UNIVERSIDADE FEDERAL DE MINAS GERAIS
FACULDADE DE MEDICINA
PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS DA SAÚDE:
INFECTOLOGIA E MEDICINA TROPICAL

VIRGINIA MARA REIS GOMES

Desenvolvimento de um escore de risco para mortalidade em pacientes com covid-19 admitidos em unidades de terapia intensiva

BELO HORIZONTE
2024

VIRGINIA MARA REIS GOMES

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Dissertação apresentada ao Programa de Pós-graduação em Ciências da Saúde: Infectologia e Medicina Tropical, da Faculdade de Medicina, da Universidade Federal de Minas Gerais, para obtenção do título de Mestre.

Orientadora: Prof. Dra. Milena Soriano Marcolino

Co-orientadores: Profa. Dra. Polianna Delfino Pereira
Prof. Dr. Vandack Alencar Nobre Júnior

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ATA DE DEFESA DE DISSERTAÇÃO

Aos quinze dias do mês de maio de dois mil e vinte e quatro (15/05/2024), às 14:00 (quatorze) horas, no Canal do CETES - Plataforma LIFESIZE, realizou-se a sessão pública para a 452ª defesa de dissertação de **VIRGINIA MARA REIS GOMES**, número de registro 2022686432, graduada no curso de MEDICINA, como requisito parcial para a obtenção do grau de Mestre em CIÊNCIAS DA SAÚDE - INFECTOLOGIA E MEDICINA TROPICAL. A presidência da sessão coube a professora **MILENA SORIANO MARCOLINO**, orientadora. Inicialmente, a presidente fez a apresentação da Comissão Examinadora assim constituída: **PROFA. MILENA SORIANO MARCOLINO - ORIENTADORA (UFMG), PROFA. POLIANNA DELFINO PEREIRA – COORIENTADORA (INAPÓS)**, **PROF. VANDACK ALENCAR NOBRE JÚNIOR – COORIENTADOR (UFMG), PROFA. CAROLINA COIMBRA MARINHO (UFMG), PROF. LEANDRO UTINO TANIGUCHI (USP), PROFA. CECILIA GÓMEZ RAVETTI (UFMG).** Em seguida, a candidata fez a apresentação do trabalho que constitui sua **Dissertação de Mestrado**, intitulada: ***"Desenvolvimento de um escore de risco para mortalidade em pacientes com covid-19 admitidos em unidades de terapia intensiva".*** Seguiu-se a arguição pela Comissão Examinadora, com a respectiva defesa da aluna. Logo após, a Comissão reuniu-se sem a presença da candidata e do público para julgamento e expedição do resultado da dissertação e considerou-a **APROVADA.** O resultado final foi comunicado publicamente à candidata e ao público, pela presidente da Comissão. Conforme arts. 76 e 77 das Normas Gerais de Pós-Graduação da UFMG, as defesas de dissertação e tese são públicas. A aluna e os membros da banca estão cientes e autorizaram a gravação desta defesa, que ficará disponibilizada em acervo da Universidade. Nada mais havendo a tratar, a presidente encerrou a sessão, sendo lavrada a presente ata que, depois de lida e aprovada, foi assinada eletronicamente por todos os membros titulares da Comissão Examinadora presente através do SEI (Sistema Eletrônico de Informações) do Governo Federal.

Belo Horizonte, 15 de maio de 2024.

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DEDICATÓRIA

A todas as vítimas da covid-19.

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EPÍGRAFE

“Se eu vi mais longe, foi por estar sobre os ombros de gigantes”.

Isaac Newton, 1676

RESUMO

Introdução: Vários escores de risco foram desenvolvidos e testados durante a pandemia da covid-19, a fim de estratificar os pacientes de maior risco, alocando adequadamente os recursos e proporcionando melhor prognóstico. Apesar disso, a maioria deles está limitada por falhas metodológicas e utiliza dados anteriores ao surgimento de novas variantes e ao amplo uso da vacinação, o que pode impactar o desempenho dos escores. Ainda falta um escore de risco de mortalidade confiável para pacientes com covid-19 internados em unidades de terapia intensiva (UTI). **Objetivos:** Desenvolver um escore de risco de mortalidade para pacientes com covid-19 à admissão em UTI e compará-lo a outros escores existentes. **Métodos:** Trata-se de um estudo retrospectivo observacional multicêntrico, que incluiu pacientes adultos com covid-19, admitidos em UTI de 18 hospitais de nove cidades brasileiras, de setembro de 2021 a julho de 2022. Os preditores em potencial foram selecionados através de revisão da literatura. Modelos Aditivos Generalizados (GAM) foram usados para avaliar a relação entre os preditores e o desfecho. A regressão LASSO (*least absolute shrinkage and selection operator*) foi usada para derivar a pontuação do escore. **Resultados:** De 558 pacientes incluídos, a idade mediana foi 69 anos (intervalo interquartil 58-78), 56,3% eram homens, 19,7% necessitaram de ventilação mecânica invasiva (VMI) e a mortalidade geral foi de 44,8%. O modelo final incluiu seis variáveis: idade (***A**ge*), pO_2/FiO_2, função respiratória (frequência respiratória e se em VM) (***B**reathing*), doença pulmonar obstrutiva crônica (***C**OPD*) e **O**besidade. O AB_2CO teve uma área sob a curva característica de operação do receptor (AUROC) de 0,781 (intervalo de confiança 95% 0,744-0,819), uma boa performance geral e excelente curva de calibração (slope=1.063, intercept=0.015, p-value=0.834). O escore foi comparado com outros já existentes (ABC_2-SPH, Atschul et al., CHA_2DS_2-VASc Modificado, COVID-SOFA, CURB-65, SOARS, SOFA, NEWS2 e 4C *Mortality Score*) e demonstrou melhor poder de discriminação que a maioria deles, e com melhor curva de calibração. **Conclusões:** O AB_2CO é um escore simples, rápido e objetivo, baseado em apenas seis variáveis, variando de 0 a 16 pontos, com desempenho superior a outros escores. Além disso, foi desenvolvido utilizando dados mais recentes da pandemia, tornando-o ainda mais fidedigno ao atual cenário. Entretanto, estudos posteriores são necessários para realizar a validação externa do escore.

Palavras-chave: Covid-19; SARS-CoV-2; unidade de terapia intensiva; prognóstico; mortalidade; fatores de risco.

ABSTRACT

Introduction: Several risk scores were tested during the COVID-19 pandemic in order to stratify those patients most at risk, properly allocating resources and giving better chances of a successful outcome. Despite that, most of them are bounded by methodological flaws and they use data before the emergence of new variants and the broad use of vaccination, which may impact scores' performance. A reliable mortality risk score for COVID-19 patients admitted to intensive care units (ICUs) is still lacking. **Objectives:** To develop a mortality risk score for patients with covid-19 upon admission to ICU and compare it with other existing scores. **Methods:** This is a multicenter observational retrospective study, which included adult patients with COVID-19 admitted to the ICU of 18 hospitals in 9 Brazilian cities, from September 2021 to July 2022. Potential predictors were selected through review of the literature. Generalized Additive Models (GAM) were used to evaluate the relationship between the predictors and the outcome. LASSO (least absolute shrinkage and selection operator) regression was used to derive the score score. **Results:** Of the 558 patients included, the median age was 69 years (IQR 58-78), 56.3% were men, 19.7% required invasive mechanical ventilation (IMV), and overall mortality was 44.8%. The final model included 6 variables: **A**ge, **B**reathing (pO_2/FiO_2, and respiratory function [respiratory rate and whether on IMV]), **C**OPD (chronic obstructive pulmonary disease) and **O**besity. AB_2CO had an area under the the receiver operating characteristic curve (AUROC) of 0.781 (95% confidence interval 0.744-0.819), a good overall performance and excellent calibration curve (slope=1.063, intercept=0.015, p-value=0.834). The score was compared with other existing ones (ABC_2-SPH, Atschul et al., Modified CHA_2DS_2-VASc, COVID-SOFA, CURB-65, SOARS, SOFA, NEWS2, and 4C Mortality Score) and demonstrated better discrimination power than most of them, and with a better calibration curve. **Conclusions:** AB_2CO is a simple, quick and objective score, based on just 6 variables, ranging from 0 to 16 points, with better performance than other scores. It was developed using the most recent data from the pandemic, making it even more reliable to the current scenario. However, further studies are necessary to carry out external validation of the score.

Keywords: COVID-19; SARS-CoV-2; intensive care unit; prognosis; mortality; risk factors.

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LISTA DE ABREVIATURAS E SIGLAS

ALT: Alanino aminotransferase

AMIB: Associação de Medicina Intensiva Brasileira

AST: Aspartato aminotransferase

AVC: Acidente vascular cerebral

AUROC: Área sob a curva de característica de operação do receptor

bpm: Batimentos por minuto

CIEGES: Centro de Informações Estratégicas para a Gestão Estadual do SUS

COVID-19: Coronavírus 2019

CDC: *Centers for Disease Control and Prevention*

DPOC: Doença pulmonar obstrutiva crônica

ECG: Escala de Coma de Glasgow

FiO_2: Fração inspirada de oxigênio

GAM: Modelos aditivos generalizados

HCO_3: Bicarbonato

IC: Intervalo de confiança

IIQ: Intervalo interquartil

IMC: Índice de massa corporal

irpm: Incursões respiratórias por minuto

LASSO: *Least absolute shrinkage and selection operator*

MICE: imputação multivariada por equações encadeadas

NEWS2: *National Early Warning Score 2*

OMS: Organização Mundial da Saúde

PCR: Proteína C-reativa

pCO_2: Pressão parcial de gás carbônico

pO_2: Pressão parcial de oxigênio

PROBAST: *Prediction model Risk Of Bias Assessment Tool*

PTTa: Tempo de tromboplastina parcial ativada

RNI: Relação normatizada internacional

RNL: Razão neutrófilo/linfócito

ROC: Característica de operação do receptor

RR: Razão de risco

RT-PCR: *Reverse transcription - polymerase chain reaction*

SARS-CoV-2: Coronavírus 2 da síndrome respiratória aguda grave

SOFA: *Sequential Organ Failure Assessment*

SpO_2: Saturação de oxigênio

SUS: Sistema Único de Saúde

TRIPOD: *Transparent Reporting of a multivariable prediction model for Individual Prediction Or Diagnosis*

UTI: Unidade de terapia intensiva

VMI: Ventilação mecânica invasiva

SUMÁRIO

1. CONSIDERAÇÕES INICIAIS

Durante a pandemia de covid-19, algumas medidas foram realizadas a fim de tentar atender à demanda extraordinária e crescente nos serviços de saúde. Entre essas medidas, podemos citar a expansão do número de leitos, com hospitais trabalhando em sua capacidade máxima, contratação de novos profissionais da saúde, além da criação dos chamados hospitais de campanha. Apesar de todos os esforços, os serviços de saúde ficaram sobrecarregados, levando a possíveis piores desfechos clínicos. Iniciou-se então, um esforço conjunto de pesquisadores em todo o mundo, em busca de melhorar a qualidade e eficácia do atendimento a pacientes com covid-19.

Nesse contexto, surgiu o "Registro Hospitalar Multicêntrico Nacional de Pacientes com Doença Causada pelo SARS-CoV-2 (covid-19)", um estudo multicêntrico observacional que inicialmente incluiu 37 hospitais, em 17 cidades, localizados em três das cinco regiões brasileiras (1). Em dezembro de 2020, iniciei minha participação no projeto, ainda como acadêmica de iniciação científica, atuando em coleta de dados, apresentação de resumos em congressos e auxílio na elaboração de artigos científicos. Em 2021, participei da comissão organizadora do 1º e 2º Congresso Brasileiro de Evidências Clínicas na Covid-19, além do 1º Congresso Acadêmico de Evidências Clínicas na Covid-19, e outros dois eventos on-line e completamente gratuitos, voltados a disseminar informações confiáveis à população geral. Essa foi uma iniciativa do grupo de pesquisa do referido projeto, que contou com o apoio da Universidade Federal de Minas Gerais e teve mais de 30 mil visualizações no YouTube, em apenas um dos dias do evento.

Diante dos desafios impostos pela pandemia, a quantificação do risco de mortalidade, baseado em parâmetros de fácil obtenção à admissão, poderia facilitar o fluxo e alocação de recursos àqueles pacientes em maior risco, potencializando as chances de um tratamento com sucesso. Nesse sentido, o referido grupo de pesquisa desenvolveu o escore ABC_2-SPH, para avaliar o risco de mortalidade intra-hospitalar dos pacientes com covid-19, usando variáveis obtidas à admissão hospitalar (2). Apesar de ter apresentado um excelente desempenho geral para sua aplicação neste contexto, o ABC2-SPH demonstrou performance insuficiente para utilização à admissão em unidades de terapia intensiva (UTI) (3). Com isso, surgiu a ideia de desenvolver um novo escore, específico para pacientes criticamente

enfermos, utilizando dados da coorte do "Registro Hospitalar Multicêntrico Nacional de Pacientes com Doença Causada pelo SARS-CoV-2 (covid-19)".

2. INTRODUÇÃO

Em março de 2020, a Organização Mundial da Saúde (OMS) declarou situação de pandemia pela covid-19 (4). Neste período, o mundo testemunhou sobrecarga dos hospitais e dos profissionais de saúde, especialmente com o surgimento de novas variantes e a alta taxa de transmissibilidade (5).

Até o momento, a pandemia de covid-19 produziu números expressivos de infectados e de óbitos em todo o mundo, com aproximadamente sete milhões de mortes, afetando de forma mais importante países com menor índice de desenvolvimento e cujas políticas públicas não obedeceram às orientações das maiores autoridades em saúde internacionais. Como principal exemplo, podemos destacar o Brasil, o terceiro país em número de casos e o segundo em número de mortes durante o período (6).

O avanço das pesquisas, que ocorreu em tempo recorde, incluiu também o desenvolvimento de escores prognósticos, buscando sistematizar a avaliação dos pacientes, já que outros escores já existentes apresentaram baixa sensibilidade e especificidade quando aplicados a pacientes com covid-19 (7,8).

Entre os escores desenvolvidos e aplicados à essa população, podemos incluir os que predizem mortalidade à admissão hospitalar, como o ABC_2-SPH (2), desenvolvido através de dados obtidos do Projeto Registro Covid-19, que incluiu 36 hospitais, localizados em 17 cidades, de cinco estados brasileiros. Este escore apresentou boa discriminação nas coortes de validação brasileira (0,859 [95% CI 0,833-0.885]) e espanhola (0,894 [95% CI 0,870-0,919), e demonstrou ser o de melhor desempenho na população brasileira (2).

Por se tratar de uma ferramenta rápida, barata e que utiliza dados facilmente obtidos à admissão hospitalar (idade [***A**ge*], ureia [***B**lood urea nitrogen*], proteína **C**-reativa, número de **C**omorbidades, **S**pO_2/FiO_2, **P**laquetas, frequência cardíaca [***H**eart rate*]), o ABC_2-SPH é de um instrumento de grande utilidade (2). Entretanto, em um estudo recente (3), este escore demonstrou poder de discriminação apenas regular para predição de mortalidade, quando usados dados à admissão em UTI. Foi observada limitação semelhante no contexto de doentes críticos com covid-19 com o uso de outros escores, parte utilizada para outras finalidades e parte desenvolvida exclusivamente para pacientes com covid-19. Assim, os resultados desse estudo demonstraram que não havia um escore prognóstico de boa acurácia quando usando dados de pacientes com covid-19 à admissão na UTI.

Com isso, nosso objetivo foi desenvolver um escore de risco de mortalidade intra-hospitalar para pacientes brasileiros com covid-19 internados em UTIs, usando dados obtidos à admissão neste setor.

3. REFERENCIAL TEÓRICO

3.1 Covid-19

3.1.1 Etiopatogenia e origem do vírus

O coronavírus é um patógeno envelopado de ácido ribonucleico (RNA) de fita simples, pertencente à família *Coronaviridae*, que está presente entre humanos e outros mamíferos e em alguns pássaros (9,10). Quatro destes vírus são mais prevalentes como patógenos em seres humanos, causando resfriado comum em indivíduos imunocompetentes. Já os vírus coronavírus da síndrome respiratória aguda do Oriente Médio (MERS-CoV) e o coronavírus da síndrome respiratória aguda (SARS-CoV-1 e SARS-CoV-2) possuem origem zoonótica e estão associados com desfechos mais graves em humanos. (9,10).

No final de dezembro de 2019, foi identificada uma série de pacientes com pneumonia de causa indeterminada, na província de Wuhan, na China, quando, posteriormente, o Centro de Controle de Doenças da China iniciou uma investigação que detectou o novo coronavírus nestes pacientes (10). Inicialmente, suspeitava-se que estavam epidemiologicamente relacionados a um mercado de peixe, onde diversos outros animais não aquáticos estavam sendo vendidos, como pássaros e coelhos (11).

3.1.2 Transmissão

A principal via de transmissão do SARS-Cov-2 é a respiratória, podendo ocorrer por gotículas ou durante procedimentos que geram aerossois, que permanecem suspensas no ar por algumas horas e podem ser carregadas por correntes de ar por distâncias maiores. Além disso, estudos demonstraram que o contato íntimo prolongado e a ventilação reduzida são determinantes na transmissão (12,13).

Outros estudos sugeriram que a transmissão poderia ocorrer através de fômites, sendo, por exemplo, o risco aumentado para profissionais da saúde com higiene das mãos precária (12). Entretanto, não foi possível descartar completamente a transmissão respiratória nos casos relatados, e acredita-se que os níveis de RNA viral em superfícies não seriam suficientes para causar infecção (12).

Outras possíveis vias de transmissão do SARS-Cov-2 são a fecal-oral, vertical ou por meio de outros fluidos corporais, ainda que haja evidências limitadas acerca dessa possibilidade (12).

3.1.3 Manifestações clínicas e espectros de gravidade

Desde o início da pandemia, observou-se que a apresentação clínica dos pacientes infectados pelo SARS-Cov-2 é bastante variável, podendo manifestar desde formas assintomáticas até quadros graves ou fatais (14). A caracterização dos diversos espectros de gravidade da covid-19 é importante para o entendimento da história natural da doença e os possíveis desfechos esperados que esses pacientes poderiam enfrentar.

Foram relatados casos de pessoas com covid-19 que não apresentaram sintomas, mas com carga viral semelhante àquela dos sintomáticos, demonstrando a indivíduos sem manifestações clínicas da infecção também podem transmitir a infecção (15). Acredita-se que cerca de 30% dos pacientes infectados apresentam-se na forma assintomática (16). Estimar a prevalência de casos assintomáticos é um desafio, como observado em uma revisão sistemática e metanálise que demonstrou uma grande heterogeneidade, entre 14% a 50% nos diferentes estudos (17).

Muitos pacientes apresentam sintomas leves, semelhantes a um resfriado comum, e frequentemente não requerem hospitalização (1). Os sintomas mais prevalentes são tosse, odinofagia, dispneia e expectoração. Outros sintomas incluem febre, fadiga, cefaleia, fraqueza muscular, diarreia, náuseas e vômitos. Há ainda relatos de outras manifestações menos frequentes, como alterações cutâneas e oculares (16).

Uma porção significativa dos casos, em geral, cerca de 14% segundo a literatura (18) progride para uma doença moderada, apresentando pneumonia, doença grave, com dificuldade respiratória, dessaturação e taquipneia. Há ainda aqueles casos mais críticos, em que ocorre uma resposta inflamatória exagerada do sistema imunológico, ocasionando na Síndrome Respiratória Aguda Grave (SRAG), podendo levar à insuficiência respiratória aguda, choque séptico e diversas outras manifestações sistêmicas. Trata-se da forma mais grave da covid-19, com demanda de internação em UTI e instituição de terapias substitutivas, tais como ventilação mecânica invasiva, uso de vasopressores e hemodiálise (19).

Alguns fatores estão relacionados ao curso da doença em pacientes com covid-19, dentre eles os grupos populacionais. Estudos sugerem que as crianças têm menor chance de agravamento do que adultos, com mortalidade mais baixa

(20,21). Já as gestantes, apresentam menor prevalência de sintomas que a população geral, sendo que muitas apresentam sintomas leves e até mesmo assintomáticas (22,23).

Além das características relativas a condições médicas, as diferentes variantes do vírus também podem influenciar. Alguns estudos sugeriram maior gravidade e mortalidade associado à variante Delta em relação à Omicron, por exemplo (24,25).

3.1.4 Fatores de risco de mortalidade

Desde o início da pandemia, diversos estudos buscaram avaliar os fatores de risco que poderiam estar relacionados a um pior prognóstico, tendo implicações clínicas importantes para o manejo e tomada de decisões (26). Esses fatores podem ser relacionados ao hospedeiro ou também ao patógeno. Entre os fatores mais importantes relacionados ao primeiro, destaca-se a idade. Acredita-se que o envelhecimento cause uma série de alterações fisiológicas, como menor imunidade e exacerbada produção de citocinas, resultando em um estado pró-inflamatório, favorável a piores desfechos (26). Nesta linha, estudos apontam para um risco maior para agravamento e mortalidade, especialmente a partir dos 60 anos de idade, aumentando progressivamente para aqueles acima dos 80 anos de idade (27,28).

Em uma revisão sistemática com metanálise, que incluiu dados de 36.470 pacientes, observou-se uma razão de risco (RR) para óbito em pacientes com mais de 70 anos de idade de 3,61 (95% IC 2,70-4.84), em comparação àqueles com uma menor faixa etária (29). Em outro estudo, incluindo 423.117 pacientes, o fator idade avançada apresentou RR de 2,61 (95% IC 1,75-3,47), enquanto a obesidade também apresentou uma associação significativa com mortalidade, com RR de 1,34 (95% IC 1,17-1,52), bem como a doença pulmonar obstrutiva crônica (DPOC) [1,58 (95% IC 1,08-2,07)] (26).

Outras condições clínicas relacionadas ao hospedeiro mostraram ter associação com a mortalidade desses pacientes, como diabetes mellitus, DPOC, hipertensão arterial sistêmica e injúria renal aguda (26). Pacientes com DPOC demonstraram maiores índices de hospitalização e mortalidade (26), provavelmente devido a infecções virais aumentarem a resposta sistêmica inflamatória, com uma recuperação mais lenta dos sintomas (30). A presença de diabetes mellitus foi

associada a maior gravidade, necessidade de ventilação mecânica invasiva, suporte intensivo e também com maior mortalidade (31).

O *Centers for Disease Control and Prevention* (CDC) lista outros fatores de risco para mortalidade nesses pacientes, como tabagismo e outras comorbidades, como câncer, hepatopatia crônica, doença cerebrovascular, doença renal crônica, doença arterial coronariana e imunossupressão (por uso de medicamentos, transplante, ou infecção pelo vírus da imunodeficiência humana [HIV]) (32).

Como resultado disso, houve uma busca urgente a fim de reduzir o risco de mortalidade e de progressão para doença severa. No último trimestre de 2022, já haviam diversas vacinas em desenvolvimento (33), tendo sua eficácia variado em até 95% (34,35). Desde então, diversos estudos têm comprovado sua eficácia e segurança nos diferentes grupos populacionais (34–37).

Quanto aos fatores relacionados ao patógeno, eles se dão em decorrência das mutações que ocorrem com a disseminação do vírus, gerando as variantes de interesse e as de preocupação, associadas a maior risco de agravamento e piores desfechos. As variantes de preocupação são aquelas com aumento de transmissibilidade ou virulência, causam redução da eficácia das medidas de saúde pública, dos diagnósticos ou vacinas disponíveis. Já as variantes de interesse são aquelas que as alterações genéticas afetam a transmissibilidade, gravidade, escape imunológico, diagnóstico ou terapêutico, e que já foi identificada como causa de transmissão de múltiplos casos em conjunto significativos, ou com outros impactos na saúde global (38).

3.1.5 Covid-19 e unidades de terapia intensiva

As UTIs representam setores hospitalares capazes de oferecer um suporte multissistêmico de alta complexidade para os pacientes com quadros clínicos mais graves (39). São classificadas seguindo níveis de cuidado, sendo o nível I o de menor risco, destinado a pacientes que estão em recuperação de condições críticas ou que têm risco de deterioração, mas que não é indicado cuidado em enfermaria. O nível II, para pacientes com alto risco, se destina a pacientes que necessitam de monitoramento e/ou suporte intensivos, porém de menor complexidade. Já o nível III de cuidados, destinada a pacientes muitos graves, com uma ou mais disfunções orgânicas, que têm risco imediato de morte (39).

A pandemia da covid-19 desencadeou um impacto significativo nas UTIs em todo o mundo. A natureza agressiva e até então imprevisível e desconhecida da doença exigiu intervenções médicas intensivas a milhares de pacientes simultaneamente, gerando uma sobrecarga para os sistemas de saúde em muitos países. A alta demanda por leitos de UTI e equipamentos médicos especializados levaram à necessidade de criação e abertura de novos leitos (40), conforme demonstrado na Figura 1.

Figura 1. Total de leitos de unidades de terapia intensiva (UTI) com financiamento federal no Brasil, de janeiro a setembro de 2021. **Fonte:** Adaptado do Centro de Informações Estratégicas para a Gestão Estadual do SUS (CIEGES) (41).

Dada a desigualdade de distribuição destes leitos, demonstrado na Figura 2, especialmente em regiões com falha de estrutura hospitalar histórica, o desenvolvimento de ferramentas de predição de desfechos torna-se necessária para a utilização racional de recursos e maior sobrevida.

Figura 2. Número total de leitos de unidades de terapia intensiva (UTI) por cada 10 mil habitantes em cada região do Brasil em 2020. **Fonte:** Adaptado de “AMIB apresenta dados atualizados sobre leitos de UTI no Brasil” (AMIB, 2020) (42).

3.2 Escores de risco de mortalidade

3.2.1 Desenvolvimento de escores prognósticos

Os escores desempenham um papel fundamental na prática médica, com informações importantes sobre estimativa da probabilidade de uma determinada doença estar presente (escores diagnósticos), ou estimativa de risco de complicações, agravamento da doença ou desfechos clínicos de pacientes (escores prognósticos) (43). Essas ferramentas são desenvolvidas para fornecer uma estimativa objetiva, permitindo uma abordagem mais direcionada ao cuidado do paciente, ajudando os profissionais de saúde a tomar decisões clínicas fundamentadas (44).

A fim de melhorar a transparência e a qualidade dos modelos de predição, foi desenvolvido o *Transparent Reporting of a Multivariable Prediction Model for Individual Prediction or Diagnosis* (TRIPOD), um conjunto de diretrizes, com informações estruturadas, incluindo 22 itens, a fim de promover a reprodutibilidade, a interpretação precisa e a aplicabilidade clínica dos modelos, aprimorando a sua confiabilidade (Quadro 1). Estas informações devem ser consideradas ao desenhar, conduzir e analisar estudos de desenvolvimento e validação de escores (45).

As diretrizes geraram um *checklist que* inclui informações a respeito do título/resumo, introdução, métodos, tamanho da amostra, resultados, discussão e outras informações. Ao fornecer informações claras sobre o estudo, os pesquisadores permitem que outros cientistas realizem uma interpretação precisa dos resultados, de sua validade e utilidade, podendo ser aplicado tanto para desenvolvimento, validação externa ou ambos, em modelos de predição diagnóstica ou prognóstica (45).

Quadro 1. Checklist TRIPOD para relato transparente em um modelo prognóstico multivariável.

