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ASPECTOS RELACIONADOS À MORTALIDADE, INFECÇÃO DE CORRENTE SANGUÍNEA ASSOCIADA A CATETER E ASPERGILOSE EM PACIENTES COM COVID-19 EM UNIDADE DE TERAPIA INTENSIVA

ADRIANA LEMOS DE SOUSA NETO

UBERLÂNDIA
2024

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Tese apresentada ao Programa de Pós-Graduação em Ciências da Saúde da Faculdade de Medicina da Universidade Federal de Uberlândia, como requisito parcial para a obtenção do título de Doutor em Ciências da Saúde.

Área de concentração: Ciências da Saúde.

Orientadora: Denise Von Dolinger de Brito Röder

Coorientador: Reginaldo dos Santos Pedroso

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FOLHA DE APROVAÇÃO

ADRIANA LEMOS DE SOUSA NETO

Aspectos relacionados à mortalidade, infecção de corrente sanguínea associada a cateter e aspergilose em pacientes com COVID-19 em unidade de terapia intensiva

Presidente da banca: Profa. Dra. Denise Von Dolinger de Brito Röder

Tese apresentada ao Programa de Pós-Graduação em Ciências da Saúde da Faculdade de Medicina da Universidade Federal de Uberlândia como requisito parcial para a obtenção do título de Doutor em Ciências da Saúde. Área de concentração: Ciências da Saúde.

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DEDICATÓRIA

A Deus, pelas incontáveis bençãos recebidas até aqui, que me impulsionaram e me encorajaram a seguir em frente.

À minha mãe Dalva e à minha irmã Renata, mulheres fortes que me inspiram diariamente.

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RESUMO

Introdução: A pandemia da COVID-19 impactou o mundo todo devido ao grande número de mortes e sobrecarga aos sistemas de saúde ocasionada devido à alta transmissibilidade do vírus e à gravidade do quadro clínico dos pacientes, muitos dos quais necessitaram de hospitalização em Unidade de Terapia Intensiva (UTI). Um fator adicional de preocupação foi o crescente número de coinfecções durante o período pandêmico, que culminou em maiores índices de mortalidade. **Objetivo**: Investigar fatores de risco relacionados à mortalidade e infecção de corrente sanguínea associada a cateter (ICSAC) e relatar casos de aspergilose associada à COVID-19 (APAC) em pacientes adultos com COVID-19 hospitalizados em UTI. **Material e métodos**: Trata-se de um estudo tipo coorte retrospectivo cujos critérios de inclusão foram pacientes diagnosticados com COVID-19, com idade ≥ 18 anos, internados na UTI de um hospital universitário brasileiro em decorrência do agravamento da COVID-19, admitidos no período de março de 2020 a dezembro de 2021. **Resultados**: Foram incluídos 588 pacientes adultos admitidos na UTI, dos quais 55,27% foram a óbito (95% CI = 51,25 – 59,29; 325/588). A ventilação mecânica invasiva foi o preditor de risco de morte na UTI mais forte, juntamente com idade avançada e Simplified Acute Physiology Score 3 (SAPS3). Do total de pacientes avaliados, 413 usaram cateter venoso central por pelo menos 48 horas, dos quais 104 tiveram hemoculturas positivas para fungos e/ou bactérias. A maioria dos microrganismos encontrados foram bactérias Gram negativas (55,05%), e 55,96% eram resistentes a três ou mais antibióticos. Os patógenos mais prevalentes foram *Klebsiella pneumoniae* (17,43%), *Acinetobacter baumanni* (15,6%) e *Staphylococcus aureus* (13,76%). Nos modelos ajustados, apenas duas variáveis foram capazes de predizer infecção: a obesidade, que aumentou as chances de ICSAC em 1,39 vezes (OR = 2,39, IC95%: 1,36–4,22) e o número de dias de uso de cateter venoso central antes da infecção reduziu as chances em 0,05 vezes ao dia (OR = 0,91, IC95%: 0,91–0,99). A ICSAC aumentou o tempo de permanência do paciente na UTI e o tempo de internação hospitalar quando comparado ao tempo daqueles que não apresentaram a infecção. ICSAC isolada não foi capaz de afetar a mortalidade dos pacientes. Foram identificados oito casos de APAC, sendo 6 casos possíveis e 2 casos prováveis. Todos os casos foram à óbito e receberam corticóide durante a internação. **Conclusão**: A maioria dos pacientes com COVID-19 da amostra avaliada não sobreviveu. Pacientes com menor tempo de uso de cateter e obesidade apresentaram maior incidência de ICSAC. À medida que mais dados sobre coinfecções e mortalidade em pacientes com COVID-19 se tornam disponíveis, maiores são as oportunidades de investigação e implementação de estratégias que visem a redução da gravidade, mortalidade e impactos nos sistemas de saúde, considerando a possibilidade de novas ondas e/ou variantes da doença.

Palavras-chave: Coinfecção, Cuidado intensivo, SARS-CoV-2.

ABSTRACT

Introduction: The COVID-19 pandemic has impacted the entire world due to the large number of deaths and the burden on health systems caused by the high transmissibility of the virus and the severity of the clinical condition of patients, many of whom required hospitalization in the Intensive Care Unit (ICU). An additional cause for concern was the growing number of coinfections during the pandemic period, which led to higher mortality rates. **Objective**: identify aspects related to mortality and catheter-associated bloodstream infection (CABSI) and to report cases of COVID-19-associated aspergillosis (CAPA) in adult COVID-19 patients hospitalized in the ICU. **Material and methods**: This is a retrospective cohort study whose inclusion criteria were patients diagnosed with COVID-19, aged ≥ 18 years, admitted to the ICU of a Brazilian university hospital as a result of the worsening of COVID-19, admitted between March 2020 and December 2021. **Results**: 588 adult patients admitted to the ICU were included, of whom 55.27% died (95% CI = 51.25 - 59.29; 325/588). Invasive mechanical ventilation was the strongest predictor of risk of death in the ICU, along with advanced age and Simplified Acute Physiology Score 3 (SAPS3). Of the total number of patients evaluated, 413 had used a central venous catheter for at least 48 hours, of which 104 had positive blood cultures for fungi and/or bacteria. Most of the microorganisms found were gram-negative bacteria (55.05% of the germs), and 55.96% were resistant to three or more antibiotics. The most prevalent pathogens were *Klebsiella pneumoniae* (17.43%), *Acinetobacter baumanni* (15.6%) and *Staphylococcus aureus* (13.76%). In the adjusted models, only two variables were able to predict infection: obesity, which increased the chances of CABSI by 1.39 times (OR = 2.39, 95%CI: 1.36-4.22) and the number of days of central venous catheter use before infection reduced the chances by 0.05 times a day (OR = 0.91, 95%CI: 0.91-0.99). CABSI increased the patient's length of stay in the ICU and the length of hospital stay when compared to those who did not have the infection. CABSI alone was unable to affect patient mortality. Eight cases of CAPA were identified, 6 of which were possible cases and 2 probable cases. All the cases died and received corticosteroids during hospitalization. **Conclusion**: The majority of COVID-19 patients in the sample evaluated did not survive. Patients with a shorter duration of catheter use and obesity had a higher incidence of CABSI. As more data on coinfections and mortality in COVID-19 patients become available, there are greater opportunities for research and implementation of strategies aimed at reducing severity, mortality and impacts on health systems, considering the possibility of new waves and/or variants of the disease.

Keywords: Coinfection, Critical care, SARS-CoV-2.

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ABREVIATURAS

APAC	Aspergilose Associada à COVID-19
CAC	Candidíase Associada à COVID-19
COVID-19	Doença do Coronavírus 19
CoViNet	Rede de Coronavírus da OMS
ECMM	Confederação Europeia de Micologia Médica
ICSAC	Infecção de Corrente Sanguínea Associada a Cateter
ISHAM	Sociedade Internacional de Micologia Humana e Animal
MAC	Mucormicose Associada à COVID-19
NHSN	National Healthcare Safety Network
PAVM	Pneumonia Associada à Ventilação Mecânica
PCR	Reação em Cadeia da Polimerase
SARS-CoV-2	Coronavírus 2 da Síndrome Respiratória Aguda Grave
SDRA	Síndrome do Desconforto Respiratório Agudo
OMS	Organização Mundial de Saúde
UTI	Unidade de Terapia Intensiva

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1 INTRODUÇÃO

A pandemia da infecção pela doença do coronavírus 19 (COVID-19) foi um grande desafio para o mundo todo, com sobrecarga aos sistemas de saúde e Unidades de Terapia Intensiva (UTI) devido ao grande número de pacientes com grave quadro de insuficiência respiratória, principal manifestação da infecção pelo novo vírus (PETRIKOV; POPUGAEV; ZHURAVEL', 2022). Até o início de março de 2024, mais de 774 milhões de casos confirmados e mais de 7 milhões de mortes foram relatados globalmente (WHO, 2024). Sucessivas ondas epidêmicas com diferentes variantes do vírus ocorreram durante o período pandêmico e foram caracterizadas por um largo espectro de manifestações clínicas, cursos e desfechos, onde a maioria dos pacientes com sintomas graves requereu hospitalização (GRIMA; GUIDO; ZIZZA, 2023).

Fatores como idade, obesidade, *diabetes mellitus* e hipertensão estão entre os principais preditores de gravidade e mortalidade dos pacientes com COVID-19 (LOWHORN et al., 2024), além de menor renda familiar e taxa de analfabetismo (BALASUBRAMANI et al., 2024; HU et al., 2024). Doença cardiovascular e outras comorbidades, intubação do paciente, admissão na UTI e pneumonia também estão associadas à mortalidade e à gravidade da doença nesses pacientes (LOWHORN et al., 2024). Dessa forma, pessoas infectadas pelo vírus e que possuam os fatores de risco supracitados necessitam de vigilância intensiva, monitoramento e intervenção médica em tempo oportuno (WONDMENEH; MOHAMMED, 2024). Políticas e medidas de saúde pública como campanhas educativas destinadas à comunidades vulneráveis, acesso igualitário a testes, tratamento e vacinação são cruciais para conter e minimizar o impacto da COVID-19 (HOLDEN et al., 2024).

Um preocupação que surgiu com o aumento das internações pela COVID-19 foi o grande número de coinfecções e consequente elevação da taxa de mortalidade (ALDARHAMI et al., 2024). Durante a pandemia houve prejuízo nas práticas dos serviços de saúde devido à alta demanda de pacientes, maior carga de trabalho e escassez de recursos humanos e materiais, o que impactou na maior incidência de infecções relacionadas à assistência à saúde (IRAS), mudança no perfil das bactérias circulantes e da resistência antimicrobiana (ISMAEL et al., 2024). Houve aumento das coinfecções bacterianas e fúngicas em pacientes graves que necessitaram de hospitalização, especialmente em internados em UTI (KRSIHNAN; KUMAR; INBAKANI, 2024; YUSOF; NORHAYATI;
AZMAN, 2023).

Uma metanálise que avaliou 49 estudos sobre coinfecções bacterianas concluiu que, de forma geral, a prevalência de coinfecção bacteriana em pacientes com COVID-19 hospitalizados foi de 26,84% (YUSOF; NORHAYATI; AZMAN, 2023).

À medida que mais dados sobre coinfecções e mortalidade em pacientes com COVID-19 se tornam disponíveis, maiores são as oportunidades de investigação e implementação de estratégias que visem a redução da gravidade, mortalidade e impactos nos sistemas de saúde, considerando a possibilidade de novas ondas e/ou variantes da doença.

2 FUNDAMENTAÇÃO TEÓRICA

Declarada como pandemia pela Organização Mundial de Saúde (OMS) em 12 de março de 2020, a COVID-19 gerou impacto global devido sua alta mortalidade, principalmente em pessoas idosas e portadoras de comorbidades, o que sobrecarregou os sistemas de saúde e culminou em escassez de leitos em UTI nos hospitais devido ao aumento exponencial do número de casos (ALIZADEHSANI et al., 2021).

Com alto poder de transmissibilidade e infectividade, o vírus causador da COVID-19, identificado como um novo beta-coronavírus de RNA envelopado (denominado coronavírus 2 da síndrome respiratória aguda grave [SARS CoV-2]) (LU et al., 2020) se espalhou rapidamente, o que fez com que a medicina dispensasse tratamentos empíricos com antivirais e corticoides, e a ciência buscasse com urgência evidências de fatores de risco que contribuíssem na identificação rápida de casos graves e intervenção precoce, visando frear a mortalidade e controlar a transmissão viral (SUN et al., 2020). O SARS CoV-2 ocasiona um agravamento à saúde maior que o resfriado comum em virtude de sua patogênese, composta pelos estágios de replicação viral, hiperatividade imunológica e lesão pulmonar (HUANG et al., 2024; LI et al., 2021a).

Diante dos diferentes níveis de gravidade clínica entre os infectados pela COVID-19, a OMS definiu critérios para classificar a doença em crítica, grave e não grave. A síndrome do desconforto respiratório agudo (SDRA), sepse, choque séptico ou outras situações que requerem terapia para manutenção da vida, como ventilação mecânica (invasiva ou não invasiva) e terapia vasopressora, são condições que caracterizam o estado crítico da doença. A COVID-19 grave é definida por saturação de oxigênio <90% em ar ambiente, pneumonia grave, sinais de desconforto respiratório grave (em adultos, uso de musculatura acessória, incapacidade de completar frases completas, frequência respiratória > 30 respirações por minuto. A COVID-19 não grave ocorre quando há ausência de qualquer critério para COVID-19 grave ou crítica (WHO, 2023).

O agravamento do quadro de COVID-19 requer tratamento intensivo com a utilização de modernos esquemas e protocolos de terapia medicamentosa, ventilação mecânica e

oxigenação por membrana extracorpórea (PETRIKOV; POPUGAEV; ZHURAVEL, 2022). O tratamento medicamentoso pode ser subcategorizado em dois grandes grupos baseado no alvo: agentes antivirais e terapias direcionadas ao hospedeiro, com o objetivo de diminuir a resposta inflamatória exacerbada: esteroides, anticorpos monoclonais e policlonais, plasma convalescente e outros, sendo que a terapia combinatória apresenta vantagens comparado ao tratamento isolado (YUAN et al., 2023).

O aumento dos estados inflamatórios com liberação exacerbada de citocinas leva à ruptura da interface dos vasos sanguíneos, criando um ambiente propício à hipercoagulabilidade (HUANG et al., 2024). Além disso, na COVID-19 ocorre aumento de trombina, fibrinogênio, maior estimulação da ativação plaquetária, níveis elevados de dímero D e aumento significativo da viscoelasticidade da fibrina, levando à complicações tromboembólicas (HE; BLOMBÄCK; WALLÉN, 2024) .

Estudo de coorte realizado no Canadá analisou dados de vigilância e concluiu que a presença de comorbidades em pacientes com COVID-19 está associada ao aumento dos riscos de hospitalização, admissão em UTI e morte. Esses riscos aumentam também em pacientes não vacinados contra COVID-19 (SIMARD et al., 2023). Idade, obesidade, sexo masculino, *diabetes mellitus* e hipertensão estão associados à mortalidade mais alta. Indivíduos com comorbidades e características clínicas associadas à gravidade devem ser monitorados de perto, e os esforços preventivos devem ser implementados (LI et al., 2021b; LOWHORN et al., 2024).

O desenvolvimento e a implantação de vacinas contra o SARS-COV-2 reduziram consideravelmente as taxas de mortalidade entre as pessoas que contraem o vírus, tendo papel importante na mudança da tendência de mortalidade por COVID-19 (COLLABORATORS, 2022).

Devido ao surgimento de diversas variantes do vírus que causa COVID-19, a OMS criou, em 2020, o Grupo Técnico Consultivo na Evolução do Vírus SARS-CoV-2, e em 2024 foi instaurada uma Rede de Coronavírus da OMS (CoViNet) para facilitar a detecção precoce e precisa de coronavírus e rastreamento de variantes, incluindo a coordenação de avaliações de risco, sendo fundamental que estes sistemas sejam mantidos e que os dados sejam partilhados, à medida que o SARS-CoV-2 continua a circular em níveis elevados em todo o mundo (WHO, 2024).

2.1 Coinfecções

Coinfecções por bactérias e fungos são muito comuns em pacientes com COVID-19 internados em UTI e estão relacionadas a um pior prognóstico e maior taxa de mortalidade, sendo relevante estimar o risco combinando critérios clínicos, investigações microbiológicas e de imagens radiológicas, objetivando um diagnóstico rápido que permita a escolha de terapia apropriada e aumento da sobrevida dos pacientes (DE FRANCESCO et al., 2023).

Pacientes com COVID-19 que possuem comorbidades como hipertensão, diabetes mellitus, doença cardiovascular e doença pulmonar apresentam maior risco de coinfecção, independente do patógeno (KHAN et al., 2023). Além disso, maior tempo de hospitalização, ventilação mecânica e tratamento com esteroides também estão entre os principais fatores de risco para coinfecção nessa população (DARWISH et al., 2023). Idade avançada e comorbidades subjacentes estão associadas ao aumento da mortalidade. Esta descoberta destaca a necessidade de melhores ferramentas para diagnosticar a presença ou ausência de coinfecção bacteriana e fúngica em pacientes COVID-19 (KOTHADIA et al., 2022).

As coinfecções bacterianas e fúngicas estão relacionadas a maior tempo de internação e maior taxa de mortalidade, sendo as bactérias Gram-negativas e espécies de *Candida* spp. os microrganismos mais comumente envolvidos (ALSHREFY et al., 2022). Metanálise que abrangeu 64 estudos e objetivou avaliar coinfecções em pacientes com COVID-19 encontrou prevalência de 20,9% de coinfecção bacteriana e 12,5% de coinfecção fúngica, o que justifica a realização de testes diagnósticos para outros patógenos simultaneamente com o SARS-CoV-2, visando o tratamento adequado do paciente (PAKZAD et al., 2022).

