UNIVERSIDADE FEDERAL DO PARÁ
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PROGRAMA DE PÓS-GRADUAÇÃO EM FARMACOLOGIA E BIOQUÍMICA

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RESUMO

Introdução: A sepse é uma complicação frequente em pacientes com COVID-19. Este estudo investigou os fatores de risco relacionados a mortes por sepse em pacientes com COVID-19 internados na UTI. **Métodos:** Este é um estudo de coorte retrospectivo de pacientes com COVID-19 que morreram na UTI de um hospital universitário em Belém, Amazônia, Brasil, entre março de 2020 e dezembro de 2022. **Resultados:** Dos 83 óbitos ocorridos na UTI, 77 (92,77%) pacientes tiveram sepse, e 63 (85,13%) dos pacientes com sepse tiveram choque séptico. A sepse foi mais prevalente em homens com idade ≥ 60 anos. Os níveis elevados de creatinina (p=0,009) e AST (p=0,04) diferiram significativamente entre os grupos com sepse e sem sepse. A coinfecção bacteriana foi significativamente associada à sepse (p=0,01). Entre as carbapenemases detectadas, houve uma predominância de OXA-23 e OXA-51, que estão associadas ao microrganismo *Acinetobacter baumannii* e foi identificada uma *Klebsiella pneumoniae* coprodutora de KPC e NDM. **Conclusões:** A coinfecção bacteriana foi o principal fator de risco de morte por sepse. A identificação de um microrganismo coprodutor de carbapenemases KPC e NDM alerta-nos para possíveis alterações na resistência antimicrobiana. A vigilância da resistência antimicrobiana é crucial para melhorar a gestão clínica e reduzir a mortalidade por sepse em doentes com COVID-19.

Palavras-chave: COVID 19; SARS-CoV-2; Sepse; Fatores de Risco; Coinfecção.

ABSTRACT

Background: Sepsis is a frequent complication in COVID-19 patients. This study investigated the risk factors related to deaths from sepsis in COVID-19 patients admitted to the ICU. **Methods:** This is a retrospective cohort study of COVID-19 patients who died in the ICU of a university hospital in Belém, Amazonia, Brazil, between March 2020 and December 2022. **Results:** Of the 83 ICU deaths, 77 (92.77%) patients had sepsis, and 63 (85.13%) of the patients with sepsis had septic shock. Sepsis was most prevalent in men aged ≥ 60 years. Elevated creatinine (p=0.009) and AST (p=0.04) levels differed significantly between the sepsis and non-sepsis groups. Bacterial co-infection was significantly associated with sepsis (p=0.01). Among the carbapenemases that were detected, there was a predominance of OXA-23 and OXA-51, which are associated with the microorganism *Acinetobacter baumannii* and a *Klebsiella pneumoniae* co-producer of KPC and NDM was identified. **Conclusions:** Bacterial co-infection was the main risk factor for death from sepsis. The identification of a microorganism that was co-producing KPC and NDM carbapenemases alerts us to possible changes in antimicrobial resistance. The surveillance of antimicrobial resistance is crucial for improving clinical management and reducing sepsis mortality in COVID-19 patients.

Keywords: COVID-19; SARS-CoV-2; Sepsis, Risk Factors; Co-infection.

LISTA DE SIGLAS

ACE2 - Enzima conversora da angiotensina 2

APCs - Células apresentadoras de antígenos

COVID-19 - Doença do Coronavírus 19

DAMPs - Padrões moleculares associados a danos

IFNγ – Interferon tipo y

IL- Interleucina

ILAS - Instituto Latino-Americano de Sepse

IRAS - Infecções Relacionadas à Assistência à Saúde

KPC - Klebsiella pneumoniae carbapenemase

MERS-CoV – Coronavírus da Síndrome Respiratória do Oriente Médio

NDM - Nova Deli metalo-beta-lactamase

OMS - Organização Mundial da Saúde

PAMPs - Padrões moleculares associados a patógenos

PRRs - Receptores de reconhecimento de padrões

RNA – Ácido ribonucleico

RNL - Relação Neutrófilo-Linfócito

RPL - Relação Plaqueta-Linfócito

SARS-CoV - Coronavirus da Síndrome Respiratória Aguda Grave

SARS-CoV-2 - Síndrome Respiratória Aguda Grave Coronavírus 2

SIRS – Síndrome da Resposta Inflamatória Sistêmica

SRAG - Síndrome Respiratória Aguda Grave

SOFA - Avaliação sequencial da falência de órgãos

Sepsis-3 -Terceiro Consenso Internacional para Sepse e Choque Séptico

TMPRSS2 - Serina protease transmembrana 2

UTI - Unidade de Terapia Intensiva

SUMÁRIO

1. INTRODUÇÃO

As primeiras notificações à Organização Mundial da Saúde (OMS) sobre o surgimento de uma pneumonia de origem desconhecida em Wuhan, na província de Hubei, China, datam de 31 de dezembro de 2019. Em janeiro de 2020, um novo coronavírus foi identificado, inicialmente designado como 2019-nCoV pela OMS e posteriormente denominado Síndrome Respiratória Aguda Grave Coronavírus 2 (SARS-CoV-2). A doença resultante desse vírus recebeu o nome de COVID-19 (JIANG *et al*., 2020). Estudos retrospectivos revelaram que o primeiro caso documentado da doença remonta a 8 de dezembro de 2019 (HU *et al*., 2020) (Figura 1). Em 11 de março de 2020, a OMS declarou a COVID-19 como uma pandemia.

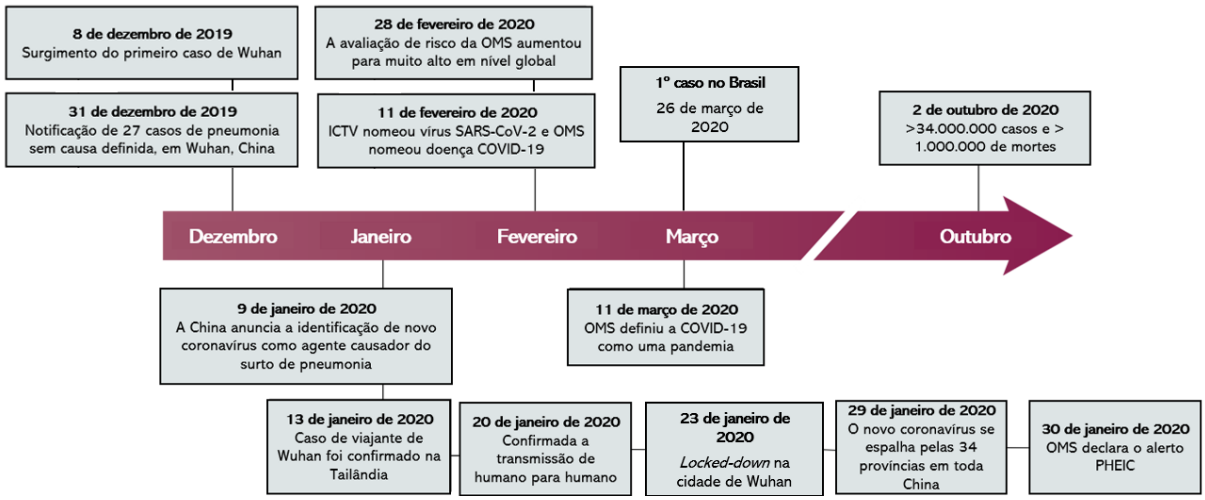
Altamente contagiosa, a doença se tornou a maior crise sanitária dos tempos modernos, resultando em elevados índices de morbidade e mortalidade (JIANG *et al*., 2020; ZHU *et al*., 2020). Até 31 de dezembro de 2022, foram registrados 6.683.993 óbitos relacionados à COVID-19 e 655.539.421 casos de infecção pelo vírus em todo o mundo (OMS, 2022). Estudos epidemiológicos indicam que o primeiro surto, que envolveu quase 2000 casos reportados até fevereiro de 2020 em Wuhan, pode ter tido origem no mercado de frutos do mar da cidade. Em certo ponto, os casos de pneumonia foram associados aos morcegos, que são hospedeiros naturais desses vírus, desencadeando investigações sobre a capacidade do vírus de infectar humanos (ZHOU *et al*., 2020; WU *et al*., 2020).