Seção/tópico	Item	Item do *checklist*
Título e resumo		
Título	1	Identificar o estudo, se de desenvolvimento e/ou validação de um modelo de predição multivariável, a população-alvo e o desfecho a ser previsto.
Resumo	2	Fornecer um resumo dos objetivos, desenho do estudo, cenário, participantes, tamanho amostral, preditores, desfecho, análise estatística, resultados e conclusões.
Introdução		
Contexto e objetivos	3a	Explicar o contexto médico (incluindo diagnóstico ou prognóstico) e justificativa para desenvolver ou validar o modelo de predição multivariável, incluindo referências a modelos existentes.
	3b	Especificar os objetivos, incluindo se o estudo descreve o desenvolvimento ou validação do modelo ou ambos.
Métodos		
Fonte dos dados	4a	Descrever o desenho do estudo ou a fonte de dados (por exemplo, estudo randomizado, coorte ou dados de registro), separadamente para os conjuntos de dados de desenvolvimento e validação, se aplicável.
	4b	Especificar as principais datas do estudo, incluindo o início e fim da coleta, e, se aplicável,

		o fim do acompanhamento.
Participantes	5a	Especificar os elementos-chave do cenário do estudo (por exemplo, atenção primária, atenção secundária, população geral), incluindo o número e local dos centros.
	5b	Descrever os critérios de elegibilidade dos participantes.
	5c	Fornecer detalhes do tratamento recebido, se relevante.
Desfecho	6a	Definir claramente o desfecho que é previsto pelo modelo, incluindo como e quando avaliado.
	6b	Relatar quaisquer ações para avaliação cega do resultado a ser previsto.
Preditores	7a	Definir claramente todos os preditores usados no desenvolvimento do modelo de predição multivariável, incluindo como e quando foram medidos.
	7b	Relatar quaisquer ações para avaliação cega de preditores para o desfecho e outros preditores.
Tamanho amostral	8	Explicar como se chegou ao tamanho amostral do estudo.
Dados faltantes	9	Descrever como os dados ausentes foram tratados (por exemplo, análise de caso completo, imputação única, imputação múltipla) com detalhes de qualquer método de imputação.
Análise estatística	10a	Descrever como os preditores foram tratados na análise.
	10b	Especificar o tipo de modelo, todos os procedimentos de construção do modelo (incluindo qualquer seleção de preditor) e métodos para validação interna.
	10c	Para validação, descrever como os preditores foram calculados.
	10d	Especificar todas as medidas usadas para avaliar a performance do modelo e, se relevante, para comparar com múltiplos modelos.

	10e	Descrever qualquer atualização do modelo (por exemplo, recalibração) decorrente da validação, se realizada.
Grupos de risco	11	Fornecer detalhes sobre como os grupos de risco foram criados, se o fizeram.
Desenvolvimento versus validação	12	Para validação, identificar quaisquer diferenças dos dados de desenvolvimento no cenário, critérios de elegibilidade, resultado e preditores.
Resultados		
Participantes	13a	Descrever o fluxo de pacientes no estudo, incluindo o número de participantes com e sem o desfecho e, se aplicável, um resumo do tempo de acompanhamento. Um diagrama pode ser útil.
	13b	Descrever as características dos participantes (dados demográficos básicos, características clínicas, preditores disponíveis), incluindo o número de participantes com dados ausentes para preditores e desfecho.
	13c	Para validação, mostrar uma comparação do desenvolvimento com os dados da distribuição de variáveis importantes (demografia, preditores e desfecho).
Desenvolvimento do modelo	14a	Especificar o número de participantes e os eventos do desfecho de cada análise.
	14b	Se realizado, relatar a associação não ajustava entre cada candidato preditor e o desfecho.
Especificação do modelo	15a	Apresentar o modelo de predição completo para permitir previsões individuais (ou seja, todos os coeficientes de regressão e a constante ou sobrevivência da linha de base em um determinado tempo).
	15b	Explicar como usar o modelo de predição.
Performance do modelo	16	Relatar as medidas de desempenho (com os intervalos de confiança) para o modelo de predição.

Atualização do modelo	17	Se realizado, relatar os resultados de qualquer atualização do modelo. (por exemplo, especificação do modelo, análise de performance).
Discussão		
Limitações	18	Discutir quaisquer limitações do estudo (como amostra não-representativa, poucos eventos por preditor, dados faltantes).
Interpretação	19a	Para validação, discutir os resultados em comparação ao desempenho nos estudos de desenvolvimento e outros dados de validação.
	19b	Fornecer uma interpretação geral dos resultados, considerando objetivos, limitações, resultados de estudos semelhantes e outras evidências relevantes.
Implicações	20	Discutir o potencial uso clínico do modelo e as implicações para estudos futuros.
Outras informações		
Informações suplementares	21	Fornecer informações sobre a disponibilidade de fontes suplementares, como protocolo do estudo, calculadora *online* e bancos de dados.
Financiamento	22	Informar a fonte de financiamento e o papel dos financiadores no estudo.

Fonte: Adaptado do TRIPOD *Checklist*.

Além disso, a fim de auxiliar na avaliação crítica da qualidade e do risco de viés nos modelos de predição, foi desenvolvido o *Prediction Model Risk Of Bias Assessment Tool* (PROBAST). Essa ferramenta fornece uma estrutura padronizada e sistemática para identificação de aspectos que podem introduzir viés aos modelos, incluindo informações sobre participantes, preditores, desfechos e análise, sendo que quanto maior a pontuação, maior a qualidade geral do modelo. Dessa forma, permite aos pesquisadores relatarem de forma consistente e transparente as limitações potenciais de seus estudos (46).

Quadro 2. Avaliação do risco de viés usando o *checklist* do PROBAST.

Domínio e item	Item do *checklist*
Participantes	
1.1	Foram utilizadas fontes de dados apropriadas, como coorte, estudos controlados randomizados, ou dados de caso-controle?
1.2	Todos os critérios de inclusão e exclusão dos pacientes foram apropriados?
Risco de viés introduzido por participantes ou fontes de dados:	
Preditores	
2.1	Os preditores foram definidos e avaliados de forma semelhante para todos os participantes?
2.2	As avaliações dos preditores foram feitas sem conhecimento dos dados de resultado?
2.3	Todos os preditores estão disponíveis no momento em que o modelo deve ser usado?
Risco de viés introduzido por preditores ou sua avaliação:	
Desfecho	
3.1	O desfecho foi determinado apropriadamente?
3.2	Foi usada uma definição de desfecho pré-especificada ou padrão?
3.3	Os preditores foram excluídos da definição do resultado?
3.4	O desfecho foi definido e determinado de forma semelhante para todos os participantes?
3.5	O desfecho foi determinado sem conhecimento das informações do preditor?

3.6	O intervalo de tempo entre a avaliação do preditor e a determinação do resultado foi apropriado?

Risco de viés introduzido por preditores ou sua avaliação:

Análise

4.1	Houve um número razoável de participantes com o resultado?
4.2	Os preditores contínuos e categóricos foram tratados adequadamente?
4.3	Todos os participantes inscritos foram incluídos na análise?
4.4	Os participantes com dados ausentes foram tratados adequadamente?
4.5	A seleção de preditores com base na análise univariável foi evitada?
4.6	As complexidades dos dados (por exemplo, censura, riscos competitivos, amostragem de pacientes de controle) foram contabilizadas adequadamente?
4.7	As medidas relevantes de desempenho do modelo foram avaliadas adequadamente?
4.8	O *overfitting* do modelo e o otimismo no desempenho do modelo foram considerados?
4.9	Os preditores e seus pesos atribuídos no modelo final correspondem aos resultados da análise multivariável relatada?

Risco de viés introduzido pela análise:

Fonte: Adaptado do PROBAST *Checklist*.

Os estudos que desenvolvem novos modelos devem incluir alguma forma de validação interna a fim de quantificar sua capacidade preditiva nos mesmos dados que o modelo foi desenvolvido (45). Além disso, uma vez desenvolvido o modelo de predição, é recomendado avaliar seu desempenho utilizando dados de participantes que não foram utilizados para o desenvolvimento (45). A validação externa pode ser realizada utilizando dados de participantes em um período amostral posterior (validação temporal) ou utilizando participantes semelhantes, mas de ambientes diferentes (validação geográfica) (45).

3.2.2 Avaliação de desempenho

A avaliação de desempenho de escores prognósticos é essencial para garantir o grau de confiabilidade e precisão destes modelos. Dentre as medidas de desempenho mais utilizadas, podemos citar a discriminação e a calibração.

A discriminação é uma métrica que avalia a capacidade de um modelo em distinguir entre os indivíduos aqueles que desenvolverão o desfecho e aqueles que não o farão. Normalmente, ela é estimada pelo índice de concordância (índice-c), que se iguala à AUROC em estudos de predição com desfechos binários, refletindo a probabilidade de que o escore designe um risco maior para o paciente com o desfecho do que o sem o desfecho.

A curva ROC é representada preferencialmente por meio de gráfico, sendo plotado entre sensibilidade (taxa de verdadeiro positivo) no eixo Y, por 1 menos especificidade (taxa de falso positivo) no eixo X, em pontos de corte consecutivos para a probabilidade do desfecho (47). A interpretação se dá com a área sob a curva característica de operação do receptor (AUROC), em que quanto mais próximo de 1, melhor a capacidade do modelo em predizer corretamente os resultados (45). Valores abaixo de 0.7 são considerados como ruins, entre 0,7 e 0,8 regulares, entre 0,8 e 0,9 como bons e acima de 0,9 excelentes (48).

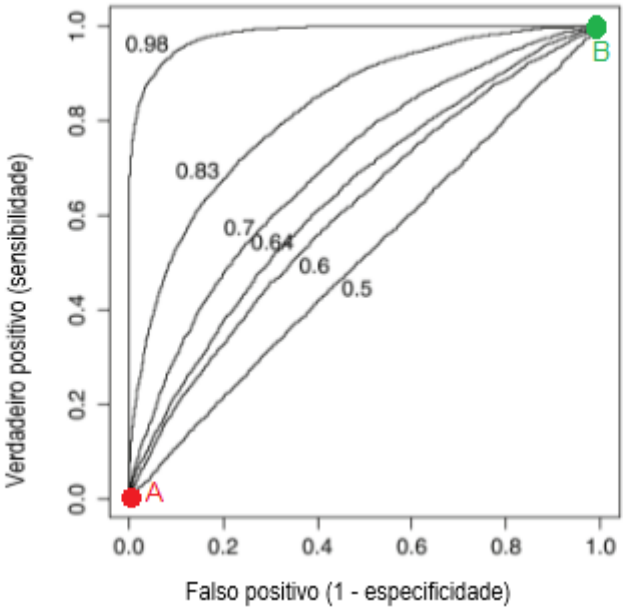

Figura 3. Interpretação da área sob a curva ROC. A: Todos os valores são preditos como zero, não havendo verdadeiros ou falsos positivos; B: Todos os valores são preditos como um, logo, todos os verdadeiros positivos são classificados

corretamente e, consequentemente, todos os falsos positivos. **Fonte:** Adaptado de "*Clinical prediction models: a practical approach to development, validation, and updating*" (Steyerberg, 2019) (47).

Já a calibração analisa o grau de concordância entre as previsões de risco feitas pelo modelo e as taxas reais observadas. Ela fornece uma representação gráfica de quão bem o modelo ajusta suas previsões à realidade. Uma curva de calibração ideal acompanha a linha de 45 graus, indicando uma previsão perfeitamente calibrada. Quanto mais acima da linha de base, mais o escore superestimou o risco, e, consequentemente, quanto mais abaixo, mais subestimou (45).

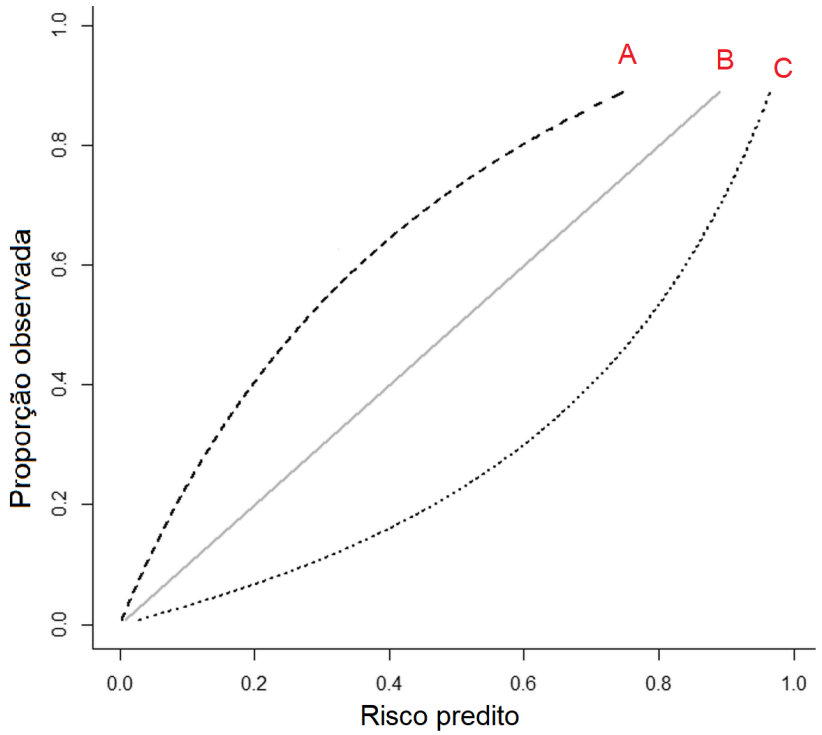

Figura 4. Interpretação da curva de calibração. A: Risco subestimado; B: Calibração ideal; C: Risco superestimado. **Fonte:** Adaptado de "*Calibration: the Achilles heel of predictive analytics*" (Calster, 2019) (49).

4. OBJETIVOS

4.1 Objetivo geral

- Desenvolver um escore de risco de mortalidade intra-hospitalar para pacientes brasileiros com covid-19 internados em UTIs, usando dados obtidos à admissão neste setor.

4.2 Objetivos específicos

- Avaliar a performance do novo escore desenvolvido;
- Comparar o novo escore desenvolvido com escores previamente desenvolvidos especificamente para pacientes com covid-19 (ABC_2-SPH, Atschul et al., Modified CHA_2DS_2-VASc, COVID-SOFA, SOARS, and 4C Mortality Score);
- Comparar o novo escore com outros escores desenvolvidos para outras condições e que foram testados previamente para covid-19 (CURB-65, SOFA, NEWS2);
- Avaliar a acurácia do escore nos subgrupos classificados por status vacinal.

5. MATERIAIS E MÉTODOS

5.1 Desenho do estudo

Esse estudo é parte do "Registro Hospitalar Multicêntrico Nacional de Pacientes com Doença Causada pelo SARS-CoV-2 (covid-19)", uma coorte multicêntrica retrospectiva, que incluiu 41 hospitais em 18 cidades, localizados em seis estados brasileiros (1,2). O desenvolvimento do escore seguiu as regras do TRIPOD e do PROBAST (45,46).

5.2 Critérios de inclusão

Foram incluídos pacientes adultos (≥ 18 anos) consecutivos, com confirmação laboratorial de covid-19, feita através do método RT-PCR (*reverse transcription - polymerase chain reaction*) ou teste de antígeno, seguindo as recomendações da Organização Mundial da Saúde (OMS) (50), admitidos em UTIs de um dos 18 hospitais participantes, durante o período de 1 de setembro de 2021 a 12 de julho de 2022. Apesar da coorte multicêntrica contar com a participação de 41 hospitais, no período específico de coleta de dados do presente estudo apenas 18 hospitais contavam com coleta de dados com admissões em UTI. A escolha do período se deu devido à grande variação de mortalidade e de perfil destes pacientes com o surgimento de novas variantes e expansão da vacinação, que poderiam potencialmente impactar no desempenho e na aplicabilidade do escore (51).

5.3 Critérios de exclusão

Foram excluídas pacientes grávidas, aqueles em tratamento paliativo exclusivo, admitidos por outro motivo e que desenvolveram covid-19 durante a internação, pacientes transferidos para outros hospitais não participantes da coorte e cujo desfecho não estava disponível.

5.4 Coleta de dados

Características clínicas, dados demográficos, achados laboratoriais, intervenções terapêuticas e desfecho foram coletados dos prontuários médicos por pesquisadores treinados. Os dados foram armazenados na plataforma REDCap (*Research Electronic Data Capture*) (52,53), no site do Centro de Telessaúde do Hospital das Clínicas da Universidade Federal de Minas Gerais (UFMG) (54). Para esta análise, foi considerada apenas a primeira admissão na UTI durante a

internação, caso o paciente tenha mais de uma.

Para garantir a precisão e qualidade dos dados, todas as informações foram verificadas periodicamente. Valores atípicos foram identificados, usando um código desenvolvido no *software* R, com base em regras estabelecidas de profissionais de referência, e posteriormente, enviados a cada hospital para verificação e correção (2).

5.5 Desfecho

O desfecho principal foi mortalidade intra-hospitalar.

5.6 Análise estatística

Variáveis contínuas foram testadas e, pelo padrão de distribuição não normal, foram então descritas usando medianas e intervalos interquartis (IIQ). Variáveis categóricas foram apresentadas em números absolutos e porcentagens. Este estudo relata intervalos de confiança de 95%, e considera p-valor <0.05 como estatisticamente relevante. Toda a análise foi realizada através do *software* R (versão 4.0.2), usando os pacotes mgcv, finalfit, mice, glmnet, pROC, rms, rmda, e psfmi.

Variáveis candidatas a preditores que estavam indisponíveis para mais de dois terços dos pacientes foram excluídas. Valores faltantes nas variáveis foram imputados utilizando imputação multivariada por equações encadeadas (MICE), exceto desfechos, cuja informação estava disponível para todos os participantes incluídos no presente estudo.

5.7 Desenvolvimento do escore de risco

Pacientes admitidos de 1 de setembro de 2021 a 12 de julho de 2022 foram incluídos na coorte de desenvolvimento. Todas as variáveis foram obtidas à admissão na UTI, exceto o desfecho. Possíveis preditores para mortalidade em UTI foram selecionados com base em literatura (Tabela 1).

Quarenta e seis possíveis preditores foram identificados. Primeiramente foi avaliada a frequência de dados faltantes, em que oito variáveis foram excluídas por mais de dois-terços de dados faltantes. Em seguida, foi avaliada a ocorrência de colinearidade. Dez preditores com alta colinearidade (forte correlação com outros) não foram incluídos.

Tabela 1. Possíveis preditores para o desenvolvimento do modelo.

Variáveis	Evidência científica	Desenvolvimento do modelo
ALT (U/L)	Radivojevic A (55)	> ⅔ dos dados faltantes
AST (U/L)	Radivojevic A (55)	> ⅔ dos dados faltantes
Bilirrubina total (mg/dL)	SOFA (56)	> ⅔ dos dados faltantes
D-dímero (ng/mL)	Dessie ZG (26); Taylor EH (57); Citu C (58)	> ⅔ dos dados faltantes
Ferritina (ng/mL)	Taylor EH (57);	> ⅔ dos dados faltantes
PTTa (segundos/controle)	Citu C (58)	> ⅔ dos dados faltantes
Temperatura (ºC)	NEWS-2 (59)	> ⅔ dos dados faltantes
Troponina	Salvatici M (60)	> ⅔ dos dados faltantes
Creatinina (mg/dL)	SOFA (56); Verfasst von AZ (61)	Alta colinearidade com ureia
HCO_3	Sada K (62)	Alta colinearidade com pCO_2 e pH
Lactato	Verfasst von AZ (61)	Alta colinearidade com proteína C-reativa
Leucócitos (cels/mm^3)	Taylor EH (57)	Alta colinearidade com RNL
Linfócitos (cels/mm^3)	Taylor EH (57)	Alta colinearidade com RNL
Neutrófilos (cels/mm^3)	Taylor EH (57)	Alta colinearidade com RNL
pH	Verfasst von AZ (61)	Alta colinearidade com pCO_2 e HCO_3
Pressão diastólica/uso de aminas	CURB-65 (63)	Alta colinearidade com pressão sistólica/uso de aminas
RNI	Zinellu A (64)	Alta colinearidade com d-dímero, PTTa e plaquetas
SpO_2/FiO_2	Choi K (65)	Alta colinearidade com pO_2/FiO_2

Acidente vascular cerebral	Singh AK (66)	Incluída no modelo
Diabetes mellitus	Dessie ZG (26); Taylor EH (57); Verfasst von AZ (61); Parohan M (67)	Incluída no modelo
Doença arterial coronariana	Dessie ZG (26); Taylor EH (57); Singh AK (66); Parohan M (67)	Incluída no modelo
Doença renal crônica	Taylor EH (57); Singh AK (66)	Incluída no modelo
DPOC	Dessie ZG (26); Taylor EH (57); Singh AK (66); Parohan M (67)	Incluída no modelo
ECG <15	SOFA (56); NEWS-2 (59); CURB-65 (63)	Incluída no modelo
Ex ou tabagismo atual	Dessie ZG (26); Taylor EH (57)	Incluída no modelo
Fibrilação atrial/Flutter	Szarpak L (68)	Incluída no modelo
Frequência cardíaca	NEWS-2 (59)	Incluída no modelo
Frequência respiratória (irpm)	NEWS-2 (59); CURB-65 (63)	Incluída no modelo
Hemoglobina (g/dL)	Jha M (69); Oh SM (70)	Incluída no modelo
Hipertensão arterial sistêmica	Dessie ZG (26); Taylor EH (57); Hofmeyr R (71); Parohan M (67)	Incluída no modelo
Idade (anos)	Dessie ZG (26); Taylor EH (57); Verfasst von AZ (61); Hofmeyr R (71); Parohan M (67); CURB-65 (63)	Incluída no modelo
Insuficiência cardíaca	Dessie ZG (26); Taylor EH (57); Singh AK (66); Parohan M (67)	Incluída no modelo
Neoplasia maligna	Dessie ZG (26); Taylor EH (57); Singh AK (66); Parohan M (67)	Incluída no modelo
Obesidade	Dessie ZG (26);	Incluída no modelo

	Najafabadi BT (72)	
pCO_2	Kaç A (73)	Incluída no modelo
Plaquetas (cels/mm^3)	SOFA (56); Taylor EH (57)	Incluída no modelo
Proteína C-reativa (mg/L)	Verfasst von AZ (61)	Incluída no modelo
pO_2/FiO_2	SOFA (56); Taylor EH (57)	Incluída no modelo
Pressão sistólica/uso de aminas	SOFA (56); CURB-65 (63); Hofmeyr R (71)	Incluída no modelo combinada com uso de inotrópicos
RNL	Liu (74)	Incluída no modelo
Sexo masculino	Dessie ZG (26); Parohan M (67)	Incluída no modelo
Sódio (mmoL)	NG WY (75); Wolf JM (76)	Incluída no modelo
Ureia (mg/L)	CURB-65 (63)	Incluída no modelo
Uso de anticoagulante profilático ou terapêutico antes da admissão na UTI	Jiang L (77); Parisi R (78)	Incluída no modelo
Uso de dexametasona ou outro corticoide oral antes da admissão na UTI	Sarma P (79)	Incluída no modelo
VMI à admissão na UTI	Taylor EH (57)	Incluída no modelo combinada com frequência respiratória

ALT: alanina aminotransferase; AST: aspartato aminotransferase; HCO_3: bicarbonato; DPOC: doença pulmonar obstrutiva crônica; ECG: escala de coma de Glasgow; pCO_2: pressão parcial de dióxido de carbono; pO_2: pressão parcial de oxigênio; FiO_2: fração inspirada de oxigênio; PTTa: tempo de tromboplastina parcial ativada; RNI: relação normatizada internacional; RNL: relação neutrófilo-linfócito; SpO_2: saturação de oxigênio; UTI: unidade de terapia intensiva; VMI: ventilação mecânica invasiva.

A seleção de preditores para a mortalidade na UTI foi realizada através dos modelos aditivos generalizados (GAM). A principal vantagem desses modelos em relação aos modelos de regressão linear ou os tradicionais modelos lineares generalizados é que os modelos GAM são mais flexíveis por buscar relações não necessariamente lineares entre os possíveis preditores e a mortalidade (80).

As variáveis contínuas selecionadas então foram categorizadas com base em pontos de corte já comumente reconhecidos, e/ou categorias de escores já estabelecidos, conforme recomendado pelo TRIPOD (45). Em seguida, foi usada a regressão logística *Least Absolut Shrinkage and Selection Operator* (LASSO) para derivar os coeficientes de cada variável que foram escalados para obter a pontuação de cada categoria e, consequentemente, a fórmula para calcular a pontuação final do escore.

Os grupos de risco foram propostos com base na probabilidade do risco de mortalidade, conforme recomendado pelo TRIPOD (45). A definição das categorias de risco (intermediário, alto e muito alto) foi feita com base em outros escores (81).

5.8 Avaliação de performance

A AUROC foi usada para descrever a discriminação do modelo. A performance geral foi avaliada pelo escore de Brier (82). A calibração foi avaliada graficamente plotando as probabilidades de mortalidade esperada e observada, com o teste de intercepto igual a zero e inclinação igual a um.

5.9 Comparação dos modelos

Em uma análise de casos completos, o modelo desenvolvido foi comparado com outros escores desenvolvidos especificamente para paciente com covid-19, como ABC_2-SPH, Altschul et al., CHA_2DS_2-VASc Modificado, COVID-SOFA, e 4C Mortality Score (2,81,83–85), além de outros escores desenvolvidos para outras condições e que foram testados previamente para covid-19, como CURB-65, SOARS, SOFA, NEWS2 (56,59,63,86) usando a AUROC. Estes escores foram identificados através de uma busca na base de dados *Medline*, sem restrições de linguagens, usando os termos “covid-19” e “coronavírus” combinados com “mortalidade” e “escore”, tendo a busca sido realizada em dezembro de 2022. Foram incluídos na análise aqueles escores que foram amplamente testados previamente para covid-19, mesmo aqueles desenvolvidos para outra finalidade ou que predizem desfechos distintos. Além disso, foram incluídos outros escores de risco já estabelecidos e usados em UTIs para pneumonia e sepse, que foram previamente aplicados para pacientes com covid-19. Entretanto, foram selecionados apenas escores com variáveis disponíveis em nossa base de dados. O método DeLong com a correção de Bonferroni foi usado para comparar o AUROC do escore desenvolvido

com os dos demais. As diferentes calibrações foram avaliadas graficamente comparando os escores que tinham dado para tal.

5.10 Aspectos éticos

O protocolo do estudo foi aprovado pela Comissão Nacional de Ética em Pesquisa (CAAE: 30350820.5.1001.0008). O consentimento informado individual foi dispensado devido à gravidade da situação e ao uso de dados não identificados, com base apenas na revisão do prontuário. Todos os procedimentos estão de acordo com os padrões éticos e com a Declaração de Helsinki de 1975.

6. RESULTADOS E DISCUSSÃO

Os resultados serão apresentados em formato de artigo científico, que foi publicado na revista *Respiratory Medicine*, Qualis A2.

AB_2CO risk score for in-hospital mortality of COVID-19 patients admitted to intensive care units

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Highlights

- An effective tool to predict in-hospital mortality in ICU COVID-19 patients is still lacking.

- The AB_2CO includes 6 variables: age, pO_2/FiO_2, respiratory rate or if in IMV, COPD, and obesity.

- The score presented a good discrimination ability and an excellent calibration plot.

- It is a simple and easy tool that may help guide clinical decisions.

Abstract

Purpose: To develop a mortality risk score for COVID-19 patients admitted to intensive care units (ICU), and to compare it with other existing scores.

Materials and Methods: It is a retrospective observational study, including consecutive adult patients with laboratory-confirmed COVID-19 admitted to ICUs of 18 hospitals from nine Brazilian cities, from 09/2021 to 07/2022. Potential predictors were selected based on the literature review. Generalized Additive Models were used to examine outcomes and predictors. LASSO regression was used to derive the mortality score.

Results: From 558 patients, median age was 69 years (IQR 58-78), 56.3% were men, 19.7% required mechanical ventilation (MV), and 44.8% died. The final model comprised six variables: age, pO_2/FiO_2, respiratory function (respiratory rate or if in MV), chronic obstructive pulmonary disease, and obesity. The AB_2CO had an AUROC of 0.781 (95% CI 0.744 to 0.819), good overall performance (Brier score=0.191) and an excellent calibration (slope=1.063, intercept=0.015, p-value=0.834). The model was compared with other scores and displayed better discrimination ability than the majority of them.

Conclusions: The AB_2CO score is a fast and easy tool to be used upon ICU admission.

Keywords: COVID-19; intensive care unit; prognosis; mortality; risk factors.

Introduction

Even with the expansion of COVID-19 vaccination worldwide, it is estimated that the disease still evolves into mortality in up to 40.3% of cases requiring intensive care units (ICU) [1,2]. Numbers are even higher in specific populations like elderly patients [3], and exceed 68% in those who require mechanical ventilation [4].