O uso indiscriminado de antibióticos em todos os pacientes com COVID-19 grave gera risco de seleção de organismos multirresistentes, sendo encorajado, nesse sentido, o uso criterioso de antimicrobianos, discernindo quais pacientes estão em risco de doença crítica e mortalidade (KOTHADIA et al., 2022). Identificar o agente infeccioso, classificar colonizações e infecções, correlacionar os dados microbiológicos com as características radiológicas, clínicas e laboratoriais são ações que podem orientar o início da antibioticoterapia apenas em pacientes que realmente necessitam de antibióticos, oportunizando o tratamento adequado aos pacientes com COVID-19 (KARACA et al., 2023; TISEO et al., 2022)

2.1.1 Coinfecções bacterianas

A coinfecção bacteriana aumenta em três vezes o risco de mortalidade dos pacientes com COVID-19 (PATTON et al., 2023), além de maior tempo de permanência hospitalar, o que torna o uso oportuno e apropriado de antibióticos, auxiliado por um diagnóstico preciso, fator crucial para melhorar o resultado do paciente e prevenir a resistência antimicrobiana (WU et al., 2022). No início da pandemia COVID-19, antimicrobianos empíricos foram prescritos em 56-90% dos pacientes devido à experiência prévia de coinfecções bacterianas que ocorrem em outras pneumonias virais respiratórias, pouco conhecimento sobre o novo coronavírus, gravidade dos pacientes e dificuldade em estabelecer ou excluir um diagnóstico de coinfecção bacteriana clinicamente, o que contribuiu para um aumento da resistência aos antimicrobianos (WU et al., 2022).

O prolongamento da hospitalização é o principal fator de risco associado à coinfecção bacteriana e ao óbito. Assim, os profissionais de saúde devem minimizar a hospitalização, bem como seguir um monitoramento contínuo para a coinfecção bacteriana entre pacientes COVID-19, para controlar a disseminação da infecção e reduzir a gravidade e a taxa de mortalidade entre pacientes COVID-19 (ALDARHAMI et al., 2024)

A infecção de corrente sanguínea associada à cateter (ICSAC) e pneumonia associada à ventilação mecânica (PAVM) são as coinfecções mais comuns em pacientes com COVID- 19 (WU et al., 2022).

2.1.1.1 Infecção de corrente sanguínea associada à cateter (ICSAC)

A ICSAC é um importante problema clínico e de saúde pública, com aumento na sua incidência observado durante a pandemia da COVID-19 (SATTA; RAWSON; MOORE, 2023). A ICSAC é definida pela National Healthcare Safety Network (NHSN) como uma infecção que ocorre ≥ 48 h após a admissão do paciente, com pelo menos uma amostra de cultura de sangue periférico positiva (CDC/NHSN, 2024). Principalmente os pacientes com COVID-19 internados em UTI apresentam maior risco de adquirirem ICSAC, e as taxas de mortalidade são maiores nos pacientes coinfectados (MASSART et al., 2021). Os microrganismos mais comumente envolvidos em ICSAC em pacientes com COVID-19 são as bactérias Gram-negativas (HLINKOVA et al., 2023).

O aumento da incidência de ICSAC nos pacientes com COVID-19 deve-se à causas multifatoriais, incluindo questões relacionadas ao paciente como comorbidades, idade avançada, sexo masculino e uso de esteroides e questões relacionadas ao processo do cuidado, como a falta de adesão às medidas de controle de IRAS.

em virtude da alta carga de trabalho e escassez de profissionais de saúde durante a pandemia (BEN-ADERET et al., 2023).

Medidas simples de prevenção de ICSAC como higienização adequada das mãos e cuidados com cateter podem ficar comprometidas quando há grandes demandas de trabalho nas equipes de saúde e falta de recursos humanos e materiais, como ocorreu durante a pandemia da COVID-19 (SATTA; RAWSON; MOORE, 2023).

2.1.1.2 Pneumonia associada à ventilação mecânica (PAVM)

A PAVM é uma das mais frequentes IRAS (com incidência de até 40% dos pacientes internados em UTI), estando intimamente relacionada ao maior tempo de ventilação mecânica e maior tempo de internação hospitalar, e cujo diagnóstico inclui suspeita clínica, novos infiltrados e diagnóstico microbiológico significando culturas microbiológicas positivas do trato respiratório inferior (PAPAZIAN; KLOMPAS; LUYT, 2020).

No entanto, esses critérios não podem ser aplicados com precisão a pacientes com COVID-19 que apresentam manifestações clínicas sobrepostas devido à infecção viral (TAN et al., 2023). Se surgirem novos sinais clínicos de deterioração respiratória que possam ser atribuídos à processo infeccioso, além da avaliação convencional com radiografia de tórax e tomografia pulmonar, é recomendado o uso de ultrassonografia pulmonar em tempo real para acompanhar pacientes com COVID-19 gravemente enfermos (DENG et al., 2022). Além disso, a procalcitonina sérica elevada e aumento de granulócitos imaturos podem atuar como biomarcadores que sugerem PAVM (DENG et al., 2022).

A PAVM é uma das complicações infecciosas mais comuns da ventilação mecânica invasiva relacionada aos cuidados de saúde e está associada a altas taxas de mortalidade, sendo os patógenos Gram-negativos os principais responsáveis pela coinfecção em pacientes com COVID-19 (ALIGUI; ABAD, 2023). Além disso, pacientes durante a ventilação mecânica em intubação orotraqueal apresentam maior incidência geral de PAVM do que aqueles em traqueostomia (TETAJ et al., 2022).

O aumento da incidência de PAVM em pacientes com COVID-19 está relacionado à ventilação mecânica prolongada e longa permanência hospitalar, imunomodulação viral, uso de esteroides, uso de agentes sedativos e bloqueadores neuromusculares, uso de vasopressores, posição prona, uso de oxigenação mecânica extracorpórea, escassez de profissionais de saúde e equipamentos de proteção inadequados (FUMAGALLI et al., 2022).

Alguns autores afirmam que mesmo que o uso de esteroides esteja associado a uma maior incidência de PAVM, a força da associação é provavelmente muito pequena, e o clínico não deve limitar seu uso quando apropriado (VACHERON et al., 2023).

A prevenção de PAVM, baseada na minimização da exposição à ventilação mecânica e no incentivo à extubação precoce, quando viável, é mais importante do que o tratamento da PAVM. E, a redução do tempo de ventilação mecânica invasiva está relacionada com a prevenção farmacológica da PAVM. Quanto ao tratamento da PAVM, os antibióticos empíricos são importantes quando há suspeita da coinfecção, havendo necessidade de atenção especial com relação ao espectro antimicrobiano e duração dos antibióticos devido à existência de bactérias resistentes aos medicamentos (DENG et al., 2022). O uso excessivo de antibióticos empíricos antes da intubação pode contribuir para o desenvolvimento desfavorável de bactérias multirresistentes, com uma alta proporção de resistência aos carbapenêmicos e microrganismos multirresistentes (TETAJ et al., 2022).

Pacientes com COVID-19 em UTI apresentam alto risco para PAVM e PAVM multirresistente. O início da PAVM é precoce em pacientes com COVID-19 comparados aos pacientes sem COVID-19, devendo ser considerado essa condição em pacientes com piora do quadro clínico (ALIGUI; ABAD, 2023).

2.1.2 Coinfecções fúngicas

As infecções fúngicas se tornaram uma preocupação durante a pandemia, especialmente em pacientes com COVID-19 gravemente doentes, desempenhando um papel fundamental em seus desfechos clínicos. Considerando que alguns sintomas de infecção fúngica podem ser semelhantes aos da COVID-19 como febre, tosse e falta de ar, o conhecimento da potencial coinfecção é crucial para evitar atraso no diagnóstico e prevenir agravamento do quadro clínico e morte (KRSIHNAN; KUMAR; INBAKANI, 2024).

A duração prolongada da ventilação mecânica, a desregulação imunológica, tratamento com corticosteroides e a exposição a antibióticos de amplo espectro criam um ambiente ideal para o desenvolvimento de infecções fúngicas invasivas (BETOLAZA et al., 2024).

Os gêneros de fungos mais comumente relacionados a essas coinfecções são espécies de *Aspergillus*, *Mucorales* e *Candida*, incluindo *Candida auris* (HOENIGL et al., 2022) e dentre os fatores de risco estão idade avançada, procedimento cirúrgico, sepse, doença pulmonar obstrutiva crônica e sexo masculino. A coinfecção ocasiona maior tempo de

internação hospitalar e em UTI, além maiores chances de mortalidade (LÓPEZ-HERRERO et al., 2024).

2.1.2.1 Aspergilose associada à COVID-19 (APAC)

Casos de aspergilose associada à COVID-19 **(**APAC) surgiram durante os primeiros meses da pandemia. No entanto, as taxas de incidência variaram amplamente, provavelmente porque APAC é difícil de diagnosticar em pacientes SDRA associada à COVID-19 (HOENIGL et al., 2022). A APAC acomete geralmente pacientes com COVID-19 em estado grave, estando relacionada a grave deterioração da função respiratória e sepse. Assim, deve-se considerar o risco potencial de aspergilose mesmo que não haja fatores de risco clássicos para esta coinfecção (KRSIHNAN; KUMAR; INBAKANI, 2024). Em estudo multicêntrico no Reino Unido que incluiu 266 pacientes com COVID-19 ventilados mecanicamente, foi encontrado uma taxa de incidência de APAC de 10,9%, (HURT et al., 2024).

Além da própria COVID-19, tratamento com esteroides, inibidor de interleucina 6 e doença pulmonar obstrutiva crônica estão entre fatores de risco para APAC, sendo importante o manejo adequado dos pacientes em cuidados intensivos (HURT et al., 2024). Somente a presença de fungos no trato respiratório não é sinônimo de doença fúngica, o que requer investigação adequada. Os critérios para o diagnóstico de micoses invasivas, que foram desenvolvidos principalmente para pacientes imunossuprimidos, são de difícil aplicação em pacientes internados em UTI devido a impossibilidade de coleta de biópsias de tecido pulmonar, a falta de fatores clássicos do hospedeiro que favoreçam a infecção fúngica, ou seja, imunossupressão, e achados radiológicos inespecíficos causados pela ventilação mecânica, além das imagens dos resultados de exames serem difíceis de interpretar devido ao quadro de infecção viral preexistente (SKÓRA et al., 2023).

O diagnóstico de APAC envolve cultura de fungo e pesquisa de galactomanana em amostras de secreção do trato respiratório inferior (KRSIHNAN; KUMAR; INBAKANI, 2024). A Confederação Europeia de Micologia Médica (ECMM) e a Sociedade Internacional de Micologia Humana e Animal (ISHAM) prepararam diretrizes que fornecem as definições de APAC comprovada, provável e possível, com recomendações para o diagnóstico e tratamento da APAC.

De acordo com as diretrizes da ECMM/ISHAM, o tratamento de primeira linha recomendado para aspergilose invasiva é o voriconazol ou isavuconazol intravenoso. A ECMM/ISHAM CAPA recomenda testes de galactomanana sérico para pacientes com SARS-

CoV-2 três vezes por semana até a alta da UTI e testes de amostras do trato respiratório inferior pelo menos uma vez por semana (KOEHLER et al., 2021).

Na ausência de um diagnóstico comprovado, o benefício da terapia antifúngica em pacientes com suspeita de APAC deve ser ponderado com cautela em relação ao custo, toxicidade, potencial de interação medicamentosa e desenvolvimento de resistência antifúngica (HURT et al., 2024). É recomendado tratamento antifúngico para APAC comprovada, provável e possível, sendo indicado início com monoterapia única ou sequencial com voriconazol, isavuconazol, posaconazol, anfotericina B lipossômica. O desoxicolato de anfotericina B e as equinocandinas podem ser considerados como uma terapia alternativa (WU et al., 2023).

Na população com APAC, outras coinfecções bacterianas com microrganismos multirresistentes são frequentemente identificadas. Essas características, juntamente com um longo tempo de permanência hospitalar e ventilação mecânica, desafiam o manejo antibacteriano e antifúngico, aumentam os custos de atenção e estão associadas a maiores taxas de mortalidade. Melhorar as capacidades diagnósticas e incluir testes de suscetibilidade a isolados de *Aspergillus* de importância clínica como padrão de tratamento e vigilância local ajudará a melhorar os desfechos em pacientes com APAC e, em geral, em todas as infecções fúngicas que ocorrem em UTIs/populações gravemente doentes (HERNÁNDEZ-SILVA et al., 2024).

2.1.2.2 Candidíase associada à COVID-19 (CAC)

Durante a pandemia da COVID-19 houve um aumento da incidência de candidíase na população infectada pelo novo coronavírus, resultando desfechos graves nos pacientes hospitalizados (TSAI et al., 2022).

Enquanto a fisiopatologia molecular não é totalmente compreendida, alguns fatores, incluindo comprometimento do sistema imunológico, deficiências de ferro e zinco e transmissões nosocomiais e iatrogênicas, predispõem os pacientes COVID-19 à candidíase (AHMED et al., 2022). Além disso, os pacientes com COVID-19 que permanecem internados por longos períodos, utilizam cateter venoso central, são submetidos a procedimentos cirúrgicos e recebem antimicrobianos de amplo espectro, estão mais sujeitos a candidemia invasiva (AL-HATMI et al., 2021). Os corticosteroides têm uma alta chance de predispor pacientes com COVID-19 à candidíase, principalmente em combinação com outras drogas imunossupressoras (AHMED et al., 2022).

A maioria dos casos de candidíase associada à COVID-19 (CAC) ocorre em UTI, sendo diagnosticado aproximadamente sete dias após a internação e apresentam duas vezes maior risco de morte quando comparados aos pacientes com candidemia sem COVID-19 (MACAULEY; EPELBAUM, 2021; PISANO et al., 2023). Assim, um diagnóstico rápido é necessário para evitar a transmissão fúngica à indivíduos não infectados e permitir tratamento oportuno aos infectados, evitando prognóstico ruim (AHMED et al., 2022).

Com relação ao tratamento, a estratégia terapêutica para o CAC causado por espécies comuns de *Candida*, como *Candida albicans*, *Candida tropicalis* e *Candida glabrata,* é semelhante à era pré-pandêmica. Para pacientes não críticos ou com baixo risco de resistência azólica, o fluconazol continua sendo a droga de escolha para candidemia. Para pacientes gravemente enfermos, aqueles com história de exposição recente a azólicos ou com alto risco de resistência ao fluconazol, as equinocandinas são recomendadas como terapia de primeira linha (WU et al., 2023). Para candidemia causada por *Candida auris*, recomendam-se equinocandinas. Se não houver evidência de resistência à anfotericina B e houver candidemia persistente após o tratamento com equinocandina, anfotericina B lipossomal ou desoxicolato de anfotericina B podem ser considerados (TSAI et al., 2022; WU et al., 2023).

A transição de *Candida* spp de comensal para patógeno, a capacidade de mudar de morfologia e formar biofilmes, a progressão da infecção por *Candida* spp. e seus fatores de virulência ainda não são bem compreendidos. Adicionalmente, os vários fatores destacados que predispõem os pacientes com COVID-19 à candidíase, suas interações, e efeitos individuais devem elucidados para evitar o desenvolvimento de coinfecções oportunistas que diminuem a sobrevida dessa população (AHMED et al., 2022).

2.1.2.3 Mucormicose associada à COVID-19 (MAC)

A mucormicose é uma infecção fúngica angioinvasiva, causada por fungos da ordem Mucorales, principalmente os pertencentes aos gêneros *Rhizopus, Mucor, Rhizomucor* e *Phycomyces*. É potencialmente letal e tem como fatores de risco *diabetes mellitus*, imunodeficiências, uso de imunossupressores e esteroides, neoplasias hematológicas e transplante de células-tronco hematológicas (HONAVAR, 2021; SKIADA; PAVLEAS; DROGARI-APIRANTHITOU, 2020). O fungo é encontrado naturalmente no ambiente, na superfície do corpo e nos orifícios. Em pessoas imunodeficientes, a micose pode afetar a pele, pulmões, rins e ainda os esporos podem inocular os seios paranasais e a nasofaringe com posterior disseminação para a órbita e cavidade intracraniana, causando a mucormicose rino-

orbitária. O patógeno invade a rede vascular causando inflamação e necrose. O diagnóstico precoce com a instituição de terapia antimicrobiana adequada é imprescindível para evitar perda da visão e morte (RAVANI et al., 2021).

Com a pandemia da COVID-19 houve um acentuado aumento de casos de mucormicose devido aos danos causados pelo SARS CoV-2, *diabetes mellitus* não controlada e uso de esteroides por esses pacientes (RAVANI et al., 2021). A mucormicose associada à COVID-19 (MAC) é definida como a identificação de *Mucorales* em cultura por testes laboratoriais, histopatologia ou reação em cadeia da polimerase (PCR) em paciente com COVID-19 e sinais e sintomas clínicos de mucormicose invasiva (SELARKA et al., 2021). A maioria dos casos de MAC relatados ocorreram na Índia por ser um país com alta prevalência de *diabetes mellitus* não controlada e que possui fatores ambientais como o clima quente e úmido que propiciam a proliferação e infecção pelo fungo (ALMYROUDI et al., 2022).

A mucormicose apresentava uma taxa de mortalidade aproximada de 50% na era pré-COVID-19, porcentagem que chegou a 85% durante a pandemia, considerando também fatores inerentes à condição pandêmica de falta de infraestrutura hospitalar, de recursos humanos e dificuldade de diagnóstico (GARCÍA-CARNERO; MORA-MONTES, 2022). Devido à alta mortalidade da doença e a ausência de sinais clínicos no início da infecção, (KUMAR et al., 2023), recomendam que o diagnóstico seja estabelecido com base em evidências de imagem, microbiologia e histopatologia.

Estudo multicêntrico realizado na Índia que avaliou 287 pacientes com mucormicose constatou que idade, envolvimento rino-órbito-cerebral e admissão em UTI foram associados com aumento das taxas de mortalidade. O tratamento com drogas antifúngicas melhorou a sobrevida dos pacientes (PATEL et al., 2021)**.** A terapia antifúngica adequada e oportuna e a ressecção cirúrgica, quando necessária, são essenciais no manejo da mucormicose. A anfotericina B lipossomal é a droga de escolha, mas o isavuconazol também é recomendado na terapia primária. Triazóis, incluindo posaconazol e isavuconazol, são indicados na fase de consolidação ou como terapia de resgate (PATEL et al., 2021). No entanto, a escolha de tratamento pode variar dependendo do tipo clínico de mucormicose: as mucormicoses pulmonar, rino-orbitária/cerebral e renal são tratadas preferencialmente com terapia antifúngica e cirúrgica concomitantes, enquanto na mucormicose cutânea utiliza-se, normalmente, apenas drogas antifúngicas (GARCÍA-CARNERO; MORA-MONTES, 2022).

Selarka et al. (2021) ressaltam a importância de maior controle glicêmico dos pacientes com COVID-19, além do uso racional de corticoides e antimicrobianos de amplo espectro, o que contribui para aumento da sobrevida dos pacientes com MAC.