Os primeiros sintomas observados em pacientes diagnosticados com o novo coronavírus incluem febre, tosse com ou sem secreções respiratórias, fadiga, mialgia, dor de cabeça, hemoptise e diarreia. As complicações da doença podem progredir para Síndrome Respiratória Aguda Grave (SRAG), lesões cardíacas ou renais, infecções secundárias e choque (HUANG *et al*., 2020). A transmissão ocorre principalmente através de partículas virais altamente infecciosas presentes em gotículas de tosse, espirros e objetos contaminados, o que levou à implementação de medidas de contenção e mitigação em todo o mundo. Isso incluiu o uso obrigatório de máscaras, práticas de distanciamento social e rigorosas medidas de higiene, enquanto se aguardava o desenvolvimento de vacinas contra o SARS-CoV-2 (CHU *et al*., 2020).

No Brasil, o primeiro caso confirmado foi registrado na cidade de São Paulo em 26 de fevereiro de 2020. A rápida propagação da doença no país resultou em um aumento significativo de casos, totalizando 177 mil casos e 12 mil mortes até 12 de

maio de 2020. Devido ao rápido crescimento do contágio pelo SARS-CoV-2, em 26 de março de 2020 foi declarada transmissão comunitária em todo o território nacional (XAVIER *et al*., 2020). Até 26 de dezembro de 2022, o novo coronavírus havia causado a morte de 693.853 pessoas e infectado 36.597.936 no país (OMS, 2022).

Figura 1. Linha do tempo dos principais eventos do surto de COVID-19**.**



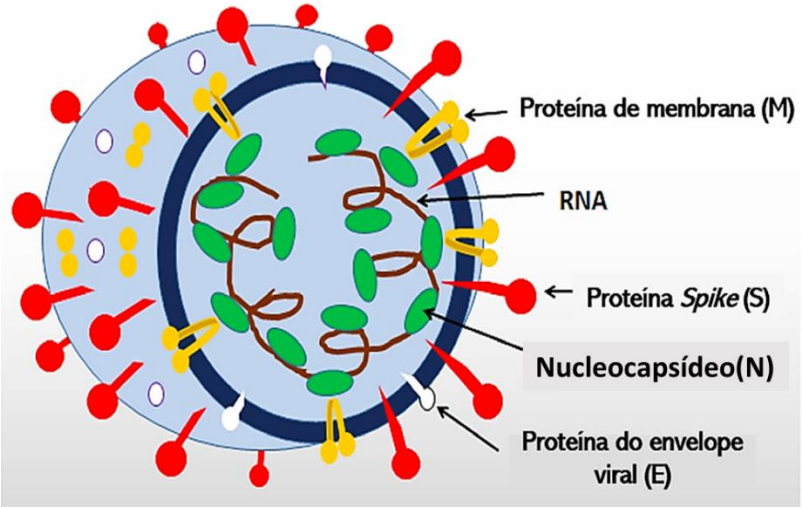
Legenda: Os primeiros casos registrados foram relatados em dezembro de 2019 em Wuhan, China. Ao longo dos 10 meses seguintes, mais de 30 milhões de casos foram confirmados em todo o mundo. COVID-19, Doença do Coronavírus 2019; ICTV, Comitê Internacional de Taxonomia de Vírus; PHEIC, Emergência de Saúde Pública de Interesse Internacional; SARS-CoV-2, Síndrome Respiratória Aguda Grave Coronavírus 2; OMS, Organização Mundial da Saúde. Fonte: Adaptado de HU *et al*., 2020 e XAVIER *et al*., 2020.

1.1 Características estruturais do SARS-CoV-2

O vírus SARS-CoV-2 faz parte do grupo de vírus envelopados com um genoma de RNA de fita simples positiva. Ele é classificado na ordem Nidovirales, família Coronaviridae, subfamília Coronavirinae e gênero Betacoronavirus. O SARS-CoV-2 é um Betacoronavírus altamente patogênico e tem uma semelhança etiológica com dois vírus previamente conhecidos: o SARS-CoV, que causou a Síndrome Respiratória Aguda Grave Coronavírus em 2003, e o MERS-CoV, responsável pela Síndrome Respiratória do Oriente Médio em 2012 (HARAPAN *et al*., 2020). De acordo com análises de sequenciamento genômico, o SARS-CoV-2 compartilha aproximadamente 79% de seu genoma com o SARS-CoV. Embora tenha uma letalidade menor em comparação com outros vírus do mesmo gênero, o SARS-CoV-2 é consideravelmente mais transmissível (JIANG *et al*., 2020).

O SARS-CoV-2 é constituído por quatro proteínas estruturais: glicoproteína spike (S), glicoproteína de envelope (E), glicoproteína de membrana (M) e proteína de nucleocapsídeo (N). Essas estruturas proteicas desempenham papéis fundamentais na replicação viral, na estruturação do vírus e na ligação do vírus aos receptores celulares (S), além de influenciar a patogenicidade do vírus (GUSEV et al., 2022) (Figura 2). O estudo dessas proteínas foi crucial para identificar alvos para respostas imunes induzidas por vacinas (DAI *et al*., 2021).

Figura 2. A estrutura principal do SARS-CoV-2.



Fonte**:** Adaptado de GUSEV *et al*., 2022.

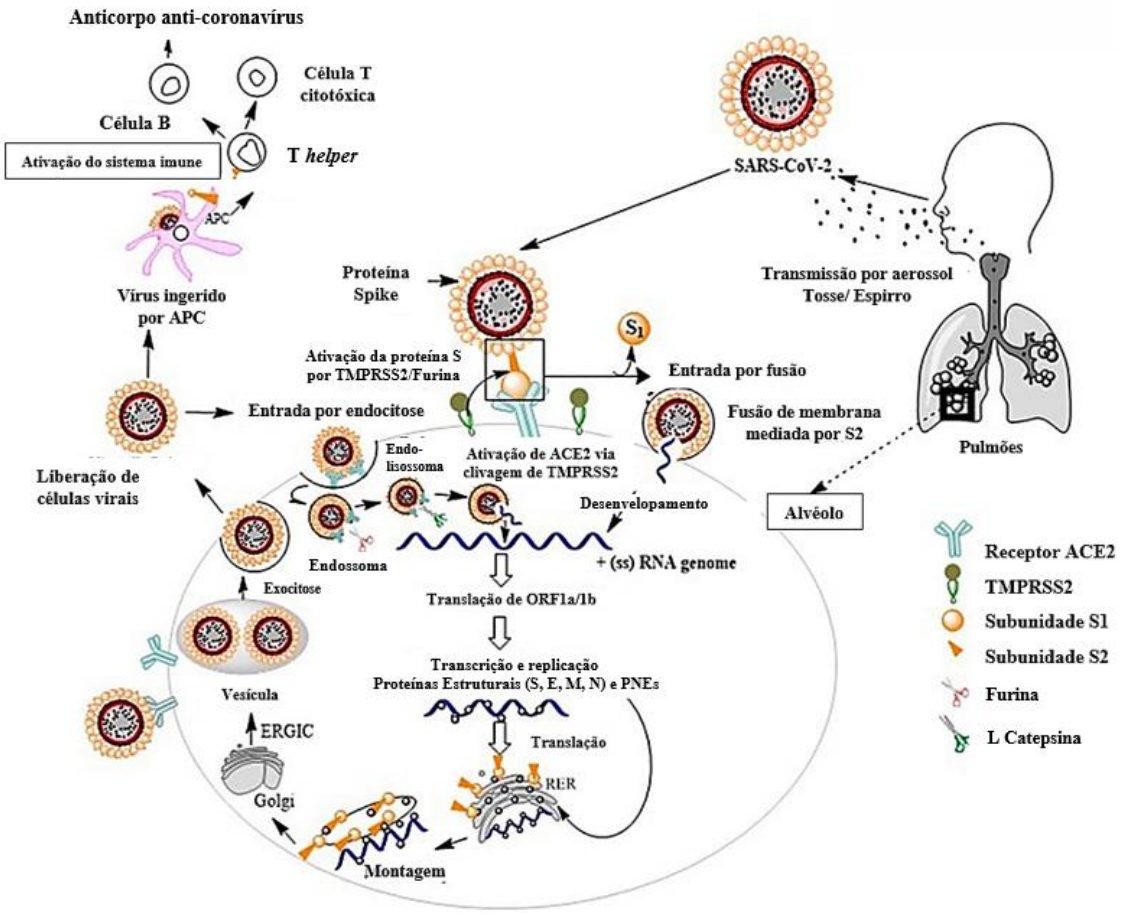
1.2 Patogênese do SARS-CoV-2

O SARS-CoV-2 usa receptores humanos da enzima conversora de angiotensina 2 (ACE2) para entrar nas células hospedeiras por meio da ligação com a proteína spike. Essa proteína é composta por dois domínios, S1 e S2. O domínio S1 se une aos receptores ACE2, enquanto o domínio S2 facilita a fusão da membrana, permitindo que o vírus entre na célula. Após a ligação do vírus com o ACE2, ocorre a clivagem no domínio S1-S2 pela ação da serina protease transmembrana 2 (TMPRSS2), facilitando a entrada do vírus na célula hospedeira. Expressa principalmente pelas células endoteliais dos tratos respiratório e digestivo, a TMPRSS2 desempenha um papel significativo na infecção por COVID-19 (SENAPATI *et al*., 2021; BEYERSTEDT *et al*., 2021).