Severity scores are commonly used in the critical care setting, to facilitate the allocation of resources to those most at risk, aiming at improving assistance and reducing mortality [5]. Previously known risk scores, as well as disease-specific new tools, have been tested in COVID-19 patients admitted to the ICU, with an average performance at most [5–7]. Despite being commonly used to predict outcomes at the ICU, those scores presented low accuracy for COVID-19. In addition, most scores were tested before the broad use of COVID-19 vaccination, which may impair overall performance significatively [5,6,8].

Although Brazil was one of the most affected countries in terms of COVID-19 cases and deaths, with a significant burden in the healthcare system, validation studies of such scores among Brazilian COVID-19 patients are scarce, and the studies available have methodological limitations [9–11]. In another study from our research group, we assessed prediction ability on a few scores using data from October 2020 to March 2022, including a score we developed to be used at the moment of hospital admission, the ABC_2-SPH. All of them showed intermediate discrimination ability with inadequate calibration plots [12].

Therefore, we aimed to develop an in-hospital mortality prediction risk score for COVID-19 patients admitted to ICU and to compare it with other existing scores.

Materials and Methods

This study is part of the Brazilian COVID-19 Registry, a retrospective multicenter cohort, which originally included 41 hospitals in 18 cities from six Brazilian states, described in detail elsewhere [13,14]. Model development followed the Transparent Reporting of a Multivariable Prediction Model for Individual Prediction or Diagnosis (TRIPOD) checklist (Supplementary file 1) and the Prediction model Risk Of Bias Assessment Tool (PROBAST) (Supplementary file 2) [15,16].

Study subjects

This study included consecutive adult patients (≥ 18 years) with laboratory-confirmed COVID-19 through SARS-CoV-2 reverse transcription-polymerase chain reaction (RT-PCR) or antigen test, according to the World Health Organization guidance [17], admitted to the ICU of one of the eighteen participating hospitals, from September 1, 2021, to July 12, 2022. Pregnant women, patients in palliative care, those admitted for another reason and who developed COVID-19 symptoms while in-hospital, patients transferred to another hospital not part of the cohort, and those whose outcome was not available were excluded (Figure 1).

Data collection

Demographic data, clinical characteristics, laboratory findings, therapeutic interventions, and outcomes were collected by trained researchers from medical records using the Research Electronic Data Capture (REDCap) electronic platform [18,19], hosted at the Telehealth Center of the *Hospital das Clínicas*, *Universidade Federal de Minas Gerais* (UFMG) [(54). The guidance manual for ICU data collection is available in the supplementary file (Supplementary file 3). For this study, we considered only the first ICU admission during the hospital stay.

To ensure data accuracy, all information was verified periodically. Values of possible data entry errors were identified by using a code developed in R software and based on expert-guided rules. Then, it was sent to each hospital for checking and correction [14].

Outcome

The primary outcome was all-cause in-hospital mortality.

Sample size

All eligible patients admitted to the participating ICUs during the study period were included.

Statistical analysis

Continuous variables were described using medians and interquartile ranges (IQR) and categorical variables were presented as absolute and relative frequencies. This study reported 95% confidence intervals, and a p-value <0.05 was considered

statistically significant. All analysis was performed with R software (version 4.0.2), using the mgcv, finalfit, mice, glmnet, pROC, rms, rmda, and psfmi packages.

Missing data

Candidate predictor variables that were unavailable for at least two-thirds of patients were excluded. Missing values on candidate explicative variables were imputed using multiple imputations with chained equations (MICE).

Development of the risk score model

Patients admitted from September 1, 2021, to July 12, 2022, were included in the development cohort. All variables used were obtained at ICU admission, except for the outcome. Potential predictors for ICU in-hospital mortality were selected based on previous literature (Supplementary file 4). Then we assessed the frequency of missing data (Supplementary file 5). Those predictors with high collinearity were not included.

Generalized Additive Models (GAM) were used to assess the relationships between outcome (in-hospital mortality) and continuous and categorical predictors (Supplementary file 6). Then, continuous variables selected were categorized for LASSO logistic regression analysis, based on commonly recognized cut points, and/or categories described in well-established score systems (Supplementary file 7). The risk groups were proposed based on the probability of mortality risk, as recommended by the TRIPOD [15] guidelines.

Performance measures

The area under the receiver operating characteristic curve (AUROC) was used to describe the model discrimination. The general performance was evaluated through the Brier score [21]. The calibration was evaluated graphically by plotting the predicted probabilities of mortality compared to the observed mortality, with an intercept test equal to zero and a slope equal to one.

Model comparisons

On a complete case analysis, the developed model was compared with other existing scores, such as ABC_2-SPH, SOFA, Atschul et al., 4C Mortality Score, CURB-65, SOARS, Modified CHA_2DS_2-VASc, NEWS2, and COVID-SOFA score

[14,22–29] using AUROC. These scores were identified through a literature search of Medline, without any language restrictions, using the terms “COVID-19” and “coronavirus” combined with “mortality”, and “score”. Additionally, other established risk scores used in ICUs for pneumonia and sepsis which were previously tested to be used for COVID-19 patients were included as well. Those scores with variables available in our database were selected. The DeLong method with Bonferroni correction was used to make pairwise comparisons between the AUROCs of the developed score and the other scores.

Subanalysis

In order to understand the accuracy of the developed model in vaccinated and unvaccinated patients, we have incorporated an analysis stratifying by vaccination status.

Results

Of 558 patients, 56.3% were men, the median age was 69 (IQR 58-78) years old, 19.7% required mechanical ventilation before or at the moment of ICU admission, and 44.8% died during hospitalization. Demographic and clinical characteristics, as well as laboratory findings for the derivation cohort, are displayed in Table 1.

Forty-six potential predictor variables were identified (Supplementary file 5). Eight variables were excluded due to excessive missing values. Ten were excluded for high collinearity. Respiratory rate and mechanical ventilation were combined into a single variable. Thus, a total of twenty-seven variables were tested. A combination of six variables was selected through GAM as the best predictors of ICU in-hospital mortality (Supplementary file 6). The final model, named AB_2CO, was composed of: age, pO_2/FiO_2, respiratory function (respiratory rate or if in mechanical ventilation), chronic obstructive pulmonary disease (COPD), and obesity.

The prognostic index was created by scaling shrink coefficients. The sum of the prediction scores ranged from 0 to 16, with a higher score indicating a higher risk of death (Tables 2 and Supplementary file 7). Risk groups were divided based on predicted death probability (Supplementary file 8) as intermediate risk (0 score, predicted mortality <15%), high risk (1-5 score, 15-49,9%), and very high risk (6-16 score, ≥50%) (Table 3).

The AB_2CO score had an AUROC of 0.781 (95% CI 0.744 to 0.819), good overall performance (Brier score=0.191), and adequate calibration (slope=1.063, intercept=0.015, p-value=0.834) (Figures 2 and 3). All other scores evaluated (ABC_2-SPH, SOFA, Atschul et al., 4C Mortality Score, CURB-65, SOARS, Modified CHA_2DS_2-VASc, NEWS2, and COVID-SOFA score) had poor to average discrimination ability.

On a complete case analysis, the AB_2CO score achieved a discrimination ability of 0.783 (CI 95% 0.743-0.822) better than SOFA, NEWS2, SOARS, Atschul et al., CURB-65 and modified CHA_2DS_2-VASc. Although not statistically significant, it showed higher AUROC than the 4C Mortality Score and COVID-SOFA, and better calibration plots than both of them, and also than ABC_2-SPH, despite slightly worse AUROC, as shown in Table 4 and Supplementary file 9.

In the subanalysis, we stratified patients through vaccination status. From a total of 558 patients, 198 (35.5%) had missing information. From 251 patients who received 2 or more vaccine shots, we had 211 complete cases (with no missing cases for the score variables and 122 deaths. The AUROC was 0.801 (95% IC 0.739-0.856). A total of 25 patients received only one shot, with 17 complete cases The AUROC was 0.700. The small sample size provided a large confidence interval (95% IC 0.417-0.917). From those 84 who did not receive any covid-19 shot, there were 68 complete cases. The AUROC of 0.781 (95% IC 0.660-0.881). Calibration curves were inadequate for those patients who received only one COVID-19 shot, slightly overestimated mortality in those at most risk who received two or more shots, and underestimated mortality in those at lower risk who did not receive any (Supplementary file 10).

Discussion

This study aimed to develop a new risk score for in-hospital mortality of COVID-19 patients admitted to 18 ICUs in Brazil. The novel score is composed of six readily available variables, three demographic characteristics (age, COPD, and obesity), and three clinical parameters observed upon ICU admission (pO_2/FiO_2, respiratory rate or whether the patient is in invasive mechanical ventilation). It showed a good discrimination ability in predicting mortality, superior to most of the scores chosen for comparison in this study, with an excellent calibration plot.

Several authors have tested the performance of severity scores traditionally used in critically ill patients. However, most of them are bound by methodological flaws which may lead to different biases [11]. Although TRIPOD guidelines have not disclosed the exact sample size needed for developing a prediction model, it is known that providing more reliable results requires larger samples. For validation studies, it is recommended a minimum of 100 events and 100 nonevents, preferably more than 250 events [30]. Many of the analyzed studies included small samples which may have overestimated the models' performance. For example, Zou et al. (2020) assessed the performance of APACHE II, SOFA, and CURB-65 scores in only 154 ICU COVID-19 patients in China, although they observed an excellent discrimination ability (APACHE II: AUROC 0.966, SOFA: 0.867, CURB-65 0.844), the small sample size from one single center does not allow the generalization of the data [31].

In this study, we reported details about missing data and imputation methods, as recommended in TRIPOD guidelines. Excluding cases with missing values in score derivation studies may reduce sample size and also lead to biases when complete cases are not representative of the whole cohort [30]. Many studies did not or poorly disclose information on missing data, like another two recently published Brazilian studies [9,10] and the Modified CHA_2DS_2-VASc used in the comparison analysis [27], and data, in general, can be missing selectively rather than fully at random, which can lead to bias [30].

Performance measurements should also be adequately reported. Calibration and discrimination are the two most used aspects. Calibration measures how well the model's predictions match the results that were actually seen, and discrimination describes a prediction model's capacity to distinguish between people who experience the outcome and those who do not [30]. An important study carried out in Brazil with 30,571 patients evaluated the SAPS-3 ability to predict mortality in ICU COVID-19 patients and the model's discrimination was highly satisfactory, with an AUROC of 0.835 (0.828–0.841). However, the calibration curve was inappropriate. Mortality was underestimated in those most at risk, and slightly overestimated in those at low to moderate risk. Additionally, the authors included data from a private healthcare network only, which may not reflect the reality of most of the Brazilian population, especially with a substantially lower mortality of 15% [32], when compared to our database (44.8%), in which 72.2% of the cohort's hospitals serve

public patients, and also, we included more updated data, being more reliable for the actual scenario.

Commonly used risk scores, such as SOFA, NEWS2, and CURB-65 showed an intermediate performance (AUROC of 0.660, 0.691 and 0.658, respectively). Those scores were widely tested for COVID-19 patients, despite being developed for other clinical situations, such as organ failure assessment, early warning for clinical deterioration, and to help determine inpatient or outpatient treatment for community-acquired pneumonia. The same was observed with other scores developed exclusively for COVID-19 patients, such as Altschul, SOARS and Modified CHA_2-DS_2-VASc (0.686, 0.680, and 0.5922 respectively). The COVID-SOFA score, developed exclusively for ICU COVID-19 patients, showed a good AUROC of 0.763, worse than our developed score. Also, despite showing a good AUROC, 4C Mortality Score and ABC_2-SPH showed poor calibration plot, showing that it is not possible to use them in actual scenarios, despite showing a good performance in their original studies when developed.

The emergence of new variants and vaccination efforts across time resulted in temporal changes in the mortality profile, as well the importance of different predictors [33]. To the extent of our knowledge, all of the developed risk scores for predicting mortality in COVID-19 patients admitted to the ICU did not consider it, and all of them were performed using patients from the early pandemic (Supplementary file 4). Therefore, they need to be validated in more recent scenarios, as it impacts the score's accuracy [33]. These reasons may explain in part the difference in results from what we have observed in the current analysis from those previously published, in addition to the aforementioned methodological limitations of the previous studies.

The AB_2CO score is a simple and objective method that can be used to determine the probability of death in COVID-19 patients using data easily and routinely obtained at ICU admission. Furthermore, this score is reliable, as we strictly follow the methodological guidelines recommended by TRIPOD and PROBAST, ensuring quality data. Additionally, the choice of the variables was made based on systematic reviews, meta-analysis, previous cohort studies, and clinical reasoning, rather than the potentially biased selection of predictors. Finally, our findings are in line with previous evidence, as the predictors included in the score are well-established risk factors associated with disease severity and poor outcomes in COVID-19 patients.

Age was contemplated as an important risk factor for mortality among COVID-19 patients [34,35], due to increased cytokine production and decreased humoral immune response [36], in addition to the presence of some chronic medical conditions related to aging [35]. Obesity was linked with worse outcomes in several studies [35,37,38]. It is hypothesized that the mechanical pressure on the chest and abdomen reducing pulmonary function and the increased proinflammatory state related to excessive ectopic visceral fat might be the reason for the increased risk [37]. COPD was associated with mortality risk in previous studies as well [35,39,40]. It might be related to impaired recovery, with increased systemic inflammation [35]. The pO_2/FiO_2 ratio is a clinical measurement that assesses the severity of respiratory dysfunction [41,42], and it have already been shown that mortality is significantly higher in patients in mechanical ventilation, partly due to the fact that patients who required mechanical ventilation have more severe disease and also, due to the inherited risks and complications of the procedure itself [43,44].

The novel score may be suitable for use in settings where accurate and rapid stratification of risk is important. To the best of our knowledge, it is the first score developed in Brazil to evaluate the in-hospital mortality of ICU COVID-19 patients considering more recent data, after the broad use of COVID-19 vaccines.

This study has some limitations. First, the inherent limitations of observational cohort studies. Second, missing information on the vaccination status of most of the patients included in the cohort, which may impair accuracy in different groups. Third, the absence of an adequate number of complete cases of SAPS-3 for comparison, as it is an important score used in ICU settings. And last, the lack of external validation analysis. Thus, before being used in clinical practice, it must be externally validated, and the model may be recalibrated accordingly whether necessary, to make sure its utilization in other healthcare settings [15]. In addition, further studies are needed to validate the score in the coming years, properly allocating resources, giving better chances of successful treatment and outcomes, with the new rising variants and vaccination expansion.

Conclusion

The AB_2CO score is a simple, objective, and easy tool to be used in ICU admission, based on only six variables: age, PaO_2/FiO_2, respiratory function

(respiratory rate or if in mechanical ventilation), COPD, and obesity, obtained routinely in institutions. This score showed a good discrimination ability and an excellent calibration curve when compared to other scores.

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Declarations

Ethics approval and consent to participate

The study protocol was approved by the Brazilian National Commission for Research Ethics (CAAE: 30350820.5.1001.0008). Individual informed consent was waived due to the severity of the situation and to the use of deidentified data, based on medical chart review only.

Data availability statement

Data is available upon reasonable request.

Guidance manual for data collection availability

The full guidance manual for data collection is available upon request.

Data Access, Responsibility, and Analysis

The lead authors (MSM and VMRG) had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Transparency declaration

The lead authors (MSM and VMRG) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

Conflicts of interest

The author(s) declared no potential conflicts of interest concerning the research, authorship, and/or publication and/or competing financial of this article.

Role of the funder/sponsor

The sponsors had no role in study design; data collection, management, analysis and interpretation; writing the manuscript; and decision to submit it for publication. MSM and VMRG had full access to all the data in the study and had responsibility for the decision to submit it for publication.

Author contribution

Substantial contributions to the conception or design of the work: VMRG, MCP and MSM.

Substantial contributions to the acquisition, analysis, or interpretation of data for the work: all authors.

Drafted the work: VMRG, PDP, VN and MSM.

Revised the manuscript critically for important intellectual content: all authors.

Final approval of the version to be published: all authors.

Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: VMRG, MCP and MSM.

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Figures

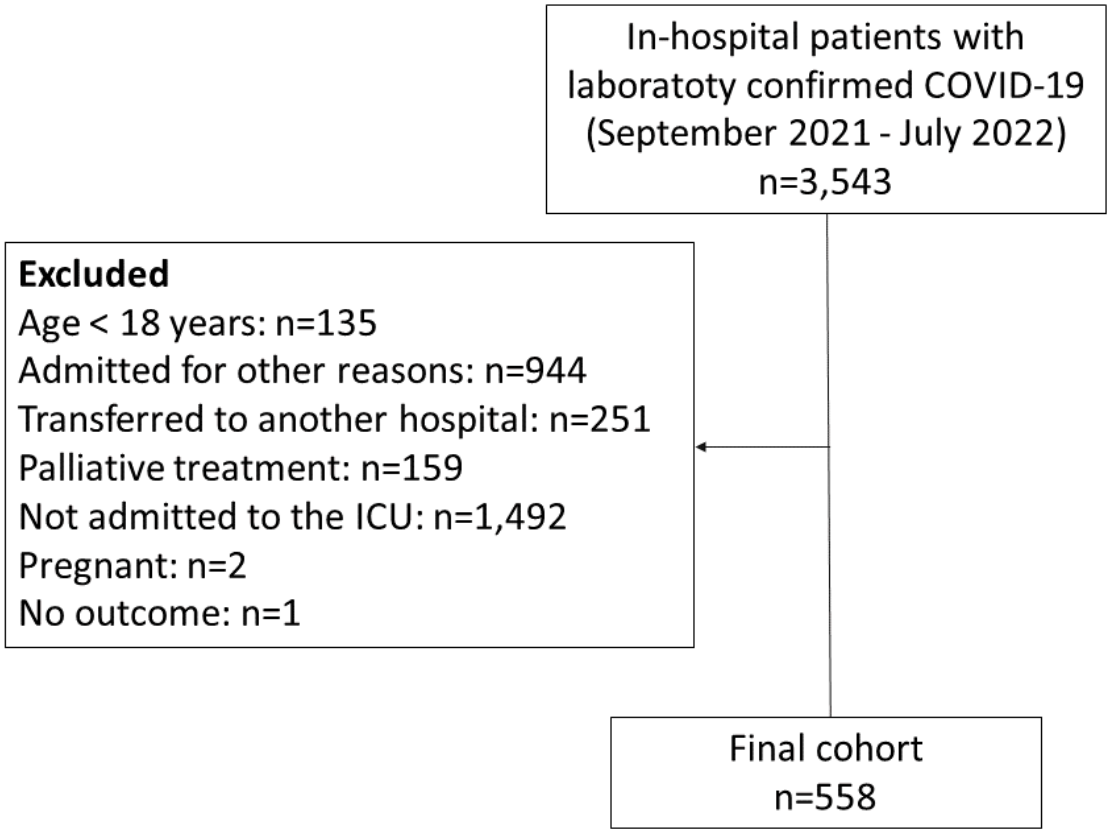

Figure 1. Flowchart of COVID-19 patients included in the study.

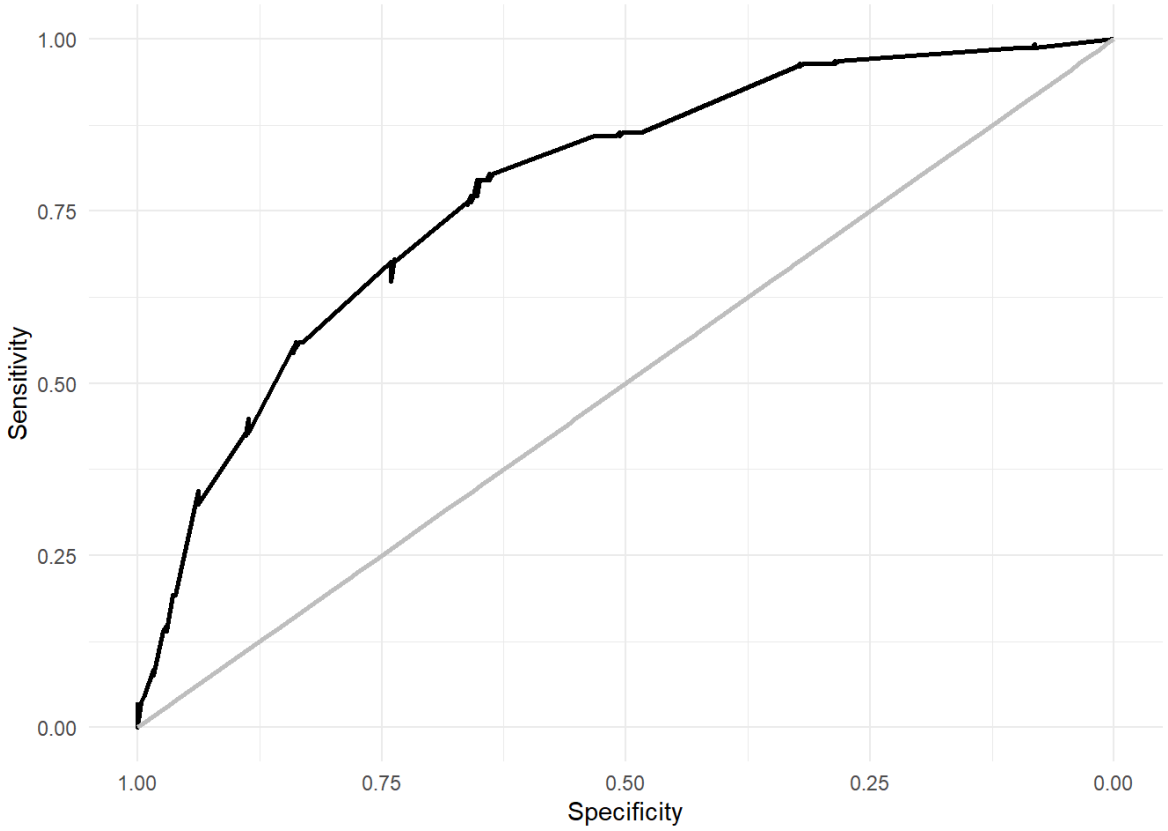

Figure 2. Area under the ROC curve of the AB_2CO risk score.

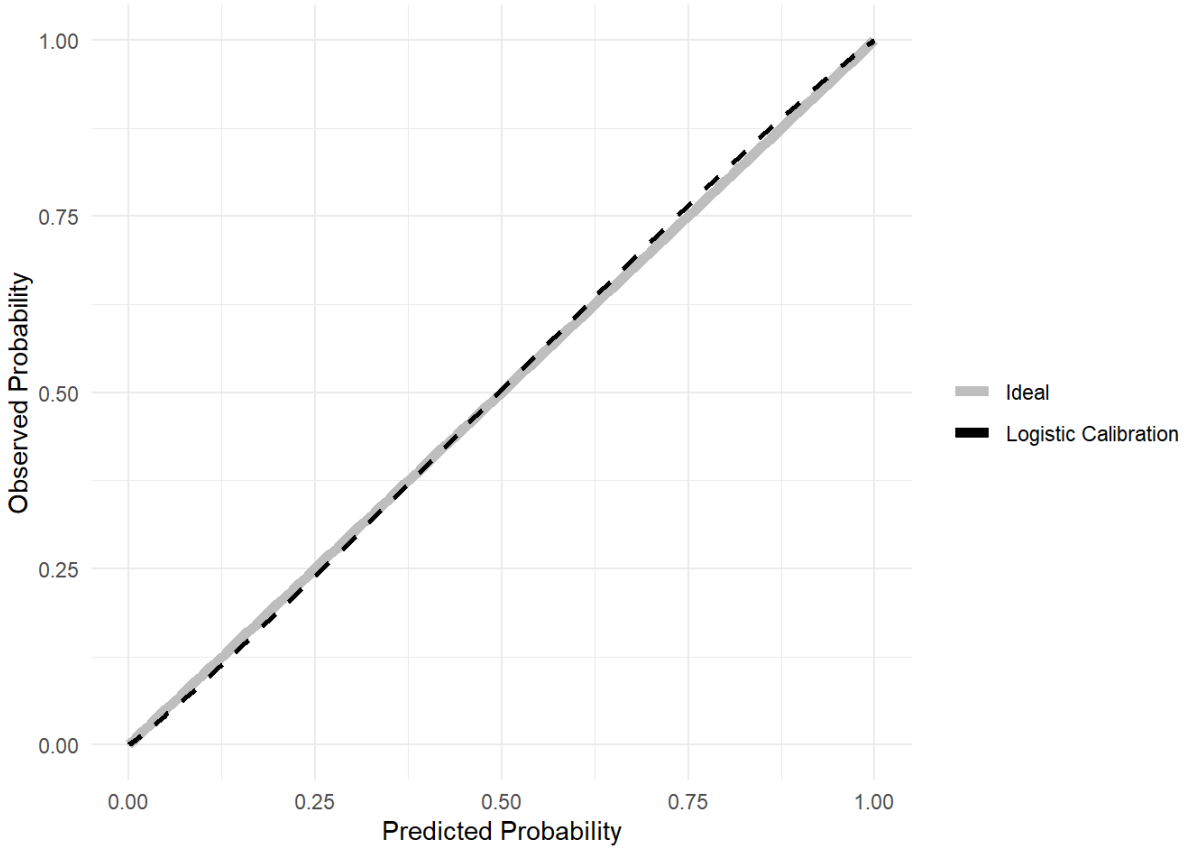

Figure 3. Calibration plot of the AB_2CO risk score

Tables

Table 1. Clinical and demographic characteristics of patients included in this study (n=558).