3 OBJETIVOS

3.1 Objetivo Geral

Identificar aspectos relacionados à mortalidade e ICSAC e relatar casos de APAC em pacientes adultos com COVID-19 hospitalizados em uma UTI da rede pública da cidade de Uberlândia, Minas Gerais.

3.2 Objetivos Específicos

a) Identificar e compreender os preditores de mortalidade em pacientes com COVID-19;
b) Conhecer a frequência de ICSAC, identificar microrganismos envolvidos e preditores dessa coinfecção;
c) Relatar casos de pacientes com APAC na UTI em estudo.

4 RESULTADOS

Artigo 1. Revisiting the COVID-19 pandemic: mortality and predictors of death in adult patients in the intensive care unit

Submetido ao periódico Life em julho de 2024

Artigo 2. Factors Influencing Central Venous Catheter-Associated Bloodstream Infections in COVID-19 Patients

Publicado no periódico Microbiology Research em junho de 2024

Artigo 3. Aspergillosis and COVID-19 in an intensive care unit in Brazil: a series of cases

Publicado no periódico Diversitas Journal em abril de 2023

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Article

Revisiting The Covid-19 Pandemic: Mortality And Predictors Of Death In Adult Patients In The Intensive Care Unit

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Abstract: COVID-19 has generated global impact due to its contagiousness and high lethality rates, with a large number of deaths mainly in intensive care units (ICUs). This study aimed to verify the occurrence and understand the factors related to mortality in adult patients with COVID-19 admitted to the ICU in a tertiary hospital. This is a retrospective cohort study, which included COVID-19 patients admitted between March 2020 and December 2021. A total of 588 patients were included, of whom the majority (55.27%) did not survive. Invasive mechanical ventilation was the strongest predictor of risk of death in the ICU with OR = 97.85 (95%CI = 39.10 - 244.86; p <0.001), along with age and SAPS3, and length of ICU stay were protective. Evaluating patients on invasive mechanical ventilation in isolation, using an adjusted model, we found that the following risk factors were observed: use of vasopressin, renal replacement therapy, red cell distribution width >15, use of hydrocortisone, age in years and are protective days of mechanical ventilation use, being admitted from another service and being of female sex. Identifying early predictors of mortality in patients with COVID-19 who require hospitalization is essential in the search for actions to prevent and manage complications that can increase the survival of these patients and reduce the impact on health services.

Keywords: COVID-19; preditors; mortality; intensive care unit

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1. Introduction

Coronavirus disease 2019 (COVID-19), declared a pandemic by the World Health Organization (WHO) on March 12, 2020, has generated global impact due to the high number of deaths, especially among the elderly and those with comorbidities, which has overloaded health systems and culminated in a shortage of intensive care units (ICUs) in hospitals due to the exponential increase in the number of cases [1]. As of March 3, 2024, more than 774 million confirmed cases and more than 7 million deaths have been reported globally [2]. Because it is a highly contagious respiratory disease and involves several factors that affect its severity and mortality, ICU admission is in many cases indispensable [3,4].

Clinical and biochemical parameters reflecting acute pulmonary, hepatic and renal dysfunction, acid-base disturbance, coagulation impairment and systemic inflammation are among the factors related to the survival of COVID-19 patients in the ICU [5]. Age, gender, hypertension, cardiovascular disease and chronic kidney disease are also related to the mortality of these patients [4]. The literature points to a mortality rate of around 30% in ICU patients with COVID-19, in addition to the greater susceptibility to infections

of this population, which justifies not only establishing conducts aimed at infection control and appropriate antimicrobial management, but also seeking clinical evidence of other variables that may contribute to high mortality rates [5,6].

Although the end of the pandemic has already been decreed in May 2023, revisiting the data of specific populations can be essential as a preventive mechanism. Specifically in Brazil, there is a shortage of ICU beds; and the occurrence of healthcare-related infections has increased length of stay, increased hospital costs and reduced the availability of ICU beds for public service systems [7,8]. The population sampled here has shown the occurrence of both co-infections [9], and the early onset of healthcare-associated infections such as catheter-associated bloodstream infection [10]. Patients with COVID-19 have been shown to be more susceptible to infections and secondary complications during hospitalization. Despite this, retrospective studies of the epidemiology of the disease and its associated factors are complex. Few population-based studies are available at the municipal level regarding strains such as [11], or even the behavior of waves that have clearly been affected by local issues and actions, as in the population sampled here [12]; or even the profile and occurrences of the outcomes in these populations; facts that may have made it difficult to manage the pandemic locally.

Reducing and understanding these negative outcomes can strongly affect health systems. Understanding the outcomes of patients who have been infected with the SARS-CoV-2 virus and the high rate of ICU admissions, associated with the significant mortality of COVID-19 patients in the first two years of the pandemic, will enable future actions in the event of new epidemics by this or other viruses, and the development of strategies that can contribute to favorable outcomes. Therefore, this study aimed to verify the occurrence and understand the predictors of mortality in adult patients with COVID-19 admitted to the ICU in a tertiary hospital in the interior of Brazil during the pandemic period.

2. Methods

2.1. Type of study and data collection

This is a retrospective cohort study whose inclusion criteria were patients diagnosed with COVID-19, laboratory confirmed by reverse transcriptase polymerase chain reaction (RT-PCR), aged ≥ 18 years, admitted to the ICU of a Brazilian university hospital as a result of the worsening of COVID-19, admitted between March 2020 and December 2021. This hospital has approximately 500 beds and offers highly complex treatment, is tertiary and a reference for the macro-region. The research was submitted to and approved by the Human Research Ethics Committee of the University to which the hospital is linked, CAAE: 51805021.5.0000.5152, number 5.043.636/2021.

The following patient characteristics were assessed: age, gender, comorbidities, clinical data such as symptoms on admission to hospital, duration of symptoms and vital signs on the first day of hospitalization, laboratory results on admission and treatments carried out in the ICU. All the data were collected electronically from the hospital information system and the patients' physical and electronic medical records.

2.2. Data recoding

For tests that showed significance and were included in the regression models, the data were dichotomized according to the reference values followed at the institution. Hematocrit was dichotomized into normal (if ≥ 35 and ≤ 45) and non-normal (if < 35 or > 45). The red blood cell distribution range (RDW) was dichotomized into ≥ 15 or not (if < 15). Prothrombin activation time (PAT) was dichotomized into abnormal (if ≤ 70) or normal (if > 70). The International Normalized Ratio (INR) was dichotomized into abnormal (if ≥ 1.2) or normal (if < 1.2). The neutrophil-to-platelet ratio (NPR) was dichotomized into abnormal (if > 58.41) and normal (if ≤ 58.41). This value was based on the third quartile. In addition, all the tests categorized as normal and abnormal were tested, but most of the results were not different from the absolute values or showed a low occurrence in one of

the levels. In the case of abnormal, for each test it was also considered and tested whether it was below the reference value or above. To simplify the analysis, not all the parameters evaluated are shown.

For the blood count, some ratios or derived indices that have been evaluated in the literature were tested [13–15]. The neutrophil/lymphocyte ratio (NeLR) was tested by dividing the number of neutrophils by the number of lymphocytes. The platelet/lymphocyte ratio (PlaLiR) was obtained by dividing the number of platelets in thousands (platelets/1000) by the number of lymphocytes. The derived neutrophil/lymphocyte ratio (d-NLR) was obtained using the equation d-NLR=N/([L*1000]-N), where N is the number of neutrophils and L is the number of lymphocytes. The myelocyte/lymphocyte ratio (MLR) was calculated by dividing the number of myelocytes by the number of lymphocytes. The neutrophil/platelet ratio (NPR) was the number of neutrophils divided by the number of platelets. The systemic immuno-inflammation index (SII) was obtained using the equation SII =(N*P)/(L*1000), where N is the number of neutrophils, P the number of platelets and L the number of lymphocytes. In both cases, multiplying by 1000 served to improve the scale of the variable [13–15].

2.3. Statistical analysis

The analyses and tests were carried out separately for patients on invasive mechanical ventilation (IMV) and for all patients together (see results). One of the most important points justifying this approach is the presence of few deaths in the group that did not receive IMV (five deaths out of 164 patients), which would not allow us to adequately estimate the statistical trend values and the associations to be tested. In the group that received IMV, there were 320 deaths out of 424 patients. IMV alone is already the main risk factor for mortality in COVID-19 patients (see results).

For the quantitative data, the median, first quartile and third quartile were calculated, given the lack of normality assessed by the Kolmogorov-Smirnov Lilliefors test. For the qualitative data, the relative frequency in percentage and its 95% confidence interval (95%CI) were calculated for each level of the variables. To compare the ICU death and survivor groups in the association analyses, the likelihood ratio test was used for qualitative variables and the Mann-Whitney test for quantitative variables. Simple and multiple logistic regression analyses were used to predict the occurrence of death in the ICU. For the logistic regression models, the obesity variable was chosen due to the lower sample loss in relation to weight. When necessary, the variables were dichotomized for better estimation. Simple regression models (unadjusted) were built for all available variables in both cases. Due to insufficient data in the records, multiple models could not be built for all variables. For the multiple models, priority variables were chosen with sufficient sample size, the presence of representative deaths and survivors, and without dependence on others. In addition, for the (adjusted) multiple regression, models were built only for the variables that had already shown a significant difference in the previous association analyses and were not dependent on others. The multiple models were presented in full and reduced form. The Wald test probability (p-value < 0.05) and the backward method were used to select the model. In addition, the Odds Ratio and its 95% confidence interval were calculated for all models, crude or adjusted. All the analyses were carried out using SPSS software version 20.0. A 5% significance level was adopted for all analyses.

3. Results

The study included 588 adult patients admitted to the ICU, of whom 55.27% died (95%CI = 51.25 - 59.29; 325/588). Among all the patients, 164 did not use IMV and 424 did. Among the patients who did not use IMV, 3.05% died (95%CI = 0.42 - 5.68; 5/164). Among the patients who used IMV, 75.47% died (95%CI = 71.38 - 79.57; 320/424). Given these differences in mortality associated with IMV, the patients were allocated into two groups for statistical analysis. The first group was the general group, which included all patients, and

the second group included only patients who received IMV. In addition, exploratory analyses demonstrated the dependence between some variables, such as patients who received IMV were also those who used vasoactive drugs, used sedatives, received invasive procedures, and used medications or underwent interventions more commonly associated with mortality and/or worsening of the condition.

In the general group, which included all patients, female gender proved to be a protective factor OR = 0.62 (95% CI = 0.44 - 0.87; p = 0.005). The median age was 53 years (IQR = 40.5 - 65.5) for survivors and 65 (IQR = 52 - 73) for non-survivors. The occurrence of diabetes mellitus was higher in the group that died (32.92 versus 19.01%), proving to be a risk factor OR = 2.09 (95%CI = 1.42; 3.07, p < 0.001). ICU stay in days had a median of 8 (IQR = 4 - 17) for survivors and 11 (IQR = 6 - 22) for non-survivors; similar behavior to the length of stay with a median of 15 and 19 days, respectively Survivors had a median Simplified Acute Physiology Score 3 (SAPS 3), a score that assesses the severity of the patient in the first hour of admission, 49 (IQR = 38 - 58) and non-survivors 61 (IQR = 49 - 71). Patients who died also had more comorbidities than survivors, despite the same median (Table 1).

Table 1. Some admission variables related to all survivors and deaths patients with COVID-19 admitted in an adult intensive care unit.

	% Yes (95% Confidence interval) [n]		p-	Odds-Ratio (95%
Trait	Survivor (n= 263)	Non-survivor (n=325)	value	Confidence interval)
Admitted from another service	67.30 (61.63-72.97) [177]	63.38 (58.15-68.62) [206]	0.321	0.84 (0.60; 1.19)
Female sex	45.25 (39.23-51.26) [119]	33.85 (28.70-38.99) [110]	0.005	0.62 (0.44; 0.87)
Obesity presence	35.74 (29.95-41.53) [94]	32.62 (27.52-37.71) [106]	0.427	0.87 (0.62; 1.23)
Systemic arterial hypertension presence	48.29 (42.25-54.33) [127]	53.23 (47.81-58.66) [173]	0.233	1.22 (0.88; 1.69)
Diabetes mellitus presence	19.01 (14.27-23.75) [50]	32.92 (27.81-38.03) [107]	<0.001	2.09 (1.42; 3.07)
Cardiovascular disease presence	10.65 (6.92-14.37) [28]	12.92 (9.28-16.57) [42]	0.395	1.25 (0.75; 2.07)
Asthma presence	1.90 (0.25-3.55) [5]	1.54 (0.20-2.88) [5]	0.736	0.81 (0.23; 2.82)
Chronic obstructive pulmonary disease presence	7.60 (4.40-10.81) [20]	11.38 (7.93-14.84) [37]	0.120	1.56 (0.88; 2.76)
Chronic kidney disease presence	7.22 (4.10-10.35) [19]	10.15 (6.87-13.44) [33]	0.210	1.45 (0.81; 2.62)
Etilism habit presence	4.94 (2.32-7.56) [13]	8.00 (5.05-10.95) [26]	0.134	1.67 (0.84; 3.32)
Smoking habit presence	18.63 (13.93-23.34) [49]	23.08 (18.5-27.66) [75]	0.187	1.31 (0.88; 1.96)
COVID-19 vaccine previous hospital admission	17.11 (12.56-21.66) [45]	20.31 (15.93-24.68) [66]	0.323	1.23 (0.81; 1.88)
Mechanical ventilation use	39.54 (33.63-45.45) [104]	98.46 (97.12-99.80) [320]	<0.001	97.85 (39.1; 244.86)
	Median (Quartile 1-Quartile 2) [n]		p-	Odds-Ratio (95%
Trait	Survivor (n= 263)	Non-survivor (n=325)	value	Confidence interval)
Age in years	53 (40.5-65.5) [263]	65 (52-73) [325]	<0.001	1.03 (1.02; 1.04)
Total number of comorbidities	1 (0-2) [263]	1 (1-2) [325]	0.007	1.19 (1.03; 1.36)
Time in days from symptom to ICU admission	11 (8-14) [245]	11 (7-14) [285]	0.229	0.99 (0.96; 1.02)
Simplified Acute Physiology Score 3 score	49 (38-58) [263]	61 (49-71) [325]	<0.001	1.05 (1.04; 1.06)
Simplified Acute Physiology Score in %	15.9 (6-31.5) [263]	39.8 (19-58.5) [325]	<0.001	1.04 (1.03; 1.05)
Length of stay at the ICU in days	8 (4-17) [263]	11 (6-22) [325]	<0.001	1.02 (1.00; 1.03)
Length of stay at the Hospital in days	19 (11-31) [263]	15 (7-27) [325]	<0.001	

Protective factors for patients who received IMV were those admitted from another service OR = 0.59 (95% CI = 0.36; 0.97; p = 0.033), and those who received tracheotomy OR = 0.24 (95% CI = 0.14; 0.39; p < 0.001), although in the latter case the association was due to

the longer duration of IMV use in the surviving patients. In the group receiving IMV, female gender was a protective factor OR = 0.36 (95% CI = 0.23; 0.56; p < 0.001). The median age was 49..50 years (IQR = 38 - 61) for survivors and 64 (IQR = 51 - 72) for non-survivors. Diabetes mellitus almost doubled the risk of death OR = 1.96 (95% CI = 1.15; 3.33; p = 0.010). Smoking acted as a predictor of mortality in the unadjusted model OR = 2.35 (95% CI = 1.22; 4.52; p = 0.006), as did the use of noradrenaline, vasopressin and hydrocortisone, all three variables with a p-value < 0.001. With an increase of more than six times in the risk of death, OR = 6.29 (95% CI = 3.65; 10.85; p <0.001), renal replacement therapy was also among the predictors of mortality in the unadjusted models (Table 2). ICU stay in days had a median of 21.5 (IQR = 13-33.5) for survivors and 12 (IQR = 6-22) for non-survivors. Survivors had a median SAPS 3 score of 51 (IQR = 37.75-62) and non-survivors 61 (IQR = 49-71). The duration of IMV use, in days, was a protective factor, as there was greater survival among patients who used IMV for longer (Table 3). This may be related to the greater severity of the disease in some patients at the time of admission to the ICU, who presented with severe respiratory failure and died shortly after being put on IMV. And those patients who managed to overcome the first few days of greater severity of the lung condition were able to benefit from intensive treatment, with the help of IMV, and survive the disease.

Table 2. Some categorical variables related to survivors and deaths patients in mechanical ventilation with COVID-19 admitted in an adult intensive care unit.

