the use of evidence-based bundles of treatment have contributed to support organic failures and increase survival of critically ill patients who would die due to multiple organic dysfunction. Concomitantly, the growth of patients with persistence inflammatory status (PICS) and dependent on intensive care for long periods was observed. Chronic critical illness (CCI) is marked by worst hospital and functional outcomes, high cost and worst long-term outcomes after intensive care unit (ICU) discharge. For many years CCI has been defined by dependence on prolonged ventilatory support. However, recently a new definition was developed with the proposal to be more sensitive to identify chronic patients within the critically ill population.

Objectives: This thesis consists of two studies. **Study 1:** In the first study, the objective was to evaluate the four most commonly used CCI definitions, including a recently developed definition, regarding the ability to identify the population of chronic patients in ICU admissions. Also, in the same research protocol, the current definition was used to identify a sample of patients with CCI and evaluate 12-months survival and functional status after ICU discharge. **Study 2:** The objective of the second study was to characterize the epidemiology of CCI in the population of patients assisted by the public health system in Brazil.

Materials and methods: Study 1: Historical cohort with patient selection with the four most commonly used CCI definitions for assessment of hospital outcomes and predictive capacity for in-hospital mortality. A sample of patients with CCI current definition was evaluated for 12-months functional status and survival. Patients were selected in an institutional database of an ICU of a private hospital of high complexity in capital of southern of Brazil. **Study 2:** Historical cohort performed in a database of the public health system in Brazil. All ICU hospitalizations between June 2018 and May 2019 in the state of Rio Grande do Sul were included. The current CCI definition was used to select chronic patients and to differentiate them from the group of acute patients. Clinical characteristics, hospital outcomes, financial impact and risk factors to develop CCI were evaluated.

Results and conclusions: Study 1: We selected 146 hospitalizations with definition of CCI of ≥14 days of mechanical ventilation (MV), 79 hospitalizations with ≥21 days of MV, 89 hospitalizations with definition of CCI due to the need for tracheostomy by prolonged MV and 494 hospitalizations with the current definition (≥8 days of ICU plus one of the following conditions: tracheostomy, MV ≥96 hours, sepsis, severe wounds, stroke or head trauma). The characteristics between hospitalizations in the four CCI definitions groups were similar. A lower mortality in the CCI definitions due to tracheostomy and the current definition compared to definitions by MV ≥14 and ≥21 days (52.8%, 46% and 61%, 65.8%, respectively) was verified. The specificity of the four definitions in predicting mortality was similar, but sensitivity was higher using the current definition (8.6%, 41.7% and 16.2%, 9.5%, respectively). For the second objective of the study, 55 patients with the current CCI definition were evaluated 12 months after ICU discharge. Functional status between 3 and 6 months after ICU discharge was significantly lower than pre-hospitalization, trending to functional recovery at 12 months. Survival in 12-months was 74.5%. The current CCI criterion is more sensitive than those previously used to predict the main outcome of this condition, the mortality. Patients with CCI have worse functional outcome between three and six months after ICU discharge, but tend to resume basal functional capacity up to 12 months after discharge. **Study 2:** 48,708 acute hospitalizations and 8056 hospitalizations with CCI criteria were included. The prevalence of CCI was 16.5%. Hospital mortality was higher in chronic hospitalizations (20.5% and 31.7%, respectively), the mean cost for hospitalization was also higher in the CCI hospitalizations (R$: 4,157.25 higher than acute ICU hospitalizations). Hospitalizations emergency source (RR 1.67, 95% CI 1.51 – 1.85), middle-size hospital (RR 1.28, 95% CI 1.19 – 1.38), medical cause reason hospitalizations (RR 1.27, 95% CI 1.20 – 1.34) and the infections (RR 5.75, 95% CI 5.5 – 6.01) were risk factors for CCI. The age groups < 1 year and >35 years marked higher mortality in hospitalizations with CCI compared to acute critical hospitalizations. This study confirms that it is possible to evaluate the epidemiology of CCI in the database of the Brazilian public health system. The data show a high prevalence of CCI as well as higher mortality and higher cost for the health system for chronic critical hospitalizations than acute critical hospitalizations. Infection, medical ~~reason~~

hospitalizations, emergency hospital source and hospitalizations in middle-sized hospitals were risk factors for CCI.

Conclusions of the thesis: The data of the studies that compose this thesis show that the newly proposed CCI definition is more sensitive than those previously proposed to identify the main outcome of this population, hospital mortality. Similar clinical characteristics between definition groups show that they seem to be the same patients at different phases of temporal evolution of CCI. Chronic critically ill patients have decline in functional status within six months of ICU discharge, but tend to regain functional status after one-year discharge. We confirm that it is possible to evaluate the CCI epidemiology in the Brazilian public health system database. The high prevalence, with high morality and higher cost to the health system highlight this condition as an important public health problem.

Keywords: critically ill patient, artificial respiration, prolonged mechanical ventilation, tracheostomy, chronic critical illness, chronically critically ill patient, survival, mortality, physical functional performance, costs.

LISTA DE FIGURAS

REVISÃO DA LITERATURA

Figura 1: Estratégia de busca de referências bibliográficas.....19

Figura 2: Respirador artificial: pulmão de aço.....21

Figura 3: Respirador de couraça.....22

Figura 4: Representação da resposta inflamatória em uma modelo de sepse.....23

Figura 5: Representação da resposta inflamatória e evolução com PICS.....25

Figura 6: Marco conceitual teórico da tese.....36

LISTA DE FIGURAS DO PRIMEIRO ARTIGO

Figure 1: One-year Kaplan-Meier survival curve of the 55 CCI current definition patients……48

Figure 2: One-year Barthel index of the 55 CCI current definition patients after ICU discharge…….…….49

LISTA DE FIGURAS DO SEGUNDO ARTIGO

Figure 1: Mortality by age group in CCI and acute critically ill…….....64

Figure 2: Kaplan-Meier curve for Chronic and Acute Critical Illness……..…….65

Figure 3: Risk-factors for chronic critical illness……66

LISTA DE TABELAS

REVISÃO DA LITERARURA

Tabela 1: Conceitos de doença crítica crônica ao longo dos anos.....27

PRIMEIRO ARTIGO

Table 1: CCI characteristics population on four definitions selected from 2007 to 2010 ICU admissions……..…….……45

Table 2: Sensitivity, specificity and accuracy of CCI definitions……...46

Table 3: Hospital outcomes in CCI definitions……...……45

Table 4: CCI characteristics population for current definition selected from 2014 to 2017 ICU admissions……..….....47

SEGUNDO ARTIGO

Table 1: Characteristics of CCI and acute critical hospitalizations in public health system ……..…62

Table 2: Amount paid for hospitalizations, length-of-stay and outcome in CCI and acute critically ill……..…64

Supplementary table: procedure codes (SIGTAP) and diagnoses codes (ICD-10) used to select critical hospitalizations with CCI definition…….59

.

LISTA DE ABREVIATURAS

APACHE II: Acute Physiology and Chronic Health Evaluation II

ARDS: acute respiratory distress syndrome

ARF: acute renal failure

ASPEN – American Society of Parenteral and Enteral Nutrition

CTI – Centro de tratamento intensivo

CCI: chronic critical illness

DCC: doença crítica crônica

DMOS: disfunção de múltiplos órgãos e sistemas

DPOC - doença pulmonar obstrutiva crônica

EN: enteral nutrition

FiO2 – fração inspirada de oxigênio

HD: hemodiálise convencional

HDVVC: hemodiálise venovenosa contínua

IMC – Índice de massa corporal

MHz – Mega-hertz (unidade de medida)

MRC – Medical Research Council

MV: mechanical ventilation

PAM – Pressão arterial média

PaO2 – preção parcial arterial de oxigênio

PAV: pneumonia associada à ventilação mecânica

SAPS 3 - Simplified Acute Physiology Score 3

SARA: síndrome da angústia respiratória aguda

SDRA – síndrome da angústia respiratória no adulto

SOFA: Sequential Organ Failure Assessment Score

SPSS: Statistical Package for the Social Sciences

UTI: Unidade de tratamento intensivo

VM: ventilação mecânica

VMP: ventilação mecânica prolongada

SUMÁRIO

CAPÍTULO I – INTRODUÇÃO

1. Introdução.....16

CAPÍTULO II – REVISÃO SISTEMATIZADA DA LITERARURA

1. Descrição da estratégia de busca de dados.....18

2. História da medicina intensiva.....21

3. Resposta metabólica ao trauma e síndrome da resposta inflamatória sistêmica (SIRS).....23

4. Doença crítica crônica e síndrome da inflamação persistente crônica.....25

5. Epidemiologia da doença crítica crônica.....28

6. Impacto econômico da doença crítica crônica.....29

7. Desfechos funcionais da doença crítica crônica após a alta hospitalar.....29

8. Referências bibliográficas.....30

CAPITULO III – CONCEITO, JUSTIFICATIVA E OBJETIVOS

1. Mapa conceitual.....35

2. Justificativa.....37

3. Objetivos.....38

3.1 Objetivo geral.....38

3.2 Objetivos específicos.....38

CAPÍTULO IV – ARTIGOS

1. Definitions and long-term outcomes in Chronic Critical Illness: a cohort study……...……..39

2. Mortality, risk factors and costs of Chronic Critical Illness in a low-income country……...…...55

CAPÍTULO V – CONCLUSÃO DA TESE

1. Considerações finais.....73

2. Perspectivas futuras.....74

CAPITULO VI – ANEXOS

1. STROBE - Definitions and long-term outcomes in Chronic Critical illness……..…..75

2. STROBE - Mortality, risk factors and costs of Chronic Critical Illness in a low-income country…….78

3. Certificado de tradução - Mortality, risk factors and costs of Chronic Critical Illness in a low-income country…….……..81

4. CAPÍTULO I – INTRODUÇÃO

1. Introdução

O atendimento a pacientes graves e o suporte a disfunções orgânicas evoluiu ao longo das últimas décadas[1]. Rapidamente as unidades de tratamento intensivo cresceram em número e em complexidade, sendo capazes de dar suporte a múltiplas disfunções orgânicas simultaneamente[2]. Se por um lado conquistamos redução da mortalidade de pacientes que anteriormente morriam por disfunção de múltiplos órgãos e sistemas (DMOS)[3], por outro lado observamos o surgimento de uma população de pacientes críticos que permanece dependente do suporte da unidade de tratamento intensivo (UTI) por longos períodos[4].

Este subgrupo de pacientes caracteriza-se por sobreviver ao insulto inicial que motivou a internação na UTI, mas persiste em um estado inflamatório crônico decorrente de novos insultos, em geral infecciosos[5]. Como consequência desenvolvem perda de massa muscular, fraqueza muscular, delírium, edema, lesões de pele e predisposição a novas infecções[5]. Comparativamente à população de críticos agudos, apresentam maior mortalidade hospitalar e menor sobrevida após a alta, além de piores desfechos funcionais a longo prazo[5].

Desde a primeira descrição da doença crítica crônica (DCC), diversas definições foram propostas pela literatura, a maioria delas baseadas no tempo de ventilação mecânica (VM) durante a internação na UTI[6]. Estas definições foram criticadas pela simplicidade frente a uma condição clínica complexa e novas definições baseadas não somente no tempo de suporte ventilatório foram propostas[7]. Recentemente, motivada por questões de ressarcimento de seguradoras de saúde, uma nova definição que considera o tempo de internação na UTI associado à presença de condições como sepse, traqueostomia e necessidade de ventilação mecânica, lesões de pele e disfunções orgânicas foi proposta[8]. Essa definição tem o objetivo de ser capaz de identificar a população de pacientes com DCC de forma mais sensível que as definições até então propostas. Por outro lado, ainda foi pouco testada em populações diferentes daquela onde foi desenvolvida[9].

Independente do critério utilizado, a DCC vem crescendo entre a população de pacientes críticos. Apesar de algumas coortes mostrarem alguma melhora da

sobrevida ao longo dos anos, desfechos funcionais após a alta hospitalar têm sido um desafio no cuidado após a alta destes pacientes[10].

A divergência de definições entre os estudos que avaliam características clínicas e desfechos da DCC configura-se em uma considerável limitação ao avanço das pesquisas com este grupo de pacientes. Testar a nova definição em outras populações pode consolidar um único critério diagnóstico e viabilizar pesquisas que caracterizem a epidemiologia desta condição em diferentes populações. Este conhecimento pode não só auxiliar em pesquisas que tentam desvendar aspectos da fisiopatologia da DCC, mas também subsidiar o planejamento de sistemas de saúde para atender necessidades específicas, principalmente quanto à reabilitação desta população de pacientes críticos.

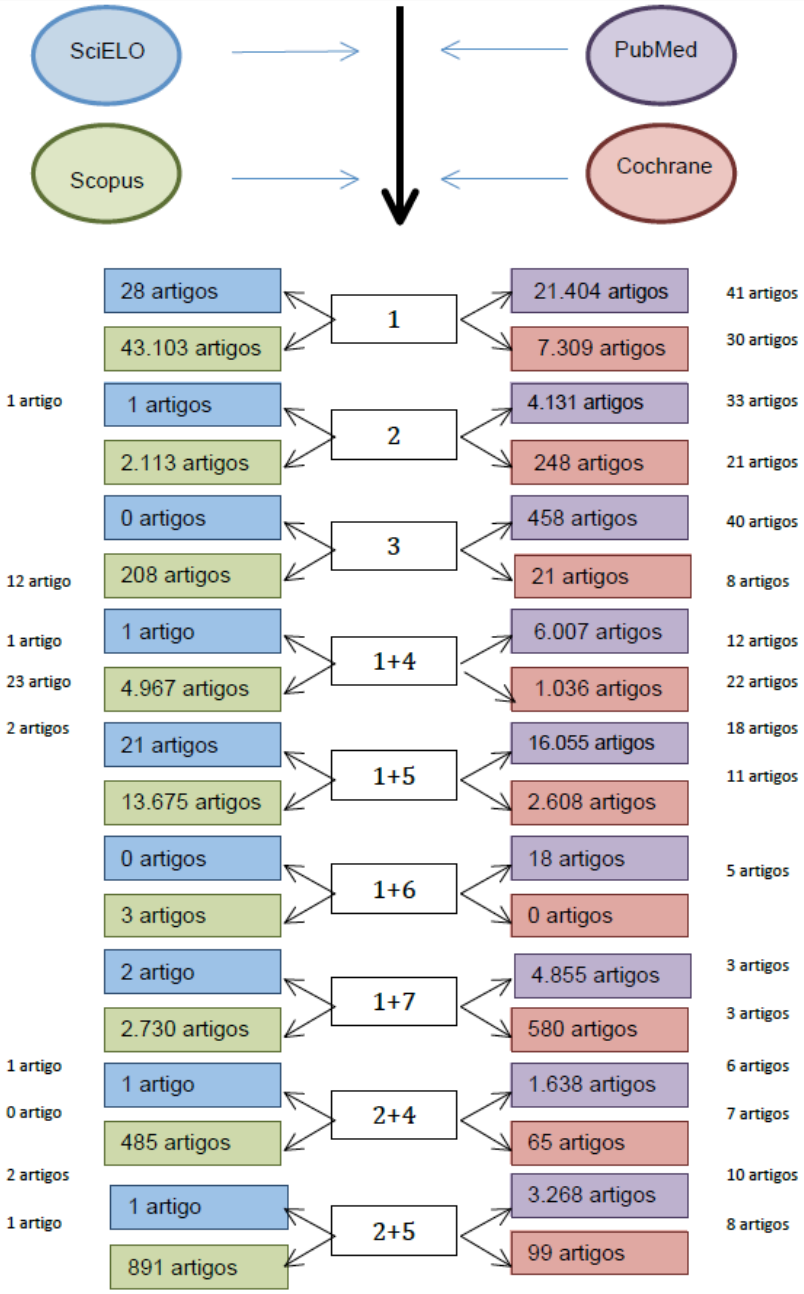
CAPÍTULO II – REVISÃO SISTEMATIZADA DA LITERARURA

1. Descrição da estratégia de busca

A revisão da literatura está focada no grupo de pacientes críticos que evolui com dependência prolongada do suporte intensivo, grupo conhecido como doentes críticos crônicos. Também está focada nos desfechos mortalidade, tempo internação, custos e capacidade funcional. A estratégia de busca envolveu quatro bases de dados: SciELO, Pubmed, Scopus e Cochrane. Os descritores usados foram: *(1) critical illness, (2) prolonged mechanical ventilation, (3) chronic critical illness, (4) length of stay, (5) mortality, (6) physical functional performance e (7) costs.*

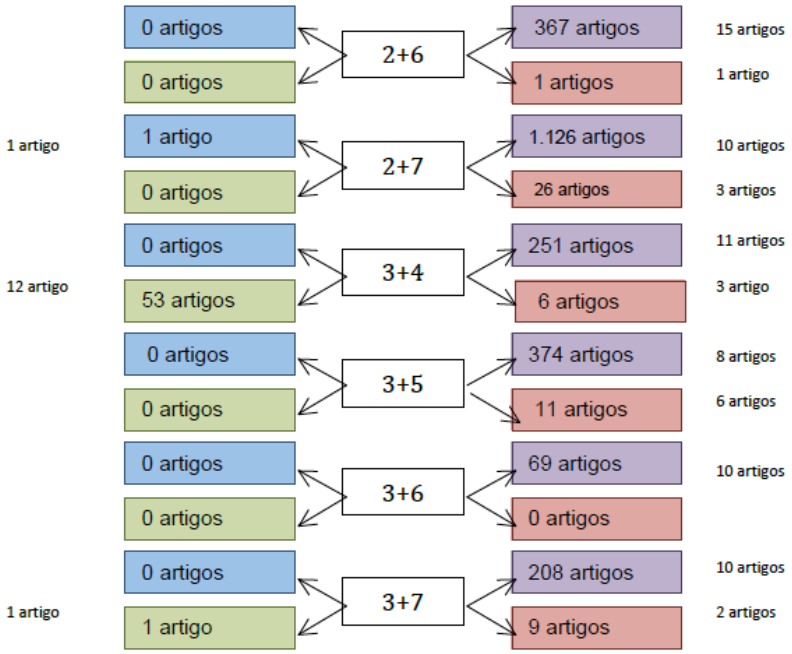
A metodologia de busca está descrita na Figura 1.

