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IMPACTO DE DIFERENTES AGENTES ETIOLÓGICOS VIRAIS NOS PACIENTES HOSPITALIZADOS DEVIDO A PRESENÇA DE SÍNDROME RESPIRATÓRIA AGUDA GRAVE DURANTE A PANDEMIA DA *CORONAVIRUS DISEASE* (COVID)-19 NO BRASIL

Bragança Paulista
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À minha família com amor.

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"Vou passar meu céu fazendo o bem sobre a terra"

St. Teresinha do Menino Jesus

RESUMO

A *coronavirus disease* (COVID)-19 impactou negativamente os sistemas de saúde globais. Especialmente no Brasil, a situação foi agravada pelas infecções causadas por outros vírus respiratórios e suas respectivas co-detecções. Dessa forma, o presente estudo visa descrever o perfil epidemiológico dos pacientes hospitalizados e infectados pelo vírus influenza A e B e com suas possíveis co-detecções virais durante a pandemia da COVID-19 no Brasil e associar esse perfil ao risco de óbito. Neste contexto, foi realizada uma análise epidemiológica a partir de dados da plataforma OpenDataSUS. Os pacientes foram agrupados de acordo com o tipo de vírus respiratório e seus marcadores epidemiológicos foram utilizados como preditores para o risco de óbito. A partir dos dados óbitos foram realizados dois estudos, no primeiro estudo foram notificados 22.067 casos de infeção pelo vírus influenza, sendo 20.330 (92,1%) do tipo A. Houve predomínio do sexo feminino (53,7%) e da raça branca (62,1%) e de residentes em zona urbana (95,2%). Adultos e idosos foram mais propensos a infecção viral. Os sinais e sintomas clínicos mais frequentes foram os de origem respiratória. A maioria dos pacientes apresentou pelo menos uma comorbidade. A unidade de tratamento intensiva (UTI) foi utilizada em 28,4% dos sujeitos sendo que a maioria deles necessitou de suporte ventilatório. O óbito foi descrito em 3.212 (14,6%) dos indivíduos sendo o maior risco associado à presença do vírus influenza A [OR=2,031 (IC95%=1,701-2,424)], idade avançada, ser autodeclarado como preto, miscigenado, presença de infeção nosocomial, sinais e sintomas clínicos respiratórios, comorbidades prévias, necessidade de UTI e de suporte ventilatório invasivo. No segundo estudo, buscou-se avaliar o perfil da co-detecção viram em pacientes hospitalizados devido à infecção pelo vírus influenza. Dos 477 pacientes incluídos, 400 (83,9%) foram detectados com o vírus influenza A. A co-detecção foi mais comum na presença de vírus sincicial respiratório (53,0%), rinovírus (14,0%) e adenovírus (13,4%), principalmente em homens (50,7%) e infanto-juvenis de 0-12 anos (65,8%). Os sintomas mais frequentes foram a tosse (90,6%), dispneia (78,8%) e febre (78,6%). A necessidade de UTI ocorreu em 147 (30,8%) casos, com 66,8% requerendo suporte ventilatório. Houve 33 (6,9%) óbitos, sendo os principais preditores a infecção pelo bocavírus e metapneumovírus, cardiopatia e necessidade de UTI. Dessa forma, podemos concluir que infecções pelo vírus influenza A, predominantemente em mulheres brancas acima de 25 anos, resultaram em mortalidade de ~15%, especialmente na presença de fenótipos mais graves e que necessitam de hospitalização em UTI e de suporte ventilatório. Co-detecções com vírus respiratórios como vírus sincicial respiratório, rinovírus e adenovírus foram comuns em homens jovens e aumentaram o risco de morte, especialmente na presença de bocavírus e metapneumovírus. Ademais, na co-detecção, fatores como raça, doenças cardíacas e necessidade de UTI também foram associados ao maior risco de óbito.

Palavras-chave: Epidemiologia. Infecções. Influenza humana.

ABSTRACT

The coronavirus disease (COVID)-19 has impacted global health systems. Especially in Brazil, the situation has been worsened by infections caused by other respiratory viruses and their respective co-detections. Therefore, the present study aims to describe the epidemiological profile of hospitalized patients infected with influenza A and B viruses and their possible viral co-detections during the COVID-19 pandemic in Brazil and associate this profile with the risk of death. In this context, an epidemiological analysis was carried out using data from the OpenDataSUS platform. Patients were grouped according to the type of respiratory virus and their epidemiological markers were used as predictors for the risk of death. Two studies were carried out based on death data. In the first study, 22,067 cases of influenza virus infection were reported, 20,330 (92.1%) of type A. There was a predominance of females (53.7%) and white race (62.1%) and residents in urban areas (95.2%). Adults and the elderly were more prone to viral infections. The most frequent clinical signs and symptoms were of respiratory origin. The majority of patients had at least one comorbidity. The intensive care unit (ICU) was used in 28.4% of the subjects, with the majority of them needing ventilatory support. Death was described in 3,212 (14.6%) of individuals, with the greatest risk being associated with the presence of the influenza A virus [OR=2.031 (95%CI=1.701-2.424)], advanced age, being self-declared as black, mixed race, presence of nosocomial infection, respiratory clinical signs and symptoms, previous comorbidities, need for ICU and invasive ventilatory support. In the second study, we sought to evaluate the co-detection profile seen in patients hospitalized due to influenza virus infection. Of the 477 patients included, 400 (83.9%) were detected with influenza A virus. Co-detection was more common in the presence of respiratory syncytial viruses (53.0%), rhinovirus (14.0%) and adenovirus (13, 4%), mainly in men (50.7%) and children aged 0 to 12 years (65.8%). The most common symptoms were cough (90.6%), dyspnea (78.8%) and fever (78.6%). The need for ICU occurred in 147 (30.8%) cases, with 66.8% requiring ventilatory support. There were 33 (6.9%) deaths, with the main predictors being infection by bocavirus and metapneumovirus, heart disease and the need for ICU. Therefore, we can conclude that infections with the influenza A virus, predominantly in white women over 25 years of age, resulted in mortality of ~15%, especially in the presence of more severe phenotypes that require hospitalization in the ICU and ventilatory support. Co-detections with respiratory viruses such as respiratory syncytial virus, rhinovirus, and adenovirus were common in young men and increased the risk of death, especially in the presence of bocavirus and metapneumovirus. Furthermore, in co-detection, factors such as race, heart disease and need for ICU were also associated with a higher risk of death.

Keywords: *Epidemiology*. *Infections. Human Influenza.*

LISTA DE SÍMBOLOS E ABREVIAÇÕES

CEP - Comitê de Ética em Pesquisa

cmH_2O - Centímetro de água

COVID-19 - do inglês *coronavirus disease*

DNA - Ácido desoxirribonucleico

H1N1 - Variante do vírus influenza A

H3N2 - Variante do vírus Influenza A

HBoV - Bocavírus humano

HPIVs - Vírus da Parainfluenza humana

MCMC - do inglês *Markov Chain Monte Carlo*

mmHg - milímetros de mercúrio

mRNA - ácido ribonucleico mensageiro

NIPALS - do inglês *Nonlinear Iterative Partial Least Squar*es

OMS - Organização Mundial da Saúde

OpenEpi - Estatísticas Epidemiológicas de Fonte Aberta para Saúde Pública

OR - do inglês *odds ratio*

PaO_2/FiO_2 - Relação de pressão parcial de oxigênio pela fração inspirada de oxigênio

$PaCO_2$ - Pressão parcial de gás carbônico

PEEP - do inglês *Positive End-Expiratory Pressure*

pH - Potencial hidrogeniônico

RNA - Ácido Ribonucleico

RT-PCR - Reação da transcriptase reversa seguida de reação em cadeia da polimerase

SARS - Síndrome respiratória aguda grave

SARS-CoV-2 - do inglês *severe acute respiratory syndrome coronavirus* 2

SPSS - do inglês *Statistical Package for the Social Sciences*

XLSTAT - do inglês *Statistical Software for Excel*

% - porcentagem

SUMÁRIO

1. INTRODUÇÃO

A *coronavirus disease* (COVID)-19 foi declarada uma pandemia pela Organização Mundial da Saúde (OMS) em 11 de março de 2020 sendo uma das pandemias com maior taxa de mortalidade do mundo, o que causou um grande impacto na saúde e economia global (PERK et al., 2021; MAJUMDER; MINKO, 2021). Aproximadamente quatro anos após o início da pandemia, boa parte da população já foi vacinada contra o SARS-CoV-2 (*severe acute respiratory syndrome coronavirus* 2) (VERGANA et al., 2021; DROZDZAL et al., 2021). Neste período foi possível identificar fármacos eficazes para o manejo da COVID-19, por exemplo o Sotrovimab, Casirivimab, Imdevimab, Abdol, Anakinra, Apremilaste, Azitromicina, Vitamina D, Dexametasona e Tocilizumabe (DROZDZAL et al., 2021; *COVID-19 Treatment Guidelines Panel*, 2021; *Food and Drug Administration,* 2020; 2021b).

Entretanto, a circulação do SARS-CoV-2, principalmente, de novas variantes como a Omicron, ainda oferece riscos à saúde pública no Brasil e no mundo (TAO et al., 2022). Concomitantemente, na literatura, diversos estudos descrevem a incidência de outras infecções virais respiratórias isoladamente ou em concomitância com o SARS-CoV-2, durante a pandemia, sendo as mais frequentes causadas pelo rinovírus, vírus influenza (principalmente dos subtipos A e B), vírus sincicial respiratório, metapneumovírus, vírus parainfluenza (subtipos 1, 2, 3, e 4) e outros vírus da família do coronavírus (CoV, vírus da bronquite infecciosa aviária-estirpe Beaudette, estirpe bovina ENT-coronavirus, cepa coronavírus humano-229E, cepa A59 do vírus da hepatite murina, cepa Purdue 115 da gastroenterite transmissível suína e cepa CV777 do vírus da diarreia epidêmica suína) (AGCA et al., 2021; BOSCHIERO et al., 2022; BRIEN; BARIC, 2005).

1.1. Características associadas ao SARS-CoV-2

Os primeiros registros da doença causada pelo SARS-CoV-2, a COVID-19, ocorreram em Wuhan, na China, em dezembro de 2019, após relatos de 41 casos de pneumonia de origem desconhecida (SOUZA et al., 2022; BOSCHIERO et al., 2022). Depois de estudos epidemiológicos e genéticos, foi descoberta uma nova cepa da família *Coronaviridae*, então denominada de SARS-CoV-2 (CONSTANZA et al., 2022; TAO et al., 2022). O SARS-CoV-2 recebeu esse nome devido a semelhança genética e estrutural com o SARS-CoV, que foi responsável por duas epidemias anteriores; a saber, a síndrome respiratória aguda grave (SARS-CoV – 2003) e a síndrome respiratória do oriente médio (2012) (CONSTANZA et al., 2022; COSTA et al., 2020).

O SARS-CoV-2 é um vírus que pertence ao subgrupo beta da família *Coronaviridae*, cujo material genético se constitui de RNA de fita simples. São vírus envelopados com polaridade positiva e cadeia única (AGCA et al., 2021). Em relação à doença causada pelo SARS-CoV-2, a COVID-19 é uma infecção que afeta, principalmente, o sistema respiratório, ocasionando desde o resfriado comum até a *severe acute respiratory syndrome* (SARS). Dessa forma, a COVID-19 se tornou um importante fator de morbidade e mortalidade no mundo (AGCA et al., 2021; da COSTA et al., 2020; de FRANCESCO et al., 2021).

1.1.1. Sintomatologia associada a infecção pelo SARS-CoV-2

A infecção pelo novo coronavírus é assintomática na maioria dos casos, mas na presença de sintomas, estes incluem, principalmente, tosse, dispneia, dor de garganta, febre e mialgia (da COSTA et al., 2020; PERK et al., 2021; SANSONE et al., 2022). Em casos mais graves da infecção, o paciente pode evoluir para uma pneumonia grave, SARS e, dessa forma, progredir para o óbito. No início dos sintomas, alguns pacientes não apresentam quadro de febre, com sintomas leves, como calafrios e sintomas respiratórios, porém a maioria dos pacientes, mesmo em casos leves, evoluem com novos sinais pulmonares em exames de imagem [por exemplo, opacidades pulmonares em vidro fosco] (HOSSEINI et al., 2020).

Outros achados em pacientes infectados pelo vírus foram a infecção respiratória superior, a diminuição dos glóbulos brancos ou linfócitos e o aumento de alanina aminotransferase, aspartato aminotransferase, lactato desidrogenase, creatinofosfoquinase e proteína C reativa (GUAN et al., 2020). Sabe-se que características como idade avançada e a presença de comorbidades como a obesidade, a diabetes mellitus e as doenças cardiovasculares estão relacionados ao aumento da gravidade da doença e, concomitantemente, com o maior risco de óbito (SANSONE et al., 2022). Diante dos sintomas e evolução da doença, é importante salientar que a clínica de cada indivíduo será diferente e variável de acordo com a raça, país, tempo de vacinação, hábitos de vida, histórico de saúde prévio, idade e sexo (STASI et al., 2020; GUAN et al., 2020).

1.1.2. Forma de transmissão do SARS-CoV-2

O SARS-CoV-2 é um vírus facilmente transmitido por meio de contato direto ou por meio de fômites (da COSTA et al., 2020; TAO et al., 2022). Recentemente a transmissão do vírus foi identificada como advinda de morcegos e/ou outros animais provenientes de mercados locais de venda de frutos do mar na Cidade Wuhan, na China (CHAN et al., 2020). Sabe-se que além da forma de transmissão animal-humano, existe a transmissão entre humanos, sendo a última forma é considerada a principal forma de transmissão do vírus. Neste caso, a transmissão ocorre principalmente pelas gotículas respiratórias (por ex. tosse e espirro) liberadas por um indivíduo que está infectado pelo vírus (SHARMA; AHMAD FAROUK; LAL, 2021). O que pode explicar a disseminação do vírus por aerossóis é que, quando o indivíduo infectado com SARS-CoV-2, espirra ou tosse, o vírus é excretado e torna-se um bio-aerossol e esse causa a transmissão por via aérea efeitva, e as gotículas maiores são fixadas em superfícies e as menores são dissipadas por centenas de metros e podem permanecer por muito tempo neste ambiente (TABATABAEIZADEH, 2021; DOREMALEN et al., 2020).

1.1.3. Diagnóstico da infecção causada pelo SARS-CoV-2

Os métodos de diagnóstico do SARS-CoV-2 são relevantes para as estratégias de redução da infecção pelo vírus e podem auxiliar em futuras pandemias, para isso é importante entender as propriedades genéticas e estruturais do vírus para a elaboração de ferramentas de diagnóstico eficazes (SAFIABADI et al., 2021).

É importante salientar que para a detecção precisa de qualquer doença infecciosa é necessária a coleta adequada de amostras no local anatômico referente à infecção, quando o patógeno esteja presente (LIPPI; SIMUNDIC; PLEBANI, 2020). A coleta de material do trato respiratório superior é utilizada para diagnóstico do SARS-CoV-2 pelo uso do *swab* flocado da nasofaringe, *swabs* nasais e orofaríngeos, amostragem das narinas anteriores, lavagens/aspirados de nasofaringe, nariz ou garganta (WHO et al., 2020; de VIRGILIO et al., 2020). Contudo, com a evolução da doença, o trato respiratório inferior pode ser afetado e seu material pode ser coletado, como o fluido de lavagem broncoalveolar, secreções endotraqueais ou escarro (MURPHY et al., 2020).

No Brasil, o principal exame utilizado para o diagnóstico da infecção pelo SARS-CoV-2 (causando a COVID-19) é o teste rápido, que detecta a presença de antígeno viral. No entanto, este exame tem como principal limitação uma menor sensibilidade e eficácia quando comparado aos outros exames de diagnóstico (AGCA et al., 2021; CHONG et al., 2021). Na literatura, a técnica referida como padrão-ouro para o diagnóstico das infecções virais respiratórias é a reação da transcriptase reversa seguida de reação em cadeia da polimerase (RT-PCR), em que é necessária a coleta de *swab* de nasofaringe e orofaringe, amostras de saliva ou aspirados do trato respiratório inferior (da COSTA et al., 2020). Após uma análise abrangente, verificou-se a presença confiável do RNA do SARS-CoV-2 na saliva, com sensibilidade e especificidade comparáveis aos métodos convencionais de *swabs* de nasofaringe. Contudo, para consolidar a saliva como método diagnóstico, são necessários estudos clínicos mais amplos que incluam diferentes estágios da infecção, no entanto a saliva se mostra promissora como abordagem menos invasiva e direcionada a marcadores específicos, representando um potencial avançado nas estratégias rápidas e eficazes de detecção viral (FERNANDES et al., 2020).

A RT-PCR foi extensivamente utilizada no Brasil, no entanto, em vários momentos da pandemia, seu uso foi limitado devido à falta de insumos e dificuldades associadas ao transporte de materiais para os laboratórios credenciados para o diagnóstico (LIU et al., 2020). Entretanto, no Brasil, o diagnóstico dos demais vírus respiratórios, geralmente, não é realizado por meio da RT-PCR e, dessa forma, no nosso país um possível subdiagnóstico destes é descrito (BOSCHIERO et al., 2022).

Os exames laboratoriais que abrangem marcadores hematológicos, bioquímicos e químicos também são utilizados para identificar possíveis indícios de um estado grave de doença e com o intuito de realizar diagnósticos diferenciais. Dentre esses exames, podem ser citados os testes como contagem de glóbulos brancos, marcadores para condições inflamatórias (proteína C-reativa), procalcitonina ou interleucina 6, testes de anticoagulação e indicadores de danos teciduais (alanina aminotransferase, aspartato aminotransferase, lactato desidrogenase e creatina quinase) (SAFIABADI et al., 2021; STEGEMAN et al., 2020; Ó'SHEA et al., 2020).

Outras formas de diagnósticos complementares da infecção pelo SARS-CoV-2 são os exames de imagem como, radiografia de tórax, tomografia computadorizada de alta resolução e ultrassonografia (CAO et al., 2020; LARICI et al., 2020), o qual o último citado se destacou como método emblemático de triagem em cenários emergenciais devido à sua praticidade e precisão em ambientes de atendimento imediato e capacidade de fornecer imagens em tempo real (DI SERAFINO et al., 2020).

Os principais achados nos exames de imagem do sujeito infectado pela COVID-19 são opacidades pulmonares, aspecto conhecido como "vidro fosco" multifocais bilaterais, alterações reticulares sobrepostas às alterações alveolares que refletem o acometimento intersticial, consolidações focais e até mesmo achados cardíacos (ESPOSITO et al., 2020; FIELDS et al., 2020).

Um novo método de diagnóstico da COVID-19 tem sido realizado, o qual analisa as proteínas do SARS-CoV-2 diretamente de amostras clínicas do trato respiratório (*swab* de nasofaringe e orofaringe), chamado teste por proteômica, o qual abre caminhos para expandir a análise da fisiologia do vírus e seu potencial infectante, além de reduzir os riscos na manipulação das amostras em decorrência do transporte poder ser realizado em ar ambiente, conter confiabilidade nos resultados e possuir alto rendimento. Esta técnica é procedente da tecnologia de espectrometria de massas, sendo que as proteínas são extraídas por partículas magnéticas e digeridas em moléculas menores, chamadas de peptídeos. A mistura desses é submetida a um processo automatizado de cromatografia, que gera a purificação e separação dos peptídeos por polaridade. Em seguida, os peptídeos são identificados por espectrometria de massas. Com os resultados de vários desses peptídeos, a proteína é identificada, logo, em caso de resultado positivo para a presença de proteína do vírus na amostra, a suspeita da COVID-19 pode ser confirmada (MANIRUZZAMAN et al., 2022; MCARDLE et al., 2021).

1.1.4. Manejo dos pacientes acometidos pelo SARS-CoV-2

Os pacientes acometidos pelo SARS-CoV-2 e seus respectivos desfechos irão variar de acordo com a gravidade do caso, que pode ser de leve a grave (AGCA et al., 2021). O tratamento do paciente irá variar de acordo com a sua necessidade, iniciando-se na realização do diagnóstico da positividade do vírus, seja por exames hematológicos, laboratoriais e de imagens, não descartando a clínica do paciente (WANG et al., 2019). O tratamento dos casos leves deve considerar a sintomatologia apresentada e, quando necessário, para casos selecionados deve ser utilizado antibióticos, corticoides e anti-inflamatórios (DROZDZAL et al., 2021). Conforme a gravidade evolui, é necessária a avaliação da necessidade do uso de oxigênio suplementar, que é comum nas insuficiências respiratórias de leve a moderadas que evoluem com hipoxemia, porém este recurso não deve ser utilizado em excesso, deve-se manter a saturação alvo entre 93-95% (LIU; LIU, 2020; ÓDRISCOLL et al., 2017; YUAN; YEUNG; YANG, 2022).

A cânula nasal de alto fluxo foi um método bastante utilizado para fornecer suporte ventilatório no manejo do desconforto respiratório em pacientes com o SARS-CoV-2, em especial quando associado ao aumento do trabalho respiratório, e quando a relação de pressão parcial de oxigênio pela fração inspirada de oxigênio (PaO_2/FiO_2) fosse descrita entre 150 e 300. No entanto, após 24 horas de uso contínuo da cânula nasal de alto fluxo, se a oxigenação se mantivesse em relação aos seus parâmetros, recomendava-se a ventilação não invasiva com pressão positiva, que pode ser utilizada de forma isolada ou com medicações associadas e oxigênio suplementar, dependendo da evolução do quadro clínico do paciente (YUAN; YEUNG; YANG, 2022; LIU; LIU, 2020; ÓDRISCOLL et al., 2017; WINDISCH et al., 2020). Com o insucesso deste último recurso, na COVID-19, é indicado a intubação orotraqueal acoplada à ventilação mecânica invasiva com pressão positiva – tratamento eficaz para casos de insuficiência respiratória grave, em especial quando realizada de forma protetora, que inclui oferta de volume corrente individualizado, pressão expiratória final positiva adequada (PEEP, do inglês *Positive End-Expiratory Pressure*) titulada e recrutada quando necessária, FiO_2 capaz de manter saturação entre 93-95%, evitando hiperóxia e parâmetros ventilatórios ajustados de acordo com o quadro clínico de cada paciente (WINDISCH et al., 2020; PFEIFER et al., 2020; MENG et al., 2020).

Para os pacientes com SARS e índice de oxigenação menor que 100 e PEEP maior que 10 cmH_2O, existe a recomendação da posição prona (MUNCH et al., 2017) – a conduta melhora a ventilação/perfusão e recruta os segmentos pulmonares dorsais –, consequentemente, gera a abertura dos alvéolos colapsados, resultando na melhora da troca gasosa e oxigenação (CHUA et al., 2021; DING et al., 2020).

A oxigenação por membrana extracorpórea é uma opção de terapia utilizada no manejo da infecção pelo SARS-CoV-2. A oxigenação por membrana extracorpórea é uma estratégia de suporte à oxigenação, ventilação e fornecimento de suporte circulatório, em especial, para pacientes com hipoxemia refratária, com PaO_2/FiO_2 menor que 50 mmHg por mais de três horas,

PaO_2/FiO_2 menor que 80 mmHg por mais de seis horas, PaO_2/FiO_2 menor que 100 mmHg, FiO_2 de 100%, potencial hidrogeniônico (pH) menor que 7,25 e pressão parcial de gás carbônico ($PaCO_2$) maior que 60 mmHg por mais de seis horas e parada cardíaca ou choque cardiogênico (LIU; LIU, 2020; FICHTNER et al., 2018; KLUGE et al., 2020).

1.1.5. Vacinação contra o SARS-CoV-2

A vacinação é um direito humano e possui um importante papel no desenvolvimento da saúde no mundo, em especial, na prevenção e no controle de surtos de doenças infecciosas (FEDELE et al., 2021). A pandemia da COVID-19 desafiou os sistemas de saúde mundialmente, sendo necessária a criação de novas estratégias preventivas, portanto, em 2020, a busca por vacinas contra este vírus iniciou-se após a descrição do perfil genômico do SARS-CoV-2 (KANGABOM et al., 2021).

Atualmente diversas vacinas contra o SARS-CoV-2 foram licenciadas, de modos de ação e eficácia distintas (POLACK et al., 2020). A vacina de mRNA BioNTech/Pfizer BNT162b2 conferiu 95% de proteção contra a COVID-19, a Astrazeneca 70,4% e a J&J/Janssen, uma proteção de 66,3% (POLACK et al., 2020; KNOLL; WONODI, 2021; SADOFF et al., 2021). No entanto, uma nova variante do SARS-CoV-2 foi identificada recentemente, denominada Delta, e têm se mostrado mais transmissível em relação às outras variantes, e ser moderadamente resistente a vacinas, em especial em sujeitos que receberam apenas uma dose (POLACK et al., 2020; VITIELLO et al., 2021).

Estudos expõem que a vacina contra o SARS-COV-2 protege contra sintomas graves da doença, reduz a disseminação do vírus e a taxa de infecção, entretanto ainda existe uma heterogeneidade entre a distribuição da vacinação nos países; sendo que essas diferenças podem causar o surgimento de novas variantes e estender a disseminação do vírus. Neste contexto, é de grande importância a continuidade do esquema vacinal e o aprimoramento de políticas públicas que incentivem a vacinação da população em massa (LEVINE et al., 2021; PETTER et al., 2021).

1.2. Outros vírus respiratórios associados a doença pulmonar grave

1.2.1. Rinovírus

O rinovírus, agente responsável pelo resfriado comum, destaca-se por sua alta prevalência e facilidade de transmissão, especialmente pelo trato respiratório superior. Essa adaptabilidade explica sua recorrência constante na população.

Os rinovírus humanos possuem RNA de fita positiva e são vírus não envelopados da família *Picornaviridae*, gênero *Enterovirus* e são categorizados em três espécies (RV-A, B e C), os quais se diferenciam de acordo com critérios de sequência filogenética e características genômicas (BOCHKOV; GERN, 2016). O rinovírus causa infecções respiratórias de vias aeríferas superiores e afeta milhões de pessoas em todo o mundo sendo uma das principais causas de morbidade em crianças menores de cinco anos de idade (LIMA et al., 2016). A infecção pelo rinovírus acarreta sintomas que variam de leves até graves, em especial em pacientes com exacerbação de doença pulmonar obstrutiva crônica ou de asma (KERR; MATHEW; GHILDYAL, 2021). Normalmente, o rinovírus causa o resfriado comum, apresentando congestão nasal, febre, tosse, espirro, cefaleia e mialgia, podendo haver complicações pulmonares em alguns pacientes. Em relação à sintomatologia, o paciente pode apresentar um espectro clínico condizente com a infecção pelo SARS-CoV-2 (de FRANCESCO et al., 2021).

1.2.2. Vírus influenza A, B e C

O vírus da influenza vem da família *Orthomyxoviridae* com genoma de RNA segmentado. O vírus influenza é dividido em três tipos: A, B e C. Sabe-se que a hemoglutinina é a glicoproteína primordial na superfície desses vírus, o que impacta na entrada do mesmo na célula e em cada etapa na sua “hospedagem” (GAMBLIN et al., 2021). Curiosamente, o vírus influenza A foi classificado em 20 subtipos (H1–H20) (GAITONDE; MOORE; MORGAN, 2019). Os vírus influenza B e C têm apenas um subtipo cada e esses dois vírus só foram descritos em humanos (GAITONDE; MOORE; MORGAN, 2019; NYPAVER et al., 2021). A infecção pelo vírus influenza gera sintomas como febre, tosse, dor no corpo e coriza e ocorre com mais frequência no inverno (LUO, 2012). Os grupos de indivíduos mais acometidos por estes vírus são idosos, crianças de seis meses a cinco anos, trabalhadores da área de saúde, da educação, gestantes e puérperas, indígenas e portadores de doenças que aumentam o risco de complicações em decorrência da influenza (KEILMAN et al., 2019; GAITONDE; MOORE; MORGAN, 2019). É muito comum a população equivocar-se acerca da distinção da gripe e do resfriado, essa diferença reside na intensidade e na natureza dos sintomas. A gripe, induzida pelo vírus influenza, manifesta-se com febre elevada, calafrios, mialgia e fadiga pronunciada, podendo resultar em complicações graves, como pneumonia. Em contraste, o resfriado comum, frequentemente provocado pelo rinovírus, apresenta um quadro mais brando, caracterizado por coriza, dor de garganta e espirros, sem febre significativa. Além disso, a gripe é mais contagiosa e tende a ter uma duração maior em comparação ao resfriado (MOORE; MORGAN, 2019).

Os subtipos de influenza A H1N1 e H3N2 são linhagens originárias de aves e suínos, respectivamente, e são subtipos reconhecidos por sua ampla circulação em humanos (CONSTANZA et al., 2022). O H1N1 já foi responsável por uma pandemia que teve início em junho de 2019; no entanto, na atualidade, tanto H1N1 quanto o H3N2, têm apresentado um aumento de sua incidência sazonalmente (SALOMON et al., 2020; AOKI et al., 2022). Na literatura está descrito que os casos da COVID-19, geralmente, são mais graves do que os casos de infecção pelo H1N1, uma vez que, evoluem mais facilmente/rapidamente para a SARS, sendo necessária a atenção hospitalar com maior frequência (da COSTA et al., 2020).

1.2.3. Vírus parainfluenza

Os vírus da parainfluenza humana (HPIVs) são vírus de RNA envelopados de fita simples da família *Paramyoviridaie* e são agrupados em quatro sorotipos (1 a 4) que causam doenças respiratórias. HPIV1 e HPIV3 são membros do gênero *Respirovirus*; HPIV2 e HPIV4 são membros do gênero *Rubulavirus*. O HPIV4 humano é subdividido em dois subgêneros (HPIV4a e HPIV4b). Os vírus parainfluenza ligam-se e replicam-se nas células epiteliais ciliadas do trato respiratório superior e inferior e a extensão da infecção correlaciona-se com a localização acometida no trato respiratório (BRANCHE; FALSEY, 2016). A infecção pelo vírus da parainfluenza humana é um importante motivo de doenças do trato respiratório inferior, principalmente, em crianças e está associado a resfriados, bronquiolite viral e pneumonia em adultos (CONSTANZA et al., 2022). Os sintomas mais comuns da infecção pelo vírus da parainfluenza são: rouquidão, laringite, laringotraqueobronquite, tosse e estridor devido à obstrução decorrente da inflamação da traqueia, podendo evoluir para o aumento do trabalho respiratório devido a obstrução, fadiga e hipóxia e insuficiência respiratória. No adulto, em geral, a doença é leve, embora a hiperresponsividade das vias aeríferas possa ocorrer em pessoas com asma devido à liberação de citocinas e quimiocinas (BRANCHE; FALSEY, 2016).

1.2.4. Metapneumovírus

O metapneumovírus faz parte da família *Paramyxoviridae*, que são vírus envelopados com RNA de cadeia simples, não segmentado. *Paramyxoviridae* inclui as subfamílias *Paramyxovirinae* e *Pneumovirinae*, esta última é ainda subdividida nos gêneros *Pneumovirus* e *Metapneumovirus* (HERMOS; VARGAS; MC ADAM, 2010). O metapneumovírus humano é um Paramixovírus descrito em 2001 sendo reconhecido como uma das principais causas de infecções do trato respiratório em crianças e adultos, com sintomas que incluem febre, coriza, tosse, rinite, faringite, otalgia e membrana timpânica anormal (HERMOS; VARGAS; MC ADAM, 2010; SCHUSTER et al., 2021). São divididos em tipo A e B, onde o tipo A gera infecções mais graves, pois são infecções mais propensas à pneumonia (BALLEGEER; SAELENS, 2020). Em geral, a infecção primária antecede aos cinco anos de idade e, com o passar do tempo, os humanos são reinfectados (SCHUSTER; WILLIAMS, 2014). O metapneumovírus estimula uma baixa resposta imunológica de memória, por este motivo as reinfecções ao longo da vida são comuns (CONSTANZA et al., 2022). A população de risco para a sintomatologia de maior gravidade, bem como, risco de óbito, associada a infecção por este vírus são os adultos mais velhos devido a redução da imunidade humoral (SCHUSTER; WILLIAMS, 2014).

1.2.5. Vírus sincicial respiratório

O vírus sincicial respiratório acomete principalmente crianças pequenas, especialmente aquelas com menos de 2 anos, sendo uma das principais causas de internação hospitalar causada por bronquiolite e pneumonia em bebês. Contudo, também pode afetar adultos, especialmente aqueles com sistemas imunológicos enfraquecidos, idosos ou pessoas com doenças respiratórias preexistentes (PIEDIMONTE; PEREZ, 2014).

O vírus sincicial respiratório é um vírus de RNA de fita simples da família *Paramyxoviridae*, cujo genoma inclui dez genes que codificam 11 proteínas e é o patógeno respiratório mais comum em bebês e crianças (BORCHERS et al., 2013; BLOUNT; MORRIS; SAVAGE, 1956). Existe um único sorotipo deste vírus, com dois subgrupos antigênicos principais, A e B, onde suas cepas frequentemente circulam, de maneira concomitante; no entanto, geralmente um dos subtipos apresenta maior prevalência (GLICA et al., 2006). A fase aguda associada a infecção pelo vírus é representada por episódios de sibilos, que podem ocorrer por meses ou anos, podendo resultar no diagnóstico de asma, onde apresentarão quadros de hiperreatividade brônquica (PIEDIMONTE; PEREZ, 2014). Os sinais e sintomas apresentados em geral são os respiratórios típicos, que podem ser acompanhados de letargia, irritabilidade e má alimentação (BORCHERS et al., 2013). A infecção por esse vírus inicia-se no epitélio da nasofaringe e pode evoluir rapidamente para as vias aéreas inferiores por transmissão intercelular, onde a replicação deste vírus é mais eficiente e incluem consequências patológicas diretas como a presença de descamação das células epiteliais necróticas – expõe a rede subepitelial de fibras nervosas nociceptivas, formando o ramo aferente para o reflexo da tosse (TRISTAM et al., 1998; VILLENAVE et al., 2012). O influxo inicial de neutrófilos polimorfonucleares nas vias aeríferas é rapidamente substituído por infiltração, predominantemente, linfomononuclear dos tecidos peribronquiolares e pelo aumento da permeabilidade microvascular, levando a edema, sendo que este pode ser submucoso (BORCHERS et al., 2013). As secreções mucosas aumentam em quantidade e viscosidade e tendem a se acumular devido à perda do epitélio ciliado, resultando em tamponamento mucoso disseminado (PIEDIMONTE; PEREZ, 2014).