Characteristics	Overall[1]	Discharge[1]	Death[1]	p-value
Age (years)	69.0 (58.0, 78.0)	65,0 (53,0, 76,0)	73.0 (64.0, 81.0)	<0.001
Sex at birth (Male)	314 (56.3%)	167 (54.2%)	147 (58.8%)	0.278
Comorbidities				
Number of comorbidities				
0	120 (21.5%)	75 (24.4%)	45 (18.0%)	
1	136 (24.4%)	77 (25.0%)	59 (23.6%)	
2	169 (30.3%)	92 (29.9%)	77 (30.8%)	
3	93 (16.7%)	45 (14.6%)	48 (19.2%)	
4	29 (5.2%)	16 (5.2%)	13 (5.2%)	
5	9 (1.6%)	3 (1.0%)	6 (2.4%)	
6	2 (0.4%)	0 (0.0%)	2 (0.8%)	
Hypertension	348 (62.4%)	189 (61.4%)	159 (63.6%)	0.588
Coronary artery disease	47 (8.4%)	27 (8.8%)	20 (8.0%)	0.746
Heart failure	72 (12.9%)	41 (13.3%)	31 (12.4%)	0.749
Atrial fibrillation or flutter	26 (4.7%)	12 (3.9%)	14 (5.6%)	0.342
Stroke	28 (5.0%)	16 (5.2%)	12 (4.8%)	0.832
COPD	60 (10.8%)	22 (7.1%)	38 (15.2%)	0.002
Asthma	196 (35.1%)	101 (32.8%)	95 (38.0%)	0.200
Diabetes Mellitus	95 (17.0%)	44 (14.3%)	51 (20.4%)	0.056
Obesity (BMI >30 kg/m^2)	5 (0.9%)	1 (0.3%)	4 (1.6%)	0.179
Malignant neoplasm	49 (8.8%)	22 (7.1%)	27 (10.8%)	0.129
Chronic kidney disease	58 (10.4%)	30 (9.7%)	28 (11.2%)	0.574

HIV infection	9 (1.6%)	5 (1.6%)	4 (1.6%)	>0.999
Current smoker	46 (8.2%)	26 (8.4%)	20 (8.0%)	0.850
Ex-smoker	109 (19.5%)	51 (16.6%)	58 (23.2%)	0.049
Clinical assessment at ICU admission				
GCS < 15	81 (19.0%)	43 (16.2%)	38 (23.6%)	0.057
pO_2/FiO_2	160.0 (98.7, 285.7)	194.4 (115.6, 336.2)	128.3 (85.2, 186.5)	<0.001
Respiratory rate (breaths/minute)				<0.001
≤ 24	253 (45.3%)	180 (58.4%)	73 (29.2%)	
> 24	195 (34.9%)	100 (32.5%)	95 (38.0%)	
MV	110 (19.7%)	28 (9.1%)	82 (32.8%)	
Heart rate (beats/minute)	83.0 (74.0, 97.0)	80.0 (72.0, 94.0)	86.0 (76.0, 102.0)	<0.001
Systolic blood pressure (mmHg)				<0.001
≥ 90 (mmHg)	463 (85.9%)	275 (92.3%)	188 (78.0%)	
< 90 (mmHg)	11 (2.0%)	4 (1.3%)	7 (2.9%)	
Diastolic blood pressure (mmHg)				<0.001
> 60 (mmHg)	390 (73.0%)	233 (78.7%)	157 (66.0%)	
≤ 60 (mmHg)	79 (14.8%)	44 (14.9%)	35 (14.7%)	
Inotrope requirement	75 (13.6%)	24 (7.9%)	51 (20.7%)	<0.001
Laboratory parameters at ICU admission				
Urea (mg/dL)	53.9 (36.8, 85.2)	47.3 (32.0, 69.1)	62.1 (42.0, 95.5)	<0.001
Creatinine (mg/dL)	1.0 (0.8, 1.6)	0.9 (0.7, 1.3)	1.3 (0.9, 2.1)	<0.001
C-reactive protein (mg/dL)	113.5 (54.3, 192.0)	92.0 (40.7, 169.6)	144.5 (77.8, 218.5)	<0.001
pH	7.4 (7.3, 7.5)	7.4 (7.4, 7.5)	7.4 (7.3, 7.4)	<0.001

pO_2 (mmHg)	93.8 (70.3, 126.4)	96.9 (72.0, 125.1)	90.7 (67.6, 126.1)	0.297
pCO_2 (mmHg)	35.5 (31.3, 41.4)	35.1 (31.6, 40.0)	36.4 (31.0, 47.4)	0.018
HCO_3 (mg/dL)	22.6 (19.5, 25.4)	23.2 (20.6, 25.9)	21.4 (18.1, 25.0)	<0.001
Hemoglobin (g/L)	12.4 (10.6, 13.6)	12.4 (11.1, 13.6)	12.4 (10.3, 13.7)	0.664
Platelets (cels/mm^3)	197,000.0 (148,000.0, 258,000.0)	203,000.0 (159,000.0, 265,000.0)	183,000.0 (135,000.0, 246,750.0)	0.006
NLR	9.2 (5.3, 14.9)	7.3 (4.4, 12.0)	11.0 (7.1, 18.0)	<0.001
Sodium	138.0 (135.0, 141.0)	138.0 (135.0, 141.0)	138.0 (136.0, 142.0)	0.095
Leucocytes (cels/mm^3)	9,252.5 (6,707.5, 12,900.0)	8,800.0 (6,565.0, 11,860.0)	10,375.0 (7,120.0, 14,407.5)	<0.001
Neutrophils (cels/mm^3)	7,426.0 (5,097.5, 10,682.5)	6,826.0 (4,699.2, 9,307.2)	8,540.5 (5,507.2, 11,699.2)	<0.001
Lymphocytes (cels/mm^3)	830.0 (534.0, 1,278.5)	914.0 (581.0, 1,362.0)	727.5 (480.5, 1,120.8)	<0.001
Medications before ICU admission				
Dexamethasone	237 (42.5%)	123 (39.9%)	114 (45.6%)	0.178
Other oral corticosteroid	29 (5.2%)	18 (5.8%)	11 (4.4%)	0.445
Budesonide	15 (2.7%)	8 (2.6%)	7 (2.8%)	0.883
Other inhalatory corticosteroid	12 (2.2%)	7 (2.3%)	5 (2.0%)	0.825
Prophylactic anticoagulation	157 (28.1%)	77 (25.0%)	80 (32.0%)	0.067
Therapeutic anticoagulation	33 (5.9%)	19 (6.2%)	14 (5.6%)	0.777
Tocilizumabe	11 (2.0%)	8 (2.6%)	3 (1.2%)	0.360
Imunossupressor	24 (4.3%)	9 (2.9%)	15 (6.0%)	0.075
Outcomes				
Mechanical ventilation at ICU admission	110 (19.7%)	28 (9.1%)	82 (32.8%)	<0.001
In-hospital mortality	250 (44.8%)			

[1]Statistics presented: Median (IQR); n (%). BMI: body mass index; COPD: chronic obstructive pulmonary disease; FiO_2: fraction of inspired oxygen; GCS: Glasgow Coma Score; HCO_3: bicarbonate; HIV: immune deficiency virus; MV: mechanical ventilation; NLR: lymphocyte/neutrophil ratio; pCO_2: partial pressure of carbon dioxide; PaO_2: partial pressure of oxygen; SF ratio: SpO_2/FiO_2 ratio; SpO_2: Oxygen saturation.

Table 2. AB_2CO score for ICU mortality in patients with COVID-19.

	Variables	Score
A	**Age (years)**	
	<60	0
	60-79	1
	≥80	3
B_2	**pO_2/FiO_2**	
	>200	0
	100-200	1
	<100	4
	Respiratory function	
	≤24 breaths/minute	0
	>24 breaths/minute	1
	In mechanical ventilation	6
C	**COPD**	
	No	0
	Yes	2
O	**Obesity**	
	No	0
	Yes	1

COPD: chronic obstructive pulmonary disease; FiO_2: fraction of inspired oxygen; pO_2: partial pressure of oxygen.

Table 3. Predicted mortality and mortality rates in risk groups.

Risk	Score	Predicted mortality	Number of patients	Number of deaths (%)
Intermediate	0	< 15%	25	1 (6.3%)
High	1 - 5	15 - 49,9%	270	85 (31.5%)
Very high	6 - 16	≥ 50%	162	118 (72.8%)
	Overall	-	457	204 (44.6%)

Table 4. Discrimination ability for each risk score applied in the Brazilian database of COVID-19 patients admitted to the intensive care unit, and comparison of the derived and other existing scores.

Compared score	p-value	AUROC of the score used in the comparison	N*
ABC_2-SPH	0.380	0.785 (0.7412-0.8301)	380
SOFA	0.025	0.660 (0.5829-0.7317)	202
NEWS2	0.004	0.691 (0.6101-0.7709)	173
4C Mortality Score	0.790	0.744 (0.6843-0.8018)	254
SOARS	< 0.001	0.680 (0.6358-0.7226)	508
Altschul et al.	0.014	0.686 (0.6249-0.7429)	298
CURB-65	< 0.001	0.658 (0.6139-0.7043)	470
Modified CHA_2DS_2-VASc	< 0.001	0.592 (0.5447-0.6367)	558
COVID-SOFA	0.700	0.763 (0.6953-0.8221)	201

NEWS2: national early warning score; SOFA: sequential organ failure assessment.
*Complete case analysis. Alpha = 0.0056. AUROC: area under the ROC curve.
*Due to the multiple comparisons, alpha was corrected using Bonferroni method.

Supplementary files

Supplementary file 1. TRIPOD checklist for transparent reporting on a multivariable prognostic model.

Section/topic	Item	Checklist item	Page
Title and abstract			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted	1
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	5
Introduction			
Background and objective	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models	7
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both	7
Methods			
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable	7
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up	8

Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres	8
	5b	Describe eligibility criteria for participants	8
	5c	Give details of treatments received, if relevant	Table 1
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed	8
	6b	Report any actions to blind assessment of the outcome to be predicted	NA
Predictors	7a	Clearly define all predictors used in developing the multivariable prediction model, including how and when they were measured	Table S4, table S5 and table S6
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors	NA
Sample size	8	Explain how the study size was arrived at	Figure 1

Section/topic	**Item**	**Checklist item**	**Page**
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method	9
Statistical analysis methods	10a	Describe how predictors were handled in the analyses	9
	10b	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation	9

	10c	For validation, describe how the predictions were calculated	NA
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models	9-10
	10e	Describe any model updating (e.g., recalibration) arising from the validation, if done	NA
Risk groups	11	Provide details on how risk groups were created, if done	9
Development vs. validation	12	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors	NA
Results			
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful	8, Figure 1
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome	Table 1
	13c	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome)	NA
Model development	14a	Specify the number of participants and outcome events in each analysis	Table 1
	14b	If done, report the unadjusted association between each candidate predictor and outcome	NA

Model specification	15a	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point)	Table S4
	15b	Explain how to use the prediction model	25
Model performance	16	Report performance measures (with CIs) for the prediction model	10
Model updating	17	If done, report the results from any model updating (i.e., model specification, model performance)	NA
Discussion			
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data)	13
Interpretation	19a	For validation, discuss the results with reference to performance in the development data, and any other validation data	NA
	19b	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence	11-13
Implications	20	Discuss the potential clinical use of the model and implications for future research	13
Other information			
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets	31-55
Funding	22	Give the source of funding and the role of the funders for the present study	4

Supplementary file 2. Risk of bias assessment using PROBAST checklist.

Domain and Item	Checklist item	Development	Validation
Participants			
1.1	Were appropriate data sources used, e.g., cohort, RCT, or nested case–control study data?	Yes (a cohort design has been used)	NA
1.2	Were all inclusions and exclusions of participants appropriate?	Yes (participants correspond to unselected participants of interest)	NA
Predictors			
2.1	Were predictors defined and assessed in a similar way for all participants?	Yes (definitions of predictors and their assessment were similar for all participants)	NA
2.2	Were predictor assessments made without knowledge of outcome data?	Yes (outcome information was stated as not used during predictor assessment)	NA
2.3	Are all predictors available at the time the model is intended to be used?	Yes (all included predictors were available at the time the model was intended to be used for prediction)	NA
Outcome			
3.1	Was the outcome determined appropriately?	Yes (objective outcome was used: mortality)	NA
3.2	Was a prespecified or standard outcome definition used?	Yes (objective outcome was used: mortality)	NA
3.3	Were predictors excluded from the outcome definition?	Yes (none of the predictors are	NA

		included in the outcome definition)	
3.4	Was the outcome defined and determined in a similar way for all participants?	Yes (outcomes were defined and determined in a similar way for all participants)	NA
3.5	Was the outcome determined without knowledge of predictor information?	Yes (predictor information was not known when determining the outcome status)	NA
3.6	Was the time interval between predictor assessment and outcome determination appropriate?	Yes (time interval between predictor assessment and outcome determination was appropriate)	NA
Analysis			
4.1	Were there a reasonable number of participants with the outcome?	Yes (high number of events per variable).	NA
4.2	Were continuous and categorical predictors handled appropriately?	Yes (continuous predictors are examined for nonlinearity using thin-plate splines and then categorical predictor groups were defined using widely accepted cut points, current evidence and/or categories defined in established rapid scoring systems).	NA
4.3	Were all enrolled participants included in the analysis?	Yes (all participants enrolled in the study were included in the data analysis).	NA

4.4	Were participants with missing data handled appropriately?	Yes (missing values were handled using multiple imputation methods)	NA
4.5	Was selection of predictors based on univariable analysis avoided?	Yes (the predictors were not selected on the basis of univariable analysis prior to multivariable modeling)	NA
4.6	Were complexities in the data (e.g., censoring, competing risks, sampling of control participants) accounted for appropriately?	Yes (a full cohort approach was used - median follow-up time was 7 days)	NA
4.7	Were relevant model performance measures evaluated appropriately?	Yes (both calibration and discrimination were evaluated appropriately)	NA
4.8	Were model overfitting and optimism in model performance accounted for?	Yes (10-fold cross-validation has been used).	NA
4.9	Do predictors and their assigned weights in the final model correspond to the results from the reported multivariable analysis?	Yes (the predictors and regression coefficients in the final model correspond to reported results from multivariable analysis)	NA

Supplementary file 3. Guidance manual for data collection for COVID-19 intensive care unit patients.

List of Abbreviations

aPPT	Activated Partial Prothrombin Time
ARDS	Acute Respiratory Distress Syndrome
BAV	Atrioventricular Block
BAVT	Total Atrioventricular Block
BMI	Body Mass Index
bpm	Beats per Minute
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease 2019
CRP	C-Reactive Protein
CVA	Cerebral Vascular Accident (Stroke)
DVT	Deep Vein Thrombosis
ECG	Electrocardiogram
ECMO	Extracorporeal Membrane Oxygenation
FiO_2	Fraction of Inspired Oxygen
FM	Face Mask
HCO_3^-	Bicarbonate
HIV	Human Immunodeficiency Virus
IBP	Intra-Arterial Pressure (invasive arterial pressure)
ICU	Intensive Care Unit
IMV	Invasive Mechanical Ventilation
Inc/min	Respiratory Incursions per Minute
INR	International Normalized Ratio
LDH	Lactate Dehydrogenase
LMWH	Low Molecular Weight Heparin
LV	Left Ventricle
MRS	Myocardial Revascularization Surgery
NC	Nasal Catheter
NR	Not Performed
O_2	Oxygen
pCO_2	Partial Carbon Dioxide Pressure
PE	Pulmonary Embolism
AST/GOT ALT/GPT	Aspartate Aminotransferase / Glutamic Oxaloacetic Transaminase Alanine Aminotransferase / Glutamic Pyruvic Transaminase
pH	Potential of Hydrogen
pO_2	Partial Oxygen Pressure
QTc	Corrected QT Interval

RT-PCR	Reverse transcription polymerase chain reaction
SAPS-3	Simplified Acute Physiological Score
SARS-COV-2	Severe Acute Respiratory Syndrome - coronavirus 2
SC	Subcutaneous
SDRA	Acute Respiratory Distress Syndrome
SOFA	Sequential Organ Failure Assessment
SV	Supraventricular
TC	Tomography
UFH	Unfractionated Heparin
V-tach	Ventricular Tachycardia

Presentation

This manual for completion of the **form** on the electronic platform REDCap® was created to help the applicant, to make this filling-in process easier and quicker. This is a practical tool, in which the main questions on the form are explained in detail, so that the applicant may easily find the instructions and immediately clarify any doubts with regard to the possibilities of responses and the correct way to fill in the form.

The instructions for the answering of the questions follow the **structure** of the form and the order of the questions. In possession of this manual, the applicant can previously become aware of the main questions and refer to the form whenever doubts arise during the application of the questionnaire.

The filling-in of the form, following the instructions in this manual, is essential to allow the identification of different outcomes and make sure of the quality of the evidence that originated from the study.

Goal

The goal of this **Guidance Manual** is to present the content of the form of the REDCap® electronic platform for the standardization of the data collection process.

The form, which is the source object of this manual, is the instrument used for the "**National Multicentre Hospital Registration of Patients with a Disease Caused by SARS-COV-2 (COVID 19)"** as approved by CONEP (CAAE 30350820.5.0000.0008).

Target Population

The eligible population consists of registrations of patients who have been admitted to hospital institutions (be it through spontaneous demand, transferred from another service, or referred by the pre-hospital service) and who have had a confirmed positive diagnosis for COVID-19 based on detectable RT-PCR or positive IgM in serum testing (conventional serology or rapid test) between March 1 and December 30, 2022.

Data Collection

The files of eligible patients shall be selected and the data shall be collected in three different moments (admission to hospital, hospitalization period, and hospital discharge or death).

Availability and Period of Application

The data shall be collected through an electronic platform (REDCap®). The researchers responsible for data collection shall sign up through the Internet link http://telessaude.hc.ufmg.br/cursos/AcessoRedCap.php. Once the registration has been made, the coordination of the project shall authorize access by electronic mail (e-mail). The researchers of each institution shall only have access to the data on patients from their own institution. Each researcher must use his or her own password.

The files of eligible patients shall be included on the database as from local ethics approval or when opened by the institution, up to 30 September 2020.

Place of Application

The forms shall be filled in at the participating institutions.

Responsibility for Filling In the Form

The **form** shall be filled in by the researchers of each institution, as assigned for the project, who have been duly trained in the study protocol and application manual. The data shall be monitored by the coordinator of the registration process. In case of any doubts, the local researchers shall be contacted.

Application time

The time needed to fill in the **form** is variable. We estimate that the average time to dill in the form shall be 40 minutes per patient.

Questions

The form contains 205 variables, divided into four separate moments of data collection (admittance to hospital, hospitalization, and hospital discharge or death).

Methodology

Preparation

The applicants shall access the **form** on the REDCap® electronic platform.

The **form** will be filled in based on data taken from the **medical files** of patients admitted to the partner hospitals (made by reading and extraction of the data present on medical files), the **system of medical tests** (in many institutions, not all tests and tests are copied onto the medical files) and **medical prescriptions**, in a r**etrospective** manner.

Before starting data collection, make sure that you are able to put into practice all the guidance that was supplied during training given by the technical team of the project. Should you have any doubts, please contact the collaborators of the project.

We now present some general guidance about how to proceed while the medical files are being appraised. This guidance is essential to guide the conduct of the researcher while data is being collected:

- Never make any changes to the registration (do not include new information, and do not erase any information that already exists)
- .When data is collected on a physical form, contact the person responsible for the files or the system of medical files at the institution, and book in advance times so that the data may be collected.
- Remember to always carry the consent letter from the institution with you, should there be a need for clarifications with regard to your access to

the files. Be prepared to solve any doubts as may occur regarding the execution of the project at the institution.

- For collection of data based on an electronic file, make sure that you still have active access to the system.

Guidance for Data Collection

Form Number
This is an automatic number, generated by REDCap®. If one researcher from a given centre fills in the REDCap® off-line and another researcher fills it in online, then it is possible that the same form numbers may initially be assigned, and then, when the offline data is imported into an online setting, the numbering of the form may be changed.

Centre Number
Each research centre shall have a corresponding 4-digit number (centre number). Make sure of your centre number before you start data collection. In case of any doubt, contact the technical team responsible for the Project.

Identification Number (ID) within the Project
The patient number (ID within the Study) is a field with seven digits, combining the centre number (4 digits) and the sequential identifier of the patient (3 digits). For example: 1001001 is the first patient number corresponding to centre 1001.

Filling in the Form
The form is divided into three different moments of data collection:

1. **Admittance to Hospital:** This includes primary identification and past medical history, clinical appraisal at the moment of admittance to hospital, and additional tests carries out within 24 hours as from the moment of admittance to hospital;
2. **Hospitalization**: This includes clinical evaluation at the moment of admittance to hospital, therapy implemented, support care during the hole hospitalization;
3. **Hospital Discharge or Death**: outcomes.

Type of Response Option

1. **Mandatory:** The variable must be supplied for all patients in all situations (if the information is not available, use “NA”).
2. **Non-Mandatory:** The variable is not mandatory, and this can be answered by one or more of the options or by no option of answer. Whenever possible, refrain from leaving an item unanswered, so that the coordination of the Project may be able to distinguish between an absence through forgetting, from unavailable information (use “NA”).
3. **Personalized Information**: This is a variable with an open-ended field, to be completed as established in the details within the guidance for completion. Such a variable can be either mandatory or **non-mandatory**.
4. **Conditional:** The variable shall be available depending on the answer to the previous question. For example, on selecting “Sex: Female”, the variable “Pregnant” will be accessible, to specify the gravidic condition of the woman. Such a variable can be either mandatory or **non-mandatory**.

It is important to fill in the form supplying as **much information as possible**. On finalizing each part of the form, there is a question about "*form status – complete?*", with the options "*incomplete*", "*unverified*" e "*complete*". After supplying all available data, at the end of the form, you should update the status to "*complete*". Should it not be possible to fill in the whole form at that moment, then you should mark "*incomplete*". Should it be necessary to review the completed form at a later moment, then it is possible to mark it as "*unverified*". This choice shall establish what color shall be assigned to each stage of the form on the "*record home page*", respectively green, red, and yellow.

The variables are detailed as follows:

1. **Admittance to Hospital**

Primary Identification		
Item	**Options for Answer**	**Guidance for Completion**
ID of the study	Mandatory	Fill in with the **four digits representing the centre number,** followed by the **three digits**, that represent the **patient ID** at the institution, which must be **sequential**
Initials	Mandatory	Supply the **initials of the name and also the initials of the second and last surnames** (for example: for Joseph Anthony Smith, use JAS, for name and surname)
Method of confirmation of COVID-19	Mandatory	Select the options: 1- RT-PCR; 2- Rapid antigen test; 3- Rapid serologic test; 4- Unknown rapid test
Medical File	Mandatory	Supply the number of the medical file or registration at the hospital
Date of Birth	Mandatory	Inform using the DD/MM/YYYY format, or select the date using the calendar.
Sex at Birth	Mandatory	Select one of the options: male or female.
Pregnant	Conditional	Select the option, yes or no. If the 'male' option is selected in the previous item, 'sex at birth', then this variable shall be inactive.
How many weeks pregnant?	personalized Information	Inform the number of weeks. If 'no' was selected in the previous item, or if 'male' was selected as the sex at birth, then this variable shall be inactive.

Date of Admittance to Hospital	Mandatory	Inform the date of admittance to the current hospital institution **If the patient is admitted to hospital for a different reason and then, during the process of hospitalization, starts to show symptoms of COVID-19, which were not present at the moment of admission to hospital, then the date considered as the date of admission to hospital shall be that of onset of symptoms.**
Transferred from another service?	Mandatory	Select the option which best represents the situation of the patient, out of the following: 1 – No; 2 – Emergency Unit; 3 – Hospital institution in the same city; 4 – Hospital institution in a different city; 5 – Campaign Hospital; 6 – No information
City of Residence	Mandatory	Inform the name of the patient's municipality of origin

Past History*		
Item	**Options for Answer**	**Guidance for Completion**
Vaccination status	Mandatory	Was the patient vaccinated? Select yes or no. If yes, answer above
Which vaccine?	Mandatory	Select the option: 1-Astrazeneca; 2-Coronavac; 3-Janssen; 4-Pfizer; 5-Sputnik; ou 6- Unknown
How many shots?	Mandatory	Check the option: 1- One; 2- Two; 3-Three; 4- Unknown
Date of the last shot	Conditional	Fill in with the date of the last COVID-19 shot DD-MM-AAAA. If only the month available, consider as day 15th (half the month)
Cardiovascular System	Mandatory	Select the option(s) that apply to the patient (multiple answers are accepted): 1- Hypertension, 2- Coronary Artery Disease, 3- Heart Failure, 4- Fibrillation / Atrial flutter; 5- Ischaemic CVA (stroke); 6- Chagas' Disease; 7- Any other cardiovascular diseases (which ones?); 8- No relevant diseases or illness.

Describe any other cardiovascular disease(s) or illness(es)	Conditional	On selecting the 'any other cardiovascular diseases' option, please specify, in this item, the disease or illness shown. If the option 'any other cardiovascular diseases' is not marked, then this item shall not be available.
Respiratory Tract	Mandatory	Select the option(s) that apply to the patient (multiple answers are accepted): 1- Asthma; 2- COPD; 3 – Pulmonary Fibrosis; 4- Active tuberculosis; 5- Past tuberculosis; 6- None of the above.
Metabolic Disorders	Mandatory	Select the option(s) that apply to the patient (multiple answers are accepted): 1 – Diabetes Mellitus; 2 – Obesity (BMI > 30kg/m2); 3 – Neither of the above.
Other Health Conditions	Mandatory	Select the option(s) that apply to the patient (multiple answers are accepted): 1 – Cirrhosis; 2 – Dementia; 3 - Psychiatric Disorders; 4 – Chronic Kidney Disease; 5 – Rheumatologic Disease; 6- Thyroid disturbance; 7 – HIV Infection;86 – Malignant Neoplasm; 9 – Postpartum < 6 weeks; 10 – Prior Transplant; 11 – Other Relevant Health Condition; 12 – No relevant health conditions
Chronic renal failure with need of dialysis?	Conditional	If checked the option "Chronic renal failure", inform if there is any need of dialysis before the COVID-19 hospitalization. Select yes or no.
Which thyroid disease?	Conditional	If checked the option thyroid disease", inform which disease: 1- Hypothyroidism; 2-Hyperthyroidism; 3-Other; 4-Unknown
HIV in treatment?	Conditional	If checked "HIV infection", inform if the patient is in treatment: 1- Yes; 2- No; 3- Unknown
Viral load available? If yes, fill in	Conditional	If checked "HIV infection", fill in the last viral load available in the medical record.
CD4 value available? If yes, fill in	Conditional	If checked "HIV infection", fill in the last CD4 value available in the medical record.

Type of neoplasm	Conditional	If checked “Malignant neoplasm”, check the option: 1- Haematologic; 2- Solid organs with metastasis; 3- Solid organs without metastasis or with no information regarding this; 4- No information about type of neoplasm.
Site of the primary neoplasm	Conditional	If checked “Malignant neoplasm”, inform the site of the primary neoplasm. If not available, write ND.
Treatment in use	Conditional	If checked “Malignant neoplasm”, inform the treatment in use (eg. radiotherapy, chemotherapy and the name of medication)
Type of Transplant	Conditional	If the option “Prior Transplant” has been selected as part of the “Other Health Conditions” item, then please select the option which best represents the type of transplant: 1 – Hematological; 2 – Solid Organs; 3 – No information.
Which organ transplantation?	Conditional	If checked “Solid organ”, inform which one.
Describe the other relevant health condition	personalized Information	If you have selected the “Other – which one(s)’ option in the “Other Health Conditions” item,. Here please inform the name of the health condition reported, in the event of it being a relevant disease or illness.
Medication of Continuous Use [α]	Mandatory	Select the option(s) applicable to the patient (multiple answers accepted): 1 – Oral anticoagulant; 2- Inhalatory non-steroidal drugs; 3 – Oral non-steroidal drugs; 4 – Immunosuppressants; 5 – Does not use medication
Lifestyle	Mandatory	Select the option(s) applicable to the patient. Multiple answers accepted): 1 – Illicit Drugs; 2 – Alcohol Consumption; 3 – Current smoker; 4 – Former smoker; 5 – None of the above.

Functional status	Mandatory	Select the option referring to the patient before falling ill with Covid-19: 1- Robust - includes very active (he exercised regularly), active (no active symptoms of the disease, he exercised occasionally) and regular (health issues well controlled); 2- Vulnerable or mild frailty - not dependent, but slower, tired throughout the day; or need help with instrumental activities (finance, transport, work domestic, medicines); 3- Moderately frail (needs help with bathing and support to dress); 4- Severely or very severely frail (totally dependent on ADLs); 5-Terminally ill (life expectancy < 6 months); 6- No information

* For purposes of **past history**, the following definitions shall be considered:

Comorbidities

- **Cardiovascular System:**
  - **Hypertension**: prior diagnosis of systemic hypertension as reported on a medical file, and/or use of medication against hypertension, regardless of whether this is regular or irregular treatment, and on whether the blood pressure is controlled or not.
  - **Arterial Coronary Disease**: History of prior angioplasty, myocardial revascularization surgery (MRS), acute heart attack, or angina.
  - **Heart Failure**: Annotations on medical records confirming heart failure, regardless of whether the ejection fraction is preserved or has been reduced.
  - **Atrial Fibrillation or Atrial Flutter**: Annotation of any atrial fibrillation (paroxystic or permanent) or atrial flutter, in the medical records.
  - **Ischaemic CVA**: Past history of cerebral ischaemia, noted down in medical records
- **Respiratory Tract:**
  - **Asthma**: Reports of asthma or “bronchitis”, with compatible prior symptoms, in adulthood, regardless of the use of medication for control (such as corticoids/LABA), in the case of adults. For pediatric patients, it should be considered as asthma whenever there has been an asthmatic crisis or a bout of “bronchitis”, at any moment within childhood.
  - **COPD**: Report of COPD regardless of the use of inhalatory medication for control, but with compatible risk factors (Example: cigarette smoking > 20 years/pack, or prolonged use of wood ovens) OR patients using inhalatory medicines compatible with the treatment of COPD (LABA, LAMA, or a combination of these, whether associated to inhalatory corticoids or not) and associated risk factors. .
  - **Pulmonary Fibrosis:** Registered on medical file.
  - **Active tuberculosis:** Registered on medical file
  - **Past tuberculosis:** Registered on medical file
- **Metabolic Disorders:**

- **Diabetes Mellitus**: Diabetes reported on the medical file, of whatever type, be it insulin-dependent or not.
- **Obesity**: BMI > 30Kg/m^2 registered on medical file or as past medical history

- **Medication for Continuous Use:** Mark the medication that the patient is taking, according to the medical records.
- **Lifestyle – Medical File Information**:
  - Alcohol Consumption: When reported on the medical file, except when there is a report mentioning 'social drinking' or a consumption of up to two standards units of drink per day: 2 cans of beer, 2 doses of Brazilian firewater (*cachaça*), two glasses of wine, or two glasses of whisky.
  - Present and past smoker: Mentioned on medical file, regardless of time and quantity;
  - Use of other illicit drugs: Reported in medical file, regardless of quantity.