Figura 1: estratégia de busca de referencias bibliográficas



Em cada box central os números indicados correspondem aos descritores de fator de estudo: *(1)critical illness, (2)prolonged mechanical ventilation, (3)chronic critical illness,* e aos descritores de desfecho: *(4)lenght of stay, (5)mortality, (6) Physical functional performance (7) costs*. Cada box lateral corresponde a uma base de dados conforme coloração indicativa. Na coluna mais lateral esta descrito quantos artigos foram utilizados de cada busca.

Figura 1: estratégia de busca de referencias bibliográficas *(continuação)*



Em cada box central os números indicados correspondem aos descritores de fator de estudo: *(1)critical illness, (2)prolonged mechanical ventilation, (3)chronic critical illness,* e aos descritores de desfecho: *(4)lenght of stay, (5)mortality, (6) Physical functional performance e (7) costs*. Cada box lateral corresponde a uma base de dados conforme coloração indicativa. Na coluna mais lateral esta descrito quantos artigos foram utilizados de cada busca.

2. História da medicina intensiva

O reconhecimento do benefício do conceito de atendimento em unidades com equipes especializadas data do século 19 com o atendimento a feridos de guerra[11]. Porém, foi nos anos 50, durante a epidemia de poliomielite em Copenhagen, que a terapia com suporte respiratório artificial desenvolveu-se e o conceito de unidade de tratamento intensivo foi sendo criado[12].

Até então, respiradores artificiais eram usados em poucos pacientes e sem o conceito de unidade especializada. O hospital Blegham, em Copenhagen, tinha no início da epidemia, apenas um respirador que usava pressão negativa (Figura 2) e seis respiradores de couraça (Figura 3). Entretanto, passou a receber diariamente 40 pacientes em insuficiência respiratória. Foi então que a técnica de traqueostomia, anteriormente usada e abandonada por apresentar desfechos pouco promissores, foi usada pelo anestesista Bjor Ibsen viabilizando o uso de ventilação com pressão positiva e aspiração de secreções respiratórias[13].

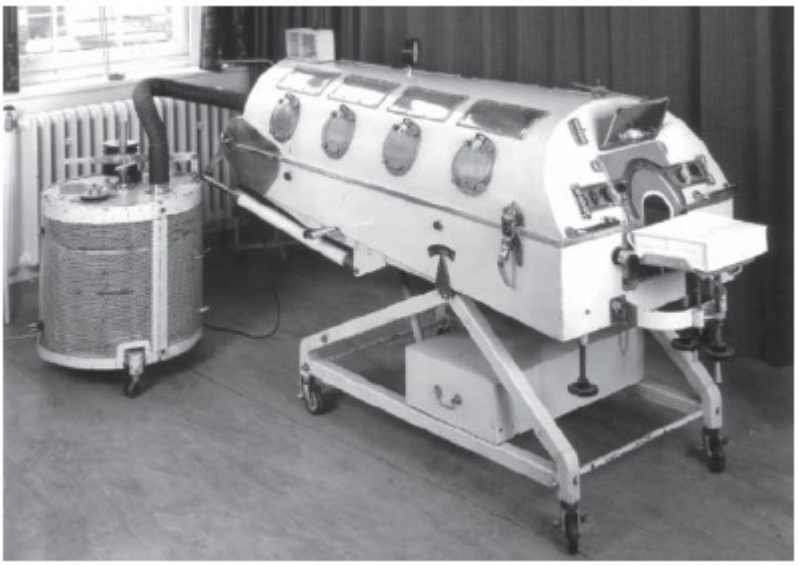


Figura 2: Respirador artificial: pulmão de aço[12]

Figura 3: Respirador de couraça[12].

Rapidamente a necessidade de reunir estes pacientes em unidades especializadas foi percebida[13] e a mortalidade da poliomielite naquela epidemia caiu de 80% para 40%[12]. A partir de então, unidades intensivas com cuidados especializados foram sendo criadas a passaram a espalhar-se pela Europa e América. Na California, anos mais tarde, foi criada a primeira unidade de choque que iniciou com quatro leitos críticos[14].

As unidades foram, então, crescendo e tecnologias foram sendo desenvolvidas a incorporadas à monitorização, como por exemplo a gasometria arterial. As terapias de suporte especializado foram evoluindo até o arsenal tecnológico como conhecemos hoje. Como consequência, surgiu a necessidade de equipes especializadas e monitoramento contínuo[15], incluindo recentemente técnicas de monitoramento à distância por telemetria[16].

No Brasil, registros na literatura nacional relatam que as primeiras UTIs no modelo que conhecemos hoje foram criadas no Hospital das Clínicas em São Paulo na década de 60 e já na década de 70 o hospital Sírio Libanês montou a primeira unidade planejada com 12 leitos.

3. Resposta metabólica ao trauma e síndrome da resposta inflamatória sistêmica (SIRS)

A doença crítica é caracterizada por uma resposta do organismo a uma agressão, seja ela uma infecção, um trauma cirúrgico, uma cirurgia de grande porte ou ainda qualquer outra doença capaz de causar reação inflamatória em grande escala, levando a uma resposta sistêmica[17].

A síndrome da resposta inflamatória sistêmica (SIRS) é caracterizada por liberação de citocinas inflamatórias em tecidos periféricos, que ativam células inflamatórias e potencializam a reação local, levando progressivamente a uma escala sistêmica[18]. A liberação de óxido nítrico em tecidos periféricos provoca intensa vasodilatação e consequente hipotensão capaz de ser detectada por barorreceptores que ativam respostas neuronais, de ação rápida, como resposta à agressão[19]. A Figura 4 resume de forma esquemática as alterações teciduais inflamatórias. A partir daí, estímulo do eixo hipotalâmico-hipofisário-adrenal provoca a liberação de hormônios de fase aguda como adrenalina e cortisol[19]. Estes irão acionar vias metabólicas a fim de preparar o organismo para reagir à agressão em proporções sistêmicas.

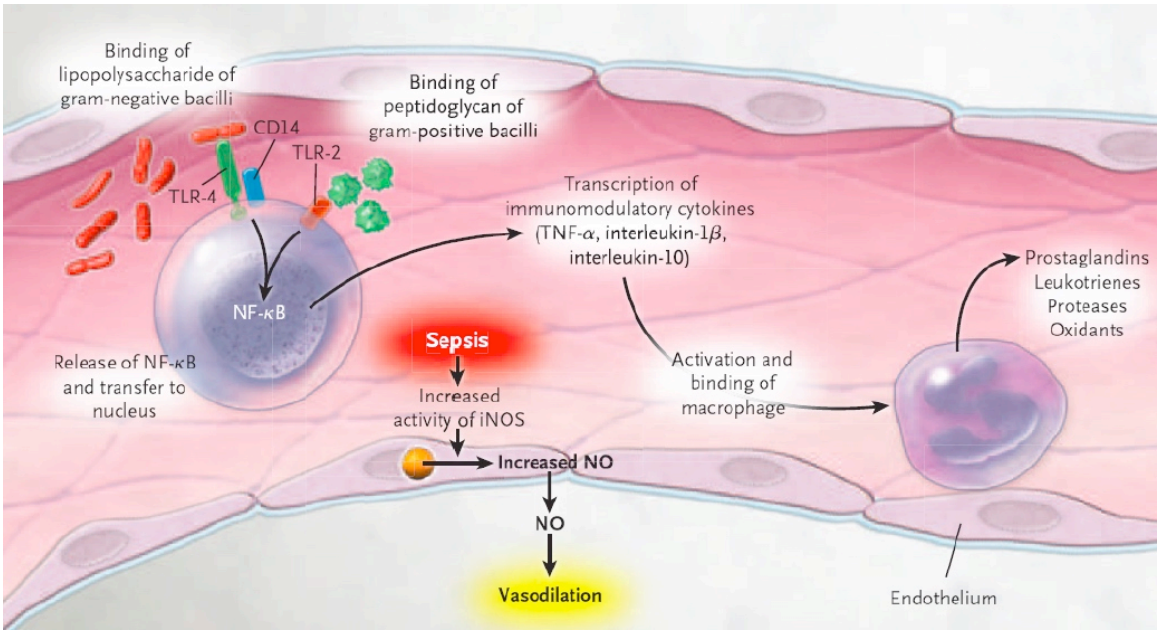


Figura 4: Representação da resposta inflamatória em uma modelo de sepse. [18]

Taquicardia, taquipnéia, febre, leucocitose e alteração da consciência são características da SIRS, sendo a evolução natural para DMOS[20] passível de ser

abortada pela introdução de suporte intensivo às disfunções orgânicas, enquanto a causa base é diagnosticada e tratada.

A liberação de hormônicos de fase aguda promove reações catabólicas a fim de mobilizar moléculas capazes de produzir a energia demandada por reações inflamatórias sistêmicas. Entretanto, diferente do catabolismo relacionado ao estado de jejum, a inflamação sistêmica provoca resistência à ação da insulina e consequente hiperinsulinemia[21]. O efeito é a dificuldade de mobilização de ácidos graxos como fonte energética e a priorização de proteínas como fonte primária de energia, já que as reservas de carboidratos duram poucas horas. A consequência deste catabolismo inflamatório é a perda intensa de massa muscular, levando à caquexia[22].

O reconhecimento desta consequência metabólica passou a ser motivo de preocupação à medida que os primeiros estudos mostraram uma forte associação com perda da massa magra com piores desfechos funcionais, maior risco de infecção e maior mortalidade[23,24].

Tentativas de amenizar a resposta inflamatória com uso de imunossupressores já foram tentadas e tiveram resultados frustrantes. Esta evidência sugere que a inflamação sistêmica possa não tratar-se de uma "resposta exagerada" do organismo, mas uma reação necessária que, quando não está presente, também leva a piores desfechos[25].

Na tentativa de amenizar as consequências do catabolismo, o desenvolvimento de métodos de suporte nutricional cresceu ao longo dos anos. Tentativas de comprovar seu benefício tem sido motivo de intensa discussão na literatura. Pacientes com baixo risco nutricional e baixa gravidade tendem a ter pouco ou nenhum benefício com o suporte nutricional. Por outro lado, evidências apontam que pacientes com múltiplas disfunções e com algum comprometimento do estado nutricional têm benefício de medidas que garantam aporte calórico próximo a 80% das necessidades energéticas diárias[26]. Estes benefícios têm sido traduzidos em redução do tempo de hospitalização, menos infecções e menor mortalidade. Outros estudos têm mostrado benefício na síntese muscular, mesmo durante a fase aguda, com a garantia de suporte nutricional durante a SIRS[27].

4. Doença critica crônica e síndrome da inflamação persistente crônica

Alguns pacientes críticos sobrevivem ao insulto inicial, mas persistem em um estado inflamatório mais brando por período prolongado. Esta condição é descrita como estado de inflamação persistente crônica (*persistent inflammation chronic syndrome* – PICS). Representa uma parcela de pacientes críticos que, após a fase aguda, sofrem novas agressões e desenvolvem um estado inflamatório mais brando, porém suficiente para desenvolver catabolismo, fraqueza muscular, predisposição a infecções e dependência de algum suporte intensivo (Figura 5)[28].

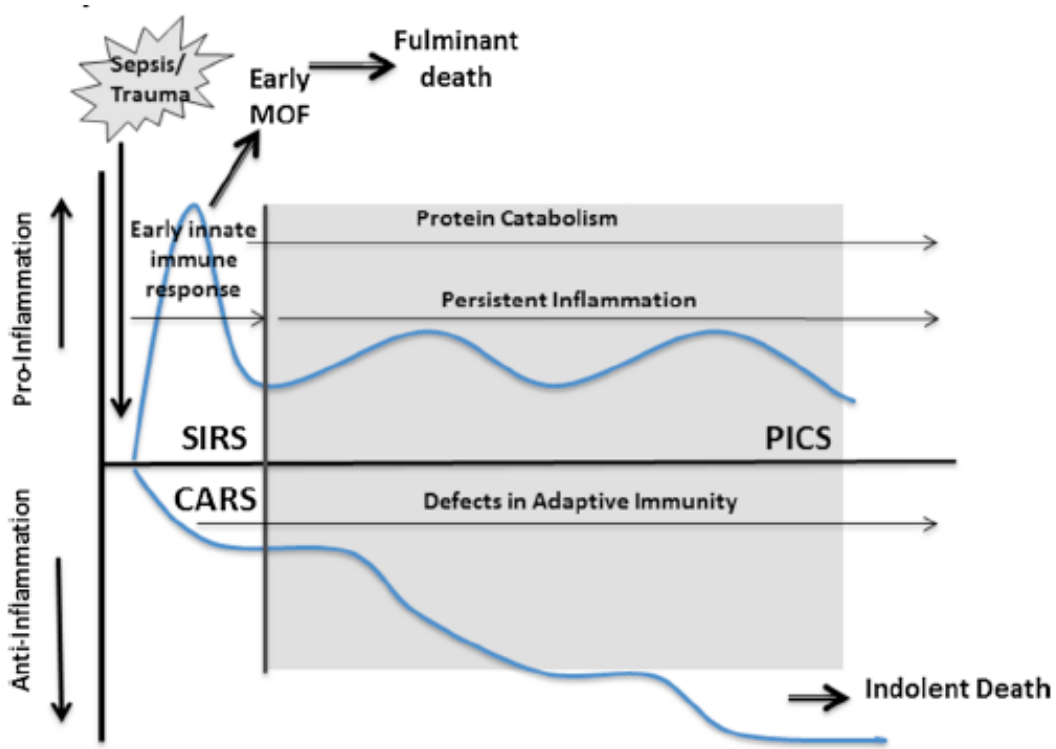


Figura 5: Representação da resposta inflamatória e evolução com PICS[28]

Esta condição fisiopatológica tem sido considerada como a gênese da doença crítica crônica[5]. População já descrita desde a década de 80 na literatura médica e que tem sido fonte de discussão quando a sua definição[6]. A Tabela 1 descreve os conceitos usados ao longo dos últimos 30 anos para reconhecer a DCC na população de pacientes críticos[6]. A grande maioria baseia-se no tempo de dependência do suporte ventilatório, tendo os pontos de corte de 14 e 21 dias de VM como as definições mais aceitas ao longo dos anos[7].