O palivizumabe é um anticorpo monoclonal utilizado como profilaxia para prevenir infecções graves causadas pelo vírus sincicial respiratório em grupos de risco, como bebês prematuros e crianças com comorbidades. Ao inibir a replicação do vírus sincicial respiratório nas vias respiratórias, o palivizumabe e as vacinas, como por exemplo a Novavax, Arexvy, entre outras, têm mostrado reduzir hospitalizações e complicações respiratórias. Embora seja eficaz na prevenção de infecções pelo vírus sincicial respiratório, seu impacto sobre a mortalidade e eventos adversos é limitado, sendo necessária mais pesquisa sobre seu uso em diferentes contextos e populações vulneráveis (GAREGNANI et al., 2021; GRIFFITHS et al., 2017).

1.2.6. Adenovírus

O adenovírus humano é um grupo de vírus pertencentes ao gênero *Mastadenovirus* da família *Adenoviridae* (LYNCH; KAJON, 2016), possuem DNA linear de fita dupla que exibem tamanhos de genoma que variam de 34 a mais de 37 kb com aproximadamente 40 genes e uma organização semelhante do genoma [regiões precoce, intermediária e tardia] que correspondem ao ciclo infeccioso e refletem os padrões de transcrição gênica (LION, 2014). Foram classificados em sete espécies (HAdV-A a HAdV-G), onde as espécies A, B, C, D, E e F circulam mundialmente e participaram dos surtos de infecção em humanos (LEE; CHOI; LEE, 2010). Os adenovírus normalmente causam infecções leves envolvendo o trato respiratório superior ou inferior, incluindo febre, faringite, amigdalite, tosse e dor de garganta e febre faringoconjuntival podendo afetar o trato gastrointestinal ou a conjuntiva. Concomitantemente, o vírus afeta comumente crianças, em especial pelo déficit da imunidade humoral (LYNCH; KAJON, 2016). A infecção pelo adenovírus pode gerar manifestações raras como: cistite hemorrágica, hepatite, colite hemorrágica, pancreatite, nefrite ou encefalite (LYNCH; FISHBEIN; ECHAVARRIA, 2011).

1.2.7. Bocavírus

O bocavírus humano é um *Parvovírus* classificado taxonomicamente dentro da subfamília *Parvovirinae*, na família *Parvoviridae,* agrupado em subtipos denominados de HBoV2, HBoV3 e HBoV4 (GUIDO et al., 2016; SILVA et al., 2010). São detectados em especial no início da vida de crianças de seis a 24 meses de idade com infecção respiratória aguda ou em amostras de fezes, de pacientes com gastroenterite (JARTTI et al., 2012; KESEBIR et al., 2006). O quadro clínico e sintomatologia, frequentemente, incluem tosse, febre, rinorreia, exacerbação da asma, bronquiolite, sibilância aguda e pneumonia (DINA et al., 2009; FRY et al., 2007). As duplas infecções são observadas com frequência, mostrando uma elevada taxa de coinfecções com outros patógenos respiratórios e gastroenterites virais e bacterianos, como o rinovírus, adenovírus, norovírus e rotavírus (GUIDO et al., 2016).

1.3. Circulação do vírus e medidas preventivas

A circulação viral apresenta diferentes aspectos dinâmicos, principalmente, associados às mudanças de estações durante o ano. Por exemplo, os vírus do tipo influenza, o vírus sincicial respiratório e os CoVs têm pico de infecção no período de inverno; em contrapartida, o rinovírus circula durante todo o ano e possui picos de infecção descritos na primavera e no outono. Até o momento, apenas o SARS-CoV-2 e influenza têm vacinas disponíveis (de FRANCESCO et al., 2021).

Além das vacinas, as medidas preventivas de higiene e distanciamento social foram popularizadas na pandemia do H1N1 em 2009 e na pandemia do SARS-CoV-2, em que também se tornou obrigatório o uso de máscara em locais públicos e as medidas de proteção como, lavagem correta das mãos, distanciamento social, limpeza das mãos com álcool em gel, foram intensificadas (da COSTAS et al., 2020; de FRANCESCO et al., 2021). Isso ocorre porque a maioria dos casos das demais infecções virais apresenta sintomas leves (sem a necessidade de internação) e, dessa forma, sem a necessidade de implementação de normas mais restritivas (PARK et al., 2021).

A determinação de medidas profiláticas como o uso de máscara, a adoção de hábitos de higiene e o distanciamento social causaram um grande impacto no padrão epidemiológico de infecções respiratórias a nível global durante a pandemia da COVID-19 (SHARMA; AHMAD FAROUK; LAL, 2021). Por exemplo, epidemias sazonais causadas pelo vírus influenza e vírus sincicial respiratório não registraram o aumento sazonal esperado (TAO et al., 2022). Um estudo mostrou que em janeiro e fevereiro de 2020 houve um pico de infecções pelos vírus respiratórios citados, com queda a partir de março desse mesmo ano, mês em que foram estabelecidas as estratégias de prevenção da infecção pelo SARS-CoV-2 em nível global (de FRANCESCO et al., 2021). Na Austrália, por exemplo, o reaparecimento do vírus sincicial respiratório só ocorreu após a redução das medidas restritivas (BINNS et al., 2022). Levantamentos realizados na Coréia, Malásia, Estados Unidos da América e Canadá também identificaram um declínio no número de infecções pelos vírus sazonais (CHONG et al., 2021; LOEVINSOHN et al., 2022; PARK et al., 2021; YANG; YEUNG; YANG, 2022; YUM et al., 2021). Por exemplo, um levantamento realizado em Nova Iorque mostrou que nos primeiros meses da pandemia da COVID-19 houve um declínio do número de infecções por parainfluenza, metapneumovírus e rinovírus (YANG; YEUNG; YANG, 2022).

Entretanto, observou-se que a redução foi menor nos casos de rinovírus, que pode ser justificada pela sua estrutura não envelopada que promove maior estabilidade do vírus em diferentes condições do ambiente. Enquanto, vírus envelopados, como o vírus influenza e o SARS-CoV-2 são facilmente inativados pela lavagem das mãos e desinfetantes comuns, o rinovírus se mostra mais resistente. Concomitantemente, a máscara facial é mais eficiente como barreira contra vírus envelopados (de FRANCESCO et al., 2021; LOEVINSOHN et al., 2022; SMEDBERG et al., 2022). Também não houve redução significativa na incidência de adenovírus (SAINT-PIERRE CONTRERAS; GOMEZ; OJEDA, 2021).

Observou-se também que a solicitação de exames para detecção dos vírus respiratórios foi menor durante a pandemia, uma vez que, pacientes que apresentavam sintomas correspondentes eram encaminhados, preferencialmente, para realizar o teste para o SARS-CoV-2 (VANDENBERG et al., 2021). Por exemplo, um levantamento realizado em um laboratório da Turquia, mostrou que a solicitação de testes para outros vírus respiratórios caiu 58,9% após o início da pandemia da COVID-19 (AGCA et al., 2021).

Como as vias de transmissão das diferentes infecções virais respiratórias são parecidas, tornando mais provável que ocorram na mesma época, as interações virais também foram sugeridas como possíveis fatores que impactaram na mudança do padrão epidemiológico dos vírus sazonais, tendo em vista que estes podem alterar a história natural uns dos outros (YANG; YEUNG; YANG, 2022).

É importante ressaltar que com a diminuição das infecções pelos demais vírus respiratórios pode haver alterações (redução) na imunidade contra eles. O que faz com que as infecções futuras possam ser mais graves e, por isso, deve ser reforçada a necessidade de vacinação também contra a gripe causada pelo vírus influenza. Com a retomada das atividades antes restritas e a flexibilização das medidas de proteção, espera-se um aumento no número de casos de infecção por vírus sazonais (de FRANCESCO et al., 2021; UJIIE et al., 2021). E, como esperado, já se observa em alguns países um aumento dos casos de influenza, vírus sincicial respiratório e parainfluenza desde 2021 (HU et al., 2022).

Um aspecto importante a ser ressaltado é que as semelhanças dos sintomas entre o SARS-CoV-2 e os demais vírus respiratórios dificultam o diagnóstico diferencial. No entanto, identificar o agente etiológico responsável pela infecção respiratória é essencial para o acompanhamento e tratamento dos pacientes, além de sua importância para o monitoramento da vigilância e estabelecimento de estratégias de proteção coletivas e individuais (CONSTANZA et al., 2022). Embora o painel viral ofereça diagnóstico rápido e preciso, sua utilidade na saúde pública pode ser limitada em casos leves, pois o tratamento para essas infecções é tipicamente sintomático e não depende da identificação específica do patógeno. No entanto, em casos graves e durante surtos, a identificação precisa do vírus pode direcionar terapias específicas e estratégias de manejo mais eficazes. Além disso, ele facilita o monitoramento e controle da disseminação de doenças, sendo uma ferramenta valiosa na resposta a crises sanitárias e na alocação eficiente de recursos.

Conhecer os padrões de circulação dos vírus respiratórios antes e depois da pandemia da COVID-19 pode contribuir para a determinação de estratégias sanitárias, medidas de prevenção e tratamento contra essas doenças.

2. OBJETIVOS

2.1. Objetivo geral

Descrever o perfil epidemiológico dos pacientes hospitalizados e infectados pelo vírus influenza A e B e com suas possíveis co-detecções virais durante a pandemia da COVID-19 no Brasil e associar esse perfil ao risco de óbito.

2.2. Objetivos específicos

(i) Categorizar o perfil epidemiológico dos pacientes internados com diagnóstico de síndrome respiratória aguda grave em decorrência da infecção pelo vírus influenza durante a pandemia da COVID-19 no Brasil e associar ao risco de óbito;

(ii) Analisar a prevalência da co-detecção entre vírus influenza e outros vírus respiratórios, com exceção do SARS-CoV-2, em pacientes brasileiros hospitalizados na pandemia da COVID-19 e associar ao risco de óbito.

3. CAPÍTULO I: Artigo Submetido

Title: Epidemiological Profile of Patients Hospitalized Due to Severe Acute Respiratory Syndrome Caused by Influenza A and B Virus Infection in Brazil During the Coronavirus Disease (COVID)-19 Pandemic: An Observational Study

Short title: Influenza Virus and Severe Infection

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Ethical approval: The study was conducted in accordance with the Declaration of Helsinki and approved by the Institution's Ethics Committee (Certificate of Presentation of Ethical Appreciation nº 67241323.0.0000.5514; Study Approval Technical Opinion nº 5.908.611).
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Abstract

Introduction: The coronavirus disease (COVID)-19 pandemic had a negative impact on the world's health systems, and, among them, Brazil was one of the most affected due to being one of the epicenters of the disease. At the same time, in Brazil, infection with influenza A and B viruses was experienced, which culminated in additional challenges for the health system already overloaded by the pandemic. In this context, the study describes the clinical and epidemiological profile of patients hospitalized due to infection with influenza A and B viruses during the COVID-19 pandemic in Brazil and associates this profile with the propensity to die.

Methods: Patients' clinical and epidemiological data were collected from the open access platform entitled "OpenDataSUS" made available by the Brazilian Ministry of Health. The following markers were collected: sex, age, race, living in a flu outbreak area, presence of hospital infection, use of antivirals to treat signs and symptoms of flu, comorbidities, clinical signs and symptoms upon hospitalization, need for treatment in an intensive care unit (ICU) and mechanical ventilatory support, and outcomes. Patients were grouped according to the type of influenza virus (A and B) and the markers were used as predictors for the risk of death. Statistical analysis was performed considering an alpha error of 0.05.

Results: We found 22,067 cases of influenza virus infection reported, of which 20,330 (92.1%) were type A and 1,737 (7.9%) were type B. There was a predominance of females (53.7%) and white race individuals (62.1%) living in urban areas (95.2%). Adults and elderly people were more prone to viral infection. The most frequent clinical signs and symptoms were those of respiratory origin (dyspnea, respiratory distress, and peripheral oxygen saturation <95%). A total of 12,224 (55.4%) individuals had at least one comorbidity, the most common of which were cardiomyopathy and diabetes mellitus. The ICU was used for 6,277 (28.4%) of the individuals, and most of them required ventilatory support (59.2%), mainly non-invasive. The number of deaths recorded was 3,212 (14.6%) individuals, with the highest risk of death being associated with the presence of influenza A versus B viruses [OR=2.031 (95%CI=1.701-2.424)]. Markers such as advanced age, being self-declared as black, multiracial background or indigenous, living in peri-urban regions, presence of nosocomial infection, clinical signs and symptoms such as dyspnea, respiratory distress, peripheral oxygen saturation <95% and fatigue/asthenia, comorbidities such as chronic respiratory disease, cardiomyopathy, diabetes mellitus, neurological or liver disease, need for ICU and invasive and non-invasive ventilatory support were more commonly observed in the group of patients who died.

Conclusion: Patients hospitalized due to influenza virus infection, predominantly type A, were mostly white women over 25 years old and living in urban areas. They frequently presented respiratory symptoms and previous comorbidities, with a 14.7% mortality rate. The highest risk of death was associated with type A of the virus with the need for ICU and ventilatory support. Other factors were associated with a greater predisposition to death, with emphasis on advanced age, presence of respiratory symptoms and clinical signs, living in peri-urban areas and presenting specific comorbidities.

Keywords: Data Science; Health Science; Epidemiology; Viral Infection; Influenza; Pandemic; Public Health.

1. Introduction

The coronavirus disease (COVID)-19 pandemic triggered a series of significant and interconnected impacts on global public and private health (1). When facing this unprecedented crisis, health systems, mainly of public origin, went through huge difficulties, with millions of confirmed cases and an impressive number of deaths related to the disease (2). At the same time, the economy was severely affected, which culminated in increased unemployment rates (3,4). Given this scenario, the adaptation of the education system in Brazil to distance learning resulted in the deterioration of the quality of education, exposing disparities in students' access to it (4,5). Furthermore, there was a significant increase in cases of anxiety and depression, highlighting the pandemic impact on the mental health of the population (4,6–8). Although challenges remain related to the equitable distribution of vaccines and unequal access to them and to the health system, significant and fast progress has been made in obtaining vaccines against COVID-19 and implementing mass vaccination campaigns that have resulted in the control of the COVID-19 spread at the global level (9–12). In addition to the immediate challenges associated with the COVID-19 pandemic in Brazil and around the world, (4,13–15) the presence of complex interactions can be described between COVID-19 and other viral agents, including the influenza virus (16–20). The coexistence of infection by both viruses created additional challenges for a health system already overloaded by the pandemic, especially regarding the diagnosis of the pathogen and management of patients with severe illnesses and the need for hospitalization (21–23).

The influenza virus also emerged as a result of a flu outbreak in 2009, starting in Mexico, due to infection with the H1N1 virus of swine origin, causing fast viral spread (24,25). In just a few months, the infection spread across the world and became a pandemic (24,25). This epidemiological event triggered a series of challenges for the public health at that time, which aimed to control the mortality of ~500,00 people/year (24,25).

Among the viruses classified as influenza, four types (A, B, C and D) are identified, with types A and B being responsible for causing diseases with a phenotype that is clinically relevant to human health and is able to cause seasonal epidemics (26). The type A influenza virus is associated with the most severe form of viral infection, being considered the main etiological agent of seasonal epidemics and pandemics (27–29). The greater severity of the disease caused by the influenza virus is associated with the need for hospitalization and the presence of complications of respiratory and non-respiratory origin, which can affect the cardiovascular system, the central nervous system and other organic systems, thus culminating in death (30). The highest mortality rates are associated, in particular, with high-risk populations, mainly children under six months of age, the elderly, patients with comorbidities and pulmonary complications (31). Approximately 5 million adults are estimated to be hospitalized each year due to infections caused by the influenza virus (32). However, these estimates may not be representative of the reality due to insufficient and incomplete diagnosis of etiological agents, as occurred with the COVID-19 (33–36).

The influenza virus infection diagnosis is essentially determined through the evaluation of clinical signs, the epidemiological context and, whenever possible, a laboratory approach focusing on molecular genetics (37). In the initial stage of the disease, generic symptoms stand out, including fever, chills, headache, myalgia and loss of appetite (38). As a consequence, flu treatment is symptomatic in mild cases, taking into account adequate hydration, the use of antipyretic and analgesic medications, rest and withdrawal from activities, aiming to reduce the flu virus spread (39). In individuals with more severe clinical phenotypes, it may be necessary to use antivirals, which are more effective when the treatment begins within 48 hours of the onset of symptoms (40). Moreover, vaccination is a fundamental strategy to reduce the spread of the influenza virus and minimize the disease impact on public health (18,41,42).

In Brazil, influenza virus infection in the hospital environment has a significant association between intensive care unit (ICU) hospitalization and mortality rates with advancing age and the presence of comorbidities (43). For example, we observed that among 0-4-year-old children, the ICU admission rate was 2.1% for those without comorbidities and 4.3% in the presence of comorbidities (43). On the other hand, among adults over 65 years old, hospitalizations represented 3.9% of those without comorbidities and 16.9% among those with comorbidities (43).

The specific literature highlights the implications of influenza virus infection in terms of mortality (44–49). Furthermore, we must consider that the influenza virus has a high potential to undergo genetic variability, which can culminate in the emergence of new viral strains (50,51). Such new viral strains might become resistant to the antivirals available and reduce the immunity effect acquired through vaccination (52), thus favoring the appearance of flu outbreaks, and in more severe cases, even resulting in pandemics (53,54). Therefore, it is crucial to ensure constant immunological updates and seek alternative forms of treatment, such as the use of monoclonal antibodies (52).

The infection caused by the influenza virus is a seasonal disease and is associated with ongoing challenges due to the genetic variability of the virus, which can culminate in resistance to the existing treatments. In such context, research for effective treatment(s) and prevention strategy(ies), such as vaccination, is essential to mitigate the infection impact on global health. Moreover, it is important to highlight that the acute respiratory distress syndrome can represent a serious complication associated with the influenza virus, exponentially increasing treatment costs and the risk of patients' death. Taking that into consideration, the importance of epidemiological surveillance and patient management must be emphasized, especially those with the most severe respiratory phenotypes when facing influenza virus infection.

Therefore, the primary objective of this study was to categorize the epidemiological profile of patients hospitalized due to a diagnosis of severe acute respiratory syndrome as a result of influenza virus infection during the COVID-19 pandemic in Brazil. The secondary objectives were to associate the epidemiological profile with the risk of death and the type of influenza virus (A or B) diagnosed during infection.

2. Methods

2.1. General aspects of the epidemiological analysis

An epidemiological analysis was carried out with data available on the open platform called OpenDataSUS (https://opendatasus.saude.gov.br/). The data were tabulated in accordance with the surveillance of severe acute respiratory infection by the Brazilian Ministry of Health and computed on the Information System Platform for Influenza Epidemiological Surveillance, which became relevant due to the swine flu pandemic (H1N1) (55). The data collection period was from December 19, 2019 to April 6, 2023 – 3 years since the beginning of the COVID-19 pandemic in Brazil. The database described has been used for epidemiological studies on topics related to this study, especially during the COVID-19 pandemic, demonstrating that it presents robust and validated data of importance for health, especially public health in Brazil (16,18,33,34,56–64).

The study addressed three analyses linked to the primary and secondary objectives, as follows: (a) descriptive analysis of the epidemiological profile of patients hospitalized due to the presence of severe respiratory syndrome resulting from influenza virus infection in Brazil, (b) association of the epidemiological profile of patients hospitalized due to the presence of severe respiratory syndrome resulting of influenza virus infection in Brazil with the risk of death, and (c) association of the epidemiological profile of hospitalized patients due to the presence of severe respiratory syndrome resulting from influenza virus infection in Brazil according to the viral type (A or B). The viral profile was carried out according to molecular and/or biochemical-immunological tests depending on the availability of the institution that included the marker in the database.

Inclusion criterion

All individuals who were hospitalized in Brazil during the COVID-19 pandemic due to infection with the influenza A virus or the influenza B virus were included.

Non-inclusion criteria

All individuals infected with other respiratory viruses, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), were excluded from the database. At the same time, the following were not included: (i) individuals without information for the main outcome of the study – presence of death or clinical recovery followed by hospital discharge, (ii) individuals without confirmatory laboratory tests for infection by the influenza A or B virus, (iii) individuals hospitalized in Brazil, however, originally coming from another country, (iv) individuals with influenza virus infection, but without determining the viral type (A or B), (v) individuals with co-detection of influenza A or B and respiratory viruses other than SARS-CoV-2 and (vi) individuals who died during hospitalization due to other causes not described in the database.

2.2. Data acquisition

Initially, the .csv file was obtained from OpenDataSUS (https://opendatasus.saude.gov.br/). The file was downloaded from the database and its structure was analyzed using the Statistical Package for the Social Sciences (SPSS) software (IBM SPSS Statistics for Macintosh, version 27.0, IBM inc, Armonk NY, USA). After the first survey on the database, the raw data to be evaluated was obtained. In the resulting dataset, the following markers were described and fitted:

(i) demographic profile, including the federation unit in which the patient's residence was located (states and federal district of Brazil), date on which hospitalization was notified to the Brazilian Ministry of Health due to severe acute respiratory syndrome, gender (male and female), age (<1 year, 1 to 12 years, 13 to 24 years, 25 to 60 years, 61 to 72 years, 73 to 85 years and +85 years), skin color/self-declared race [white, black, multiracial background (in Brazil, described as mixed race or *pardo*), Asian and indigenous] (62,63,65,66), education (no education/illiterate, elementary education – 1st cycle, elementary education – 2nd cycle, high school and higher education) and place of residence (urban, rural and peri-urban);

(ii) virus infection data such as type and subtype of influenza A and B viruses, residence in a place with an influenza outbreak, presence of hospital-acquired (nosocomial) infection, vaccination status against the influenza virus and use of antiviral medications for the treatment of influenza virus infection. influenza virus (management of clinical signs and symptoms);

(iii) presence of comorbidities [comorbidities (any), cardiomyopathy, hematological disease, Down syndrome, liver disease, asthma, diabetes mellitus, neurological disease, systemic arterial hypertension, chronic respiratory disease, immunosuppressive disease, kidney disease, obesity and others (excluding the above)];

(iv) clinical symptoms and signs related to severe acute respiratory syndrome [fever, cough, sore throat, dyspnea, respiratory distress, peripheral oxygen saturation <95%, diarrhea, vomiting, abdominal pain, fatigue, loss of smell, loss of taste and other symptoms (excluding the above)];

(v) result obtained from lung imaging performed during viral infection. The results were computed in the database using two exams: chest X-ray and high-resolution computed tomography of the chest;

(vi) need for treatment in the ICU, need for mechanical ventilation support (there was no need for ventilation or mechanical ventilation was not performed, non-invasive mechanical ventilation and invasive mechanical ventilation) and outcomes (recovery or death).

For greater accuracy, three researchers reviewed the individuals' clinical and epidemiological data obtained from the dataset. Furthermore, categorical data were coded numerically to assign values to missing data and to perform descriptive and inferential statistical analyses. The SPSS dataset was saved as an .xls file for the input missing data.

2.3. Analysis of missing data

Missing data was imputed for some characteristics due to: (i) the presence of more than 5% of missing data in the database, (ii) the lack of missing data only for the dependent variable (after the exclusion of some participants), and (iii) the assumption that the absence of data in the variables occurred completely by chance. Moreover, characteristics with more than 40% missing data were excluded. Missing data were thus imputed using XLSTAT Statistical Software for Excel (Addinsoft Inc, Paris, Île-de-France, France). Missing qualitative data (categorical data) were estimated using the NIPALS (Nonlinear Iterative Partial Least Squares) algorithm. The XLSTAT statistical software generated a new Excel data set (.xls) which was used to perform statistical analyses in the SPSS software.

2.4. Statistical analysis

2.4.1. Descriptive analysis

The descriptive analysis was conducted using the number of individuals (N) and percentages (%) for categorical data. In inferential statistical analyses, whenever applicable, the Odds Ratio (OR, likelihood ratio) values and the 95% confidence interval (95%CI) referring to each previously calculated OR were also presented.

2.4.2. Bivariate analysis

Bivariate statistical analysis was performed using SPSS and OpenEpi software (OpenEpi: Open Source Epidemiological Statistics for Public Health, Version. www.OpenEpi.com, 2013/04/06)(67). The χ^2 test was applied to evaluate the distribution of data regarding death and the classification for the influenza virus type (A or B) according to the study clinical and epidemiological markers. The OR and 95% CI were calculated to estimate the association of each marker with the presence of death and the classification for the type of influenza virus (A or B). The OR was calculated using OpenEpi software for 2 × 2 tables, the value for each patient's characteristic was included manually. The results were compiled in tables and figures. Figures were created using GraphPad Prism version 8.0.0 for Mac (http://www.graphpad.com, GraphPad Software, San Diego CA, USA). An alpha error of 0.05 was considered in all bivariate analyses carried out in this study.

2.4.3. Multivariate analysis

Multivariate analysis was performed using the Binary Logistic Regression Model with the Backward Stepwise method. Markers with $P \leq 0.05$ in the bivariate analysis were included in the regression model. The response variable was the health outcome (recovery – hospital discharge or death) or the type of influenza virus (A or B) identified as the causal factor for hospitalization. Data for comorbidities (any) or others, symptoms (other) and patient characteristics with $P > 0.05$ were not used. In the Logistic Regression Model, we presented the (i) coefficient B [including SE (standard error)], which for the constant was called the intercept, (ii) the Wald χ^2 test and its significance, (iii) degrees of freedom for the Wald χ^2 test and (iv) Exp(B) which represents the exponentiation of the B coefficient (OR) including its 95% CI. Multicollinearity among the study markers considering cutoff points <0.1 for tolerance and >10 for the variance inflation factor was tested before carrying out the statistical inference analysis. The results were compiled in tables and figures. Figures were created using GraphPad Prism version 8.0.0 for Mac (http://www.graphpad.com, GraphPad Software, San Diego CA, USA). The alpha error of 0.05 was also considered in the multivariable analyses carried out in this study.

2.4. Research ethical aspects

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee (Certificate of Presentation of Ethical Review nº 67241323.0.0000.5514; Study Approval Technical Opinion nº 5.908.611).

3. Results

3.1. Distribution and evolution of influenza virus infection in Brazil during the COVID-19 pandemic

In Brazil, during the COVID-19 pandemic period, 22,067 cases of infection with the influenza virus were reported. The flowchart for inclusion of participants in the study is presented in **Figure 1**.

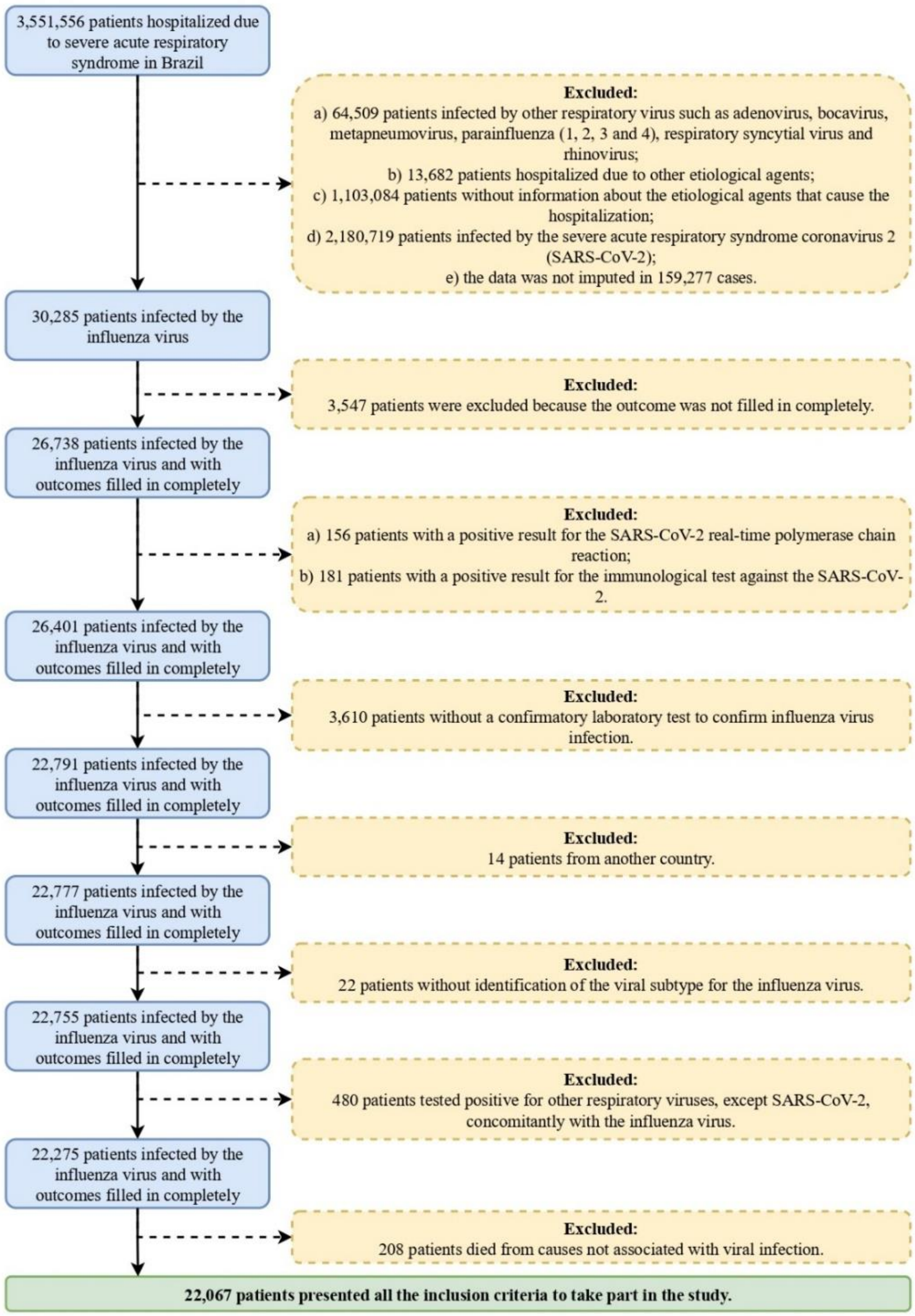

FIGURE 1. Flowchart of participants' inclusion in the study. The flowchart shows the number of participants excluded at each stage of creation of the database used in the inferential analysis. The data used in the epidemiological analysis were obtained from information available on the open platform called OpenDataSUS (https://opendatasus.saude.gov.br/). The data were tabulated according to the surveillance of severe acute respiratory infection by the Brazilian Ministry of Health and were computed on the Information System Platform for Influenza Epidemiological Surveillance. The data collection period was from December 19, 2019 to April 6, 2023 – 3 years since the beginning of the coronavirus disease (COVID)-19 pandemic in Brazil. As a final inclusion criterion, we included all individuals who were hospitalized in Brazil during the COVID-19 pandemic due to infection by the influenza A virus or the influenza B virus and who presented data regarding the hospital outcome in the absence of infection by other viruses, including adenovirus, bocavirus, metapneumovirus, parainfluenza (1, 2, 3 and 4), rhinovirus, severe acute respiratory syndrome coronavirus 2, and respiratory syncytial virus.

The states most affected by the infection, in absolute number, were São Paulo [7,637 (34.6%)], Paraná [2,199 (10.0%)], Rio de Janeiro [1,677 (7.6%)], Minas Gerais [1,121 (5.1%)], and Rio Grande do Sul [1,091 (4.9%)] **(Table 1)**.

TABLE 1. Distribution of recorded cases of infection by influenza A and B viruses and need for hospitalization according to the Brazilian federative units during the period of the coronavirus disease (COVID)-19 pandemic.

States and Federal District	N (%)
Acre	59 (0.3%)
Alagoas	119 (0.5%)
Amazonas	199 (0.9%)
Amapá	24 (0.1%)
Bahia	1,049 (4.8%)
Ceará	924 (4.2%)
Federal District	718 (3.3%)
Espírito Santo	370 (1.7%)
Goiás	614 (2.8%)
Maranhão	594 (2.7%)
Minas Gerais	1,121 (5.1%)
Mato Grosso do Sul	983 (4.5%)
Mato Grosso	205 (0.9%)
Pará	163 (0.7%)
Paraíba	174 (0.8%)
Pernambuco	736 (3.3%)
Piauí	94 (0.4%)
Paraná	2,199 (10.0%)
Rio de Janeiro	1,677 (7.6%)
Rio Grande do Norte	117 (0.5%)
Rondônia	221 (1.0%)
Roraima	13 (0.1%)
Rio Grande do Sul	1,091 (4.9%)
Santa Catarina	563 (2.6%)
Sergipe	352 (1.6%)
São Paulo	7,637 (34.6%)
Tocantins	51 (0.2%)

N, number of patients hospitalized due to the influenza A and/or B virus in Brazil in the 3-year period since the COVID-19 pandemic outbreak; %, percentage; Federal District indicates the city of Brasilia. The data collection period was from December 19, 2019, to April 6, 2023.
The data used in the epidemiological analysis were obtained from information available on the open platform called OpenDataSUS (https://opendatasus.saude.gov.br/). The data were tabulated according to the surveillance of severe acute respiratory infection by the Brazilian Ministry of Health and were computed on the Information System Platform for Influenza Epidemiological Surveillance. The data collection period was from December 19, 2019, to April 6, 2023 – 3 years since the beginning of the COVID-19 pandemic in Brazil. As a final inclusion criterion, we included all individuals who were hospitalized in Brazil during the COVID-19 pandemic due to infection with the influenza A virus and/or the influenza B virus and who presented data regarding the hospital outcome in the absence of infection by other viruses, including adenovirus, bocavirus, metapneumovirus, parainfluenza (1, 2, 3 and 4), rhinovirus, severe acute respiratory syndrome coronavirus 2 and respiratory syncytial virus.

We also present the evolution in the absolute and relative number of cases of influenza A and B viruses in hospitalized patients in Brazil **(Figure 2)**. In the evolution of the number of cases of viral infection, it is noteworthy that the influenza A virus presented a greater number of cases of infection requiring hospitalization and that there was a large peak in cases in the period coinciding with the transition between the years 2021 and 2022.