Após a entrada na célula hospedeira, o RNA viral é liberado e age como mRNA funcional para os ribossomos. Esses ribossomos traduzem algumas das novas

cadeias de RNA para produzir componentes essenciais para a montagem de novas partículas virais, incluindo as proteínas S (spike), M (membrana), E (envelope) e N (nucleocapsídeo). Durante esse processo, também são sintetizadas proteínas acessórias, como Orf1a e Orf1b. Inicialmente, as proteínas M interagem com as proteínas S e E para formar as estruturas básicas das novas partículas virais. Posteriormente, as proteínas M se ligam às proteínas N e ao RNA genômico para formar o nucleocapsídeo. Finalmente, os novos vírus são liberados por exocitose, prontos para infectar novas células. (SENAPATI *et al*., 2021; LUBIN *et al*., 2022.) (Figura 3).

Figura 3. Mecanismo de interação e patogênese do SARS-CoV-2.



Legenda: O SARS-CoV-2 entra e se liga ao receptor ACE2. Ocorre a clivagem pela ação da TMPRSS2 nos domínios S1-S2 da proteína S. O genoma de RNA de fita simples de sentido positivo (+ssRNA) traduz outras proteínas estruturais e não estruturais e replica as proteínas estruturais (S, M, E, N). As proteínas virais são traduzidas e processadas através do retículo endoplasmático rugoso (RER) e do retículo endoplasmático do compartimento intermediário de Golgi (ERGIC). Após a montagem estrutural dentro de vesículas endossomais, as novas partículas virais são liberadas por exocitose. Os vírus são fagocitados por células apresentadoras de antígenos (APCs) que apresentam peptídeos S virais para células T auxiliares que ativam células B e células T citotóxicas. Fonte: Adaptado de SENAPATI *et al*., 2021.

A patogênese da doença também está relacionada à distribuição dos correceptores do coronavírus. O receptor de ACE-2 é abundantemente expresso nos epitélios pulmonares e em outros órgãos humanos, sugerindo possíveis vias de entrada para o SARS-CoV-2 através do contato com o ar ambiente pelas células pulmonares. Essa expressão epitelial é um primeiro passo crucial para compreender a patogênese das principais manifestações da doença, especialmente no pulmão, como tosse, pneumonia e Síndrome Respiratória Aguda Grave (SRAG) (HUERTAS *et al*., 2020).

Estudos realizados com pacientes em estado crítico em Wuhan relataram que a complicação mais frequentemente observada foi a sepse, seguida de falência respiratória, síndrome do desconforto respiratório agudo, parada cardíaca e choque séptico (ZHOU *et al*., 2020). A COVID-19 grave é considerada uma forma de sepse viral, e há semelhanças nos sinais apresentados por pacientes sépticos e por pessoas com COVID-19 grave (ZHANG *et al*., 2022).

1.3 Sepse

A sepse é uma disfunção orgânica ameaçadora à vida secundária à resposta desregulada do hospedeiro a uma infecção (SEYMOUR *et al*., 2016). É uma das condições mais comuns e uma das principais causas de morte em todo o mundo. De acordo com um estudo do *Institute for Health Metrics and Evaluation*, estima-se que ocorram cerca de 49 milhões de casos de sepse e 11 milhões de mortes associadas à sepse por ano (RUDD *et al*., 2020). Segundo o ILAS, quase 30% dos leitos das UTIs brasileiras estão ocupados com pacientes em sepse ou choque, com a mortalidade elevada para 55,4% (ILAS, 2020).

No Pará, um levantamento epidemiológico realizado em um hospital de referência observou que dos 212 pacientes internados em UTI, 181 apresentaram sepse nas diferentes gravidades, cuja mortalidade foi de 63%, principalmente nos pacientes com choque séptico (53%) e seguida da sepse grave (8,3%). O estudo verificou também que os fatores de risco associados ao agravamento da sepse foram: maior tempo médio de internação na UTI, idade superior que 65 anos, elevada frequência de comorbidades e utilização de procedimentos invasivos (Barros *et al*., 2016).

A patologia pode evoluir com profundas anormalidades circulatórias, celulares e metabólicas, elevando substancialmente a mortalidade (SECKEL *et al*., 2016). Além

disso, a sepse pode ser desencadeada por vírus, bactérias, fungos ou protozoários, sendo que estudos apontam que a principal causa é de origem bacteriana (MAYR *et al*., 2014). A presença de patógenos potencialmente multirresistentes também é de extrema importância para o agravamento da sepse (PRADIPTA *et al*., 2013).

As definições do Terceiro Consenso Internacional para Sepse e Choque Séptico (Sepsis-3) estabeleceram critérios claros para operacionalizar o diagnóstico da sepse. Clinicamente, é necessário que haja suspeita ou identificação de um agente infeccioso associado à infecção, juntamente com a presença de sinais e sintomas que sugiram disfunção orgânica. Definiu-se como disfunção orgânica para preenchimento do critério de sepse o aumento em 2 pontos no escore Sequential Organ Failure Assessment (SOFA) especialmente em pacientes de UTI (Tabela 1). Em ambientes fora da UTI, para agilizar a identificação de sepse, utiliza-se a pontuação denominada quickSOFA (qSOFA), que é uma avaliação rápida de falha orgânica, sendo positivo para possível diagnóstico de sepse, quando o paciente apresentar dois ou mais pontos na avaliação. O qSOFA corresponde a uma frequência respiratória maior ou igual a 22/min, alteração do estado mental e a pressão sistólica menor ou igual a 100mmHg (SEYMOUR *et al*., 2016; SINGER *et al*., 2016).

Tabela 01. Escore SOFA segundo o Sepsis-3.

	Score				
Sistema	**0**	**1**	**2**	**3**	**4**
Respiratório PaO_2/FiO_2 mmHg (kPa)	>400 (53,3)	<400 (53,3)	<300(40)	<200 (26,7) com suporte respiratório	<100 (13,3) com suporte respiratório
Coagulação Plaquetas, $x10^3$/uL	≥150	<150	<100	<50	<20
Hepático Bilirrubina:mg/dL (umol/L)	<1,2	1,2 - 1,9 (20-30)	2 - 5,9 (33-101)	6 - 11,9 (102-204)	>12 (204)
Cardiovascular	PAM ≥ 70mmHg	PAM< 70mmHg	Dopamina <5; dobutamina	Dopamina5-15; epinefrina<0,1; Norepinefrina<0,1	Dopamina5-15; epinefrina≥0,1; Norepinefrina>0,1
Nervoso Central Escala de Glasgow (coma)[a]	15	13 - 14	10 - 12	6 - 9	<6
Renal Creatinina:mg/dL (umol/L) Débito Urinário (mL/d)	< 1.2 (110)	1,2 - 1,9 (110-170)	2 - 3,4 (171-299)	3,5 - 4,9 (300-440) <500	>5 (440) <200

Abreviações: FiO2. Fração inspirada de oxigênio; PAM. Pressão Arterial Média; PaO2. Pressão parcial de oxigênio.
[a] O escore da Escala de Coma Glascow é de 3-15, quanto mais alto melhor a função neurológica.