Entretanto, a DCC representa um conjunto mais amplo de alterações metabólicas e, à medida que a medicina intensiva foi ampliando a capacidade de suporte a outras disfunções e cuidados intensivos mais complexos, surgiu a necessidade de ampliar esta definição[7]. Motivada por questões de pagamentos de serviços de saúde por seguradoras norte-americanas, uma nova definição foi criada[8]. Foi proposta, então, uma definição mais ampla que leva em consideração oito ou mais dias de internação na UTI somada a uma entre cinco condições: (1) traqueostomia, (2) ≥96 horas de VM, (3) sepse, (4) lesões graves de pele ou (5) disfunções orgânicas[8].

A partir de então, outros estudos usaram esta definição a fim de caracterizar a epidemiologia da DCC em outras populações[9]. Cabe salientar que o critério disfunções orgânicas tem sido questionado e há uma preferência por utilizar em seu lugar apenas informações que caracterizem comprometimento de funções neurológicas: acidente vascular encefálico (AVE) isquêmico e hemorrágico e traumatismo cranioencefálico[9].

Tabela 1: Conceitos de doença crítica crônica ao longo dos anos

Ano	Autor	Conceito
2014	Kahn et al	8 dias ou mais na UTI com uma ou mais entre seis condições: ventilação mecânica, traqueostomia, AVE, TCE, sepse ou ferimentos graves.
2013	Loss et al	14 dias de ventilação mecânica ou traqueostomia por dependencia de suporte ventilatório.
2012	Carson at al	21 dias ou mais de ventilação mecânica por pelo menos 6h/dia.
2011	Boniatti et al	Traqueostomia pordependência da de suporte ventilatório ou 21 dias ou mais de ventilação mecânica
2008	Zilberberg et al	Suporte ventilatório por causa agurda por tempo maior ou igual a 96h.
2007	Scheinhorn et al	Ventilação prolongada por falência respiratória.
2005	MacIntyre et al	Necessidade de ventilação mecânica por 21 dias consecutivos e ou tempo maior ou igual a 6h por dias.
2005	Daly et al	Pacientes necessitando de ventilação mecânica por tempo maior ou igual a 72h que sobrevivem a alta hospitalar.
2004	Nelson et al	Uma síndrome de significante deteriorização do metabolismo e de funções neuroendocrinas, neuropsiquiátricas e imunológicas. Definida pela realiazação de traqueostomia por falência de desmame da ventilação mecânica.
2002	Nierman	Pacientes que sobrevivem a doença crítica, mas ficam com significante comprometimento functional e dependência de cuidados intensivos de enfermagem e de tecnologia avançada.
2002	Carson and Bach	Pacientes que necessitam de cuidados contínuo e ventilação mecânica prolongada em uma UTI por semana ou meses; 21 dias de UTI indica que as condições mais facilmente reversíveis teriam sido resolvidas.
2000	Nasraway et al	Uma pequena parcela de pacientes de UTI que por causa de doenças subjacentes ou complicações sofrem uma prolongada e complicada evolução. Sobrevidentes da doença aguda severamente enfraquecidos frequentemente dependents de ventilação mecânica ou diálise renal.
1997	Douglas et al	Pacientes que necessitam de e de cuidados intensivos de enfermagem tratamento medico para dienca primária; geralmente com estada na UTI de duas semanas.
1985	Girard and Raffin	Paceintes de UTI que não sobrevivem a despeito do extraordiário suporte de vida por semanas a meses.

Extraído e modificado de *Wiencek, C. Winkelman, C. Chronic critical illness: prevalence, profile, and pathophysiology. AACN Adv Crit Care 2010.* **UTI,** unidade de tratamento intensivo; **AVE**, acidente vascular encefálico; **TCE**, traumatismo crânioencefálico.

5. Epidemiologia da doença crítica crônica

A DCC tem emergido como uma condição crescente nas UTIs do mundo todo[10]. Independente do critério utilizado, a prevalência da DCC nas UTIs varia entre 5% a 10% das internações críticas[29,30]. Coortes mostram uma tendência de crescimento anual da prevalência da DCC e uma tendência à redução da mortalidade ao longo dos anos[9].

A DCC está associada à recorrência de episódios de instabilidade, reinfecção, maior incidência de delirium, alterações cognitivas, maior permanência hospitalar, necessidade de cuidadores ou *home care*, maior ocorrência de reinternações, maior mortalidade hospitalar, em geral próxima a 50%, e piores desfechos funcionais um ano após a alta, bem como maior custo ao sistema de saúde [31, 32].

Uma coorte conduzida em Porto Alegre identificou uma mortalidade de 30% neste grupo de pacientes ainda na UTI e 54% de mortalidade hospitalar[33]. Neste estudo, nos 41 pacientes com DCC avaliados, os fatores de risco associados a esta condição foram necessidade de VM, presença de hiperglicemia nos primeiros quatro dias da internação na UTI, internação prolongada previamente à internação na UTI e baixa oferta calórica[33].

Outros estudos também buscaram identificar marcadores de mortalidade para esta condição. Um estudo conduzido por Carson S *e cols* validou um modelo de predição de mortalidade em pacientes com tempo de VM ≥21 dias. Identificou que necessidade de vasopressor, hemodiálise, contagem de plaquetas < 150.000 e idade maior ou igual a 50 anos foram preditores de mortalidade na população de DCC[34].

Uma coorte com 817 pacientes com VM por tempo ≥48h encontrou piores desfechos no primeiro ano nos pacientes mais velhos, que apresentavam piores índices prognósticos e mais comorbidades[35, 36]. Outro estudo buscou variáveis preditores de DCC (definição de ≥14 dias de VM) no momento da intubação. Identificou que acidose, disfunção renal e taquicardia foram preditores de DCC[37].

Diversos fatores dificultam estabelecer a epidemiologia da DCC. Eles residem na baixa ocorrência (5% a 10% dos pacientes críticos), na diversidades de definições adotadas e na necessidade de seguimento prolongado para identificar este grupo de

pacientes. Além disso, avaliações de desfechos após a alta são muito caras e complexas. Demandam coortes multicêntricas e financiamentos robustos.

6. Impacto econômico da doença crítica crônica

O custo das internações de pacientes com DCC está relacionado ao maior tempo de internação e às complicações clinicas. Lesões de pele, colonização por germe multirresistente, uso de antimicrobianos de amplo espectro, demanda por cuidados de enfermagem e medidas de reabilitação são fatores que impactam no maior custo para tratamento desta população de pacientes[38, 39].

Um estudo recente, usando a definição atual de DCC, avaliou o impacto econômico da DCC no sistema de saúde norte-americano. Os dados apontam um custo anual crescente, chegando em 2009 a 26 bilhões de dólares gastos com 380.001 internações[9]. Outro estudo, usando ainda definição de VMP de 21 dias ou mais em pacientes idosos encontrou uma relação custo benefício ruim, avaliando sobrevida e qualidade de vida a longo prazo, comparando com pacientes que tiveram VM suspensa após 21 dias de suporte[40].

Na tentativa de minimizar o significativo impacto no custo hospitalar, medidas de desospitalização têm sido testadas em pacientes com DCC. Elas mostraram resultado financeiro positivo, porém sem impacto nos desfechos clínicos[41,42]. Por outro lado, os cuidadores destes pacientes apresentam alta prevalência de ansiedade e de depressão[43, 44].

7. Desfechos funcionais da doença crítica crônica após a alta hospitalar

À medida que a população com DCC foi crescendo e mais pacientes foram sobrevivendo a longas internações, cresceu a demanda por reabilitação e cuidados de enfermagem após a alta hospitalar. Desta forma, diversos estudos buscaram medir desfechos funcionais nos pacientes críticos crônicos sobreviventes à internação na UTI. A baixa prevalência e a elevada mortalidade levam a coortes pequenas e com muitas perdas de seguimento.

Um estudo multicêntrico envolvendo 17 UTIs realizou seguimento de 141 pacientes com DCC por 57 meses. Observou que a capacidade funcional dos

sobreviventes era significativamente menor do que a da população geral[45]. Outro estudo menor, acompanhou 28 pacientes crônicos após a alta da UTI durante 24 meses. Da mesma forma, observou capacidade funcional reduzida para atividades diárias[46].

Além dos desfechos funcionais, a qualidade de vida após a UTI tem sido fonte de pesquisa. Uma coorte de 30 pacientes com DCC mostrou piores escores de qualidade de vida nesta população. Este estudo também avaliou capacidade funcional encontrando desfechos semelhantes a outras coortes[47]. Uma coorte de pacientes críticos gerais também avaliou qualidade de vida e capacidade funcional após a alta. Um dos achados interessantes deste estudo foi que pacientes com traumatismo cranioencefálico apresentaram piores desfechos[48], justamente um dos critérios atualmente usados para a definição de DCC.

8. Referências bibliográficas

1. Weil MH, Tang W. From intensive care to critical care medicine: a historical perspective. Am J Respir Crit Care Med. 2011 Jun 1;183(11):1451-3.
2. Puri, N. Puri, V. Dellinger, R. P. History of technology in the intensive care unit. Crit Care Clin 2009; 25(1): 185-200.
3. Nelson JE, Cox CE, Hope AA, Carson SS. Chronic critical illness. Am J Respir Crit Care Med 2010; 182: 446–54.
4. Carson SS, Bach PB. The epidemiology and costs of chronic critical illness. Crit Care Clinc 2002; 18: 461-76
5. Mira JC, Gentile LF, Mathias BJ et al. Sepsis Pathophysiology, Chronic Critical Illness and PICS. Crit Care Med. 2017 February ; 45(2): 253–262.
6. Wiencek, C. Winkelman, C. Chronic critical illness: prevalence, profile, and pathophysiology. AACN Adv Crit Care 2010; 21(1): 44-61
7. Loss SH, Nunes DSL, Franzosi OS et all. Chronic critical illness: are we saving patients or creating victims? Rev Bras Ter Intensiva. 2017;29(1):87-95

8. Kandilov AM, Ingber MJ, Morley M, et al.: Chronically Critically Ill Population Payment Recommendations. Research Triangle Park, NC, RTI International, 2014
9. Kahn JM, Le T, Angus DC, Cox CE, Hough CL, White DB, Yende S, Carson SS; ProVent Group Study Investigators. The epidemiology of chronic critical illness in the United States. Crit Care Med. 2015;43(2):282-7.
10. Kamel AY, Rosenthal CM, Brakenridge S, et all. Chronic Critical Illness: Application of What We Know. Nutr Clin Pract. 2018 Feb; 33(1): 39–45.
11. NIGHTINGALE, F. *Notes on Hospitals*; 3. ed., Londres: Longman Green, l863.
12. Kelly FE, Fong K, Hirsch N, et al. Intensive care medicine is 60 years old: the history and future of the intensive care unit. Clinical Medicine 2014 Vol 14, No 4: 376–9.
13. Reisner-Sénélar, L. The birth of intensive care medicine: Björn Ibsen's records. Intensive Care Med 2011; 31(7): 1084-6.
14. Tang W, Sun S. Max Harry (Hal) Weil – a leader, mentor, friend, and wonderful colleague. *Resuscitation* 2011;82:1481–2.
15. Weil MH, Tang W. From intensive care to critical care medicine: a historical perspective. Am J Respir Crit Care Med. 2011 Jun 1;183(11):1451-3.
16. Lilly CM, Mickelson JT. Evolution of the Intensive Care Unit Telemedicine Value Proposition. Crit Care Clin. 2019 Jul;35(3):463-477.
17. Chakraborty RK; Burns B. Systemic Inflammatory Response Syndrome. StatPearls [Internet]. 2019 Sep 21.
18. Russell JA. Managemente of sepsis. N Engl J Med. 2006 Oct 19;355(16):1699-713.
19. Hotchkiss RS, Karl IE. The Pathophysiology and Treatment of Sepsis. N Engl J Med 2003; 348:138-150.
20. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 1992;20:864-874
21. Cuesta JM[1], Singer M. The stress response and critical illness: a review. Crit Care Med. 2012 Dec;40(12):3283-9.

22. Klaude M, Mori M, Tjäder I, Gustafsson T, Wernerman J, Rooyackers O. Protein metabolism and gene expression in skeletal muscle of critically ill patients with sepsis. Clin Sci. 2012 Feb;122(3):133–42.
23. Windsor JA[1], Hill GL. Weight loss with physiologic impairment. A basic indicator of surgical risk. Ann Surg. 1988 Mar;207(3):290-6.
24. Chlan LL, Tracy MF, Guttormson J, Savik K. Peripheral muscle strength and correlates of muscle weakness in patients receiving mechanical ventilation. Am J Crit Care. 2015 Nov;24(6):e91-98.
25. Alaniz C. An Update on Activated Protein C (Xigris) In the Management of Sepsis. Pharmacy and Therapeutics. 2010 Sep; 35(9): 504-508, 529.
26. Heyland DK, Cahill, N, Day AG. Optimal amount of calories for critically ill patients: Depends on how you slice the cake! Crit Care Med 2011;39: 2619-2626.
27. Punthucheary ZA, Astin R, McphailMJW et al. Metabolic phenotype of skeletal muscle in early critical illness. Thorax. 2018 Oct;73(10):926-935.
28. Gentile L F, Cuenca A G, Efron P A, Ang D, Bihorac A, McKinley B A, et al. Persistent inflammation and immunosuppression: A common syndrome and new horizon for surgical intensive care. J Trauma Acute Care Surg. Jun 2012; 72(6): 1491–1501.
29. MacIntyre N R. Chronic Critical Illness: The growing Challenge to Health Care. Respiratory Care 2012; 57(6):1021-27.
30. Carson S S. Definitions and epidemiology of the chronically critically ill. Resp Care 2012; 57(6): 848-56.
31. Carson S, Cox C, Holmes G, Howard A, Carey T. The changing epidemiology of mechanical ventilation: a population-based study. J Int Care Med. 2006;21:173–182.
32. Nelson J, Mercado A, Camhi S, et al. Communication about chronic critical illness. Arch Int Med. 2007;167(22): 2509–2515.
33. Loss S H, Marchese C B, Boniatti M M, Wawrzeniak I C, Oliveira R P. Nunes L N, Victorino J A. Prediction of chronic critical illness in a general intensive care unit. Rev Assoc Med Bras 2013 59(3): 241-247.

34. Carson SS, Garrett J, Hanson L C, Lanier J, Govert J, Brake M, et al. A prognostic model for one-year mortality in patients requiring prolonged mechanical ventilation. Crit Care Med 2008; 36(7): 2061-9.
35. Chelluri L, Rotondi A J, Sirio C A, Donahoe M P, Pinsky M R, Mendelsohn A B, et al. 2-Month mortality and functional status of critically ill adult patients receiving prolonged mechanical ventilation. Chest 2002; 121(2): 549-558.
36. Chelluri L, Im K A, Belle S H, Schulz R, Rotondi A J, Donahoe M P, et al. Long-term mortality and quality of life after prolonged mechanical ventilation. Crit care Med 2004; 32(1): 61-69.
37. Clark PA, Lettieri C J. Clinical model for predicting prolonged mechanical ventilation. Journal of Critical Care 2013; 28(5): 880.e1-880.e7
38. Donahoe M P. Current venues of care and related costs for the chronically critically ill. Respir Care 2012; 57(6): 867-86.
39. Bigatello L M, Stelfox H T, Berra L, Schmidt U, Gettings E M. Outcome of patients undergoing prolonged mechanical ventilation after critical illness. Crit Care Med 2007; 35(11):2491-7.
40. Cox C E, Carson S S, Govert J A, Chelluri L, Sanders G D. An economic evaluation of prolonged mechanical ventilation. Crit Care Med 2007; 35(8): 1918-27.
41. Dermot Frengley J, Sansone GR, Shakya K, Kaner R. Prolonged mechanical ventilation in 540 seriously ill older adults: effects of increasing age on clinical outcomes and survivalJ. J Am Geriatr Soc 2007; 62(1): 1-9.
42. Douglas SL, Daly BJ, Kelley CG, O'Toole E, Montenegro H. Chronically critically ill patients: health-related quality of life and resource use after a disease management intervention. Am J Crit 2007; 16(5): 447-57.
43. Douglas SL, Daly BJ, Kelley CG, O'Toole E, Montenegro H. Impact of a disease management program upon caregivers of chronically critically ill patients. Chest 2005; 128(6): 3925-36.
44. Douglas S L, Daly B J, O'Toole E, Hickman R L. Depression among white and nonwhite caregivers of the chronically critically ill. J Crit Care 2010; 25(2): 364.e11-9.