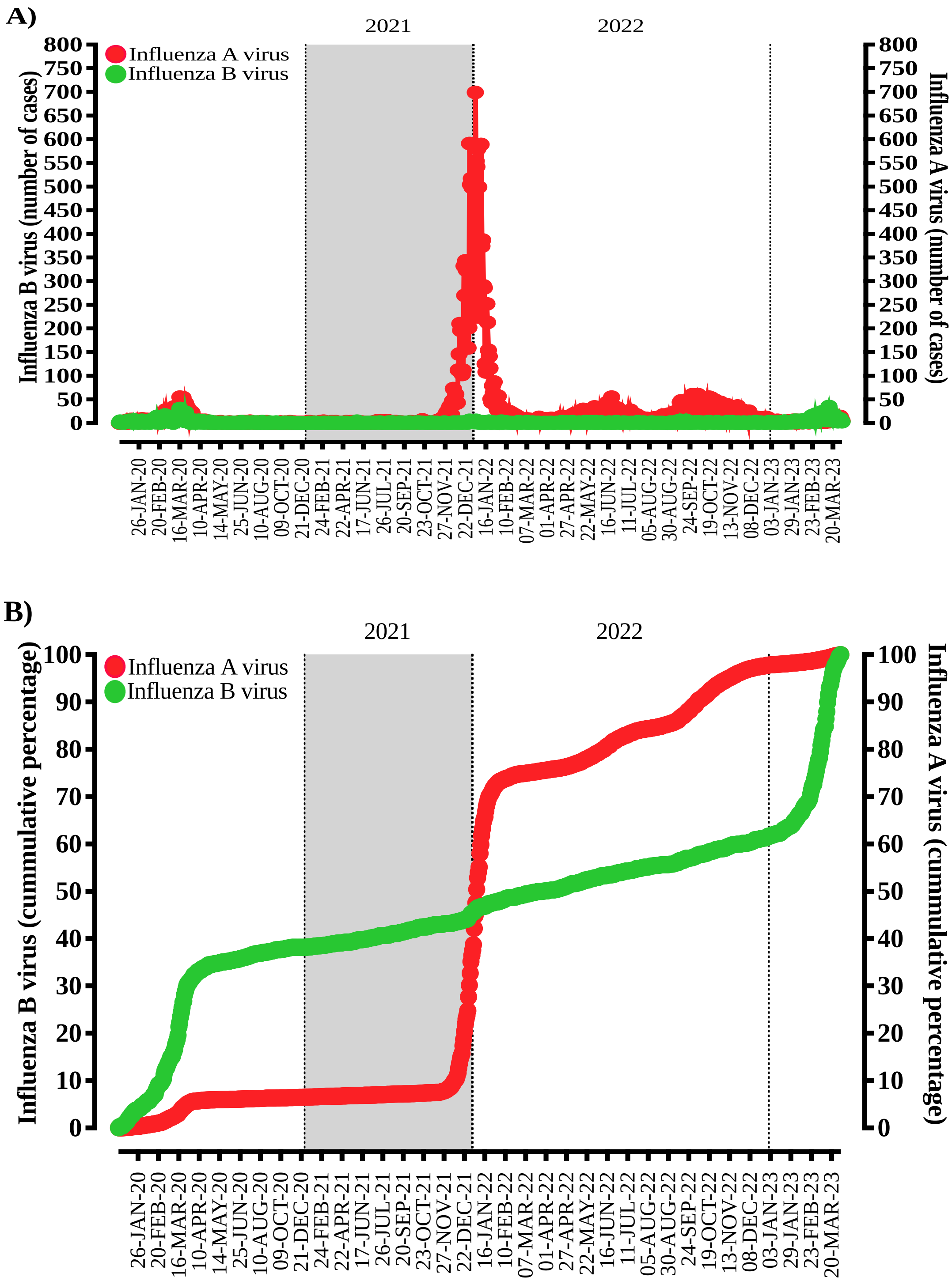

FIGURE 2. Evolution in the absolute (A) and relative (B) number of cases of infection caused by influenza A and B viruses in hospitalized patients in Brazil during the period of the coronavirus disease (COVID)-19

pandemic. A) Absolute data are presented for both viruses evaluated, demonstrating that the influenza A virus presented a greater number of cases of infection requiring hospitalization, with a large peak in the period coinciding with the transition between the years 2021 and 2022. B) Relative data for each type of influenza virus (A or B) responsible for hospitalization is presented as a cumulative percentage. The percentage was calculated separately for each viral type. As described in Table 2, cases of co-detection of influenza A and B viruses were considered infection by influenza A virus for the purposes of descriptive analysis in Figure 2 and in the inferential analyses carried out in the study. The x-axis of the figure shows the temporal demarcation of the data collection period and, for graphic purposes, the periods in which new cases were not computed were disregarded. The data used in the epidemiological analysis were obtained from information available on the open platform called OpenDataSUS (https://opendatasus.saude.gov.br/). The data were tabulated according to the surveillance of severe acute respiratory infection by the Brazilian Ministry of Health and were computed on the Information System Platform for Influenza Epidemiological Surveillance. The data collection period was from December 19, 2019 to April 6, 2023 – 3 years since the beginning of the COVID-19 pandemic in Brazil.

3.2. Description of the viral profile associated with the influenza virus in Brazil during the COVID-19 pandemic

In the sample evaluated, type A influenza virus was identified in 20,330 (92.1%) participants, while 1,737 (7.9%) individuals presented type B influenza virus (**Figure 3; Table 2**). Regarding influenza virus subtypes, due to the limitations of laboratory diagnosis in Brazil, only a few pathogens were completely identified, namely: (i) influenza A (H1N1)pdm09 virus [1,376 (6.2%)], (ii) influenza A virus (H3N2) virus [8,932 (40.5%)], (iii) influenza B Victoria virus [73 (0.3%)] and (iv) influenza B Yamagatha virus [6 (<0.1%)] (**Figure 3; Table 2**). The sample also presented some cases of co-detection between (i) influenza A (H1N1)pdm09 virus and influenza B virus [4 (<0.1%)], (ii) influenza A (H3N2) virus and influenza B virus [2 (<0.1%)] and (iii) influenza A virus and influenza B virus [4 (<0.1%)] (**Figure 3; Table 2**). **Figure 3** shows the patients' mortality rate according to the viral profile, with the rate being higher in the presence of influenza A virus infection (CFR = 11.3%), mainly for the H3N2 subtype (CFR = 19 .6%).

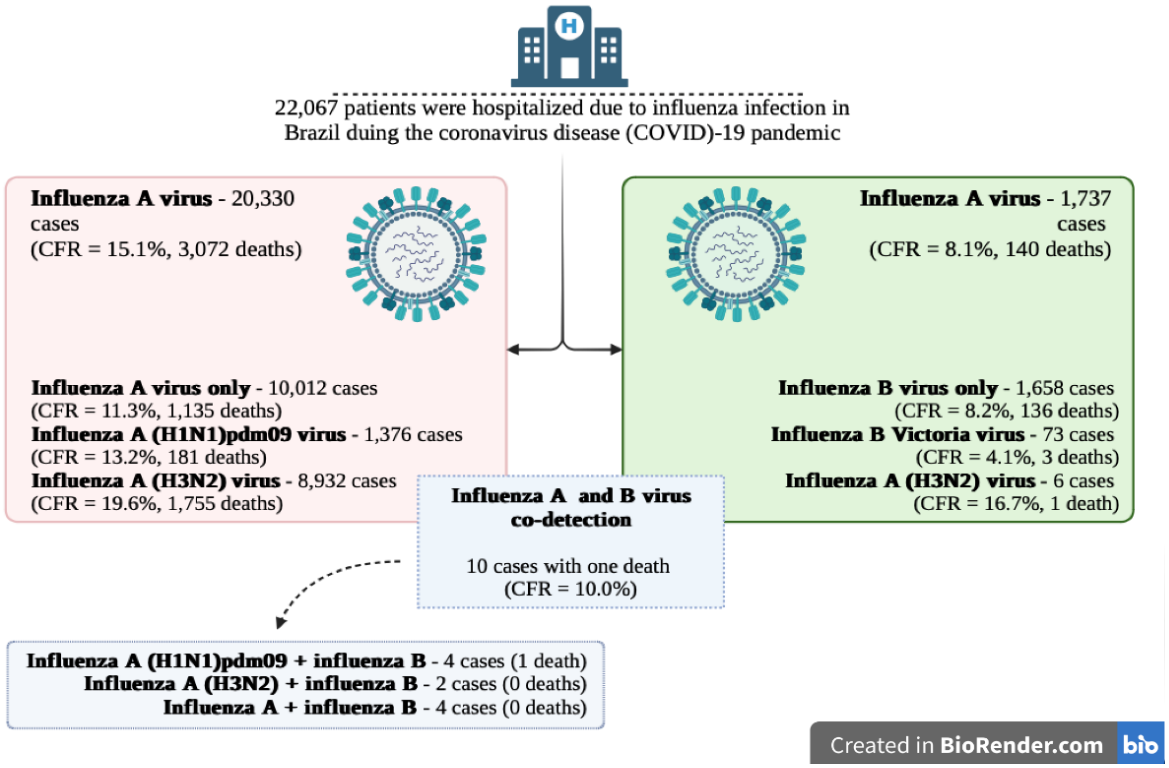

FIGURE 3. Description of the viral profile associated with influenza A and/or B viruses in Brazil during the coronavirus disease (COVID)-19 pandemic. In the figure, the data is presented according to the number of cases and the number of deaths. Furthermore, the calculation of the case fatality rate (CFR) was carried out according to the following formula: [number of deaths/number of cases of hospitalization and with virus infection proven by laboratory methods]*100.

The data used in the epidemiological analysis were obtained from information available on the open platform called OpenDataSUS (https://opendatasus.saude.gov.br/). The data were tabulated according to the surveillance of severe acute respiratory infection by the Brazilian Ministry of Health and were computed on the Information System Platform for Influenza Epidemiological Surveillance. The data collection period was from December 19, 2019 to April 6, 2023 – 3 years since the beginning of the coronavirus disease (COVID)-19 pandemic in Brazil. As a final inclusion criterion, we included all individuals who were hospitalized in Brazil during the COVID-19 pandemic due to infection by the influenza A virus or the influenza B virus and who presented data regarding the hospital outcome in the absence of infection by other viruses, including adenovirus, bocavirus, metapneumovirus, parainfluenza (1, 2, 3 and 4), rhinovirus, severe acute respiratory syndrome coronavirus 2, and respiratory syncytial virus.

TABLE 2. Classification of the influenza virus according to subtypes A and B in patients that required hospitalization during the coronavirus disease (COVID)-19 pandemic in Brazil.

Virus Classification	**N (%)**
Influenza A	10,012 (45.4%)
Influenza A (H1N1)pdm09	1,376 (6.2%)
Influenza A (H1N1)pdm09 + influenza B*	4 (<0.1%)
influenza A (H3N2)	8,932 (40.5%)
Influenza A (H3N2) + influenza B*	2 (<0.1%)
Influenza A + influenza B*	4 (<0.1%)
Influenza B	1,658 (7.5%)
Influenza B Victoria	73 (0.3%)
Influenza B Yamagatha	6 (<0.1%)
Grouped Classification	**N (%)**
Influenza A	20,330 (92.1%)
Influenza B	1,737 (7.9%)

N, number of patients hospitalized due to the influenza A and/or B virus in Brazil in the 3-year period since the COVID-19 pandemic outbreak; %, percentage.
*, the patients were grouped as infected by the influenza A virus for the classification used in the inference statistical analysis.
The data used in the epidemiological analysis were obtained from information available on the open platform called OpenDataSUS (https://opendatasus.saude.gov.br/). The data were tabulated according to the surveillance of severe acute respiratory infection by the Brazilian Ministry of Health and were computed on the Information System Platform for Influenza Epidemiological Surveillance. The data collection period was from December 19, 2019, to April 6, 2023 – 3 years since the beginning of the COVID-19 pandemic in Brazil. As a final inclusion criterion, we included all individuals who were hospitalized in Brazil during the COVID-19 pandemic due to infection with the influenza A virus and/or the influenza B virus and who presented data regarding the hospital outcome in the absence of infection by other viruses, including adenovirus, bocavirus, metapneumovirus, parainfluenza (1, 2, 3 and 4), rhinovirus, severe acute respiratory syndrome coronavirus 2 and respiratory syncytial virus.

3.3. Description of clinical and epidemiological markers of patients hospitalized due to influenza virus infection

In this study, some markers were excluded due to the high occurrence of missing data, namely [number of missing cases (percentage relative to the sample of cases evaluated)]: (i) education [14,367 (65.1%)], (ii) living in a region with a flu outbreak [20,803 (94.3%)], (iii) presence of abdominal pain [8,956 (40.6%)], (iv) presence of loss of smell [9,202 (41.7%)], (v) presence of loss of taste [9,251 (41.9%)], (vi) vaccination status in recent years against the influenza virus [14,449 (65.5%)], (vii) type of antivirals used to manage clinical signs and symptoms in the face of viral infection [16,398 (74.3%)] and (viii) results obtained in the lung imaging examination performed through chest X-ray [15,549 (70.5%)] and in the high-resolution computed tomography of the chest [17,643 (80.0%)].

Among patients infected with the influenza A or B virus in Brazil during the COVID-19 pandemic, there was a predominance of females [11,855 (53.7%)] and individuals who self-declared as being of the white race [13,708 (62.1%)] or multiracial background [7,266 (32.9%)] (**Table 3**). The age groups with the highest prevalence of infection were, respectively, 25 to 60 years [5,381 (24.4%)], 1 to 12 years [4,626 (21.0%)] and 73 to 85 years [3,923 (17.0%)] 8%)] (**Table 3**). Most of the study participants lived in urban areas at the time of hospitalization [21,006 (95.2%)] (Table 3). Nosocomial infection occurred in 365 (1.7%) individuals; Furthermore, the most frequent clinical signs and symptoms were mainly of respiratory origin, including cough [19,719 (89.4%)], fever [17,886 (81.1%)], dyspnea [15,903 (72.1%)], respiratory discomfort [14,006 (63.5%)] and presence of peripheral oxygen saturation <95% [13,000 (58.9%)] (**Table 3**). Regarding comorbidities, a total of 12,224 (55.4%) individuals had at least one positive personal history. Among those, the most frequent were cardiomyopathy [8,014 (36.3%)], diabetes mellitus [6,093 (27.6%)], chronic respiratory disease [3,543 (16.1%)], asthma [1,963 (8.9%)] and neurological disease [1,792 (8.1%)] (**Table 3**).

The use of antivirals to treat the influenza signs and symptoms was described in 5,848 (26.5%) cases (**Table 3**). Treatment in the ICU was required by 6,277 (28.4%) individuals, and most of them also required ventilatory support [13,046 (59.2%)], both (i) non-invasive [10,759 (48.8%)] and (ii) invasive [2,287 (10.4%)], while 9,021 (40.9%) were not subjected to ventilatory support (**Table 3**). The most reported hospital outcome criterion was laboratory [21,797 (98.8%)]. Most of the patients hospitalized due to influenza virus infection were clinically cured (discharged from hospital) [18,855 (85.4%)], while death was reported in 3,212 (14.6%) cases (**Table 3)**.

TABLE 3. Description of the clinical and epidemiological markers evaluated in the study of recorded cases of infection by influenza A and B viruses and the need for hospitalization during the period of the coronavirus disease (COVID)-19 pandemic in Brazil.

Marker	Group	N (%)
Sex	Male	10,212 (46.3%)
	Female	11,855 (53.7%)
Age	<1 year old	1,288 (5.8%)
	1 to 12 years old	4,626 (21.0%)
	13 to 24 years old	1,595 (7.2%)
	25 to 60 years old	5,381 (24.4%)
	61 to 72 years old	3,134 (14.2%)
	73 to 85 years old	3,923 (17.8%)
	+85 years old	2,120 (9.6%)
Race	White	13,708 (62.1%)
	Black	840 (3.8%)
	Asian	163 (0.7%)
	Multiracial background*	7,266 (32.9%)
	Indigenous	90 (0.4%)
Place of residence	Urban	21,006 (95.2%)
	Peri-urban	875 (4.0%)
	Rural	186 (0.8%)
Nosocomial infection	Yes	365 (1.7%)
	No	21,702 (98.3%)
Clinical signs and symptoms upon hospitalization		
Fever	Yes	17,886 (81.1%)
	No	4,181 (18.9%)
Cough	Yes	19,719 (89.4%)
	No	2,348 (10.6%)
Sore throat	Yes	4,501 (20.4%)
	No	17,566 (79.6%)
Dyspnea	Yes	15,903 (72.1%)
	No	6,164 (27.9%)
Respiratory distress	Yes	14,006 (63.5%)
	No	8,061 (36.5%)
Peripheral oxygen saturation	<95%	13,000 (58.9%)
	≥95%	9,067 (41.1%)
Diarrhea	Yes	1,662 (7.5%)
	No	20,405 (92.5%)
Vomit	Yes	2,288 (10.4%)
	No	19,779 (89.6%)
Fatigue and/or asthenia	Yes	6,485 (29.4%)

	No	15,582 (70.6%)
Other symptoms	Yes	10,641 (48.2%)
	No	11,426 (51.8%)
Comorbidities described upon hospitalization		
Risk factor (any comorbidity)	Yes	12,224 (55.4%)
	No	9,843 (44.6%)
Cardiomyopathy	Yes	8,014 (36.3%)
	No	14,053 (63.7%)
Hematological disease	Yes	279 (1.3%)
	No	21,788 (98.7%)
Down Syndrome	Yes	87 (0.4%)
	No	21,980 (99.6%)
Liver disease	Yes	185 (0.8%)
	No	21,882 (99.2%)
Asthma	Yes	1,963 (8.9%)
	No	20,104 (91.1%)
Diabetes mellitus	Yes	6,093 (27.6%)
	No	15,974 (72.4%)
Neurological disease	Yes	1,792 (8.1%)
	No	20,275 (91.9%)
Chronic respiratory disease	Yes	3,543 (16.1%)
	No	18,524 (83.9%)
Immunosuppression	Yes	656 (3.0%)
	No	21,411 (97.0%)
Kidney disease	Yes	674 (3.1%)
	No	21,393 (96.9%)
Obesity	Yes	803 (3.6%)
	No	21,264 (96.4%)
Other comorbidities	Yes	6,852 (31.1%)
	No	15,215 (68.9%)
Use of antiviral to treat flu signals and symptoms	Yes	5,848 (26.5%)
	No	16,219 (73.5%)
Need for intensive care unit treatment	Yes	6,277 (28.4%)
	No	15,790 (71.6%)
Need for ventilatory support during hospitalization	Invasive	2,287 (10.4%)
	Non-invasive	10,759 (48.8%)
	No	9,021 (40.9%)
Hospital outcome criterion	Laboratory	21,797 (98.8%)
	Clinic	270 (1.2%)
Evolution (patient's outcome)	Cured (hospital discharge)	18,855 (85.4%)
	Death	3,212 (14.6%)

N, number of patients hospitalized due to the influenza A and/or B virus in Brazil in the 3-year period since the COVID-19 pandemic outbreak; %, percentage.

*, in Brazil, individuals are described as multiracial background or *pardo*.

The data used in the epidemiological analysis were obtained from information available on the open platform called OpenDataSUS (https://opendatasus.saude.gov.br/). The data were tabulated according to the surveillance of severe acute respiratory infection by the Brazilian Ministry of Health and were computed on the Information System Platform for Influenza Epidemiological Surveillance. The data collection period was from December 19, 2019, to April 6, 2023 – 3 years since the beginning of the COVID-19 pandemic in Brazil. As a final inclusion criterion, we included all individuals who were hospitalized in Brazil during the COVID-19 pandemic due to infection with the influenza A virus and/or the influenza B virus and who presented data regarding the hospital outcome in the absence of infection by other viruses, including adenovirus, bocavirus, metapneumovirus, parainfluenza (1, 2, 3 and 4), rhinovirus, severe acute respiratory syndrome coronavirus 2 and respiratory syncytial virus.

3.4. Association between clinical and epidemiological markers with the risk of death of hospitalized patients due to influenza virus infection in Brazil

Risk of death was associated with statistical significance of the several clinical and epidemiological markers evaluated in the study. Among the markers, the presence of the influenza A virus, rather than the influenza B virus, was associated with a greater chance of death [OR=2.031 (95%CI=1.701-2.424)] (**Table 4, Figure 4A, Supplementary Table 1**).

Regarding age groups, compared to individuals under the age of 1 year, adults and the elderly were more likely to die: (i) 25 to 60 years [OR=5.681 (95%CI=3.919-8.235)], (ii) 61 to 72 years [OR=11.660 (95%CI=8.041-16.920])], (iii) 73 to 85 years [OR=14.120 (95%CI=9.758-20.420)] and (iv) +85 years [OR= 20.670 (95%CI=14.230-30.020)] (**Table 4, Figure 4A, Supplementary Table 1**).

In the sample, in relation to those self-declared as being of the white race, a higher chance of death was observed for individuals self-declared as being of the black race [OR=1.656 (95%CI=1.386-1.979)], multiracial background [OR=1.444 (95%CI=1.335-1.563)] and indigenous [OR=1.841 (95%CI=1.107-3.061)] (**Table 4, Figure 4A, Supplementary Table 1**). In relation to the place of residence, individuals residing in peri-urban regions [OR=1.577 (95%CI=1.334-1.864)] were more likely to die, while residents of rural regions [OR=0.411 (95%CI=0.229- 0.739) were less likely to die during hospitalization (**Table 4, Figure 4A, Supplementary Table 1**).

The presence of nosocomial infection was also a factor associated with a greater chance of death [OR=1.351 (95%CI=1.036-1.764)], as well as the presence of clinical signs and symptoms, mainly associated with respiratory conditions, such as dyspnea [OR=4.090 (95%CI=3.628-4.610)], respiratory distress [OR=3.777 (95%CI=3.414-4.178)], peripheral oxygen saturation <95% [OR=5.681 (95%CI=5.106-6.322)] and fatigue and asthenia [OR=2.579 (95%CI=2.389-2.784)] (**Table 4, Figure 4A, Supplementary Table 1**).

Among the comorbidities, the presence of at least one personal history [OR=3.484 (95%CI=3.187-3.809)] and, mainly, the presence of chronic respiratory disease [OR=5.267 (95%CI=4.847-5.723)], cardiomyopathy [OR=3.289 (95%CI=3.027-3.532)], diabetes mellitus [OR=3.292 (95%CI=3.048-3.555)], neurological disease [OR=2.868 (95%CI=2.573-3.197)] and liver disease [OR =2.254 (95%CI=1.629-3.119)] were risk factors for death (**Table 4, Figure 4A, Supplementary Table 1**).

Treatment with antivirals to alleviate flu signs and symptoms reduced the chance of death [OR=0.638 (95%CI=0.581-0.700). Furthermore, individuals who required ICU treatment [OR=4.583 (95%CI=4.240-4.954)] and invasive [OR=34.500 (95%CI=30.150-39.480)] and non-invasive ventilatory support [OR=3.989 (95%CI) =3.541-4.494)] were more likely to die (**Table 4, Figure 4A, Supplementary Table 1**).

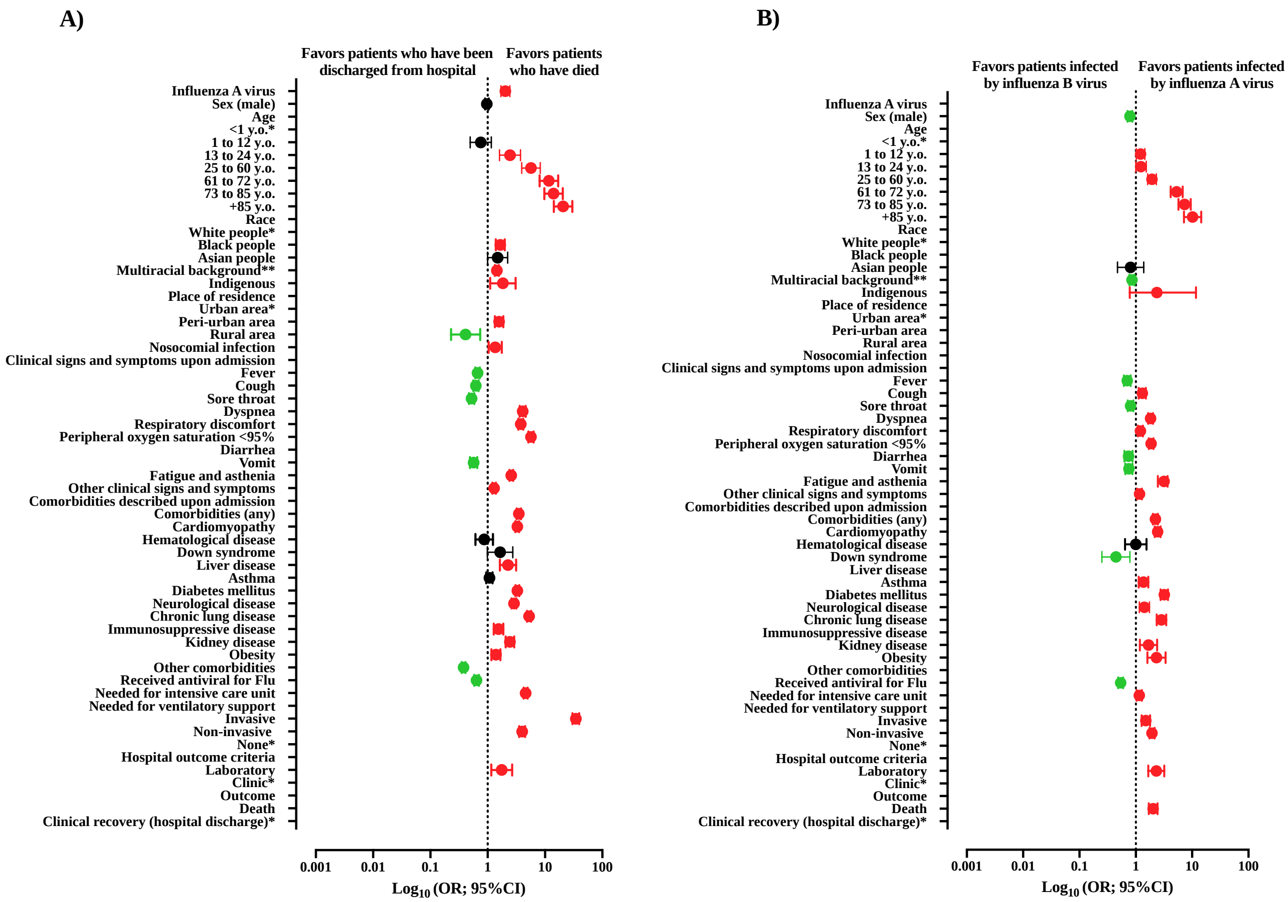

Figure 4. Association of clinical and epidemiological markers with the risk of death and classification as being infected by the influenza A virus rather than the influenza B virus in patients hospitalized due to severe acute respiratory syndrome in Brazil during the period of the coronavirus disease (COVID)-19 pandemic. A) Association of clinical and epidemiological markers with the risk of death. Markers that presented statistical significance in the bivariate analysis, favoring the greatest risk for the patient's progression to death are shown in red. Markers that presented statistical significance in the bivariate analysis, favoring a greater chance of hospital discharge are shown in green. Data that were not statistically significant are shown in black. B) Associations of clinical and epidemiological markers with the chance of being classified as being infected by the influenza A virus rather than the influenza B virus. Markers that presented statistical significance in the bivariate analysis favoring (most common) infection by the influenza virus A are shown in red. Markers that showed statistical significance in the bivariate analysis favoring (most common) infection by the influenza B virus are shown in green. Data that were not statistically significant are shown in black. *, reference group for calculating the Odds Ratio (OR, likelihood ratio); **, in Brazil individuals are described as being mixed race or *pardo*. 95%CI, 95% confidence interval. Data are presented on the log10 scale. The data used in the epidemiological analysis were obtained from information available on the open platform called OpenDataSUS (https://opendatasus.saude.gov.br/). The data were tabulated according to the surveillance of severe acute respiratory infection by the Brazilian Ministry of Health and were computed on the Information System Platform for Influenza Epidemiological Surveillance. The data collection period was from December 19, 2019 to April 6, 2023 – 3 years since the beginning of the coronavirus disease (COVID)-19 pandemic in Brazil. As a final inclusion criterion, we included all individuals who were hospitalized in Brazil during the COVID-19 pandemic due to infection by the influenza A virus or the influenza B virus and who presented data regarding the hospital outcome in the absence of infection by other viruses, including adenovirus, bocavirus, metapneumovirus, parainfluenza (1, 2, 3 and 4), rhinovirus, severe acute respiratory syndrome coronavirus 2, and respiratory syncytial virus.

TABLE 4. Association of clinical and epidemiological markers evaluated in the study with the chance of death and classification as being infected by the influenza A virus rather than the influenza B virus among cases of patients registered with influenza virus infection and requiring hospitalization during the period of the coronavirus disease (COVID)-19 pandemic in Brazil.*

Marker	Groups	Death**	Cured (hospital discharge)**	*P*	Influenza A virus**	Influenza B virus**	*P*	Total
Influenza virus	Influenza A virus	3,072 (15.1%)	17,258 (84.9%)	**<0.001**	NA	NA	NA	20.330
	Influenza B virus	140 (8.1%)	1,597 (91.9%)		NA	NA	NA	1.737
Sex	Male	1,463 (14.3%)	8,749 (85.7%)	0.370	9,313 (45.8%)	899 (51.8%)	**<0.001**	10,212 (46.3%)
	Female	1,749 (14.8%)	10,106 (85.2%)		11,017 (54.2%)	838 (48.2%)		11,855 (53.7%)
Age* **	<1 year old	30 (2.3%)	1,258 (97.7%)		1,086 (5.3%)	202 (11.6%)		1,288 (5.8%)
	1 to 12 years old	82 (1.8%)	4,544 (98.2%)	0.238	4,012 (19.7%)	614 (35.3%)	**0.026**	4,626 (21.0%)
	13 to 24 years old	88 (5.5%)	1,507 (94.5%)	**<0.001**	1,386 (6.8%)	209 (12.0%)	**0.049**	1,595 (7.2%)
	25 to 60 years old	642 (11.9%)	4,739 (88.1%)	**<0.001**	4,910 (24.2%)	471 (27.1%)	**<0.001**	5,381 (24.4%)
	61 to 72 years old	682 (21.8%)	2,452 (78.2%)	**<0.001**	3,028 (14.9%)	106 (6.1%)	**<0.001**	3,134 (14.2%)
	73 to 85 years old	988 (25.2%)	2,935 (74.8%)	**<0.001**	3,826 (18.8%)	97 (5.6%)	**<0.001**	3,923 (17.8%)
	+ 85 years old	700 (33.0%)	1,420 (67.0%)	**<0.001**	2,082 (10.2%)	38 (2.2%)	**<0.001**	2,120 (9.6%)
Race* **	White	1,740 (12.7%)	11,968 (87.3%)		12,672 (62.3%)	1,036 (59.6%)		13,708 (62.1%)
	Black	163 (19.4%)	677 (80.6%)	**<0.001**	791 (3.9%)	49 (2.8%)	0.075	840 (3.8%)
	Asian	29 (17.8%)	134 (82.2%)	0.068	148 (0.7%)	15 (0.9%)	0.522	163 (0.7%)
	Multiracial background[#]	1,261 (17.4%)	6,005 (82.6%)	**<0.001**	6,632 (32.6%)	634 (36.5%)	**0.003**	7,266 (32.9%)
	Indigenous	19 (21.1%)	71 (78.9%)	**0.026**	87 (0.4%)	3 (0.2%)	0.670	90 (0.4%)
Place of residence	Urban	3,017 (14.4%)	17,989 (85.6%)		19,339 (95.1%)	1,667 (96.0%)		21,006 (95.2%)
	Peri-urban	183 (20.9%)	692 (79.1%)	**<0.001**	818 (4.0%)	57 (3.3%)	0.143	875 (4.0%)
	Rural	12 (6.5%)	174 (93.5%)	**0.001**	173 (0.9%)	13 (0.7%)	0.734	186 (0.8%)
Nosocomial Infection	Yes	68 (18.6%)	297 (81.4%)	**0.026**	340 (1.7%)	25 (1.4%)	0.465	365 (1.7)
	No	3,144 (14.5%)	18,558 (85.5%)		19,990 (98.3%)	1,712 (98.6%)		21,702 (98.3%)
Clinical signs and symptoms upon hospitalization								
Fever	Yes	2,417 (13.5%)	15,469 (86.5%)	**<0.001**	16,400 (80.7%)	1,486 (85.5%)	**<0.001**	17,886 (81.1%)
	No	795 (19.0%)	3,386 (81.0%)		3,930 (19.3%)	251 (14.5%)		4,181 (18.9%)
Cough	Yes	2,730 (13.8%)	16,989 (86.2%)	**<0.001**	18,211 (89.6%)	1,508 (86.8%)	**<0.001**	19,719 (89.4%)
	No	482 (20.5%)	1,866 (79.5%)		2,119 (10.4%)	229 (13.2%)		2,348 (10.6%)
Sore throat	Yes	407 (9.0%)	4,094 (91.0%)	**<0.001**	4,088 (20.1%)	413 (23.8%)	**<0.001**	4,501 (20.4%)
	No	2,805 (16.0%)	14,761 (84.0%)		16,242 (79.9%)	1,324 (76.2%)		17,566 (79.6%)
Dyspnea	Yes	2,894 (18.2%)	13,009 (81.8%)	**<0.001**	14,865 (73.1%)	1,038 (59.8%)	**<0.001**	15,903 (72.1%)
	No	318 (5.2%)	5,846 (94.8%)		5,465 (26.9%)	699 (40.2%)		6,164 (27.9%)
Respiratory distress	Yes	2,727 (19.5%)	11,279 (80.5%)	**<0.001**	12,976 (63.8%)	1,030 (59.3%)	**<0.001**	14,006 (63.5%)
	No	485 (6.0%)	7,576 (94.0%)		7,354 (36.2%)	707 (40.7%)		8,061 (36.5%)
Peripheral oxygen saturation	<95%	2,795 (21.5%)	10,205 (78.5%)	**<0.001**	12,225 (60.1%)	775 (44.6%)	**<0.001**	13,000 (58.9%)