1.4 Sepse e COVID-19

A sepse com subsequente disfunção multiorgânica é uma das principais causas de morte em pacientes com COVID-19. Essa condição está associada a distúrbios circulatórios observados em pacientes em estágios avançados da infecção e nos casos mais graves da doença causada pelo SARS-CoV-2 (TANG *et al*., 2021).

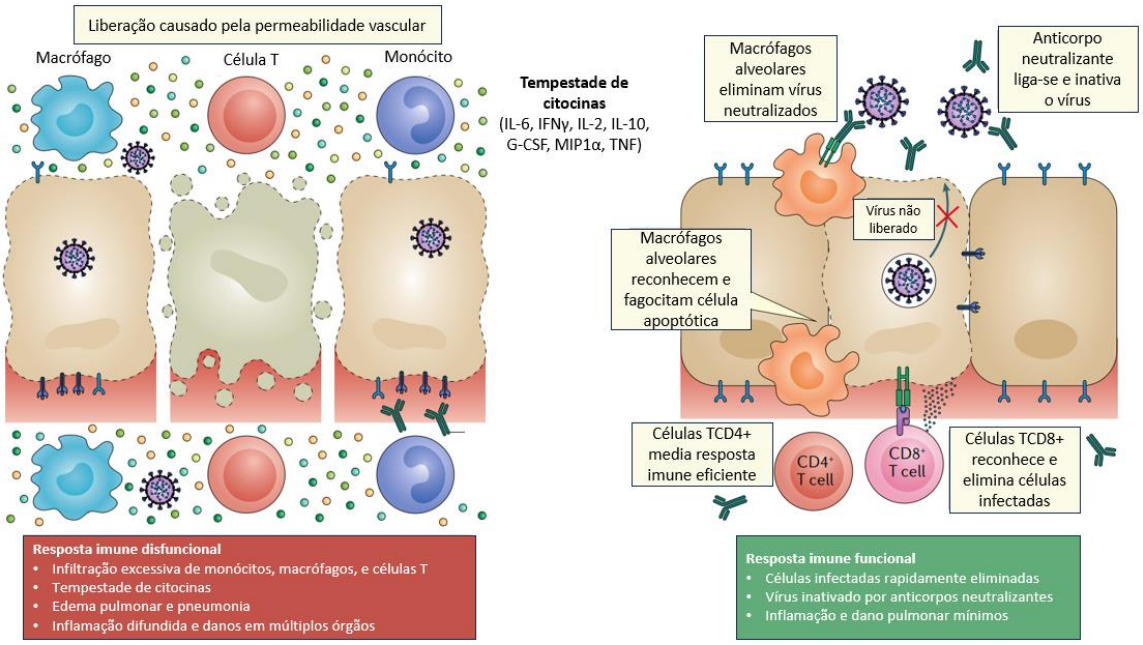
O surgimento da pandemia de COVID-19 desencadeou um debate e aumentou a conscientização sobre a sepse viral, tornando-se uma causa importante de sepse, independentemente de infecções secundárias causadas por bactérias ou fungos. Vários estudos indicam que, embora existam algumas características únicas relevantes ao COVID-19, muitas de suas manifestações agudas são semelhantes à sepse causada por outros patógenos (PATIL *et al*., 2021; TUFAN *et al*., 2021).

1.4.1 Resposta do organismo à infecção pelo SARS-CoV-2

Durante a infecção pelo SARS-CoV-2, as células epiteliais alveolares e os macrófagos alveolares detectam os padrões moleculares associados a patógenos (PAMPs), como RNA viral, e padrões moleculares associados a danos (DAMPs), por meio de uma variedade de receptores de reconhecimento de padrões (PRRs). Esse processo desencadeia uma resposta inflamatória local, caracterizada pelo aumento na secreção de citocinas pró-inflamatórias e quimiocinas, como IL-6, IFNγ, MCP1 e IP-10, no sangue dos pacientes afetados. A secreção dessas citocinas e quimiocinas atrai células imunes, principalmente monócitos e linfócitos T, para o local infectado, enquanto não há recrutamento de neutrófilos. Esse processo pode explicar a linfopenia e o aumento da relação neutrófilo-linfócito observados em cerca de 80% dos pacientes com infecção por SARS-CoV-2 (TAY *et al*., 2020) (Figura 4).

O aumento das citocinas pró-inflamatórias com linfopenia de células T predispõe pacientes com COVID-19 grave à tempestade de citocinas, resultando em apoptose linfocítica e falência de múltiplos órgãos (CHAN *et al*., 2020).

Figura 4. Mecanismo de resposta à infecção pelo SARS-CoV-2.



Legenda: **Resposta imune funcional**: a inflamação inicial atrai células T específicas do vírus para o local da infecção, onde elas eliminam as células infectadas antes que o vírus se espalhe. Anticorpos neutralizantes bloqueiam a infecção viral, e os macrófagos alveolares reconhecem e eliminam o vírus neutralizado e as células apoptóticas. Esses processos colaboram para eliminar o vírus e minimizar os danos pulmonares, permitindo a recuperação do paciente. **Resposta imune disfuncional**: pode resultar em danos pulmonares graves (infiltração celular excessiva, edema, pneumonia). A tempestade de citocinas resultante pode se espalhar para outros órgãos, causando danos sistêmico. Fonte: Adaptado de TAY *et al*., 2020.

1.5 Fatores de risco associados ao óbito por COVID-19

1.5.1 Alteração de biomarcadores

Evidências recentes destacam a importância dos biomarcadores como preditores de gravidade, prognóstico adverso ou mortalidade na COVID-19. Alterações nas enzimas cardíacas, aumento da lactato desidrogenase (LDH), contagem elevada de leucócitos, aumento do lactato, linfopenia, diminuição da contagem de plaquetas, aumento da contagem de neutrófilos, elevação da creatinina, Proteína C Reativa elevada e níveis elevados de enzimas hepáticas são fatores de risco para óbito por COVID-19 (SHARMA *et al*., 2021; GARDINASSI *et al*., 2023).

Além dos biomarcadores conhecidos, destacam-se como biomarcadores inflamatórios sistêmicos, os neutrófilos e as plaquetas que, obtidos do hemograma completo, são divididos pelo número absoluto de linfócitos, configurando a Relação

Neutrófilo-Linfócito (RNL) e a Relação Plaqueta-Linfócito (RPL), respectivamente (HOU *et al*., 2021).

Os parâmetros inflamatórios RPL e RNL elevados têm associações aos processos inflamatórios, bem como aos resultados desfavoráveis em determinadas condições patológicas. Estudos também destacam a RNL e a RPL como potenciais marcadores biológicos para SIRS e sepse, devido a capacidade desses parâmetros em indicar o estado inflamatório e imunológico do paciente, como observado na avaliação desses indicadores em doenças como reumatismo, tumores, doenças cardiovasculares e doenças do sistema respiratório (EL-MENYAR *et al*., 2022; KRIPLANI et al., 2022; LI; XIE, 2021).

1.5.2 Coinfecção e Resistência Antimicrobiana

A diminuição das células B, células T e células NK durante a infecção por SARS-CoV-2 compromete o sistema imunológico durante o curso da doença. Essa redução dos linfócitos e da função imunológica do hospedeiro pode ser a principal razão para a coinfecção com outros agentes patogênicos. Pacientes graves com COVID-19 têm maior probabilidade de receber terapias invasivas, como ventilação mecânica, traqueostomia e hemodiálise. A ventilação mecânica aumenta o risco de pneumonia bacteriana secundária, um fator de risco potencial para pacientes críticos, predispondo-os a infecções secundárias causadas por patógenos multirresistentes, como *Acinetobacter baumannii*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Enterococcus spp*, *Stenotrophomonas maltophilia* e *Klebsiella pneumoniae* (CHEN *et al*., 2020; FAZEL *et al*., 2023). Além disso, o uso ampliado de antimicrobianos de largo espectro cria um ambiente propício para infecções oportunistas e o desenvolvimento de resistência antimicrobiana (RAWSON *et al*., 2020).