[α] With regard to medication, the following list presents the most significant examples within each class:

Class	**Medication**
Oral Anticoagulants	Apixaban, Dabigatran, Edoxaban, Rivaroxaban, Warfarin.
Oral Corticoids	Betamethasone, Dexamethasone, Prednisolone, Prednisone, Deflazacort.
Inhalatory Corticoids	Beclomethasone, Budesonide, Ciclesonide, Dexamethasone, Fluticasone, Mometasone, Triancinolone.
Imunossupressants	Azatioprin, Cyclophosphamide, Cyclosporin, Everolimos, Methotrexate, Mycophenolate Sodium, Mycophenolate Mophetil, Sirolimos, Tacrolimos.

2. **Clinical assessment on ICU admission**

Clinical Assessment on Admission		
Item	**Options for Answer**	**Guidance for Completion**
Date of Onset of First Symptom	Mandatory	Inform the date of onset of first symptom using the DD/MM/YYYY format, or fill in the date using the calendar.
Main reason of admission	Mandatory	Check one 1- Covid-19; 2- Other reason

What was the other reason for hospitalization?	Conditional	If checked “other reason”, inform which one(s): 1- Cardiogenic shock; 2- Coronary artery disease; 3- Cerebrovascular disease; 4- Hepatic encephalopathy; 5- Gastrointestinal hemorrhage; 6- Decompensated heart failure; 7- Infection; 8- Sepsis; 9- Septic shock; 10- Trauma; 11- Pulmonary embolism; 12- Labor; 13- Other
Which other?	Conditional	If checked other above, write which one
Was the patient suspicious of Covid-19 when admitted?	Mandatory	If hospitalization for other reasons, answer yes or no.
Clinical signs and symptoms	Mandatory	Please select the options that apply to the patient (multiple responses are accepted): 1 – Adinamia; 2 – Ageusia (loss of taste); 3 – Anosmia (loss of smell); 4 – Arthralgia; 5 – Headache; 6 – Coryza; 7 – Diarrhea; 8 – Dyspnoea; 9 – Sore throat; 10 – Fever; 11 – Haemoptysis; 12 – Hyporexia; 13 – Neurological symptoms; 14 – Myalgia; 15 – Nausea and vomiting; 16 – Cough; 17 - No Symptoms; 18 – Others
What neurological symptoms?	Conditional	If checked “neurological symptoms”, check which one (ones): 1- Stroke; 2- Seizure; 3- Delirium; 4-Others
Which other neurological symptoms?	Conditional	If checked “others” above, describe which ones.
Which other signs or symptoms?	Conditional	If you have checked “others” in “clinical signs and symptoms”, please describe which ones.

Was the patient admitted straight to the ICU, without passing through the emergency department or other place?	Mandatory	Fill in the yes or no option. In this case, you must mark the option yes only if there is no clinical examination before the ICU. If yes, the next variables related to the clinical evaluation on admission and laboratory findings on admission are inactive, and the next variable to be filled will be in the form related to ICU admission
Glasgow Coma Scale	Mandatory / personalized Information	Please fill in with the patient's Glasgow score at the moment of admission. If not available, then please use ND. **If there is a record on the file of an alert and lucid patient, or use of the abbreviations LOTE, BOTE or LOCV, then consider a Glasgow score of 15.** **If the patient is under continuous sedation, then fill in with NA (not applicable).**
State / Level of Consciousness	Conditional	If the information about the Glasgow Coma Scale is not complete or not available, then please select the option(s) that best apply to the patient, choosing between: 1 – Lucid and alert; 2 – Confused; 3 -Disoriented; 4 – Drowsy; 5 – In a state of torpor; 6 – Comatose. **If the patient is in a state of continuous sedation, then please mark "comatose".**
Systolic Blood Pressure	Mandatory / personalized Information	Inform the systolic blood pressure in mmHg. Complete with NA if not available.
Diastolic Blood Pressure	personalized Information	Inform the diastolic blood pressure in mmHg. Complete with NA if not available.
If there is monitoring of IBP; mean arterial pressure (mmHg)	personalized Information	If this is a patient with monitoring of invasive arterial pressure, then please inform the mean arterial blood pressure. Put NA if the information is not available.

Is there any use of vasoactive amines?	Mandatory	Fill in with either ‘yes’ or ‘no’ at the moment of confirmation of the pressure as registered in the previous items.
Heartbeat Frequency	Mandatory/ personalized Information	Supply the value of the heartbeat frequency in beats per minute (bpm). Put NA if the information is not available.
Respiratory rate	Mandatory/ personalized Information	Supply the breathing frequency in Inc/min. Put NA if the information is not available.
Temperature	personalized Information	Inform the temperature in ºC. Put NA if the information is not available.
Saturation of O_2	Mandatory/ personalized Information	Inform the level of saturation of O_2 in %. Put NA if the information is not available.
Environmental Air	Mandatory	Select one of the options, ‘yes’ or ‘no’, according to the supply of O_2 when the saturation of the previous item is registered.
Nasal Catheter (NC)	Mandatory/ Conditional	If the ‘no’ option is selected in the ‘Environmental Air’ item, then the option of oxygen supply through a NC shall become available. Select one of the options, ‘yes’ or ‘no’
Flow	personalized Information	Inform the flow (L/min) of O_2 offered by the nasal catheter. This item shall only be available for completion if ‘yes’ is selected in the previous item. Put NA if the information is not available.
Face Mask	Mandatory/ Conditional	If the ‘no’ option is selected in the ‘Environmental Air’ and ‘Nasal Catheter’ items, then the option of supply of oxygen through FM shall become available. Select one of the options: ‘yes’ or ‘no’.
Flow	personalized Information	Inform the flow (L/min) of O_2 offered by the face mask. This item shall only be available if ‘yes’ is selected in the previous item. Put NA if the information is not available.

Invasive mechanical ventilation	Mandatory/ Conditional	If the 'no' option is selected in the 'Environmental Air', 'Nasal Catheter', and 'Face Mask' items, then the option of supply of oxygen through IMV shall become available. Select one of the options: 'yes' or 'no'.
Which FiO_2?	Conditional	If in IMV, fill in the FiO_2 registered in the medical record.

Laboratory Findings on ICU Admission		
Item	**Options for Answer**	**Guidance for Completion**
Hemoglobin (g/dL)	personalized Information	Inform the value of hemoglobin content on the CBC made at the admission of the patient to hospital. Put NA if this laboratory test is not available.
Leukocytes (cells/mm^3)	Mandatory/ personalized Information	Inform the absolute global leukocyte count on the CBC made at the admission of the patient to hospital. Put NA if this laboratory test is not available.
Neutrophils (cells/mm^3)	personalized Information	Inform the value of hemoglobin content on the CBC made at the admission of the patient to hospital. Put NA if this laboratory test is not available.
Lymphocytes (cells/mm^3)	Mandatory/ personalized Information	Inform the absolute lymphocyte count as on the CBC made at the admission of the patient to hospital. Put NA if this laboratory test is not available.
Platelets (cells/mm^3)	Mandatory/ personalized Information	Inform the absolute platelet count as in the test made at the admission of the patient to hospital. Put NA if this laboratory test is not available.
Total Bilirubin (mg/dL)	Mandatory/ personalized Information	Inform the total bilirubin value as in the test made at the admission of the patient to hospital. Put NA if this laboratory test is not available.
Creatinine (mg/dL)	Mandatory/ personalized Information	Inform the creatinine level as in the test made at the admission of the patient to hospital. Put NA if this laboratory test is not available.
D-dimer (ng/mL)	Mandatory/ personalized Information	Inform the D-dimer value as in the test made at the admission of the patient to hospital. Put NA if this laboratory test is not available.

D-dimer reference value	Mandatory/ personalized Information	Inform the D-dimer maximum reference value.
Ferritin (ng/mL)	Mandatory/ personalized Information	Inform the ferritin value as in the test made at the admission of the patient to hospital. Put NA if this laboratory test is not available.
Lactate	Mandatory	Fill in this field if the lactate is: 1 – Arterial; 2 – Venous; 3 – Not applicable, if the test is not performed.
Lactate Unit	personalized Information	Inform the measuring unit as registered in the previous unit (mmol/L or mg/dL) used as part of the tests performed on the admission of the patient to hospital.
CRP (mg/L)	personalized Information	Inform the CRP value in the test made on the patient's admission to hospital. Put NA in the test is not available.
aPPT (seconds) / control	personalized Information	Inform the aPTT value in the test made on the patient's admission to hospital. Put NA if the test is not available.
RNI	personalized Information	Inform the RNI value in the test made on the patient's admission to hospital. Put NA if the test is not available.
Sodium (mmol)	Mandatory/ personalized Information	Inform the Sodium level in the test made on the patient's admission to hospital. Put NA if the test is not available.
GOT/AST (U/L)	Mandatory/ personalized Information	Inform the GOT/AST level in the test made on the patient's admission to hospital. Put NA if the test is not available.
GPT/ALT (U/L)	Mandatory/ personalized Information	Inform the GOT/ALT level in the test made on the patient's admission to hospital. Put NA if the test is not available.
Troponin	personalized Information	Inform the troponin level in the test made on the patient's admission to hospital. Put NA if the test is not available.
Troponin reference value	personalized Information	Inform the maximum troponin reference value.
Urea (mg/dL)	personalized Information	Inform the urea level in the test made on the patient's admission to hospital. Put NA if the test is not available.
pH	personalized Information	Inform the pH as part of the arterial gasometry test, on the patient's admission to hospital. Put NA if the test is not available.
Arterial pCO_2	personalized Information	Inform the pCO_2 value within the arterial gasometry test on the patient's admission to hospital. Put ND if the test is not available.

Arterial pO_2	Mandatory/ personalized Information	Inform the pCO_2 value within the arterial gasometry test on the patient's admission to hospital. Put ND if the test is not available.
HCO_3^-	personalized Information	Inform the HCO_3^- value within the arterial gasometry test on the patient's admission to hospital. Put ND if the test is not available.
FiO_2 (at the moment of collection of gasometrics)*	Mandatory/ personalized Information	Inform the FiO_2 value at the moment of collection for the arterial gasometry test on the patient's admittance to hospital. Put NA if the test is not available. **This item of data is essential for the calculation of the ratio between PaO2/FiO2, meaning that it is very important to try to obtain this.**

* If the patient is not in mechanical ventilation, the use of the following estimates for FiO_2 has been agreed:

Device	**Flow (L/min)**	**Approximate value of FiO2 to be used in the collection form**
No – regular room air	0	0.21
Nasal Cannula	1	0.24
	2	0.28
	3	0.32
	4	0.36
	5	0.40
	6	0.44
Simple Mask	5	0.40
	6	0.50
	7	0.60
Mask with Non-Reinhaling Reservoir	6	0.60
	7	0.70
	8-9	0.80
	10-15	0.95

3. **Hospitalization**

Therapeutic Intervention		
Item	**Options for Answer**	**Guidance for Completion**
Therapies used during hospitalization	Mandatory	Select the option(s) referring to the therapy used during the whole period of hospitalization of the patient (multiple answers are accepted):\ 1 – Antibiotics for nosocomial infections; 2 – Anticoagulants; 3 – Antifungal Drugs; 4 –

		Neuromuscular blocker for intubation; 5 – Oral or IV corticotherapy; 6 – Inhaled corticoids; 7 – None of the Above.
Which Anticoagulant?	Mandatory/ Conditional	If the 'Anticoagulant' option has been chosen in item 128, then select the item that refers to what anticoagulant was used: 1 – Unfractionated Heparin; 2 – Low Molecular Weight Heparin; 3 – Fondaparinux; 4 – Warfarin; 5 – Others.
Unfractionated Heparin Dose*	Mandatory/ Conditional	If the option 'Unfractionated Heparin' is selected in item 128.1, please select the option referring to the dose of anticoagulants: 1 – Prophylactic; 2 – Therapeutic
Start of Treatment with Unfractionated Heparin	Mandatory/ personalized Information	If the option 'Unfractionated Heparin' is selected in item 128.1, please inform the date when the medication started to be used, in DD/MM/YYYY format.
End of Treatment with Unfractionated Heparin	Mandatory/ personalized Information	If the option 'Unfractionated Heparin' is selected in item 128.1, please inform the date when the medication stopped being used, in DD/MM/YYYY format.
Dose of Low Molecular Weight Heparin [α]	Mandatory/ Conditional	If the option 'Low Molecular Weight Heparin' is selected in item 128.1, please select the option referring to the dose of anticoagulants: 1 – Prophylactic; 2 – Therapeutic
Start of Treatment with Low Molecular Weight Heparin	Mandatory/ personalized Information	If the option 'Low Molecular Weight Heparin' is selected in item 128.1, please inform the date when the medication started to be used, in DD/MM/YYYY format.
End of Treatment with Low Molecular Weight Heparin	Mandatory/ personalized Information	If the option 'Low Molecular Weight Heparin' is selected in item 128.1, please inform the date when the medication stopped being used, in DD/MM/YYYY format.
Dose of Fondaparinux[ł]	Mandatory/ Conditional	If the option 'Fondparinux' is selected in item 128.1, please select the option referring to the dose of anticoagulants: 1 – Prophylactic; 2 – Therapeutic
Start of Treatment with Fondparinux	Mandatory/ personalized Information	If the option 'Fondparinux' is selected in item 128.1, please inform the date when the medication started to be used, in DD/MM/YYYY format.
End of Treatment with Fondparinux	Mandatory/ personalized Information	If the option 'Fondparinux' is selected in item 128.1, please inform the date when the medication stopped being used, in DD/MM/YYYY format.
Start of Treatment with Warfarin	Mandatory/ personalized Information	If the option 'Warfarin' is selected in item 128.1, please inform the date when the medication started to be used, in DD/MM/YYYY format.

End of Treatment with Warfarin	Mandatory/ personalized Information	If the option 'Warfarin' is selected in item 128.1, please inform the date when the medication stopped being used, in DD/MM/YYYY format.
What other anticoagulant?	Conditional/ personalized Information	If the option 'Others' is selected in item 128.1, please inform which other anticoagulant is being used.
Start of Treatment with Other Anticoagulant	Mandatory/ personalized Information	If the option 'Other Anticoagulant' is selected in item 128.1, please inform the date when the medication started to be used, in DD/MM/YYYY format.
End of Treatment with Other Anticoagulant	Mandatory/ personalized Information	If the option 'Other Anticoagulant' is selected in item 128.1, please inform the date when the medication stopped being used, in DD/MM/YYYY format.
How is the neuromuscular blocker used?	Mandatory/ personalized Information	If selected the option "neuromuscular blocker", choose one: 1- Bolus; 2- Continuous infusion; 3- No information
For how many days was the neuromuscular blocker used?	Mandatory/ personalized Information	If selected the option "neuromuscular blocker", fill in for how many days.
Which Corticoid?	Mandatory/ Conditional	If the option 'Corticoid' is selected in item 128, then please mark if the corticoid used was: 1 – Dexamethasone, 2 – Another Corticoid.
Start of Treatment with Corticoid	Conditional/ personalized Information	If the option 'Corticoid' is selected in item 128, please inform the date when the medication started to be used, in DD/MM/YYYY format.
Duration of the Treatment with Corticoid (days)	Conditional/ personalized Information	If you select the option "corticoid", fill in how many days. If the patient used more than one type of corticoid, add the total use days. The day of start is day 1
Dose of Dexamethasone (mg/dia)?	Mandatory/ personalized Information	If you select the option "dexamethasone", put the diary dose.
Dose of hydrocortisone (mg/dia)?	Mandatory/ personalized Information	If you select the option "hydrocortisone", put the diary dose.
Dose of methylprednisolone (mg/dia)?	Mandatory/ personalized Information	If you select the option "methylprednisolone", put the diary dose.
Dose of prednisone or prednisolone (mg/dia)?	Mandatory/ personalized Information	If you select the option "prednisone or prednisolone", put the dairy dose.
Dose of other corticosteroid (mg/dia)?	Mandatory/ personalized Information	If you select the option "other corticosteroid", put the diary dose.

Therapy Introduced Specifically for Covid-19	Mandatory	Select the option(s) referring to the therapies as used during the whole of the hospitalization period (multiple answers are accepted): 1 – Antibiotic in the acute phase; 2 – Immunoglobulin; 3 – Convalescent Plasma; 4 – Remdesivir; 5 – Sarilumab; 6 – Tocilizumab; 7 – Other (Which?) 8 – None.
Describe Other Therapy Used	Mandatory/ personalized Information	If the option 'Other – which one?' has been selected under 'Therapy Introduced Specifically for COVID-19", please describe the other therapy used.
Support Care	Mandatory	Select the option(s) related to support care as provided during the whole period of hospitalization: 1 – Vasoactive Amines; 2 – ECMO; 3 – Respiratory physiotherapy; 4 - Motor physiotherapy 5 - Prone position (non-IMV); 6- Prone position (on IMV); 7 – Volemic Resuscitation; 8 – Non-Invasive Mechanical Ventilation; 9 – None of these
Date and time of the start of ECMO	Conditional	If checked "ECMO", inform the date and time of the start of ECMO.
Date and time of the indication of ECMO	Conditional	If checked "ECMO", inform the date and time of the indication of ECMO.
Date of the end of ECMO	Conditional	If checked "ECMO", inform the date of the end of ECMO.
Were there any ECMO complications?	Conditional	If checked "ECMO", answer with yes or no..
Which ECMO complications?	Conditional	Se assinalado "sim" na variável anterior, descrever qual complicação
Definition of Palliative Care for the Patient	Mandatory	Answer with 'yes' or 'no'.
Was the definition of Palliative Care for the Patient established at the moment of admission?	Mandatory	If checked "yes" above, inform if the indication was clearly established at hospital admission: 1- Yes; 2- No; 3- Not clear

*** Dose of unfractionated heparin (UFH):** Doses considered **prophylactic** are UFH 5,000 UI applied subcutaneously (SC) every 12 hours (12/12h) or every 8 hours (8/8h). The **therapeutic** dose is normally given based on the weight of the patient, in a continuous infusion pump, with monitoring of aPPT. In exceptional cases, there are therapeutic doses at 320UI/kg of attack weight and 250UI/kg of weight 12/12h SC, without any monitoring of aPPT.

[α] **Dose of low molecular weight heparin:** Examples of **prophylactic** doses: enoxaparin 40mg SC 24/24h or dalteparin 5000UI 24/24h. Examples of **therapeutic** doses include: enoxaparin 1mg/Kg of body weight SC 12/12h or 1.5mg/Kg of body weight, every 24 hours; dalteparin 200UI/Kg SC every 24 hours. The therapeutic dose could be adjusted if there is kidney failure.

[ł] **Dose of fondaparinux:** The prophylactic dose of fondaparinux is 2.5 mg SC every 24 hours. The therapeutic dose depends on weight, being set at 5mg if <50Kg, 7.5mg if 50-100Kg, and 10mg if >100Kg, SC, every 24 hours.

1. **Discharge or Death**

Outcomes		
Item	**Options for Answer**	**Guidance for Completion**
Date of Hospital Discharge / Death / Transfer	Mandatory	Inform the date of hospital discharge or death, using the DD/MM/YYYY format.
Was there a transfer to another institution?	Mandatory	Answer ‘yes’ or ‘no’, with regard to transfer to another institution.
Which Institution?	Mandatory/ Conditional	If the answer to the previous item was ‘yes’, then describe the institution of transfer.
Was there any need for mechanical ventilation?	Mandatory	Answer ‘yes’ or ‘no’, with regard to the need for mechanical ventilation
Date of intubation	Conditional	If checked for IMV, fill in with the date of the first intubation.
Days of mechanical ventilation	Mandatory/ personalized Information	If the answer to the previous item is ‘yes’, then please inform the number of days when the patient remained under mechanical ventilation.
Was there any need for a tracheostomy?[α]	Mandatory/ personalized Information	Answer ‘yes’ or ‘no’.
Was there any need for replacement kidney therapy (dialysis)?[ł]	Mandatory	Answer ‘yes’ or ‘no’, with regard to the need for dialysis during the hospitalization period.
Intercurrences during hospitalization?	Mandatory	Select the option(s) that correspond to the support care provided during the whole hospitalization period (multiple answers are accepted): 1. Arrhythmia; 2- Pneumonia with bronchiolitis (check CT thorax); 3- Septic Shock; 4 - Acute HF (new case, or

		decompensated chronic case); 5 - Hospital Infection; 6 - Heart Attack; 7 - Renal failure; 8 - Myocarditis; 9 - Pericarditis; 10 - Haemorrhage; 11 - ARDS; 12 - Vascular Thrombosis; 13 - Other; 14 - None
Which arrhythmia?	Mandatory/ Conditional	If you checked “1- Arrhythmia” check which ones:: 1- Fibrilação/ atrial flutter; 2- atrioventricular block with need of pacemaker; 3- Multifocal atrial rhythm; 4- Supraventricular tachycardia; 5- Monomorphic ventricular tachycardia; 6- Polymorphic ventricular tachycardia; 7-Other.
Site of the Haemorrhage?	Mandatory/ Conditional	If ‘Hemorrhage’ was selected as part of ‘Intercurrences during hospitalization’, then please inform the site of the hemorrhage.
How serious was the hemorrhage?	Mandatory/ Conditional	If ‘Hemorrhage’ was selected as part of ‘Intercurrences during hospitalization’, then choose one of the following alternatives: 1. Serious; 2. Not serious, but clinically relevant; 3. Not serious.[T]
What kind of thromboembolic event?	Mandatory/ Conditional	If ‘Vascular Thrombosis’ was selected under ‘Intercurrences During hospitalization’, then select one option corresponding to the type of thromboembolic event: 1 – DVT; 2 – TEP; 3 – Arterial Thrombosis.
Any other complications?	Mandatory/ Conditional	If ‘Other’ was selected under ‘Intercurrences During hospitalization’, then please select the other complication that was shown.
Any gestational complications?	Mandatory/ Conditional	If pregnant, answer yes or no.
Which gestational complication?	Mandatory/ Conditional	Select which complications: 1- Miscarriage; 2- Ectopic gestation; 3- Pre-eclampsia; 4- Eclampsia; 5-HELLP syndrome; 6- Puerperium or labor hemorrhage;7- Hysterectomy, 8- Puerperal infection; 9-Other
Which other gestational complication?	Mandatory/ Conditional	If you checked “other” above, inform which one.
labor during hospitalization?	Mandatory/ Conditional	Answer yes or no.
Type of labor	Mandatory/ Conditional	If checked yes above, check the type of labor:1- Natural childbirth; 2- Cesarean delivery; 3- Unknown
Was the child born alive?	Mandatory/ Conditional	Answer yes or no.
Weight of the newborn (g)	personalized Information	Fill in the weight of the newborn.
APGAR on the 1st minute	personalized Information	Fill in the APGAR score on the 1st minute

APGAR on the 5th minute	personalized Information	Fill in the APGAR score on the 5th minute
Death	Mandatory	Answer with ‘yes’ or ‘no’.

*** Need for mechanical ventilation:** Annotation on the medical record, confirming the need for mechanical ventilation

[α] **Fault of extubation:** Record on the medical file, confirming fault of extubation.

[ł] **Need for replacement kidney therapy:** An annotation on the medical records mentioning dialysis during hospitalization that was started during hospitalization (meaning that prior dialytics are excluded).

[Ŧ]Consider the following definition for intercurrences during hospitalization:

1. **Septic Shock:** Annotation on the medical file mentioning septic shock; or, in the case of patients with evidence of infectious process: presence of shock; use of amines and lactate persistently over 2 mmol/L (18 mg/dL), despite appropriate volemic resuscitation
2. **Widespread Intravascular Coagulation:** Annotation on medical files or score as proposed by the *International Society on Thrombosis and Haemostasis* of ≥5, with this score being calculated automatically based on the information supplied on the form, taking into account factors such as platelet count, D-dimer, coagulogram and fibrinogen.
3. **Acute heart failure:** A new, or a decompensated chronic case of heart failure, regardless of whether the ejection fraction is preserved or reduced.
4. **Hospital Infection:** Record of a bacterial infectious process in any site, or at an undetermined site, diagnosed 48 hours after admission to hospital.
5. **Heart Attack (Myocardial Infarction)**: Medical files recording an acute myocardial infarction of any type.
6. **Renal failure:** diagnosis of acute kidney injury (or failure) recorded in medical records, or an increase of at least 0.3 mg/dL in creatinine, in relation to baseline creatinine.
7. **Myocarditis:** Diagnosis of myocarditis, duly recorded on the medical file.
8. **Pericarditis:** Diagnosis of pericarditis, duly recorded on the medical file.
9. **Hemorrhage:** Medical file mentioning hemorrhagic complication(s) which could be considered as (Variable 146.2):

- **Serious Hemorrhage:** Clinically evident bleeding leading to any of the following situations: death; involvement of a key anatomic site (intracranial; spinal; pericardial; articular; retroperitoneal; or intramuscular, with compartment syndrome); fall of at least 2 g/dL in the concentration of hemoglobin; shock; transfusion of at least 2 units of entire blood or RBC concentrate; or permanent invalidity.
- **Hemorrhage not serious, but clinically relevant:** Presence of evident bleeding that does not meet the criteria for defining serious bleeding, but which warranted medical intervention, temporary interruption of treatment, or that generated any kind of pain.
- **Hemorrhage not serious:** Do not fall under any of the previous criteria.

10. **Adult Respiratory Distress Syndrome:** Medical file mentioning adult breathing distress syndrome, ARDS, SDRA; or a diagnosis of disproportional hypoxaemia, registered on the medical file, through arterial gasometry with pO_2/FiO_2<200 at any moment; or through maneuvers of alveolar recruitment.
11. **Vascular Thrombosis:** Diagnosis of arterial thrombosis registered on a medical file; deep venous thrombosis confirmed by imaging test (duplex scan or compression ultrasound); and/or pulmonary embolus by imaging test (angiotomography, scintillography; or, if there is haemodynamic instability and in the absence of confirmation through previous testing, changes that would suggest acute overload of the right ventricle, in an echocardiogram or bedside ultrasound).

12. **Gestational complications:**

1- Miscarriage: termination of pregnancy before the 20th week of gestational age.
2- Ectopic pregnancy: select this option if there is a description in the pregnancy record that develops outside the uterine cavity.
3- Pre-eclampsia: description of pre-eclampsia in the medical record.
4- Eclampsia: description in the eclampsia chart.
5- HELLP syndrome: description in the medical record of HELLP syndrome (hemolysis, increased liver enzymes and thrombocytopenia.
6- Hemorrhage in childbirth or puerperium: excessive loss of blood after childbirth, which has been described in the medical record.
7- Hysterectomy: postpartum uterus removal procedure due to complications of childbirth, as described in the chart.
8- Puerperal infection: any infection of the genital tract that occurs during the puerperium. Examples: endometritis, episiotomy infection (EPIS) or vaginal lacerations, surgical site infection.

Supplementary file 4. Literature search for finding risk scores for COVID-19 ICU patients.