	≥95%	417 (4.6%)	8,650 (95.4%)		8,105 (39.9%)	962 (55.4%)		9,067 (41.1%)
Diarrhea	Yes	223 (13.4%)	1,439 (86.6%)	0.171	1,494 (7.3%)	168 (9.7%)	**<0.001**	1,662 (7.5%)
	No	2,989 (14.6%)	17,416 (85.4%)		18,836 (92.7%)	1,569 (90.3%)		20,405 (92.5%)
Vomit	Yes	211 (9.2%)	2,077 (90.8%)	**<0.001**	2,062 (10.1%)	226 (13.0%)	**<0.001**	2,288 (10.4%)
	No	3,001 (15.2%)	16,778 (84.8%)		18,268 (89.9%)	1,511 (87.0%)		19,779 (89.6%)
Fatigue and asthenia	Yes	1,537 (23.7%)	4,948 (76.3%)	**<0.001**	6,271 (30.8%)	214 (12.3%)	**<0.001**	6,485 (29.4%)
	No	1,675 (10.7%)	13,907 (89.3%)		14,059 (69.2%)	1,523 (87.7%)		15,582 (70.6%)
Other symptoms	Yes	1,725 (16.2%)	8,916 (83.8%)	**<0.001**	9,864 (48.5%)	777 (44.7%)	**0.002**	10,641 (48.2%)
	No	1,487 (13.0%)	9,939 (87.0%)		10,466 (51.5%)	960 (55.3%)		11,426 (51.8%)
Comorbidities described upon hospitalization								
Risk factor (any comorbidity)	Yes	2,527 (20.7%)	9,697 (79.3%)	**<0.001**	11,577 (56.9%)	647 (37.2%)	**<0.001**	12,224 (55.4%)
	No	685 (7.0%)	9,158 (93.0%)		8,753 (43.1%)	1,090 (62.8%)		9,843 (44.6%)
Cardiomyopathy	Yes	1,952 (24.4%)	6,062 (75.6%)	**<0.001**	7,669 (37.7%)	345 (19.9%)	**<0.001**	8,014 (36.3%)
	No	1,260 (9.0%)	12,793 (91.0%)		12,661 (62.3%)	1,392 (80.1%)		14,053 (63.7%)
Hematological disease	Yes	36 (12.9%)	243 (87.1%)	0.431	257 (1.3%)	22 (1.3%)	0.993	279 (1.3%)
	No	3,176 (14.6%)	18,612 (85.4%)		20,073 (98.7%)	1,715 (98.7%)		21,788 (98.7%)
Down syndrome	Yes	19 (21.8%)	68 (78.2%)	0.054	73 (0.4%)	14 (0.8%)	**0.004**	87 (0.4%)
	No	3,193 (14.5%)	18,787 (85.5%)		20,257 (99.6%)	1,723 (99.2%)		21,980 (99.6%)
Liver disease	Yes	51 (27.6%)	134 (72.4%)	**<0.001**	177 (0.9%)	8 (0.5%)	0.072	185 (0.8%)
	No	3,161 (14.4%)	18,721 (85.6%)		20,153 (99.1%)	1,729 (99.5%)		21,882 (99.2%)
Asthma	Yes	301 (15.3%)	1,662 (84.7%)	0.306	1,845 (9.1%)	118 (6.8%)	**0.001**	1,963 (8.9%)
	No	2,911 (14.5%)	17,193 (85.5%)		18,485 (90.9%)	1,619 (93.2%)		20,104 (91.1%)
Diabetes mellitus	Yes	1,624 (26.7%)	4,469 (73.3%)	**<0.001**	5,897 (29.0%)	196 (11.3%)	**<0.001**	6,093 (27.6%)
	No	1,588 (9.9%)	14,386 (90.1%)		14,433 (71.0%)	1,541 (88.7%)		15,974 (72.4%)
Neurological disease	Yes	543 (30.3%)	1,249 (69.7%)	**<0.001**	1,688 (8.3%)	104 (6.0%)	**0.001**	1,792 (8.1%)
	No	2,669 (13.2%)	17,606 (86.8%)		18,642 (91.7%)	1,633 (94.0%)		20,275 (91.9%)
Chronic respiratory disease	Yes	1,325 (37.4%)	2,218 (62.6%)	**<0.001**	3,428 (16.9%)	115 (6.6%)	**<0.001**	3,543 (16.1%)
	No	1,887 (10.2%)	16,637 (89.8%)		16,902 (83.1%)	1,622 (93.4%)		18,524 (83.9%)
Immunosuppression	Yes	135 (20.6%)	521 (79.4%)	**<0.001**	582 (2.9%)	74 (4.3%)	**0.001**	656 (3.0%)
	No	3,077 (14.4%)	18,334 (85.6%)		19,748 (97.1%)	1,663 (95.7%)		21,411 (97.0%)
Kidney disease	Yes	193 (28.6%)	481 (71.4%)	**<0.001**	641 (3.2%)	33 (1.9%)	**0.004**	674 (3.1%)
	No	3,019 (14.1%)	18,374 (85.9%)		19,689 (96.8%)	1,704 (98.1%)		21,393 (96.9%)
Obesity	Yes	152 (18.9%)	651 (81.1%)	**<0.001**	774 (3.8%)	29 (1.7%)	**<0.001**	803 (3.6%)
	No	3,060 (14.4%)	18,204 (85.6%)		19,556 (96.2%)	1,708 (98.3%)		21,264 (96.4%)
Other comorbidities	Yes	5,234 (76.4%)	1,618 (23.6%)	**<0.001**	6,558 (32.3%)	294 (16.9%)	**<0.001**	6,852 (31.1%)
	No	13,621 (89.5%)	1,594 (10.5%)		13,772 (67.7%)	1,443 (83.1%)		15,215 (68.9%)
Use of antiviral to treat flu signals and symptoms	Yes	630 (10.8%)	5,218 (89.2%)	**<0.001**	5,174 (25.5%)	674 (38.8%)	**<0.001**	5,848 (26.5%)
	No	2,582 (15.9%)	13,637 (84.1%)		15,156 (74.5%)	1,063 (61.2%)		16,219 (73.5%)

Need for intensive care unit treatment	Yes	1,872 (29.8%)	4,405 (70.2%)	**<0.001**	5,828 (28.7%)	449 (25.8%)	**0.012**	6,277 (28.4%)
	No	1,340 (8.5%)	14,450 (91.5%)		14,502 (71.3%)	1,288 (74.2%)		15,790 (71.6%)
Need for ventilatory support during hospitalization	Invasive	1,341 (58.6%)	946 (41.4%)	**<0.001**	2,121 (10.4%)	166 (9.6%)	**<0.001**	2,287 (10.4%)
	Non-invasive	1,515 (14.1%)	9,244 (85.9%)	**<0.001**	10,141 (49.9%)	618 (35.6%)	**<0.001**	10,759 (48.8%)
	No[a]	356 (3.9%)	8,665 (96.1%)		8,068 (39.7%)	953 (54.9%)		9,021 (40.9%)
Hospital outcome criterion	Laboratory	3,188 (14.6%)	18,609 (85.4%)	**0.008**	20,104 (98.9%)	1,693 (97.5%)	**<0.001**	21,797 (98.8%)
	Clinic	24 (8.9%)	246 (91.1%)		226 (1.1%)	44 (2.5%)		270 (1.2%)
Evolution (patient's outcome)	Cured	NA	NA		17,258 (84.9%)	1,597 (91.9%)	**0.001**	18,855 (85.4%)
	Death	NA	NA		3,072 (15.1%)	140 (8.1%)		3,212 (14.6%)

N, number of patients hospitalized due to the influenza virus in Brazil in the 3-year period since the COVID-19 pandemic outbreak; NA, not applicable; %, percentage.

*, the data statistical analysis was performed using the χ^2 test; **, the percentage was calculated per line using the group of each clinical and epidemiological marker evaluated in the study as a reference; ***, age and race classification was carried out in accordance with the literature; #, in Brazil individuals are described as being mixed race or *pardo*; [a], ventilatory support was not offered to the hospitalized patient. Data with significant values are presented in bold. An alpha error of 0.05 was adopted in the statistical analyses carried out in the study. The data used in the epidemiological analysis were obtained from information available on the open platform called OpenDataSUS (https://opendatasus.saude.gov.br/). The data were tabulated according to the surveillance of severe acute respiratory infection by the Brazilian Ministry of Health and were computed on the Information System Platform for Influenza Epidemiological Surveillance. The data collection period was from December 19, 2019 to April 6, 2023 – 3 years since the beginning of the COVID-19 pandemic in Brazil. As a final inclusion criterion, we included all individuals who were hospitalized in Brazil during the COVID-19 pandemic due to infection with the influenza A virus and/or the influenza B virus and who presented data regarding the hospital outcome in the absence of infection by other viruses, including adenovirus, bocavirus, metapneumovirus, parainfluenza (1, 2, 3 and 4), rhinovirus, severe acute respiratory syndrome coronavirus 2 and respiratory syncytial virus.

SUPPLEMENTARY TABLE 1. Association of clinical and epidemiological markers evaluated in the study with the chance of death among cases of patients registered with infection by the influenza A and/or B virus and with need for hospitalization during the period of the coronavirus disease (COVID)-19 pandemic in Brazil.*

Marker	Groups	Death**	Cured (hospital discharge)**	Total	*P*	Odds ratio	95%CI
Influenza virus	Influenza A virus	3,072 (15.1%)	17,258 (84.9%)	20.330	**<0.001**	**2.031**	**1.701-2.424**
	Influenza B virus	140 (8.1%)	1,597 (91.9%)	1.737		1	Reference
Sex	Male	1,463 (14.3%)	8,749 (85.7%)	10.212	0.370	0.966	0.896-1.042
	Female	1,749 (14.8%)	10,106 (85.2%)	11.855		1	Reference
Age* **	<1 year old	30 (2.3%)	1,258 (97.7%)	1.288		1	Reference
	1-12 years old	82 (1.8%)	4,544 (98.2%)	4.626	0.238	0.757	0.496-1.155
	13-24 years old	88 (5.5%)	1,507 (94.5%)	1.595	**<0.001**	**2.449**	**1.607-3.731**
	25-60 years old	642 (11.9%)	4,739 (88.1%)	5.381	**<0.001**	**5.681**	**3.919-8.235**
	61-72 years old	682 (21.8%)	2,452 (78.2%)	3.134	**<0.001**	**11.660**	**8.041-16.920**
	73-85 years old	988 (25.2%)	2,935 (74.8%)	3.923	**<0.001**	**14.120**	**9.758-20.420**
	+ 85 years old	700 (33.0%)	1,420 (67.0%)	2.120	**<0.001**	**20.670**	**14.230-30.020**
Race* **	White	1,740 (12.7%)	11,968 (87.3%)	13.708		1	Reference
	Black	163 (19.4%)	677 (80.6%)	840	**<0.001**	**1.656**	**1.386-1.979**
	Asian	29 (17.8%)	134 (82.2%)	163	0.068	1.489	0.993-2.231
	Multiracial background[#]	1,261 (17.4%)	6,005 (82.6%)	7.266	**<0.001**	**1.444**	**1.335-1.563**
	Indigenous	19 (21.1%)	71 (78.9%)	90	**0.026**	**1.841**	**1.107-3.061**
Place of residence	Urban	3,017 (14.4%)	17,989 (85.6%)	21.006		1	Reference
	Peri-urban	183 (20.9%)	692 (79.1%)	875	**<0.001**	**1.577**	**1.334-1.864**
	Rural	12 (6.5%)	174 (93.5%)	186	**0.001**	**0.411**	**0.229-0.739**
Nosocomial infection	Yes	68 (18.6%)	297 (81.4%)	365	**0.026**	**1.351**	**1.036-1.764**
	No	3,144 (14.5%)	18,558 (85.5%)	21.702		1	Reference
Clinical signs and symptoms in hospitalization							
Fever	Yes	2,417 (13.5%)	15,469 (86.5%)	17.886	**<0.001**	**0.666**	**0.609-0.727**
	No	795 (19.0%)	3,386 (81.0%)	4.181		1	Reference
Cough	Yes	2,730 (13.8%)	16,989 (86.2%)	19.719	**<0.001**	**0.622**	**0.558-0.693**
	No	482 (20.5%)	1,866 (79.5%)	2.348		1	Reference
Sore throat	Yes	407 (9.0%)	4,094 (91.0%)	4.501	**<0.001**	**0.523**	**0.469-0.584**
	No	2,805 (16.0%)	14,761 (84.0%)	17.566		1	Reference
Dyspnea	Yes	2,894 (18.2%)	13,009 (81.8%)	15.903	**<0.001**	**4.090**	**3.628-4.610**
	No	318 (5.2%)	5,846 (94.8%)	6.164		1	Reference
Respiratory distress	Yes	2,727 (19.5%)	11,279 (80.5%)	14.006	**<0.001**	**3.777**	**3.414-4.178**
	No	485 (6.0%)	7,576 (94.0%)	8.061		1	Reference
Peripheral oxygen saturation	<95%	2,795 (21.5%)	10,205 (78.5%)	13.000	**<0.001**	**5.681**	**5.106-6.322**
	≥95%	417 (4.6%)	8,650 (95.4%)	9.067		1	Reference
Diarrhea	Yes	223 (13.4%)	1,439 (86.6%)	1.662	0.171	0.903	0.780-1.045
	No	2,989 (14.6%)	17,416 (85.4%)	20.405		1	Reference
Vomit	Yes	211 (9.2%)	2,077 (90.8%)	2.288	**<0.001**	**0.568**	**0.490-0.658**
	No	3,001 (15.2%)	16,778 (84.8%)	19.779		1	Reference
Fatigue and asthenia	Yes	1,537 (23.7%)	4,948 (76.3%)	6.485	**<0.001**	**2.579**	**2.389-2.784**
	No	1,675 (10.7%)	13,907 (89.3%)	15.582		1	Reference
Other symptoms	Yes	1,725 (16.2%)	8,916 (83.8%)	10.641	**<0.001**	**1.293**	**1.200-1.394**
	No	1,487 (13.0%)	9,939 (87.0%)	11.426		1	Reference
Comorbidities described upon hospitalization							
Risk factor (any comorbidity)	Yes	2,527 (20.7%)	9,697 (79.3%)	12.224	**<0.001**	**3.484**	**3.187-3.809**
	No	685 (7.0%)	9,158 (93.0%)	9.843		1	Reference
Cardiomyopathy	Yes	1,952 (24.4%)	6,062 (75.6%)	8.014	**<0.001**	**3.289**	**3.027-3.532**
	No	1,260 (9.0%)	12,793 (91.0%)	14.053		1	Reference
Hematological disease	Yes	36 (12.9%)	243 (87.1%)	279	0.431	0.868	0.611-1.234
	No	3,176 (14.6%)	18,612 (85.4%)	21.788		1	Reference

Down Syndrome	Yes	19 (21.8%)	68 (78.2%)	87	0.054	1.644	0.987-2.738
	No	3,193 (14.5%)	18,787 (85.5%)	21.980		1	Reference
Liver disease	Yes	51 (27.6%)	134 (72.4%)	185	**<0.001**	**2.254**	**1.629-3.119**
	No	3,161 (14.4%)	18,721 (85.6%)	21.882		1	Reference
Asthma	Yes	301 (15.3%)	1,662 (84.7%)	1.963	0.306	1.070	0.940-1.217
	No	2,911 (14.5%)	17,193 (85.5%)	20.104		1	Reference
Diabetes mellitus	Yes	1,624 (26.7%)	4,469 (73.3%)	6.093	**<0.001**	**3.292**	**3.048-3.555**
	No	1,588 (9.9%)	14,386 (90.1%)	15.974		1	Reference
Neurological disease	Yes	543 (30.3%)	1,249 (69.7%)	1.792	**<0.001**	**2.868**	**2.573-3.197**
	No	2,669 (13.2%)	17,606 (86.8%)	20.275		1	Reference
Chronic respiratory disease	Yes	1,325 (37.4%)	2,218 (62.6%)	3.543	**<0.001**	**5.267**	**4.847-5.723**
	No	1,887 (10.2%)	16,637 (89.8%)	18.524		1	Reference
Immunosuppression	Yes	135 (20.6%)	521 (79.4%)	656	**<0.001**	**1.544**	**1.273-1.873**
	No	3,077 (14.4%)	18,334 (85.6%)	21.411		1	Reference
Kidney disease	Yes	193 (28.6%)	481 (71.4%)	674	**<0.001**	**2.442**	**2.057-2.899**
	No	3,019 (14.1%)	18,374 (85.9%)	21.393		1	Reference
Obesity	Yes	152 (18.9%)	651 (81.1%)	803	**<0.001**	**1.389**	**1.159-1.664**
	No	3,060 (14.4%)	18,204 (85.6%)	21.264		1	Reference
Other comorbidities	Yes	5,234 (76.4%)	1,618 (23.6%)	6.852	**<0.001**	**0.379**	**0.351-0.409**
	No	13,621 (89.5%)	1,594 (10.5%)	15.215		1	Reference
Use of antiviral to treat flu signals and symptoms	Yes	630 (10.8%)	5,218 (89.2%)	5.848	**<0.001**	**0.638**	**0.581-0.700**
	No	2,582 (15.9%)	13,637 (84.1%)	16.219		1	Reference
Need for intensive care unit treatment	Yes	1,872 (29.8%)	4,405 (70.2%)	6.277	**<0.001**	**4.583**	**4.240-4.954**
	No	1,340 (8.5%)	14,450 (91.5%)	15.790		1	Reference
Need for ventilatory support	Invasive	1,341 (58.6%)	946 (41.4%)	2.287	**<0.001**	**34.500**	**30.150-39.480**
	Non-invasive	1,515 (14.1%)	9,244 (85.9%)	10.759	**<0.001**	**3.989**	**3.541-4.494**
	No[a]	356 (3.9%)	8,665 (96.1%)	9.021		1	Reference
Hospital outcome criterion	Laboratory	3,188 (14.6%)	18,609 (85.4%)	21.797	**0.008**	**1.756**	**1.153-2.675**
	Clinic	24 (8.9%)	246 (91.1%)	270		1	Reference

N, number of patients hospitalized due to the influenza virus in Brazil in the 3-year period since the COVID-19 pandemic outbreak; %, percentage; 95%CI, 95% confidence interval.

*, the data statistical analysis was performed using the χ^2 test; **, the percentage was calculated per line using the group of each clinical and epidemiological marker evaluated in the study as a reference; ***, age and race classification was carried out in accordance with the literature; #, in Brazil individuals are described as being mixed race or *pardo*; [a], ventilatory support was not offered to the hospitalized patient. Data with significant values are presented in bold. An alpha error of 0.05 was adopted in the statistical analyses carried out in the study. The data used in the epidemiological analysis were obtained from information available on the open platform called OpenDataSUS (https://opendatasus.saude.gov.br/). The data were tabulated according to the surveillance of severe acute respiratory infection by the Brazilian Ministry of Health and were computed on the Information System Platform for Influenza Epidemiological Surveillance. The data collection period was from December 19, 2019 to April 6, 2023 – 3 years since the beginning of the COVID-19 pandemic in Brazil. As a final inclusion criterion, we included all individuals who were hospitalized in Brazil during the COVID-19 pandemic due to infection with the influenza A virus and/or the influenza B virus and who presented data regarding the hospital outcome in the absence of infection by other viruses, including adenovirus, bocavirus, metapneumovirus, parainfluenza (1, 2, 3 and 4), rhinovirus, severe acute respiratory syndrome coronavirus 2 and respiratory syncytial virus.

3.5. Multivariate analysis to determine the main predictors for greater chance of death among those hospitalized due to influenza A and/or influenza B virus infection during the COVID-19 pandemic period in Brazil

The multivariate analysis was able to obtain significant data to predict the risk of death among those affected by influenza virus infection in Brazil. The markers that showed a statistically significant association included: (i) age [13 to 24 years – OR=2.802 (95%CI=1.778-4.417), 25 to 60 years – OR=5.409 (95%CI=3.637-8.045), 61 to 72 years old – OR=8.041 (95%CI=5.395-11.985), 73 to 85 years old – OR=10.817 (95%CI=7.823-16.067) and +85 years old – OR=19.752 (95%CI=13.232-29.485)] , (ii) race [black – OR=1.860 (IC95%=1.494-2.315), multiracial background – OR=1.795 (IC95%=1.626-1.981) and indigenous – OR=2.596 (IC95%=1.368-4.929)], (iii) peri-urban place of residence [OR=1.410 (95%CI=1.144-1.738)], (iv) presence of nosocomial infection [OR=1.490 (95%CI=1.070-2.076)], (v) clinical signs and symptoms [dyspnea – OR=1.175 (95%CI=1.005-1.375), respiratory distress – OR=1.444 (95%CI=1.260-1.655) and transcutaneous oxygen saturation <95% – OR=1.524 (95%CI=1.321-1.757)], (vi) comorbidities [neurological disease – OR=1.651 (95%CI=1.441-1.891) and chronic respiratory disease – OR=2.114 (95%CI=1.894-3.259)], (vii) need for ICU treatment [OR=1.664 (95%CI=1.502-1.843)] and (viii) need for ventilatory support [invasive – OR=13.751 (95%CI=11.649-16.233) and non-invasive – OR=1.564 (95%CI=1.365-1.792)]. Among the markers that showed a significant association, some demonstrated association with a lower chance of death, among them, the use of antivirals for the treatment of clinical signs and symptoms associated with influenza outstood [OR=0.537 (95%CI=0.478-0.602)] (**Table 5**).

TABLE 5. Multivariate analysis to determine the main death predictors in patients hospitalized due to influenza A and/or B virus infection during the coronavirus disease (COVID)-19 pandemic in Brazil.*

Markers[a]	**B**	**SE**	**Wald**	**df**	***P***	**OR**	**IC95%**
Age							
<1 year old			874.812	6	**<0.001**		
1 to 12 years old	-0.260	0.229	1.296	1	0.255	0.771	0.493-1.207
13 to 24 years old	1.030	0.232	19.692	1	**<0.001**	**2.802**	**1.778-4.417**
25 to 60 years old	1.688	0.202	69.499	1	**<0.001**	**5.409**	**3.637-8.045**
61 to 72 years old	2.085	0.204	104.827	1	**<0.001**	**8.041**	**5.395-11.985**
73 to 85 years old	2.381	0.202	139.178	1	**<0.001**	**10.817**	**7.283-16.067**
+85 years old	2.983	0.204	213.033	1	**<0.001**	**19.752**	**13.232-29.485**
Race							
White			151.490	4	**<0.001**		
Black	0.621	0.112	30.844	1	**<0.001**	**1.860**	**1.494-2.315**
Asian	0.090	0.245	0.136	1	0.712	1.095	0.677-1.770
Multiracial background**	0.585	0.050	134.936	1	**<0.001**	**1.795**	**1.626-1.981**
Indigenous	0.954	0.327	8.512	1	**0.004**	**2.596**	**1.368-4.929**
Place of residence							
Urban			10.611	2	**0.005**		
Peri-urban	0.343	0.107	10.348	1	**0.001**	**1.410**	**1.144-1.738**
Rural	0.207	0.367	0.318	1	0.573	1.230	0.599-2.524
Nosocomial infection	0.399	0.169	5.576	1	**0.018**	**1.490**	**1.070-2.076**
Clinical signs and symptoms							
Cough	-0.550	0.073	57.565	1	**<0.001**	**0.577**	**0.500-0.665**
Sore throat	-0.279	0.067	17.232	1	**<0.001**	**0.756**	**0.663-0.863**
Dyspnea	0.162	0.080	4.097	1	**0.043**	**1.175**	**1.005-1.375**
Respiratory distress	0.368	0.069	28.005	1	**<0.001**	**1.444**	**1.260-1.655**
Peripheral oxygen saturation <95%	0.421	0.073	33.589	1	**<0.001**	**1.524**	**1.321-1.757**
Comorbidities							
Neurological disease	0.501	0.069	52.159	1	**<0.001**	**1.651**	**1.441-1.891**
Chronic respiratory disease	0.748	0.056	178.586	1	**<0.001**	**2.114**	**1.894-2.359**
Kidney disease	0.205	0.108	3.614	1	0.057	1.228	0.994-1.517
Obesity	-0.494	0.111	19.747	1	**<0.001**	**0.610**	**0.491-0.759**
Use of antiviral to treat flu	-0.623	0.058	113.628	1	**<0.001**	**0.537**	**0.478-0.602**
Intensive care unit	0.509	0.052	95.217	1	**<0.001**	**1.664**	**1.502-1.843**
Ventilatory support							
Invasive	2.621	0.085	958.704	1	**<0.001**	**13.751**	**11.649-16.233**
Non-invasive	0.447	0.069	41.597	1	**<0.001**	**1.564**	**1.365-1.792**
None			1,330.611	2	**<0.001**		
Constant (intercept)	-5.004	0.218	527.410	1	**<0.001**	**0.007**	

SE, standard error; df, degrees of freedom; OR, odds ratio; 95%CI, 95% confidence interval.
*, The data collection period was from December 19, 2019 to April 6, 2023 – 3 years since the beginning of the COVID-19 pandemic in Brazil.; **, in Brazil individuals are described as being mixed race or *pardo*.
The multivariate analysis was carried out using the Binary Logistic Regression Model with the Backward Stepwise method. In the regression Logistic Regression model, we presented (i) B coefficient (including SE), which for the constant was called intercept, (ii) the Wald χ^2 test and its significance, (iii) degrees of freedom for the Wald χ^2 test, and (iv) Exp(B), which represents the B coefficient exponentiation B (OR) including its95%CI.
The 0.05 alpha error was adopted in the multivariate analysis.
[a.] Markers inserted in phase 1 of the multivariate analysis ($P \leq 0.05$ in bivariate analysis): (i) viral profile for the influenza A and B types, (ii) age, (iii) race, (iv) place of residence, (v) presence of nosocomial infection, (vi) clinical signs and symptoms (Fever, Cough, Sore throat, Dyspnea, Respiratory distress, Peripheral oxygen saturation <95%, Vomit, fatigue and asthenia), (vii) comorbidities (cardiopathy, liver disease, diabetes mellitus, neurological disease, chronic respiratory disease, immunosuppression, kidney disease, and obesity), (viii) use of antiviral to treat the flu

clinical signs and symptoms, (ix) need for intensive care unit treatment, and (x) need for invasive and non-invasive ventilatory support.

The data used in the epidemiological analysis were obtained from information available on the open platform called OpenDataSUS (https://opendatasus.saude.gov.br/). The data were tabulated according to the surveillance of severe acute respiratory infection by the Brazilian Ministry of Health and were computed on the Information System Platform for Influenza Epidemiological Surveillance. The data collection period was from December 19, 2019 to April 6, 2023 – 3 years since the beginning of the COVID-19 pandemic in Brazil. As a final inclusion criterion, we included all individuals who were hospitalized in Brazil during the COVID-19 pandemic due to infection with the influenza A virus and/or the influenza B virus and who presented data regarding the hospital outcome in the absence of infection by other viruses, including adenovirus, bocavirus, metapneumovirus, parainfluenza (1, 2, 3 and 4), rhinovirus, severe acute respiratory syndrome coronavirus 2 and respiratory syncytial virus.

3.6. Risk for the classification of patients hospitalized due to influenza in Brazil as being infected by the influenza A virus in relation to the influenza B virus.

Infection resulting from the influenza A virus was less likely to occur in males [OR=0.788 (95%CI=0.714-0.869)] and in individuals who self-declared as multiracial background [OR=0.855 (95%CI=0.771-0.948)] (**Table 4, Figure 4B, Supplementary Table 2**). In relation to the age groups evaluated, compared to individuals under the age of 1 year, all others were more likely to be infected by the influenza A virus: (i) 1 to 12 years [OR=1.215 (95% CI=1.023-1.444)], (ii) 13 to 24 years [OR=1.233 (95%CI=1.001-1.529)], (iii) 25 to 60 years [OR=1.939 (95%CI=1.624-2.316)], (iv) 61 to 72 years [OR=5.313 (95%CI=4.159-6.789)], (v) 73 to 85 years [OR=7.337 (95%CI=5.706-9.433)] and (vi) +85 years [OR=10.190 (95CI%=7.151-14.520)] (**Table 4, Figure 4B, Supplementary Table 2**).

Regarding clinical symptoms upon hospitalization, individuals hospitalized due to influenza A virus infection presented a higher frequency of symptoms such as cough [OR=1.305 (95%CI=1.128-1.510)], dyspnea [OR=1.832 (95%CI=1.656-2.026)], respiratory distress [OR=1.211 (95%CI=1.096-1.338)], peripheral oxygen saturation <95% [OR=1.872 (95%CI=1.696-2.066)] and fatigue and asthenia [OR=3.174 (95CI%=2.473-3.674)] (**Table 4, Figure 4B, Supplementary Table 2**). Among the comorbidities, the presence of at least one personal previous history was associated with a higher prevalence of influenza A virus [OR=2.228 (95%CI=2.014-2.465)], especially in individuals diagnosed with diabetes mellitus [OR=3.212 (95%CI=2.760-3.738)], chronic respiratory disease [OR=2.861 (95%CI=2.359-3.468)], cardiomyopathy [OR=2.444 (95%CI=2.165-2.759)], obesity [OR=2.331 (95%CI= 1.604-3.388)], and kidney disease [OR=1.681 (95%CI=1.181-2.394)] (**Table 4, Figure 4B, Supplementary Table 2**). The use of antivirals to manage clinical signs and symptoms associated with influenza was less recurrent in individuals infected with the influenza A virus than with the influenza B virus [OR=0.538 (95%CI=0.486-0.596)] (**Table 4, Figure 4B, Supplementary Table 2**).

The need for ICU admission was more prevalent in individuals infected with the influenza A virus [OR=1.153 (95%CI=1.031-1.289)] (**Table 4, Figure 4B, Supplementary Table 2**). Concomitantly, the same group of patients presented greater demands for invasive [OR=1.509 (95%CI=1.271-1.792)] and non-invasive [OR=1.938 (95%CI=1.744-2.154)] ventilatory support (**Table 4, Figure 4B, Supplementary Table 2**). Moreover, those individuals presented a higher death rate [OR=2.031 (95%CI=1.701-2.424)] and, as hospital outcome criteria, the profile of laboratory tests was more prevalent [OR=2.312 (95%CI=1.668-3.205)] (**Table 4, Figure 4B, Supplementary Table 2**).