Trait	% Yes (95% Confidence interval) [n]		p-value	Odds-Ratio (95% Confidence interval)
	Survivor	Non-survivor		
Admitted from another service	74.04 (65.61-82.46) [77]	62.81 (57.52-68.11) [201]	0.033	0.59 (0.36; 0.97)
Female sex	57.69 (48.2-67.19) [60]	32.81 (27.67-37.96) [105]	<0.001	0.36 (0.23; 0.56)
Obesity presence	38.46 (29.11-47.81) [40]	33.13 (27.97-38.28) [106]	0.322	0.79 (0.5; 1.25)
Systemic arterial hypertension presence	45.19 (35.63-54.76) [47]	53.13 (47.66-58.59) [170]	0.160	1.37 (0.88; 2.14)
Diabetes mellitus presence	20.19 (12.48-27.91) [21]	33.13 (27.97-38.28) [106]	0.010	1.96 (1.15; 3.33)
Cardiovascular disease presence	7.69 (2.57-12.81) [8]	12.81 (9.15-16.47) [41]	0.140	1.76 (0.8; 3.89)
Asthma presence	0 (0-0) [0]	1.56 (0.2-2.92) [5]	0.092	
Chronic obstructive pulmonary disease presence	4.81 (0.70-8.92) [5]	11.56 (8.06-15.07) [37]	0.032	2.59 (0.99; 6.77)
Chronic kidney disease presence	2.88 (0-6.1) [3]	10.31 (6.98-13.64) [33]	0.009	3.87 (1.16; 12.9)
Etilism habit presence	5.77 (1.29-10.25) [6]	8.13 (5.13-11.12) [26]	0.417	1.44 (0.58; 3.61)
Smoking habit presence	11.54 (5.40-17.68) [12]	23.44 (18.8-28.08) [75]	0.006	2.35 (1.22; 4.52)
COVID-19 vaccine previous admission	13.46 (6.90-20.02) [14]	20.31 (15.9-24.72) [65]	0.109	1.64 (0.88; 3.06)
Blood transfusion	26.92 (18.40-35.45) [28]	31.56 (26.47-36.65) [101]	0.368	1.25 (0.76; 2.05)
Use of noradrenaline	90.38 (84.72-96.05) [94]	99.38 (98.51-100.00) [318]	<0.001	16.92 (3.64; 78.55)
Use of vasopressin	17.31 (10.04-24.58) [18]	70.94 (65.96-75.91) [227]	<0.001	11.66 (6.65; 20.47)
Use of hydrocortisone	29.81 (21.02-38.6) [31]	71.56 (66.62-76.51) [229]	<0.001	5.93 (3.65; 9.63)
Use of neuroblocker	71.15 (62.45-79.86) [74]	68.13 (63.02-73.23) [218]	0.560	0.87 (0.53; 1.41)
Use of midazolam	94.23 (89.75-98.71) [98]	91.25 (88.15-94.35) [292]	0.315	0.64 (0.26; 1.59)
Use of fentanyl	98.08 (95.44-100.72) [102]	93.44 (90.72-96.15) [299]	0.045	0.28 (0.06; 1.21)
Use of propofol	59.62 (50.19-69.05) [62]	51.25 (45.77-56.73) [164]	0.136	0.71 (0.46; 1.12)
Use of ketamine	37.5 (28.20-46.8) [39]	44.06 (38.62-49.5) [141]	0.238	1.31 (0.83; 2.07)
Use of non-invasive ventilation	62.5 (53.20-71.8) [65]	61.56 (56.23-66.89) [197]	0.864	0.96 (0.61; 1.52)

Use of indwelling bladder catheter	100 (100-100) [104]	97.19 (95.38-99.00) [311]	0.024	
Use of tracheostomy	40.38 (30.95-49.81) [42]	13.75 (9.98-17.52) [44]	<0.001	0.24 (0.14; 0.39)
Use of central venous catheter	100 (100-100) [104]	98.75 (97.53-99.97) [316]	0.132	
Renal replacement therapy	18.27 (10.84-25.7) [19]	58.44 (53.04-63.84) [187]	<0.001	6.29 (3.65; 10.85)
Haematocrit abnormal	33.65 (24.57-42.74) [35]	48.28 (42.79-53.76) [154]	0.009	1.84 (1.16; 2.82)
Red cell distribution width >15	13.46 (6.9-20.02] [14]	27.59 (22.68-32.49] [88]	0.002	2.45 (1.32; 4.53)
Neutrophil to platelet ratio abnormal	17.48 (10.14-24.81] [18]	33.54 (28.34-38.75] [106]	0.001	2.38 (1.36; 4.17)
Prototombin activation time abnormal	6.12 (1.38-10.87] [6]	19.02 (14.61-23.42] [58]	0.001	3.60 (1.50; 8.63)
International Normalized Ratio abnormal	5.1 (0.75-9.46] [5]	15.84 (11.73-19.95] [48]	0.003	3.50 (1.35; 9.06)

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Table 3. Some quantitative variables related to survivors and deaths patients in mechanical ventilation with COVID-19 admitted in an adult intensive care unit. 191 192

	Median (Quartile 1 - Quartile 2) [n]			Odds-Ratio (95%
Trait	Survivor	Non-survivor	p-value	Confidence interval)
Age in years	49.50 (38-61) [104]	64.00 (51-72) [320]	<0.001	1.05 (1.03; 1.06)
Total number of comorbidities	1 (0-2) [104]	1 (1-2) [320]	0.003	1.31 (1.08; 1.6)
Time in days from symptom to ICU admission	11 (8-13.75) [98]	11 (7-14) [282]	0.676	0.99 (0.95; 1.03)
Length of stay at the ICU in days	21.5 (13-33.5) [104]	12 (6-22) [320]	<0.001	0.97 (0.96; 0.98)
Simplified Acute Physiology Score 3 score	51 (37.75-62) [104]	61 (49-71) [320]	<0.001	1.04 (1.02; 1.05)
Simplified Acute Physiology Score in %	20.25 (6-39.8) [104]	39.8 (19-58.5) [320]	<0.001	1.03 (1.02; 1.04)
Days of mechanical ventilation use	15.5 (9-27.25) [104]	11.5 (5-19) [312]	<0.001	0.98 (0.97; 1.00)
Hemoglobin in g/dL	12.6 (11.18-14.13) [104]	12.4 (10.8-14.05) [319]	0.641	0.97 (0.88; 1.06)
Leukocytes in 1000/mm^3	11.3 (7.58-13.7) [104]	11.9 (8.4-17.05) [319]	0.056	1.05 (1.01; 1.09)
Haematocrit in %	37.65 (34.18-41.58) [104]	37.3 (32.7-41.55) [319]	0.631	0.99 (0.96; 1.02)
Mean Corpuscular Volume in fL	88.9 (85.35-91.2) [104]	88.9 (85.1-93.2) [319]	0.275	1.02 (0.99; 1.05)
Mean Corpuscular Hemoglobin in pg	29.65 (28.8-30.6) [104]	29.9 (28.6-31.1) [319]	0.219	1.06 (0.97; 1.16)
Mean Corpuscular Hemoglobin Concentration in g/dL	33.5 (32.2-34.63) [104]	33.6 (32.45-34.6) [319]	0.873	0.98 (0.86; 1.13)
Red cell distribution width in %	13.9 (13.2-14.6) [104]	14.1 (13.2-15.2) [319]	0.097	1.16 (1.00; 1.34)
Mean platelet volume in fL	10.5 (10-11.1) [103]	10.7 (10-11.4) [314]	0.405	1.05 (0.84; 1.32)
Myelocytes in units by mm^3	0 (0-0) [104]	0 (0-0) [319]	0.590	1.00 (1.00; 1.00)
Rods in units by mm^3	601 (298-1349) [104]	755 (377.5-1444.5) [319]	0.177	1.00 (1.00; 1.00)
Segmented in units by mm^3	8406 (5901.5-11436.25) [104]	9480 (6335.5-13751) [319]	0.044	1.00005 (1.00001; 1.0001)
Lymphocytes in units by mm^3	810.5 (483.5-1120.5) [104]	687 (385-1150) [319]	0.256	1.00 (1.00; 1.00)
Monocytes in units by mm^3	380 (271-633) [102]	426 (282-750) [317]	0.215	1.00 (1.00; 1.00)
Neutrophils in units by mm^3	9400 (6499-12578.25) [104]	10250 (7138-15178) [319]	0.057	1.00 (1.00; 1.00)
Platelet in units/1000 by mm^3	234 (190.5-299) [103]	215 (167.25-292) [316]	0.040	0.998 (0.996; 1.00)
Neutrophils Lymphocytes Ratio	11.63 (7.86-17.65) [104]	14.67 (8.96-23.5) [319]	0.017	0.999 (0.996; 1.002)
Platelet Lymphocytes Ratio	299.43 (209.61-477.12) [104]	308.97 (191.26-483.73) [318]	0.798	1.00 (1.00; 1.00)
Creatinine in mg/dL	0.81 (0.61-1.09) [104]	1.22 (0.85-2.24) [318]	<0.001	1.52 (1.21; 1.91)
Albumin in mg/dl	3.23 (2.85-3.56) [84]	3.13 (2.65-3.44) [265]	0.060	1.01 (0.97; 1.05)

Glutamic-oxaloacetic transaminase in U/L	50.1 (37.98-73.18) [100]	52.9 (33.8-85.6) [283]	0.845	1.00 (1.00; 1.01)
Glutamic-pyruvic transaminase in U/L	45.05 (28.45-74.7) [100]	37.15 (22.4-59.68) [282]	0.061	1.00 (1.00; 1.00)
Lactic dehydrogenase in U/L	562 (432.5-670) [87]	615 (453-856) [233]	0.016	1.00 (1.00; 1.01)
Polymerase Chain Reaction in mg/dL	12.64 (7.41-19.1) [102]	13.4 (6.95-21.69) [300]	0.499	1.01 (0.99; 1.04)
D-dimer in ng/mL	1135 (628.5-4063) [91]	2381 (826.2-6545) [263]	0.009	1.0003 (0.999; 1.0001)
Interleukin 6 in pg/mL	48.7 (26.57-142.68) [76]	89.37 (40.86-178.4) [219]	0.024	0.9999 (0.9995; 1.0003)
Prototombin activation time in %	100.00 (96.5-100) [98]	96.00 (75-100) [305]	<0.001	0.97 (0.96; 0.99)
International Normalized Ratio	1.00 (1.00-1.02) [98]	1.01 (1.00-1.12) [303]	<0.001	5.32 (1.07; 26.51)
Neutrophils Lymphocytes derivate Ratio	7.33 (5.25-10.11) [104]	7.33 (5.25-11.5) [319]	0.180	1.04 (1.00; 1.08)
Myelocytes Lymphocytes Ratio	0.60 (0.33-0.8) [102]	0.67 (0.33-1.18) [317]	0.049	1.48 (1.07; 2.06)
Neutrophils Platelet Ratio	38.80 (28.52-51.39) [103]	47.35 (33.09-67.27) [316]	0.001	1.02 (1.01; 1.03)
Systemic immune-inflammation index	2.86 (1.63-4.54) [104]	3.31 (1.70-5.39) [319]	0.187	0.99 (0.98; 1.01)
Length of stay at the Hospital in days	31.5 (22.75-48.50) [104]	15.50 (7.00-27) [320]	<0.001	

IMV was the strongest predictor of the risk of death in the ICU in the unadjusted models with OR = 97.85 (95%CI = 39.10 - 244.86; p <0.001). Based on this, a prediction model was proposed for all patients (Table 4), and another only for patients on IMV (Table 4). The use of mechanical ventilation was also associated with greater use of vasoactive drugs and use of devices (data not shown); and as there were few deaths in the group without IMV, it was not possible to build models that took this interaction into account (use or not of IMV and death in the ICU).

After applying the multiple logistic regression model, the overall group had as predictors of mortality the use of IMV, OR = 306.74 (95% CI = 87.47-1075.71; p < 0.001), age, OR = 1.04 (95% CI = 1.03-1.06; p < 0.001) and SAPS 3 score, OR= 1.03 (95% CI = 1.01-1.04; p = 0.001). While Length of stay at the ICU in days was a protective factor in this group OR= 0.96 (95% CI = 0.85 - 0.98; p < 0.001)

When the adjusted model was applied to the group receiving IMV, there was age, OR = 1.03 (95% CI = 1.01-1.05; p = 0.006), use of vasopressin, OR = 7.87 (95% CI= 3.54-17.46, p < 0.001), use of hydrocortisone, OR = 2. 33 (95% CI= 1.05-5.16; p = 0.038), RDW >15, OR = 3.84 (95% CI = 1.60-9.21; p = 0.003) and renal replacement therapy OR = 5.42 (95%CI= 2.55-11.51; p < 0.001) as predictors of mortality. In this group, days of use of mechanical ventilation OR = 0.95 (95%CI = 0.93 - 0.97; p < 0.001), being admitted from another service OR = 0.43 (95%CI = 0.21-0.86; p < 0.001) and being female OR = 0.42 (95%CI = 0.22 - 0.82; p < 0.001). (Table 4).

Table 4. Logistic regression models and odds ratios related to death in patients with COVID-19 in an adult intensive care unit evaluated in different scenarios (models for all patients or only to patients in mechanical ventilation).

Model applied to all patients				
	Full Multiple model		Reduced multiple model	
Traits included	p-value	Odds Ratio (95% Confidence Interval)	p-value	Odds Ratio (95% Confidence Interval)
Mechanical ventilation use	<0.001	351.70 (95.94; 1289.22)	<0.001	306.74 (87.47; 1075.71)
Age in years	<0.001	1.05 (1.03; 1.07)	<0.001	1.04 (1.03; 1.06)
Simplified Acute Physiology Score 3 score	0.001	1.03 (1.01; 1.05)	0.001	1.03 (1.01; 1.04)
Length of stay at the ICU in days	<0.001	0.96 (0.95; 0.98)	<0.001	0.96 (0.95; 0.98)

Asthma presence	0.299	6.13 (0.20; 187.18)
Chronic kidney disease presence	0.331	1.80 (0.55; 5.93)
Diabetes mellitus presence	0.288	1.44 (0.74; 2.80)
COVID-19 vaccine previous hospital admission	0.491	1.29 (0.62; 2.68)
Obesity presence	0.415	1.26 (0.72; 2.22)
Smoking habit presence	0.728	1.16 (0.51; 2.61)
Time in days from symptom to ICU admission	0.701	1.01 (0.96; 1.06)
Etilism habit presence	0.995	1.00 (0.27; 3.61)
Cardiovascular disease presence	0.791	0.87 (0.32; 2.36)
Chronic obstructive pulmonary disease presence	0.616	0.75 (0.24; 2.33)
Admitted from another service	0.118	0.64 (0.36; 1.12)
Systemic arterial hypertension presence	0.095	0.59 (0.32; 1.10)

Model applied to patients in mechanical ventilation

	Full Multiple model		Reduced multiple model	
Traits included	p-value	Odds Ratio (95% Confidence Interval)	p-value	Odds Ratio (95% Confidence Interval)
Use of vasopressin	<0.001	7.49 (3.29; 17.05)	<0.001	7.87 (3.54; 17.46)
Renal replacement therapy	<0.001	5.19 (2.23; 12.09)	<0.001	5.42 (2.55; 11.51)
Red cell distribution width >15	0.011	3.52 (1.34; 9.26)	0.003	3.84 (1.60; 9.21)
Use of hydrocortisone	0.030	2.57 (1.10; 6.03)	0.038	2.33 (1.05; 5.16)
Age in years	0.041	1.03 (1.00; 1.05)	0.006	1.03 (1.01; 1.05)
Days of mechanical ventilation use	<0.001	0.94 (0.92; 0.96)	<0.001	0.95 (0.93; 0.97)
Admitted from another service	0.026	0.43 (0.21; 0.90)	0.020	0.43 (0.21; 0.87)
Female sex	0.035	0.47 (0.23; 0.95)	0.010	0.42 (0.22; 0.82)
Use of noradrenaline	0.060	15.67 (0.90; 274.17)		
Neutrophil to platelet ratio abnormal	0.088	2.18 (0.89; 5.32)		
Diabetes mellitus presence	0.492	1.54 (0.45; 5.22)		
Haematocrit abnormal	0.478	1.30 (0.63; 2.67)		
Smoking habit presence	0.733	1.19 (0.44; 3.18)		
Time from symptom to ICU admission	0.510	1.02 (0.96; 1.09)		
Simplified Acute Physiology Score 3 score	0.527	1.01 (0.98; 1.03)		
Total number of comorbidities	0.712	0.91 (0.55; 1.50)		
Chronic kidney disease presence	0.862	0.84 (0.13; 5.68)		
Chronic obstructive pulmonary disease presence	0.675	0.72 (0.16; 3.29)		
Use of Fentanyl	0.050	0.13 (0.02; 1.00)		

4. Discussion

In this study, the majority (55.27%) of COVID-19 patients admitted to the ICU did not survive. A review that evaluated different studies published during the pandemic found that the mortality rate for COVID-19 patients in the ICU reached 84.6%. This high rate may have been due to the severity of the disease, the population served, comorbidities, difficulties faced by health systems and socioeconomic status [16,17]. As the pandemic progressed, mortality rates fell to close to 40%, a fact that may be related to the

rapid availability of scientific studies related to guidelines for the clinical management of COVID-19 [16], and the advent of vaccines in record time and their effectiveness [18].

The SAPS3 score was effective in predicting mortality in the general group of patients. This score shows good applicability in predicting mortality in ICUs and in patients with COVID-19, both in patients admitted to private Brazilian ICUs [19] as in public institutions [20]. The score should be used with caution and future studies should test its calibration for each population studied and for specific diseases, taking into account other comorbidities such as diabetes; since they can interfere with the calibration result [21].

Age was associated with higher mortality as an independent factor, both in the group of patients who received IMV and in the general group, which corroborated data from a meta-analysis of COVID-19 cases from five countries that concluded that age was an important predictor of mortality in this population [22]. In Brazil, the age factor was also preponderant in mortality rates; although aspects of the municipality were also essential in defining mortality [23], probably related to differences in the local management of the pandemic or the conditions of the municipal health network. Another important factor was the higher mortality in men who received IMV. There are indications of higher mortality in men compared to women, even more prevalent in older people; although the causal effects are still unknown and are probably related to the virus infection itself [24]. Some comorbidities seem to play an important role in the evolution of COVID-19. Diabetes mellitus acted as a predictor of mortality in the univariate analysis of this study, both for the general group and for the group of patients who received IMV. The high mortality from COVID-19 in patients with diabetes can be explained by some processes, such as the permissibility of pluripotent stem cells derived from pancreatic beta cells for infection by SARS-CoV-2 [25]. There is also greater insulin resistance in COVID-19 patients due to the exaggerated action of angiotensin II, and insulin resistance triggers activation of the inflammatory response and the cytokine storm [26]. Thus, the release of different inflammatory mediators into the blood that SARS-CoV-2 causes is exacerbated in patients with diabetes [13,27]. Analysis of pancreatic autopsies of patients infected with COVID-19 showed that beta cells were infiltrated by SARS-CoV-2 in all patients [28]. COVID-19 patients with better glycemic control have better outcomes [29]. Diabetic patients are also those with the highest risk of using mechanical ventilation (adjusted OR = 2.20; p = 0.004; 95%CI: 1.29 - 3.75; full model not shown), and this may justify not including them in the adjusted models; since the impact of IMV overlaps with other variables. Other comorbidities may also be important, as we observed that an increase in the number of comorbidities increases the risk of death, as observed in the literature, but due to the low representativeness and experimental difficulties, assessing the impact of each of them may be complex [30]. Further studies, such as case-control studies, should assess the increased risk of death from the comorbidities that we found to play a significant role here, such as Cardiovascular disease presence, Chronic obstructive pulmonary disease presence, Chronic kidney disease presence, Smoking habit presence, correcting for confounding variables for each comorbidity.