45. Combes A, Costa MA, Trouillet JL, Baudot J, Mokhtari M, Gibert C, Chastre J. Morbidity, mortality, and quality-of-life outcomes of patients requiring >or=14 days of mechanical ventilation. Crit Care Med. 2003; 31(5):1373-81.
46. Delle Karth G, Meyer B, Bauer S, Nikfardjam M, Heinz G. Outcome and functional capacity after prolonged intensive care unit stay. Wien Klin Wochenschr. 2006; 118(13-14):390-6.
47. Montuclard L, Garrouste-Orgeas M, Timsit JF, Misset B, De Jonghe B, Carlet J. Outcome, functional autonomy, and quality of life of elderly patients with a long-term intensive care unit stay. Crit Care Med 2000; 28(10):3389-95.
48. Delle Karth G, Meyer B, Bauer S, Nikfardjam M, Heinz G. Outcome and functional capacity after prolonged intensive care unit stay. Wien Klin Wochenschr. 2006; 118(13-14):390-6.

CAPITULO III – CONCEITO, JUSTIFICATIVA E OBJETIVOS

1. MAPA CONCEITUAL

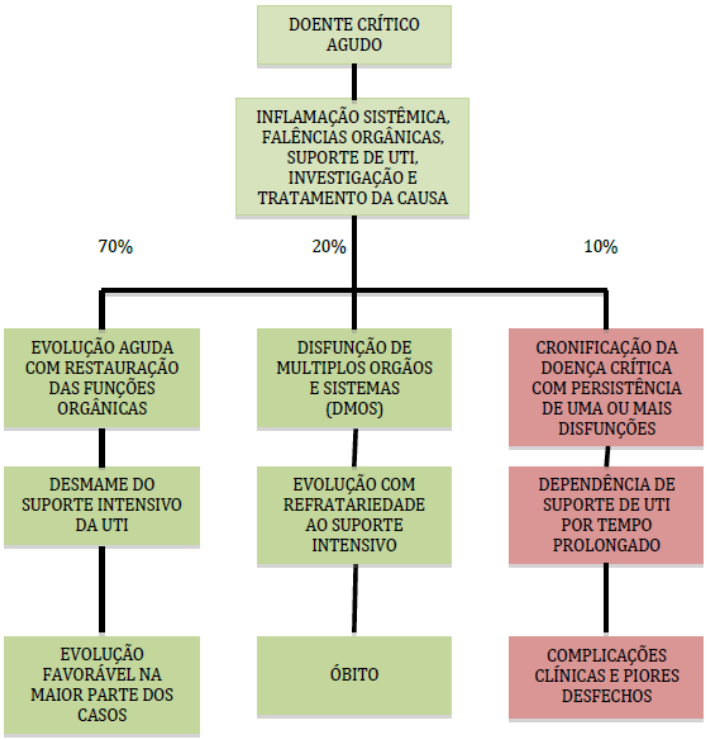
A doença crítica aguda tem sua gênese no processo de inflamação exacerbada decorrente de um insulto. Este pode ocorrer por infecção, por trauma cirúrgico em cirurgias de grande porte, por trauma devido a causas externas como em grandes queimados ou ainda por outras doenças com capacidade de provocar inflamação sistêmica.

Uma parcela importante de pacientes consegue esfriar esta resposta inflamatória sistêmica concomitantemente à resolução ou controle da causa base, retomando funções orgânicas. Este grupo consegue abandonar o suporte de UTI e tem, em geral, boa evolução. Por outro lado, uma parcela de pacientes críticos apresenta resposta inflamatória intensa e disfunção de múltiplos órgãos e sistemas refratária à capacidade da UTI em proporcionar suporte de vida. Nestes casos, a evolução para óbito é inexorável.

Existe ainda um terceiro grupo de pacientes críticos. Ele caracteriza-se por conquistar o controle parcial do quadro agudo. Entretanto sofre novas agressões, em geral infecciosas, e evolui com inflamação persistente crônica. Consequentemente, necessita de suporte intensivo por período prolongado. Ainda sem explicação fisiopatológica clara, estes pacientes caracterizam-se por apresentarem piores desfechos tanto hospitalares quanto em longo prazo.

A Figura 6 representa de forma esquemática o marco teórico do estudo.

Figura 6: Mapa conceitual da tese



UTI: unidade de tratamento intensivo, **DMOS:** disfunção de múltiplos órgãos e sistemas

2. JUSTIFICATIVA

Apesar de ser descrita há mais de 30 anos, a doença crítica crônica vem sofrendo mudanças de conceitos à medida que a medicina intensiva desenvolve novas formas de suporte de vida. A busca por uma definição de DCC mais sensível, que viabilize o reconhecimento e intervenções precoces, sempre foi um desafio para comunidade científica.

Testar em outras populações de pacientes críticos a definição recentemente proposta de DCC, sua capacidade preditiva e acurácia, comparativamente a outras definições mais usadas na literatura poderá auxiliar a consolidar uma definição única de DCC. A diversidade de definições torna difícil a comparação entre estudos e consequente evolução de pesquisas que busquem desvendar a fisiopatologia desta condição e desenvolver estratégias terapêuticas.

Outro ponto importante é a escassez de dados populacionais sobre DCC no Brasil. Estudos em outros países apontam para um crescimento anual significativo da população de críticos crônicos. Desenvolver uma metodologia capaz de fornecer a epidemiologia da DCC no Brasil e testar esta metodologia em bases de dados do sistema público pode produzir informações importantes para planejamento de políticas de saúde para população de pacientes críticos.

3. OBJETIVOS

3.1 OBJETIVO GERAL

Comparar desfechos hospitalares entre as definições mais usadas de DCC, caracterizar a epidemiologia da DCC e avaliar sobrevida e capacidade funcional após alta da UTI nesta população.

3.2 OBJETIVOS ESPECÍFICOS

Comparar as principais definições de DCC usadas na literatura quanto a características clínicas e desfechos hospitalares.

Avaliar desfechos funcionais em até 12 meses após a alta da UTI em uma amostra de pacientes críticos crônicos usando a definição atualmente proposta.

Avaliar a epidemiologia da DCC nas internações financiadas pelo sistema público de saúde do Brasil usando a definição atualmente proposta.

CAPÍTILO IV - ARTIGOS

1. Definitions and long-term outcomes in Chronic Critical Illness: a cohort study.

Authors: Nunes DSL[1], Franzosi OS[1], Teixeira C[2], Oliveira R P[2], Sganzerla D[3], Rosa RG[3], Vieira SRR[3].

[1]Student of post-graduation - UFRGS

[2] Professor of School of Medicine - UFCSPA

[3] Researcher member of Moinhos de Vento Hospital

[4] Professor of School of Medicine - UFRGS

Abstract

Introduction: Chronic critical illness (CCI) has been changing in definitions as long as long-stay patients need different types of intensive care. Similarly, there is a growing interest in studying long-term outcomes, especially functional outcomes, among survivors. The aim of this study is to measure hospital outcomes in four CCI definitions and to evaluate 12-months survival and functional status in a sample of CCI patients selected through current definition.

Methodology: Single center historical cohort study. The sample was selected using the four relevant CCI definitions described in the literature. To meet the first objective we applied the CCI definitions on an institutional database and measured clinical characteristics, length-of-stay and hospital mortality. To meet the second objective we applied the current CCI definition on a specific period of database and selected a convenient sample that have 12-months of follow-up. To measure functional status we used Barthel index.

Results: We selected 146 patients using CCI definition by mechanical ventilation (MV) ≥14 days, 79 using MV ≥21 days, 89 using tracheotomy CCI definition and 494 patients using CCI current definition. The clinical characteristics were similar among these four groups. Hospital mortality was lower in tracheotomy and current definition

groups (61%, 65.8%, 52.8% and 46%, respectively). However, the current CCI definition was more sensitive than the others to predict hospital mortality. The 12-months survival among the 55 CCI patients selected using current definition after ICU discharge was 74.5%. The functional capacity in 3-6 months after ICU discharge were lower than before ICU admission and tended to recover to baseline among the survivors at 12-months.

Conclusion: The current CCI definition is more sensitive to predict hospital mortality than those previously proposed. The prevalence of obesity among CCI patients is high. The 12-months functional status of CCI patients decreased after ICU discharge and tended to recover to baseline at 12-months.

INTRODUCTION

The capacity to provide support for ever more severe organ failure has resulted in greater survival of critically ill patients[1,2,3]. However, there is a population of critically ill patients who survive the acute critical phase, but remain dependent on some type of intensive care for long periods[4,5].

This population is characterized by high hospital length-of-stay, development of sarcopenia and acquired muscle weakness, severe wounds, infections, and worse hospital outcomes [6,7,8,9]. It is also associated with increased expenditure by the health system and long-term dependence on specialized care and has been linked with psychological and social consequences for caries, such as anxiety and depression[5,10,11].

These conditions have been referred to as chronic critical illness (CCI) since the 80s, although the definition criteria have changed over the years, being characterized for many years by the dependence on ventilatory support for long periods[7,12,13]. However, in 2014, due to payment issues within the North-American healthcare system, a wider criterion was proposed which is not based solely on dependence on ventilatory support[14]. Since then, this new more comprehensive definition has been accepted by the scientific community and has been used in studies designed to investigate the epidemiology of CCI in different population[15].

Similarly, CCI data about hospital outcomes and, especially long-term functional status, are scarce and different CCI definitions for select patients have been applied. This study aims to evaluate the hospital outcomes of CCI using the most relevant criteria described in the literature. It also aims to evaluate the survival and evolution of functional status after the ICU discharge in a sample of chronic patients selected by the currently definition of CCI.

METHODOLOGY

Design: Historic cohort study

Description of the study site: Medical-surgical 31-bed ICU intended for the hospitalization of adult patients (≥14 years), located in Moinhos de Vento Hospital, a tertiary care hospital, reference in high complexity in the private health system of Porto Alegre, capital of a state of southern Brazil. The Hospital is accredited by the Joint Commission International (JCI). The ICU has a specialized medical and multidisciplinary team, rigorous continuing education program and medical residency program in intensive care medicine. The unit has an institutional database and all hospitalizations have been recorded since 2007. This allowed the selection of patients that have the inclusion criteria.

Patients: All ICU admissions of adult patients (≥14 years old) from January 2007 to December 2010 and, in a second period from May 2014 to December 2017. The CCI definitions used were the four most relevant described in previous studies: (1) mechanical ventilation (MV) ≥14 days, (2) VM ≥21 days, (3) tracheostomy for MV time need and, (4) the most current and accepted of them, which consists of staying for 8 or more days in ICU added by one of the following conditions: (a) tracheostomy, (b) MV for ≥96 hours, (c) sepsis, (d) severe wounds and (e) stroke (ischemic or hemorrhagic) or head trauma. From 2014 to 2017 only the current definition of CCI was used for patient selection[6].

Patient selection description: The ICU where the study was conducted has institutional database indicators in which all hospitalizations with more than 24 hours of ICU stay are recorded. Identification data such as name and medical records,

demographic data such as age and gender, clinical data (hospitalization cause, unit before ICU, the reason for ICU admission, length of stay, acquired dysfunctions, severity, ICU supports used, complications during ICU stay, ICU discharge condition and hospital discharge information) is registered. The period from January 2007 to December 2016 was analyzed for the quantity and quality of records by the study authors. We identified 5.393 hospitalizations in ICU. After quality analyses of the records, we excluded 1.212 and 4.181 hospitalizations were divided into two periods. To evaluate hospital outcomes according to the definitions of CCI, patients were selected between hospitalizations incurred from January 2007 to December 2010 (3.023 hospitalizations). To evaluate survival and functional status after ICU discharge, patients with the current CCI definition were selected for convenience among hospitalizations that occurred from May 2014 to December 2016 (1.158 hospitalizations). For this analysis, the definition adopted for CCI was the currently accepted in the literature: ≥8 days of ICU stay added by one of the five conditions (tracheostomy, MV ≥96h, sepsis, severe wounds, stroke or severe head trauma).

Outcomes: hospital length-of-stay and hospital and ICU mortality were measured in patients with CCI criteria selected among hospitalizations that occurred between January 2007 and December 2010. Functional status was measured in three to six months and in 12 months after ICU discharge among hospitalizations that occurred from May 2014 to December 2016. We also measured 12-months survival after ICU discharge. For both post discharge analysis we used a convenience sample of CCI patients selected by the current definition.

The measure of outcomes after ICU discharge: A convenience sample was selected among those patients whose functional outcome and 12-months mortality after ICU discharge had been evaluated in another research protocol in the same institution[16]. Among 1164 critically ill patients hospitalizations from May 2014 to December 2016, 55 had CCI by current definition and 12-months follow-up record and were included. In this sample, only the most recent criterion was applied to select patients with CCI.

Evaluation of functional capacity: patients who survived ICU hospitalization were selected in an independent research protocol between 24 and 120 hours after ICU discharge[16]. After patient consent, the follow-up started by functional status

evaluation before hospitalization through Barthel index. This first evaluation refers to the functional status before hospitalization (recordatory). After that, telephone contact was made by a central with trained interviewers, and functional capacity and survival were evaluated at three, six and 12 months after ICU discharge using the same instrument. The Barthel index is an evaluation of independence in various basic activities of daily living, such as feeding, bathing, grooming, dressing, intestinal and urinary sphincters control, toilet use, transfer and mobility from the chair to bed, ambulation and ladder. It has a variation from zero to 100 points, being the highest functionality represented by a higher score. It has a validated Portuguese version[17].

Statistical analysis: To evaluate functional status, the Barthel index of three and six months were analyzed together, considering the short interval between these evaluations. We expected a longer time for functional recovery of chronic patients. The correlation between the Barthel index was evaluated by generalized estimating equations (GEE). For each CCI definition the sensitivity, specificity and accuracy were performed. The normality of the variables was tested with Kolmogorov-Smirnov test. The quantitative variables were described by mean and standard deviation and categorical deviations by absolute and relative frequencies. The associations between categorical variables were performed using the Chi-square test and for the comparison of means, the T-student test was applied. The level of significance adopted was 5%. Statistical analysis was performed with the Software SPSS version 21.0.

Ethical aspects: The project was elaborated and conducted according to the resolution 466/12 of the National Health Council (CNS) and was approved by the ethics committee of the institution under the number CAAE 04307518.4.3001.5330. The objective of follow-up after ICU discharge was also approved in a second research protocol (CAAE: 04258312.4.1001.5330) that included the population and objectives of the first one. This second protocol subsidized follow-up functional status and 12-months survival that allowed the analysis of follow-up after hospital discharge using the same methodology to measure the outcomes provided in the first protocol. Informed consent was obtained from all included patients after the procedures had been explained. The consent form included information on the study aims, data collection and recording methods. Confidentiality and anonymity was ensured. When data collection was restricted to the use of information from institutional databases

and medical records, the signing of the consent form was waived and the authors signed an agreement to preserve patient and staff anonymity regarding the use of the data.

RESULTS

Among 3.023 hospitalizations we selected 146 patients using CCI definition by MV ≥14 days, 79 using MV ≥21 days, 89 using tracheotomy CCI definition and 494 patients using CCI current definition. The characteristics of CCI patients in the analysis that address the first objective of this study are described in Table 1. We can observe the demographic and clinical variables in the four definitions used for selection of CCI patients: (1) MV ≥14 days, (2) MV ≥ 21days, (3) tracheostomy and (4) the current definition. Due to overlap between the CCI definitions, it was not possible to apply a statistical test to compare the differences between the groups. However, we observed that the four CCI definitions groups have similar demographic and clinical characteristics, including severity scores. A high proportion of obese patients was verified (BMI >30) in all CCI groups (74%, 74.7%, 68.5%, and 71.9% respectively). The presence of sepsis also had a high prevalence in all CCI definitions (67.8%, 79.7%, 71.9%, and 65%, respectively). Similarly, in all four definitions used, medical hospitalization was more prevalent (71.2%, 69.6%, 70.8%, and 74.1% respectively). Disease severity measured by the SOFA and APACHE II scores and the number of clinical comorbidities was also similar among the four groups.