A detecção de *Klebisiela pneumoniae* co-produtora de KPC e NDM eleva a preocupação com a resistência antimicrobiana, principalmente em ambiente de UTI, pois a presença do gen codificador de NDM favorece os mecanismos de multirresistência, pela facilidade de transferência gênica para outras espécies de cepas pertencentes à família Enterobacteriaceae (Casale *et al*.,2023), tornando-se um desafio adicional no tratamento de pacientes com sepse associada à COVID-19.

No contexto brasileiro, a elevada incidência de Infecções Relacionadas à Assistência à Saúde (IRAS) provocadas por microrganismos multirresistentes é motivo de preocupação devido às possíveis sequelas e aos custos elevados de

tratamento, os quais impactam adversamente o sistema de saúde pública (Massarine *et al*., 2023).

Assim, a identificação precoce da sepse em pacientes com COVID-19 é essencial para um bom prognóstico, pois possibilita a introdução de manejo clínico adequado nas primeiras horas da doença (Evans *et. al*., 2021; Gavelli *et al*.,2021).

Desse modo, pode-se afirmar a relevância desse estudo, pois o manejo e tratamento da sepse geram altos custos hospitalares às instituições de saúde. Em razão disso, pesquisas referentes a essa temática podem auxiliar na prevenção da sepse e no diagnóstico precoce, com objetivo de melhorar o desfecho dos casos clínicos, reduzir possíveis sequelas e minimizar a resistência bacteriana ocasionada pelo alto índice de utilização de antimicrobianos.

2. OBJETIVOS

2.1 Objetivo Geral

Investigar fatores de risco intrínsecos e extrínsecos associados ao óbito relacionado à sepse em pacientes com COVID-19, admitidos em unidade de terapia intensiva.

2.2 Objetivos Específicos

- Analisar o perfil dos pacientes com COVID-19 com desfecho óbito por sepse;
- Analisar os biomarcadores associados ao desfecho fatal;
- Descrever os principais microrganismos associados ao óbito por sepse;
- Descrever os microrganismos produtores de carbapenemases na população estudada.

3. RESULTADOS

3.1. Artigo submetido à revista *Viruses* - MDPI

Fatores de risco associados a mortes relacionadas à sepse em pacientes com COVID-19

RISK FACTORS ASSOCIATED WITH SEPSIS-RELATED DEATH IN COVID-19 PATIENTS

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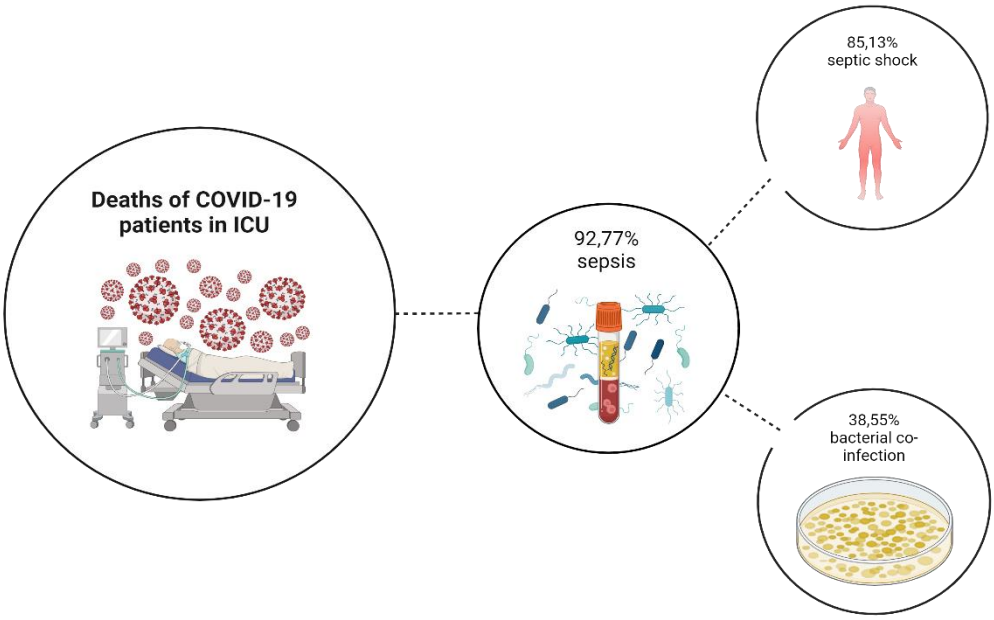


Abstract: Background: Sepsis is a frequent complication in COVID-19 patients. This study investigated the risk factors related to deaths from sepsis in COVID-19 patients admitted to the ICU. Methods: This is a retrospective cohort study of COVID-19 patients who died in the ICU of a university hospital in Belém, Amazonia, Brazil, between March 2020 and December 2022. Results: Of the 83 ICU deaths, 77 (92.77%) patients had sepsis, and 63 (85.13%) of the patients with sepsis had septic shock. Sepsis was most prevalent in men aged ≥ 60 years. Elevated creatinine (p=0.009) and AST (p=0.04) levels differed significantly between the sepsis and non-sepsis groups. Bacterial co-infection was significantly associated with sepsis (p=0.01). Among the carbapenemases that were detected, there was a predominance of OXA-23 and OXA-51, which are associated with the microorganism *Acinetobacter baumannii* and a *Klebsiella pneumoniae* co-producer of KPC and NDM was identified. Conclusions: Bacterial co-infection was the main risk factor for death from sepsis. The identification of a microorganism that was co-producing KPC and NDM carbapenemases alerts us to possible changes in antimicrobial resistance. The surveillance of antimicrobial resistance is crucial for improving clinical management and reducing sepsis mortality in COVID-19 patients.

Keywords: COVID-19; SARS-CoV-2; sepsis, risk factors; co-infection

1. Introduction

First detected in China in December 2019, a new coronavirus was identified as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which causes Coronavirus disease 19 (COVID-19) [1]. COVID-19 took on pandemic proportions in 2020 [2] and continues to be a major public health concern, although the rate of infection and mortality has decreased as a result of immunization. However, the virus has undergone many modifications in its structure, mainly in the spike protein, which has resulted in different variants of the virus, such as the Omicron variant—identified at the end of 2021—that was responsible for the second wave of COVID-19, which was a cause for great concern due to its high transmissibility rates and potential for immune escape [3,4]. Omicron's sub-capsids are continuously monitored due to the large number of mutations detected in its genome, which could generate new outbreaks of transmission [5]. In Brazil, by December 2022 the new coronavirus was responsible for the deaths of 693,853 people and for the infection of 36,597,936 people according to the World Health Organization (WHO) [6].

Several studies have shown that critically ill patients with COVID-19 have developed clinical manifestations that are typical of septic shock and fulfil the diagnostic criteria for sepsis and shock according to the International Sepsis Consensus-3 [7,8]. In the first COVID-19 cases reported in Wuhan, sepsis was the most common complication observed in critically ill patients, followed by respiratory failure, Severe Acute Respiratory Syndrome (SARS), cardiac arrest and septic shock [9]. In the evolution of infectious sepsis, pulmonary lesions, hepatic, renal and micro-circulatory dysfunctions are manifestations that fit the criteria for sepsis and septic shock according to the Sepsis-3 International Consensus [10]. The progression of patients with severe COVID to a septic condition may be related to the dysregulation of the immune system that is caused by SARS-CoV-2 infection, which causes the death of lymphocytes—especially B, T and NK cells—and consequently leads to immunosuppression that promotes secondary infection. In addition, these patients still need invasive devices such as catheters and orotracheal tubes that also promote secondary infections, particularly by multi-resistant bacteria such as *Acinetobacter baumannii*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Enterococcus spp*., *Stenotrophomonas maltophilia* and *Klebsiella pneumoniae* [11].

The association between bacterial sepsis and Severe Acute Respiratory Syndrome, caused by SARS-CoV-2, can be potentiated by conditions that are intrinsic and extrinsic to the host such as secondary bacterial pneumonia related to mechanical ventilation, which is a potential risk factor for critically ill patients [12]. In addition, the widespread use of broad-spectrum antimicrobials creates an environment that is conducive to opportunistic infections and the development of antimicrobial resistance, especially in patients who have progressed to sepsis [13]. Epidemiological analyses have shown that bacterial co-infection rates in COVID-19 patients are low. However, rates of secondary bacterial infection, which manifest later, are 10% to 20% higher, especially for healthcare-related infections and those that are associated with the use of invasive devices [14].