The use of IMV was the strongest independent predictor of mortality in the patients evaluated (OR = 97.85), and should receive more attention in the clinical management of the patient. Mechanical ventilation is necessary as a support measure for many COVID-19 patients with acute respiratory syndrome and directly reflects the severity of the disease. The use of non-invasive mechanical ventilation did not prove to be a protective factor in our study, possibly due to the rapid and progressive evolution of the pulmonary condition in these patients. Despite the possible complications inherent in this therapy, IMV, such as barotrauma with alveolar rupture and superimposed bacterial pneumonia, was a strategy widely used in the clinical management of patients. These complications can be minimized if imaging tests are carried out frequently, in addition to rigorous monitoring of the patient's clinical condition, with a view to early diagnosis of pneumonia, complications that would lead to appropriate management [31]. In this sense the presence

of other comorbidities with significant effect observed by us as cronic obstructive Pulmonary disease presence and Smoking Habit presence could reinforce this lethality. On the other hand, it is important to identify the ideal time to introduce mechanical ventilation, since its late installation can reduce patient survival. Multicenter study that evaluated about 1900 patients with COVID-19 in ICU in the United States concluded that early initiation of mechanical ventilation reduces the chance of mortality compared to those patients who receive late intervention [32]. Patients died with a median of 11.5 days of mechanical ventilation use and survivors had a median of 15.5 days under IMV. Prospective cohort observed survivors with median of 27 days of IMV use and non-survivors 10 days [33].

In the analysis of patients in the general group, the length of stay in the ICU acted as a protective factor against mortality, that is, the longer the stay in the ICU, the lower the chance of mortality. The justification for this finding may be due to the extreme severity of the clinical picture by COVID-19 of some patients admitted to the ICU, leading to early death. Another factor to discuss is that the time of ICU and or hospitalization in these cases can work as an associated outcome and not a predictor. Those patients who survived the first days of hospitalization received the appropriate intensive care necessary for health recovery. However, a long time in the ICU increases the risk of other unfavorable outcomes such as the risk of infection related to health care, impairs mental health and family relationships of patients, in addition to the higher cost and burden on health systems [34,35], which consequently increase the risk of death. In Brazil, the occurrence of infections related to health care has already been clearly related to overload and increased health costs for the public health system [7,8]. Thus, the length of stay in ICU is an important measure for planning the capacity of beds and hospital resources if the SARS-CoV-2 presents a seasonal pattern [36]. Reducing hospitalization time and preventing health care-related infections are an important indicator for health services. In the patients evaluated here we observe both the presence of infections secondary to covid as aspergillosis [9], and the early installation of infections related to health care as catheter associated bloodstream infection [10]. There is a difficulty in defining the presence and classification of care-related infections based on international criteria in Brazil, since compulsory notifications in Brazil follow criteria of Brazilian regulatory bodies. Despite this, we observed the positivity of positic cultures for microorganisms both for blood, urine and tracheal aspirate (data not shown).

Patients with COVID-19 who have acute kidney injury have a substantial increased risk of death, especially if they require renal replacement therapy [37], association that was observed in patients admitted with high levels of creatinine on admission also in the group of patients in IMV who received renal replacement therapy of this study, after multiple logistic regression analysis. Vasopressin is commonly used in respiratory failure caused by COVID-19 to replace other drugs, because it does not impair renal function and does not cause overload in the right ventricle [38]. However, in patients with non-septic shock, vasopressin associated with catecholamines should be avoided because it is related to possible hyponatremia and volume overload [39]. In the group of IMV patients in this study, vasopressin increased by almost eight times the risk of death (OR = 7,87).

The use of hydrocortisone was associated with higher mortality in the group of patients in IMV (OR=2.33). However, meta-analysis including seven randomized controlled trials, including 1,703 patients, concluded that mortality was lower among patients receiving corticosteroids, including dexamethasone, hydrocortisone or methylprednisolone, compared to those who received placebo or conventional treatment [40]. Infusion of intravenous hydrocortisone in severe patients with COVID-19 reduces the amount of interleukin 6 in the lungs, thus reducing the inflammation that occurs in acute respiratory syndrome related to COVID-19 [41]. The findings of this study may be related to the late start of hydrocortisone therapy. However, this hypothesis was not analyzed due to the lack of accurate data that confirmed the exact date on which the drug was introduced in the treatment of patients. Studies of the impact of using one drug or another are still complex in

retrospective studies in Brazil given the low quality of patient records in the medical record. Digital and structured data in eletronic health records in Brazil are incipientes [42].

In the analysis of blood counts, the group of patients who received IMV had RDW > 15 as a predictor of mortality (OR = 3.84). The dysfunction in the size and aggregatibility of erythrocytes contributes to the impairment of capillary blood flow and microangiopathy/microthrombosis in patients with COVID-19 [43]. RDW, as well as platelets and leukocytes, are biomarkers that can predict disease progression and mortality in patients with COVID-19. Thus, these combined parameters should deserve special attention from the beginning of hospitalization in case of future waves of COVID-19 [44]. The altered markers for platelets, Neutrophil to platelet ratio abnormal, Prototombin activation time abnormal and International Normalized Ratio abnormal were independently associated with higher risk of mortality and reflect changes in the coagulation pattern of patients as observed in the literature [45,46], probably associated to vascular endothelial cell dysfunction, a hyperinflammatory immune response; and hypercoagulability [47]. Markers related to hemograms and their indices or derived reasons have had diverse findings in the literature but has shown great predictive potential of outcomes [13–15]. In Brazil, NLR greater than 10 has been associated with higher mortality, independently or associated with Dimero D [48]; although there is no consensus on the reference values for most of these indices.

At the height of the COVID-19 pandemic and with the increasing number of cases and deaths from the disease, researchers were looking for biomarkers in patient admission that could predict mortality. In this study, in the group receiving IMV, high levels of lactic dehydrogenase (LDH), D-dimer and creatinine ($p=0.016$, $p=0.009$, $p<0.001$, respectively) were associated with mortality. However, when multivariate logistic regression models were applied, these variables did not have statistical significance alone. Probably these patients with high values for the tests are also the same who received IMV and or other risk factors for death. Elevated levels of LDH on admission are associated with an approximate six-fold increase for the development of severe disease and an increase of about 16-fold in the chances of mortality in patients with COVID-19 [49].

Serum LDH is a prognostic marker of pulmonary injury of rapid, effective and accessible to predict higher risk of mortality in patients with COVID-19, and its measurement should be prioritized to enhance actions aimed at reducing mortality in these patients [50]. The level of serum D dimer collected on admission is a product of fibrin degradation and reflects the activation of coagulation and fibrinolysis, being a biomarker used to predict the mortality of patients with COVID-19 [51]. Meta-analysis that evaluated 2911 patients concluded that increased rates of this biomarker can increase up to four times the risk of death [52]. Serum creatinine level at admission can predict mortality in patients with COVID-19 and the literature points to 1.12 mg/dL as a cutoff point for this prediction [53]. Our study found a median of 1.22 mg/dL of creatinine among the nonsurvivors who received IMV, when an unadjusted statistical model was applied.

Some aspects that could affect mortality rates in the population studied here are difficult to control. There are records of the differential distribution of the incidence of COVID-19 in different neighborhoods of the city [54], which could reflect socio-economic differences and access to health services. Studies of the behavior of the waves and the Prevalencia of the strains in the municipality are absent or do not cover the entire pandemic periphery, and the municipality did not follow the guidelines for the virus content recommended by the state which clearly affected the occurrence of cases in the municipality [11,12]. Thus, these confounding factors could not be corrected in our study. The hosptial is also a macroregional reference, with patients from different municipalities information that is not always present in the medical records. Compulsory notification data from the municipalities served in the microregion of Uberlandia, in the initial phase of the pandemic had already demonstrated the impact of the size of the municipality of origin (small, medium or large) and decentralized policies to control the spread of the pandemic [55].

This study has important limitations because it is single-center, presents great data loss of some variables not recorded in medical records, and the absence of a prospective follow-up with control group without COVID-19, which prevented in-depth analysis and generalization of results. The results found, however, contribute to the elucidation of factors associated with mortality, directing future research, controlled the possible confounders, which provide the creation of intensive care protocols for patients with COVID-19 in order to mitigate mortality in this population. Local data are of paramount importance for the management of the municipalities, since they may present marked differences in behavior in relation to the state and or even the country.

5. Conclusion

Most patients with COVID-19 admitted to the ICU did not survive. IMV was a risk predictor strongly associated with mortality, age, diabetes mellitus and high SAPS 3 score for the general group of patients. In the group of patients receiving IMV, age, vasopressin, RDW >15, renal replacement therapy and were hydrocortisone associated with mortality. Early identification of predictors of mortality in patients with COVID-19 that require hospitalization in the ICU is paramount in the search for prevention and management of complications that may increase the survival of these patients.

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Brief Report

Factors Influencing Central Venous Catheter-Associated Bloodstream Infections in COVID-19 Patients

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Abstract: During the pandemic of COVID-19, the rates of bloodstream infection associated with ve- nous catheter in patients infected with the disease admitted to an intensive care unit rose significantly. In this study, we evaluated the occurrence of bloodstream infections in patients with SARS-CoV-2 and the variables that made the patients more susceptible to the catheter-associated bloodstream infection (CABSI). Blood culture results from patients interned between March 2020 and December 2021 (n= 109) were collected electronically from the hospital information system and then analyzed. The following variables presented statistical relevance after an adjusted model as follows: obesity (p = 0.003) and time of use of catheter before infection (p = 0.019). In conclusion, patients with shorter catheter use time and obesity had higher incidence of CABSI.

Keywords: COVID-19;, central venous cathter, secondary bloodstream infection;

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1. Introduction

The serious global health crisis caused by the coronavirus disease 2019 (COVID-19) pandemic caused the health workforce, and material and financial resources routinely used to prevent healthcare-associated infections (HAIs), to be redirected to manage the pandemic [1]. Added to this, patients who develop the severe form of COVID-19 are more prone to HAI due to the pathogenic mechanism of the virus and the use of immuno-suppressive medications, along with other risk factors such as staying in intensive care units (ICU) [2,3]. Studies, including systematic reviews and meta-analyses, indicate an up to 24% higher incidence of secondary infections, whether bacterial or fungal, in patients hospitalized with COVID-19 [4–6]. Furthermore, higher rates of catheter-associated blood-stream infection (CABSI) are observed in these patients compared to those not infected with COVID-19 [7].

Bloodstream infections are among the most serious in critically ill COVID-19 pa- tients [8], an diabetes and obesity [9]. These factors are associated with greater clinical severity and the need fo susceptible to CABSI [10]. It is reported that up to 50% of patients with COVID-19 who died frequency of CABSI, finding related microorganisms and factors associated with infection contr HAIs. Especially for COVID-19 patients, the need to know this frequency is reinforced given that th stay and patient morbidity and mortality [12], reducing the availability of resources and beds, pandemic.Thus, this study aimed to describe the occurrence of CABSI in patients with COVID-19 admitted to an intensive care units and its related factors.

2. Materials and Methods

This is a retrospective cohort whose inclusion criteria were patients aged over 18 years and who had used a central venous catheter (CVC) for at least 48 h. This was because the objective of the study was to analyze the population of adults admitted to an ICU due to the worsening of COVID-19, and because CABSI is defined as an infection occurring at least 48 h after central line insertion [13]. The patients selected had been admitted from March 2020 to December 2021. The study was carried out at a Brazilian public university and tertiary hospital. This hospital has approximately 500 beds and offers complex treatments. There were no exclusion criteria. The research was approved by the local Human Research Ethics Committee, CAAE: 51805021.5.0000.5152, under opinion number 5.043.636/2021.

The following characteristics were evaluated: age, sex, comorbidities, clinical data such as symptoms upon admission to the hospital, duration of symptoms and vital signs on the first day of hospitalization, laboratory results upon admission and treatments performed in the ICU. All data, including blood culture results from blood samples obtained by peripheral venipuncture, were collected electronically from the hospital information system and the patients' electronic medical records. In this case, the identified germs and the resistance profile of the antibiogram were collected, following the institution's protocol. For classification of resistance, the following definition was considered: resistant (R), microorganisms that present resistance to at least one class of antimicrobial; multidrug-resistant microorganisms (MDR), resistant to three or more classes of antimicrobials after accounting for intrinsic resistance; extensively resistant (XDR), resistant to most standard antimicrobials; pandrug resistant (PDR), resistant to all antimicrobials [14].

2.1. Defining the Outcome of Catheter-Associated Bloodstream Infection

CABSI is defined as an infection occurring at least 48 h after central line insertion, with at least one positive peripheral blood culture sample. In our study, the date of infection was defined as the date of positive blood culture collection. Microorganisms classified by the Centers for Disease Control and Prevention (CDC) as commensal, present on the skin, such as coagulase-negative staphylococci (including *S. epidermidis*) and *viridians* group streptococci, which are identified by the culture of two or more blood samples collected on separate occasions, were not considered in this study due to the lack of a second sample that could differentiate from contamination. Infections were defined according to CDC standards [13].

2.2. Statistical Analysis

For quantitative data, the median, first quartile and third quartile were calculated, given the absence of normality assessed by the Kolmogorov–Smirnov Lilliefors test. For qualitative data, the relative frequency in percentage and 95% confidence interval were calculated for each of the variable levels. To compare groups with and without CABSI in association analyses, the likelihood ratio test was used for qualitative variables and the Mann–Whitney test for quantitative variables. To control confounding variations, logistic regression models were used. For the logistic regression models, we chose the variable obesity due to lower sample loss compared to weight. To predict the presence of CABSI, simple and multiple logistic regression analysis was used. The simple (unadjusted) and multiple (adjusted) regression models were only built for variables that had previously shown a significant difference in prior association analyses and without data absence to avoid convergence and parameter estimation problems, since we had a lot of missing data in some variables. These variables with missing data were maintained in text for better patient characterization. The adjusted model included the presence of obesity, COVID-19 vaccination prior to hospital admission, hydrocortisone use prior to CABSI, 3 or more antibiotic use prior to CABSI, use of antifungal prior to CABSI, lactate dehydrogenase in U/L and days of central venous catheter use until diagnosis. Furthermore, the odds ratio and its 95% confidence interval were calculated for all models, unadjusted or adjusted.

All analyses were conducted using SPSS software version 20.0. A significance level of 5% was adopted for all analyses.

3. Results

During the study period, 596 COVID-19 patients were evaluated, of which 413 used CVC for at least 48 h and were included in the study. A total of 62.5% were male and had a median age close to 60 years. Patients with CABSI had shorter catheter use times before infection (median 9 vs. 11 days) compared to those who did not have infection (Tables 1 and 2). Furthermore, they showed higher weight and body mass index values, reflecting the higher prevalence of obesity (43.27 vs. 32.04%) and use of the COVID vaccine (25.0 vs. 16.18%), together with lower prevalence of hydrocortisone use before infection (48.8 vs. 59.87%), use of more than three antibiotics before infection (25.0 vs. 39.48%) and antifungals before infection (10.58 vs. 21.04%) (Tables 1 and 2). The hematological parameters of patients upon admission to the ICU did not differ between the two groups.

Table 1. Qualitative variables related to catheter-associated bloodstream infection (CABSI) in patients with COVID-19 in an adult intensive care unit.

Variables	*N* of Yes (% of Yes) [95% Confidence Interval]		*p*-Value
	CABSI Presence (*n* = 104)	CABSI Absence (*n* = 309)	
Admitted from another service	69 (66.35) [57.26–5.43]	200 (64.72) [59.4–70.5]	0.764
Obesity presence	45 (43.27) [33.75–57.79]	99 (32.04) [26.84–37.24]	0.040
Systemic arterial hypertension presence	60 (57.69) [48.2–67.19]	155 (50.16) [44.59–55.74]	0.183
Diabetes mellitus presence	35 (33.65) [24.57–42.74]	89 (28.8) [23.75–33.85]	0.354
Cardiovascular disease presence	14 (13.46) [6.9–20.02]	34 (11) [7.51–14.49]	0.505
Chronic obstructive pulmonary disease presence	10 (9.62) [3.95–15.28]	32 (10.36) [6.96–13.75]	0.828
Chronic kidney disease presence	11 (10.58) [4.67–16.49]	24 (7.77) [4.78–10.75]	0.384
Etilism habit presence	7 (6.73) [1.92–11.55]	25 (8.09) [5.05–11.13]	0.649
Smoking habit presence	22 (21.15) [13.3–29]	65 (21.04) [16.49–25.58]	0.980
COVID-19 vaccine prior to hospital admission	26 (25) [16.68–33.32]	50 (16.18) [12.07–20.29]	0.050
Renal replacement therapy prior to CABSI	40 (38.46) [29.11–47.81]	142 (45.95) [40.4–51.51]	0.181
Hydrocortisone use prior to CABSI	50 (48.08) [38.47–57.68]	185 (59.87) [54.41–65.34]	0.036
Antibiotic use prior to CABSI	83 (79.81) [72.09–87.52]	253 (81.88) [77.58–86.17]	0.642
3 or more antibiotics use prior to CABSI	26 (25) [16.68–33.32]	122 (39.48) [34.03–44.93]	0.007
Use of cephalosporin prior to CABSI	19 (18.27) [10.84–25.7]	56 (18.12) [13.83–22.42]	0.973
Use of carbapenem prior to CABSI	41 (39.42) [30.03–48.82]	153 (49.51) [43.94–55.09]	0.073
Use of antifungal prior to CABSI	11 (10.58) [4.67–16.49]	65 (21.04) [16.49–25.58]	0.013

Table 2. Quantitative variables related to catheter-associated bloodstream infection (CABSI) in patients with COVID-19 in an adult intensive care unit.