Regarding hospital outcomes according to CCI definitions, we observed a higher ICU mortality in those patients that use MV ≥14 days and ≥21days (51.4% and 60.8%, respectively). The tracheostomy criteria and the current definition had lower mortality rates than others (39.3% and 36.2%, respectively). A similar result was observed for hospital mortality (61%, 65.8%, and 52.8%, 46.4%, respectively).

Table 1: CCI characteristics population on four definitions selected from 2007 to 2010 ICU admissions

	CCI MV ≥14days 146	CCI MV ≥21days 79	CCI tracheotomy 89	CCI Current definition* 494
Age in years	69.2 (±18)	69.5 (±17.1)	70.9 (±16.3)	69 (±17.8)
Female sex	58 (39.7)	31 (39.2)	35 (39.3)	211 (42.7)
BMI				
< 18.5 underweight	5 (3.4)	3 (3.8)	--	7 (1.4)
18.5 – 24.9 normalweight	21 (14.4)	10 (12.7)	15 (16.9)	81 (16.4)
25 – 29.9 overweight	12 (8.2)	7 (8.9)	13 (14.9)	51 (10.3)
≥ 30 obesity	74 (74.0)	59 (74.7)	61 (68.5)	355 (71.9)
At ICU admission source				
Ward	55 (37.7)	30 (38.0)	25 (28.1)	164 (33.2)
Emergency room	36 (24.7)	17 (21.5)	24 (27.0)	150 (30.4)
Operation room	21 (14.4)	17 (21.5)	13 (14.6)	60 (12.1)
Transfers	25 (17.1)	10 (12.7)	19 (21.3)	89 (18.0)
Other	9 (6.1)	5 (6.3)	8 (9.0)	31 (6.3)
Reason for ICU admission				
Medical	104 (71.2)	55 (69.6)	63 (70.8)	366 (74.1)
Surgical	18 (12.3)	15 (19.0)	11 (12.4)	48 (9.7)
Surgical emergency	16 (11.0)	4 (5.1)	7 (7.9)	52 (10.5)
Oncologic	3 (2.1)	2 (2.5)	1 (1.1)	7 (1.4)
Cardiologic	1 (0.7)	--	1 (1.1)	3 (0.6)
Neurologic	3 (2.1)	3 (3.8)	6 (6.7)	14 (2.8)
Obstetric	--	--	--	--
Trauma	1 (0.7)	--	--	4 (0.8)
Number of preexisting diseases				
None	30 (20.6)	13 (16.5)	16 (18.0)	95 (19.2)
One	35 (24.0)	19 (24.1)	24 (27.0)	106 (21.5)
Two	28 (19.2)	17 (21.5)	15 (16.9)	96 (19.4)
More than two	53 (36.3)	30 (38.0)	34 (38.2)	197 (39.9)
Sepsis	99 (67.8)	63 (79.7)	64 (71.9)	321 (65.0)
Severity at ICU: day 1				
APACHE II	22 (±6.2)	21.4 (±6.3)	21 (±6.4)	20.5 (±7.1)
SOFA	6 (3-8)	5 (3-8)	5 (3-8)	5 (3-8)

CCI: Chronic critical illness, MV: mechanical ventilation, BMI: body mass index, ICU: intensive care unit, APACHE II: Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment

In Table 2 we shows sensitivity, specificity and accuracy for mortality in the four definitions. The specificity was similar in the four groups (97.7% for MV ≥14 days, 98.8% for MV ≥ 21days, 98.1% for tracheostomy and 88.1% for current CCI definition). The current CCI definition has the highest sensitivity (16.2% for MV ≥14 days, 9.5%% for MV ≥21 days, 8.6% for tracheostomy and 41.7% for current CCI

definition). Accuracy was similar in the four definitions. The mortality according to the four CCI definitions is represented in Table 3.

Table 2: Sensitivity, especificity and acuracy according to CCI definitions for ICU mortality

	CCI MV ≥14days 146	CCI MV ≥21days 79	CCI tracheotomy 89	CCI current criteria* 494
Sensitivity	16.2	9.5	8.6	41.7
Especificity	97.4	98.8	98.1	88.1
PPV	61.0	65.8	52.8	46.4
PNV	82.5	81.6	81.3	86.0
Acuracy	81.4	81.1	80.4	78.9

CCI: chronic critical illness, MV: mechanical ventilation, PPV: preditive positive value, PNV: preditive negative value

Table 3: hospital outcomes according to CCI definitions

	CCI MV ≥14days 146	CCI MV ≥21days 79	CCI tracheotomy 89	CCI current criteria* 494
ICU lengh of stay	31 (22-45)	39 (30-56)	35 (22-50)	17 (12-29)
Hospital lengh of stay	42 (27-70)	46 (31-81)	50 (34-83)	29 (16-48)
ICU death	75 (51.4)	48 (60.8)	35 (39.3)	179 (36.2)
Hospital death	88 (61.0)	52 (65.8)	47 (52.8)	229 (46.4)

CCI: chronic critical illness, MV: mechanical ventilation, ICU: intensive care unit, *8 days ICU stay plus one of other conditions: tracheotomy, MV ≥96h, sepsis and other severe infection, severe wounds, stroke (ischemic or hemorrhagic) or traumatic brain injury

To meet the second objective of the study, we evaluated functional status and 12-months survival after ICU discharge. Among 1.158 hospitalizations from May 2014 to December 2016 we identified 179 chronic ill patients defined by current definition. Among this group we selected a convenient sample of 55 CCI patients to evaluate 12-months survival and functional status. Table 4 shows the characteristics of patients selected among hospitalizations from May 2014 to December 2016. We observed a mean age of 66.3 years (±18.8), 45.5% male. The emergency unit was the main source of patients (41.8%) and medical reasons were the main cause of ICU admissions (69.1%). The median APACHE II was 16 (11-20). The infection rate at the time of ICU admission was 63.6% and ICU-acquired weakness and delirium rates were 43.6% and 58.2%, respectively. We also observed a median ICU stay of 17 (10-

27) days and a median hospital stay of 18 (8-19) days. The hospital mortality rate was not evaluated in this analysis.

Table 4: CCI characteristics population for current definition selected from 2014 to 2017 ICU admissions

Characteristic	CCI current definition* 55
Age in years	66.3 (±18.8)
Female sex	30 (54.5)
At ICU admission source	
Ward	12(21.8)
Emergency room	23 (41.8)
Operation room	11 (20)
Transfers	8 (14.5)
Other	1 (1.8)
Reason for ICU admission	
Medical	38 (69.1)
Surgical	7 (12.7)
Surgical emergency	10 (18.2)
Severity at ICU: day 1	
APACHE II	16 (11-20)
Organ failure (n)	3 (2-3)
Infection on admission	
Infections	35 (63.3)
Sepsis	23 (41.8)
During ICU stay	
Vasoactive drug use	47 (85.5)
Sedative drug use	49 (89.1)
Neuromuscular blockers dug use	11 (20.0)
RRT	15 (27.3)
ICU-AW	24 (43.6)
Delirium	32 (58.2)
New infection	26 (47.3)
ICU Stay	17 (10-27)

CCI: chronic critical illness, MV: mechanical ventilation , ICU: intensive care unit, RRT - renal replacement therapy, ICU-AW: muscular weakness acquired in ICU. *8 days ICI stay plus one of other conditions: tracheotomy, MV ≥96h, sepsis and other severe infection, severe wounds, stroke (ischemic or hemorrhagic) or traumatic brain injury.

Survival after ICU discharge among CCI current definition patients is represented by the survival curve in Figure 1. The mortality rate among chronic patients who had an ICU discharge was 25.5% in 12-months follow-up.

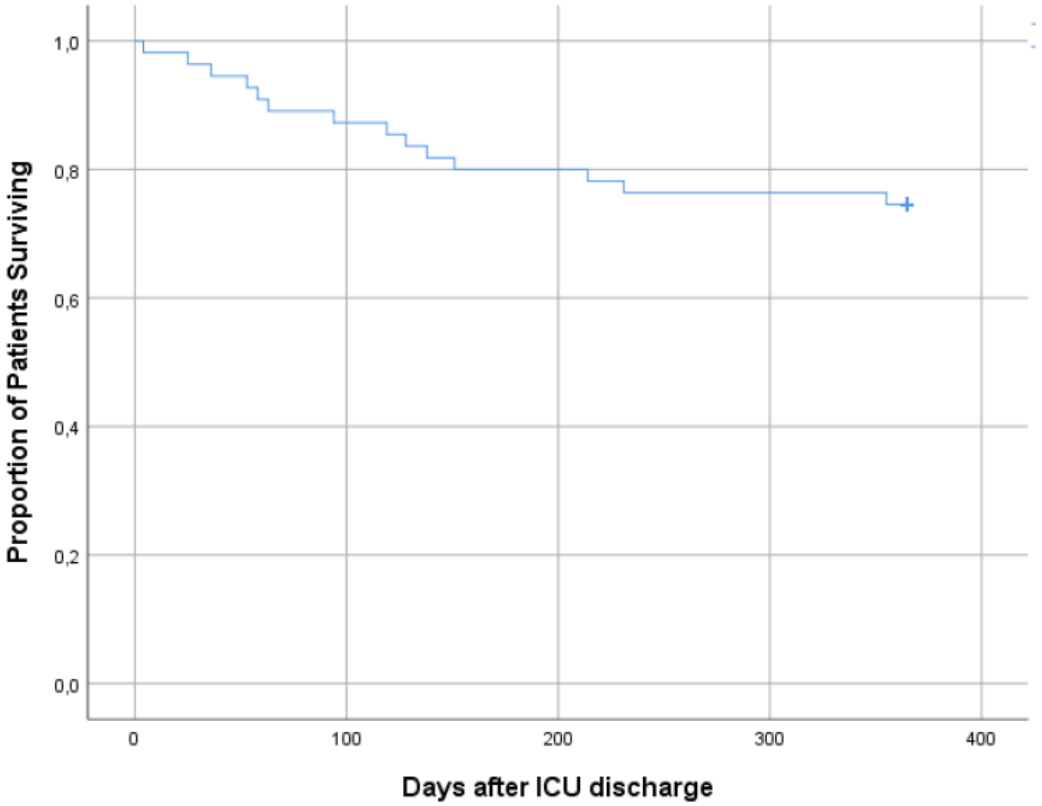


Figure 1: One-year Kaplan-Meier survival curve of the 55 CCI current definition patients.

The evolution of functional status among CCI patients after ICU discharge is shown in Figure 2. We can observe that functional status in the first evaluation (between 3 and 6 months after ICU discharge) was lower than the functional status before ICU admission. On the other hand, at the end of 12-months of follow-up, survivors had a tendency to recover functional status near baseline. Analyses using GEE shows statistical difference between Barthel index before ICU-stay and 3-6 months after ICU discharge. However, there was no statistically difference between the Barthel index before the ICU and the 12-month index.

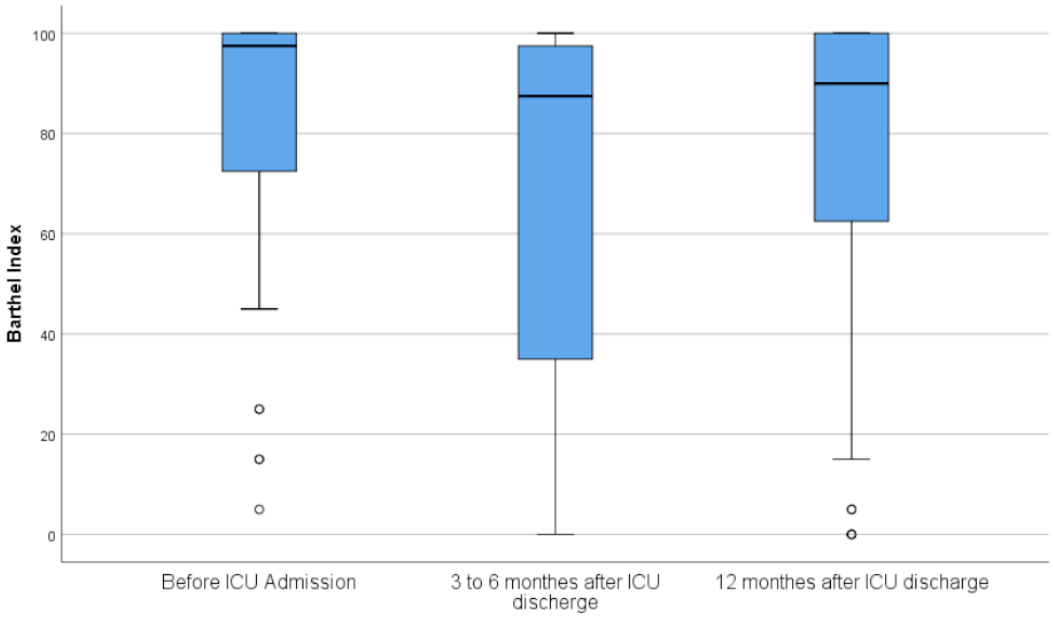


Figure 2: One-year Barthel index of the 55 CCI current criteria patients after ICU discharge

DISCUSSION

To our knowledge, this is the first study that compares hospital outcomes among the main CCI definitions in a Brazilian population. Also, it evaluates the accuracy of four definitions in predicting one of the most important outcomes of CCI, hospital mortality. We observed that the current CCI definition has similar specificity to those previous definitions, but has greater sensitivity, without losing accuracy. This result reinforces the proposal of the current CCI definition to be more sensitive in identifying CCI patients showing similar performance as the original study [14,15]. Hospital mortality rate in this cohort was similar to other studies in CCI populations regardless of the criteria used[18].

Although the CCI is often associated with undernutrition throughout hospitalization, we observed a large proportion of obese patients (BMI >30 kg/m²) among the CCI population regardless of the CCI definition adopted. A recent study analyzed metabolic characteristics of long-stay critically ill patients and showed a high overweight rate regardless outcome[19]. Critically ill obese patients have gained attention due to the increasing prevalence of this condition in the general population[20]. Studies show a relationship between obesity and higher mortality[20]. Factors related to

insulin resistance, difficulty in fatty acid mobilization and prioritization of proteins as a primary energy source during critical disease would be implicated in the development of cachexia and higher mortality[21,22,23]. We did not compare chronic and acute patients, therefore, we cannot attribute obesity as a risk factor for mortality in chronic patients. On the other hand, the high obesity rate in this cohort of chronic patients should motivate further research for the correlation of body composition and outcomes in CCI patients.

To address the second objective of this study, a sample of patients identified by current definition was selected to a 12-months follow-up analysis. After ICU discharge, the 12-months survival was 74.5%. Another study showed one-year survival of 61% after ICU discharge. However, the definition applied was MV ≥14 days requirement[24]. Another recent study evaluating patients on prolonged MV (≥21 days) showed a one-year survival of 66.9%[25,26].

Functional outcomes after hospital discharge have been studied in several centers. CCI has been associated with worse long-term functional outcomes. The tools used to measure functional status and quality of life differ between studies, likewise, the definition of CCI[27,28,29,30]. Our data showed a significant reduction in functional status in the first evaluation after ICU discharge (3 to 6 months). However, among patients who survived 12-months, the functional status tended to recover to previous ICU admission levels. This finding may have been caused by either the recovery of patient`s functional status or the death of patients with worst functional capacity.

This tendency to recovery to baseline functional status is not usual in other studies. However, it is important to highlight that previous studies are based on different CCI definitions and could select patients with poor functional status. Therefore, longer time for functional recovery could be required. Our data suggest that functional status from three to six months is worst in CCI patients. Despite that, we found a tendency of long-term functional recovery in survivors. Longer follow-up periods and multi-center studies with larger sampling are needed to elucidate this finding.

As far as we know, this is the first study that applied the current CCI definition on a 12-months follow-up. However, our study has some limitations. First, we

evaluated the functional status in a convenience sample. Second, the sample size was estimated for 3 to 6 months functional status follow-up. Thus, it is probably that the absence of significant difference between functional status at 12-months may be caused by reduced sample power. Other limitations should be pointed. We used a database and recording data. In the attempt to minimize bias we analyzed the quality data base and excluded the poor quality fraction. Equally, we did not compare CCI patients with acute patients because the database excluded less 24 hours ICU-stay patients.