Recent evidence has highlighted the importance of biomarkers as predictors of severity, adverse prognosis, or mortality from COVID-19. Altered cardiac enzymes, increased lactate dehydrogenase (LDH) levels, leukocytosis with neutrophilia, lymphopenia, increased lactate levels, decreased platelet counts, increased creatinine levels, elevated C-reactive protein levels and elevated levels of liver enzymes are intrinsic risk factors for death from COVID-19 [15,16]. Thus, the early identification of sepsis in COVID-19 patients is essential for a good prognosis, as this makes it possible to introduce appropriate clinical management within the first hours of the disease [17,18].

This study is therefore relevant because the management and treatment of sepsis generate high hospital costs for health institutions. As a result, research on this subject can help to prevent sepsis and to provide early diagnosis, with the aim of improving the outcome of clinical cases, reducing sequelae, and minimizing the development of bacterial resistance that is caused by the current high rate of antimicrobial use. In this context, this study aimed to investigate the intrinsic and extrinsic risk factors that are associated with sepsis-related deaths in COVID-19 patients who have been admitted to an intensive care unit.

2. Materials and Methods

2.1. Type of study and ethical aspects

This retrospective, descriptive, observational cohort study aimed to identify the most relevant risk factors that are associated with sepsis-related deaths in COVID-19

patients who were admitted to the intensive care unit of an infectious disease's referral hospital in Belém, Amazonia, Brazil, between March 2020 and December 2022.

This study was approved by the Ethics Committee for Research Involving Human Beings of the João de Barros Barreto University Hospital, opinion no. 5.694.252, CAAE 56902322.7.0000.0017.

2.2. *Study population and data collection*

Between March 2020 and December 2022, 533 COVID-19 patients were admitted to the hospital and 102 required intensive care; of these 102 patients, 83 died. This study included patients who died after being admitted to the ICU, and who had a laboratory diagnosis of COVID-19 that was obtained either through the detection SARS-CoV-2 using the RT-PCR (Reverse Transcription Polymerase Chain Reaction) assay in samples collected from the nasopharynx or through a positive Rapid Antigen Test (TR-Ag) result. Patients were excluded from this study if they were discharged from hospital, did not receive a laboratory diagnosis of COVID-19, were under the age of 18 years, or had an ICU stay of less than 24 hours (Figure 1).

Data were obtained from patients' electronic medical records and from the study hospital's clinical analysis laboratory database. Patient data that were collected consisted of demographic information, clinical history, the presence of comorbidities, the use of invasive therapy (mechanical ventilation/hemodialysis), levels of laboratory biomarkers (D-dimer, C-reactive protein, creatinine, AST (aspartate aminotransferase), ALT (alanine aminotransferase), lactate, platelet count, neutrophils and lymphocytes) and the presence of co-infection (microbiological analysis).

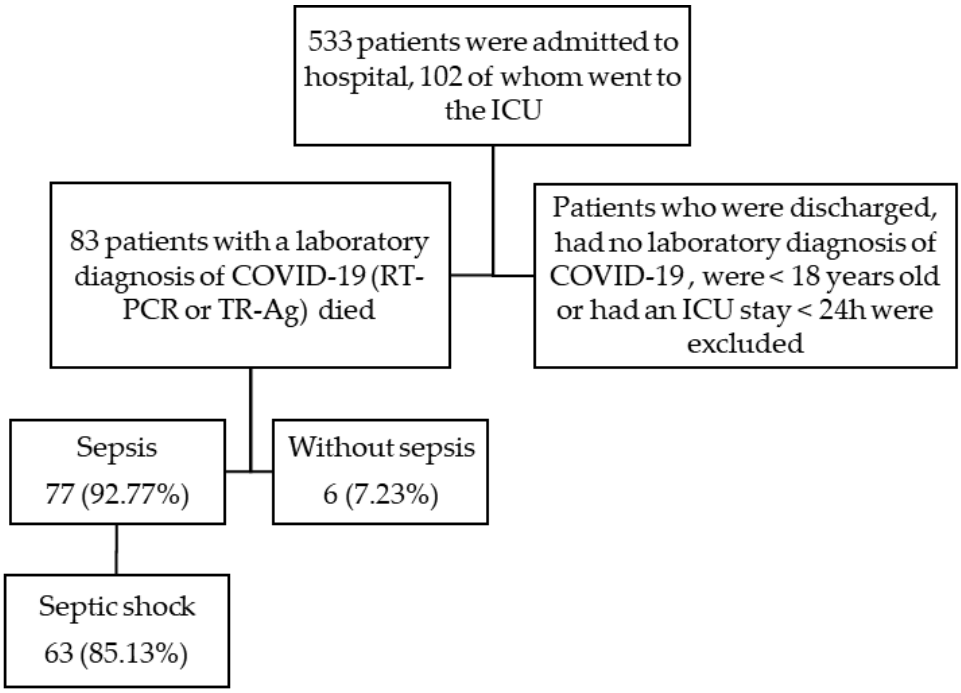


Figure 1. Flowchart of the study design

2.3. Statistical analysis

The statistical analysis used data from COVID-19 patients who died after being admitted to the ICU during the study period. The data were organized in Microsoft Office Excel 365 software and presented in tables as a total number (no.) and percentage (%). The sepsis and non-sepsis groups were preliminarily characterized and possible associations with the variables of age, gender, comorbidities, the use of invasive devices and the presence of co-infection were analyzed by the G test using BioEstat 5.0 software. Associations between patient outcomes and laboratory biomarkers were analyzed by the Mann–Whitney test using GraphPad Prism 9.0.0. A significance level of 5% ($p < 0.05$) was used. Graphs were generated in GraphPad Prism 9.0.0.

3. Results

The results showed that of the 83 deaths of COVID-19 patients that occurred in the ICU, 77 (92.77%) patients developed sepsis, and 63 (85.13%) of the patients with sepsis had septic shock. The analyses that were conducted after patients were categorized into sepsis and non-sepsis groups showed that sepsis was most prevalent

among men (53.24%) and patients aged ≥ 60 years (59.74%). Among the patients with sepsis, 87.01% had comorbidities and 59.74% required invasive devices as therapeutic support (mechanical ventilation/hemodialysis). The association of co-infection between sepsis and non-sepsis patients was statistically significant (G test, p=0.01) and had a prevalence of 41.56% in the sepsis group. There were no other statistically significant differences between these groups (Table 1).

Table 1. General characteristics of study patients who were admitted to the ICU and died between March 2020 and December 2022.

Variables	Sepsis (no.=77)	Without sepsis (no.=6)	p-value
Sex			0.52
Female	36 (46.76%)	2 (33.33%)	
Male	41 (53.24%)	4 (66.67%)	
Age			0.73
18–59 years	31 (40.26%)	2 (33.33%)	
≥60 years	46 (59.74%)	4 (66.67%)	
Comorbidities			0.20
Yes	67 (87.01%)	6 (100%)	
No	10 (12.99%)	0	
Ventilation/Hemodialysis			0.21
Yes	46 (59.74%)	2 (33.33%)	
No	31 (40.26%)	4 (66.67%)	
Co-infections			0.01*
Yes	32 (41.56%)	0	
No	45 (58.44%)	6 (100%)	

*—statistically significant with $p < 0.05$.