Variable	Median (Quartile 1–Quartile 3) [*n*]		*p*-Value
	CABSI Presence	CABSI Absence	
Age in years	60 (45.75–68) [104]	61 (49–71) [309]	0.396
Weight in Kg	80 (71–95) [94]	75.5 (68–87.2) [248]	0.007
Height in m	1.68 (1.64–1.73) [101]	1.67 (1.6–1.72) [256]	0.782
Body Mass Index in Kg/m^2	28.03 (25.01–33.3) [93]	26.99 (24.69–31.24) [235]	0.008
Total number of comorbidities	1 (1–3) [104]	1 (0–2) [309]	0.070
Simplified Acute Physiology Score	57 (44.75–70) [104]	59 (46–69) [309]	0.417
Simplified Acute Physiology Score prognosis in %	32 (11.75–57.25) [104]	34 (13–56.5) [309]	0.362
Days of central venous catheter use until diagnosis	9 (6–14) [99]	11 (6–20) [294]	0.043
Creatine in mg/dL	1.06 (0.76–1.75) [104]	1.1 (0.78–1.9) [308]	0.945
Albumin in mg/dL	3.15 (2.73–3.44) [248]	3.22 (2.63–3.52) [93]	0.362
Glutamic-Oxaloacetic Transaminase in U/L	49.65 (39–71.85) [100]	50.75 (33–86.48) [276]	0.852
Pyruvic Glutamic Transaminase in U/L	38.9 (29.8–53.9) [99]	39 (23–66.4) [277]	0.819
Lactate Dehydrogenase in U/L	636 (519–850) [75]	563 (423–800) [241]	0.042
Polymerase Chain Reaction in mg/dL	13.61 (7.83–20.28) [101]	12.77 (6.92–20.86) [293]	0.654
D-Dimer in mg/dL	2149 (595.5–5845) [87]	1928 (775.14–5897) [257]	0.537
Interleukin-6 in pg/dL	74.55 (23.77–124.38) [72]	86.22 (34.64–186) [217]	0.114
Prothrombin Activity Time in %	100 (83.75–100) [98]	100 (77–100) [295]	0.262
International Standardized Prothrombin Ratio	1 (1–1.08) [98]	1 (1–1.1) [293]	0.334

In the simple models, all variables that showed a difference between the two groups were also efficient in predicting CABSI, except for lactic dehydrogenase (OR = 1.00) (Table 3). Obesity was considered a risk factor, and prior vaccination for COVID-19, the use of hydrocortisone, use of three or more antibiotics and use of antifungals were considered protective factors. When the models were adjusted, we saw that only two variables were able to predict infection, with obesity increasing the chances of CABSI by 1.39 times (OR = 2.39; 95%CI: 1.36–4.22) and the number of days of CVC use prior to infection reducing the chances by 0.05 times per day (OR = 0.91; 95%CI: 0.91–0.99) (Table 3). CABSI increased the patient's length of stay in the ICU (median of 20.5 vs. 12 days) and the length of hospital stay (median of 26.5 vs. 19 days) when compared to the times of those who did not have the infection. CABSI alone was not able to affect patient mortality, with mortality in the group without CABSI being 72.2% (95% CI:67.85–77.78; *n* = 225 deaths) and in the group with CABSI being 75.96% (95% CI:67.65–84.17, *n* = 79 deaths) with an odds ratio of 1.18 (95% CI:0.70–1.97; *p*-value = 0.597). This result needs to be evaluated with caution, as confounding factors were not considered.

Table 3. Simple (or unadjusted) and multiple (or adjusted) logistic regression models related to presence of catheter-associated bloodstream infection (CABSI) in patients with COVID-19 in an adult intensive care unit.

Significant Variables in the Association Tests	Odds Ratio (95% Confidence Interval)			
		Simple Model		Multiple Model
	p-Value	Unadjusted	*p*-Value	Adjusted
Obesity presence	0.038	1.62 (1.03–2.55)	0.003	2.39 (1.36–4.22)
COVID-19 vaccination prior to hospital admission	0.046	1.73 (1.01–2.96)	0.232	1.50 (0.77–2.91)
Hydrocortisone use prior to CABSI	0.036	0.62 (0.40–0.97)	0.585	0.85 (0.48–1.51)
3 or more antibiotics use prior to CABSI	0.008	0.51 (0.31–0.88)	0.597	1.21 (0.60–2.42)
Use of antifungal prior to CABSI	0.020	0.44 (0.22–0.88)	0.242	0.56 (0.22–1.47)
Lactate Dehydrogenase in U/L	0.940	1.00 (1.00–1.00)	0.647	0.99 (0.9996–1.0003)
Days of central venous catheter use until diagnosis	0.002	0.96 (0.94–0.99)	0.019	0.95 (0.91–0.99)

A total of 109 positive blood cultures for bacteria or fungi were found in 104 patients (of which five had simultaneously positive samples for fungus and bacteria). Most microorganisms found were gram negative bacteria (55.05% of germs), with 55.96% of germs resistant to three or more antibiotics. The most prevalent germs were *Klebsiella pneumoniae* (17.43%), *Acinetobacter baumanni* (15.6%) and *Staphylococcus aureus* (13.76%). These germs also showed the highest number of samples with resistance (Tables 4 and 5, Figure 1).

Table 4. Microorganisms isolated in 109 blood cultures from patients admitted with COVID-19 to an intensive care unit and evaluated for the presence or absence of catheter-associated bloodstream infection (CABSI).

Variable	Level	% (*n*) [95% Confidence Interval]
Isolated microorganism	*Staphylococcus aureus*	13.76 (15) [7.29–20.23]
	Enterococcus faecium	3.67 (4) [0.14–7.2]
	Proteus mirabilis	0.92 (1) [0–2.71]
	Acinetobacter baumanni	15.6 (17) [8.78–22.41]
	Enterecoccus faecalis	12.84 (14) [6.56–19.13]
	Klebisiela pneumoniae	17.43 (19) [10.31–24.55]
	Pseudomonas aeruginosa	5.5 (6) [1.22–9.79]
	Stenotropomonas maltophilia	3.67 (4) [0.14–7.2]
	Burkholderia cepacia	0.92 (1) [0–2.71]
	Serratia mascescens	0.92 (1) [0–2.71]
	Escherichia coli	0.92 (1) [0–2.71]
	Pasteurella sp.	0.92 (1) [0–2.71]
	Klebisiella oxytoca	0.92 (1) [0–2.71]
	Streptococcus viridans	0.92 (1) [0–2.71]
	Candida peliculosa	0.92 (1) [0–2.71]
	Candida tropicalis	0.92 (1) [0–2.71]
	Candida albicans	11.01 (12) [5.13–16.89]
	Candida utilis	0.92 (1) [0–2.71]
	Candida glabrata	0.92 (1) [0–2.71]
	Aspergillu sp.	1.83 (2) [0–4.35]
	Geotrichum candidum	0.92 (1) [0–2.71]

Table 4. *Cont.*

Variable	Level	% (*n*) [95% Confidence Interval]
Agent classification	Gram positive bacteria	27.52 (30) [19.14–35.91]
	Gram negative bacteria	55.05 (60) [45.71–64.38]
	Fungi	17.43 (19) [10.31–24.55]
ESBL resistance mechanism	No	96.63 (86) [92.88–100.38]
	Yes	3.37 (3) [0–7.12]
Resistant to 3 or more antibiotics	No	55.96 (61) [46.64–65.28]
	Yes	44.04 (48) [34.72–53.36]

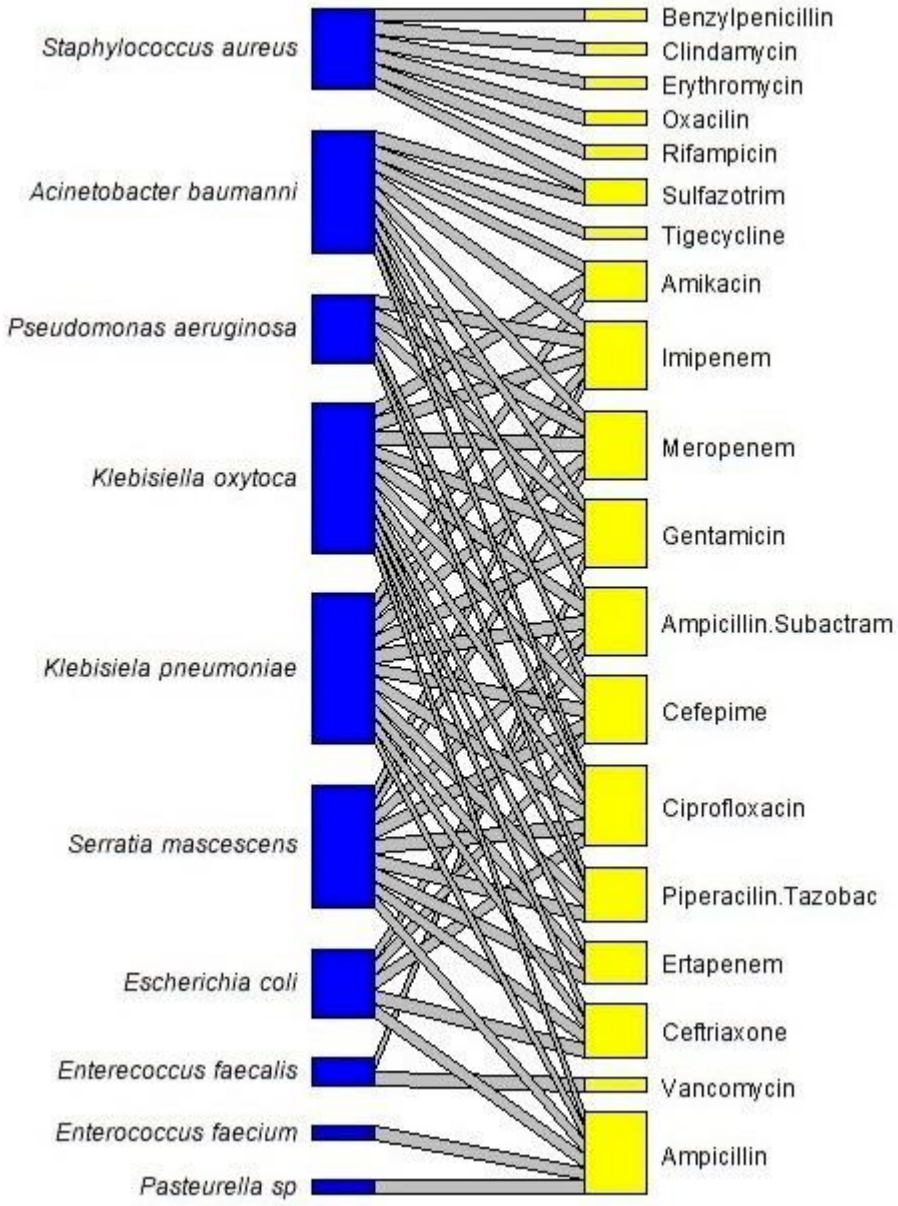

Figure 1. Antimicrobial resistance from microorganism (in blue) to antibiotics (in yellow) represented in a bipartide network for 109 cultures from patients admitted with COVID-19 to an intensive care unit and evaluated for the presence or absence of catheter-associated bloodstream infection (CABSI). The bars represent the resistance of each microorganism to each antimicrobial. Note: *Stenotrophomonas maltophilia*, *Streptococcus viridans* and *Burkholderia cepacia* did not show any resistance. See Table 5 for frequency of resistance in each pair.

Table 5. Frequency of resistance in microorganisms isolated in 109 blood cultures from patients admitted with COVID-19 to an intensive care unit and evaluated for the presence or absence of catheter-associated bloodstream infection (CABSI).

Antibiotics	Microorganisms [1]									
	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10
Amikacin	2	0	0	0	1	1	0	0	0	0
Ampicillin	0	0	4	1	18	1	1	0	3	0
Ampicilin-Sulbactam	14	0	0	1	16	1	0	0	3	0
Benziylpenicillin	0	0	0	0	0	0	0	0	0	13
Cefepime	14	0	0	1	15	1	0	0	2	0
Ceftriaxone	0	0	0	1	17	1	0	0	2	0
Ciprofloxacin	14	0	0	1	15	1	0	1	1	0
Clindamycin	0	0	0	0	0	0	0	0	0	10
Erythomicin	0	0	0	0	0	0	0	0	0	12
Ertapenem	0	0	0	0	14	1	0	0	1	0
Gentamicin	4	6	0	0	12	1	0	1	0	0
Imipenem	13	0	0	0	14	1	0	1	1	0
Meropenem	13	0	0	0	14	1	0	1	1	0
Oxacilin	0	0	0	0	0	0	0	0	0	7
Piperacilin-Tazobac	0	0	0	0	13	1	0	3	1	0
Rifampicin	0	0	0	0	0	0	0	0	0	1
Sulfazotrim	1	0	0	0	0	0	0	0	0	2
Tigecycline	3	0	0	0	0	0	0	0	0	0
Vancomycin	0		0	0	0	0	0	0	0	0

4. Discussion

COVID-19 has negatively affected health services in several ways, including an increase in HAI rates [15]. Patients with CABSI had had a shorter time using a catheter before infection compared to those who did not have infection. This was also observed in another study that compared CABSI in a pre-COVID-19 cohort and a COVID-19 co- hort, showing in its results that, in the pre-pandemic period, the length of catheter use was approximately 4 days and after the pandemic the length of use was approximately 3 days [16]. The hypothesis is that with a shorter period of time using a catheter, the patient with COVID-19 in the ICU with a predisposition to CABSI will already need to undergo several invasive procedures, thus becoming susceptible to greater exposure and infection by different microorganisms [17]. As a result, the infection sets in soon after exposure and contamination. A study assessed that the incidence of CABSI before COVID-19 was equal to 1.89 per 1000 patients admitted, and during the pandemic the incidence increased to 5.53 per 1000 patients admitted [18], which may suggest a lower quality of care in maintenance and insertion of the catheter during the pandemic, possibly caused by the stress of healthcare professionals faced with exposure to the new virus and decreased adherence to standard precautions, as shown by some studies [9,15,16]. We saw obesity as a risk factor for CABSI. Obesity contributes to worse prognoses in patients with established COVID-19. Furthermore, metabolic deregulations, which are common in the obese population and closely related to an impaired immune system, together with an altered response to viral infection can lead to a greater predisposition to other infections and greater virulence, duration and severity of the disease [19]. Regarding length of stay, it was found that CABSI was associated with higher values both in the ICU and in the hospital. This result is in line with other studies, wherein prolonged hospitalization was also associated with the presence of CABSI [20,21]. An elevated serum DHL level was seen in patients with infection, as in another study, resulting from the greater release of this enzyme into the bloodstream because of cellular damage caused by the infectious processes to which these patients are

subjected [20]. Patients with more severe cases of COVID-19 infection have higher levels of DHL than patients with milder cases, this being a biomarker that can be used to show the severity of patients' status in relation to COVID-19 [22].

The use of hydrocortisone, three or more antibiotics and antifungals were protective factors for CABSI, which corroborated other studies in which patients with concomitant use of antibiotics showed a lower association with CABSI [23,24]. Although the literature links corticosteroid therapy with increased rates of fungemia [10,25], there are reports of the protective effect of hydrocortisone against candidemia in patients with severe COVID-19 [26]. The Pan American Health Organization points to a reduction in the risk of death for pa- tients with COVID-19 with the use of corticosteroids, such as hydrocortisone, due to the effectiveness of this medication in treating and controlling the inflammatory process caused by COVID-19 [27]. The microorganisms isolated in the observed blood cultures were Gram negative, with a predominance of *Klebsiella pneumoniae* and *Acinetobacter baumanni*. Gram negative bacilli present greater multidrug resistance, being more resistant after the COVID-19 pandemic [24] and presenting a need for greater control of the use of antimicrobials. A study that compared COVID-19 ICUs with non-COVID-19 ICUs showed that *Acinetobacter baumanni* had increased resistance to carbapenems. However, during the pandemic there was a significant increase in the consumption of broad-spectrum antimicrobials, disproportionate to the increase in infections with MDR microorganisms. Considering the need to avoid excessive use of antimicrobials but without delaying the start of effective treatment, it is important to create antimicrobial management programs, in addition to spreading greater knowledge of infection rates and the microorganisms involved [16]. This is important to minimize morbidity, mortality, hospitalization time and costs.

Studies show that the more invasive procedures are conducted, the greater the exposure to such microorganisms and, so, to CABSI [28–30]. Is important to remember the importance of knowing the risk factors involved in co-infections, which contribute to the development of preventive actions, thus ensuring greater quality in the care provided and reducing morbidity, mortality and patient hospitalization times. The occurrence of HAIs in general has increased patients' length of stay and hospital costs, thus creating an overload on health systems. Reducing infection rates related to HAIs both reduces hospital costs and increases the availability of ICU beds in the world [31], which are still scarce, and were even more scarce during the COVID-19 pandemic.

There was a higher incidence of CABSI in vaccinated patients compared to those who were not vaccinated, although we were unable to verify how long ago the patient had been vaccinated or whether the vaccination schedule had been completed. A justification for this finding may be related to the vaccination of risk groups, corroborating this hypothesis with the fact that, in the adjusted models, only obesity remained a risk factor. The occur- rence of CABSI is associated with greater severity of COVID-19 and risk factors prior to hospitalization in these patients. In a retrospective cohort study conducted in Hungary, no statistical difference was seen relating vaccinated patients to bloodstream infections [32], but that was in a more accelerated vaccination context compared to Brazil.

This study brought interesting information about the association of obesity, time of catheter use, CABSI and COVID-19 infection. Although the pandemic has ended, COVID-19 infections will continue to occur and new previously unknown variants of the virus may appear, which requires the preparation of health services in terms of caring for the population and preventing other complications due to hospitalization. In this way, the results found can collaborate with future studies.

Our findings also contribute to elucidating the risk factors and risk indicators for the development of CABSI in patients seriously ill due to COVID-19, emphasizing the need for greater control and prevention of infections during other pandemic periods, not only COVID-19. Furthermore, other studies in other regions of the world will contribute to better evaluating the robustness of the data found in this study. Future studies, involving large control centers in this country and others, will be able to point out the variables that best relate to the outcome of patients infected with diseases such as COVID-19 and will

also be able investigate health care actions that can mitigate the occurrence of catheter-associated bloodstream infections, especially in vulnerable patients such as those requiring intensive care.

The study, however, has some limitations, such as the lack of prospective analysis and a control group without COVID-19, in addition to the fact that data collection was conducted in a single center, and records had a high loss of information in some variables, preventing in-depth analysis, which limits the generalization of results.

5. Conclusions

Patients with a shorter time using a catheter and with obesity had a higher incidence of CABSI compared to patients with a longer period of use and without obesity. The occurrence of CABSI also increased patients' length of stay in the ICU and in the hospital.

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Informed Consent Statement: Patient consent was waived due to it being a retrospective study, using medical records and the patients not being hospitalized any longer.

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Aspergillosis and COVID-19 in an intensive care unit in Brazil: a series of cases

Aspergilose e COVID-19 em unidade de terapia intensiva brasileira: uma série de casos

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INFORMAÇÕES DO ARTIGO

ABSTRACT

COVID-19-Associated Pulmonary Aspergillosis (CAPA) is one of the main complications of severely ill patients with COVID-19. Thus, this study aimed to report cases of CAPA in patients hospitalized in an intensive care unit of a tertiary hospital. Method: Descriptive and retrospective study that included patients with CAPA admitted between March 2020 and December 2021 in the intensive care unit of a high complexity hospital. Results: Of the eight patients with CAPA described in this study, six were classified as possible cases and two as probable cases. Conclusion: Preventive actions and active investigation of invasive pulmonary aspergillosis in critical COVID-19 patients should be performed through appropriate screening and diagnostic protocols, considering the high risk of co-infection of these patients.