CONCLUSION

Our data shows that the current CCI definition has greater sensitivity to predict hospital mortality compared to the previous CCI definitions used. The clinical characteristics and outcomes were similar regardless the CCI criterion. Therefore, probably CCI definitions represent the same patients in different stages. We also observed a poor functional status in chronic patients. However, a tendency of functional status recover in 12-months was noticed. Perhaps sample power issues are implicated in this result and further studies using the current CCI definition in follow-up after ICU are necessary.

REFERENCES

1. Kelly FE, Fong K, Hirsch N, Nolan JP. Intensive care medicine is 60 years old: the history and future of the intensive care unit. Clin Med. 2014 Aug;14(4):376-9.
2. Reisner-Sénélar, L. The birth of intensive care medicine: Björn Ibsen's records. Intensive Care Med 2011; 31(7): 1084-6.
3. Puri, N. Puri, V. Dellinger, R. P. History of technology in the intensive care unit. Crit Care Clin 2009; 25(1): 185-200.
4. Nelson JE, Cox CE, Hope AA, Carson SS. Chronic critical illness. Am J Respir Crit Care Med 2010; 182: 446–54.

5. Carson SS, Bach PB. The epidemiology and costs of chronic critical illness. Crit Care Clinc 2002; 18: 461-76
6. Loss SH, Nunes DSL, Franzosi OS et all. Chronic critical illness: are we saving patients or creating victims? Rev Bras Ter Intensiva. 2017;29(1):87-95
7. Carson, S. S. Definitions and epidemiology of the chronically critically ill. Resp Care 2012 57(6): 848-56.
8. Nelson JE, Kinjo K,Meier DE, Ahmed K, Morrison RS. When critical illness become chronic: informational needs of patients end families. J Crit Care 2005; 20: 79-89.
9. Van den Berghe G, de Zegher F, Bouillon R. Acute and Prolonged Critical Illness as Different Neuroendocrine Paradigms. J Neuroendocrinol Metab. 1998; 83: 1827-84.
10. Douglas SL, Daly BJ, Kelley CG, O'Toole E, Montenegro H. Impact of a disease management program upon caregivers of chronically critically ill patients. Chest 2005; 128(6): 3925-36.
11. Douglas S L, Daly B J, O'Toole E, Hickman R L. Depression among white and nonwhite caregivers of the chronically critically ill. J Crit Care 2010; 25(2): 364.e11-9.
12. Girard K, Raffin TA. The chronically critically ill: to save or let die? Respir Care 1985;30:339–347.
13. Wiencek, C. Winkelman, C. Chronic critical illness: prevalence, profile, and pathophysiology. AACN Adv Crit Care 2010; 21(1): 44-61
14. Kandilov AM, Ingber MJ, Morley M, et al.: Chronically Critically Ill Population Payment Recommendations. Research Triangle Park, NC, RTI International, 2014
15. Kahn JM, Le T, Angus DC, Cox CE, Hough CL, White DB, Yende S, Carson SS; ProVent Group Study Investigators. The epidemiology of chronic critical illness in the United States. Crit Care Med. 2015;43(2):282-7.
16. Robinson cc, Rosa RG, Kochhann R, et all. Quality of life after intensive care unit: a multicenter cohort study protocol for assessment of long-term outcomes among intensive care survivors in Brazil. Rev. bras. ter. intensiva vol.30 no.4 São Paulo Oct./Dec. 2018 Epub Jan 10, 2019

17. Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index. Md State Med J. 1965;14:61-5.
18. Loss SH, de Oliveira RP, Maccari JG, Savi A, Boniatti MM, Hetzel MP, et al. The reality of patients requiring prolonged mechanical ventilation: a multicenter study. Rev Bras Ter Intensiva. 2015 Mar;27(1):26–35.
19. Viana MV, Pantet O, Bagnoud G, et all. Metabolic and Nutritional Characteristics of Long-Stay Critically Ill Patients. J Clin Med. 2019 Jul 7;8(7)
20. Gallagher D, DeLegge M. Body composition (sarcopenia) in obese patients: implications for care in the intensive care unit. JPEN J Parenteral Enteral Nutr. 2011 Sep;35(5 Suppl):21S-8S.
21. Jeevanandam M, Young DH, Schiller WR. Obesity and the metabolic response to severe multiple trauma in man. J Clin Invest. 1991 Jan;87(1):262–9.
22. Breen HB. Lipid oxidation and nitrogen balance in critically ill obese patients. Nutr Clin Pract. 2005 Feb;20(1):98–102.
23. Weijs PJM, Looijaard WGPM, Dekker IM, Stapel SN, Girbes AR, Oudemans-van Straaten HM, et al. Low skeletal muscle area is a risk factor for mortality in mechanically ventilated critically ill patients. Crit Care. 2014 Jan 13;18(2):R12.
24. Bigatello L M, Stelfox H T, Berra L, Schmidt U, Gettings E M. Outcome of patients undergoing prolonged mechanical ventilation after critical illness. Crit Care Med 2007; 35(11):2491-7.
25. Jubran A, Grant BJB, Duffner LA, et all. Long Term Outcome after Prolonged Mechanical Ventilation. A Long-Term Acute-Care Hospital Study. Am J Respir Crit Care Med. 2019 Jun 15;199(12):1508-1516.
26. Jubran A, Grant BJB, Duffner LA, et all. Effect of pressure support vs unassisted breathing through a tracheostomy collar weaning durations in patients requiring prolonged mechanical ventilation: a randomized trial. JAMA. 2013 Feb 20;309(7):671-7.

27. Combes A, Costa MA, Trouillet JL, Baudot J, Mokhtari M, Gibert C, Chastre J. Morbidity, mortality, and quality-of-life outcomes of patients requiring >or=14 days of mechanical ventilation. Crit Care Med. 2003; 31(5):1373-81.
28. Montuclard L, Garrouste-Orgeas M, Timsit JF, Misset B, De Jonghe B, Carlet J. Outcome, functional autonomy, and quality of life of elderly patients with a long-term intensive care unit stay. Crit Care Med 2000; 28(10):3389-95.
29. Delle Karth G, Meyer B, Bauer S, Nikfardjam M, Heinz G. Outcome and functional capacity after prolonged intensive care unit stay. Wien Klin Wochenschr. 2006; 118(13-14):390-6.
30. Cabral CR, Teixeita C, Oliveira RP, Hass JS, Azzolin KO. Avaliação da mortalidade e qualidade de vida dois anos após a alta do CTI: dados preliminares de uma coorte prospectiva. Rev Bras Ter Intensiva. 2009; 21(1):18-24.

2. Mortality and risk-factors of Chronic Critical Illness in a low-income country

Authors: Nunes DSL[1], Franzosi OS[1], Teixeira C[2], Oliveira R P[2], Grando AM[3], Loss SH[1], Vieira SRR[3].

[1]Student of post-graduation UFRGS

[2] Professor of School of Medicine UFCSPA

[3] Scientific Technician of Public Health Department

[4] Professor of School of Medicine - UFRGS

Abstract

Introduction: Chronic critical illness (CCI) has been growing like an important public health problem. Current CCI definition, characterized by ≥8 days of ICU-stay plus one of the following conditions: tracheostomy, MV ≥96 hours, sepsis, severe wounds, stroke or head trauma, has been accepted by scientific community as more sensitive than older criterion. The objective of this study is characterizing the epidemiology of CCI in a southern state of Brazil using a public health ICU hospitalization databases.

Methodology: Historical cohort in a database of the public health system in Brazil. All ICU hospitalizations between June 2018 and May 2019 in the state of Rio Grande do Sul were included. Clinical characteristics, hospital outcomes, costs and risk factors to develop CCI were evaluated.

Results: 48,708 acute hospitalizations and 8056 hospitalizations with CCI criteria were included. The prevalence of CCI was 16.5%. Hospital mortality was higher in chronic hospitalizations (20.5% and 31.7%, respectively), the mean cost for hospitalization was also higher in the CCI hospitalizations (R$: 6.363,48 and R$ 10.520,73, respectively). Emergency source (RR 1.67, 95% CI 1.51 – 1.85), middle-size hospitalizations (RR 1.28, 95% CI 1.19 – 1.38), medical reason hospitalizations (RR 1.27, 95% CI 1.20 – 1.34) and infection (RR 5.75, 95% CI 5.5 – 6.01) were risk factors for CCI. The age groups ≥35 years marked higher mortality in hospitalizations with CCI compared to acute critical hospitalizations.

Conclusion: It is possible to evaluate the epidemiology of CCI in the database of the Brazilian public health system. The data evaluated show a high prevalence of CCI as well as higher mortality and higher cost for the health system for chronic critical

hospitalizations than acute critical hospitalizations. Infection was an important risk factor for CCI development.

INTRODUCTION

Advances in intensive care medicine have increased survival rates among critical patients. Paradoxically, a subset of patients has emerged and grown in number who need long-term support for dysfunctions and require intensive care[1,2]. Since the 1980s, these conditions have been known as chronic critical illness (CCI), but the concept has been changing as dependence on types of life support and intensive care other than mechanical ventilation (MV) have proven necessary for long periods[3].

Regardless of the different concepts adopted in the scientific literature over the years, CCI is characterized by patients with a high prevalence of muscle weakness, combined with cachexia, delirium and cognitive disorders, loss of pulsatile release of certain hormones, such as pituitary hormones, loss of renal function, requiring hemodialysis, skin peeling and pressure ulcers, immunodeficiencies, and colonization by multiresistant microorganisms[4,5,6]. This population has worse hospital outcomes, imposes elevated costs on health systems, and has worse functional outcomes over the long term[7,8].

Chronic critical illness has been studied in many different populations because of the increasing prevalence, the modest reductions in mortality rates over the years, the social impacts, and the financial burden on public health systems and social security.[9, 10, 11] Epidemiological studies of this population should provide valuable tools for public policy planning in low-income countries with universal access healthcare systems, deficient primary care, and modest development of home care.

A recent definition of CCI based on wider criteria than the definitions based on time on MV (≥14 or ≥21 days or tracheostomy) was proposed in 2014 and has been accepted as more comprehensive in the scientific community, becoming the preferred definition.[12] Since this definition was developed and tested using a health insurance database, based on identification of codes for procedures and diagnoses, it can be applied to other databases.

The objective of this study is to report the epidemiological profile of CCI and hospital outcomes using the hospital admissions information system (HIS) maintained by the Brazilian public healthcare system (SUS - Sistema Único de Saúde).

METHODOLOGY

Study design: Historic cohort study. Data were selected on a public database maintained by the Brazilian public healthcare service. Records were selected for all hospital admissions from June 2018 to May 2019 in the state of Rio Grande do Sul. The choice of state was based on the authors' assessment of the local audit process and local HIS data treatment. The HIS is a database that stores information on hospital admissions that are registered, audited, and paid for healthcare service providers contracted by the government. Each town has contracting autonomy, but the data recording format is standardized for the entire country and payment for services is dependent on correctly registered information. The HIS contains demographic information, dates of hospital admission and discharge, condition at discharge, codes for procedures performed, information on primary and secondary diagnoses, using the International Classification of Diseases (ICD-10) codes, and the sums paid for the procedures performed.[13] The HIS is a public domain database that can be accessed over the internet (http://sihd.datasus.gov.br/principal/index.php) and which does not identify patients.

Profile of investigated admissions: Admissions that took place during the period analyzed were subdivided into those during which the patient spent time in the intensive care unit (ICU) and those with no ICU admission. From the subset of critical patients, those that met criteria for chronic critical illness were selected. The definition used was that developed by the Research Triangle Institute (RTI).

CCI definition used: As part of a contract with the United States' Centers for Medicare & Medicine Service (CMS), the RIT developed a more comprehensive CCI definition than the usual which was based on ≥14 or ≥21 days on MV[12]. The objective was developing a more sensitivity CCI definition able to identify the subset of critical patients that demand greater resource expenditure, long hospital-stay, have more

complications and poor outcomes. This current definition has been used in epidemiological studies to describe de CCI characteristics and outcomes.

In order to identify admissions that met the CCI criteria according to the currently accepted definition, we selected admissions involving an ICU-stay ≥8 days added by one of the following conditions: (1) mechanical ventilation (≥96 hours), (2) tracheostomy, (3) sepsis or serious infection, (4) severe skin wounds (pressure ulcers), or (5) ischemic or hemorrhagic stroke or traumatic brain injury. The RTI also included presence of two or more organ failures as a condition that defines CCI. However, the procedures and diagnostic codes used in the HIS do not enable identification of all organ failures. Moreover, some authors consider that the condition organ failures is weak compared to the other conditions that define CCI[14]. The diagnostic and procedure codes for each criterion were defined by consensus among the authors after the health care system procedures codes table (SIGTAP) and the ICD-10 disease codes analysis and are described in a supplementary Table.

Supplementary table: procedure codes (SIGTAP) and diagnoses codes (ICD-10) used to select critical hospitalizations with CCI definition.

Clinical conditions (requiring ≥8 critical care days)	Description of CCI definition codes	Hospitalizations
Tracheotomy	• SIGTAP: 0404010377- tracheotomy; 0412010127 – tracheotomy plus tracheal prothesis; 0412020076 – mediastinal tracheotomy; 0416030297 tracheotomy in oncology • ICD-10: Z90.3	655
Mechanical ventilation	• SIGTAP: non • ICD-10: J96; J96.0; J96.1; J96.9	968
Sepsis	• SIGTAP: 0303010037: other bacterial disease treatment; 0408060611: surgical treatment of infections in arthroplasty of middle and medium port; 0408060620: surgical treatment of infections in arthroplasty of large port; 0412040190: surgical treatment of trauma, necrosis and infections; 0303010061: bowel infections treatment; 0303140151: Pneumonia and influenza treatment; 0412020084: Mediastinitis treatment; 0303060158: Endocarditis treatment in prosthetic valve; 0303060166: Endocarditis treatment in native valve0303140038: Suppurative and necrotic infections in upper respiratory tract treatment; 0303140100: upper respiratory tract treatment; 0303140143: Other low respiratory tract infections treatment; 0303040041 – Brain abscess medical treatment; 0408030470 – Surgical treatment of infections in ileo-psoas muscle; 0409010138 – surgical treatment of kidney abscess; 0409020010 – Surgical treatment of peri-urethral infections; 0409030015 – Surgical treatment of prostatic abscess; 0409040010 and 0409040029 – Surgical treatment of scrotal abscess; 0410010014 – Surgical treatment of breast abscess; 0412020033 - Surgical treatment of mediastinal abscess; 0412030101 – pleurostomy for infection diseases; 0303010010 – Dengue treatment; 0303010029 – hemorrhagic Dengue treatment; Bacterial zoonotic disease treatment; 0303010053 – protozoarn disease treatment; 0303010070 – haemorrhagic fever caused by virus; 0303010088 – Hanseniasis treatment; 0303010100 – helminteiasis treatment; 0303010118 – viral hepatites treatment; 0303010126 – sexually transmitted infections treatment; 0303010142 – Central nervous system viral infections treatment; 0303010150 -Malaria treatment; 0303010169 – mycosis treatment; 0303010177 – Chlamydia	5264

Supplementary table: continuation

	infections treatment; 0303010185 – other spirochetes infections treatment; 0303010193 – other viral infections treatment. 0303010207 – poliomyelitis; 0303010215 - Tuberculosis treatment; 0303040297 – Spinal cord infections treatment; 0303050144 – Ophthalmic infections treatment; 0303080060 - Staphylococcus intections treatment; 0303080078 – Streptococcus infections treatment; 0303140070 – external ear, middle ear and mastoid infections treatment; 0303180030 – HIV bowel infections treatment; 0303180056 – HIV respiratory infections; 0303180064 – disseminated infections in HIV disease treatment; 0407020039 and 0407020047 – surgical appendicitis treatment; 0407020152 – surgical rectal abscess treatment; 0407030166 - Surgical abscess treatment; 0407030174 – marsupialization abscess; 0407040013 – surgical pelvic abscess treatment. 0407040021 – surgical sub-phrenic abscess treatment; 0407040030 – surgical peritoneal abscess treatment; 0408020296 and 0408050330 – infection treatment in pos amputation treatment; 0408060557, 0408060565, 0412030071 and 0408060565 – surgical infection arthritis treatment; 0412030012, 0412030063 and 0412030055 – surgical treatment of lung and pleural infections; 0415040027 – necrotizing fasciitis debridement; 0506020045, 0506020053, 0506020061, 0506020070, 0506020088, 0506020096, 0506020100 and 0506020118 – post-transplant intercurrence treatment plus ICD-10 codes of infection diseases. • ICD -10: A41, from A41.0 to A41.9	
Severe wounds	• SIGTAP: 0415040027 – necrotizing fasciitis debridement; 0415040035 – skin ulcer debridement; 0415040043 – ulcer or necrosis debridement; 0303080094 – other skin diseases treatment • ICD-10: L89; L98.9; A48.0	237
Stroke and TBI	• SIGTAP: 0303040149 Stroke treatment (ischemic or haemorrhagic); 0303040300 – Stroke treatment using thrombolytic therapy • ICD-10: from I.60 to I.69	1589

CCI: chronic critical ill, ICU: intensive care unit, SIGTAP: procedure codes of public health system, ICD-10: International Code Diseases - 10th edition, TBI: trauma brain injure.