SUPPLEMENTARY TABLE 2. Association of clinical and epidemiological markers evaluated in the study with the chance of being classified as being infected by the influenza A virus rather than the influenza B virus among cases of patients registered with influenza virus infection and requiring hospitalization during the coronavirus disease (COVID)-19 pandemic period in Brazil.*

Marker	Group	Influenza A virus**	Influenza B virus**	Total	*P*	Odds ratio	95%CI
Sex	Male	9,313 (45.8%)	899 (51.8%)	10,212 (46.3%)	**<0.001**	**0.788**	**0.714-0.869**
	Female	11,017 (54.2%)	838 (48.2%)	11,855 (53.7%)		1	Reference
Age* **	<1 year old	1,086 (5.3%)	202 (11.6%)	1,288 (5.8%)		1	Reference
	1-12 years old	4,012 (19.7%)	614 (35.3%)	4,626 (21.0%)	**0.026**	**1.215**	**1.023-1.444**
	13-24 years old	1,386 (6.8%)	209 (12.0%)	1,595 (7.2%)	**0.049**	**1.233**	**1.001-1.529**
	25-60 years old	4,910 (24.2%)	471 (27.1%)	5,381 (24.4%)	**<0.001**	**1.939**	**1.624-2.316**
	61-72 years old	3,028 (14.9%)	106 (6.1%)	3,134 (14.2%)	**<0.001**	**5.313**	**4.159-6.789**
	73-85 years old	3,826 (18.8%)	97 (5.6%)	3,923 (17.8%)	**<0.001**	**7.337**	**5.706-9.433**
	+ 85 years old	2,082 (10.2%)	38 (2.2%)	2,120 (9.6%)	**<0.001**	**10.190**	**7.151-14.520**
Race* **	White	12,672 (62.3%)	1,036 (59.6%)	13,708 (62.1%)		1	Reference
	Black	791 (3.9%)	49 (2.8%)	840 (3.8%)	0.075	1.320	0.982-1.773
	Asian	148 (0.7%)	15 (0.9%)	163 (0.7%)	0.522	0.807	0.473-1.377
	Multiracial background[#]	6,632 (32.6%)	634 (36.5%)	7,266 (32.9%)	**0.003**	**0.855**	**0.771-0.948**
	Indigenous	87 (0.4%)	3 (0.2%)	90 (0.4%)	0.670	2.371	0.783-11.740
Place of residence	Urban	19,339 (95.1%)	1,667 (96.0%)	21,006 (95.2%)		1	Reference
	Peri-urban	818 (4.0%)	57 (3.3%)	875 (4.0%)	0.143	1.237	0.941-1.625
	Rural	173 (0.9%)	13 (0.7%)	186 (0.8%)	0.734	1.147	0.651-2.020
Infection nosocomial	Yes	340 (1.7%)	25 (1.4%)	365 (1.7)	0.465	1.165	0.774-1.753
	No	19,990 (98.3%)	1,712 (98.6%)	21,702 (98.3%)		1	Reference
Clinical signs and symptoms upon hospitalization							
Fever	Yes	16,400 (80.7%)	1,486 (85.5%)	17,886 (81.1%)	**<0.001**	**0.705**	**0.614-0.809**
	No	3,930 (19.3%)	251 (14.5%)	4,181 (18.9%)		1	Reference
Cough	Yes	18,211 (89.6%)	1,508 (86.8%)	19,719 (89.4%)	**<0.001**	**1.305**	**1.128-1.510**
	No	2,119 (10.4%)	229 (13.2%)	2,348 (10.6%)		1	Reference
Sore throat	Yes	4,088 (20.1%)	413 (23.8%)	4,501 (20.4%)	**<0.001**	**0.807**	**0.719-0.906**
	No	16,242 (79.9%)	1,324 (76.2%)	17,566 (79.6%)		1	Reference
Dyspnea	Yes	14,865 (73.1%)	1,038 (59.8%)	15,903 (72.1%)	**<0.001**	**1.832**	**1.656-2.026**
	No	5,465 (26.9%)	699 (40.2%)	6,164 (27.9%)		1	Reference
Respiratory distress	Yes	12,976 (63.8%)	1,030 (59.3%)	14,006 (63.5%)	**<0.001**	**1.211**	**1.096-1.338**
	No	7,354 (36.2%)	707 (40.7%)	8,061 (36.5%)		1	Reference
Peripheral oxygen saturation	<95%	12,225 (60.1%)	775 (44.6%)	13,000 (58.9%)	**<0.001**	**1.872**	**1.696-2.066**
	≥95%	8,105 (39.9%)	962 (55.4%)	9,067 (41.1%)		1	Reference
Diarrhea	Yes	1,494 (7.3%)	168 (9.7%)	1,662 (7.5%)	**<0.001**	**0.741**	**0.627-0.876**
	No	18,836 (92.7%)	1,569 (90.3%)	20,405 (92.5%)		1	Reference

Vomit	Yes	2,062 (10.1%)	226 (13.0%)	2,288 (10.4%)	**<0.001**	**0.755**	**0.652-0.874**
	No	18,268 (89.9%)	1,511 (87.0%)	19,779 (89.6%)		1	Reference
Fatigue and asthenia	Yes	6,271 (30.8%)	214 (12.3%)	6,485 (29.4%)	**<0.001**	**3.174**	**2.473-3.674**
	No	14,059 (69.2%)	1,523 (87.7%)	15,582 (70.6%)		1	Reference
Other symptoms	Yes	9,864 (48.5%)	777 (44.7%)	10,641 (48.2%)	**0.002**	**1.164**	**1.055-1.285**
	No	10,466 (51.5%)	960 (55.3%)	11,426 (51.8%)		1	Reference
Comorbidities described upon hospitalization							
Risk factor (any comorbidity)	Yes	11,577 (56.9%)	647 (37.2%)	12,224 (55.4%)	**<0.001**	**2.228**	**2.014-2.465**
	No	8,753 (43.1%)	1,090 (62.8%)	9,843 (44.6%)		1	Reference
Cardiomyopathy	Yes	7,669 (37.7%)	345 (19.9%)	8,014 (36.3%)	**<0.001**	**2.444**	**2.165-2.759**
	No	12,661 (62.3%)	1,392 (80.1%)	14,053 (63.7%)		1	Reference
Hematological disease	Yes	257 (1.3%)	22 (1.3%)	279 (1.3%)	0.993	0.998	0.644-1.547
	No	20,073 (98.7%)	1,715 (98.7%)	21,788 (98.7%)		1	Reference
Down Syndrome	Yes	73 (0.4%)	14 (0.8%)	87 (0.4%)	**0.004**	**0.444**	**0.250-0.787**
	No	20,257 (99.6%)	1,723 (99.2%)	21,980 (99.6%)		1	Reference
Liver disease	Yes	177 (0.9%)	8 (0.5%)	185 (0.8%)	0.072	1.898	0.933-3.861
	No	20,153 (99.1%)	1,729 (99.5%)	21,882 (99.2%)		1	Reference
Asthma	Yes	1,845 (9.1%)	118 (6.8%)	1,963 (8.9%)	**0.001**	**1.369**	**1.129-1.661**
	No	18,485 (90.9%)	1,619 (93.2%)	20,104 (91.1%)		1	Reference
Diabetes mellitus	Yes	5,897 (29.0%)	196 (11.3%)	6,093 (27.6%)	**<0.001**	**3.212**	**2.760-3.738**
	No	14,433 (71.0%)	1,541 (88.7%)	15,974 (72.4%)		1	Reference
Neurological disease	Yes	1,688 (8.3%)	104 (6.0%)	1,792 (8.1%)	**0.001**	**1.422**	**1.159-1.744**
	No	18,642 (91.7%)	1,633 (94.0%)	20,275 (91.9%)		1	Reference
Chronic respiratory disease	Yes	3,428 (16.9%)	115 (6.6%)	3,543 (16.1%)	**<0.001**	**2.861**	**2.359-3.468**
	No	16,902 (83.1%)	1,622 (93.4%)	18,524 (83.9%)		1	Reference
Immunosuppression	Yes	582 (2.9%)	74 (4.3%)	656 (3.0%)	**0.001**	**0.662**	**0.517-0.848**
	No	19,748 (97.1%)	1,663 (95.7%)	21,411 (97.0%)		1	Reference
Kidney disease	Yes	641 (3.2%)	33 (1.9%)	674 (3.1%)	**0.004**	**1.681**	**1.181-2.394**
	No	19,689 (96.8%)	1,704 (98.1%)	21,393 (96.9%)		1	Reference
Obesity	Yes	774 (3.8%)	29 (1.7%)	803 (3.6%)	**<0.001**	**2.331**	**1.604-3.388**
	No	19,556 (96.2%)	1,708 (98.3%)	21,264 (96.4%)		1	Reference
Other comorbidities	Yes	6,558 (32.3%)	294 (16.9%)	6,852 (31.1%)	**<0.001**	**2.337**	**2.055-2.658**
	No	13,772 (67.7%)	1,443 (83.1%)	15,215 (68.9%)		1	Reference
Use of antiviral to treat flu signals and symptoms	Yes	5,174 (25.5%)	674 (38.8%)	5,848 (26.5%)	**<0.001**	**0.538**	**0.486-0.596**
	No	15,156 (74.5%)	1,063 (61.2%)	16,219 (73.5%)		1	Reference
Need for intensive care unit treatment	Yes	5,828 (28.7%)	449 (25.8%)	6,277 (28.4%)	**0.012**	**1.153**	**1.031-1.289**
	No	14,502 (71.3%)	1,288 (74.2%)	15,790 (71.6%)		1	Reference
	Invasive	2,121 (10.4%)	166 (9.6%)	2,287 (10.4%)	**<0.001**	**1.509**	**1.271-1.792**

Need for ventilatory support	Non-invasive	10,141 (49.9%)	618 (35.6%)	10,759 (48.8%)	**<0.001**	**1.938**	**1.744-2.154**
	No[a]	8,068 (39.7%)	953 (54.9%)	9,021 (40.9%)		1	Reference
Hospital outcome criterion	Laboratory	20,104 (98.9%)	1,693 (97.5%)	21,797 (98.8%)	**<0.001**	**2.312**	**1.668-3.205**
	Clinic	226 (1.1%)	44 (2.5%)	270 (1.2%)		1	Reference
Evolution (Patient's outcome)	Cured (hospital discharge)	17,258 (84.9%)	1,597 (91.9%)	18,855 (85.4%)	**0.001**	**2.031**	**1.701-2.424**
	Death	3,072 (15.1%)	140 (8.1%)	3,212 (14.6%)		1	Reference

N, number of patients hospitalized due to the influenza virus in Brazil in the 3-year period since the COVID-19 pandemic outbreak; %, percentage; 95%CI, 95% confidence interval.

*, the data statistical analysis was performed using the χ^2 test; **, the percentage was calculated per line using the group of each clinical and epidemiological marker evaluated in the study as a reference; ***, age and race classification was carried out in accordance with the literature; #, in Brazil individuals are described as being mixed race or *pardo*; [a], ventilatory support was not offered to the hospitalized patient. Data with significant values are presented in bold. An alpha error of 0.05 was adopted in the statistical analyses carried out in the study. The data used in the epidemiological analysis were obtained from information available on the open platform called OpenDataSUS (https://opendatasus.saude.gov.br/). The data were tabulated according to the surveillance of severe acute respiratory infection by the Brazilian Ministry of Health and were computed on the Information System Platform for Influenza Epidemiological Surveillance. The data collection period was from December 19, 2019 to April 6, 2023 – 3 years since the beginning of the COVID-19 pandemic in Brazil. As a final inclusion criterion, we included all individuals who were hospitalized in Brazil during the COVID-19 pandemic due to infection with the influenza A virus and/or the influenza B virus and who presented data regarding the hospital outcome in the absence of infection by other viruses, including adenovirus, bocavirus, metapneumovirus, parainfluenza (1, 2, 3 and 4), rhinovirus, severe acute respiratory syndrome coronavirus 2 and respiratory syncytial virus.

3.7. Multivariate analysis to determine the main predictors for influenza A virus infection in relation to influenza B virus in hospitalized patients during the COVID-19 pandemic period in Brazil

The multivariate analysis obtained significant data to predict the risk of infection by the influenza A virus compared to the influenza B virus in hospitalized patients in Brazil. The markers showing statistically significant association included: (i) age [25 to 60 years – OR=1.657 (95%CI=1.375-1.998), 61 to 72 years – OR=3.851 (95%CI=2.975-4.985), 73 to 85 years old – OR=5.072 (95%CI=3.888-6.617) and +85 years old – OR=7.336 (95%CI=5.095-10.561)], (ii) clinical signs and symptoms [cough – OR=1.212 (95 %IC=1.039-1.414), dyspnea – OR=1.233 (95%CI=1.089-1.396), and fatigue and asthenia – OR=1.972 (95%CI=1.676-2.321)], comorbidities [asthma – OR=1.291 (95%CI=1.054-1.581) and diabetes mellitus – OR=1.346 (95%CI=1.099-1.648)], and need for non-invasive ventilatory support [OR=1.240 (95%CI=1.093-1.406)]. Among the markers that showed a significant association, some demonstrated an association with a lower chance of infection by the influenza A virus in relation to the influenza B virus, among them, the need for hospitalization in the ICU [OR=0.872 (95%CI=0.764- 0.996)] and the use of antivirals for the treatment of clinical signs and symptoms associated with influenza outstood [OR=0.601 (95%CI=0.540-0.668)] (**Table 6**).

TABLE 6. Multivariate analysis to determine the main markers of the influenza A virus infection rather than the influenza B virus in patients hospitalized during the coronavirus disease (COVID)-19 pandemic in Brazil.*

Markers[a]	**B**	**SE**	**Wald**	**df**	***P***	**OR**	**95%CI**
Age							
<1 year old			315.020	6	**<0.001**		
1 to 12 years old	0.172	0.090	3.646	1	0.056	1.188	0.995-1.418
13 to 24 years old	0.105	0.111	0.900	1	0.343	1.111	0.894-1.381
25 to 60 years old	0.505	0.095	28.025	1	**<0.001**	**1.657**	**1.375-1.998**
61 to 72 years old	1.348	0.132	104.770	1	**<0.001**	**3.851**	**2.975-4.985**
73 to 85 years old	1.624	0.136	143.275	1	**<0.001**	**5.072**	**3.888-6.617**
+85 years old	1.993	0.186	114.834	1	**<0.001**	**7.336**	**5.095-10.561**
Race							
White			8.761	4	0.067		
Black	0.277	0.154	3.245	1	0.072	1.320	0.976-1.785
Asian	-0.336	0.284	1.404	1	0.236	0.714	0.410-1.246
Multiracial background**	-0.050	0.054	0.849	1	0.357	0.951	0.855-1.058
Indigenous	0.982	0.594	2.734	1	0.098	2.670	0.834-8.552
Clinical signals and symptoms							
Cough	0.192	0.079	5.997	1	**0.014**	**1.212**	**1.039-1.414**
Sore throat	-0.105	0.063	2.755	1	0.097	0.901	0.796-1.019
Dyspnea	0.209	0.063	10.873	1	**0.001**	**1.233**	**1.089-1.396**
Respiratory distress	-0.368	0.065	32.492	1	**<0.001**	**0.692**	**0.610-0.785**
Peripheral oxygen saturation <95%	0.125	0.068	3.374	1	0.066	1.133	0.992-1.295
Diarrhea	-0.196	0.089	4.895	1	**0.027**	**0.822**	**0.691-0.978**
Fatigue and asthenia	0.679	0.083	66.848	1	**<0.001**	**1.972**	**1.676-2.321**
Comorbidities							
Cardiomyopathy	-0.192	0.085	5.043	1	**0.025**	**0.825**	**0.698-0.976**
Asthma	0.255	0.103	6.117	1	**0.013**	**1.291**	**1.054-1.581**
Diabetes mellitus	0.297	0.103	8.232	1	**0.004**	**1.346**	**1.099-1.648**
Immunosuppression	-0.634	0.133	22.554	1	**<0.001**	**0.531**	**0.408-0.689**
Use of antiviral to treat flu	-0.509	0.054	88.068	1	**<0.001**	**0.601**	**0.540-0.668**
Intensive care unit treatment	-0.136	0.068	4.083	1	**0.043**	**0.872**	**0.764-0.996**
Ventilatory support							
Invasive	0.009	0.107	0.007	1	0.932	1.009	0.818-1.246
Non-invasive	0.215	0.064	11.225	1	**0.001**	**1.240**	**1.093-1.406**
None			13.255	2	**0.001**		
Constant	1.657	0.113	215.155	1	**<0.001**	**5.243**	

SE, standard error; df, degrees of freedom; OR, odds ratio; 95%CI, 95% confidence interval.
*, The data collection period was from December 19, 2019 to April 6, 2023 – 3 years since the beginning of the COVID-19 pandemic in Brazil.; **, in Brazil individuals are described as being mixed race or *pardo*.
The multivariate analysis was carried out using the Binary Logistic Regression Model with the Backward Stepwise method. In the regression Logistic Regression model, we presented (i) B coefficient (including SE), which for the constant was called intercept, (ii) the Wald χ^2 test and its significance, (iii) degrees of freedom for the Wald χ^2 test, and (iv) Exp(B), which represents the B coefficient exponentiation B (OR) including its95%CI.
The 0.05 alpha error was adopted in the multivariate analysis.
[a], Markers inserted in phase 1 of the multivariate analysis ($P \leq 0.05$ in bivariate analysis): (i) viral profile for the influenza A and B types, (ii) age, (iii) race, (iv) place of residence, (v) presence of nosocomial infection, (vi) clinical signs and symptoms (Fever, Cough, Sore throat, Dyspnea, Respiratory distress, Peripheral oxygen saturation<95%, Vomit, fatigue and asthenia), (vii) comorbidities (cardiopathy, liver disease, diabetes mellitus, neurological disease, chronic respiratory disease, immunosuppression, kidney disease, and obesity), (viii) use of antiviral to treat the flu clinical signs and symptoms, (ix) need for intensive care unit treatment, and (x) need for invasive and non-invasive ventilatory support, and (ix) outcome.
The data used in the epidemiological analysis were obtained from information available on the open platform called OpenDataSUS (https://opendatasus.saude.gov.br/). The data were tabulated according to the surveillance of severe

acute respiratory infection by the Brazilian Ministry of Health and were computed on the Information System Platform for Influenza Epidemiological Surveillance. The data collection period was from December 19, 2019 to April 6, 2023 – 3 years since the beginning of the COVID-19 pandemic in Brazil. As a final inclusion criterion, we included all individuals who were hospitalized in Brazil during the COVID-19 pandemic due to infection with the influenza A virus and/or the influenza B virus and who presented data regarding the hospital outcome in the absence of infection by other viruses, including adenovirus, bocavirus, metapneumovirus, parainfluenza (1, 2, 3 and 4), rhinovirus, severe acute respiratory syndrome coronavirus 2 and respiratory syncytial virus.

4. Discussion

The results of this study exposed a new scenario experienced in Brazil during the COVID-19 pandemic, in which there was a significant increase in reports of influenza virus infection requiring hospitalization. States such as São Paulo, Paraná and Rio de Janeiro were severely affected, especially by the type A influenza virus, which presented high peaks of contamination and, consequently, was associated with greater patient mortality. Women and self-declared white people aged 25 to 60 years were more susceptible to contamination by the influenza A or B viruses. The most frequent clinical signs and symptoms were of respiratory origin, including cough, fever, and dyspnea. Regarding patients who required ICU treatment, the majority required ventilatory support and were more likely to die. The use of antivirals to treat clinical signs and symptoms related to influenza was associated with a lower chance of death.

During the COVID-19 pandemic in Brazil, 22,067 cases of influenza virus infection were reported. The predominance of type A influenza virus was noticeable, comprising a significant 92.1% of cases, while type B influenza virus represented only 7.9% of cases. The higher prevalence of influenza A virus is well documented in the literature (32,68). For example, the numbers described in our study are similar to those obtained in an observational study carried out in the United Kingdom that described a higher prevalence of influenza A virus (55.9%) in relation to influenza type B virus (27), as well as in a study carried out in Spain, in which most of the samples were positive for the influenza A virus (60.2%), while 39.8% tested positive for the influenza B virus (69). However, in sporadic cases, influenza B virus infection may prevail over type A. In such context, in China, in the period between 2020-2021, type B influenza viruses were responsible for the majority of influenza infections throughout the country to the detriment of type A influenza viruses, which contrasts with the prevalence of the latter in most countries during the same period (70). The influenza virus is an RNA virus responsible for numerous influenza pandemics over the years, including the Spanish Flu (1918-1919) caused by H1N1, the Asian Flu (1957-1958) whose causal agent is represented by H2N2, the Hong Kong Flu (1968-1969) caused by H3N2 and, more recently, the H1N1pdm09 pandemic in 2009 (45,71–75). The Spanish Flu, in particular, was responsible for millions of deaths. Influenza B pandemics are less common, but also contribute to seasonal epidemics (75).

The physiology of the infection by influenza A and B viruses influences their different prevalences. Virus A shows a remarkable ability to undergo antigenic shifts, allowing new variants to emerge and contributing to seasonal epidemics and pandemics. Such genetic changes occur due to instability in viral genes, challenging acquired immunity. In contrast, the influenza B virus presents a more stable and slower mutation rate, resulting in a predominant main lineage over time. These physiological differences explain the prevalence of virus A in pandemic events and the contribution of virus B to regular seasonal epidemics (76,77).In this study, a small sample of the population was laboratory tested to identify the subtype of the influenza virus, demonstrating that Brazil still lacks laboratory tools, mainly molecular ones, to carry out its epidemiological surveillance (78,79). This fact became even more evident during the COVID-19 pandemic, which highlighted the country's difficulty in promoting the diagnosis of a large part of its population when facing the pandemic situation (4,14,15,33,80–82). However, among those evaluated for viral subtypes, the prevalence of influenza A (H3N2) and influenza A (H1N1)pdm09 outstood. The subtypes (Yamagatha and Victoria) of influenza B virus were rarely identified. A study carried out in the United States of America evaluated samples from 38,995 individuals who were identified at the level of viral subtype (68). Among the samples, higher prevalence of influenza A (H1N1)pdm09 virus (56.6%) was observed, followed by influenza A (H3N2) virus (43.6%) (68). Interestingly, the viral infection seasonal fluctuation was demonstrated as a common factor associated with influenza, since the influenza A (H1N1)pdm09 virus predominated in relation to most of the viruses circulating throughout the country only during the period between October 2018 and early February 2019. From the end of February 2019 onwards, the influenza A (H3N2) virus was detected more frequently when compared to the influenza A (H1N1)pdm09 virus (68). Moreover, regarding the influenza B virus lineage, there was a higher prevalence of the Victoria subtype (63.3%) followed by the Yamagata subtype (36.7%) (68).

Assessment of the viral subtype is essential in several aspects of public health, namely, predicting pandemics, properly formulating seasonal vaccines to ensure efficacy, monitoring antiviral resistance, and effectively implementing control measures in outbreaks. Furthermore, this assessment contributes to understanding the dynamics of influenza in the community, informing public health strategies, and driving scientific research to develop new treatments, thus reducing the death rate due to the virus.

Although the effectiveness of the flu vaccine in a spectrum related to critical illness and death remains poorly characterized, some authors were able to demonstrate, in the period between October 2019 and February 2020, in a sample of 638 hospitalized patients, with an average age of 57 years and with signs of respiratory distress syndrome in the ICU, that 286 patients were treated in the ICU and 42 (6.6%) died during hospitalization. Among cases and controls, respectively, 45% and 61% were vaccinated, resulting in an overall influenza vaccine efficacy of 32%, including 28% against influenza A virus and 52% against influenza B virus. The overall vaccine intake was higher in adults aged 18 to 49 years than in those aged 50 to 64 years and ≥65 years. Overall vaccine efficacy was significantly greater against influenza-associated death (80%) than non-death-associated influenza illness (83).

Beginning in 2019, the Center for Disease Control and Prevention (CDC) of the United States prioritized select groups of high-risk patients for vaccination against the influenza virus, including individuals over the age of 65, young children, and those with neurological conditions, pregnant women, patients with underlying diseases such as asthma, diabetes mellitus, heart disease and immunosuppressed patients (patients infected with the human immunodeficiency virus causing acquired immunodeficiency syndrome and individuals with cancer in a state of immunosuppression) (84). However, in Brazil, a recent study on childhood vaccination coverage (CVC) demonstrated that between 2015 and 2018 there was an increase in CVC in relation to all vaccines evaluated. However, from 2018, after the presidential elections, the CVC reduced significantly, showing an even more pronounced decrease with the start of the COVID-19 pandemic, especially in relation to BCG (bacillus Calmette and Guerin) and pentavalent vaccines which raised questions regarding anti-vaccine movements, highlighting the importance of public management in disseminating information to raise the population's awareness of health problems resulting from reduced CVC (85).

In a study of Phase 4 clinical trials in the era of the COVID-19 pandemic and their importance in the optimization of the vaccination against COVID-19, the authors demonstrated that simultaneous vaccination against COVID-19 and seasonal flu did not increase safety problems, producing acceptable levels of adverse reactions, and preserving antibody responses against SARS-CoV-2. The article also highlighted the issue of implementing health policies, especially public policies related to the coordination of vaccination campaigns against COVID-19 aimed at individuals who have a low immunological response, issues that can be extrapolated to other diseases that require special vaccination schedule, aiming to enable adjustments to the vaccination calendar in national vaccination programs, especially those administered by public health, which is the Brazilian model (10). Moreover, vaccination against the influenza virus was apparently associated with benefits during hospitalization resulting from COVID-19, with a lower death rate observed in Brazil among those vaccinated for both etiological agents (influenza virus and SARS-CoV-2) (18).

Although vaccination is a fundamental pillar in the prevention of infectious diseases, including influenza caused by the influenza virus, growing vaccine hesitancy and anti-vaccine movements have represented challenges for global health, a fact that can be ascribed to several factors, such as misinformation, concerns about safety, distrust in health institutions, or even barriers to access vaccination. During the COVID-19 pandemic, conspiracy theories and false information were rapidly spread on social media, contributing to vaccine hesitancy. These movements could compromise public health efforts, decreasing adherence to vaccination campaigns and increasing the risk of outbreaks of preventable diseases (9,12,86).

The clinical and epidemiological profile of the cases examined outstood for several distinct characteristics. Among the demographic data, there was a prevalence of females and white people, these data is similar to another Brazilian study that showed a higher prevalence of infection in females and in white individuals (87). The most affected age group in this study was associated with young adults (25 and 60 years old), which is also similar to data presented in the literature (32). On the other hand, another large cohort study carried out in New Zealand, with unvaccinated subjects, showed that children presented the highest contamination rate by the influenza virus, which can be explained by the functional immaturity of the immune system and the inability to distinguish the antigens from the influenza virus (88).

The predominance of viral infections was observed in urban areas, which may be related to high population density, physical proximity between people, intensive use of public transport, and crowds in public spaces, in addition to urban environmental conditions leading to viral stability (89). In contrast, those who lived in peri-urban and rural regions were more likely to die, possibly due to specific challenges that hamper their treatment, such as less access to health services, geographical distances that make fast medical care difficult and the presence of older populations susceptible to worse clinical outcomes (90).

Among the symptoms observed, the most prevalent was cough, followed by the presence of fever, dyspnea, respiratory discomfort, peripheral oxygen saturation below 95% and fatigue/asthenia. The clinical markers described are common in respiratory infections associated with viruses, including those caused by the influenza virus (89,91).

Furthermore, it is noteworthy that COVID-19 presents a clinical profile similar to that associated with infections caused by influenza viruses types A and B, as described in the literature (29,92,93). The main clinical signs and symptoms described above and referring to respiratory system impairment were identified as predisposing factors to death. In this context, the respiratory symptoms described may be linked to respiratory failure, while fatigue and asthenia might result from the pronounced systemic response to infection, reflecting the severity of the impact of the virus on the body (94).

Regarding comorbidities, most cases presented at least one underlying condition, the most prevalent were cardiomyopathies, diabetes mellitus, chronic respiratory disease, asthma, and neurological disease. The results of this research are supported by a meta-analysis, which identified advanced age, diabetes mellitus and chronic lung disease as risk elements for hospitalization due to the seasonal influenza virus. On the other hand, being under five years old and having asthma were indicated as risk factors associated with the development of pneumonia (95). Among the comorbidities, the progression to death was more prevalent in the presence of comorbidities common to Brazilians, with emphasis on the presence of chronic respiratory diseases, cardiomyopathies, diabetes mellitus, neurological diseases, and liver disease. The literature indicates that influenza virus infection may be a risk factor for cardiovascular mortality, renal failure and other systemic outcomes (96).

Increased risk of death in influenza virus infection is not limited to pre-existing conditions, it might also occur due to the impairment of the immune system, which makes it difficult to respond effectively against the virus. The presence of systemic inflammation associated with some comorbidities not only intensifies complications but also contributes to the worsening of the situation. In addition, there are factors related to advanced age and the propensity for secondary complications. This intricate interplay of variables makes people with comorbidities more vulnerable to fatal outcomes during the influenza virus infection (97,98).

Given the factors that increase the risk of death from influenza virus infection in people with comorbidities, it is crucial to adopt a comprehensive approach. Priority actions include vaccination campaigns for this risk group, promotion of social isolation to reduce the spread of the virus and improvements in the capacity of the health system to effectively manage serious cases. This includes ensuring adequate resources such as hospital beds, ventilatory support and medicines, in addition to training health professionals to provide specialized care for patients with comorbidities. Furthermore, investing in continuous research and fast dissemination of updated information contributes to a more efficient and informed response to this complex interaction of risk factors (99).

Infection caused by the influenza virus has been related to increased hospitalization and cardiovascular mortality and, in the literature, some authors raise the hypothesis that vaccination against the influenza virus may be associated with a lower risk of occurrence of these events. Thus, in a meta-analysis of six clinical trials with a total of 9,001 patients, the influenza virus vaccine was associated with a lower risk of general cardiovascular events. That study also reported that vaccination against the influenza virus was associated with a 34% lower risk of major adverse cardiovascular events and individuals with recent acute coronary syndrome showed a 45% lower risk. Those authors also emphasized that because influenza represents a threat to the population’s health, including during the COVID-19 pandemic period, it is essential for all countries to carry out mass vaccination (100). Such results can be extrapolated to other cardiovascular diseases, such as stroke. In a population-based study carried out in Canada on a sample of

4,141,209 adults, the authors found that the risk of stroke was reduced among people who had recently been vaccinated against influenza, compared to those who had not. This association extended to the entire adult population and was not limited to individuals with a high initial risk of stroke (101).

Regarding therapeutic interventions, the use of antivirals was recorded in few cases. This restricted use may be ascribed to the variable efficacy of these medications, especially when introduced later in the treatment, and the potential development of viral resistance that limits their application (94). The management of hospitalized patients in our series was mainly carried out outside the ICU and under non-invasive ventilatory support. The data analyzed in this study is similar to a study carried out in Hong Kong that indicated the need for an ICU in only 16.4% of individuals infected with the influenza virus (102).

Death occurred in 14.6% of the cases analyzed, this value was three times higher than that described in a French study that reported a 5.8% rate among 45,819 hospitalized individuals (92). In this study, several factors were significantly associated with a greater probability of death, among them, the identification of the influenza A virus outstood, a fact previously described in the literature (29,68,87,95). The influenza A virus may present greater lethality when compared to influenza B due to factors such as the variable virulence of different subtypes of influenza A, different population susceptibility, mutations (pathogenic variants), and more significant antigenic variations in this viral type, in addition to the greater possibility of affecting more vulnerable demographic groups (41).

The ability of the influenza A virus to undergo more substantial mutations, with concomitant acquisition of pathogenic variants that can modulate the expression and/or activity of surface proteins, contributes to greater partial escape from the existing immunity, which can result in more severe cases of viral infection (41,97). However, it is important to highlight that mortality rates are subject to seasonal variations and depend on the specific characteristics of each flu season, the predominant strains and the effectiveness of vaccination, thus highlighting the importance of continuous annual immunization as a preventive measure (32,103). In such context, a survey of global data demonstrated the following scenarios as extreme: (mortality due to infection by the influenza A/B virus) ranged from 77% in Indonesia to 0.1% in Rwanda, (mortality due to infection by the influenza A virus) ranged from 33% in Vietnam to 0.4% in Kuwait, and (mortality due to influenza B virus infection) ranged from 12.5% in Spain to 0.9% in France 1/2/2025 9:53:00 PM(29).

In this study, the presence of a nosocomial infection, acquired in a hospital environment, was identified as an additional factor that contributes to a greater chance of death. Multiple factors can be associated with nosocomial infection, including the presence of underlying medical conditions and compromised immune systems, which makes them more susceptible to serious complications from influenza, the virus contagious nature, physical proximity between patients, and potential exposure to more virulent viral strains in the hospital environment (104). Therefore, aiming to prevent hospital infections, simple and effective measures should be taken by health professionals such as cleaning hands and materials before contact with each patient and wearing masks that cover the mouth and nose.

Adult and older individuals were more susceptible to death, possibly due to a weakened immune system, making the elderly less able to effectively combat viral infections, a fact that can be intensified by the presence of comorbidities (105). In summary, exacerbated inflammatory response, lower physiological reserve and immune deterioration in the elderly may contribute to a greater risk of serious complications (84,95,106). Furthermore, race was also a predictive element for a higher risk of death, especially among those self-declared as black, multiracial background and indigenous. However, the literature lacks studies that discuss and provide more information regarding the association between the severity of the infection caused by the influenza virus and different racial groups. However, in relation to other viral infections, such as that caused by SARS-CoV-2, the highest death rate among those belonging to the aforementioned racial groups is clear, mainly due to the neglect of public health specific to these groups, as well as their greater difficulty of access to health services (63,94).

The need for ventilatory support was also associated with a greater chance of mortality, highlighting the severity of respiratory compromise as a crucial indicator in the unfavorable progression of the disease. Since the complication resulting from the influenza virus infection can provoke alveolar flooding, this might cause the development of acute respiratory distress syndrome in response to the intrinsic pathogenicity of the virus and related to its specific targeting of the host's airways and alveolar epithelial cells (73,107). Moreover, although the host's robust innate immune response is essential for viral clearance, it may worsen the severity of lung lesions (108). These findings provide valuable insights for the identification of higher-risk populations and more effective intervention strategies in the influenza management.

Furthermore, when comparing the clinical and epidemiological profile of infections caused by influenza A virus and influenza B virus, there are noticeable differences in susceptibility. One of them is a greater prevalence of the influenza A virus in females, especially after puberty, due to the reduction in estrogen and testosterone levels, resulting in an increased chance of inflammation (109–112). Also, when analyzing age groups, greater probability of infection by the influenza B virus was observed in individuals under 1 year old. Other studies also carried out surveys regarding age groups, indicating that patients infected by the influenza A virus were older (89,113). Regarding clinical signs and symptoms, cough, dyspnea, respiratory discomfort, peripheral oxygen saturation below 95%, fatigue, and asthenia were indicators of a greater probability of classification by the influenza A virus, which agrees with the literature (114–116).

Previous comorbidities were also more common among those infected by the influenza A virus, with a study carried out in Italy showing similar results in this regard, demonstrating that 69% of subjects infected by the influenza A virus presented at least one underlying medical condition (117). The need for ICU admission was more prevalent in cases of influenza A virus, highlighting the potential severity of the infection and the importance of intensive interventions in more critical situations. When investigating more serious cases, the analysis revealed a greater demand for ventilatory support, which may indicate the complexity of the respiratory impairment associated with this viral strain. Finally, in terms of outcome, a higher death rate was observed in cases classified as infected by the influenza A virus, indicating a possible differentiation in prognosis when compared to other strains of the virus. This suggests that the type A virus infects most of the population and is associated with higher mortality. However, mortality rates were similar to those obtained in another study carried out in Mexico, which demonstrated that, out of 6,945 confirmed cases of influenza A, 7% were hospitalized and survived and <1% died (118).

When comparing the COVID-19 pandemic with cases of influenza virus infection in Brazil, both are seen to represent significant challenges for the health system and the general population. Although the influenza virus is a known and common pathogen with well-defined seasonality, the rapid spread of SARS-CoV-2 resulted in an unprecedented disease burden. COVID-19 provoked the collapse of healthcare systems around the world due to its high transmissibility and the severity of associated complications, resulting in substantially higher numbers of hospitalizations and deaths than seasonal flu (119).

The COVID-19 patients' hospitalization characteristics and the influenza virus can be compared, highlighting that patients hospitalized due to COVID-19 tend to be predominantly male, elderly and aged between 40 and 59 years, often presenting comorbidities such as diabetes mellitus, chronic cardiovascular, kidney and pulmonary diseases. In contrast, in this study, Brazilian patients hospitalized due to infection by influenza virus were mainly women, aged over 25 years and of white race/color, with a prevalence of comorbidities such as cardiomyopathy, diabetes mellitus, chronic respiratory disease, asthma, and neurological disease (87).

In addition, the COVID-19 pandemic revealed the importance of epidemiological surveillance, fast response capacity, and the need for effective public health measures to control the spread of the virus and mitigate its socioeconomic impacts. While both diseases share similarities in terms of symptoms and preventative measures, the magnitude and consequences of the COVID-19 pandemic underscore the importance of adapted and innovative strategies to address emerging public health challenges (4,120).

Aiming at improving health policies in response to the results found, it is essential to strengthen epidemiological surveillance systems, promote public awareness campaigns, ensure equitable access to tests and treatment, reinforce the health system's response capacity and coordinate actions between different sectors. Investments in research and development are also essential to prepare for future pandemics. These measures aim to protect the population, reduce the incidence and severity of cases and promote a more effective and coordinated response to these infectious diseases.

Limitations

The study has limitations that require caution when interpreting the results. The data source, coming from the "OpenDataSUS" platform, may present representativeness and accuracy restrictions, affecting the generalization of findings. Collecting data exclusively from hospitalized patients introduces potential selection bias, limiting the representativeness of the diversity of influenza virus infection in the general population. Generalization to other populations is restricted by the specificity of the Brazilian context during the COVID-19 pandemic. The definition of comorbidities may lack uniformity and the lack of exploration of socioeconomic variables and vaccination history may impact the understanding of the mortality risk determinants.

5. Conclusion

Patients hospitalized due to influenza virus infection, predominantly type A, were mostly white women over the age of 25 and living in urban areas. They frequently presented respiratory symptoms and previous comorbidities, with a 14.7% mortality rate. The highest risk of death was associated with type A of the virus with the need for ICU and ventilatory support. Other factors were associated with a greater predisposition to death, with emphasis on advanced age, presence of respiratory symptoms and clinical signs, living in peri-urban areas and specific comorbidities.

6. References

1. Wang H, Paulson KR, Pease SA, Watson S, Comfort H, Zheng P, et al. Estimating excess mortality due to the COVID-19 pandemic: a systematic analysis of COVID-19-related mortality, 2020–21. The Lancet. 2022 Apr 16;399(10334):1513–36.

2. Martín Sánchez FJ, Martínez-Sellés M, Molero García JM, Moreno Guillén S, Rodríguez-Artalejo FJ, Ruiz-Galiana J, et al. Insights for COVID-19 in 2023. Rev Esp Quimioter. 2023 Apr;36(2):114–24.

3. Asogwa NU. The harm in and of COVID-19. Dev World Bioeth. 2021 Sep 16;10.1111/dewb.12335.

4. Martins JP, Siqueira BA, Sansone NMS, Marson FAL. COVID-19 in Brazil: A Three-Year Update. Diagnostic Microbiology and Infectious Disease. 2023 Aug 27;116074.

5. Battisti A, Lazzaro G, Varuzza C, Vicari S, Menghini D. Distance learning during COVID-19 lockdown: Impact on adolescents with specific learning disorders and their parents. Front Psychiatry. 2022;13:995484.