Title	Author	Patient time span	Setting/ Country of derivation	Sample size (n)	Inclusion criteria	Variables included	CI/AUROC	Limitation
External validation of 4C ISARIC mortality score in critically ill COVID-19 patinets from Saudi Arabia	Aletreby et al.	January 1, 2020 and June 30, 2021	ICU at King Saud Medical City (KSMC), Riyadh, Saudi Arabia	1,493	All patients admitted to our ICU, as long as they were COVID-19 positive, confirmed by RT-PCR, and of adult age (18 years or above)	Age, gender, number of comorbidities, respiratory rate at hospital admission, peripheral oxygen saturation (SpO_2) on room air at hospital admission, Glasgow Coma Scale (GCS) at hospital admission, first available blood urea level (mmol/L) and C-reactive protein (CRP) (mg/L).	0.81 (95% CI: 0.79 – 0.83, $p < 0.001$)	The development and validation cohorts were entirely of the United Kingdom population. The inherent limitation within the retrospective design. This remains a single center study, reflecting the management in only our ICU. They chose not to use imputation methods on missing data and it may have reduced the sample size and impacted results. The cohort lacked several ethnicities, so the results may not be applicable in other regions of the world, and finally, generalizability of our results may be limited to only critically ill patients, as we didn't include non-ICU admissions.
A novel severity score to predict	Altschul et al.	March 1st to April 16th, 2020	New York, USA	4711 Derivation: 2355 Validation: 2356	All patients admitted to a hospital within a large healthcare network that	22 variables	Derivation: of 0.824 (95% CI 0.814–0.851)	The limitations of this study are its retrospective design, its cohort, which is primarily a minority urban

inpatient mortality in COVID-19 patients					were positive by detection of SARS-CoV-2 RT-PCR		Validation: AUC of 0.798 (95% CI 0.789–0.818)	population, and the epoch at which the data was required. Since the data and outcomes were recorded during the highest surge of the pandemic this may bias the results towards higher mortality as this was a great strain on treating hospitals at the time. Given the sociodemographic background of the patient population the score may again be biased towards higher mortality risk.
Severity Scores in COVID-19 Pneumonia: a Multicenter, Retrospective, Cohort Study	Artero et al.	March 1 and May 28, 2020	Spain	10,238	Patients with SARS-CoV2 infection, aged ≥18 years, and with CAP who were hospitalized	PSI, CURB-65, qSOFA, and MuLBSTA (multilobar infiltrates, lymphocytes, bacterial infection, active smoker, prior smoker, hypertension, and age ≥60 years)	Mortality PSI: 0.835 CURB-65: 0.825 qSOFA: 0.728 MuLBSTA: 0.715 Admission to ICU PSI: 0.539 CURB-65: 0.562 qSOFA: 0.616 MuLBSTA: 0.658 Mechanical Ventilation PSI: 0.560 CURB-65: 0.572 qSOFA: 0.624 MuLBSTA: 0.678	Due to its retrospective design, some possible confounding variables were not recorded and thus we could not calculate prognostic scores in 3.4 to 9.5% of cases. They focused only on hospitalized patients and as such, we cannot be certain that their findings can be extrapolated to outpatients. By excluding patients still hospitalized as of May 29, 2020, the case fatality rate in our study does not reflect the true mortality rate of COVID-19. This study was conducted in multiple centers in Spain

								and its results may not be applicable to other settings with different populations or healthcare systems. The results of the secondary outcomes may be biased by the availability of ICU beds and ventilators in the first months of the pandemic.
Mortality Predictive Value of APACHE II and SOFA Scores in COVID-19 Patients in the Intensive Care Unit	Beigmohammadi et al.	Not clear	ICUs of the general tertiary Imam Khomeini hospital complex, Tehran University of Medical Science, Tehran, Iran	204	Positive SARS COV 2 RT-PCR from nasopharyngeal swab or respiratory secretions, from both sexes, and age>16 years, who had been diagnosed with severe/critical COVID-19.	SOFA and APACHE II	89.5% for SOFA and 73% for the APACHE II score	It is a retrospective study, and the data were collected in a critical condition. The hospital is a tertiary mega hospital and referral center that includes three hospitals with multiple intensive units that may be the reason for the study's high mortality.
Early prognostication of COVID-19 to guide hospitalization versus outpatient monitoring using a point-of-test	Chua et al.	1 March and 16 May 2020	Emergency department (ED) at Watford Hospital, West Hertfordshire NHS Hospitals. England.	983	All individuals aged 18 or older who tested positive for SARS-CoV-2 nucleic acid by RT-PCR	SOARS (SpO2, Obesity, Age, Respiratory Rate, Stroke history)	Derivation: AUROC 0.82 Validation: The longer score Aintree (AUROC 0.87) ISARIC cohort (0.77). SOARS 0.80 (Aintree) and 0.74 (ISARIC).	The occurrence of missing information despite prospective data collection. The use of multiple imputation to estimate missing values for multivariate regression and the availability of nearly 85% of observations for constructing the risk stratification rule helped to mitigate against underestimating their role.

risk prediction score								The modest sample size of the derivation cohort was dictated by the incident caseload during the pandemic. Reduced score calibration at the high-risk end suggests that SOARS may overestimate the probability of death in the highest risk cases.
Coronavirus Disease 2019 ICU Patients Have Higher-Than-Expected Acute Physiology and Chronic Health Evaluation–Adjusted Mortality and Length of Stay Than Viral Pneumonia ICU Patients	Higgins et al.	Covid: March 14, and June 17, 2020 Viral pneumonia: January 1, 2014, and December 31, 2019.	Covid: 43 hospitals Viral pneumonia : 132 hospitals in the United States	Covid: 1,491 and 4,200 patients with a primary (*n* = 2,544) or secondary (*n* = 1,656) admitting diagnosis of noncoronavirus disease viral pneumonia receiving ICU care. Viral pneumonia: 202	Positive test for COVID-19 admitted between March 14, and June 17, 2020, with historical data collected between January 1, 2014, and December 31, 2019, on patients age greater than or equal to 18 with a primary or secondary admission diagnosis of VP.	Age and APACHE-IVb severity of Illness	Not disclosed	It included only hospitals voluntarily participating in the APACHE database and temporal bias in comparing VP from 2014 to 2019 with COVID-19 where data were only available for early 2020.
Developing a mortality risk prediction model using data of 3663 hospitalized COVID-19	Kandil et al.	April 2020 to the end of February 2021	Isolation areas of ASUHs including buildings of El-Obour, Geriatrics,	3,663	Laboratory confirmed diagnosis of COVID-19 based on real-time reverse-transcriptase –polymerase-chain-reaction (RT–PCR) test	Basic model: age, presence/absence of comorbidities, and the severity level	Basic model AUC = 0.832 (95% CI 0.816-0.847) and other model AUC = 0.842 (95% CI 0.812-0.873).	Being a hospital-based study, determination of mortality predictors may be a subject of collider bias with possible inflation of associations. It is a retrospective hospital-based

patients: a retrospective cohort study in an Egyptian University Hospital			and Field hospitals			of the condition on admission Other model: with added INR		study. It was not externally validated.
Risk stratification of patients admitted to hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: development and validation of the 4C Mortality Score	Knight et al	Derivation: 6 Feb to 20 May, 2020 Validation: 21 May to 29 June, 2020	260 hospitals in England, Scotland, or Wales	35,463 (derivation) 22,361 (validation)	Consecutive patients ≥18 years admitted to hospital with covid-19 at least four weeks before final data extraction	Age, sex, number of comorbidities, respiratory rate, peripheral oxygen saturation, glasgow coma scale, urea level and C reactive protein	Derivation: AUROC 0.79, 95% confidence interval 0.78 to 0.79; Validation cohort: 0.77, 0.76 to 0.77	They were unable to evaluate the predictive performance of several existing scores that require a large number of parameters, as well as several other covid-19 prognostic scores that use computed tomography findings or uncommonly measured biomarkers. Several potentially relevant comorbidities, such as hypertension, previous myocardial infarction, and stroke, were not included in data collection. A proportion of recruited patients (3.3%) had incomplete episodes. The patient cohort on which the 4C Mortality Score was derived comprised patients admitted to hospital who were seriously ill (mortality rate of 32.2%) and were of advanced age (median age 73 years). The model is not for use in the community and could perform differently

								in populations at lower risk of death.
SAPS-3 performance for hospital mortality prediction in 30,571 patients with COVID-19 admitted to ICUs in Brazil	Kurtz et al.	Feb 26, 2020 to Apr 30, 2021	188 ICUs of 45 hospitals (Rede D'Or São Luiz), Brazil	30,571	All adult patients (>16 years) with RT-PCR-confirmed SARS-CoV-2 infection admitted to 188 ICUs	SAPS-3 score	AUROC=0.835 [95% CI 0.828–0.841]	Not disclosed
Prediction of 28-day mortality in critically ill patients with COVID-19: Development and internal validation of a clinical prediction model	Leoni et al.	Feb 22, 2020 to Apr 3, 2020	Guglielmo da Saliceto Hospital of Piacenza, Italy	242	Consecutive critically ill patients admitted to ICU. Critically ill patients were defined as those admitted to ICU who required mechanical ventilation or had a fraction of inspired oxygen (FiO2) of at least 60% or more.	Age, obesity, procalcitonin, SOFA score and PaO2/FiO2	C-statistic for the predicted 28-day mortality risk: 0.821 (95% CI 0.766–0.876) and 0.822 (95% CI 0.770–0.873) in the original and bootstrap models, respectively.	It is possible that some data present inaccuracies that might introduce some bias in the study results. They did not collect data about complications during ICU length of stay. They did not collect D-dimer, IL-6 and thrombosis data in every patient. They did not collect the cause of death and type of mechanical ventilation used. Absence of an external validation.
COVID-19 ICU mortality prediction: a machine learning approach using	Lorenzoni et al.	Feb 28, 2020 to Apr 4, 2021	ICUs of the COVID-19 VENETO ICU network, Italy	1,616 (1293 models training and 124 external validation and a further cohort of 199 was used as additional	All adult patients with confirmed SARS-CoV-2 infection admitted to the ICUs of the COVID-19 VENETO ICU network. The first group, i.e., "training	Age was identified as the most important predictive parameter in every model investigated.	Model 3 0.85 Models 1 and 2: 0.75.	Clinical variables investigated in the study represent only a small number of parameters potentially relevant and able to affect critically ill patients' outcomes. Several patients had incomplete records.

SuperLearner algorithm				external validation)	set," included patients admitted to the ICUs from 28th of February to 28th of April 2020 plus from 27th of November to 4th of March 2021, and was used for model training. The second group (named "test set 1"), composed by patients admitted to the ICUs from 5th of March to 4th of April 2021, was used for external validation of the model.	Secondary, total SOFA score at ICU admission, the level of daily activity and the need of different types of respiratory supports were important parameters for Model 1, 2 and 3.		
Evaluation and calibration of SAPS 3 in patients with COVID-19 admitted to intensive care units	Metnitz et a.l	January 1st, 2020, to January 31st, 2021	90 participating ICUs, Austria	1,464	Patients with documented SARS-CoV-2 infection admitted to participating ICUs	SAPS 3	0.745 (95% CI 0.719–0.770).	Not disclosed
Development and Internal Validation of a New Prognostic Model Powered to Predict	Moisa et al.	April 2020 to November 2021	Two tertiary centers in Romania	425	Patients ≥ 18 years, COVID-19 pneumonia confirmed through RT-PCR and chest Rx or CT scan, ARDS secondary to COVID-19 pneumonia requiring	Age, neutrophil-to-lymphocyte ratio and SOFA score	0.796 (95% CI: 0.755-0.833, p<0.001)	First, the study design, lack of racial diversity, and patients were from only two tertiary centers. Secondly, they included patients without confirmed or suspected bacterial co-infection at ICU

28-Day All-Cause Mortality in ICU COVID-19 Patients - The COVID-SOFA Score					non-invasive or invasive MV or high-flow oxygen therapy, SOFA score ≥ 2 and ICU length of stay ≥ 72 h			admission or the first 48h after ICU admission. Reduced number of vaccinated patients and the subsequent inability to make assumptions about this population. Lastly, lack of external validation on a different cohort.
Predicting mortality in COVID-19: Comparison of novel score with apache IV	Onyambu et al.	March 1 to May 30, 2020	Not clear	40	All data ware retrospectively collected from electronic health records of COVID-19 patients on day 1 of admission to our ICU	Neutrophil/lymphocyte ratio (NLR), CRP, Ferritin levels (F), and D-dimer levels (D) as follows CSS = (NLR X CRP X F X D)/10,000.	AUC = 0.75 ± 0.05 for CSS compared to 0.70 ± 0.05 for APACHE IV ($p < 0.0001$).	Not disclosed
Analysis of Critical Care Severity of Illness Scoring Systems in Patients With Coronavirus Disease 2019: A Retrospective Analysis of Three U.K. ICUs	Stephens et al.	March 10, 2020, to May 22, 2020	Three teaching hospitals in London, UK	242	All critically unwell patients with COVID-19 admitted to ICUs	APACHE II, SAPS II, and ICNARC	Not disclosed.	APACHE II, SAPS II and ICNARC might be unsuitable for quantifying disease severity, predicting mortality or prognosis, assessing ICU performance, and stratifying patients for clinical trials for COVID-19 patients, grossly underestimating actual mortality risk and poorly stratifying disease severity.

Early Warning Scores at Time of ICU Admission to Predict Mortality in Critically Ill COVID-19 Patients	Tyagi et al.	After September 10, 2020 (1-mo period)	COVID dedicated large public hospital in northern India	140	Laboratory confirmed COVID-19 patients aged between 18 and 95 y admitted to ICUs over a 1-mo period	CRB-65, NEWS2 and GCS	CRB-65 (AUC: 0.720 [95% confidence interval [CI]: 0.630-0.811]) NEWS2 (AUC: 0.712 [95% CI: 0.622-0.803]). Glasgow Coma Scale score at time of admission ($P < 0.001$; adjusted hazard ratio = 0.808 [95% CI: 0.715-0.911]).	Lack of follow-up for long term survival after ICU discharge. This was a single center study spread over a short period. Thus, regional and temporal trends cannot be inferred.
Comparison of mortality risk evaluation tools efficacy in critically ill COVID-19 patients	Vicka et al.	Not clear	A Tertiary university hospital	249	Patients >18 years who were admitted to ICU in a tertiary referral university hospital in the year of 2020 and tested positive for SARS-CoV-2.	4C Mortality score, SAPS II, APACHE II and SOFA	APACHE II: AUC 0.772 (95% CI 0.714-0.830; p<0.001). 4C Mortality Score: AUC 0.754 (95% CI 0.694-0.814; p<0.001). SOFA: AUC 0.679 (95% CI 0.611-0.747; p<0.001) SAPS II: AUC 0.755 (95% CI 0.695-0.815; p<0.001)	The study design has a potential for bias. They designed this study with evaluations at two points in time, indeed, in some cases, occurring at the same time, when the patient is being admitted directly to the ICU and, in some cases, at two different points in time.
Acute Physiology and Chronic Health Evaluation II Score as a Predictor of Hospital Mortality in Patients of	Zou et al.	January 10, 2020, to February 10, 2020	ICU of Tongji hospital, China	154	Inpatients cared in the ICU who have been diagnosed as COVID-19, according to World Health Organization interim guidance	APACHE II score, SOFA and CURB65	APACHE II: 0.966 (95% CI, 0.942–0.990), SOFA: 0.867 (95% CI, 0.808–0.926), CURB65 0.844 (95% CI, 0.784–0.905)	Retrospective, single-center study with a relatively small sample size. Most patients were transferred from other hospitals or isolation units. These patients were more likely to progress to adverse outcomes. Therefore, the mortality of patients with COVID-19 in this study may

Coronavirus Disease 2019	be much higher than the general population. The treatments may influence the outcomes of patients with COVID-19.

ARDS: acute respiratory distress syndrome; ICU: intensive care unit; MV: mechanical ventilation; RT-PCR: reverse transcription polymerase chain reaction.

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Supplementary file 5. Evaluating potential predictors for the model development and percentage of missing.

Potential variables	Missing (%)
Ferritin (ng/mL)	81.4%
Temperature (^oC)	62.2%
Troponin	58.8%
D dimer (ng/mL)	54.7%
Total bilirubin (mg/dL)	38.4%
AST (U/L)	35.5%
aPTT (seconds/control)	35.5%
ALT (U/L)	35.3%
C-reactive protein (mg/L)	28.1%
GCS <15	23.5%
IRN	22.9%
Lactate	21.7%
pO_2/FiO_2	18.1%
pCO_2	9.7%
HCO_3	9.7%
pH	9.1%
Respiratory rate (irpm)	7.7%
Sodium (mmoL)	7.7%
Platelet count (cels/mm^3)	5.2%
Neutrophils (cels/mm^3)	4.7%
NLR	4.7%
Urea (mg/L)	4.7%
Hemoglobin (g/dL)	4.3%
Diastolic pressure/amines use	4.3%

Lymphocytes (cels/mm^3)	4.1%
Leucocytes (cels/mm^3)	3.9%
Creatinine (mg/dL)	3.4%
SpO_2/FiO_2	3.4%
Systolic pressure/amines use	3.4%
Heart rate	0.7%
Mechanical ventilation at ICU admission	0%
Age	0%
Gender	0%
Arterial hypertension	0%
Coronary artery disease	0%
Heart failure	0%
Atrial fibrillation/Flutter	0%
Stroke	0%
COPD	0%
Diabetes mellitus	0%
Obesity	0%
Malignant neoplasm	0%
Chronic kidney disease	0%
Ex or current smoker	0%
Dexamethasone or other oral corticosteroid use before ICU admission	0%
Prophylactic or therapeutic anticoagulant therapy before ICU admission	0%

ALT: alanine aminotransferase; AST: aspartate aminotransferase; FiO_2: fraction of inspired oxygen; GCS: Glasgow coma scale; HCO_3: bicarbonate; ICU: intensive care unit; INR: international normalized ratio; NLR: neutrophil/lymphocyte ratio; pCO_2: partial pressure of carbon dioxide; pO_2: partial pressure of oxygen; aPTT: activated partial thromboplastin time; SAPS-3: Simplified Acute Physiology Score III; SOFA score: Sequential Organ Failure Assessment.

Supplementary file 6. Variable selection based on generalized additive model (GAM).

Variable	Deviance explained (%)	R-sq.(adj)	UBRE	D1-statistics (p-value)	D2-statistics (p-value)
All variables included	0.310	0.322	294.586		
Age (years)**	0.295	0.292	0.135	0.001	0.001
Heart rate (bpm)	0.329	0.335	0.086	0.997	0.998
Platelet count (10^9/L)	0.310	0.318	0.100	0.745	0.760
C-reactive protein (mg/dL)	0.317	0.321	0.101	0.554	0.860
Sodium (mmol/L)	0.323	0.331	0.088	0.999	1.000
Hemoglobin (g/dL)	0.327	0.335	0.085	1.000	1.000
Urea (mg/dL)	0.324	0.332	0.084	1.000	1.000
pCO_2	0.295	0.310	0.102	0.999	0.897
pO_2/FiO_2**	0.286	0.293	0.133	0.966	0.037
NLR	0.306	0.314	0.104	1.000	0.340
Sex at birth	0.328	0.335	0.084	0.671	0.686
Arterial hypertension	0.326	0.332	0.089	0.110	0.110
Coronary artery disease	0.327	0.335	0.084	0.786	0.818
Heart failure	0.327	0.336	0.085	0.577	0.592
Atrial fibrillation/Flutter	0.328	0.335	0.084	0.853	0.843
Stroke	0.328	0.336	0.084	0.701	0.709
COPD**	0.319	0.327	0.093	0.050	0.049
Diabetes mellitus	0.326	0.332	0.086	0.257	0.259
Obesity**	0.324	0.326	0.097	0.004	0,004
Malignant neoplasm	0.330	0.336	0,085	0.377	0,380
Chronic kidney disease	0.329	0.336	0.084	0.683	0,695

GCS <15	0.329	0.336	0.084	0.938	0,827
Systolic pressure/amines use	0.319	0.329	0.088	0.150	0,181
Ex or current smoker	0.328	0.335	0.084	0.790	0,808
Dexamethasone or other oral corticosteroid before ICU admission	0.327	0.335	0.085	0.561	0,569
Prophylactic or therapeutic anticoagulant therapy before ICU admission	0.327	0.334	0.085	0.592	0,603
Respiratory rate or if in IMV**	0.312	0.318	0.103	0.003	0,003

COPD: chronic obstructive pulmonary disease; D1: multivariate Wald test; D2: pools test statistics from the repeated analyses; GCS: glasgow coma scale; HCO_3: bicarbonate; ICU: intensive care unit; IMV: invasive mechanical ventilation; NLR: neutrophils-to-lymphocytes count ratio; Obesity: (BMI>30kg/m^2); pCO_2: partial pressure of carbon dioxide; UBRE: Unbiased risk estimator. ** Variable included in final model (p-value <0.05).

Supplementary file 7. L1 penalized shrunk coefficients and scaled coefficients from LASSO logistic regression.

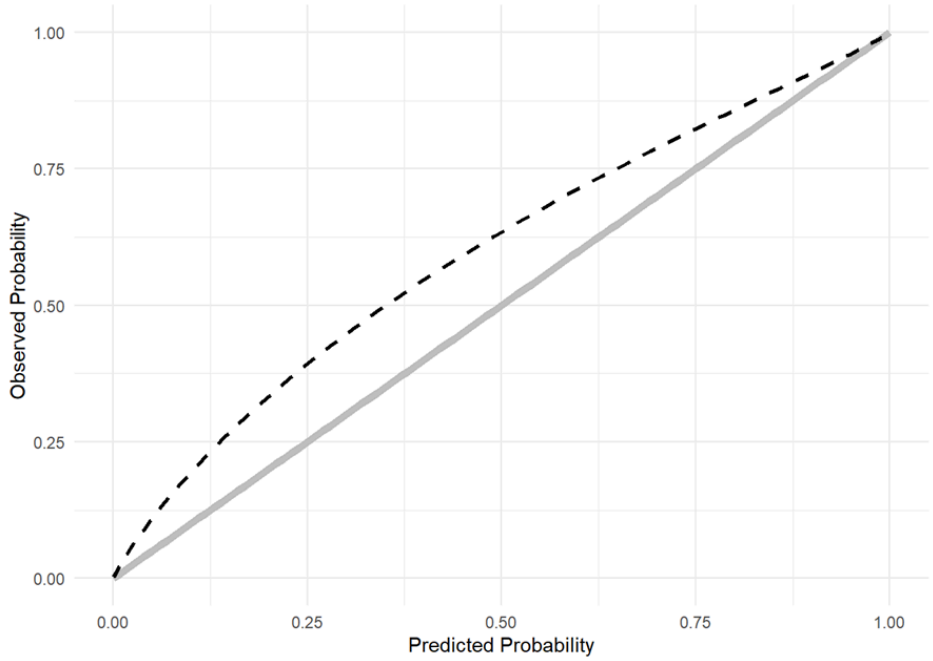
Variable	Coefficients	Scaled coefficients (x4)
Intercept	-1.407	-6
Age (years)		
60 - 69	0.125	1
70 - 79	0.326	1
> 80	0.850	3
pO_2/FiO_2		
< 100	0.956	4
100 - 200	0.338	1
Respiratory function		
>24 irpm	0.372	1
Mechanical ventilation	1.527	6
COPD		
Yes	0.393	2
Obesity		
Yes	0.240	1

BMI: body mass index; COPD: chronic obstructive pulmonary disease; LASSO: least absolute shrinkage and selection operator logistic regression; Obesity: body mass index > 30 kg/m^2.

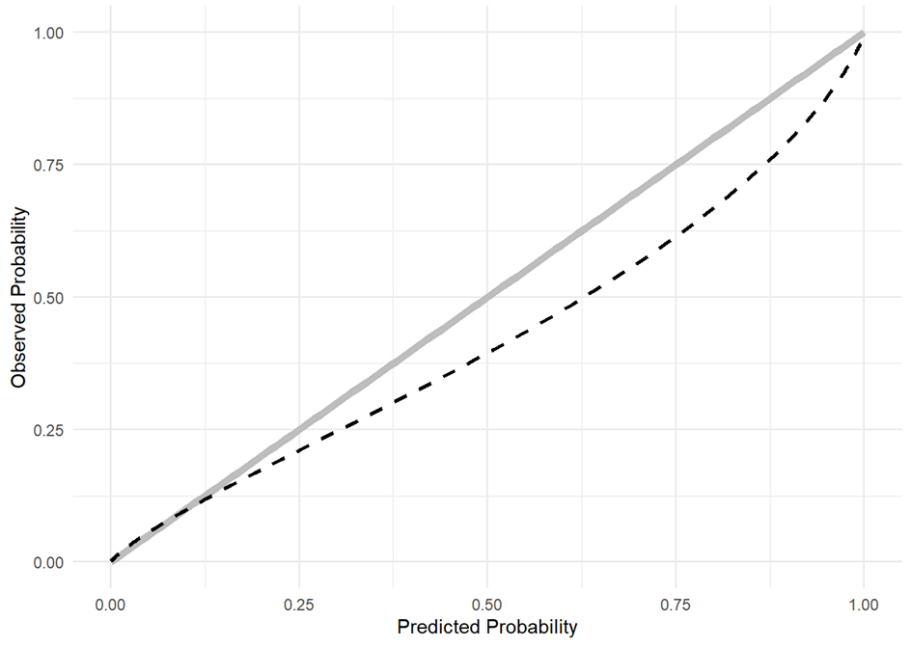
Supplementary file 8. Deaths according to the derived score.

New score	Patients	Deaths (n)	Deaths (%)	Expected deaths (%)
0	25	1	4.0%	14.4%
1	60	5	8.3%	19.3%
2	72	24	33.3%	25.4%
3	46	14	30.4%	32.6%
4	42	20	47.6%	40.8%
5	50	22	44.0%	49.4%
6	38	24	63.2%	58.2%
7	35	20	57.1%	66.4%
8	39	32	82.1%	73.8%
9	13	11	84.6%	80.0%
10	16	13	81.2%	85.0%
11	10	8	80.0%	89.0%
12	3	2	66.7%	92.0%
13	4	4	100.0%	94.2%
14	2	2	100.0%	95.9%
15	2	2	100.0%	97.1%
16	0	0	0%	97.9%

Supplementary file 9. Calibration plot of the risk scores used for comparison.