Variables and outcomes: The following demographic variables were selected from among those available on the HIS: age, sex, skin color, town, and size of hospital. Towns were then categorized as state capital, metropolitan zone, or interior of the state. Hospitals were classified by total number of beds (up to 50 beds = small; 51-150 beds = medium; 151-500 beds = large; and >500 beds = large with extra

capacity)[15]. The clinical variables selected for analysis were type of intervention (elective or urgent), type of admission (medical; pediatric; obstetric; or surgical), hospital-stay, ICU-stay, principal diagnosis, and procedures performed. Secondary diagnoses were not used because the treating teams do not usually fill in this field and it is not a requirement for payment. In contrast, the principal diagnosis is mandatory and is checked for code compatibility (electronic checking) and is audited against clinical data. The outcomes analyzed were hospital discharge or death. There is no information about destination after discharge. This study does not analyze data on follow-up after hospital discharge. The amount paid by the SUS to hospital service providers were also extracted from the HIS database (total cost of admission and sums paid for days in the ICU).

Ethical considerations: This study employs HIS data from the SUS that is freely available for public access and does not identify patients. This is an epidemiological database that can be accessed by anyone over the internet.

Statistical analysis: Age was stratified into bands to enable analysis of hospital mortality comparing acute and chronic critical patients. Quantitative variables were expressed as means and standard deviations and categorical variables as absolute and relative frequencies. Associations between categorical variables were identified using the chi-square test and Student's *t* test was used to compare means. Survival curves for CCI and acute critical patients were plotted using the Kaplan-Meier method. Poisson regression was used to identify variables that confer a risk of developing CCI and a risk of death. The variables selected were analyzed using SPSS version 21.0. A 5% significance level was adopted.

RESULTS

The characteristics of the study population are listed in Table 1. During the period analyzed, a total of 747,125 hospital admissions in the state of Rio Grande do Sul were identified and 56,767 of these involved time in the ICU. Of the total number of admissions involving ICU-stay, 8,057 (16.5%) met the criteria for CCI. Table 2 lists the amount paid for hospital services for chronic and acute critical admissions.

The mean cost of a chronic critical admission is greater than the mean cost of an acute critical admission (R$ 10,520.73 vs. R$ 6,363.48, respectively p<.001). The median length of stay in the ICU and in the hospital was greater in the CCI subset, as was mortality (31.7% vs. 20.5%, respectively p<.001). The median length of ICU-stay was 14 days (10 – 20) for CCI patients and 3 days (2 -6) for acute patients (p<.001). The median length of total hospital-stay was also different in the two groups: 19 days (13 - 30) days for CCI and 8 days (4 – 15) for acute admissions (p<.001).

Table 1: Characteristics of CCI and acute critical hospitalizations in public health system

Charateristic	CCI 8057	Acute 48.708	*p*
Female sex	3597 (44.6)	21686 (44.5)	*ns*
Race			
Calcasian	5748 (71.3)	36984 (75.9)	*ns*
Black	361 (4.5)	2144 (4.4)	*ns*
Brown	393 (4.9)	2086 (4.3)	*ns*
Yellow	40 (0.5)	346 (0.7)	*ns*
Native	9 (0.1)	51 (0.1)	*ns*
Non-information	1506 (18.7)	7097 (14.6)	*ns*
City			
Capital	2237 (27.8)	17922 (36.8)	*< .001*
Metropolitan aera	1655 (20.5)	6371 (13.1)	*< .001*
Other cities	4165 (51.7)	24415 (50.1)	*< .001*
Hospital size			
Medium-size	2206 (27.4)	8823 (18.1)	*<.001*
Large-size	3951 (49.0)	24890 (51.1)	*<.001*
Extra-large	1900 (23.6)	14994 (30.8)	*<.001*
Hospital admission source			
Non-urgency	329 (4.1)	5990 (12.3)	*<.001*
Urgency	7728 (95.9)	42718 (87.7)	*<.001*
Reason for hospital admission			
Medical	4402 (54.6)	16983 (34.9)	*<.001*
Surgical	1834 (22.8)	23190 (47.6)	*<.001*
Obstetric	17 (0.2)	179 (0.4)	*<.001*
Pediatric	1804 (22.4)	8356 (17.1)	*<.001*
Diagnoses at hospital admission			
Infections	5122 (63.6)	7162 (14.7)	*<.001*
CNS diseases	1044 (13.0)	2356 (4.8)	*<.001*
Cardiovascular diseases	37 (0.5)	12141 (24.9)	*<.001*
Lung diseases	1132 (14.0)	4047 (8.3)	*<.001*
Cancer	29 (0.4)	4385 (9.0)	*<.001*
Trauma	87 (1.1)	1661 (3.4)	*<.001*
Bowel diseases	9 (0.1)	2586 (5.3)	*<.001*
Childbirth-related fetal conditions	50 (0.6)	5812 (12.0)	*<.001*
Other	547 (6.7)	8558 (17.6)	*<.001*

CCI: chronic critical illness, CSN: central nervous system

The relative risk of death associated with CCI was 1.10 (95%CI: 1.06 – 1.14 p<.001). However, when we analyzed mortality rates by age groups, we observed that results differed by age band. Figure 1 illustrates that there were significant differences in mortality rates between the subset of admissions that met criteria for CCI and the acute subset in the under 1 year age range and from the 35-39 years band all the way up to the ≥85 years age group. In contrast, there were no differences in hospital mortality between the two subsets for the age groups from 1 to 34 years.

Table 2: Amount paid for hospitalizations, length-of-stay and outcome in CCI and acute critically ill.

	CCI 8057	**Acute** 48.708	*p*
Amount one-year paid (R$)	84.765.547,65	309.952.348,28	
Amount one-year paid for ICU care (R$)	64.850.131,92	135.498.456,72	
Average value per hospitalization (R$)	10.520,73	6.363,48	*< 0.001*
ICU length-of-stay (days)	14 (10-20)	3 (2-6)	*< 0.001*
Hospital length-of-stay (days)	19 (13-30)	8 (4-15)	*< 0.001*
Mortality	2551 (31,7)	9978 (20,5)	*< 0.001*

CCI: chronic critical illness, ICU: intensive care unit

Analysis of hospital mortality using a Kaplan-Meier curve (Figure 2) shows that mortality is higher among acute critically ill patients than among CCI patients over the first 30 days in hospital. This relationship then inverts from 30 days in hospital onwards, and thereafter mortality in the CCI subset remains significantly higher than among acute patients.

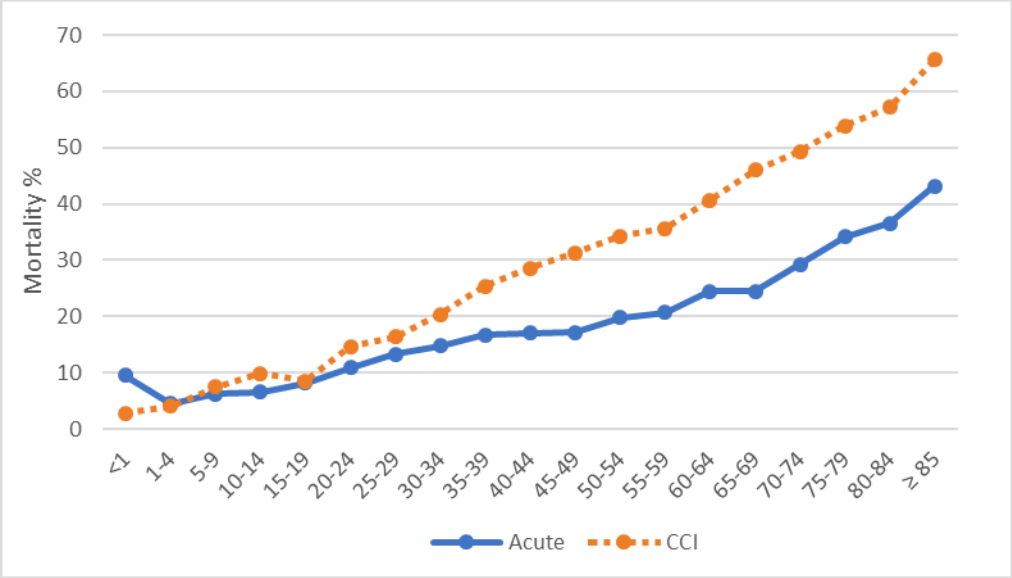


Figure 1: Mortality by age group in CCI and acute critically ill.

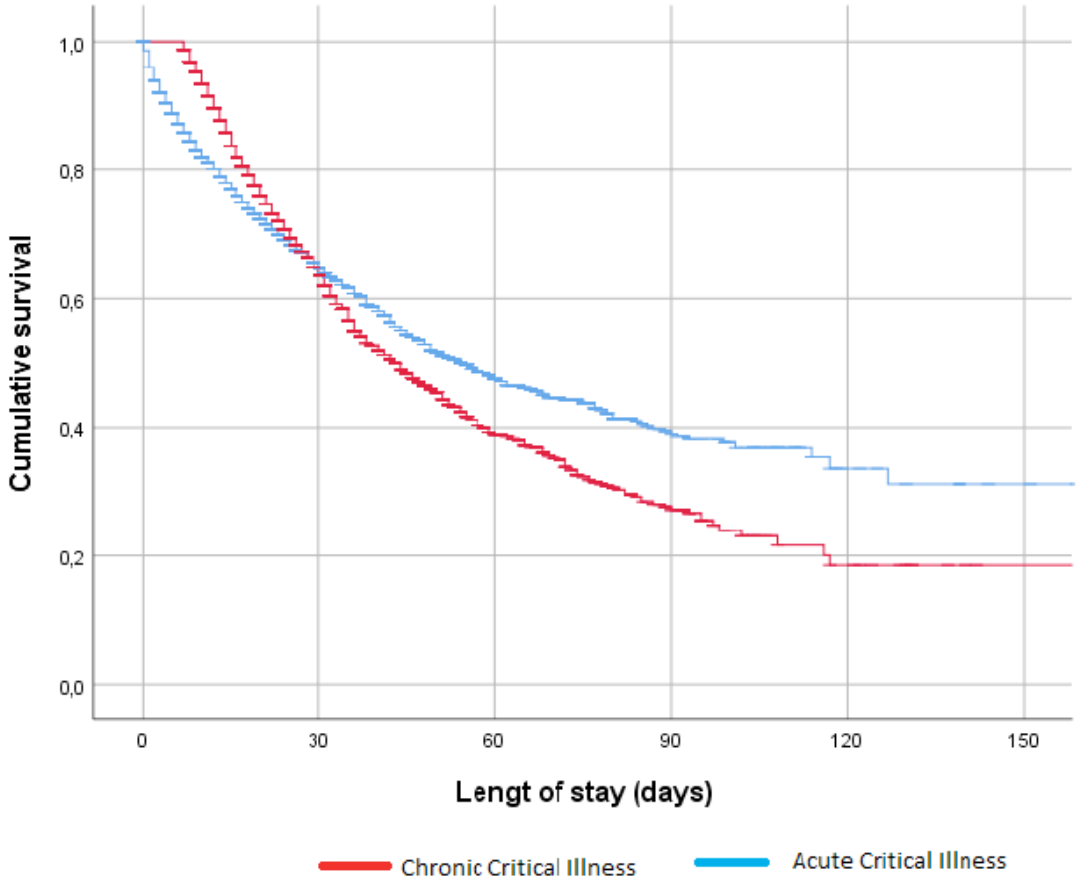


Fig. 2: Kaplan-Meier curve for Chronic and Acute Critical Illness.

Poisson regression was used to analyze risk factors for CCI, as illustrated in Figure 3. It can be observed that emergency source hospitalizations (RR 1.67, 95% CI 1.51 – 1.85), middle-size hospitals (RR 1.28, 95% CI 1.19 – 1.38), medical reason hospitalizations (RR 1.27, 95% CI 1.20 – 1.34) and infection (RR 5.75, 95% CI 5.5 – 6.01) were risk factors for CCI development.

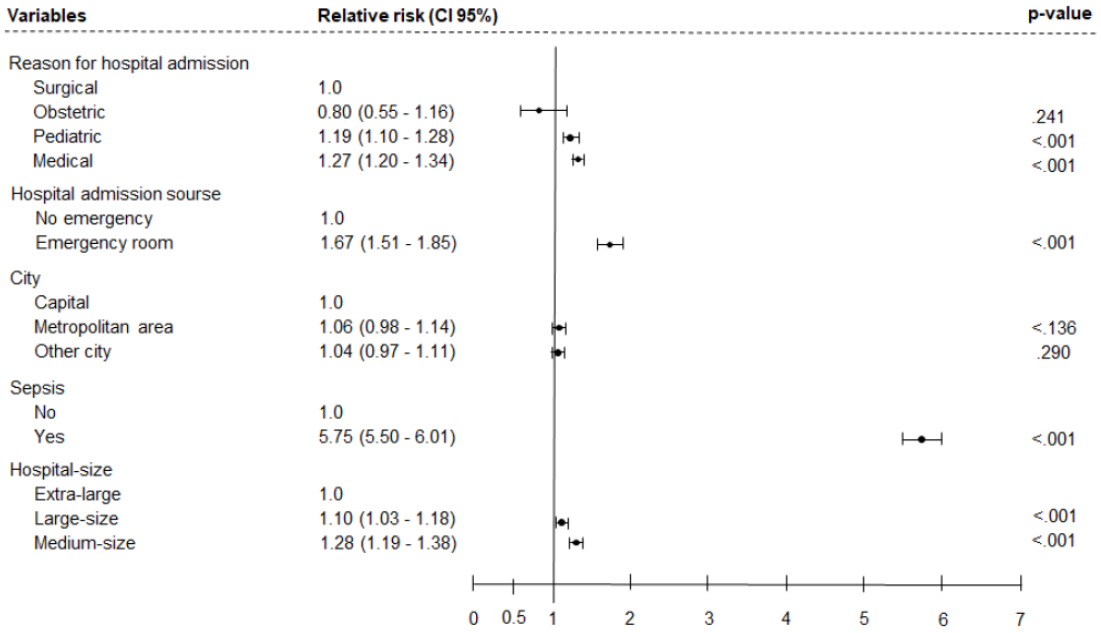


Figure 3: Risk factors for chronic critical illness.

DISCUSSION

In our knowledge, this data constitute the first analysis of a public healthcare database analyzing the profile of chronic critically ill patients and their impact on use of resources by the Brazilian healthcare system. We observed that this population can be identified using the HIS diagnosis and procedure codes available on the public healthcare system's database.

Our data show a CCI prevalence of 16.5% among critical care admissions on the public healthcare system, as soon as a hospital mortality of 31.7%. It also found that this population spends longer time in hospital and has higher costs when compared with acute critical admissions during the same period. The mean amount paid by the healthcare system to hospital service providers was 1.6 times higher for chronic critical admissions than for acute critical admissions. However, the CCI subset spent 2.8 times longer in hospital.