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COVID-19, SARS-CoV-2, Aspergillosis, Critical care, Mycoses, Coronavirus

RESUMO

A Aspergilose Pulmonar Associada à COVID-19 (APAC) é uma das principais complicações de pacientes com COVID-19 gravemente doentes. Dessa forma, esse estudo objetivou relatar casos de APAC em pacientes internados em unidade de terapia intensiva de um hospital terciário. Método: Estudo descritivo e retrospectivo que incluiu pacientes com APAC admitidos entre março de 2020 a dezembro de 2021 na unidade de terapia intensiva de um hospital de alta complexidade. Resultados: Do total de oito pacientes com APAC descritos nesse estudo, seis foram classificados como casos possíveis e dois como casos prováveis. Conclusão: Ações preventivas e investigação ativa de aspergilose pulmonar invasiva em pacientes com COVID-19 críticos devem ser realizadas por meio de protocolos de rastreamento e diagnóstico adequados, considerando o alto risco de coinfecção desses pacientes.

Palavras-chave:
COVID-19, SARS-CoV-2, Aspergilose, Cuidados Críticos, Micoses, Coronavirus

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Introduction

COVID-19 marked world history for the unprecedented damage generated in a pandemic that recorded more than 6.6 million deaths between March 2020 and November 2022 (*WHO Coronavirus (COVID-19) Dashboard | WHO Coronavirus (COVID-19) Dashboard With Vaccination*, 2022). The virus that causes COVID-19 was called SARS-CoV-2 due to is genetic similarity with the coronavirus of severe acute respiratory syndrome (SARS-CoV) (Zhu et al., 2020). This virus causes severe pneumonia with clinical symptoms different from known and rapidly evolving ones that have challenged health services worldwide (Castagnoli et al., 2020).

Since the beginning of the pandemic, bacterial and fungal coinfections have been reported in patients with COVID-19 and among the main genera of pathogens involved are *Acinetobacter, Klebsiella, Pseudomonas, Candida,* and *Aspergillus* (Musuuza et al., 2021). COVID-19-Associated Pulmonary Aspergillosis (CAPA) is one of the main complications of severely ill patients with COVID-19 (Calderón-Parra et al., 2022; Hashim et al., 2022), occurring in approximately 10% of patients admitted to the Intensive Care Unit (ICU) worldwide (Calderón-Parra et al., 2022; Hashim et al., 2022) and higher mortality rate compared with patients without CAPA (Bartoletti, 2020; Calderón-Parra et al., 2022; Chong et al., 2022). Recent reports from Netherlands, Brazil and Spain report invasive aspergillosis in 19%, 16% and 11% patients with severe COVID-19 pneumonia, respectively (Koehler et al., 2020; de Almeida Jr et al., 2022; Marta et al., 2022).

The diagnosis of CAPA is complex due to nonspecific symptoms, difficulty in performing biopsies and imaging tests that do not adequately differentiate lung damage caused by COVID-19 or invasive aspergillosis (Caggiano et al., 2022). Given the different definitions of CAPA used in research published at the beginning of the pandemic, the European Confederation of Medical Mycology/International Society for Human and Animal Mycoses (ECMM/ISHIM) proposed, based on validated tests, to classify the CAPA as proven, probable and possible. This classification allows researchers to homogeneously classify patients, conferring higher quality to studies and, to health professionals, adequate clinical management (Koelher, 2021). 2020 ECMM/ISHAM consensus definitions provide support for standardization of CAPA clinical research and surveillance studies based on conventional biomarkers and micrology of lower respiratory tract samples, such as microscopy and culture for fungi, in order to meet the microbiological diagnostic criteria (Permpalung et al., 2021).

The aim of this study was to report cases of COVID-19-associated pulmonary aspergillosis in patients admitted to the ICU of a tertiary hospital, from March 2020 to December 2021, with description of clinical characteristics, diagnosis, treatment and outcome.

Method

Design and ethical aspects of the study

This descriptive and retrospective study included patients with CAPA, adults (≥18 years), admitted between March 2020 and December 2021 in the ICU of a high complexity hospital, which has approximately 500 beds and is a reference in the southeastern region of Brazil.

The research was submitted and approved by the Human Research Ethics Committee, CAAE: 51805021.5.0000.5152.

Data collection and definitions

Patient data were collected in the electronic medical record including clinical and microbiological information, prescribed treatment and outcome. As there was no screening or screening protocol for CAPA in the period evaluated, the investigations occurred upon clinical suspicion.

The laboratory diagnosis of COVID-19 occurred by polymerase chain reaction with reverse transcriptase (RT-PCR). For the diagnosis of CAPA, the criteria of the 2020 ECMM/ISHAM consensus were used (Koelher, 2021), which classifies CAPA as proven, probable and possible: CAPA is proven by histopathological or direct microscopic detection, or both, of fungal elements that are morphologically consistent with *Aspergillus* sp, showing invasive growth into tissues with associated tissue damage, or (with or without) aspergillus recovered by culture or detected by microscopy, in histology studies or by a sterile aspiration or biopsy from a pulmonary site, showing an infectious disease. The diagnosis of probable and possible pulmonary PACA requires a pulmonary infiltrate combined with mycological evidence by culture of the respiratory tract obtained via non-bronchoscopic lavage or detection of biomarkers, being probable when the serum galactomannan index or bronchoscopic lavage is >0.5 and possible when galactomannan detected in non-bronchoscopic lavage, index >1,2.

The cases described in this report could not be proven due to the absence of samples obtained by biopsy or bronchoscopy. *Aspergillus* species were obtained in culture of tracheal secretion aspirate and serum galactomannan was obtained by enzyme immunosorbent assay (ELISA). The antimicrobial sensitivity profile of the isolated fungus species was not determined. The eight cases included in this study were described and relevant data were categorized.

Results

We identified 588 patients with COVID-19 admitted to the ICU during the study period, of which 170 had tracheal secretion cultures positive for bacteria or fungi. The consensus criteria followed included identification of *Aspergillus* sp in culture of tracheal secretion and serum

galactomannan >0.5, which allowed to classify eight cases of CAPA, six as possible CAPA and two as probable CAPA (Table 1).

Table1.
Characteristics of patients with COVID-19 Associated Pulmonary Aspergillosis (CAPA) in an Intensive Care Unit

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Age	51 years	50 years	74 years	59 years	67 years	61 years	59 years	61 years
Sex	male	female	male	male	female	male	male	male
Comorbidities	Grade III obesity, DM, SAH	Grade III obesity	SAH, gastric ulcer	Grade II obesity, SAH	Grade II obesity, SAH	Grade I obesity; MD; SAH; CVD; CKD	Grade I obesity, DM, SAH	Grade I obesity, SAH
SAPS 3	66 points	34 points	not calculated	79 points	70 points	60 points	not calculated	76 points
Length of stay until identification of the fungus in culture	16 days	12 days	5 days	11 days	9 days	6 days	5 days	14 days
Time of mechanical ventilation until identification of the fungus in culture	11 days	10 days	4 days	8 days	9 days	3 days	3 days	12 days
Time between admission to the ICU and identification of the fungus in culture	11 days	10 days	5 days	9 days	9 days	5 days	5 days	11 days
Length of ICU stay/days	28 days	48 days	7 days	12 days	9 days	5 days	14 days	27 days
Hemodialysis	yes	no	yes	yes	no	yes	yes	yes
Length of hospital stay	33 days	50 days	7 days	14 days	9 days	6 days	14 days	30 days
Prone position	yes	yes	no	yes	yes	no	no	yes
Serum GM (positive: index >0.5)	Positive (0.8)	Negative*	not performed	Negative*	not performed	not performed	Positive*(1.25)	Negative*
Germ identified in Fungal Culture of Tracheal Aspirate	*Aspergillus sp.*	*Aspergillus sp.*	*Aspergillus fumigatus*	*Aspergillus sp.*	*Aspergillus fumigatus*	*Aspergillus fumigatus*	*Aspergillus fumigatus*	*Aspergillus fumigatus*
CAPA classification according to ECMM/ISHAM	Probable	Possible	Possible	Possible	Possible	Possible	Probable	Possible
Coinfection with other germs	no	*Klebsiela pneumoniae*	no	no	no	no	*Candida albicans*	*Acinetobacter baumanni*
Antifungal therapy	Empirical fluconazole and voriconazole replaced by liposomal amphotericin B after identification of *Aspergillus*	Voriconazole followed by Liposomal Amphotericin B	not started due to death	Liposomal amphotericin B	not started due to death	not started due to death	Liposomal amphotericin B	Liposomal amphotericin B

*Abbreviations: DM: diabetes mellitus; SAH: systemic arterial hypertension; CVD: cardiovascular disease; CKD: chronic kidney disease; SAPS 3: Simplified Acute Physiology Score 3; GM: galactomannan. Symbol: *: exam collected the day after the identification of Aspergillus in a culture of tracheal secretion aspirate.*

Common profile of the cases

The eight patients included in this report were admitted to the hospital due to symptoms of COVID-19 and then transferred to the ICU where they received invasive mechanical ventilation, used intravenous corticosteroid and had *Aspergillus* species identified in tracheal secretion culture. All patients underwent at least one chest computed tomography scan during hospitalization, indicating ground-glass pulmonary opacity. The eight patients progressed to death.

Presentation of the cases

Case 1

Male patient, 51 years old, with diabetes mellitus, systemic arterial hypertension and grade III obesity. Diagnosed with COVID-19 four days before admission. Chest tomography was performed on the day of admission with areas of ground glass with involvement of 20% of the pulmonary area. Due to worsening of the respiratory pattern was transferred to the ICU in D5 (fifth day of hospital stay), when it required mechanical ventilation and initiated renal replacement therapy. He presented persistent fever and infectious leukogram, even with broad-spectrum empirical antibiotic therapy and, in D9, fluconazole was also prescribed empirically. With a positive galactomannan test on D14, voriconazole was administered instead of fluconazole. In tracheal aspirate secretion collected on D16 was isolated *Aspergillus* sp and staggered treatment for liposomal amphotericin B. There was a worsening of the clinical picture and identification of *Acinetobacter baumannii* in aspirated tracheal secretion collected in D30. He died in D32

Case 2

Female patient, 50 years old, grade III obesity, with a history of smoking for 40 years, abstaining for 10 years. Admitted due to diagnosis of COVID-19 the day before hospitalization and symptoms of dyspnea and cough five days before hospitalization. Chest tomography of the day of admission with bilateral ground glass opacities occupying more than 90% of the pulmonary parenchyma. It presented progressive worsening of the respiratory pattern, being transferred to the ICU with two days of hospitalization, D2, the day in which mechanical ventilation was installed. Due to persistent fever cultures were collected on D12, with identification of *Aspergillus* sp and *Klebisiella pneumoniae* in endotracheal aspirate secretion, instituted therapy with voriconazole on D16, maintained empirical meropenem started on D10 and associated inhaled gentamicin. After 15 days of treatment with voriconazole, this was replaced by liposomal amphotericin B in D31 due to alteration in hepatogram. In D35 was identified *Acinetobacter baumannii* in tracheal secretion culture. The patient presented worse ventilatory parameters and died in D50.

Case 3

Male patient, 74 years old, with systemic arterial hypertension. He went to the health service with cough and high digestive bleeding due to a gastric ulcer. On the day of admission, COVID-19 was confirmed and thorax tomography was performed with ground glass opacity occupying 40% of the total lung area, followed by transfer to ICU. On the second day of hospitalization, D2, presented worsening of the respiratory pattern, agitation and mental confusion, being installed mechanical ventilation. *Aspergillus fumigatus* isolate in endotracheal aspirate culture collected on D5 due to persistent fever. Renal replacement therapy initiated on D6. He presented hemodynamic instability and progressed to death in D7, the day on which the culture result was released, prior to the beginning of antifungal therapy.

Case 4

Male patient, 59 years old, with systemic arterial hypertension and grade II obesity. Admitted to the service the day he was diagnosed with COVID-19, with complaints of flu symptoms. He was transferred to the ICU the day after admission, D2 and, on the fourth day of hospitalization, D4, was intubated and installed mechanical ventilation, after presenting a progressive decrease in oxygen saturation, not responsive to other measures, and the imaging showed bilateral pulmonary opacity. In D9, renal replacement therapy was started. He presented persistent fever, leukocytosis and increased C-reactive protein, and broad-spectrum antibiotic therapy was started. In D11, *Aspergillus* sp was identified in endotracheal aspirate secretion concomitant to the worsening of the clinical picture. Started treatment with liposomal amphotericin B on D12, when the patient evolved to death.

Case 5

Female patient, 67 years old, with systemic arterial hypertension and grade II obesity. Diagnosed with COVID-19 five days before hospital admission. Admitted with major dyspnea, being intubated and referred to ICU on admission. Chest tomography performed at admission showed 40 to 60% of lung involvement. He presented persistent fever and, in D9, *Aspergillus fumigatus* was identified in endotracheal aspirate secretion and liposomal amphotericin B was prescribed. However, due to the worsening of the clinical picture the patient evolved to death before the beginning of treatment.

Case 6

Male patient, 61 years old, with diabetes mellitus, systemic arterial hypertension, grade I obesity, congestive heart failure and chronic kidney disease, undergoing conservative treatment until admission to the ICU, where the disease worsened and required renal

replacement therapy. Diagnosed with COVID-19 seven days before admission. He presented 25% of pulmonary involvement in chest tomography performed on the date of admission. Transferred to ICU in D2 and D4 mechanical ventilationwas installed due to the worsening of the respiratory pattern. In D6, *Aspergillus fumigatus* was identified in endotracheal aspirate secretion, the day the patient died.

Case 7

Male patient, 59 years old, with diabetes mellitus, grade I obesity and hypertension.

Prior to hospitalization, he received a dose of vaccine against COVID-19, whose date and manufacturer information were not recorded in the medical record. The diagnosis of COVID-19 occurred 11 days before hospitalization. Admission chest tomography showed 70% of lung involvement. He presented respiratory worsening and was transferred to ICU in D1. He needed mechanical ventilation in D2 and after three days renal replacement therapy was started due to alteration of renal function. Due to persistent fever and worsening of the clinical picture, in D5 cultures were collected with identification of *Aspergillus fumigatus* and *Candida albicans* in tracheal aspirate secretion and started treatment with liposomal amphotericin B. Collected serum galactomannan in D6, with index 1.25. The patient presented a worsening of the clinical picture with persistent fever, not responsive to the measures and prescribed broad-spectrum antibiotic therapy, evolving to death on D14.

Case 8

Male patient, 61 years old, with systemic arterial hypertension and grade I obesity, previous history of smoking, no record of time of cigarette use, and current history of alcoholism. Diagnosed with COVID-19 five days before admission. Submitted to orotracheal intubation and transferred to ICU in D4. Due to persistent fever and infectious leukogram, cultures and isolate *Aspergillus fumigatus* and *Acinetobacter baumannii* were collected in tracheal secretion within 15 days of hospitalization, when antifungal therapy was initiated with liposomal amphotericin B and replaced with empirical meropenem and teicoplanin by polymyxin and tigecycline. In D17, renal replacement therapy was started and, in the following days, there was a worsening of the clinical picture that culminated in the death of the patient in D30.

Discussion

Brazil is, along with the United States and India, among the countries with the highest number of cases and deaths from COVID-19 (Oliveira et al., 2022). CAPA has been of interest to scholars due to its ability to increase morbidity and mortality in critical patients and the need for better definitions regarding its clinical manifestations (Calderón-Parra et al., 2022; Koehler et al., 2020). Studies indicate significantly higher mortality among patients with CAPA than in patients without CAPA (Borman et al., 2022; Hashim et al., 2022; Singh et al., 2021; Tio et al., 2021). In this report all patients evolved to death. However, it is worth mentioning the existence of comorbidities such as hypertension, obesity, diabetes and advanced age, in addition to the early clinical worsening by COVID-19 presented by the cases, given the high scores of Simplified Acute Physiology Score 3 (SAPS 3) obtained at the time of admission to the ICU. The SAPS 3 is a validated hospital mortality predictor system, which is based on variables of acute physiological disorders, conditions and health status prior to interventions occurred in hospitalization, since the calculation is performed with data from the first hour after the patient's admission to the ICU. This score can vary between zero and 120 and the higher the score, the higher the probability of death (Moreno et al., 2005).

Considering the greater possibility of poor outcomes in patients with COVID-19 coinfected by invasive pulmonary aspergillosis (Singh et al., 2021), it is relevant to mention the risk factors for the emergence of CAPA mentioned in the literature and also found in patients who composed the sample of this report, among which are the lung damage caused by COVID-19 itself, need for hospitalization in ICU, corticosteroid use, prolonged hospitalization, invasive mechanical ventilation, and advanced age (Arastehfar et al., 2020; Calderón-Parra et al., 2022; Er et al., 2022; Nasir et al., 2020), which is why routine screening is essential for early screening and decision-making (Caggiano et al., 2022; Gangneux & Dannaoui, 2022).

The diagnosis of aspergillosis in critical patients with COVID-19 is a topic widely discussed due to the difficulty in distinguishing between colonization by *Aspergillus* spp. or invasive infection, considering the frequent unavailability of histological findings and lack of

clinical and radiological characteristics, which was observed in our cases and corroborated with other studies (Calderón-Parra et al., 2022; Koehler et al., 2020; Tio et al., 2021). Bronchoscopy to obtain samples free of contaminants is generally avoided due to the possibility of aerosol transmission during the procedure, and many patients were not clinically fit for a lung biopsy at the time of suspicion of CAPA. Likewise, imaging tests may not be feasible due to the clinical instability of patients or, when performed, they may not differentiate acute respiratory syndrome in COVID-19 and invasive pulmonary aspergillosis (Nasir et al., 2020).