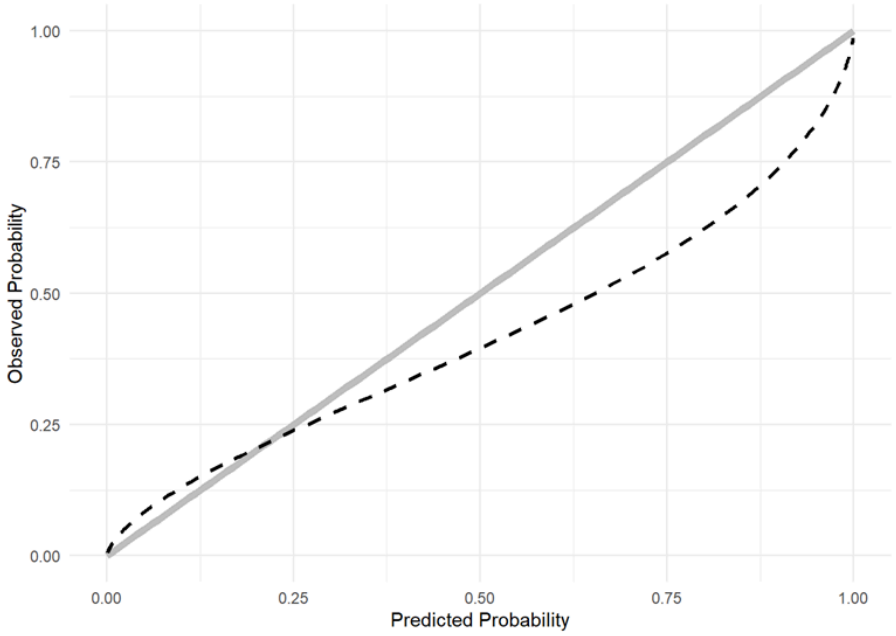


9A. 4C Mortality Score calibration plot

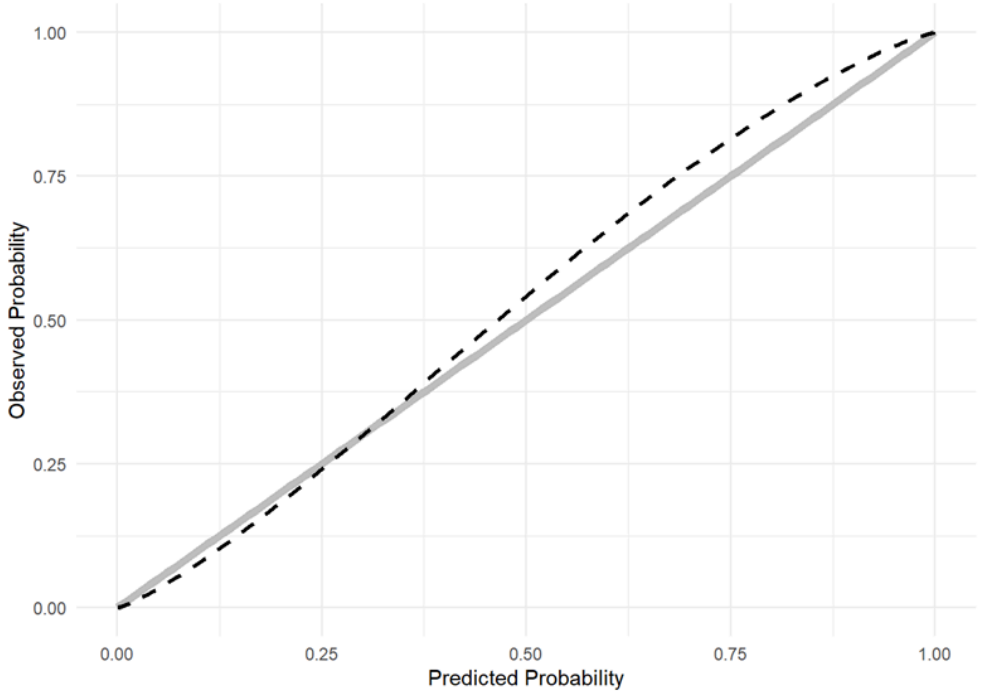


9B. ABC_2-SPH calibration plot

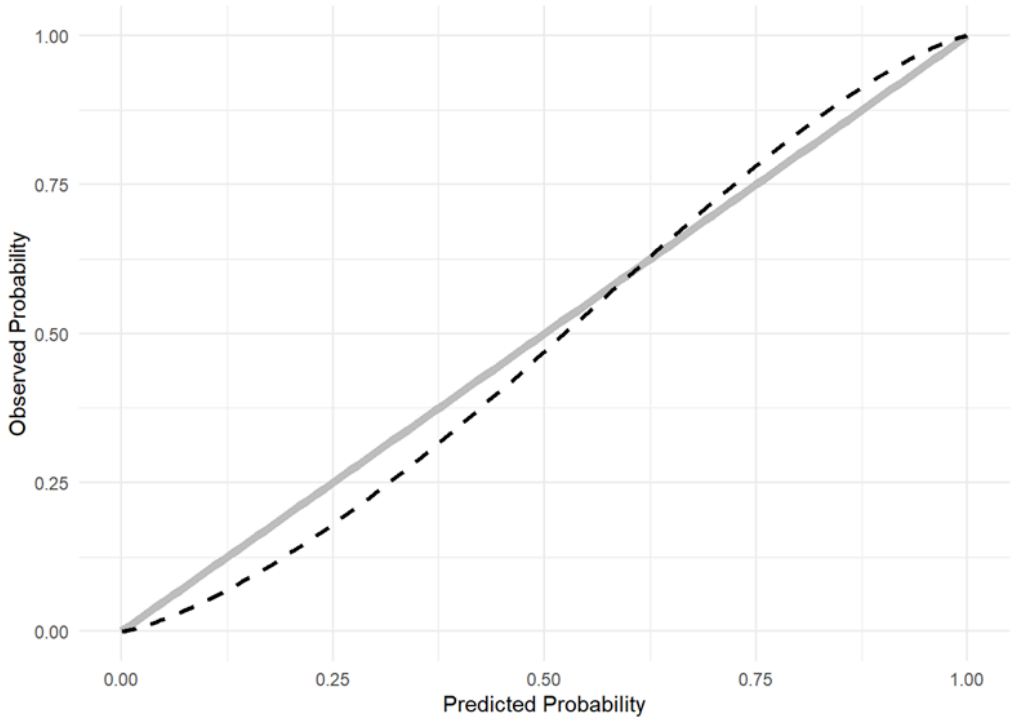
Supplementary file 10. Calibration plot of the sub analysis of vaccination status stratification.



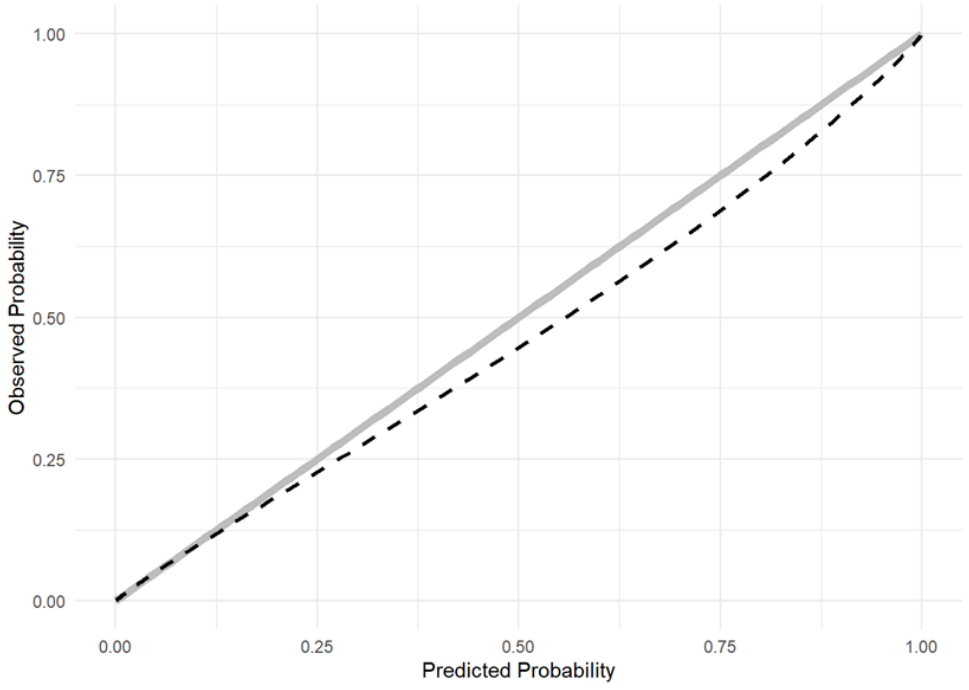
10A. Patients received one covid-19 shot.



10B. Patients received two or more covid-19 shots.



10C. Patients who did not receive any covid-19 shot.



10D. Patients lacking information on vaccination status.

7. COMENTÁRIOS DA BANCA EXAMINADORA

A banca sugeriu a realização de uma curva de calibração com intervalo de confiança, que foi obtida através do pacote "*Calibration Curves*" no programa "R". A curva foi representada na Figura 5, que apresenta três traçados, sendo a linha ideal em vermelho, que representa a calibração perfeita, a linha preta tracejada, que representa a calibração do modelo e, por último, a linha preta contínua, que representa uma calibração mais flexível usando a técnica de suavização "Loess", que mostra como a calibração do modelo varia ao longo das diferentes faixas de probabilidade. Há ainda a banda acinzentada ao redor desta, que indica o intervalo de confiança 95%. Com isso, o gráfico mostra que, na maioria das vezes, o modelo se aproxima do ideal, entretanto, o alargamento da faixa cinza do lado direito do gráfico indica maior incerteza nas previsões para altas probabilidades.

Como proposta para estudos futuros, foi discutida a importância da validação externa para o avaliar a possibilidade de uso do novo escore. Além disso, foi sugerido ainda que, com a queda significativa do número de casos de pacientes com covid-19 internados em unidades de terapia intensiva, seja avaliada a possibilidade de validar o escore para outras condições, como pneumonia, já que muitas das variáveis do AB_2CO também são consideradas como fatores de risco de mortalidade para outras condições, especialmente respiratórias.

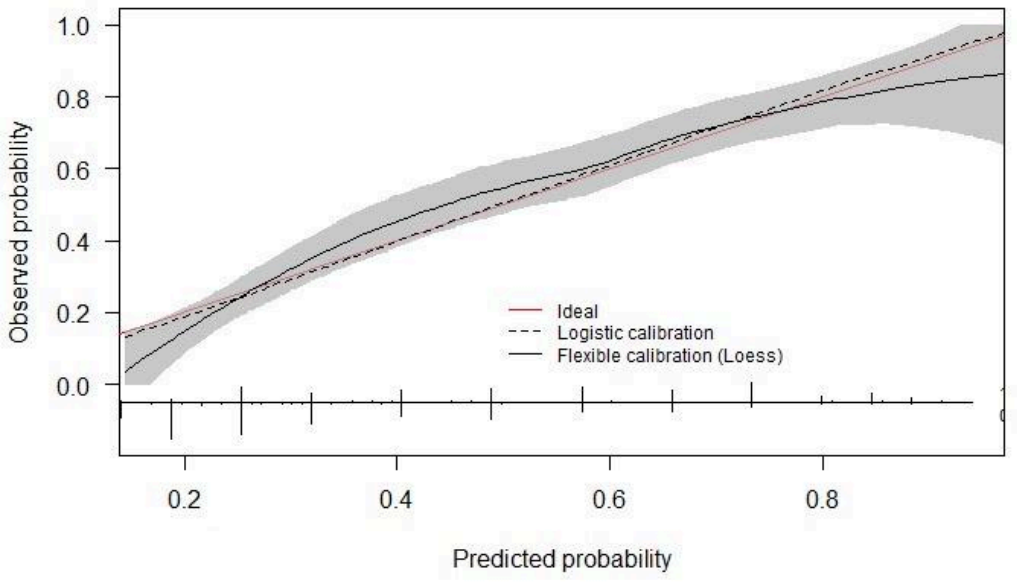


Figura 5: Curva de calibração do AB_2CO.

8. CONSIDERAÇÕES FINAIS

Neste estudo, desenvolvemos o escore AB_2CO, baseado em apenas seis variáveis: (i) idade, (ii) PaO_2/FiO_2, (iii) frequência respiratória se o paciente apresenta-se em ventilação espontânea, (iv) ventilação mecânica invasiva, (v) DPOC e (vi) obesidade. Trata-se de uma ferramenta simples, rápida, objetiva, barata e de fácil utilização à admissão em UTI, com variáveis rotineiramente obtidas nas instituições hospitalares. O AB_2CO mostrou uma boa capacidade de discriminação e uma excelente curva de calibração, demonstrando melhor desempenho que outros escores testados, ao utilizar dados mais recentes da covid-19, após o surgimento de novas variantes e ampla disponibilidade de vacinação. Entretanto, estudos futuros necessitam validar o escore para que seu uso seja recomendado, o que tem sido um grande desafio encontrar uma coorte parceira para tal.

A disponibilidade de um escore prognóstico confiável, especialmente desenvolvido para a população brasileira, é de suma importância. Logo, o desenvolvimento científico em um momento de extrema fragilidade, tem sido um incentivo para continuidade dos estudos, que busca o uso mais eficiente de recursos e melhoria assistencial - com tomada de decisões mais assertivas e melhores prognósticos, impactando vidas em uma escala global.

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APÊNDICES

APÊNDICE A - Aprovação da Comissão Nacional de Ética em Pesquisa (CONEP)

COMISSÃO NACIONAL DE ÉTICA EM PESQUISA

PARECER CONSUBSTANCIADO DA CONEP

DADOS DA EMENDA

Título da Pesquisa: Registro hospitalar multicêntrico nacional de pacientes com doença causada pelo SARS-COV-2 (COVID-19)

Pesquisador: Milena Soriano Marcolino

Área Temática:

Versão: 19

CAAE: 30350820.5.1001.0008

Instituição Proponente: Faculdade de Medicina da UFMG

Patrocinador Principal: Financiamento Próprio
FUNDACAO DE AMPARO A PESQUISA DO ESTADO DE MINAS GERAIS

DADOS DO PARECER

Número do Parecer: 6.086.943

Apresentação do Projeto:

As informações elencadas nos campos "Apresentação do Projeto", "Objetivo da Pesquisa" e "Avaliação dos Riscos e Benefícios" foram retiradas do arquivo Informações Básicas da Pesquisa (PB_INFORMAÇÕES_BÁSICAS_2045391_E18.pdf, de 10/04/2023).

INTRODUÇÃO

Coronavírus é o nome dado a um grupo de vírus RNA, com alta capacidade de mutação e estrutura microscópica com espículas, parecida com uma coroa (1). É uma grande família encontrada em animais como porcos, camelos, morcegos e gatos. Alguns desses vírus conseguem, através de mutações, atravessar a barreira interespécie, infectando os humanos. Em 1937 foram isolados os primeiros coronavírus humanos. Até dezembro de 2019, havia seis diferentes coronavírus isolados capazes de infectar os seres humanos e de causar respiratórias de diferentes gravidades (1). Entretanto, em dezembro de 2019, descreveu-se pela primeira vez o SARS-CoV-2 (2). Infecções provenientes do SARS-CoV-2, chamadas COVID-19, rapidamente se alastraram pelo mundo. Até dia 7 de abril de 2020, tivemos mais de 1.428.428 casos ao redor do mundo e mais de 82.020 mortes pela COVID-19 (3). Os países mais acometidos são: Estados Unidos, Espanha e Itália, com seus respectivos números de casos confirmados: 398.185, 141.942, 135.586 (Situation report, World Health Organization) (4). No Brasil, até dia 6 de abril de 2020, temos 14.034 casos

confirmados e 686 mortes até o momento, sendo 304 no estado de São Paulo e 71 no estado do Rio de Janeiro. No dia 20 de março de 2020, todo o país foi considerado como transmissão comunitária (Ministério da Saúde) (5). Dados do Brasil ainda são escassos e limitados. A análise da incidência de mortalidade e complicações, além da análise de fatores relacionados à ocorrência dos desfechos têm grande importância para profissionais da linha de frente, gestores e para a Saúde Pública. Nenhum estudo foi realizado até o momento com os pacientes confirmados pelo vírus no Brasil. Dessa forma, objetiva-se com esse estudo, a análise de casos confirmados da doença, a fim de observa-se padrões e peculiaridades da dinâmica e progresso natural da doença no cenário brasileiro. Como objetivo específico, tem-se gerar informações sobre custo real e seus determinantes do manejo de pacientes com SARS-COV-2 para subsidiar cientificamente estratégias de reembolso em formato de bundled nas perspectivas de saúde pública e suplementar.

HIPÓTESE

1. Questão – As descrições apresentadas na literatura internacional sobre infecções pelo novo coronavírus 2019 são aplicáveis para a realidade brasileira?

Hipótese – As descrições apresentadas na literatura acadêmica existentes sobre o perfil clínico, laboratorial, radiológico e terapêutico dos pacientes diagnosticados com o novo coronavírus 2019 e admitidos em hospitais brasileiros são diferentes, fator que faz fundamental a consideração das peculiaridades brasileiras durante o rastreio, diagnóstico e tratamento dessa enfermidade.

2. Questão - Quais os principais sintomas apresentados pelos pacientes soropositivos para o SARS-CoV-2 brasileiros, em especial, dos pacientes admitidos nas diferentes unidades federativas do Brasil?

Hipótese – As manifestações clínicas mais comuns nos pacientes brasileiros associados testados para o coronavírus estão relacionadas a febre, mialgia, sintomas respiratórios e cefaleia.

3. A mortalidade hospitalar dos pacientes admitidos em hospital com COVID-19 é semelhante à descrita na literatura?

Hipótese - O perfil de mortalidade hospitalar dos pacientes admitidos em hospitais brasileiros com COVID-19 não é semelhante à apresentada na literatura.

4. Qual o custo do tratamento hospitalar dos pacientes com COVID-19 considerando as comorbidades dos pacientes?

Hipótese – O custo do tratamento hospitalar dos pacientes com COVID-19 tem variação em função das comorbidades observadas entre os pacientes.

5. É possível subsidiar cientificamente estratégias de reembolso em formato de bundled nas perspectivas de saúde pública e suplementar?
Hipótese – O custo do tratamento hospitalar dos pacientes com COVID-19 e os desfechos esperados têm variação em função das comorbidades observadas entre os pacientes e podem ser analisados de forma conjunta para subsidiar estratégias e reembolso em formato de bundled.

METODOLOGIA
Trata-se de estudo observacional, baseado na coleta de dados de pacientes confirmados com doença causada pelo novo coronavírus 2019 (SARSCoV-2), por sorologia ou RT-PCR. A coleta de dados poderá ser realizada por dois métodos: 1. Análise retrospectiva de prontuários dos pacientes admitidos nos hospitais parceiros (feita por leitura e extração de dados presentes nos prontuários médicos) e 2. Análise prospectiva dos pacientes internados nos respectivos centros hospitalares (análise e extração diária da evolução dos pacientes hospitalizados). Ademais, diante da existência de sistemas de notificação compulsória do Ministério da Saúde, dados adicionais poderão ser obtidos por esta plataforma mediante solicitação formal a esta instituição estadual (Secretarias Estaduais de Saúde). A vigência dos dados será de 12 meses consecutivos/retrospectivos, avaliando-se possíveis variações sazonais. Os dados coletados serão vinculados a protocolos pré-estabelecidos de atendimentos, típicos de atendimento de clínica médica ou pediátrica, em que é identificado sexo, idade, queixa principal, história da moléstia atual, comorbidades prévias, sintomas associados, história epidemiológica ou de viagem, avaliação primária laboratorial (exames sanguíneos como hemograma, proteína-C reativa, dímero, enzimas hepáticas, marcadores inflamatórios, e testes para outros patógenos), avaliação radiológica, terapêutica implementada e desfechos (mortalidade, síndrome da angústia respiratória do adulto, complicações cardiovasculares, complicações hemorrágicas, eventos tromboembólicos, choque séptico, coagulação intravascular disseminada, infecção nosocomial, necessidade de terapia intensiva, ventilação mecânica e terapia renal substitutiva, falência de extubação). Além disso, dados associados a exame físico presentes nos prontuários ou obtidos pelos integrantes do grupo de pesquisa serão obtidos. Para a análise de custos e proposição de modelo de remuneração, a orientação da literatura sobre condução de estudos de microcusteio, permitindo a análise em nível individual por paciente, e uso do método de custeio baseado em atividades e tempo serão seguidos para estruturar a coleta de dados (6-8).A partir do mapeamento da jornada do paciente, desde a chegada na emergência ou hospital de campanha até a alta ou o óbito, os dados de consumo de recursos (profissionais, estrutura hospitalar, materiais e medicamentos), serão

coletados de forma retrospectiva pela revisão de registros de evoluções clínicas e bases de dados administrativos das instituições. Também serão coletados os dados de investimentos específicos em equipamentos para preparar as estruturas hospitalares no atendimento dos pacientes com SARS-COV-2, e de necessidade de reestruturações de práticas de controle de qualidade e segurança, vigilância e esterilização de equipamentos e ambiente. O Formulário I apresenta a orientação para coleta de dados de custos de cada unidade nos hospitais, investimentos de capital realizados para o tratamento do COVID-19, remuneração atualizada e escala de profissionais especiais para o atendimento hospitalar dos pacientes e o Formulário II a orientação para coleta de dados de consumo de recursos em nível individual por paciente. O Formulário I deverá ser respondido por gestor da instituição que será convidado a colaborar com a pesquisa, sendo o aceite o convite o consentimento do profissional em participar da pesquisa. O Formulário II deve ser utilizado por pesquisador interno da instituição para a coleta de dados em prontuário de forma retrospectiva. Ressalta-se que dados de identificação dos pacientes não serão obtidos em momento nenhum do estudo.

CRITÉRIOS DE INCLUSÃO
Serão incluídos nesse estudo pacientes com COVID-19 confirmada (testes serológicos de RT-PCR ou teste sorológico), admitidos em hospitais brasileiros. Faremos a inclusão de todos os pacientes diagnosticados, independente de faixa etária, perfil de comorbidades previamente diagnosticadas, assim como rede hospitalar admitida (pública ou privada).

CRITÉRIOS DE EXCLUSÃO
Eventos médicos associados a outras enfermidades infectocontagiosas, como influenza e dengue, não serão contabilizados nesse estudo.

Objetivo da Pesquisa:
OBJETIVOS PRIMÁRIOS
Determinar o perfil clínico, laboratorial, radiológico, prática terapêutica e mortalidade de pacientes confirmados com infecção do novo coronavírus 2019 admitidos em hospitais da rede SUS, privados e filantrópicos no Brasil.
Identifica, avaliar desfechos primários como mortalidade, admissão em Unidade de Terapia Intensiva (UTI), tempo de hospitalização, duração em ventilação mecânica e terapia renal substitutiva.

OBJETIVOS SECUNDÁRIOS

i. Avaliar complicações: incidência de síndrome de disfunção respiratória do adulto, miocardite e outras complicações cardiovasculares, necessidade de ventilação mecânica e terapia intensiva, além de dias de terapia intensiva em pacientes admitidos nos centros hospitalares parceiros;

ii. Obter e comparar dados dos eventos relacionados aos dados obtidos com dados apresentados na literatura internacional.

iii. Gerar informações sobre custo real e seus determinantes do manejo de pacientes com SARS-COV-2 para subsidiar cientificamente estratégias de reembolso em formato de bundled nas perspectivas de saúde pública e suplementar.

iv. Derivar e validar escores prognósticos para mortalidade, necessidade de terapia renal substitutiva e tromboembolismo venoso em pacientes com COVID-19, a partir de dados clínicos e laboratoriais.

v. Analisar desfechos e fatores prognósticos em subgrupos de interesse, como gestantes, crianças, pacientes oncológicos, pacientes com história de transplante prévio, pacientes com miocardiopatia chagásica, pacientes com manifestações neurológicas e pessoas vivendo com HIV/Aids.

vi. Realizar a validação externa do escore ABC2-SPH desenvolvido em etapa anterior deste estudo (doi.org/10.1101/2021.02.01.21250306) em pacientes admitidos em UTI.

vii. Identificar características hospitalares associadas a mau prognóstico em pacientes com COVID-19.

viii. Realizar comparação entre a utilização da análise estatística tradicional e a aprendizagem de máquina para a elaboração de modelos para predição de mortalidade causada pelo COVID-19.

ix. Comparar o perfil clínico, laboratorial, radiológico e complicações de pacientes confirmados com COVID-2019 no ano de 2020, com o perfil dos anos subsequentes;

x. Avaliar a incidência dos diferentes sintomas da forma pós-aguda da COVID-19 em pacientes que receberam alta das instituições parceiras.

Avaliação dos Riscos e Benefícios:

RISCOS

Os riscos em que a pesquisa está relacionada são descritos nos tópicos a seguir, assim como medidas atenuantes respectivas:

i. Possibilidade de extravio e furto de dados; medida resolutiva: informações pessoais/tematicamente identificáveis não serão permanentemente armazenadas em drivers manuais, celulares smartphones ou laptops, exceto em casos em que tais dados estejam submetidos à encriptação. Ademais, os conjuntos de dados obtidos e armazenados serão

memorizados em um servidor institucional seguro, inacessível ao público em geral.
ii. Risco à imagem de pessoas físicas (passageiros/pacientes) atrelados a pesquisa; medida resolutiva: cada indivíduo de pesquisa receberá um código de caso (Record Locator Number- RLN), estruturado da seguinte forma:
1. Sigla da Instituição médica
2. Número contínuo do caso
3. Cidade em que o paciente foi admitido. Ressalta-se que a obtenção de dados pessoais retroativos, vinculados aos pacientes do estudo encontra-se respaldada na Lei 13.709, de 14 de agosto de 2018, que dispõe sobre a proteção de dados pessoais e altera a Lei 12.965, de 23 de abril de 2014.
Os resultados da pesquisa serão tornados públicos ao final do projeto, através de publicações nacionais, internacionais e relatórios às classes médicas, ao Ministério da Saúde e à Anvisa.

BENEFÍCIOS
Mormente, vale destacar que os benefícios associados com a execução deste projeto científico são múltiplos.
1. Desenvolvimento de literatura específica e fidedigna Inicialmente, frente a lacuna literária detectada, espera-se desenvolver referências bibliográficas confiáveis e que reflitam a realidade brasileira, considerando todas as singularidades nacionais.
2. Análise da realidade epidemiológica brasileira e delineamento de atendimento emergencial aos pacientes infectados pelo COVID-19 Concomitantemente, deseja-se conhecer o cenário existente de pandemia, auxiliando as instituições relacionadas com eventos relacionados à saúde em doenças infectocontagiosas na elaboração de medidas preventivas, protocolos de atendimento e melhor treinamento da equipe (médicos e outros profissionais de saúde) nas intercorrências existentes.
3. Promoção de práticas educativas e de formação De forma similar, almeja-se a consolidação de campanhas informativas para diversas camadas populacionais (e seus nichos epidemiológicos), em parceria com o Conselho Federal de Medicina e universidades públicas e privadas, a fim de treinar profissionais da saúde para o atendimento de casos de COVID-19 no Brasil.

Comentários e Considerações sobre a Pesquisa:
Emenda 18

Justificativa da Emenda:

COMISSÃO NACIONAL DE ÉTICA EM PESQUISA

"Solicitamos no presente adendo, alterar o cronograma de execução, prorrogando a finalização do projeto. Além disso, foi corrigida a data de início das análises estatísticas (no cronograma anteriormente o item era finalização das análises, foi corrigido para realização das análises, com data de início e previsão de término). As modificações feitas no projeto original aprovado na CONEP foram destacadas no texto do projeto na cor vermelha.".

O documento alterado na presente emenda foram:

1. BROCHURA DO INVESTIGADOR, documento intitulado:
Brochura do investigador COVID-19, (word) de 10 de abril de 2023.

Considerações sobre os Termos de apresentação obrigatória:
Verificar item "Conclusões ou Pendências e Lista de Inadequações".

Recomendações:
Verificar item "Conclusões ou Pendências e Lista de Inadequações".

Conclusões ou Pendências e Lista de Inadequações:
Não foram identificados óbices éticos nesta emenda.

Considerações Finais a critério da CONEP:
Diante do exposto, a Comissão Nacional de Ética em Pesquisa - Conep, de acordo com as atribuições definidas na Resolução CNS nº 466 de 2012 e na Norma Operacional nº 001 de 2013 do CNS, manifesta-se pela aprovação da emenda proposta ao projeto de pesquisa.

Situação: Emenda aprovada.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_2045391_E18.pdf	10/04/2023 18:14:17		Aceito
Projeto Detalhado / Brochura Investigador	E18_Brochura_COVID19_Plataforma_Brasil.docx	10/04/2023 18:11:52	POLIANNA DELFINO PEREIRA	Aceito

Endereço: SRTVN 701, Via W 5 Norte, lote D - Edifício PO 700, 3º andar
Bairro: Asa Norte **CEP:** 70.719-040
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COMISSÃO NACIONAL DE ÉTICA EM PESQUISA

Outros	E18_Carta_Adendo.docx	10/04/2023 18:11:39	POLIANNA DELFINO PEREIRA	Aceito
Folha de Rosto	FRA.pdf	07/04/2020 22:12:43	ISRAEL JUNIOR BORGES DO NASCIMENTO	Aceito

Situação do Parecer:
Aprovado

BRASILIA, 30 de Maio de 2023

Assinado por:
Laís Alves de Souza Bonilha
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ANEXOS

ANEXO A - Publicação do artigo

Respiratory Medicine 227 (2024) 107635

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Original Research

AB_2CO risk score for in-hospital mortality of COVID-19 patients admitted to intensive care units

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ABSTRACT

Purpose: To develop a mortality risk score for COVID-19 patients admitted to intensive care units (ICU), and to compare it with other existing scores.
Materials and methods: This retrospective observational study included consecutive adult patients with laboratory-confirmed COVID-19 admitted to ICUs of 18 hospitals from nine Brazilian cities, from September 2021 to July 2022. Potential predictors were selected based on the literature review. Generalized Additive Models were used to examine outcomes and predictors. LASSO regression was used to derive the mortality score.
Results: From 558 patients, median age was 69 years (IQR 58–78), 56.3 % were men, 19.7 % required mechanical ventilation (MV), and 44.8 % died. The final model comprised six variables: age, pO_2/FiO_2, respiratory function (respiratory rate or if in MV), chronic obstructive pulmonary disease, and obesity. The AB_2CO had an AUROC of 0.781 (95 % CI 0.744 to 0.819), good overall performance (Brier score = 0.191) and an excellent calibration (slope = 1.063, intercept = 0.015, p-value = 0.834). The model was compared with other scores and displayed better discrimination ability than the majority of them.
Conclusions: The AB_2CO score is a fast and easy tool to be used upon ICU admission.