The prevalence of CCI observed in our study was 16.5%. This is much higher than rates observed in cohorts from developed countries using the same criteria as this study. However, mortality was similar[14]. An important publication from 2015, using

the same criteria for CCI as used in our study, observed a downward year-on-year trend in CCI mortality in North-American states and a prevalence of 7.6%. Another observation that was also similar to the Brazilian data was the association between infection and CCI. In Brazil, mortality from sepsis in public hospitals can be as high as 49.1%[16]. Difficulties with recognition and with application of early intervention protocols do not only impact on mortality, they can also contribute to development of CCI[17]. Confirming this finding, our study found that 66.3% of admissions in the CCI subset were because of infectious diseases, whereas this proportion was 14.7% of acute critical admissions. This high prevalence of infection diagnoses in the CCI population may, at least partially, explain the high prevalence and high mortality rate of CCI in the Brazilian cohort.

Age has proven to be an important characteristic of critical illness, especially in CCI. Some studies have found associations between CCI and older age groups[18]. Other studies have also found that age is a marker of mortality in CCI and also of worse long-term functional outcomes[19]. Our data showed that age was a marker of mortality in critical illness. A new and interesting finding in this study was mortality of critical patients by age group. Admissions of patients less than 1 year old and over the age of 35 years had higher mortality for CCI than for acute admissions. This appears to be an important observation because age tends to be a variable that is considered in prognostic assessments for many diseases and also when evaluating whether to limit treatment. The present analysis suggests, that in the range from 1 to 34 years, age is not a determinant factor of different outcomes in CCI patients, since they have the same hospital prognosis as patients with acute illness.

The survival analysis shown in Figure 3 illustrates that over the first 30 days in hospital, survival among CCI patients is greater than among acute patients. The relationship inverts after the 30th day in hospital. This inversion suggests that the condition of the initial insult is not more severe in chronic patients than among acute cases. Also, that possibly a second insult superimposed on the initial critical illness leads to an additional risk, increasing the likelihood of an unfavorable outcome. There is evidence indicative of a second cause, different from the cause of the initial admission, among patients who spend prolonged periods in the ICU[20, 21]. Infectious

complications were considerably more common among chronic patients[22]. Our data support this finding, showing a strong association between CCI and infection.

Infection has been associated with persistent chronic inflammation in several studies[23]. After several unsuccessful attempts to control hyperinflammation, these researchers began to question the universally accepted explanation for the body's exacerbated reaction in severe sepsis[22]. Recently, a two-phase model, with an inflammatory phase followed by an immunosuppression phase has attracted researchers' attention once more[22]. Studies in critically ill patients, have shown that survivors of sepsis have period of immune deficiency after acute illness.[24]. It is not yet clear what immune mechanism or groups of cells predominate in this anti-inflammatory response. But immunosuppression has been identified as a potential cause of the predisposition to infections in patients who survive the critical acute phase and then develop further complications, tending to progress to CCI and its worse outcomes[23].

A diagnosis of infection at admission was an important risk factor for development of CCI in this analysis, with an RR of 5.75 (95%CI: 5.5 – 6.01, p<.001). The association between CCI and infection is related with other studies and could be a reason for the higher mortality in the Brazilian CCI cohort than in other populations. Currently, sepsis mortality is high in Brazilian public hospitals. Data from the Latin American Sepsis Institute for 2008 showed that mortality rates were 49.1% and 36.7% in public and private hospitals in Brazil respectively[16]. Mortality of critical patients in general is also different in public and private hospitals, with rates in public ICUs that can be as high as 25.4%, which is a considerably higher percentage than seen in private ICUs in Brazil (14.6%) and in cohorts in developed countries (14.5%)[25,26]. Recently, an important multi-center study conduced by Machado FR et all shows a high mortality around 55% of sepsis in brazilian ICUs[27]. Factors such as difficulties with flows of patient referrals through the healthcare network, overcrowding, and too few specialized professionals may be related to the worse outcomes in the public system[15].

Other risk factors that we identified in the Brazilian CCI cohort were medical and pediatric admissions reasons, which may be interrelated with infections related to

CCI. Another observation was the association between CCI and admission source via the emergency department and to medium to large hospitals. The availability of professionals specialized in intensive care and emergency medicine (specialties that have been consolidated recently in Brazil) tends to be concentrated in extra-large size hospitals, where the working conditions and the payment are more attractive. A recent study that assessed care for sepsis in emergency departments showed that results were better in emergency units that had specific qualifications professionals related critically ill patients [28].

Finally, our study has some limitations. These data are from just one of the 26 states that make up Brazil. However, this state is the sixth most populous in the country and fifth most populous of the states in the South, Southeast, and Mid West regions. Another point is related to the representativeness of the epidemiological profile. States with sub-tropical climates have a different health profile to states with a tropical climate. The study's external validity for states in the North and Northeast of Brazil should be treated with caution. In the attempt to minimize bias we chose using the database of a state which database process is well known to us. Also, we perform preliminary analysis to check the consistency database information with other literature studies.

CONCLUSION

This study showed the possibility to describe the epidemiology of CCI in the public health brazilian database. Chronic critical illness has a significant impact on hospital-stay and consequent consumption of resources. The association between CCI and infections reveals an opportunity to intervene with protocols for early recognize and treatment of sepsis in the pre-hospital and hospital settings. The methodology developed for this study could be applied to the HIS databases for other states and other periods. This would expand knowledge on CCI in a developing country and provide tools for planning public health policies.

REFERENCES

1. Reisner-Sénélar L. The birth of intensive care medicine: Björn Ibsen's records. Intensive Care Med 2011; 31(7): 1084-6.
2. Puri N, Puri V, Dellinger R P. History of technology in the intensive care unit. Crit Care Clin 2009; 25(1): 185-200.
3. Loss SH, Nunes DSL, Franzosi OS et all. Chronic critical illness: are we saving patients or creating victims? Rev Bras Ter Intensiva. 2017;29(1):87-95
4. Carson, S. S. Definitions and epidemiology of the chronically critically ill. Resp Care 2012 57(6): 848-56.
5. Nelson JE, Kinjo K,Meier DE, Ahmed K, Morrison RS. When critical illness become chronic: informational needs of patients end families. J Crit Care 2005; 20: 79-89.
6. Van den Berghe G, de Zegher F, Bouillon R. Acute and Prolonged Critical Illness as Different Neuroendocrine Paradigms. J Neuroendocrinol Metab. 1998; 83: 1827-84.
7. Douglas SL, Daly BJ, Kelley CG, O'Toole E, Montenegro H. Impact of a disease management program upon caregivers of chronically critically ill patients. Chest 2005; 128(6): 3925-36.
8. Douglas S L, Daly B J, O'Toole E, Hickman R L. Depression among white and nonwhite caregivers of the chronically critically ill. J Crit Care 2010; 25(2): 364.e11-9.
9. Zilberberg M, deWit M, Pirone J, Shorr A. Growth in adult prolonged acute mechanical ventilation: implications for health care delivery. Crit Care Med. 2008;36:1451–1455.
10. Donahoe M P. Current venues of care and related costs for the chronically critically ill. Respir Care 2012; 57(6): 867-86.
11. Bigatello L M, Stelfox H T, Berra L, Schmidt U, Gettings E M. Outcome of patients undergoing prolonged mechanical ventilation after critical illness. Crit Care Med 2007; 35(11):2491-7.
12. Kandilov AM, Ingber MJ, Morley M, et al.: Chronically Critically Ill Population Payment Recommendations. Research Triangle Park, NC, RTI International, 2014

13. Brasil. Ministério da Saúde/ Secretaria de Atenção à Saúde/ Departamento de Regulação, Avaliação e Controle/Coordenação Geral de Sistemas de Informação. SIH – Sistema de Informação Hospitalar do SUS: Manual Técnico Operacional do Sistema 2017.
14. Kahn JM, Le T, Angus DC, Cox CE, Hough CL, White DB, Yende S, Carson SS; ProVent Group Study Investigators. The epidemiology of chronic critical illness in the United States. Crit Care Med. 2015;43(2):282-7.
15. De Negri Filho A, Barbosa Z. O Papel dos Hospitais nas Redes de Atenção a Saúde. Elementos para pensar em uma agenda estratégica para o SUS. CONSENSUS 2014; 11: 42-9.
16. SOGAYAR AM, MACHADO FR et al. A multicentre, prospective study to evaluate costs of septic patients in Brazilian intensive care units. Pharmacoeconomics. 2008. 26(5): 425-34.
17. Mira JC, Gentile LF, Mathias BJ et al. Sepsis Pathophysiology, Chronic Critical Illness and PICS. Crit Care Med. 2017 February ; 45(2): 253–262.
18. Loss S H, Marchese C B, Boniatti M M, Wawrzeniak I C, Oliveira R P. Nunes L N, Victorino J A. Prediction of chronic critical illness in a general intensive care unit. Rev Assoc Med Bras 2013 59(3): 241-247.
19. Dermot Frengley J, Sansone GR, Shakya K, Kaner R. Prolonged mechanical ventilation in 540 seriously ill older adults: effects of increasing age on clinical outcomes and survivalJ. J Am Geriatr Soc 2007; 62(1): 1-9.
20. Hotchkiss, R. S., G. Monneret, and D. Payen. Immunosuppression in sepsis: a novel understanding of the disorder and a new therapeutic approach. Lancet Infect. 2013 Dis. 13: 260–268.
21. Otto, G. P., M. Sossdorf, R. A. Claus, J. Ro¨del, K. Menge, K. Reinhart, M. Bauer, and N. C. Riedemann. 2011. The late phase of sepsis is characterized by an increased microbiological burden and death rate. Crit. Care 15: R183.
22. Kalb, T. H., and S. Lorin. 2002. Infection in the chronically critically ill: unique risk profile in a newly defined population. Crit. Care Clin. 18: 529–552.

23. Efron PA, Mohr AM, Bihorac A, et al. Persistent inflammation, immunosuppression, and catabolism and the development of chronic critical illness after surgery. Surgery 164 (2018) 178–184.
24. Borken F, Markwart R, Requardt RP et all. Chronic Critical Illness from Sepsis Is Associated with an Enhanced TCR Response. *J Immunol* 2017; 198:4781-4791.
25. Nogueira LS, Sousa RMC et al. Características clínicas e gravidade de pacientes internados em UTIs públicas e privadas. Texto contexto - enferm. 2012. 21(1): 59-67.
26. Graf J, Wagner J et al. Five-year survival, quality of life, and individual costs of 303 consecutive medical intensive care patients--a cost-utility analysis. Crit Care Med. 2005. 33(3): 547-55.
27. Machado FR, Cavalcanti AB, Bozza FA et all. The epidemiology of sepsis in Brazilian intensive care units (the Sepsis PREvalence Assessment Database, SPREAD): an observational study. Lancet Infect Dis. 2017 Nov;17(11):1180-1189.
28. Gunnerson KJ, Benjamin Bassin BS, Havey AR, et all. Association of an Emergency Department–Based Intensive Care Unit With Survival and Inpatient Intensive Care Unit Admissions. *JAMA Network Open.* 2019;2(7):e197584.

8. CONSIDERAÇÕES FINAIS

Os resultados apresentados nos dois estudos acrescentam dados novos na literatura sobre a população de pacientes críticos crônicos. Em primeiro lugar, testamos a sensibilidade e a especificidade das definições de DCC mais usadas e recentes da literatura, mostrando que o critério proposto recentemente tem maior sensibilidade para predizer mortalidade hospitalar que as definições anteriores, além de detectar um maior número de pacientes crônicos entre a população de pacientes críticos.

Corroborando outros estudos, observamos que a capacidade funcional dos pacientes com DCC apresenta redução após a alta da UTI. Por outro lado, observamos uma tendência de retorno ao status funcional prévio à internação na UTI após um ano de seguimento.

Também conseguimos mostrar ser viável avaliar dados de desfecho hospitalar na população de pacientes críticos usando a base de dados do sistema público de saúde do Brasil. O estudo desta condição nas hospitalizações financiadas pelo sistema público de saúde pode subsidiar a tomada de decisão no planejamento de políticas públicas envolvendo a população de pacientes crítico.

9. PERSPECTIVAS FUTURAS

A conquista de uma definição mais sensível de DCC e a possibilidade de identificar esta condição mais precocemente durante o curso do paciente na UTI traz uma oportunidade de estabelecer o prognóstico e desenvolver um plano terapêutico direcionado a necessidades singulares desta população de pacientes críticos. São exemplos de intervenções a atenção com risco aumentado de infecção, a instituição de medidas de reabilitação, o suporte nutricional prevendo o curso longo de convalescência e o planejamento dos cuidados após a alta hospitalar: centros de reabilitação, hospitais de longa permanência e *home care*.

Identificar a DCC e acompanhar dados de prevalência e mortalidade ao longo do tempo, usando a base de dados do sistema público de saúde, pode monitorar o efeito de intervenções sobre potenciais causas que têm sido apontadas como contribuidoras para o desenvolvimento de DCC. Estão entre estas causas o atraso no reconhecimento e na intervenção sobre a sepse e o choque séptico em unidades de hospitalares e pré-hospitalares do sistema público de saúde.

Entender a fisiopatologia da DCC é o ponto mais desafiador para ciência. O consenso acerca da definição desta condição viabiliza a uniformização dos critérios de inclusão em estudos, permitindo a comparação entre eles e a colaboração entre centros de pesquisa. O desafio agora concentra-se em desvendar processos moleculares e bioquímicos da resposta metabólica e sua evolução para a inflamação e catabolismo crônicos.

CAPITULO VI – ANEXOS

1. STROBE Statement—Checklist of items that should be included in reports of ***cohort studies*** for first paper: **Definitions and long-term outcomes in Chronic Critical Illness: a cohort study.**

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	39
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	39
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	40
Objectives	3	State specific objectives, including any prespecified hypotheses	41
Methods			
Study design	4	Present key elements of study design early in the paper	41
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	41
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	42
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	--
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	42
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	42 43

Bias	9	Describe any efforts to address potential sources of bias	50 51
Study size	10	Explain how the study size was arrived at	41 42
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	42
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	43
		(*b*) Describe any methods used to examine subgroups and interactions	--
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	42
		(*e*) Describe any sensitivity analyses	43
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	45 tab.1
		(b) Give reasons for non-participation at each stage	42
		(c) Consider use of a flow diagram	--
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	45 47
		(b) Indicate number of participants with missing data for each variable of interest	-- --
		(c) Summarise follow-up time (eg, average and total amount)	44 46
Outcome data	15*	Report numbers of outcome events or summary measures over time	47 48

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	48
		(*b*) Report category boundaries when continuous variables were categorized	--
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	--
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	44 46
Discussion			
Key results	18	Summarise key results with reference to study objectives	49
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	50 51
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	49 50
Generalisability	21	Discuss the generalisability (external validity) of the study results	50 51
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	--

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

2. STROBE Statement—Checklist of items that should be included in reports of ***cohort studies*** for first paper: **Mortality and risk-factors of Chronic Critical Illness in a low-income country.**

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	55
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	55
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	56
Objectives	3	State specific objectives, including any prespecified hypotheses	57
Methods			
Study design	4	Present key elements of study design early in the paper	57
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	57
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	57
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	--
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	57 58
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	57
Bias	9	Describe any efforts to address potential sources of bias	69

Study size	10	Explain how the study size was arrived at	58 59
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	61
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	61
		(*b*) Describe any methods used to examine subgroups and interactions	--
		(*c*) Explain how missing data were addressed	--
		(*d*) If applicable, explain how loss to follow-up was addressed	--
		(*e*) Describe any sensitivity analyses	--
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	62
		(b) Give reasons for non-participation at each stage	61
		(c) Consider use of a flow diagram	--
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	62
		(b) Indicate number of participants with missing data for each variable of interest	--
		(c) Summarise follow-up time (eg, average and total amount)	65
Outcome data	15*	Report numbers of outcome events or summary measures over time	63 a 66
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were	66

		included	
		(*b*) Report category boundaries when continuous variables were categorized	64
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	--
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	--
Discussion			
Key results	18	Summarise key results with reference to study objectives	66
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	69
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	67 69
Generalisability	21	Discuss the generalisability (external validity) of the study results	69
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	--

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Scientific

Precisamente o que você quer dizer.

EDITORIAL CERTIFICATE

This document certifies that the manuscript below was edited for correct English language usage, grammar, punctuation and spelling by a native speaker of English and qualified editor at Scientific Linguagem.

Paper Title:

Mortality and risk-factors of Chronic Critical Illness in a low-income country

Author:

Diego Silva Leite Nunes

Date certificate issued:

November 2019

For further information please contact Ms. Graça Adam at +55-51-3012.0575.