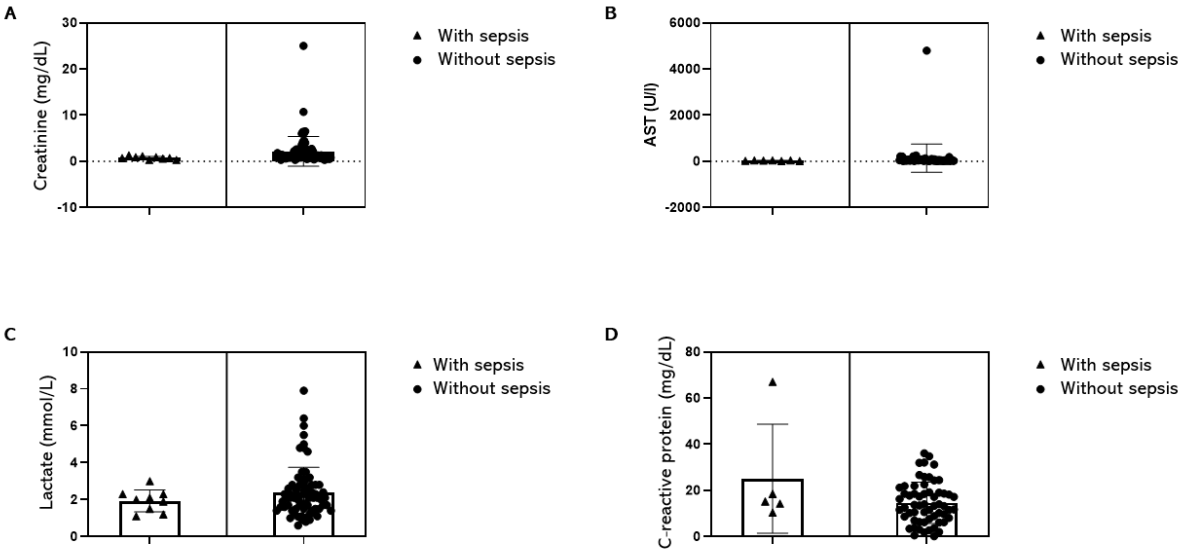
Among the 83 patients who were admitted to the ICU, 73 (87.95%) patients had comorbidities. Cancer stood out as the most common comorbidity, affecting 21.69% of patients, followed by hypertension with diabetes mellitus, which was present in 19.28% of patients. Cancer can further compromise the immune system, making patients more susceptible to COVID-19-related complications. Similarly, the combined presence of hypertension and diabetes mellitus represents an additional burden of cardiovascular and metabolic disease, which can increase the risk of adverse outcomes for patients (Table 2).

Table 2. Identification of patient comorbidities (no.=83).

Comorbidities	No.	%
Hypertension + diabetes mellitus	16	19.28
Hypertension + other	8	9.64
Diabetes mellitus	8	9.64
PLHA[1]	11	13.25
Cancer	18	21.69
Other	12	14.46
No comorbidities	10	12.05

1—PLHA, People living with HIV/AIDS.

Our findings revealed that the levels of creatinine (p=0.009) and AST (p=0.04) significantly differed between the sepsis and non-sepsis groups. However, no significant differences between groups were observed for the other biochemical and hematological parameters that were analyzed (Figure 2).



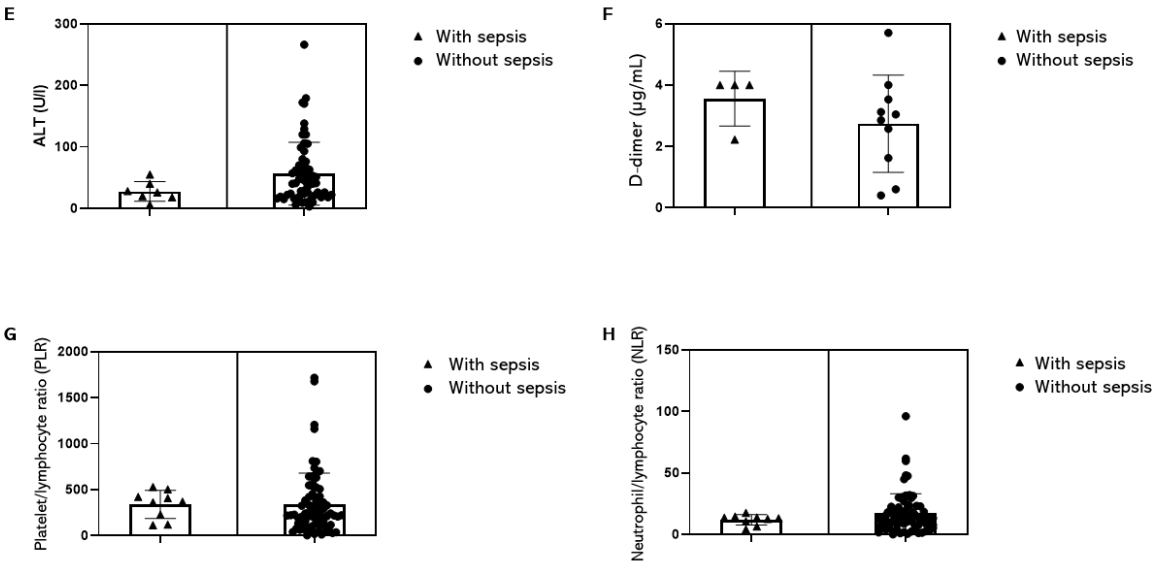


Figure 2. Comparison of hematological and biochemical biomarkers between the sepsis and non-sepsis groups. (A) Creatinine, (B) aspartate aminotransferase, (C) lactate, (D) C-reactive protein, (E) alanine aminotransferase, (F) D-dimer, (G) platelet/lymphocyte ratio, and (H) neutrophil/lymphocyte ratio.

With regard to the presence of co-infections, the results from the microbiological analysis of the patients who developed sepsis revealed a predominance of monomicrobial infections. *Klebsiella pneumoniae* was the most isolated pathogen, which affected 18.75% of patients, followed by *Acinetobacter baumannii*, which affected 9.37% of patients. The high frequencies of these microorganisms highlight the importance of monitoring and controlling these pathogens in intensive care settings, especially in COVID-19 patients (Table 3).

Table 3. Classification of microorganisms associated with co-infections (no.=32).

Microorganisms	**No.**	**%**
Monomicrobial infections		
Klebsiella pneumoniae	6	18.75
Acinetobacter baumannii	3	9.37
Candida tropicalis	2	6.25
Candida albicans	2	6.25
Candida spp.	2	6.25
Staphylococcus spp.	2	6.25
Staphylococcus haemolyticus	1	3.12
Staphylococcus aureus	1	3.12
Stenotrophomonas maltophilia	1	3.12
Escherichia coli	1	3.12
Polymicrobial infections		
Burkholderia cepacian, Candida spp.	1	3.12
Staphylococcus spp., *Candida tropicalis*	1	3.12
Pseudomonas aeruginosa, Staphylococcus aureus	1	3.12
Candida spp./Enterococcus faecium	1	3.12
Klebsiella pneumoniae/Escherichia coli	1	3.12
Candida albicans/Stenotrophomonas maltophilia	1	3.12
Acinetobacter baumannii, Staphylococcus spp.	1	3.12
Stenotrophomonas maltophilia/Staphylococcus spp.	1	3.12
Klebsiella pneumoniae, Stenotrophomonas maltophilia, Candida tropicalis	1	3.12
Pseudomonas fluorescens, Klebsiella pneumoniae, Acinetobacter spp.	1	3.12
Elizabethkingia meningoseptica, Candida spp., Acinetobacter baumannii	1	3.12

Table 4 shows that seven bacterial isolates from patients with co-infections had a resistance genotype according to the molecular identification of the mutational enzymes oxacillinase (OXA)-51, OXA-23, VanA, *Klebsiella pneumoniae* carbapenemase (KPC) and New Delhi metalobetalactamase (NDM), which was carried out by LACEN-PA. Among the carbamenemases that were detected, OXA-23 and OXA-51 were most detected and were always associated with *Acinetobacter baumannii*, followed the detection of KPC and NDM, which were expressed by a strain of *Klebsiella pneumoniae*, and then the detection of VanA, which was found in a strain *of Enterococcus faecium.*

Table 4. Resistance genes of microorganisms associated with co-infections

Microorganism	Resistance Genes						Total No. of Genes
	No.	*bla OXA-23*	*bla OXA-51*	*vanA*	*bla KPC*	*bla NDM*	
Acinetobacter baumannii	5	5	5				10
Enterococcus faecium	1			1			1
Klebsiella pneumoniae[1]	1				1	1	2
Total	7						13

Source: Central Laboratory of the State of Pará. 1—KPC- and NDM-co-producing isolate.