1. Introduction

Even with the expansion of COVID-19 vaccination worldwide, it is estimated that the disease still evolves into mortality in up to 40.3 % of cases requiring intensive care units (ICU) [1,2]. Numbers are even higher in specific populations like elderly patients [3], and exceed 68 % in those who require mechanical ventilation [4].

Severity scores are commonly used in the critical care setting, to facilitate the allocation of resources to those most at risk, aiming at improving assistance and reducing mortality [5]. Previously known risk scores, as well as disease-specific new tools, have been tested in COVID-19 patients admitted to the ICU, with an average performance at most [5–7]. Despite being commonly used to predict outcomes at the ICU, those scores presented low accuracy for COVID-19. In addition, most scores were tested before the broad use of COVID-19 vaccination, which may impair overall performance significatively [5,6,8].

Although Brazil was one of the most affected countries in terms of COVID-19 cases and deaths, with a significant burden in the healthcare system, validation studies of such scores among Brazilian COVID-19 patients are scarce, and the studies available have methodological limitations [9–11]. In another study from our research group [12], we assessed prediction ability on a few scores using data from October 2020 to March 2022, including a score we developed to be used at the moment of hospital admission, the ABC_2-SPH [13]. All of them showed intermediate discrimination ability with inadequate calibration plots [12].

Therefore, we aimed to develop an in-hospital mortality prediction risk score for COVID-19 patients admitted to ICU and to compare it with other existing scores.

2. Materials and Methods

This study is part of the Brazilian COVID-19 Registry, a retrospective multicenter cohort, which originally included 41 hospitals in 18 cities from six Brazilian states, described in detail elsewhere [14,13]. Model development followed the Transparent Reporting of a Multivariable Prediction Model for Individual Prediction or Diagnosis (TRIPOD) checklist (Supplementary file 1) and the Prediction model Risk Of Bias Assessment Tool (PROBAST) (Supplementary file 2) [15,16].

2.1. Study subjects

This study included consecutive adult patients (≥18 years) with laboratory-confirmed COVID-19 through SARS-CoV-2 reverse transcription-polymerase chain reaction (RT-PCR) or antigen test, according to the World Health Organization guidance [17], admitted to the ICU of one of the eighteen participating hospitals, from September 1, 2021, to July 12, 2022. Pregnant women, patients in palliative care, those admitted for another reason and who developed COVID-19 symptoms while in-hospital, patients transferred to another hospital not part of the cohort, and those whose outcome was not available were excluded (Fig. 1).

2.2. Data collection

Demographic data, clinical characteristics, laboratory findings, therapeutic interventions, and outcomes were collected by trained researchers from medical records using the Research Electronic Data Capture (REDCap) electronic platform [18,19], hosted at the Telehealth Center of the *Hospital das Clínicas*, *Universidade Federal de Minas Gerais* (UFMG) [20]. The guidance manual for ICU data collection is available in the supplementary file (Supplementary file 3). For this study, we considered only the first ICU admission during the hospital stay.

To ensure data accuracy, all information was verified periodically. Values of possible data entry errors were identified by using a code developed in R software and based on expert-guided rules. Then, it was sent to each hospital for checking and correction [13].

2.3. Outcome

The primary outcome was all-cause in-hospital mortality.

2.4. Sample size

All eligible patients admitted to the participating ICUs during the study period were included.

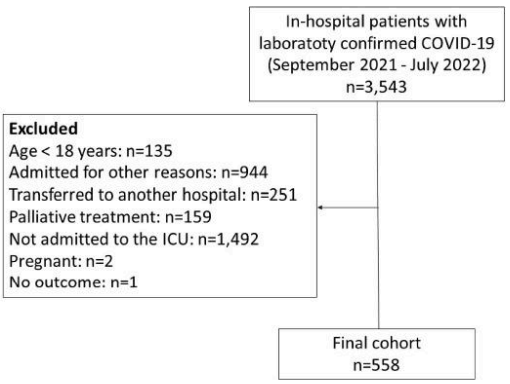

Fig. 1. Flowchart of COVID-19 patients included in the study.

2.5. Statistical analysis

Continuous variables were described using medians and interquartile ranges (IQR) and categorical variables were presented as absolute and relative frequencies. This study reported 95 % confidence intervals, and a p-value <0.05 was considered statistically significant. All analysis was performed with R software (version 4.0.2), using the mgcv, finalfit, mice, glmnet, pROC, rms, rmda, and psfmi packages.

2.6. Missing data

Candidate predictor variables that were unavailable for at least two-thirds of patients were excluded. Missing values on candidate explicative variables were imputed using multiple imputations with chained equations (MICE).

2.7. Development of the risk score model

Patients admitted from September 1, 2021, to July 12, 2022, were included in the development cohort. All variables used were obtained at ICU admission, except for the outcome. Potential predictors for ICU in-hospital mortality were selected based on previous literature (Supplementary file 4). Then we assessed the frequency of missing data (Supplementary file 5). Those predictors with high collinearity were not included.

Generalized Additive Models (GAM) were used to assess the relationships between outcome (in-hospital mortality) and continuous and categorical predictors (Supplementary file 6). Then, continuous variables selected were categorized for LASSO logistic regression analysis, based on commonly recognized cut points, and/or categories described in well-established score systems (Supplementary file 7). The risk groups were proposed based on the probability of mortality risk, as recommended by the TRIPOD [15] guidelines. Risk stratification cathegories were based on other scores [21].

2.8. Performance measures

The area under the receiver operating characteristic curve (AUROC) was used to describe the model discrimination. The general performance was evaluated through the Brier score [22]. The calibration was evaluated graphically by plotting the predicted probabilities of mortality compared to the observed mortality, with an intercept test equal to zero and a slope equal to one.

2.9. Model comparisons

On a complete case analysis, the developed model was compared with other existing scores, such as ABC_2-SPH, SOFA, Atschul et al., 4C Mortality Score, CURB-65, SOARS, Modified CHA_2DS_2-VASc, NEWS2, and COVID-SOFA score [13,23–30] using AUROC. These scores were identified through a literature search of Medline, without any language restrictions, using the terms "COVID-19" and "coronavirus" combined with "mortality", and "score". Additionally, other established risk scores used in ICUs for pneumonia and sepsis which were previously tested to be used for COVID-19 patients were included as well. Those scores with variables available in our database were selected. The DeLong method with Bonferroni correction was used to make pairwise comparisons between the AUROCs of the developed score and the other scores.

2.10. Subanalysis

In order to understand the accuracy of the developed model in vaccinated and unvaccinated patients, we have incorporated an analysis stratifying by vaccination status.

3. Results

Of 558 patients, 56.3 % were men, the median age was 69 (IQR 58–78) years old, 19.7 % required mechanical ventilation before or at the moment of ICU admission, and 44.8 % died during hospitalization. Demographic and clinical characteristics, as well as laboratory findings for the derivation cohort, are displayed in Table 1.

Forty-six potential predictor variables were identified (Supplementary file 5). Eight variables were excluded due to excessive missing values. Ten were excluded for high collinearity. Respiratory rate and mechanical ventilation were combined into a single variable. Thus, a total of twenty-seven variables were tested. A combination of six variables was selected through GAM as the best predictors of ICU in-hospital mortality (Supplementary file 6). The final model, named AB_2CO, was composed of: age, pO_2/FiO_2, respiratory function (respiratory rate or if in mechanical ventilation), chronic obstructive pulmonary disease (COPD), and obesity.

The prognostic index was created by scaling shrink coefficients. The sum of the prediction scores ranged from 0 to 16, with a higher score indicating a higher risk of death (Table 2 and Supplementary file 7). Risk groups were divided based on predicted death probability (Supplementary file 8) as intermediate risk (0 score, predicted mortality <15 %), high risk (1–5 score, 15–49,9 %), and very high risk (6–16 score, ≥50 %) (Table 3).

The AB_2CO score had an AUROC of 0.781 (95 % CI 0.744 to 0.819), good overall performance (Brier score = 0.191), and adequate calibration (slope = 1.063, intercept = 0.015, p-value = 0.834) (Figs. 2 and 3). All other scores evaluated (ABC_2-SPH, SOFA, Atschul et al., 4C Mortality Score, CURB-65, SOARS, Modified CHA_2DS_2-VASc, NEWS2, and COVID-SOFA score) had poor to average discrimination ability.

On a complete case analysis, the AB_2CO score achieved a discrimination ability of 0.783 (CI 95 % 0.743–0.822) better than SOFA, NEWS2, SOARS, Atschul et al., CURB-65 and modified CHA_2DS_2-VASc. Although not statistically significant, it showed higher AUROC than the 4C Mortality Score and COVID-SOFA, and better calibration plots than both of them, and also than ABC_2-SPH, despite slightly worse AUROC, as shown in Table 4 and Supplementary file 9.

In the subanalysis, we stratified patients through vaccination status. From a total of 558 patients, 198 (35.5 %) had missing information. From 251 patients who received 2 or more vaccine shots, we had 211 complete cases (with no missing cases for the score variables and 122 deaths. The AUROC was 0.801 (95 % IC 0.739–0.856). A total of 25 patients received only one shot, with 17 complete cases The AUROC was 0.700. The small sample size provided a large confidence interval (95 % IC 0.417–0.917). From those 84 who did not receive any covid-19 shot, there were 68 complete cases. The AUROC of 0.781 (95 % IC 0.660–0.881). Calibration curves were inadequate for those patients who received only one COVID-19 shot, slightly overestimated mortality in those at most risk who receive two or more shots, and underestimated mortality in those at lower risk who did not received any (Supplementary file 10).

4. Discussion

This study aimed to develop a new risk score for in-hospital mortality of COVID-19 patients admitted to 18 ICUs in Brazil. The novel score is composed of six readily available variables, three demographic characteristics (age, COPD, and obesity), and three clinical parameters observed upon ICU admission (pO_2/FiO_2, respiratory rate or whether the patient is in invasive mechanical ventilation). It showed a good discrimination ability in predicting mortality, superior to most of the scores chosen for comparison in this study, with an excellent calibration plot.

Several authors have tested the performance of severity scores traditionally used in critically ill patients. However, most of them are bound by methodological flaws which may lead to different biases (11).

Table 1
Clinical and demographic characteristics of patients included in this study (n = 558).

Characteristics	Overall[a]	Discharge[a]	Death[a]	p-value
Age (years)	69.0 (58.0, 78.0)	65,0 (53,0, 76,0)	73.0 (64.0, 81.0	<0.001
Sex at birth (Male)	314 (56.3 %)	167 (54.2 %)	147 (58.8 %)	0.278
Comorbidities				
Number of comorbidities				
0	120 (21.5 %)	75 (24.4 %)	45 (18.0 %)	
1	136 (24.4 %)	77 (25.0 %)	59 (23.6 %)	
2	169 (30.3 %)	92 (29.9 %)	77 (30.8 %)	
3	93 (16.7 %)	45 (14.6 %)	48 (19.2 %)	
4	29 (5.2 %)	16 (5.2 %)	13 (5.2 %)	
5	9 (1.6 %)	3 (1.0 %)	6 (2.4 %)	
6	2 (0.4 %)	0 (0.0 %)	2 (0.8 %)	
Hypertension	348 (62.4 %)	189 (61.4 %)	159 (63.6 %)	0.588
Coronary artery disease	47 (8.4 %)	27 (8.8 %)	20 (8.0 %)	0.746
Heart failure	72 (12.9 %)	41 (13.3 %)	31 (12.4 %)	0.749
Atrial fibrillation or flutter	26 (4.7 %)	12 (3.9 %)	14 (5.6 %)	0.342
Stroke	28 (5.0 %)	16 (5.2 %)	12 (4.8 %)	0.832
COPD	60 (10.8 %)	22 (7.1 %)	38 (15.2 %)	0.002
Asthma	196 (35.1 %)	101 (32.8 %)	95 (38.0 %)	0.200
Diabetes Mellitus	95 (17.0 %)	44 (14.3 %)	51 (20.4 %)	0.056
Obesity (BMI >30 kg/m^2)	5 (0.9 %)	1 (0.3 %)	4 (1.6 %)	0.179
Malignant neoplasm	49 (8.8 %)	22 (7.1 %)	27 (10.8 %)	0.129
Chronic kidney disease	58 (10.4 %)	30 (9.7 %)	28 (11.2 %)	0.574
HIV infection	9 (1.6 %)	5 (1.6 %)	4 (1.6 %)	>0.999
Current smoker	46 (8.2 %)	26 (8.4 %)	20 (8.0 %)	0.850
Ex-smoker	109 (19.5 %)	51 (16.6 %)	58 (23.2 %)	0.049
Clinical assessment at ICU admission				
GCS <15	81 (19.0 %)	43 (16.2 %)	38 (23.6 %)	0.057
pO_2/FiO_2	160.0 (98.7, 285.7)	194.4 (115.6, 336.2)	128.3 (85.2, 186.5)	<0.001
Respiratory rate (breaths/minute)				<0.001
≤ 24	253 (45.3 %)	180 (58.4 %)	73 (29.2 %)	
> 24	195 (34.9 %)	100 (32.5 %)	95 (38.0 %)	
MV	110 (19.7 %)	28 (9.1 %)	82 (32.8 %)	
Heart rate (beats/minute)	83.0 (74.0, 97.0)	80.0 (72.0, 94.0)	86.0 (76.0, 102.0)	<0.001
Systolic blood pressure (mmHg)				<0.001
≥ 90 (mmHg)	463 (85.9 %)	275 (92.3 %)	188 (78.0 %)	
< 90 (mmHg)	11 (2.0 %)	4 (1.3 %)	7 (2.9 %)	
Diastolic blood pressure (mmHg)				<0.001
>60 (mmHg)	390 (73.0 %)	233 (78.7 %)	157 (66.0 %)	
≤ 60 (mmHg)	79 (14.8 %)	44 (14.9 %)	35 (14.7 %)	
Inotrope requirement	75 (13.6 %)	24 (7.9 %)	51 (20.7 %)	<0.001
Laboratory parameters at ICU admission				
Urea (mg/dL)	53.9 (36.8, 85.2)	47.3 (32.0, 69.1)	62.1 (42.0, 95.5)	<0.001
Creatinine (mg/dL)	1.0 (0.8, 1.6)	0.9 (0.7, 1.3)	1.3 (0.9, 2.1)	<0.001
C-reactive protein (mg/dL)	113.5 (54.3, 192.0)	92.0 (40.7, 169.6)	144.5 (77.8, 218.5)	<0.001
pH	7.4 (7.3, 7.5)	7.4 (7.4, 7.5)	7.4 (7.3, 7.4)	<0.001
pO_2 (mmHg)	93.8 (70.3, 126.4)	96.9 (72.0, 125.1)	90.7 (67.6, 126.1)	0.297
pCO_2 (mmHg)	35.5 (31.3, 41.4)	35.1 (31.6, 40.0)	36.4 (31.0, 47.4)	0.018
HCO_3	22.6 (19.5, 25.4)	23.2 (20.6, 25.9)	21.4 (18.1, 25.0)	<0.001
Hemoglobin (g/L)	12.4 (10.6, 13.6)	12.4 (11.1, 13.6)	12.4 (10.3, 13.7)	0.664
Platelets (cels/mm^3)	197,000.0 (148,000.0, 258,000.0)	203,000.0 (159,000.0, 265,000.0)	183,000.0 (135,000.0, 246,750.0)	0.006
NLR	9.2 (5.3, 14.9)	7.3 (4.4, 12.0)	11.0 (7.1, 18.0)	<0.001
Sodium	138.0 (135.0, 141.0)	138.0 (135.0, 141.0)	138.0 (136.0, 142.0)	0.095
Leucocytes (cels/mm^3)	9252.5 (6707.5, 12,900.0)	8800.0 (6565.0, 11,860.0)	10,375.0 (7120.0, 14,407.5)	<0.001
Neutrophils (cels/mm^3)	7426.0 (5097.5, 10,682.5)	6826.0 (4699.2, 9307.2)	8540.5 (5507.2, 11,699.2)	<0.001
Lymphocytes (cels/mm^3)	830.0 (534.0, 1278.5)	914.0 (581.0, 1362.0)	727.5 (480.5, 1120.8)	<0.001
Medications before ICU admission				
Dexamethasone	237 (42.5 %)	123 (39.9 %)	114 (45.6 %)	0.178
Other oral corticosteroid	29 (5.2 %)	18 (5.8 %)	11 (4.4 %)	0.445
Budesonide	15 (2.7 %)	8 (2.6 %)	7 (2.8 %)	0.883
Other inhalatory corticosteroid	12 (2.2 %)	7 (2.3 %)	5 (2.0 %)	0.825
Prophylactic anticoagulation	157 (28.1 %)	77 (25.0 %)	80 (32.0 %)	0.067
Therapeutic anticoagulation	33 (5.9 %)	19 (6.2 %)	14 (5.6 %)	0.777
Tocilizumabe	11 (2.0 %)	8 (2.6 %)	3 (1.2 %)	0.360
Imunossupressor	24 (4.3 %)	9 (2.9 %)	15 (6.0 %)	0.075
Outcomes				
Mechanical ventilation at ICU admission	110 (19.7 %)	28 (9.1 %)	82 (32.8 %)	<0.001
In-hospital mortality	250 (44.8 %)			

[a] Statistics presented: Median (IQR); n (%). BMI: body mass index; COPD: chronic obstructive pulmonary disease; FiO_2: fraction of inspired oxygen; GCS: Glasgow Coma Score; HCO_3: bicarbonate; HIV: immune deficiency virus; MV: mechanical ventilation; NLR: lymphocyte/neutrophil ratio; pCO_2: partial pressure of carbon dioxide; PaO_2: partial pressure of oxygen; SF ratio: SpO_2/FiO_2 ratio; SpO_2: Oxygen saturation.

Table 2
AB_2CO score for ICU mortality in patients with COVID-19.

	Variables	Score
A	**Age (years)**	
	<60	0
	60–79	1
	≥80	3
B_2	**pO_2/FiO_2**	
	>200	0
	100–200	1
	<100	4
	Respiratory function	
	≤24 breaths/minute	0
	>24 breaths/minute	1
	In mechanical ventilation	6
C	**COPD**	
	No	0
	Yes	2
O	**Obesity**	
	No	0
	Yes	1

COPD: chronic obstructive pulmonary disease; FiO_2: fraction of inspired oxygen; pO_2: partial pressure of oxygen.

Although TRIPOD guidelines have not disclosed the exact sample size needed for developing a prediction model, it is known that providing more reliable results requires larger samples. For validation studies, it is recommended a minimum of 100 events and 100 nonevents, preferably

Table 3
Predicted mortality and mortality rates in risk groups.

Risk	Score	Predicted mortality	Number of patients	Number of deaths (%)
Intermediate	0	<15 %	25	1 (6.3 %)
High	1–5	15 - 49,9 %	270	85 (31.5 %)
Very high	6–16	≥50 %	162	118 (72.8 %)
	Overall	–	457	204 (44.6 %)

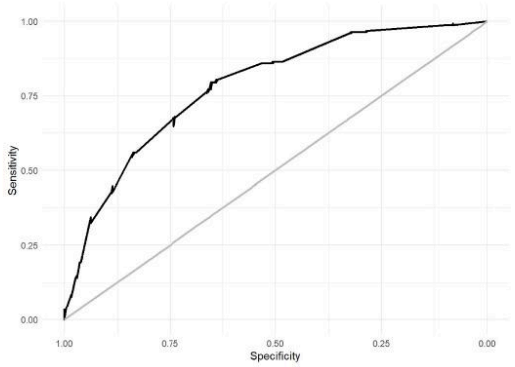

Fig. 2. Area under the ROC curve of the AB_2CO risk score.

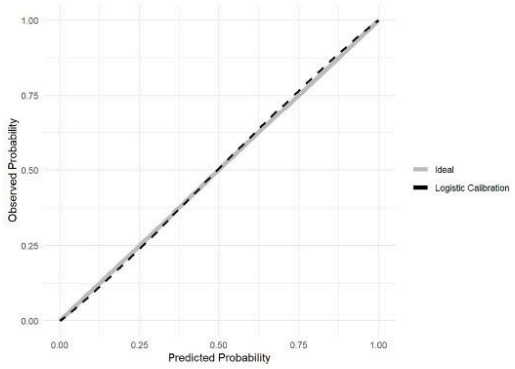

Fig. 3. Calibration plot of the AB_2CO risk score.

more than 250 events (30). Many of the analyzed studies included small samples which may have overestimated the models' performance. For example, Zou et al. (2020) assessed the performance of APACHE II, SOFA, and CURB-65 scores in only 154 ICU COVID-19 patients in China, although they observed an excellent discrimination ability (APACHE II: AUROC 0.966, SOFA: 0.867, CURB-65 0.844), the small sample size from one single center does not allow the generalization of the data [31].

In this study, we reported details about missing data and imputation methods, as recommended in TRIPOD guidelines. Excluding cases with missing values in score derivation studies may reduce sample size and also lead to biases when complete cases are not representative of the whole cohort [32]. Many studies did not or poorly disclose information on missing data, like another two recently published Brazilian studies [11,9] and the Modified CHA_2DS_2-VASc used in the comparison analysis [28], and data, in general, can be missing selectively rather than fully at

Table 4
Discrimination ability for each risk score applied in the Brazilian database of COVID-19 patients admitted to the intensive care unit, and comparison of the derived and other existing scores.

Compared score	p-value	AUROC of the score used in the comparison	N*
ABC_2-SPH	0.380	0.785 (0.7412–0.8301)	380
SOFA	0.025	0.660 (0.5829–0.7317)	202
NEWS2	0.004	0.691 (0.6101–0.7709)	173
4C Mortality Score	0.790	0.744 (0.6843–0.8018)	254
SOARS	<0.001	0.680 (0.6358–0.7226)	508
Altschul et al.	0.014	0.686 (0.6249–0.7429)	298
CURB-65	<0.001	0.658 (0.6139–0.7043)	470
Modified CHA_2DS_2-VASc	<0.001	0.592 (0.5447–0.6367)	558
COVID-SOFA	0.700	0.763 (0.6953–0.8221)	201

NEWS2: national early warning score; SOFA: sequential organ failure assessment. *Complete case analysis. Alpha = 0.0056. AUROC: area under the ROC curve. *Due to the multiple comparisons, alpha was corrected using Bonferroni method.

random, which can lead to bias [32].

Performance measurements should also be adequately reported. Calibration and discrimination are the two most used aspects. Calibration measures how well the model's predictions match the results that were actually seen, and discrimination describes a prediction model's capacity to distinguish between people who experience the outcome and those who do not [32]. An important study carried out in Brazil with 30,571 patients evaluated the SAPS-3 ability to predict mortality in ICU COVID-19 patients and the model's discrimination was highly satisfactory, with an AUROC of 0.835 (0.828–0.841). However, the calibration curve was inappropriate. Mortality was underestimated in those most at risk, and slightly overestimated in those at low to moderate risk. Additionally, the authors included data from a private healthcare network only, which may not reflect the reality of most of the Brazilian population, especially with a substantially lower mortality of 15 % [33], when compared to our database (44.8 %), in which 72.2 % of the cohort's hospitals serve public patients, and also, we included more updated data, being more reliable for the actual scenario.

Commonly used risk scores, such as SOFA, NEWS2, and CURB-65 showed an intermediate performance (AUROC of 0.660, 0.691 and 0.658, respectively). Those scores were widely tested for COVID-19 patients, despite being developed for other clinical situations, such as organ failure assessment, early warning for clinical deterioration, and to help determine inpatient or outpatient treatment for community-acquired pneumonia. The same was observed with other scores developed exclusively for COVID-19 patients, such as Altschul, SOARS and Modified CHA_2-DS_2-VASc (0.686, 0.680, and 0.5922 respectively). The COVID-SOFA score, developed exclusively for ICU COVID-19 patients, showed a good AUROC of 0.763, worse than our developed score. Also, despite showing a good AUROC, 4C Mortality Score and ABC_2-SPH showed poor calibration plot, showing that it is not possible to use them in actual scenarios, despite showing a good performance in their original studies when developed.

The emergence of new variants and vaccination efforts across time resulted in temporal changes in the mortality profile, as well the importance of different predictors [34]. To the extent of our knowledge, all of the developed risk scores for predicting mortality in COVID-19 patients admitted to the ICU did not consider it, and all of them were performed using patients from the early pandemic (Supplementary file 4). Therefore, they need to be validated in more recent scenarios, as it impacts the score's accuracy [34]. These reasons may explain in part the difference in results from what we have observed in the current analysis from those previously published, in addition to the aforementioned methodological limitations of the previous studies.

The AB_2CO score is a simple and objective method that can be used to determine the probability of death in COVID-19 patients using data

easily and routinely obtained at ICU admission. Furthermore, this score is reliable, as we strictly follow the methodological guidelines recommended by TRIPOD and PROBAST, ensuring quality data. Additionally, the choice of the variables was made based on systematic reviews, meta-analysis, previous cohort studies, and clinical reasoning, rather than the potentially biased selection of predictors. Finally, our findings are in line with previous evidence, as the predictors included in the score are well-established risk factors associated with disease severity and poor outcomes in COVID-19 patients.

Age was contemplated as an important risk factor for mortality among COVID-19 patients [35,36], due to increased cytokine production and decreased humoral immune response [37], in addition to the presence of some chronic medical conditions related to aging [36]. Obesity was linked with worse outcomes in several studies [36,38,39]. It is hypothesized that the mechanical pressure on the chest and abdomen reducing pulmonary function and the increased proinflammatory state related to excessive ectopic visceral fat might be the reason for the increased risk [38]. COPD was associated with mortality risk in previous studies as well [36,40,41]. It might be related to impaired recovery, with increased systemic inflammation [36]. The pO_2/FiO_2 ratio is a clinical measurement that assesses the severity of respiratory dysfunction [42,43], and it have already been shown that mortality is significantly higher in patients in mechanical ventilation, partly due to the fact that patients who required mechanical ventilation have more severe disease and also, due to the inherited risks and complications of the procedure itself [44,45].

The novel score may be suitable for use in settings where accurate and rapid stratification of risk is important. To the best of our knowledge, it is the first score developed in Brazil to evaluate the in-hospital mortality of ICU COVID-19 patients considering more recent data, after the broad use of COVID-19 vaccines.

This study has some limitations. First, the inherent limitations of observational cohort studies. Second, missing information on the vaccination status of most of the patients included in the cohort, which may impair accuracy in different groups. Third, the absence of an adequate number of complete cases of SAPS-3 for comparison, as it is an important score used in ICU settings. And last, the lack of external validation analysis. Thus, before being used in clinical practice, it must be externally validated, and the model may be recalibrated accordingly whether necessary, to make sure its utilization in other healthcare settings [15]. In addition, further studies are needed to validate the score in the coming years, properly allocating resources, giving better chances of successful treatment and outcomes, with the new rising variants and vaccination expansion.

5. Conclusion

The AB_2CO score is a simple, objective, and easy tool to be used in ICU admission, based on only six variables: age, PaO_2/FiO_2, respiratory function (respiratory rate or if in mechanical ventilation), COPD, and obesity, obtained routinely in institutions. This score showed a good discrimination ability and an excellent calibration curve when compared to other scores.

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Ethics approval and consent to participate

The study protocol was approved by the Brazilian National Commission for Research Ethics (CAAE: 30350820.5.1001.0008). Individual informed consent was waived due to the severity of the situation and to the use of deidentified data, based on medical chart review only.

Data availability statement

Data is available upon reasonable request.

Guidance manual for data collection availability

The full guidance manual for data collection is available upon request.

Data access, responsibility, and analysis

The lead authors (MSM and VMRG) had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Transparency declaration

The lead authors (MSM and VMRG) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

Role of the funder/sponsor

The sponsors had no role in study design; data collection, management, analysis and interpretation; writing the manuscript; and decision to submit it for publication. MSM and VMRG had full access to all the data in the study and had responsibility for the decision to submit it for publication.

Final approval of the version to be published: all authors

Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: VMRG, MCP and MSM.

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Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2024.107635.

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