In the cases reported here, five patients had serum galactomannan analysis in the period of identification of *Aspergillus* in tracheal secretion aspirate, where two had a positive result (index >0.5). Galactomannan, obtained in plasma or bronchoalveolar lavage fluid, is a biomarker that can assist in the diagnosis and prognosis of invasive pulmonary aspergillosis, being indicated its serum collection three times a week until discharge from the ICU, for CAPA screening in critical patients (Koelher, 2021; Patterson & Donnelly, 2019). Different authors defend its importance as a pre-test in situations of high probability, considering its high specificity in non-neutropenic patients (de Almeida Jr et al., 2022; Ghazanfari et al., 2022; Koelher, 2021; Lim, Jin Lee et al., 2022). Galactomannan is detectable even before the onset of clinical symptoms and thus may be useful to guide early treatment (Caggiano et al., 2022). However, it is important to consider that, especially at the serum level, galactomannan has low sensitivity and may be positive even in case of colonization (Mitaka et al., 2020).

Given the rigorous criteria required by the ECMM/ISHAM to prove CAPA, many authors were concerned about the possibility of underestimation of its incidence(Bounhiol et al., 2022; Lim, Jin Lee et al., 2022; Nasir et al., 2020; Permpalung et al., 2021). Thus, the search for microbiological findings in tracheal aspirate, bronchoalveolar lavage or through nonbronchoscopic lavage is relevant in order to mitigate morbidity and mortality from this infection and, even cases classified as possible APAC, should receive antifungal therapy (Koelher, 2021; Machado et al., 2021; Marta et al., 2022; Nasir et al., 2020). On the other hand, some authors discuss the issue of early and prolonged treatment impacting increased costs, adverse reactions, drug interactions and antimicrobial resistance in patients already highly vulnerable in ICU, emphasizing the importance of applying and refining the diagnostic criteria of CAPA, which will provide realistic prevalence rates and appropriateness of therapy (Arastehfar et al., 2020; Egger et al., 2022). New studies may contribute to greater definitions of the benefits of using early antifungal treatment or prophylaxis for patients at high risk of invasive fungal infections (Gangneux & Dannaoui, 2022).

The CAPA treatment decision should consider all patient information and clinical data. Voriconazole is recommended as a first-line antifungal in the management of CAPA, even with the possible drug interactions with treatments commonly used in COVID-19, its narrow therapeutic window and toxicity that may aggravate the clinical picture of these patients admitted to the ICU (Koelher, 2021; Tio et al., 2021). One patient, among the cases presented in this report, required replacement of voriconazole by liposomal amphotericin B due to liver alteration, an adverse event most commonly presented by patients using voriconazole

according to some authors (Eiden et al., 2007; Maertens et al., 2021). Liposomal amphotericin B is a viable option when the patient presents contraindication to triazoles due to its nephrotoxic potential and the renal alteration that commonly affects patients with severe COVID-19 (Maertens et al., 2021; Patterson et al., 2016; Ullman et al., 2018) observed in most of the patients in this report.

With clinical activity similar to voriconazole and fewer adverse effects are posaconazole and isavuconazole, safe options for the treatment of CAPA for patients who do not tolerate voriconazole or liposomal amphotericin B (Koelher, 2021; Maertens et al., 2021; Singh et al., 2021). Both drugs have a higher unit cost than voriconazole, which may justify their unavailability and non-use in some health services, although studies indicate a good cost-effectiveness of these alternative options (Floros et al., 2019; Greiner et al., 2010; Harrington et al., 2017).

This case report exemplifies the clinical difficulty in the diagnosis and management of patients with CAPA, even in large hospital centers. Among the several limitations of the study are the realization of the research in a single center, the small sample of CAPA cases, perhaps underestimated due to the lack of adequate screening and investigation, the lack of diagnostic tests that could prove CAPA and the absence of a control group without COVID-19, hospitalized in the same period, which would enable the analysis of the impact of COVID-19 on the development of invasive pulmonary aspergillosis. Thus, extensive studies that analyze risk factors, clinical manifestations, early diagnosis and therapy are necessary.

Conclusion

The high mortality, diagnostic and management complexity of patients with CAPA indicate the need for active investigation of invasive pulmonary aspergillosis in patients with COVID-19 in intensive care, through appropriate screening, diagnostic protocols, and preventive actions for patients with a high risk of co-infection.

Conflicts of interest

We declare that there are still no conflicts of interest in relation to this scientific text.

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CONSIDERAÇÕES FINAIS

A pesquisa realizada possibilitou identificar a ocorrência de ICSAC e mortalidade em pacientes com COVID-19, além de permitir a análise dos casos de APAC dentre os pacientes internados em UTI, resultados esses que contribuem para a elucidação e investigação de fatores que possam reduzir o drástico impacto causado no mundo em situações de pandemia.

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ANEXO

Parecer consubstanciado Comitê de Ética em Pesquisa da Universidade Federal de Uberlândia

UFU Comitê de Ética em Pesquisa — UNIVERSIDADE FEDERAL DE UBERLÂNDIA/MG — Plataforma Brasil

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: COINFECÇÃO FÚNGICA EM PACIENTES COM COVID-19 INTERNADOS EM UNIDADE DE TERAPIA INTENSIVA

Pesquisador: Denise Von Dolinger de Brito Röder

Área Temática:

Versão: 2

CAAE: 51805021.5.0000.5152

Instituição Proponente: Instituto de Ciências Biomédicas

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 5.043.636

Apresentação do Projeto:

INTRODUÇÃO. A COVID-19 gerou um impacto social sem precedentes em todo o mundo devido à dificuldade em prevenir a disseminação do vírus e ao grande número de pessoas infectadas, muitas das quais requerem cuidados intensivos ou até sucumbem à doença. Os pacientes criticamente doentes pela COVID-19 e internados em UTI's são suscetíveis a uma ampla gama de sequelas que podem ser fatais ou gerar complicações e repercussões em saúde pública a longo prazo. Nesse contexto, evidencia-se a coinfecção por diferentes microrganismos, visto que pacientes com piora do quadro clínico da COVID-19 apresentam maiores taxas de coinfecção por outros vírus, bactérias e fungos.

HIPÓTESE. Acredita-se que as infecções fúngicas secundárias à COVID-19 contribuem para o agravamento do quadro clínico e aumento da mortalidade dos pacientes em cuidados intensivos infectados com COVID19.

METODOLOGIA. Trata-se de um estudo de coorte retrospectiva, descritiva e exploratória com abordagem quantitativa e qualitativa. Serão analisados os dados secundários dos anos 2020 e 2021. A presente pesquisa será realizada na UTI de três hospitais públicos da cidade de Uberlândia – MG: Hospital de Clínicas da Universidade Federal de Uberlândia (HC-UFU), Hospital e Maternidade Municipal Dr. Odelmo Leão Carneiro (HMMDOLC) e Hospital Santa Catarina, os quais somam 140

leitos de Unidade de Terapia Intensiva (UTI) Adulto. Os critérios para a escolha dos hospitais supracitados foram: ofertar serviço público, de alta complexidade, e referência para Uberlândia e região na assistência à saúde. As referidas instituições serão convidadas a participar da pesquisa e, havendo consentimento, serão obtidos os termos de autorização de coparticipação. Procedimento de coleta de dados: Serão coletados dados dos pacientes que estiveram internados nas UTI's do HC-UFU, HMMDOLC e Hospital Santa Catarina, co-infectados por COVID-19/infecção fúngica, no ano 2020 e 2021, por meio de pesquisa em prontuários impressos, eletrônicos e Ficha de Notificação Compulsória. Um instrumento de coleta de dados (apêndice I) individual será utilizado para todos os pacientes incluídos no estudo e será composto pelos seguintes itens, desde que constem nos registros dos prontuários e nas Fichas de Notificação Compulsória:- Dados do perfil sociodemográfico: idade; sexo; raça (cor da pele autorreferida); estado civil; idade.- Dados sobre os hábitos de vida: se fez ou faz uso de bebida alcoólica; fumo; drogas ilícitas; se realiza atividade física.- Dados sobre antecedentes pessoais: história de comorbidades (diabetes mellitus, hipertensão arterial sistêmica, doenças cardiovasculares, doença pulmonar obstrutiva crônica, insuficiência renal crônica, doença hepática); história de neoplasias; história de doenças fúngicas; história de imunossupressão; história de transplante de órgãos; história de trombose; medicamentos em uso; transfusão sanguínea prévia.- Dados clínicos: Data da internação no serviço, data de internação na UTI sintomas na admissão no serviço, data da internação na UTI, sintomas na internação na UTI, índice de gravidade, peso, altura, Índice de Massa Corpórea (IMC), tipo
sanguíneo/fator RH, resultados de exames laboratoriais na internação (enzimas hepáticas, cardíacas, resultados de exames de hemograma e biomarcadores como galactomanana e procalcitonina), função renal, coagulograma: tempo de protrombina ativada, RNI, plaquetas, desidrogenase lática (DHL), provas de atividade inflamatória: proteína C reativa, ferritina, D-dímero, Nursing active score (carga de trabalho). - Dados sobre a infecção pela COVID-19: se trata-se de reinfecção, data do diagnóstico, método diagnóstico, medicação para tratamento da COVID-19, saturação periférica de oxigênio na data da admissão no serviço e data da admissão na UTI uso de suporte ventilatório invasivo e não invasivo, tempo de internação na UTI, tempo entre o início dos sintomas e deterioração do quadro clínico (classificada aqui como piora do quadro pulmonar com necessidade de ventilação mecânica invasiva), uso de terapia renal substitutiva, traqueostomia, lesão renal, complicações trombóticas, terapia com ECMO, disfunção hepática, uso de cateter venoso central, uso de sonda vesical de demora, evolução da doença (alta/óbito), data da alta do serviço e da UTI, causa e data do óbito, se o paciente foi vacinado contra COVID-19, se

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foi vacinado contra gripe no ano que antecede a infecção por COVID-19.- Dados sobre a infecção fúngica e/ou bacteriana: data e método do diagnóstico, sinais e sintomas, microrganismo isolado, tratamento prescrito; tempo de tratamento; evolução da doença.

CRITÉRIOS DE INCLUSÃO. Serão incluídos os prontuários de pacientes maiores de 18 anos, diagnosticados com COVID-19 em regime de internação nas unidades de terapia intensiva dos hospitais HC -UFU, HMMDOLC e anexo Hospital Santa Catarla, nos anos 2020 e 2021.

CRITÉRIOS DE EXCLUSÃO. Serão excluídos os pacientes menores de 18 anos e aqueles internados nas referidas unidades de terapia intensiva que não apresentaram COVID19 durante a internação.

Objetivo da Pesquisa:

OBJETIVOS. Investigar a prevalência de coinfecções por COVID-19/infecção fúngica em pacientes hospitalizados em UTI da rede pública da cidade de Uberlândia.

OBEJTIVOS SECUNDÁRIOS.

A) Identificar a ocorrência de coinfecção COVID-19/infecção fúngica;

B) Relacionar os fatores de risco clínicos e epidemiológicos relacionados ao COVID-19/infecção fúngica;

C) Analisar a utilização de terapêutica antifúngica, relacionando sinais clínicos, tempo de internação, tempo de tratamento e evolução clínica.

D) Comparar a ocorrência de coinfecção covid-19/infecção em pacientes internados em três hospitais públicos na cidade de Uberlândia.

Avaliação dos Riscos e Benefícios:

RISCOS. Há uma pequena chance de os participantes da pesquisa serem identificados. Para evitar tal risco, os instrumentos de coleta de dados terão apenas um código aleatório para cada indivíduo, sem identificar o mesmo em nenhuma fase da pesquisa, o que facilitará a organização e garantirá o sigilo das informações coletadas. Os pesquisadores comprometem-se a manter sigilo das informações e anonimato dos participantes, garantindo a não exposição dos prontuários utilizados. Há ainda o risco de os hospitais participantes serem identificados. No entanto, apenas a pesquisadora que irá coletar os dados saberá quais participantes estiveram internados em quais hospitais, e a mesma garante o sigilo e confidencialidade das informações coletadas. Além disso, na ficha de instrumento de coleta de

dados não haverá nome de nenhum hospital, pois serão utilizadas letras do alfabeto para diferenciá-los.

BENEFÍCIOS. Os benefícios incluem um melhor conhecimento da relação COVID-19/infecção fúngica; conhecer e correlacionar fatores clínicos e epidemiológicos bem como o diagnóstico, tratamento e evolução das infecções. Estas informações poderão ser úteis para o desenvolvimento protocolos de prevenção e manejo das doenças, de forma a reduzir sua morbimortalidade. Além de favorecer e subsidiar novos estudos acerca da temática escolhida.

Comentários e Considerações sobre a Pesquisa:
Resposta da pendências apontada no Parecer nº5.010.606 de 30 de Setembro de 2021:

1. Os prontuários que farão parte da pesquisa, são apenas de pacientes que já receberam alta dos hospitais participantes? Caso não, o TCLE não pode ser dispensado para pacientes ainda em tratamento. Desta forma, o CEP solicita esclarecimento.

RESPOSTA DOS PESQUISADORES:
Os prontuários que farão parte da pesquisa são apenas de pacientes que já receberam alta dos hospitais participantes. Trata-se de um estudo retrospectivo, com indusão de pacientes hospitalizados nos anos 2020 e 2021. A coleta de dados será realizada, conforme cronograma proposto, de dezembro de 2021 a janeiro de 2023, com análise inicial dos dados a partir das internações ocorridas em 2020 e depois, por último, as internações ocorridas em 2021. Assim, todos os pacientes terão seus prontuários analisados após a alta hospitalar. Alterado documento de justificativa da dispensa do TCLE, item questões éticas na brochura do pesquisador e item que trata sobre dispensa de TCLE na plataforma Brasil.

Considerações CEP/UFU: Pendência atendida.

Considerações sobre os Termos de apresentação obrigatória:
Folha de rosto carimbada, assinada e datada pelo diretor da unidade. Declarações das instituições coparticipantes assinados e datados. Currículos da equipe executora qualificados e identificados. Orçamento e cronograma detalhados. Documento da equipe executora assinado e datado.

Dispensa de TCLE em acordo com as normas do CEP.

Conclusões ou Pendências e Lista de Inadequações:

As pendências do parecer nº5.010.606 de 30 de Setembro de 2021 foram atendidas.

Considerações Finais a critério do CEP:

OBS.: O CEP/UFU LEMBRA QUE QUALQUER MUDANÇA NO PROTOCOLO DEVE SER INFORMADA IMEDIATAMENTE AO CEP PARA FINS DE ANÁLISE E APROVAÇÃO DA MESMA.

O CEP/UFU lembra que:

a- segundo as Resoluções CNS 466/12 e 510/16, o pesquisador deverá manter os dados da pesquisa em arquivo, físico ou digital, sob sua guarda e responsabilidade, por um período mínimo de 5 (cinco) anos após o término da pesquisa;

b- poderá, por escolha aleatória, visitar o pesquisador para conferência do relatório e documentação pertinente ao projeto.

c- a aprovação do protocolo de pesquisa pelo CEP/UFU dá-se em decorrência do atendimento as Resoluções CNS 466/12, 510/16 e suas complementares, não implicando na qualidade científica do mesmo.

Orientações ao pesquisador :

• O participante da pesquisa tem a liberdade de recusar-se a participar ou de retirar seu consentimento em qualquer fase da pesquisa, sem penalização alguma e sem prejuízo ao seu cuidado (Res. CNS 466/12 e 510/16) e deve receber uma via original do Termo de Consentimento Livre e Esclarecido, na íntegra, por ele assinado.

• O pesquisador deve desenvolver a pesquisa conforme delineada no protocolo aprovado e descontinuar o estudo somente após análise das razões da descontinuidade pelo CEP que o aprovou (Res. CNS 466/12), aguardando seu parecer, exceto quando perceber risco ou dano não previsto ao participante ou quando constatar a superioridade de regime oferecido a um dos grupos da pesquisa que requeiram ação imediata.

• O CEP deve ser informado de todos os efeitos adversos ou fatos relevantes que alterem o curso normal do estudo (Res. CNS 466/12). É papel do pesquisador assegurar medidas imediatas adequadas frente a evento adverso grave ocorrido (mesmo que tenha sido em outro centro) e enviar notificação ao CEP e à Agência Nacional de Vigilância Sanitária – ANVISA – junto com seu

posicionamento.
• Eventuais modificações ou emendas ao protocolo devem ser apresentadas ao CEP de forma clara e sucinta, destacando a parte do protocolo a ser modificada e suas justificativas. Em caso de projetos do Grupo I ou II apresentados anteriormente à ANVISA, o pesquisador ou patrocinador deve enviá-las também à mesma, junto com o parecer aprobatório do CEP, para serem juntadas ao protocolo inicial (Res.251/97, item III.2.e).

De acordo com as atribuições definidas na Resolução CNS 466/12, Resolução 510/16 e suas complementares, o CEP manifesta-se pela aprovação do protocolo de pesquisa proposto.
O protocolo não apresenta problemas de ética nas condutas de pesquisa com seres humanos, nos limites da redação e da metodologia apresentadas.

Data para entrega do Relatório Final ao CEP/UFU: JANEIRO/2024.

* Tolerância máxima de 01 mês para atraso na entrega do relatório final.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1810841.pdf	06/10/2021 15:13:43		Aceito
Outros	pendencia.docx	06/10/2021 15:12:25	Denise Von Dolinger de Brito Röder	Aceito
Outros	dispensa_tcle.pdf	06/10/2021 15:11:59	Denise Von Dolinger de Brito Röder	Aceito
Projeto Detalhado / Brochura Investigador	projetocepCOVID.pdf	06/10/2021 15:11:17	Denise Von Dolinger de Brito Röder	Aceito
Outros	curriculo_lattes.docx	16/09/2021 16:43:15	Denise Von Dolinger de Brito Röder	Aceito
Folha de Rosto	folha_de_rosto.pdf	09/09/2021 10:45:37	Denise Von Dolinger de Brito	Aceito

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UFU Comitê de Ética em Pesquisa

UNIVERSIDADE FEDERAL DE UBERLÂNDIA/MG

PlataForma Brasil

Folha de Rosto	folha_de_rosto.pdf	09/09/2021 10:45:37	Röder	Aceito
Declaração de Pesquisadores	Declaracao_pesquisadores.pdf	20/08/2021 16:25:56	Denise Von Dolinger de Brito Röder	Aceito
Declaração de Instituição e Infraestrutura	autorizacao_prefeitura.pdf	20/08/2021 16:22:57	Denise Von Dolinger de Brito Röder	Aceito
Declaração de Instituição e Infraestrutura	autorizacao_ufu.pdf	17/08/2021 17:09:52	Denise Von Dolinger de Brito Röder	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

UBERLANDIA, 18 de Outubro de 2021

Assinado por:
Igor Antônio Lourenço da Silva
(Coordenador(a))

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