4. Discussion

Sepsis is a serious complication that can arise in COVID-19 patients and significantly increase their risk of mortality. When analyzing the risk factors associated with this condition, varied factors stand out that may be related to a higher risk of death, such as the presence of comorbidities and co-infections. Male individuals who are affected by COVID-19 at an advanced age and have comorbidities are more susceptible to the severe form of the disease, which can evolve into a septic condition regardless of whether it is associated with secondary infections with a poor prognosis. Comorbidities such as cardiovascular disease, diabetes, chronic kidney disease and cancer in patients with COVID-19 are associated with high mortality rates [19,20,21]. Cancer emerged as the most prevalent of the comorbidities that were identified in our study, and it affected 21.69% of the study patients. This was followed by hypertension associated with diabetes mellitus, which showed a prevalence of 19.28%. Carethers' study [22] suggested that comorbidities play a crucial role in the severity of the disease due to the increased expression of angiotensin-converting enzyme receptor 2 (ACE2) and/or transmembrane serine protease 2 (TMPRSS2) in the hosts' lung cells. This increased expression makes patients more susceptible to SARS-CoV-2 infection, thus increasing their risk of developing the severe form of the disease and potentially dying.

In addition to the presence of comorbidities, the measurement of biomarkers plays a crucial role in the identification and prognosis of sepsis through helping to identify patients who are at greater risk of developing severe disease and requiring intensive care. Our findings revealed that high creatinine levels and AST levels were significantly associated with deaths from sepsis, thus corroborating studies that have linked increased levels of liver and kidney function tests to a poor prognosis in COVID-19 patients [23]. Previous studies have reported that between 30% and 50% of patients

who are infected with SARS-CoV-2 and require hospitalization develop some form of acute kidney injury—as observed by an increase in serum creatinine levels—which can eventually progress to chronic kidney disease [24]. The progression of the disease in chronic patients may be related to alterations in the immune system that affect the function of neutrophils, monocytes and B and T cells, thereby resulting in reduced bactericidal and antimicrobial capacities. This can lead to a greater likelihood of admission to intensive care units (ICUs) and increased mortality in this group of patients. [25,26].

Recent research has highlighted the presence of high AST levels in severe cases of COVID-19, suggesting that liver dysfunction is a significant complication of the disease. Although the exact pathways for liver damage in COVID-19 are not yet fully defined, such damage can be attributed to possible direct viral infection, increased expression of the hepatic angiotensin-converting enzyme 2 (ACE-2) receptor, muscle damage, the presence of steatosis, microthrombosis and the use of hepatotoxic drugs. The assessment of aminotransferase levels should be integrated into the clinical management of COVID-19 patients as an additional strategy to identify those who are at the greatest risk of fatal complications [27,28].

A recent meta-analysis found that 19% of COVID-19 patients had co-infections, whereas 24% developed superinfections. These conditions are associated with an unfavorable prognosis, including a significant increase in the mortality rate [29]. Our data revealed that in the presence of co-infections, *Klebsiella pneumoniae* and *Acinetobacter baumannii* were the most frequently isolated microorganisms in patients who died, in agreement with the data available in the literature. Gram-negative microorganisms such as Enterobacterales, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* have been identified as common causes of these co-infections [30]. Recent studies highlight the fact that *Klebsiella pneumoniae* and *Acinetobacter baumannii* infections are frequently identified in ICUs [31]. *Acinetobacter baumannii* infections are associated with high mortality rates, especially in ICU patients; this is due to the characteristic antimicrobial resistance of this bacterium, which emphasizes the urgency of implementing strict infection control measures to contain its spread and reduce its negative impact on patients' health [32,33]. In the Brazilian context, the high incidence of healthcare-related infections (HAIs) caused by multidrug-resistant microorganisms is a cause for concern due to the possible sequelae and high treatment costs, which adversely impact the public health system

[34]. Although the WHO recommends the use of antibiotics according to their access categories, the empirical use of these drugs may have contributed to the emergence of new multidrug-resistant microorganisms in addition to those that are already known [35,36].

It is important to note that in our study we identified five types of resistance genes in bacterial isolates that were related to co-infection. In the *Acinetobacter baumannii* strains, there was a predominance of the genes encoding OXA-23 and OXA-51. The frequent detection of OXA-23 is one of the most common facts associated with resistance [37]. Studies suggest that outbreaks of multidrug-resistant *Acinetobacter baumanii* in intensive care units have intensified during the pandemic and may have occurred due to cross-transmission of the bacteria by mechanical ventilation equipment, infusion pumps and renal replacement therapy by COVID-19 patients. In addition, in several countries, including Brazil, health teams had to spend a long time using the same personal protective equipment due to the difficulties in obtaining these items and the impossibility of receiving adequate prior training on the prevention of health-related infections [38,39].

In our research, a bacterial isolate that co-produced KPC and NDM was identified. As highlighted in the epidemiological alert, issued by the Pan American Health Organization (PAHO) in October 2021, the co-expression of different classes of carbapenemases is proliferating in several countries, thereby becoming a serious threat to public health [40]. The mechanism of resistance through NDM-1 (New Delhi metallobeta-lactamase-1) was first described in 2009. From a therapeutic perspective, this mechanism is particularly worrying as bacteria that possess it become resistant to practically all available antibiotics, with the exception of colistin and tigecycline. The detection of Klebsiella pneumoniae that are co-producing KPC and NDM in ICUs raises concerns about antimicrobial resistance due to the ease with which the multidrug resistance mechanisms of the NDM-encoding gene can be transferred to other strains within the Enterobacteriaceae family [41,42,43]. This situation represents an additional challenge in the treatment of patients with sepsis that is associated with COVID-19.

This study had some limitations. The lack of complete information describing biochemical biomarkers may have caused some bias in the detailed analysis of factors associated with sepsis and septic shock in the study population. Due to budgetary restrictions that were faced by the hospital during the pandemic, some biochemical biomarkers could not be evaluated. In addition, the data in this study comes from a

single university hospital; therefore, the sample size for the group of COVID-19 patients admitted to the ICU was small compared with the existing studies on this subject that are described in the literature. However, it is extremely important to carry out epidemiological research to identify the variables that predispose patients to sepsis and its complications to enable the subsidization of public policies aiming to provide proper management and treatment of sepsis.

5. Conclusions

Based on this study, we can infer that the rate of COVID-19 patients admitted to the ICU who developed sepsis and septic shock was high. The presence of bacterial co-infection was the most relevant risk factor that was associated with death from sepsis. The identification of a microorganism that co-produces the carbapenemases KPC and NDM is a warning of possible changes in the pattern of resistance to the recommended antimicrobial treatments, which requires rigorous monitoring. Finally, identifying and understanding the risk factors associated with sepsis in patients with COVID-19, together with ongoing surveillance of antimicrobial resistance, are fundamental to improving clinical management and reducing the mortality rate from this condition.

Author Contributions: Conceptualization, Marta Monteiro and Rosiane Figueiredo; Investigation Rosiane Figueiredo, methodology, Marta Monteiro, Lucimar Madeira and Vanessa Jóia; software – Formal Analyses, Vanessa Jóia, Sandra Lima, Allane da Paz and Rosiane Figueiredo; research and data curation, Rosiane Figueiredo, João Junior, Mayara Arthur and Zenilde Silva; writing—preparation of original draft, Rosiane Figueiredo; writing—revision and editing, Marta Monteiro and Lucimar Madeira. All authors have read and agreed with the published version of the manuscript.

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Institutional Review Board Statement: The study was carried out in accordance with the Declaration of Helsinki and was approved by the Ethics Committee for Research Involving Human Beings of the João de Barros Barreto University Hospital, opinion no. 5.694.252, CAAE 56902322.7.0000.0017.

Informed Consent Statement: Informed consent was waived due to the retrospective nature of the study.

Data Availability Statement: The authors confirm that the data supporting the findings of this study are available within the article.

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Conflicts of Interest: The authors declare no conflicts of interest.

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4. CONCLUSÃO

- Com base nos resultados da pesquisa, podemos inferir que a incidência de sepse e choque séptico em pacientes com COVID-19 admitidos em UTI foi significativamente alta.
- A presença de coinfeção bacteriana emergiu como o fator de risco mais relevante associado ao desfecho fatal por sepse.
- A detecção de microrganismos produtores de carbapenemases, como KPC e NDM, alerta para possíveis mudanças nos padrões de resistência antimicrobiana, exigindo vigilância rigorosa.
- A identificação e compreensão dos fatores de risco associados à sepse em pacientes com COVID-19, aliadas a uma vigilância contínua da resistência antimicrobiana, são essenciais para aprimorar o manejo clínico e reduzir a mortalidade associada a essa complicação.

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