6. Zhu C, Zhang T, Li Q, Chen X, Wang K. Depression and Anxiety During the COVID-19 Pandemic: Epidemiology, Mechanism, and Treatment. Neurosci Bull. 2022 Nov 21;39(4):675–84.

7. Deng J, Zhou F, Hou W, Silver Z, Wong CY, Chang O, et al. The prevalence of depression, anxiety, and sleep disturbances in COVID-19 patients: a meta-analysis. Ann N Y Acad Sci. 2021 Feb;1486(1):90–111.

8. Daly M, Robinson E. Depression and anxiety during COVID-19. Lancet. 2022 Feb 5;399(10324):518.

9. Boschiero MN, Palamim CVC, Marson FAL. The hindrances to perform the COVID-19 vaccination in Brazil. Hum Vaccin Immunother. 2021 Nov 2;17(11):3989–4004.

10. Ralise AEG, Camargo TM, Marson FAL. Phase 4 clinical trials in the era of the Coronavirus Disease (COVID-19) pandemic and their importance to optimize the COVID-19 vaccination. Hum Vaccin Immunother. 2023 Aug 1;19(2):2234784.

11. Mohseni Afshar Z, Barary M, Hosseinzadeh R, Karim B, Ebrahimpour S, Nazary K, et al. COVID-19 vaccination challenges: A mini-review. Hum Vaccin Immunother. 2022 Nov 30;18(5):2066425.

12. Boschiero MN, Palamim CVC, Marson F a. L. COVID-19 vaccination on Brazil and the crocodile side-effect. Ethics Med Public Health. 2021 Jun;17:100654.

13. Marson FAL. COVID-19 – 6 million cases worldwide and an overview of the diagnosis in Brazil: a tragedy to be announced. Diagn Microbiol Infect Dis. 2020 Oct;98(2):115113.

14. Marson F a. L, Ortega MM. COVID-19 in Brazil. Pulmonology. 2020;26(4):241–4.

15. Boschiero MN, Palamim CVC, Ortega MM, Mauch RM, Marson FAL. One Year of Coronavirus Disease 2019 (COVID-19) in Brazil: A Political and Social Overview. Ann Glob Health. 2021 May 18;87(1):44.

16. Boschiero MN, Duarte A, Palamim CVC, Alvarez AE, Mauch RM, Marson FAL. Frequency of respiratory pathogens other than SARS-CoV-2 detected during COVID-19 testing. Diagn Microbiol Infect Dis. 2022 Feb;102(2):115576.

17. Lansbury L, Lim B, Baskaran V, Lim WS. Co-infections in people with COVID-19: a systematic review and meta-analysis. J Infect. 2020 Aug;81(2):266–75.

18. Sansone NMS, Boschiero MN, Darrieux M, Marson F a. L. Effectiveness of influenza vaccination against coronavirus disease (COVID)-19 outcomes in hospitalized individuals in Brazil: an epidemiological study. Public Health. 2023 Dec;225:8–11.

19. Krumbein H, Kümmel LS, Fragkou PC, Thölken C, Hünerbein BL, Reiter R, et al. Respiratory viral co-infections in patients with COVID-19 and associated outcomes: A systematic review and meta-analysis. Rev Med Virol. 2023 Jan;33(1):e2365.

20. Conlon A, Ashur C, Washer L, Eagle KA, Hofmann Bowman MA. Impact of the influenza vaccine on COVID-19 infection rates and severity. Am J Infect Control. 2021 Jun;49(6):694–700.

21. Wu X, Cai Y, Huang X, Yu X, Zhao L, Wang F, et al. Co-infection with SARS-CoV-2 and Influenza A Virus

in Patient with Pneumonia, China. Emerg Infect Dis. 2020 Jun;26(6):1324–6.

22. Chotpitayasunondh T, Fischer TK, Heraud JM, Hurt AC, Monto AS, Osterhaus A, et al. Influenza and COVID-19: What does co-existence mean? Influenza Other Respir Viruses. 2021 May;15(3):407–12.

23. Goldman RD. Pediatric influenza in the emergency department: diagnosis and management. Pediatr Emerg Med Pract. 2021 Jan;18(1):1–20.

24. Mena I, Nelson MI, Quezada-Monroy F, Dutta J, Cortes-Fernández R, Lara-Puente JH, et al. Origins of the 2009 H1N1 influenza pandemic in swine in Mexico. eLife. 5:e16777.

25. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012 Dec 15;380(9859):2095–128.

26. Liang Y. Pathogenicity and virulence of influenza. Virulence. 2023 Dec;14(1):2223057.

27. Mabayoje DA, Cutino-Moguel T, Haigh J, Wilks M, Welch CA, Melzer M. The difference in mortality between adult patients with laboratory documented influenza A and B, a single centre retrospective observational study. J Med Virol. 2021 Jun;93(6):3949–54.

28. Ghebrehewet S, MacPherson P, Ho A. Influenza. BMJ. 2016 Dec 7;355:i6258.

29. Pormohammad A, Ghorbani S, Khatami A, Razizadeh MH, Alborzi E, Zarei M, et al. Comparison of influenza type A and B with COVID-19: A global systematic review and meta-analysis on clinical, laboratory and radiographic findings. Rev Med Virol. 2021 May;31(3):e2179.

30. Krammer F, Smith GJD, Fouchier RAM, Peiris M, Kedzierska K, Doherty PC, et al. Influenza. Nat Rev Dis Primers. 2018 Jun 28;4(1):3.

31. Cromer D, van Hoek AJ, Jit M, Edmunds WJ, Fleming D, Miller E. The burden of influenza in England by age and clinical risk group: a statistical analysis to inform vaccine policy. J Infect. 2014 Apr;68(4):363–71.

32. Lafond KE, Porter RM, Whaley MJ, Suizan Z, Ran Z, Aleem MA, et al. Global burden of influenza-associated lower respiratory tract infections and hospitalizations among adults: A systematic review and meta-analysis. PLoS Med. 2021 Mar;18(3):e1003550.

33. Lima TM, Palamim CVC, Melani VF, Mendes MF, Pereira LR, Marson FAL. COVID-19 Underreporting in Brazil among Patients with Severe Acute Respiratory Syndrome during the Pandemic: An Ecological Study. Diagnostics (Basel). 2022 Jun 20;12(6):1505.

34. Palamim CVC, Siqueira BA, Boschiero MN, Marson FAL. Increase in COVID-19 underreporting among 3,282,337 Brazilian hospitalized patients due to SARS: A 3-year report and a major concern for health authorities. Travel Med Infect Dis. 2023;54:102616.

35. Pavlovic JM, Pesut DP, Stosic MB. Influence of the COVID-19 pandemic on the incidence of tuberculosis and influenza. Rev Inst Med Trop Sao Paulo. 2021;63:e53.

36. Sam JIC. The burden of human influenza in Malaysia. Med J Malaysia. 2015 Jun;70(3):127–30.

37. Vemula SV, Zhao J, Liu J, Wang X, Biswas S, Hewlett I. Current Approaches for Diagnosis of Influenza Virus Infections in Humans. Viruses. 2016 Apr 12;8(4):96.

38. Ohmit SE, Monto AS. Symptomatic predictors of influenza virus positivity in children during the influenza season. Clin Infect Dis. 2006 Sep 1;43(5):564–8.

39. Jefferson T, Jones MA, Doshi P, Del Mar CB, Hama R, Thompson MJ, et al. Neuraminidase inhibitors for preventing and treating influenza in adults and children. Cochrane Database Syst Rev. 2014 Apr 10;2014(4):CD008965.

40. Muthuri SG, Venkatesan S, Myles PR, Leonardi-Bee J, Al Khuwaitir TSA, Al Mamun A, et al. Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. Lancet Respir Med. 2014 May;2(5):395–404.

41. Nypaver C, Dehlinger C, Carter C. Influenza and Influenza Vaccine: A Review. J Midwifery Womens Health.

2021 Jan;66(1):45–53.

42. Chen H, Huang Z, Chang S, Hu M, Lu Q, Zhang Y, et al. Immunogenicity and safety of an inactivated SARS-CoV-2 vaccine (Sinopharm BBIBP-CorV) coadministered with quadrivalent split-virion inactivated influenza vaccine and 23-valent pneumococcal polysaccharide vaccine in China: A multicentre, non-inferiority, open-label, randomised, controlled, phase 4 trial. Vaccine. 2022 Aug 26;40(36):5322–32.

43. El Guerche-Séblain C, Etcheto A, Parmentier F, Afshar M, E Macias A, Puentes E, et al. Hospital admissions with influenza and impact of age and comorbidities on severe clinical outcomes in Brazil and Mexico. PLoS One. 2022;17(11):e0273837.

44. Eiros Bouza JM, Pérez Rubio A. Influenza and its impact on mortality. Rev Clin Esp (Barc). 2021 Feb;221(2):97–8.

45. Javanian M, Barary M, Ghebrehewet S, Koppolu V, Vasigala V, Ebrahimpour S. A brief review of influenza virus infection. J Med Virol. 2021 Aug;93(8):4638–46.

46. Hong WC, Sun SF, Hsu CW, Lee DL, Lee CH. Clinical Characteristics and Predictors of Mortality in Critically Ill Adult Patients with Influenza Infection. Int J Environ Res Public Health. 2021 Apr 1;18(7):3682.

47. Read IWO, Musacchio A. Influenza pandemics throughout Brazilian history. Hist Cienc Saude Manguinhos. 2022;29(4):1013–31.

48. Martins-Filho PR, Júnior JM de O, Santos CAD. Case-fatality rates and risk of death from COVID-19 and influenza A/H3N2 in Brazil: A nationwide ecological study. Enferm Infecc Microbiol Clin. 2023 Mar;41(3):199–201.

49. Costa LMCD, Merchan-Hamann E. Pandemias de influenza e a estrutura sanitária brasileira: breve histórico e caracterização dos cenários. Rev Pan-Amaz Saude. 2016 Mar;7(1):11–25.

50. Lyons DM, Lauring AS. Mutation and Epistasis in Influenza Virus Evolution. Viruses. 2018 Aug 3;10(8):407.

51. Griffin EF, Tompkins SM. Fitness Determinants of Influenza A Viruses. Viruses. 2023 Sep 20;15(9):1959.

52. Smyk JM, Szydłowska N, Szulc W, Majewska A. Evolution of Influenza Viruses-Drug Resistance, Treatment Options, and Prospects. Int J Mol Sci. 2022 Oct 13;23(20):12244.

53. The Prevailing Pandemic of Influenza. JAMA. 2020 Apr 14;323(14):1414–5.

54. Jones JC, Yen HL, Adams P, Armstrong K, Govorkova EA. Influenza antivirals and their role in pandemic preparedness. Antiviral Res. 2023 Feb;210:105499.

55. de Souza WM, Buss LF, Candido D da S, Carrera JP, Li S, Zarebski AE, et al. Epidemiological and clinical characteristics of the COVID-19 epidemic in Brazil. Nat Hum Behav. 2020 Aug;4(8):856–65.

56. Baqui P, Bica I, Marra V, Ercole A, van der Schaar M. Ethnic and regional variations in hospital mortality from COVID-19 in Brazil: a cross-sectional observational study. Lancet Glob Health. 2020 Aug;8(8):e1018–26.

57. Boschiero MN, Lutti Filho JR, Ortega MM, Marson FAL. High case fatality rate in individuals with Down syndrome and COVID-19 in Brazil: a two-year report. J Clin Pathol. 2022 Oct;75(10):717–20.

58. Boschiero MN, Sansone NMS, Marson FAL. Hospitalized patients with X-linked disease and infected with SARS-CoV-2 in Brazil: A serial case report from the first two years of the pandemic. Respir Investig. 2023 Jul;61(4):460–6.

59. Boschiero MN, Palamim CVC, Ortega MM, Marson FAL. Clinical characteristics and comorbidities of COVID-19 in unvaccinated patients with Down syndrome: first year report in Brazil. Hum Genet. 2022 Dec;141(12):1887–904.

60. Sansone NMS, Pereira LR, Boschiero MN, Valencise FE, Fraga AMA, Marson FAL. Characterization of Clinical Features of Hospitalized Patients Due to the SARS-CoV-2 Infection in the Absence of Comorbidities Regarding the Sex: An Epidemiological Study of the First Year of the Pandemic in Brazil. Int J Environ Res Public Health. 2022 Jul 22;19(15):8895.

61. Sansone NMS, Boschiero MN, Ortega MM, Ribeiro IA, Peixoto AO, Mendes RT, et al. Severe Acute Respiratory Syndrome by SARS-CoV-2 Infection or Other Etiologic Agents Among Brazilian Indigenous Population:

An Observational Study from the First Year of Coronavirus Disease (COVID)-19 Pandemic. Lancet Reg Health Am. 2022 Apr;8:100177.

62. Sansone NMS, Boschiero MN, Marson FAL. Epidemiologic Profile of Severe Acute Respiratory Infection in Brazil During the COVID-19 Pandemic: An Epidemiological Study. Front Microbiol. 2022;13:911036.

63. Sansone NM, Boschiero MN, Valencise FE, Palamim CV, Marson FA. Characterization of demographic data, clinical signs, comorbidities, and outcomes according to the race in hospitalized individuals with COVID-19 in Brazil: An observational study. J Glob Health. 2022 Jul 25;12:05027.

64. Sansone NMS, Valencise FE, Bredariol RF, Peixoto AO, Marson FAL. Profile of coronavirus disease enlightened asthma as a protective factor against death: An epidemiology study from Brazil during the pandemic. Front Med (Lausanne). 2022;9:953084.

65. Cor ou raça | Educa | Jovens - IBGE [Internet]. [cited 2024 Jan 5]. Available from: https://educa.ibge.gov.br/jovens/conheca-o-brasil/populacao/18319-cor-ou-raca.html

66. Sze S, Pan D, Nevill CR, Gray LJ, Martin CA, Nazareth J, et al. Ethnicity and clinical outcomes in COVID-19: A systematic review and meta-analysis. EClinicalMedicine. 2020 Dec;29:100630.

67. Sullivan KM, Dean A, Soe MM. OpenEpi: A Web-based Epidemiologic and Statistical Calculator for Public Health. Public Health Rep. 2009;124(3):471–4.

68. Xu X, Blanton L, Elal AIA, Alabi N, Barnes J, Biggerstaff M, et al. Update: Influenza Activity in the United States During the 2018-19 Season and Composition of the 2019-20 Influenza Vaccine. MMWR Morb Mortal Wkly Rep. 2019 Jun 21;68(24):544–51.

69. Pérez-García F, Vásquez V, de Egea V, Catalán P, Rodríguez-Sánchez B, Bouza E. Influenza A and B co-infection: a case-control study and review of the literature. Eur J Clin Microbiol Infect Dis. 2016 Jun;35(6):941–6.

70. Huang WJ, Cheng YH, Tan MJ, Liu J, Li XY, Zeng XX, et al. Epidemiological and virological surveillance of influenza viruses in China during 2020-2021. Infect Dis Poverty. 2022 Jun 29;11(1):74.

71. Gu Y, Zuo X, Zhang S, Ouyang Z, Jiang S, Wang F, et al. The Mechanism behind Influenza Virus Cytokine Storm. Viruses. 2021 Jul 14;13(7):1362.

72. Din GU, Hasham K, Amjad MN, Hu Y. Natural History of Influenza B Virus-Current Knowledge on Treatment, Resistance and Therapeutic Options. Curr Issues Mol Biol. 2023 Dec 26;46(1):183–99.

73. Hutchinson EC. Influenza Virus. Trends Microbiol. 2018 Sep;26(9):809–10.

74. Kawaoka Y, Neumann G. Influenza viruses: an introduction. Methods Mol Biol. 2012;865:1–9.

75. Bertucci LM. [Influenza A (H1N1), a new ’Spanish flu’ ?]. Rev Assoc Med Bras (1992). 2009;55(3):230–1.

76. Avni T, Babich T, Nir A, Yahav D, Shaked H, Sorek N, et al. Comparison of clinical outcomes of influenza A and B at the 2017–2018 influenza season: a cohort study. Eur J Clin Microbiol Infect Dis. 2020;39(6):1109–14.

77. Karolyi M, Pawelka E, Daller S, Kaczmarek C, Laferl H, Niculescu I, et al. Is there a clinical difference between influenza A and B virus infections in hospitalized patients? : Results after routine polymerase chain reaction point-of-care testing in the emergency room from 2017/2018. Wien Klin Wochenschr. 2019 Aug;131(15–16):362–8.

78. Freitas FT de M, Pimentel CCP, Bianchini PR, Carvalho RM de, Serafim AP, Costa CFA. Evaluation of Severe Acute Respiratory Syndrome surveillance caused by respiratory viruses in a pediatric unit, 2013 to 2019. Rev Paul Pediatr. 2023;42:e2022215.

79. Cantarino L, Merchan-Hamann E. Influenza in Brazil: surveillance pathways. J Infect Dev Ctries. 2016 Jan 31;10(1):13–23.

80. Simões E Silva AC, Oliveira EA, Martelli H. Coronavirus Disease Pandemic Is a Real Challenge for Brazil. Front Public Health. 2020;8:268.

81. Marques NP, Silveira DMM, Marques NCT, Martelli DRB, Oliveira EA, Martelli-Júnior H. Cancer diagnosis in Brazil in the COVID-19 era. Semin Oncol. 2021 Apr;48(2):156–9.

82. Helsper CW, Van Gils CH, Van Erp NF, Siepman van den Berg MFR, Rogouti O, Van Asselt KM, et al. Impact of the COVID-19 Outbreak-Delayed Referral of Colorectal and Lung Cancer in Primary Care: A National Retrospective Cohort Study. Cancers (Basel). 2023 Feb 25;15(5):1462.

83. Grijalva CG, Feldstein LR, Talbot HK, Aboodi M, Baughman AH, Brown SM, et al. Influenza Vaccine Effectiveness for Prevention of Severe Influenza-Associated Illness Among Adults in the United States, 2019-2020: A Test-Negative Study. Clin Infect Dis. 2021 Oct 20;73(8):1459–68.

84. Mettelman RC, Thomas PG. Human Susceptibility to Influenza Infection and Severe Disease. Cold Spring Harb Perspect Med. 2021 May 3;11(5):a038711.

85. Paula Martins J, Almeida Alatzatianos G, Mendes Camargo T, Augusto Lima Marson F. Overview of childhood vaccination coverage in Brazil and the impact of the COVID-19 pandemic: Is our children's health at risk? A review of pre-COVID-19 periods and during the COVID-19 pandemic. Vaccine X. 2024 Mar;17:100430.

86. Domingues CMAS. Challenges for implementation of the COVID-19 vaccination campaign in Brazil. Cad Saude Publica. 2021 Jan 11;37(1):e00344620.

87. Niquini RP, Lana RM, Pacheco AG, Cruz OG, Coelho FC, Carvalho LM, et al. Description and comparison of demographic characteristics and comorbidities in SARI from COVID-19, SARI from influenza, and the Brazilian general population. Cad Saude Publica. 2020;36(7):e00149420.

88. Huang QS, Bandaranayake D, Wood T, Newbern EC, Seeds R, Ralston J, et al. Risk Factors and Attack Rates of Seasonal Influenza Infection: Results of the Southern Hemisphere Influenza and Vaccine Effectiveness Research and Surveillance (SHIVERS) Seroepidemiologic Cohort Study. J Infect Dis. 2019 Jan 9;219(3):347–57.

89. Pandita AK, Raina D, Arora T, Ohri P. Clinico-epidemiological profile of Influenza A H1N1 cases at a tertiary care institute of Uttarakhand. J Family Med Prim Care. 2021 Mar;10(3):1258–62.

90. Zhai Y, Santibanez TA, Kahn KE, Srivastav A, Walker TY, Singleton JA. Rural, urban, and suburban differences in influenza vaccination coverage among children. Vaccine. 2020 Nov 10;38(48):7596–602.

91. Dwibedi B, Sabat J, Dixit S, Rathore S, Subhadra S, Panda S, et al. Epidemiological and clinical profile of Influenza A(H1N1) pdm09 in Odisha, eastern India. Heliyon. 2019 Oct;5(10):e02639.

92. Piroth L, Cottenet J, Mariet AS, Bonniaud P, Blot M, Tubert-Bitter P, et al. Comparison of the characteristics, morbidity, and mortality of COVID-19 and seasonal influenza: a nationwide, population-based retrospective cohort study. Lancet Respir Med. 2021 Mar;9(3):251–9.

93. Godaert L, Cebille A, Proye E, Dramé M. COVID-19 versus Seasonal Influenza: Comparison of Profiles of Older Adults Hospitalized in a Short-Term Geriatric Ward in France. Am J Trop Med Hyg. 2021 Dec 2;106(1):108–13.

94. de Morais RB, Shimabukuro PMS, Gonçalves TM, Hiraki KRN, Braz-Silva PH, Giannecchini S, et al. Factors associated with death due to severe acute respiratory syndrome caused by influenza: Brazilian population study. J Infect Public Health. 2022 Dec;15(12):1388–93.

95. Mertz D, Kim TH, Johnstone J, Lam PP, Science M, Kuster SP, et al. Populations at risk for severe or complicated influenza illness: systematic review and meta-analysis. BMJ. 2013 Aug 23;347:f5061.

96. GBD 2017 Influenza Collaborators. Mortality, morbidity, and hospitalisations due to influenza lower respiratory tract infections, 2017: an analysis for the Global Burden of Disease Study 2017. Lancet Respir Med. 2019 Jan;7(1):69–89.

97. Keilman LJ. Seasonal Influenza (Flu). Nurs Clin North Am. 2019 Jun;54(2):227–43.

98. Gaitonde DY, Moore FC, Morgan MK. Influenza: Diagnosis and Treatment. Am Fam Physician. 2019 Dec 15;100(12):751–8.

99. Sanz-Muñoz I, Eiros JM. Old and new aspects of influenza. Med Clin (Barc). 2023 Oct 13;161(7):303–9.

100. Behrouzi B, Bhatt DL, Cannon CP, Vardeny O, Lee DS, Solomon SD, et al. Association of Influenza Vaccination With Cardiovascular Risk: A Meta-analysis. JAMA Netw Open. 2022 Apr 1;5(4):e228873.

101. Holodinsky JK, Zerna C, Malo S, Svenson LW, Hill MD. Association between influenza vaccination and risk

of stroke in Alberta, Canada: a population-based study. Lancet Public Health. 2022 Nov;7(11):e914–22.

102. Chan MKT, Chong LY, Achilles Project Working Group in Hong Kong. A prospective epidemiologic survey on the prevalence of foot disease in Hong Kong. J Am Podiatr Med Assoc. 2002 Sep;92(8):450–6.

103. Comas-García A, García-Sepúlveda CA, Méndez-de Lira JJ, Aranda-Romo S, Hernández-Salinas AE, Noyola DE. Mortality attributable to pandemic influenza A (H1N1) 2009 in San Luis Potosí, Mexico. Influenza Other Respir Viruses. 2011 Mar;5(2):76–82.

104. Naudion P, Lepiller Q, Bouiller K. Risk factors and clinical characteristics of patients with nosocomial influenza A infection. J Med Virol. 2020 Aug;92(8):1047–52.

105. Martins Gonçalves T, Mitsue Saruhashi Shimabukuro P, Nakamura Hiraki KR, Braz-Silva PH, Giannecchini S, Kai-Wang To K, et al. Severe acute respiratory syndrome by influenza and factors associated with death in older adults: a population study. J Infect Dev Ctries. 2023 Feb 28;17(2):241–50.

106. Thompson WW, Shay DK, Weintraub E, Brammer L, Cox N, Anderson LJ, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA. 2003 Jan 8;289(2):179–86.

107. Barbosa RPA, Salgado APC, Garcia CC, Filho BG, Gonçalves AP de F, Lima BHF, et al. Protective immunity and safety of a genetically modified influenza virus vaccine. PLoS One. 2014;9(6):e98685.

108. Herold S, Becker C, Ridge KM, Budinger GRS. Influenza virus-induced lung injury: pathogenesis and implications for treatment. Eur Respir J. 2015 May;45(5):1463–78.

109. Rhim JW, Go EJ, Lee KY, Youn YS, Kim MS, Park SH, et al. Pandemic 2009 H1N1 virus infection in children and adults: A cohort study at a single hospital throughout the epidemic. Int Arch Med. 2012 Mar 26;5(1):13.

110. Hackett S, Hill L, Patel J, Ratnaraja N, Ifeyinwa A, Farooqi M, et al. Clinical characteristics of paediatric H1N1 admissions in Birmingham, UK. Lancet. 2009 Aug 22;374(9690):605.

111. Eshima N, Tokumaru O, Hara S, Bacal K, Korematsu S, Tabata M, et al. Sex- and age-related differences in morbidity rates of 2009 pandemic influenza A H1N1 virus of swine origin in Japan. PLoS One. 2011 Apr 29;6(4):e19409.

112. Krementsov DN, Case LK, Dienz O, Raza A, Fang Q, Ather JL, et al. Genetic variation in chromosome Y regulates susceptibility to influenza A virus infection. Proc Natl Acad Sci U S A. 2017 Mar 28;114(13):3491–6.

113. Mehta V, Vasanth V, Balachandran C. Yellow nails following hemodialysis in chronic renal failure: is it yellow nail syndrome or a variant? Dermatol Online J. 2008 Nov 15;14(11):19.

114. Jain S, Kamimoto L, Bramley AM, Schmitz AM, Benoit SR, Louie J, et al. Hospitalized patients with 2009 H1N1 influenza in the United States, April-June 2009. N Engl J Med. 2009 Nov 12;361(20):1935–44.

115. Arbat S, Dave M, Niranjane V, Rahman I, Arbat A. Analyzing the clinical profile of swine flu/influenza A H1N1 infection in central India: a retrospective study. Virusdisease. 2017 Mar;28(1):33–8.

116. Cao B, Li XW, Mao Y, Wang J, Lu HZ, Chen YS, et al. Clinical features of the initial cases of 2009 pandemic influenza A (H1N1) virus infection in China. N Engl J Med. 2009 Dec 24;361(26):2507–17.

117. Bassetti M, Parisini A, Calzi A, Pallavicini FMB, Cassola G, Artioli S, et al. Risk factors for severe complications of the novel influenza A (H1N1): analysis of patients hospitalized in Italy. Clin Microbiol Infect. 2011 Feb;17(2):247–50.

118. Echevarría-Zuno S, Mejía-Aranguré JM, Mar-Obeso AJ, Grajales-Muñiz C, Robles-Pérez E, González-León M, et al. Infection and death from influenza A H1N1 virus in Mexico: a retrospective analysis. Lancet. 2009 Dec 19;374(9707):2072–9.

119. Bastos LS, Niquini RP, Lana RM, Villela DAM, Cruz OG, Coelho FC, et al. COVID-19 and hospitalizations for SARI in Brazil: a comparison up to the 12th epidemiological week of 2020. Cad Saude Publica. 2020;36(4):e00070120.

120. Jefferson T, Dooley L, Ferroni E, Al-Ansary LA, van Driel ML, Bawazeer GA, et al. Physical interventions to interrupt or reduce the spread of respiratory viruses. Cochrane Database Syst Rev. 2023 Jan 30;1(1):CD006207.

4. CAPÍTULO II: Artigo Publicado

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Viral co-detection of influenza virus and other respiratory viruses in hospitalized Brazilian patients during the first three years of the coronavirus disease (COVID)-19 pandemic: an epidemiological profile

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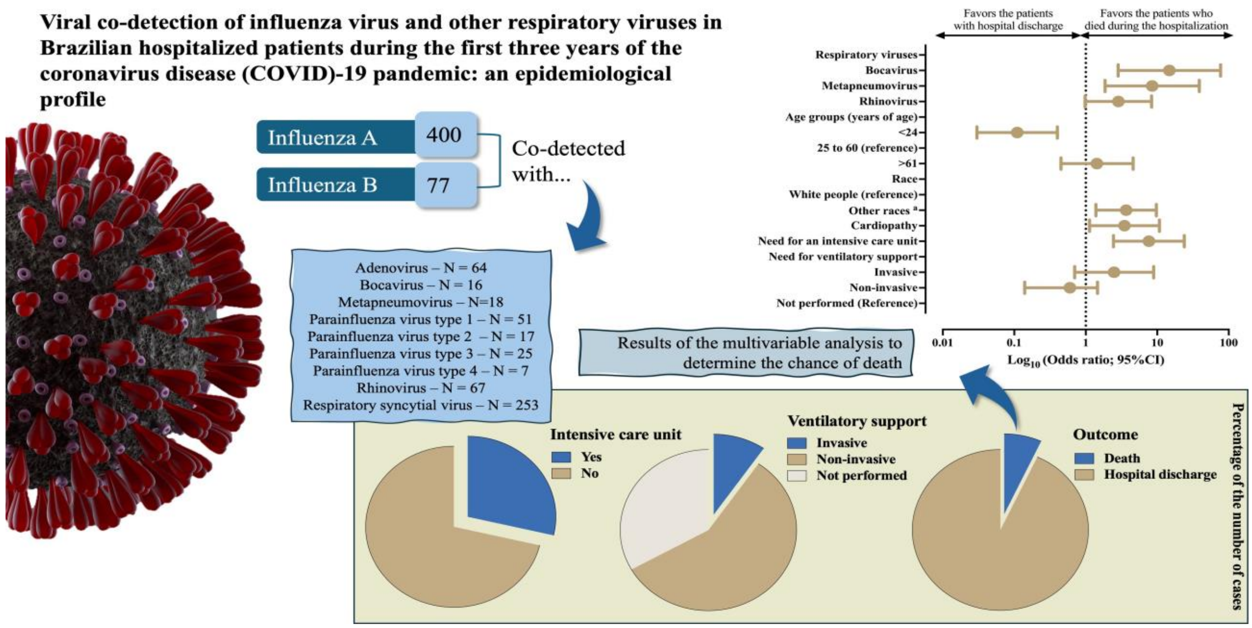
Introduction: In Brazil, few studies were performed regarding the co-detection of respiratory viruses in hospitalized patients. In this way, the study aimed to describe the epidemiological profile of hospitalized patients due to influenza virus infection that presented co-detection with another respiratory virus.

Methods: The epidemiological analysis was made by collecting data from Open-Data-SUS. The study comprised patients infected by the influenza A or B virus with positive co-detection of another respiratory virus, such as adenovirus, bocavirus, metapneumovirus, parainfluenza virus (types 1, 2, 3, and 4), rhinovirus, and respiratory syncytial virus (RSV). The markers [gender, age, clinical signs and symptoms, comorbidities, need for intensive care unit (ICU) treatment, and need for ventilatory support] were associated with the chance of death. The data was collected during the first three years of the coronavirus disease (COVID)-19 pandemic—from December 19, 2019, to April 06, 2023.

Results: A total of 477 patients were included, among them, the influenza A virus was detected in 400 (83.9%) cases. The co-detection occurred, respectively, for RSV (53.0%), rhinovirus (14.0%), adenovirus (13.4%), parainfluenza virus type 1 (10.7%), parainfluenza virus type 3 (5.2%), metapneumovirus (3.8%), parainfluenza virus type 2 (3.6%), bocavirus (3.4%), and parainfluenza virus type 4 (1.5%). The co-detection rate was higher in the male sex (50.7%), age between 0–12 years of age (65.8%), and white individuals (61.8%). The most common clinical symptoms were cough (90.6%), dyspnea (78.8%), and fever (78.6%). A total of 167 (35.0%) people had at least one comorbidity, mainly cardiopathy (14.3%), asthma (8.4%), and diabetes mellitus (7.3%). The need for ICU treatment occurred in 147 (30.8%) cases, with most of them needing ventilatory support (66.8%), mainly non-invasive ones (57.2%). A total of 33 (6.9%) patients died and the main predictors of death were bocavirus infection (OR = 14.78 [95%CI = 2.84–76.98]), metapneumovirus infection (OR = 8.50 [95%CI = 1.86–38.78]), race (other races vs. white people)



GRAPHICAL ABSTRACT
[a]Other races included the patients self-declared as Black people, Asian individuals, Mixed individuals (*Pardos*), and Indigenous peoples. The data are presented using a *log-rank* scale. 95%CI, 95% confidence interval; N, number of individuals (cases).

(OR = 3.67 [95%CI = 1.39–9.74]), cardiopathy (OR = 3.48 [95%CI = 1.13–10.71]), and need for ICU treatment (OR = 7.64 [95%CI = 2.44–23.92]).

Conclusion: Co-detection between the influenza virus and other respiratory viruses occurred, mainly with RSV, rhinovirus, and adenovirus being more common in men, white people, and in the juvenile phase. Co-detection of influenza virus with bocavirus and metapneumovirus was associated with an increased chance of death. Other factors such as race, cardiopathy, and the need for an ICU were also associated with a higher chance of death.

KEYWORDS

adenovirus, bocavirus, influenza virus, metapneumovirus, parainfluenza virus, respiratory syncytial virus, severe acute respiratory syndrome coronavirus 2, rhinovirus

1 Introduction

The flu seasonality is marked by a high incidence of acute respiratory infection, which is frequently associated with enhanced hospitalizations due to viral infections. The main virus responsible for respiratory infection is the influenza virus. Hospitalizations resulting from infection with this virus represent an ongoing challenge for healthcare professionals, due to its ability to develop into more serious complications and even death, especially in high-risk groups (Iuliano et al., 2018; Chu et al., 2020; Lafond et al., 2021).

According to the World Health Organization, the incidence of influenza worldwide can be up to 1 billion cases, being the most common respiratory infection (The burden of Influenza, 2024). Nearly 3–5 million cases of influenza can develop into severe cases, with the need for hospitalizations, being that, among those hospitalized with influenza, severe cases can vary between 5–24% (Ao et al., 2019). Most of the patients who needed an intensive care unit (ICU) or even those who died were children, had comorbidities, were also diagnosed with pneumonia, lived in large households, and prior seeking care before hospitalization (Ao et al., 2019). Furthermore, influenza infection has a relatively high mortality, with nearly 290–650 thousand deaths annually (The burden of Influenza, 2024).

The co-detection of the influenza virus and other viral agents is frequent and has significant implications for the epidemiology and treatment of the patient (Trenholme et al., 2017; Choe et al., 2020). The precise identification of these additional viruses can be fundamental for the understanding of the disease severity and to evaluate the clinical outcomes and enhanced rate of hospitalization, by providing valuable information for infection prevention and control (Pinky and Dobrovolny, 2016; Szymański et al., 2017).

Furthermore, a recent meta-analysis suggests that the co-infection of the influenza virus and other respiratory viruses, mainly the severe acute respiratory syndrome virus (SARS-CoV-2), can be associated with more severe and worse outcomes (Yan et al., 2023).

In Brazil, respiratory co-infections have a high prevalence despite the difficulty in identifying the etiological agent (Boschiero et al., 2022a). Frequently, the symptoms are treated without even considering proper underlying viral etiology, resulting in underreporting and underestimation of the true impact of viral infections (Alexander and Dobrovolny, 2022). The diagnostic gap can affect the efficacy of control and prevention measures, highlighting the urgency of a comprehensive approach in the evaluation of respiratory infections, especially those associated with influenza viruses and other viral agents (Gregianini et al., 2019; Martin-Loeches et al., 2019).

Thus, this study aims to analyze the prevalence of co-detection between influenza virus and other respiratory viruses, except SARS-CoV-2, in Brazilian hospitalized patients during the coronavirus disease (COVID)-19 pandemic.

2 Methods

2.1 General aspects and epidemiology analysis

An epidemiological analysis was conducted using data available at Open-Data-SUS.[1] All the data have been imputed according to the severe acute respiratory infection surveillance [Information System Platform for Influenza Epidemiological Surveillance—from Portuguese *Sistema de Informação da Vigilância Epidemiológica da Gripe* (SIVEP-Gripe)] administered by the Brazilian Ministry of Health, which gained relevance due to the swine flu pandemic (H1N1) (de Souza et al., 2020). The data was collected from December 19, 2019, to April 6, 2023—three years since the beginning of the COVID-19 pandemic in Brazil. The dataset described in the article has been used for several other similar studies, especially, during the COVID-19 pandemic, being considered robust data for studies of epidemiology aiming to increase the quality of public healthcare policies in Brazil (Baqui et al., 2020; Boschiero et al., 2022b; Sansone et al., 2022b).

A descriptive analysis of the epidemiological profile of hospitalized patients with severe acute respiratory syndrome due to influenza virus infection and the co-detection of other respiratory viruses was performed. It was also performed an association between epidemiological profile and the chance of death. The viral profile was performed according to molecular (real-time polymerase chain reaction) tests. In some cases, biochemical immunological tests (antibody and antigen tests) were also performed depending on the availability of tests in the institution that imputed the data into the surveillance system. The Brazilian Ministry of Health defined a severe case as any patient who presented dyspnea OR peripheral oxygen saturation <95% OR any sign of respiratory distress (for example cyanosis and the use of accessory muscle) (Ministério da Saúde, 2024).

Inclusion criteria: all individuals who have been hospitalized during the COVID-19 pandemic due to influenza A or B virus infection with co-detection for other viruses [adenovirus, bocavirus, metapneumovirus, parainfluenza virus (types 1, 2, 3, and 4), rhinovirus, and respiratory syncytial virus (RSV)] were included.

Exclusion criteria: individuals who presented a positive SARS-CoV-2 test have been excluded from the analysis. Concomitantly, the following individuals were not included: (i) individuals without data on the main outcome—death or hospital discharge; (ii) individuals without any laboratory test that confirms viral infection—molecular test; (iii) foreigners hospitalized in Brazil; (iv) individuals infected with influenza, but not specified if it is influenza A or B; and (v) individuals who died during hospitalization due to other causes not described in the dataset.

2.2 Data acquisition

Initially, the data were acquired as a .csv file from Open-Data-SUS (see text footnote 1). The structure of the file was analyzed using the Statistical Package for the Social Sciences (SPSS) software (IBM SPSS Statistics for Macintosh, Version 27.0, IBM inc. Armonk NY, United States). After the first visualization of the dataset, the raw data was acquired and analyzed. The following markers were described:

(i) Demographic profile, including federal unity of the residence (states and federal district), date of the hospitalization due to severe acute respiratory syndrome, gender (female and male), age (<1 year of age, 1–12 years of age, 13–24 years of age, 25–60 years of age, 61–72 years of age, 73–85 years of age, and +85 years of age) (Dyussenbayev, 2017), self-declared race [White people, Black people, multiracial background (in Brazil described as Mixed or *Pardos* individuals), Asian individuals, and Indigenous peoples] (Sze et al., 2020; Sansone et al., 2022b; Corouraça|Educa|Jovens—IBGE, 2024), educational level (no education/illiterate, primary education of 1° cycle, primary education of 2° cycle, high school, and college), and place of residence (urban or rural and peri-urban).

(ii) Data regarding the type and subtype of the virus infection, such as influenza A and B, adenovirus, bocavirus, metapneumovirus, parainfluenza virus (types 1, 2, 3, and 4), rhinovirus and RSV, residence in a region of flu outbreak, nosocomial infection, Flu vaccination status, and use of antiviral drugs. The patients were grouped according to the number of co-detections described as follows: one co-detected virus, two co-detected viruses, and three co-detected viruses. Furthermore, the patients were distributed according to the date of notification, as well as the month of notification and the seasons (summer, autumn, spring, and winter).

(iii) Presence of comorbidities [comorbidity (any)—presence of at least one comorbidity, cardiopathy, hematological disorder, Down syndrome, hepatic disorder, asthma, diabetes mellitus, neurological disorder, chronic respiratory disorder, immunosuppression, kidney disorder, obesity, and other comorbidities (excluding the previous ones)].

(iv) Clinical signs and symptoms related to severe acute respiratory syndrome [fever, cough, sore throat, dyspnea, respiratory discomfort, peripheral oxygen saturation <95%, diarrhea, vomiting, abdominal pain, fatigue, loss of smell, loss of taste, and other clinical signs and symptoms (excluding the previous ones)].

(v) Results of image tests performed during viral infection. In the dataset, the results were imputed using two types of tests: x-ray of the thorax and high-resolution computed tomography of the thorax.

1 https://opendatasus.saude.gov.br/

(vi) Need for ICU treatment, need for mechanical ventilatory support (not performed, non-invasive mechanical ventilatory support, and invasive mechanical ventilatory support), and outcomes (death or hospital discharge).

For better precision, two researchers (MB and FM) revised all the clinical and epidemiological data included in the study. The categorical data were numerically assigned to perform the missing data imputation and to carry out descriptive and inferential statistical analyses. The SPSS dataset was saved as an .xls file to perform the imputation of missing data values.

2.3 Missing data imputation

The inclusion of missing data for some features was performed because (i) the dataset had more than 5% missing data, (ii) the dataset did not have missing data only for the dependent variable, and (iii) the authors assumed that the variables were missing completely at random. Also, the characteristics that had more than 40% missing data were excluded. The missing data were imputed by the XLSTAT Statistical Software for Excel (Addinsoft Inc., Paris, Île-de-France, France) using the NIPALS (Nonlinear Iterative Partial Least Squares) algorithm. The XLSTAT Statistical Software generated a new Excel (.xls) data set used to perform the inferential statistical analyses in the SPSS software.

2.4 Statistical analysis

2.4.1 Descriptive analysis

The descriptive analysis was conducted using the number of individuals (*N*) and the percentage (%) for categorical data. In the results of the inferential statistical analysis, when applicable, the Odds Ratio (OR) with its 95% confidence interval (95%CI) was also calculated.

2.4.2 Bivariate analysis

A bivariate analysis was performed using the SPSS and OpenEpi (OpenEpi: Open-Source Epidemiological Statistics for Public Health, version. www.OpenEpi.com, April 04, 2013) softwares (Sullivan et al., 2009). The Chi-square test or Fisher's exact test was used to estimate the distribution of the clinical and epidemiological markers with respect to the outcomes (death or hospital discharge). The OR with 95%CI was presented with its respective values. The OR was calculated using the OpenEpi software for 2 × 2 tables, all the values being manually included for each patient.

2.4.3 Multivariable analysis

The multivariable analysis was done using the Binary Logistic Regression model with the Backward Stepwise method. Markers with $p \leq 0.05$ in the bivariate analysis were included in the regression model. The dependent variable was the health outcome (death or recovery—hospital discharge). The data for (any) comorbidity (presence of at least one comorbidity) or others, symptoms (others), and characteristics of the patients with $p > 0.05$ were not used in this model. In the Logistic Regression model, the following information was presented: (i) coefficient B [including the SE (standard error)], which for the constant was called the intercept, (ii) the Wald Chi-square test and its significance, (iii) degrees of freedom for the Wald Chi-square test, and (iv) the Exp (*B*) which represents the exponentiation of the *B* coefficient (OR) including its 95%CI. The multicollinearity among the study markers was tested considering cut-off points <0.1 for tolerance and >10 for the variance inflation factor before carrying out the statistical inference analysis.

The results were compiled into tables and figures. Figures were created using GraphPad Prism version 10.2.3 for Mac (http://www.graphpad.com, GraphPad Software, San Diego CA, United States). The alpha error of 0.05 was considered in the bivariate and multivariable analyses carried out in the study.

2.5 Ethical aspects

The study was carried out in accordance with the Declaration of Helsinki and was approved by the institutional ethics committee (Certificate of Presentation for Ethical Appreciation No. 67241323.0.0000.5514; Study Approval No. 5.908.611).

3 Results

3.1 List of excluded markers

The markers that presented more than 40% of missing data were excluded, being the following markers excluded: educational level (*N* = 248, 52.0%), place of residence in a region of flu outbreak (*N* = 443, 92.9%), abdominal pain (*N* = 192, 40.3%), flu vaccination (*N* = 335, 70.2%), loss of smell (*N* = 191, 40.0%), loss of taste (*N* = 193, 40.3%), and image tests [thorax X-ray (*N* = 245, 51.4%) and thorax high resolution computed tomography (*N* = 429, 89.9%)].

3.2 Frequency of the main respiratory viruses detected with influenza virus

Influenza A was detected in 400 (83.9%) cases; in contrast, influenza B occurred only in 77 (16.1%) of the patients. Among the subtypes of influenza, when described in the dataset, the influenza A virus subtype H3N2 presented the highest co-detection rate with other viruses [183 (38.4%)] followed by the influenza A virus subtype H1N1 [50 (10.5%)]. Only one patient had the diagnosis of an influenza B subtype that was of a Victoria lineage. The co-detection occurred, respectively, for RSV [253 (53.0%)], rhinovirus [67 (14.0%)], adenovirus [64 (13.4%)], parainfluenza virus type 1 [51 (10.7%)], parainfluenza virus type 3 [25 (5.2%)], metapneumovirus [18 (3.8%)], parainfluenza virus type 2 [17 (3.6%)], bocavirus [16 (3.4%)], and parainfluenza virus type 4 [7 (1.5%)] (Table 1). A total of 31 (6.5%) individuals presented positive co-detection with two viruses; in addition, in 5 (1.0%) cases, the co-detection occurred for three viruses. The complete viral profile is presented as Figure 1 which includes all levels of co-detection. In addition, the Brazilian federal units with the highest rate of co-detection were São Paulo [156 (32.7%)], Paraná [66 (13.8%)], and Goiás [42 (8.8%)] states (Supplementary Table S1).

TABLE 1 Epidemiological profile of viral infection in Brazilian patients hospitalized for severe acute respiratory syndrome caused by the influenza virus.

Marker	Groups	*N* (%)
Influenza virus	Influenza A virus	167 (35.0%)
	Influenza A virus H1N1 subtype	50 (10.5%)
	Influenza A virus H3N2 subtype	183 (38.4%)
	Influenza B virus	76 (15.9%)
	Influenza B virus Victoria subtype	1 (0.2%)
Group of influenza virus	Influenza A virus	400 (83.9%)
	Influenza B virus	77 (16.1%)
Respiratory virus*	Adenovirus	64 (13.4%)
	Bocavirus	16 (3.4%)
	Metapneumovirus	18 (3.8%)
	Parainfluenza virus type 1	51 (10.7%)
	Parainfluenza virus type 2	17 (3.6%)
	Parainfluenza virus type 3	25 (5.2%)
	Parainfluenza virus type 4	7 (1.5%)
	Rhinovirus	67 (14.0%)
	Respiratory syncytial virus	253 (53.0%)

%, percentage; *N*, number of individuals. *: 36 patients had more than two respiratory viruses - 31 (6.5%) with two additional viruses and 5 (1.0%) with three additional viruses. The data were collected in the Open-Data-SUS (https://opendatasus.saude.gov.br/). The data comprised the period from December 19, 2019, to April 06, 2023—three years since the beginning of the coronavirus disease (COVID)-19 pandemic in Brazil.

3.3 Distribution of respiratory viruses according to the date of notification and seasons

In our data, the season with the highest number of cases was the summer [224 (47.0%)], followed by spring [110 (23.1%)], autumn [88 (18.4%)], and winter [55 (11.5%)] (Figure 2A; Supplementary Table S2). The viral profile was similar among all the viruses, except for some particularities such as adenovirus, which had the highest number of cases during the spring [25 (39.1%)]. The complete respiratory viral profile according to seasons is presented in Figure 2A and Supplementary Table S2. In addition, the distribution of the patients according to the date of notification and the month of notification is presented in Figures 2B,C and Supplementary Table S3.

3.4 Distribution of respiratory viruses according to age

Most of the individuals with positive results for influenza A and B were <1 year of age (29.2 and 35%, respectively) and between 1 and 12 years of age (35.1 and 37.7%, respectively). In the same way, adenovirus (62.5%), bocavirus (68.7%), metapneumovirus (33.3%), parainfluenza virus type 2 (41.1%), parainfluenza virus type 3 (36%), and rhinovirus (41.8%) were more common in patients between 1 and 12 years of age. On the contrary, parainfluenza virus type 1 (25.5%) and parainfluenza virus type 4 (42.8%) were more common in patients between 25 and 60 years of age. Finally, RSV (46.6%) was more common in those <1 year of age. The complete data are presented in Figure 3 and Supplementary Table S4.

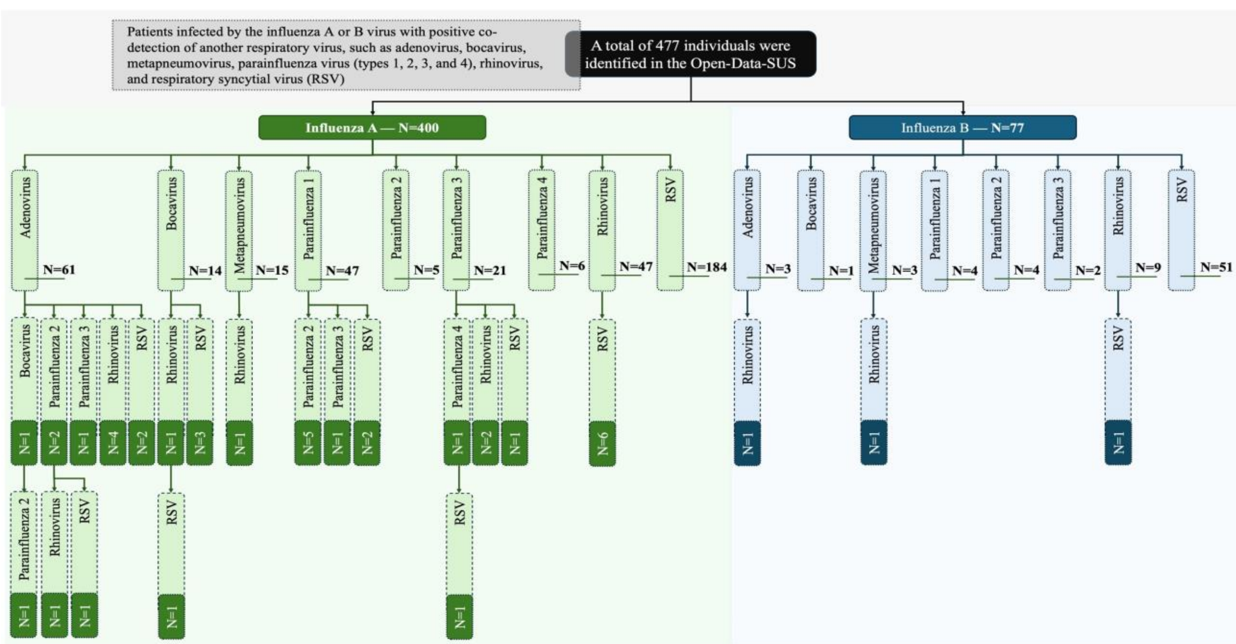


FIGURE 1
Epidemiological profile of the viral infection in Brazilian patients hospitalized for severe acute respiratory syndrome caused by the influenza virus. The data were collected in the Open-Data-SUS (https://opendatasus.saude.gov.br/). The data comprised the period from December 19, 2019, to April 06, 2023—three years since the beginning of the coronavirus disease (COVID)-19 pandemic in Brazil. *N*, number of individuals.

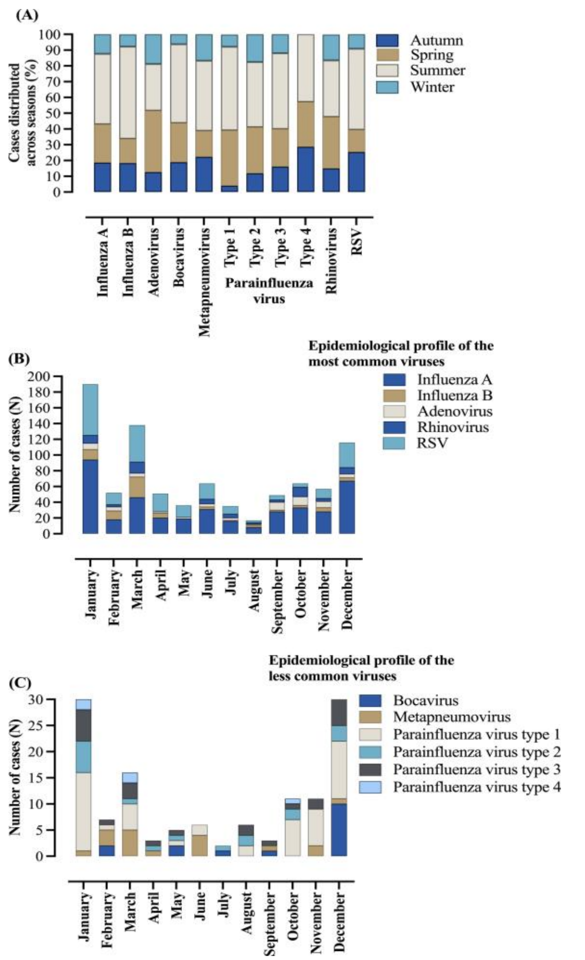


FIGURE 2
Distribution of respiratory viruses in hospitalized patients due to severe acute respiratory syndrome caused by influenza virus infection according to seasons and date of notification. **(A)** Number of cases distributed across seasons. **(B)** Epidemiological profile of the most common viruses according to date. **(C)** Epidemiological profile of the less common viruses according to date. The data comprised the period from December 19, 2019, to April 06, 2023—three years since the beginning of the coronavirus disease (COVID)-19 pandemic in Brazil. %, percentage; *N*, number of individuals; RSV, respiratory syncytial virus. Autumn from March 21 to June 21. Winter from June 21 to September 23. Spring from September 23 to December 21. Summer from December 21 to March 21. The dates were presented according to the notification periods.

3.5 Clinical and epidemiological characteristics of the patients

In the hospitalized patients due to influenza infection, the co-detection rates of respiratory viruses were higher in the male sex [242 (50.7%)], age between zero and 12 years [314 (65.8%)], white people [295 (61.8%)], and the place of residence in urban areas [461 (96.6%)]. The nosocomial infection occurred only in 15 (3.1%) cases. The most common clinical signs and symptoms were cough [432 (90.6%)], dyspnea [376 (78.8%)], fever [375 (78.6%)], respiratory discomfort [368 (77.1%)], and peripheral oxygen saturation <95% [365

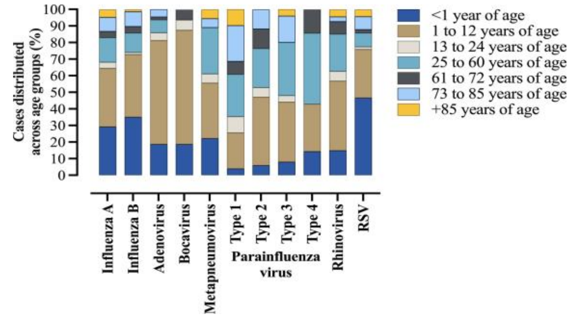


FIGURE 3
Distribution of respiratory viruses in hospitalized patients due to severe acute respiratory syndrome caused by influenza virus infection across age groups. The data comprised the period from December 19, 2019, to April 06, 2023—three years since the beginning of the coronavirus disease (COVID)-19 pandemic in Brazil. %, percentage; *N*, number of individuals; RSV, respiratory syncytial virus.

(76.5%)]. Regarding comorbidities, a total of 167 (35.0%) individuals presented at least one comorbidity, mainly cardiopathy [68 (14.3%)], asthma [40 (8.4%)], and diabetes mellitus [35 (7.3%)]. The use of antiviral drugs to treat flu symptoms was described in 137 (28.7%) cases. The need for ICU treatment occurred in 147 (30.8%) cases, with most of them needing ventilatory support [319 (66.8%)]—(i) non-invasive [273 (57.2%)] and (ii) invasive [46 (9.6%)]. Most of the patients had hospital discharge [444 (93.1%)], while 33 (6.9%) people died. The complete information is presented in Figure 4 and Table 2.

3.6 Bivariate analysis to identify the death predictors in hospitalized patients

A higher chance of death in hospitalized individuals with influenza was identified in the presence of co-detection with bocavirus (OR = 4.94 [95%CI = 1.09–17.66]) and rhinovirus (OR = 2.50 [95%CI = 1.11–5.63]). Furthermore, patients under 24 years of age presented a protective OR (OR = 0.18 [95%CI = 0.07–0.48]) for death compared to those between 25 and 60 years of age. Additionally, when all races were compared to the white race, an increased chance of death was described (OR = 3.08 [95%CI = 1.48–6.42]). Several other characteristics, such as the presence of at least one comorbidity (OR = 3.11 [95%CI = 1.50–6.42]), cardiopathy (OR = 4.60 [95%CI = 2.17–9.76]), diabetes mellitus (OR = 3.18 [95%CI = 1.22–8.32]), immunosuppression (OR = 5.94 [95%CI = 1.29–22.25]), and the presence of other comorbidities (OR = 4.33 [95%CI = 1.97–9.49]) were associated with a higher chance of death. The need for ICU (OR = 5.94 [95%CI = 2.75–12.83]) and invasive respiratory support (OR = 8.01 [95%CI = 3.22–19.95]) also increase the probability of death (Table 3; Figure 5).

3.7 Multivariable analysis to identify the main predictors of death

The multivariable analysis to identify the main predictors of death in Brazilian patients hospitalized due to influenza virus infection who

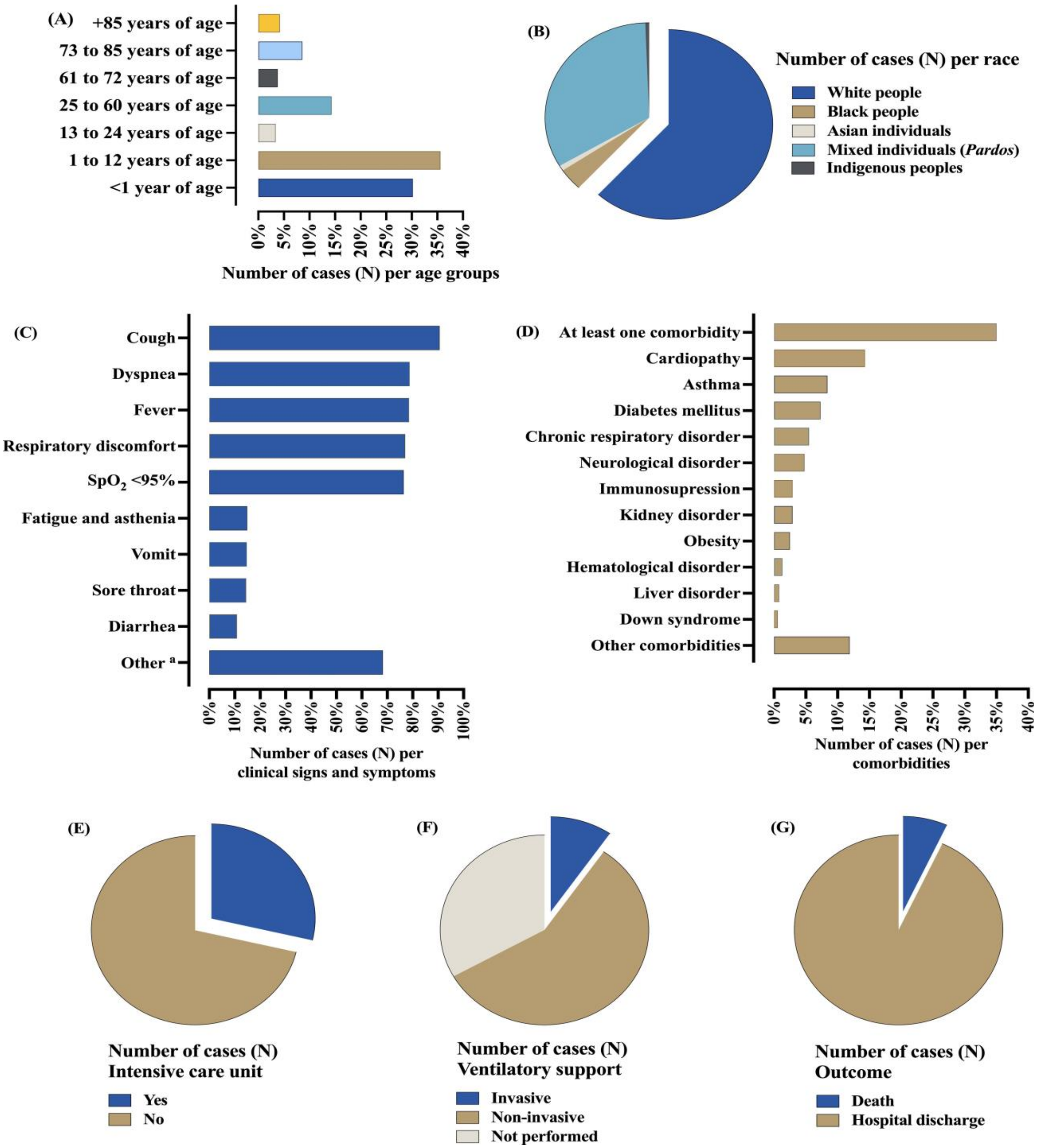


FIGURE 4
Epidemiological profile of Brazilian patients hospitalized for severe acute respiratory syndrome caused by the influenza virus who presented co-detection with other respiratory viruses. **(A)** Distribution of the patients according to the age groups. **(B)** Distribution of the patients according to the self-declared races. **(C)** Distribution of the patients according to clinical signs and symptoms. **(D)** Distribution of the patients according to the comorbidities. **(E)** Distribution of the patients according to the need for support from the intensive care. **(F)** Distribution of the patients according to the need for ventilatory support. **(G)** Distribution of the patients according to the outcome. The data comprised the period from December 19, 2019, to April 06, 2023—three years since the beginning of the coronavirus disease (COVID)-19 pandemic in Brazil. All the data is presented as the number of cases (N) in percentage. [a]: Other clinical signs and symptoms summarize all the clinical signs and symptoms that were not listed previously in the dataset. %, percentage; *N*, number of individuals; SpO_2, peripheral oxygen saturation.

TABLE 2 Epidemiological profile of Brazilian patients hospitalized for severe acute respiratory syndrome caused by the influenza virus who presented co-detection with other respiratory viruses.

Marker	Group	*N* (%)
Gender	Male	242 (50.7%)
	Female	235 (49.3%)
Age	<1 year of age	144 (30.2%)
	1 to 12 years of age	170 (35.6%)
	13 to 24 years of age	16 (3.4%)
	25 to 60 years of age	68 (14.3%)
	61 to 72 years of age	18 (3.8%)
	73 to 85 years of age	41 (8.6%)
	+85 years of age	20 (4.2%)
Race	White people	295 (61.8%)
	Black people	18 (3.8%)
	Asian individuals	4 (0.8%)
	Mixed individuals (*Pardos*)	157 (32.9%)
	Indigenous peoples	3 (0.6%)
Place of residence	Urban	461 (96.6%)
	Rural + peri-urban	16 (3.4%)
Nosocomial infection	Yes	15 (3.1%)
	No	462 (96.9%)
Clinical signs and symptoms	Cough	432 (90.6%)
	Dyspnea	376 (78.8%)
	Fever	375 (78.6%)
	Respiratory discomfort	368 (77.1%)
	Peripheral oxygen saturation < 95%	365 (76.5%)
	Fatigue and asthenia	71 (14.9%)
	Vomit	70 (14.7%)
	Sore throat	69 (14.5%)
	Diarrhea	52 (10.9%)
	Other clinical signs and symptoms[a]	326 (68.3%)
Comorbidities	At least one comorbidity	167 (35.0%)
	Cardiopathy	68 (14.3%)
	Asthma	40 (8.4%)
	Diabetes mellitus	35 (7.3%)
	Chronic respiratory disorder	26 (5.5%)
	Neurological disorder	23 (4.8%)
	Immunosuppression	14 (2.9%)
	Kidney disorder	14 (2.9%)
	Obesity	12 (2.5%)
	Hematological disorder	6 (1.3%)
	Liver disorder	4 (0.8%)
	Down syndrome	3 (0.6%)
	Other comorbidities	57 (11.9%)
Use of antivirals to treat flu symptoms[b]	Yes	137 (28.7%)
	No	340 (71.3%)
Need for an intensive care unit	Yes	147 (30.8%)
	No	330 (69.2%)
Need for ventilatory support	Invasive	46 (9.6%)
	Non-invasive	273 (57.2%)
	Not performed	158 (33.1%)
Outcome	Hospital discharge	444 (93.1%)
	Death	33 (6.9%)

%, percentage; *N*, number of individuals.
[a]Other symptoms summarize all the symptoms that were not listed previously in the dataset.
[b]The antiviral therapy was used at the discretion of the attending physician; then it was not indicated based on the severe phenotype or the need for ventilatory support. The data were collected in the Open-Data-SUS (https://opendatasus.saude.gov.br/). The data comprised the period from December 19, 2019, to April 06, 2023—three years since the beginning of the coronavirus disease (COVID)-19 pandemic in Brazil.

presented co-detection by other respiratory viruses highlights the importance of the following markers: bocavirus infection (OR = 14.78 [95%CI = 2.84–76.98]), metapneumovirus infection (OR = 8.50 [95%CI = 1.86–38.78]), race (other races versus white people) (OR = 3.67 [95%CI = 1.39–9.74]), presence of cardiopathy (OR = 3.48 [95%CI = 1.13–10.71]), and need for ICU (OR = 7.64 [95%CI = 2.44–23.92]) (Table 4; Figure 6).

4 Discussion

In our study, we observed that the co-detection of other respiratory viruses in hospitalized patients due to influenza occurred, mainly, by the RSV and rhinovirus in patients infected with the influenza A virus. In our analysis, two viruses (bocavirus and rhinovirus) were associated with an increased chance of death. Several other factors were also associated with an increased chance of death, such as race, the presence of comorbidity, the need for ICU treatment, and the need for ventilatory support. The main symptoms involved respiratory complications and the mortality rate was 6.9%.

The H3N2 lineage of the influenza A virus presented the highest prevalence in our study, being that this particular lineage was described in co-detection with other influenza A and B lineages (Gregianini et al., 2019). The presence of different viral lineages in the same host can be responsible for genetic rearrangements and result in new variants with greater adaptive resistance, which can culminate in challenges to infection control (Nelson and Vincent, 2015). Furthermore, the co-detection rate is variable and depends on the enrolled population, the age of the individuals, and social, clinical, and demographic factors. In this way, the literature describes such a wide range of co-detection, varying from 7.3% in the United States of America and 61.8% in Spain (Echenique et al., 2013; Martínez-Roig et al., 2015).

In our study, most of the respiratory viruses were most common in children, such as rhinovirus, RSV, and adenovirus, which is per the literature (Zhang et al., 2021; Dallmeyer et al., 2024; Dias et al., 2024). Classically, respiratory viruses have always been a greater threat to young children, due to the immune system that is still developing and smaller airways and lungs, which can facilitate virus infection (CDC, 2024b), in fact, most of these viruses are transmitted

TABLE 3 Association between the epidemiological profile of Brazilian patients hospitalized due to severe acute respiratory syndrome caused by the influenza virus who presented co-detection by other respiratory viruses and the outcomes after hospitalization.

Marker	Group	Death	Hospital discharge	Total	*p*-value	OR (95%CI)
Influenza A virus	Yes	28 (7.0%)	372 (93.0%)	400	1.000	1.08 (0.41–2.90)
	No	5 (6.5%)	72 (93.5%)	77		Reference
Influenza B virus	Yes	5 (6.5%)	72 (93.5%)	77	1.000	0.92 (0.34–2.47)
	No	28 (7.0%)	372 (93.0%)	400		Reference
Adenovirus	Yes	3 (4.7%)	61 (95.3%)	64	0.601	0.63 (0.12–2.12)
	No	30 (7.3%)	383 (92.7%)	413		Reference
Bocavirus	Yes	4 (25.0%)	12 (75.0%)	16	0.019	4.94 (1.09–17.66)
	No	29 (6.3%)	432 (93.7%)	461		Reference
Metapneumovirus	Yes	4 (22.2%)	14 (77.8%)	18	0.029	4.21 (0.95–14.60)
	No	29 (6.3%)	430 (93.7%)	459		Reference
Parainfluenza virus type 1	Yes	3 (5.9%)	48 (94.1%)	51	1.000	0.83 (0.16–2.81)
	No	30 (7.0%)	396 (93.0%)	426		Reference
Parainfluenza virus type 2	Yes	1 (5.9%)	16 (94.1%)	17	1.000	0.84 (0.02–5.73)
	No	32 (7.0%)	428 (93.0%)	460		Reference
Parainfluenza virus type 3	Yes	3 (12.0%)	22 (88.0%)	25	0.404	1.92 (0.35–6.94)
	No	30 (6.6%)	422 (93.4%)	452		Reference
Parainfluenza virus type 4	Yes	0 (0.0%)	7 (100.0%)	7	1.000	Not applicable
	No	33 (7.0%)	437 (93.0%)	470		-
Rhinovirus	Yes	9 (13.4%)	58 (86.6%)	67	0.035	2.50 (1.11–5.63)
	No	24 (5.9%)	386 (94.1%)	410		Reference
Respiratory syncytial virus	Yes	10 (4.0%)	243 (96.0%)	253	0.007	0.36 (0.17–0.77)
	No	23 (10.3%)	201 (89.7%)	224		Reference
Number of co-infections	One virus	30 (6.8%)	411 (93.2%)	441		Reference
	Two viruses	2 (6.5%)	29 (93.5%)	31	1.000	0.95 (0.10–4.05)
	Three viruses	1 (20.0%)	4 (80.0%)	5	0.607	3.41 (0.07–35.90)
Number of co-infections (grouped)	One virus	30 (6.8%)	411 (93.2%)	441		Reference
	+2 (two or three viruses)	3 (8.3%)	33 (91.7%)	36	0.925	1.25 (0.36–4.30)
Gender	Male	17 (7.0%)	225 (93.0%)	242	1.000	1.03 (0.51–2.10)
	Female	16 (6.8%)	219 (93.2%)	235		Reference
Age (years of age)	<24	9 (2.7%)	321 (97.3%)	330	<0.001	0.18 (0.07–0.48)
	25 to 60	9 (13.2%)	59 (86.8%)	68		Reference
	>61	15 (19.0%)	64 (81.0%)	79	0.473	1.54 (0.62–3.78)
Race	White people	12 (4.1%)	283 (95.9%)	295	<0.001	Reference
	Other races[a]	21 (11.5%)	161 (88.5%)	182		3.08 (1.48–6.42)
Place of residence	Urban	30 (6.5%)	431 (93.5%)	461	0.091	0.30 (0.08–1.12)
	Rural + peri-urban	3 (18.8%)	13 (81.2%)	16		Reference
Nosocomial infection	Yes	1 (6.7%)	14 (93.3%)	15	1.000	0.96 (0.02–6.71)
	No	32 (6.9%)	430 (93.1%)	462		Reference
Fever	Yes	23 (6.1%)	352 (93.9%)	375	0.269	0.60 (0.28–1.31)
	No	10 (9.8%)	92 (90.2%)	102		Reference
Cough	Yes	27 (6.2%)	405 (93.8%)	432	0.112	0.43 (0.17–1.11)
	No	6 (13.3%)	39 (86.7%)	45		Reference
Sore throat	Yes	6 (8.7%)	63 (91.3%)	69	0.606	1.34 (0.53–3.39)
	No	27 (6.6%)	381 (93.4%)	408		Reference

(Continued)

TABLE 3 (Continued)

Marker	Group	Death	Hospital discharge	Total	*p*-value	OR (95%CI)
Dyspnea	Yes	30 (8.0%)	346 (92.0%)	376	0.119	2.83 (0.85–14.78)
	No	3 (3.0%)	98 (97.0%)	101		Reference
Respiratory discomfort	Yes	28 (7.6%)	340 (92.4%)	368	0.297	1.71 (0.65–4.55)
	No	5 (4.6%)	104 (95.4%)	109		Reference
Peripheral oxygen saturation	<95%	25 (6.8%)	340 (93.2%)	365	1.000	0.96 (0.42–2.18)
	≥95%	8 (7.1%)	104 (92.9%)	112		Reference
Diarrhea	Yes	3 (5.8%)	49 (94.2%)	52	1.000	0.81 (0.15–2.75)
	No	30 (7.1%)	395 (92.9%)	425		Reference
Vomit	Yes	1 (1.4%)	69 (98.6%)	70	0.069	0.17 (<0.01–1.06)
	No	32 (7.9%)	375 (92.1%)	407		Reference
Fatigue and asthenia	Yes	5 (7.0%)	66 (93.0%)	71	1.000	1.02 (0.38–2.74)
	No	28 (6.9%)	378 (93.1%)	406		Reference
Other clinical signs and symptoms[b]	Yes	21 (6.4%)	305 (93.6%)	326	0.563	0.80 (0.38–1.67)
	No	12 (7.9%)	139 (92.1%)	151		Reference
Presence of at least one comorbidity	Yes	20 (12.0%)	147 (88.0%)	167	0.002	3.11 (1.50–6.42)
	No	13 (4.2%)	297 (95.8%)	310		Reference
Cardiopathy	Yes	13 (19.1%)	55 (80.9%)	68	<0.001	4.60 (2.17–9.76)
	No	20 (4.9%)	389 (95.1%)	409		Reference
Hematological disorder	Yes	0 (0.0%)	6 (100.0%)	6	1.000	Not applicable
	No	33 (7.0%)	438 (93.0%)	471		-
Down syndrome	Yes	0 (0.0%)	3 (100.0%)	3	1.000	Not applicable
	No	33 (7.0%)	441 (93.0%)	474		-
Liver disorder	Yes	2 (50.0%)	2 (50.0%)	4	0.026	14.05 (0.99–199.9)
	No	31 (6.6%)	442 (93.4%)	473		Reference
Asthma	Yes	0 (0.0%)	40 (100.0%)	40	0.098	Not applicable
	No	33 (7.6%)	404 (92.4%)	437		-
Diabetes mellitus	Yes	6 (17.1%)	29 (82.9%)	35	0.026	3.18 (1.22–8.32)
	No	27 (6.1%)	415 (93.9%)	442		Reference
Neurological disorder	Yes	3 (13.0%)	20 (87.0%)	23	0.207	2.12 (0.38–7.76)
	No	30 (6.6%)	424 (93.4%)	454		Reference
Chronic respiratory disorder	Yes	4 (15.4%)	22 (84.6%)	26	0.096	2.64 (0.62–8.53)
	No	29 (6.4%)	422 (93.6%)	451		Reference
Immunosuppression	Yes	4 (28.6%)	10 (71.4%)	14	0.012	5.94 (1.29–22.25)
	No	29 (6.3%)	434 (93.7%)	463		Reference
Kidney disorder	Yes	3 (21.4%)	11 (78.6%)	14	0.065	3.92 (0.67–15.95)
	No	30 (6.5%)	433 (93.5%)	463		Reference
Obesity	Yes	1 (8.3%)	11 (91.7%)	12	0.581	1.23 (0.03–8.96)
	No	32 (6.9%)	433 (93.1%)	465		Reference
Other comorbidities	Yes	11 (19.3%)	46 (80.7%)	57	0.001	4.33 (1.97–9.49)
	No	22 (5.2%)	398 (94.8%)	420		Reference
Antivirals to treat the flu symptoms[c]	Yes	11 (8.0%)	126 (92.0%)	137	0.553	1.26 (0.59–2.68)
	No	22 (6.5%)	318 (93.5%)	340		Reference
Need for an intensive care unit	Yes	23 (15.6%)	124 (84.4%)	147	<0.001	5.94 (2.75–12.83)
	No	10 (3.0%)	320 (97.0%)	330		Reference

(Continued)

TABLE 3 (Continued)

Marker	Group	Death	Hospital discharge	Total	*p*-value	OR (95%CI)
Need for ventilatory support	Invasive	15 (32.6%)	31 (67.4%)	46	<0.001	8.01 (3.22–19.95)
	Non-invasive	9 (3.3%)	264 (96.7%)	273	0.34	0.56 (0.22–1.45)
	Not performed	9 (5.7%)	149 (94.3%)	158		Reference

95%CI, 95% confidence interval; %, percentage; *N*, number of individuals; OR, odds ratio.
[a]Other races included the patients self-declared as Black people, Asian individuals, Mixed individuals (*Pardos*), and Indigenous peoples.
[b]Other clinical signs and symptoms summarize all the clinical signs and symptoms that were not listed previously in the dataset.
[c]The antiviral therapy was used at the discretion of the attending physician; then it was not indicated based on severe phenotype or the need for ventilatory support. The data were collected in the Open-Data-SUS (https://opendatasus.saude.gov.br/). The data comprised the period from December 19, 2019, to April 06, 2023—three years since the beginning of the coronavirus disease (COVID)-19 pandemic in Brazil. The Chi-square test or Fisher's exact test was used to estimate the distribution of clinical and epidemiological markers with respect to outcomes (death or hospital discharge). The alpha error of 0.05 was considered in the bivariate analyses carried out in the study.

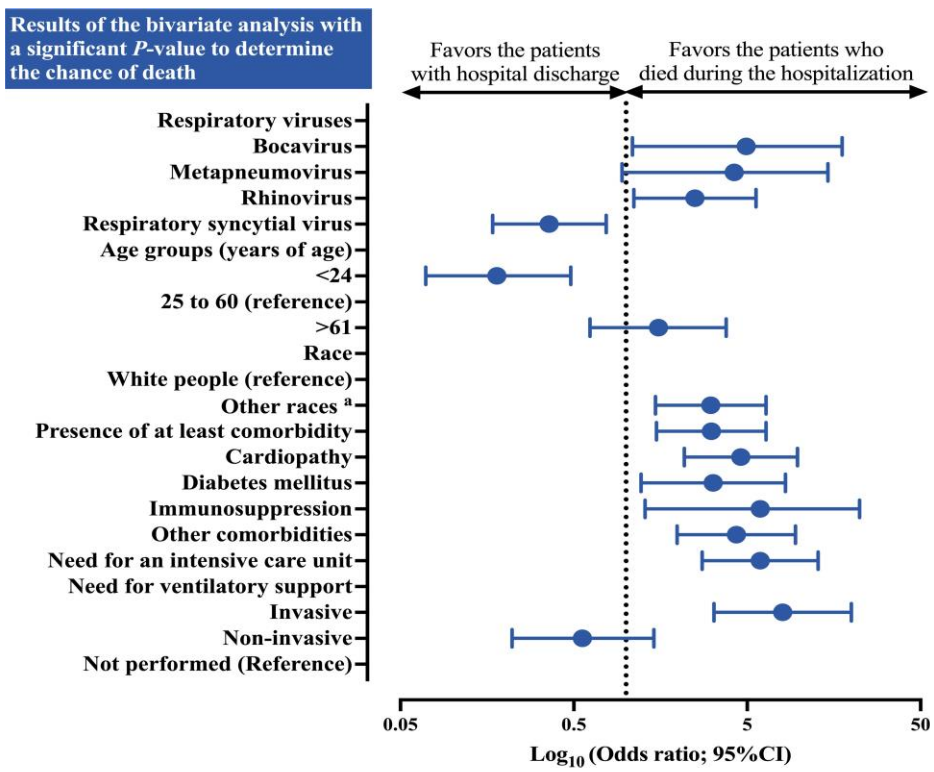


FIGURE 5
Association between the epidemiological profile of Brazilian patients hospitalized due to severe acute respiratory syndrome caused by the influenza virus who presented co-detection by other respiratory viruses and the outcomes after hospitalization. The figure presents the results of the bivariate analysis with a significant *p*-value exclusively to determine the probability of death. [a]: Other races included the patients self-declared as Black people, Asian individuals, Mixed individuals (*Pardos*), and Indigenous peoples. The data comprised the period from December 19, 2019, to April 06, 2023—three years since the beginning of the coronavirus disease (COVID)-19 pandemic in Brazil. The Chi-square test or Fisher's exact test was used to estimate the distribution of the clinical and epidemiological markers with respect to outcomes (death or hospital discharge). The alpha error of 0.05 was considered in the bivariate analyses carried out in the study. The data are presented using a *log-rank* scale. 95%CI, 95% confidence interval; OR, odds ratio.

by poor hygiene or even contact with someone who was already sick; that is why older people can protect themselves by washing hands or other hygiene measures, thus decreasing the impact of transmission.

The profile of the respiratory viruses that were co-detected with influenza was similar to those described in the literature. Depending on the co-detection profile, the patient's outcome might be more severe (Chauhan and Slamon, 2017; Noyola et al., 2019). In Brazil, in turn, few studies have evaluated respiratory viral co-detection (Martins Júnior et al., 2014; Canela et al., 2018; Costa et al., 2022; Moreira et al., 2023). Canela et al. (2018) evaluated 71 samples of patients up to 18 years of age who were treated in the ICU, the influenza virus being the most common (43%), followed by the rhinovirus (41%). The co-detection occurred in almost 22% of the samples, being described as the co-detection of H1N1 and rhinovirus/enterovirus, RSV, metapneumovirus, and seasonal influenza virus,

TABLE 4 Multivariable analysis to identify the main predictors of death in Brazilian patients hospitalized due to severe acute respiratory syndrome caused by the influenza virus who presented co-detection by other respiratory viruses.

Markers	*B*	SE	Wald	df	*p*-value	OR	95%CI
Respiratory virus							
Bocavirus	2.69	0.84	10.23	1	0.001	14.78	2.84–76.98
Metapneumovirus	2.14	0.78	7.63	1	0.006	8.50	1.86–38.78
Rhinovirus	1.05	0.54	3.73	1	0.054	2.86	0.98–8.32
Age (years of age)							
<1 to 24	−2.26	0.68	11.10	1	0.001	0.11	0.03–0.40
25 to 60 (reference)			16.28	2	0.001		
>61	0.36	0.59	0.37	1	0.545	1.43	0.45–4.59
Race (Other vs. white people)[a]	1.30	0.50	6.84	1	0.009	3.67	1.39–9.74
Cardiopathy	1.25	0.57	4.75	1	0.029	3.48	1.13–10.71
Need for an intensive care unit	2.03	0.58	12.21	1	0.001	7.64	2.44–23.92
Need for ventilatory support							
Invasive	0.91	0.65	1.97	1	0.160	2.49	0.70–8.92
Non-invasive	−0.78	0.59	1.75	1	0186	0.6	0.14–1.46
Not performed (reference)			8.20	2	0.017		
Constant	−4.15	0.73	32,54	1	0.001	0.01	

95%CI, 95% confidence interval; df, degrees of freedom; SE, standard error; OR, odds ratio. The following markers were included in the model: viral infection (bocavirus, metapneumovirus, rhinovirus, and respiratory syncytial virus), age, race, comorbidities (cardiopathy, hepatic disorder, diabetes mellitus, and immunodepression), need for an intensive care unit, and need for mechanical ventilatory support. The multivariable analysis was done using the Binary Logistic Regression model with the Backward Stepwise method. Markers with $p \leq 0.05$ in the bivariate analysis were included in the regression model. The dependent variable was the health outcome (death or recovery—hospital discharge). The alpha error of 0.05 was considered in the multivariable analyses carried out in the study.

[a]Other races included the patients self-declared as Black people, Asian individuals, Mixed individuals (*Pardos*), and Indigenous peoples. The data were collected in the Open-Data-SUS (https://opendatasus.saude.gov.br/). The data comprised the period from December 19, 2019, to April 06, 2023—three years since the beginning of the coronavirus disease (COVID)-19 pandemic in Brazil.

however, it was not possible to describe the impact of this viral profile on the outcome (Canela et al., 2018). On the other hand, Costa et al. (2022) described a more severe clinical profile of hospitalized patients with viral co-detection (Costa et al., 2022). Also, Martins Júnior et al. (2014) observed that in outpatients, the viral co-detection rate is low (3.7%), and if presented, most of the co-detection was associated with RSV (Martins Júnior et al., 2014). Nevertheless, the literature is still controversial regarding the impact of viral co-detection on clinical outcomes and what the effector role is in this outcome according to the different etiological agents detected and the ecological relationship between them.

Regarding seasonality, in our study, most of the viruses were detected in December and January, months with warmer temperatures in the South Hemisphere. Although studies described the higher incidence of the respiratory virus in colder seasons (Viegas et al., 2004; Weigl et al., 2007; Ambrosioni et al., 2014, pp. 2011–2012; García-Arroyo et al., 2022), in Brazil, previous studies observed a different trend in seasonality in respiratory virus (Gardinassi et al., 2012; Vianna et al., 2021), in which a peak of incidence was observed in spring and autumn. In our study, since most of the data were acquired from the Brazilian Ministry of Health dataset, tests were completely at the discretion of the attending physicians and availability in the Health Institutions, which could reflect a pseudo-increase in warmer temperature seasons, such as January and December. One might also speculate that the lower humidity in Brazil, especially in dry regions such as the *cerrado*, contributed to a higher incidence of respiratory viruses, since their incidence appears to increase in low-humidity regions climate (Gardinassi et al., 2012; Hofmann et al., 2023).

In general, in our study, the co-detection of other respiratory viruses than influenza was low; however, the literature seems to be controversial. A Brazilian study performed by Dias et al. (2024) observed co-detection among respiratory viruses that ranged from 0.3–1.3% (Dias et al., 2024), while in the study by De Paulis et al. (2011), 31% of the patients presented with co-detection (De Paulis et al., 2011). In the same way, co-detection also varies according to region; for example, in Cameroon, co-detection was around 6.9% (Moumbeket Yifomnjou et al., 2023, pp. 2020–2021), which is similar to countries such as France (6.5%) (Le Hingrat et al., 2021). Similarly, the effect of respiratory virus co-detections on patients' outcomes remains unclear. For example, some studies did not describe an association between co-detection of other respiratory viruses and worse outcomes (Cilla et al., 2008; De Paulis et al., 2011), in contrast, Semple et al. (2005) observed an increased risk of ICU for mechanical ventilation in pediatric patients with metapneumovirus and RSV (Semple et al., 2005). Since the real effect of co-detection on the worst outcomes is still not clear in the literature, further studies are necessary to evaluate the impact of viral co-detections in hospitalized patients. The respiratory viruses have a seasonal profile, therefore mutual infections may be the result of this natural flow (Rath et al., 2017). The interactions between respiratory viruses may present a different response depending on the first viral infection (Godinho et al., 2016; Piret and Boivin, 2022). In this context, the first virus results in a positive response (synergism or additive effect) or a negative response (antagonism effect among the virus) (Piret and Boivin, 2022). Similarly, to the outcome, severity is represented as a broad phenotypic spectrum, which, consequently, denotes the search for

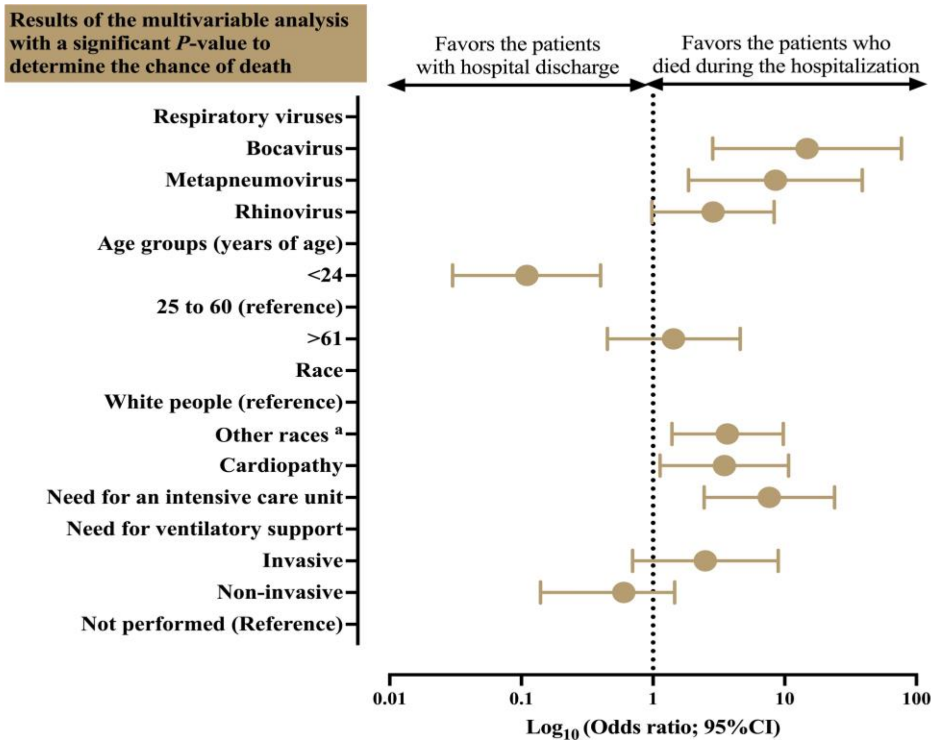


FIGURE 6
Multivariable analysis to identify the main predictors of death in Brazilian patients hospitalized due to severe acute respiratory syndrome caused by the influenza virus who presented co-detection by other respiratory viruses. The figure presents the results of the multivariable analysis (markers) with a significant *p*-value exclusively to determine the chance of death. [a]: Other races included the patients self-declared as Black people, Asian individuals, Mixed individuals (*Pardos*), and Indigenous peoples. The following markers were included in the model: viral infection (bocavirus, metapneumovirus, rhinovirus, and respiratory syncytial virus), age, race, comorbidities (cardiopathy, hepatic disorder, diabetes mellitus, and immunodepression), need for an intensive care unit, and need for mechanical ventilatory support. The data comprised the period from December 19, 2019, to April 06, 2023—three years since the beginning of the coronavirus disease (COVID)-19 pandemic in Brazil. The multivariable analysis was done using the Binary Logistic Regression model with the Backward Stepwise method. Markers with $p \leq 0.05$ in the bivariate analysis were included in the regression model. The dependent variable was the health outcome (death or recovery—hospital discharge). The alpha error of 0.05 was considered in the multivariable analysis carried out in the study. The data are presented using a *log-rank* scale. 95%CI, 95% confidence interval; OR, odds ratio.

medical support through the clinical condition. This directive search may be a conditional factor for the diagnosis of the viral profile most commonly associated with worse clinical outcomes and which may generate underreporting of milder clinical phenotypic (Szymański et al., 2017).

The juvenile was the most affected in our study; however, it was not associated with an enhanced chance of death. Younger individuals have an immature immune system, which makes these individuals more vulnerable to viral infections (Debiaggi et al., 2012; Cebey-López et al., 2015). The lack of acquired immunity to the different viruses might also enhance the co-detection (Cieślak et al., 2018). The biological and environmental markers, such as experience in educational and daycare centers, can culminate in an increase in viral infection in this age group and thus in co-detection (Cieślak et al., 2018; Kurskaya et al., 2018). Other races, such as Black people, Indigenous peoples, and mixed individuals (*Pardos*), on the other hand, were associated with an enhanced chance of death, which is similar to previous studies (Sansone et al., 2022a; CDC, 2024a). One might speculate that these people have less access to healthcare, which might culminate in delayed hospitalization and worse outcomes (Williams and Rucker, 2000; Racial and income inequalities in access to healthcare in Brazilian cities—ScienceDirect, 2024).

The death rate in the present study was relatively low considering that all patients were hospitalized for influenza virus infection. However, the literature lacks good evidence on the real impact of multiple viral infections on patient outcomes, possibly due to the low rates of diagnosis of these infections. However, the main findings favor a greater assertiveness of severity in the face of viral infections in line with those of bacterial origin (Rice et al., 2012; Diaz et al., 2016). Although the literature is uncertain, in our findings, some viruses and comorbidities were described as risk factors for death and, given the above, other studies should be listed to validate our findings (Rath et al., 2017; Kurskaya et al., 2018; Barahimi et al., 2023).

The control over viral infections in countries such as Brazil is of paramount importance for local epidemiology. Although the literature contradicts the real effect of co-detection on more serious outcomes in hospitalized patients, testing for pathogens that have specific therapy, such as the influenza virus, appears to be minimally reasonable (Wishaupt et al., 2017; Costa et al., 2022; Ambrożej et al., 2024). From an epidemiological point of view, mass testing of patients is difficult, therefore, it is extremely important to take into account not only clinical and demographic characteristics, such as age and clinical presentation, but also to take into account periods of the year, as most viruses have their seasonality (Hall, 2001; McAdam et al., 2004; Hermos et al., 2010; Ginocchio and McAdam, 2011).

Although our study mainly dealt with patients with a positive result for influenza and the co-detection of other respiratory viruses, undoubtedly, the COVID-19 pandemic played an important role in the dynamics of surveillance of flu-like syndromes. A recent report observed 21 surveillance influenza virus infections and COVID-19 surveillance systems from different countries (including Brazil) from 2021–2022 (Staadegaard et al., 2023). In most of these countries, the authors observed decreased influenza activity and a decreased number of samples tested at least temporally (Adlhoch et al., 2021; Staadegaard et al., 2023; End-to-end integration of SARS-CoV-2 and influenza sentinel surveillance: compendium of country approaches, 2024). Several reasons might explain this particular finding, such as structural changes in the surveillance system and decreased syndromic consultations (Adlhoch et al., 2021; Staadegaard et al., 2023). One might speculate that the pandemic limited the circulation of the influenza virus as shown in previous research (Adlhoch et al., 2021; Staadegaard et al., 2023), in which the rates of rhinovirus, influenza, RSV, and adenovirus decreased in 2020 compared to 2019 perhaps due to quarantine and social isolation (Kuitunen et al., 2020; Trenholme et al., 2021), highlighting the importance of COVID-19 not only as a disease itself but also disrupting other virus seasonality.

Public data surveillance of respiratory viruses is also extremely relevant worldwide, as its use has the potential to detect possible epidemics and upcoming outbreaks of already known viruses or even new viruses, as was the case with SARS-CoV-2 (Hashimoto et al., 2000; Morse, 2012; Maddah et al., 2023). Since 2009, in response to the H1N1 pandemic, Brazil has developed SIVEP-Gripe to control cases and possible viral outbreaks (da Silva et al., 2022). Notifications are made by clinics, hospitals, and also emergency departments, both public and private, which means that all strata of the population are covered (Sansone et al., 2022b; Martins et al., 2023; Palamim et al., 2023). Unfortunately, the specific virus evaluation of these patients may be underdiagnosed, as was the case with COVID-19, which can make it difficult to implement public health policies for the surveillance and control of infections.

4.1 Limitations

The study has limitations that require caution when interpreting the results. The data source, coming from the Open-Data-SUS platform, may have representativeness and accuracy restrictions, which affect the generalization of the findings. Collecting data exclusively from hospitalized patients introduces potential selection bias, limiting the representativeness of the diversity of influenza virus infection in the general population. Generalization to other populations is restricted by the specificity of the Brazilian context during the COVID-19 pandemic. The definition of comorbidities may lack uniformity and the lack of exploration of socioeconomic variables and the history of vaccination may affect understanding of the determinants of death risk. There is no information on the diagnoses of important respiratory virus infections responsible for common colds, such as those caused by OC43 and NL63 strains, since the institutions that provided the Open-Data-SUS did not test for these specific strains in Brazil. Additionally, only a small portion of hospitalized patients in Brazil have been tested for several respiratory viruses. Laboratory tests occurred randomly depending on medical requests, availability of tests in health institutions, and access to tests by patients. Therefore, one of the main limitations of the study is the difficulty in providing accurate information on the temporal analysis of infections. Furthermore, there was an outbreak of influenza virus infection at the end of 2021 which may have helped to increase cases in the months surrounding the outbreak, mainly the summer season. We excluded patients with a positive SARS-CoV-2 diagnosis since we were only interested in patients with influenza in the pandemic era. In addition, several studies were performed to understand co-detection/co-infection of respiratory viruses including SARS- CoV-2 (Kim et al., 2020; Swets et al., 2022; Morales-Jadán et al., 2023); however, we tried to understand the burden of the co-detection between influenza virus and other respiratory viruses during the COVID-19 pandemic.

5 Conclusion

The co-detection between the influenza virus and other respiratory viruses occurred, mainly with RSV, rhinovirus, and adenovirus being more common in men, white people, and in the juvenile phase. Co-detection of influenza virus with bocavirus and metapneumovirus was associated with an increased chance of death. Other factors such as race, heart disease, and the need for ICU were also associated with a higher chance of death.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the study was conducted in accordance with the Declaration of Helsinki and approved by the Institution’s Ethics Committee (Certificate of Presentation for Ethical Appreciation No. 67241323.0.0000.5514; Study Approval No. 5.908.611). The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants’ legal guardians/next of kin because the data was collected in an open database.

Author contributions

BS: Conceptualization, Data curation, Investigation, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. KB: Conceptualization, Data curation, Investigation, Resources, Validation, Writing – original draft, Writing – review &

editing. MB: Conceptualization, Investigation, Methodology, Resources, Validation, Writing – original draft, Writing – review & editing. FM: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmicb.2024.1462802/full#supplementary-material

References

Adlhoch, C., Sneiderman, M., Martinuka, O., Melidou, A., Bundle, N., Fielding, J., et al. (2021). Spotlight influenza: the 2019/20 influenza season and the impact of COVID-19 on influenza surveillance in the WHO European region. *Euro Surveill.* 26:2100077. doi: 10.2807/1560-7917.ES.2021.26.40.2100077

Alexander, P., and Dobrovolny, H. M. (2022). Treatment of respiratory viral coinfections. *Epidemiologia* 3, 81–96. doi: 10.3390/epidemiologia3010008

Ambrosioni, J., Bridevaux, P.-O., Wagner, G., Mamin, A., and Kaiser, L. (2014). Epidemiology of viral respiratory infections in a tertiary care Centre in the era of molecular diagnosis, Geneva, Switzerland, 2011–2012. *Clin. Microbiol. Infect.* 20, O578–O584. doi: 10.1111/1469-0691.12525

Ambrożej, D., Orzołek, I., Makrinioti, H., Castro-Rodriguez, J. A., Camargo, C. A., Hasegawa, K., et al. (2024). Association of respiratory virus types with clinical features in bronchiolitis: implications for virus testing strategies. A systematic review and meta-analysis. *Paediatr. Respir. Rev.* 49, 34–42. doi: 10.1016/j.prrv.2023.09.003

Ao, T., McCracken, J. P., Lopez, M. R., Bernart, C., Chacon, R., Moscoso, F., et al. (2019). Hospitalization and death among patients with influenza, Guatemala, 2008–2012. *BMC Public Health* 19:463. doi: 10.1186/s12889-019-6781-6

Baqui, P., Bica, I., Marra, V., Ercole, A., and van der Schaar, M. (2020). Ethnic and regional variations in hospital mortality from COVID-19 in Brazil: a cross-sectional observational study. *Lancet Glob. Health* 8, e1018–e1026. doi: 10.1016/S2214-109X(20)30285-0

Barahimi, E., Azad, M. H., Hesarooeyeh, Z. G., Hafshejani, N. H., Defaee, S., and Seddighi, N. (2023). Late diagnosis of respiratory syncytial virus and influenza co-infection during coronavirus disease 2019 pandemic: a case report. *J. Med. Case Rep.* 17:437. doi: 10.1186/s13256-023-04187-3

Boschiero, M. N., Duarte, A., Palamim, C. V. C., Alvarez, A. E., Mauch, R. M., and Marson, F. A. L. (2022a). Frequency of respiratory pathogens other than SARS-CoV-2 detected during COVID-19 testing. *Diagn. Microbiol. Infect. Dis.* 102:115576. doi: 10.1016/j.diagmicrobio.2021.115576

Boschiero, M. N., Palamim, C. V. C., Ortega, M. M., and Marson, F. A. L. (2022b). Clinical characteristics and comorbidities of COVID-19 in unvaccinated patients with down syndrome: first year report in Brazil. *Hum. Genet.* 141, 1887–1904. doi: 10.1007/s00439-022-02468-3

Canela, L. N. P., Magalhães-Barbosa, M. C., Raymundo, C. E., Carney, S., Siqueira, M. M., Prata-Barbosa, A., et al. (2018). Viral detection profile in children with severe acute respiratory infection. *Braz. J. Infect. Dis.* 22, 402–411. doi: 10.1016/j.bjid.2018.09.001

CDC (2024a). Racial and ethnic minority groups. Centers for Disease Control and Prevention. Available at: https://www.cdc.gov/flu/highrisk/disparities-racial-ethnic-minority-groups.html (Accessed September 6, 2024).

CDC (2024b). Respiratory viruses and young children. Respiratory illnesses. Available at: https://www.cdc.gov/respiratory-viruses/risk-factors/young-children.html (Accessed September 6, 2024).

Cebey-López, M., Herberg, J., Pardo-Seco, J., Gómez-Carballa, A., Martinón-Torres, N., Salas, A., et al. (2015). Viral co-infections in pediatric patients hospitalized with lower tract acute respiratory infections. *PLoS One* 10:e0136526. doi: 10.1371/journal.pone.0136526

Chauhan, J. C., and Slamon, N. B. (2017). The impact of multiple viral respiratory infections on outcomes for critically ill children. *Pediatr. Crit. Care Med.* 18, e333–e338. doi: 10.1097/PCC.0000000000001232

Choe, Y. J., Park, S., and Michelow, I. C. (2020). Co-seasonality and co-detection of respiratory viruses and bacteraemia in children: a retrospective analysis. *Clin. Microbiol. Infect.* 26, 1690.e5–1690.e8. doi: 10.1016/j.cmi.2020.09.006

Chu, S.-E., Seak, C.-J., Su, T.-H., Chaou, C.-H., Tseng, H.-J., and Li, C.-H. (2020). Prognostic accuracy of SIRS criteria and qSOFA score for in-hospital mortality among influenza patients in the emergency department. *BMC Infect. Dis.* 20:385. doi: 10.1186/s12879-020-05102-7

Cieślak, K., Kowalczyk, D., Szymański, K., Hallmann-Szelińska, E., and Brydak, L. B. (2018). Influenza and influenza-like viruses: frequent infections in children under 14 years of age during the 2016/2017 epidemic season. *Adv. Exp. Med. Biol.* 1114, 83–87. doi: 10.1007/5584_2018_229

Cilla, G., Oñate, E., Perez-Yarza, E. G., Montes, M., Vicente, D., and Perez-Trallero, E. (2008). Viruses in community-acquired pneumonia in children aged less than 3 years old: high rate of viral coinfection. *J. Med. Virol.* 80, 1843–1849. doi: 10.1002/jmv.21271

Corouraça|Educa|Jovens—IBGE (2024). Available at: https://educa.ibge.gov.br/jovens/conheca-o-brasil/populacao/18319-cor-ou-raca.html (Accessed January 5, 2024).

Costa, L. F., Da Silveira, H. L., Queiróz, D. A. O., Mantese, O. C., and Yokosawa, J. (2022). Respiratory virus infections in hospitalized and non-hospitalized children: determinants of severe course of the disease. *J. Infect. Dev. Ctries.* 16, 196–205. doi: 10.3855/jidc.15117

da Silva, A. D., da Veiga, A. B. G., Cruz, O. G., Bastos, L. S., and Gomes, M. F. (2022). Severe acute respiratory infection surveillance in Brazil: the role of public, private and philanthropic healthcare units. *Health Policy Plan.* 37, 1075–1085. doi: 10.1093/heapol/czac050

Dallmeyer, L. K., Schüz, M. L., Fragkou, P. C., Omony, J., Krumbein, H., Dimopoulou, D., et al. (2024). Epidemiology of respiratory viruses among children during the SARS-CoV-2 pandemic: a systematic review and meta-analysis. *Int. J. Infect. Dis.* 138, 10–18. doi: 10.1016/j.ijid.2023.10.023

De Paulis, M., Gilio, A. E., Ferraro, A. A., Ferronato, A. E., Sacramento, P. R., Botosso, V. F., et al. (2011). Severity of viral coinfection in hospitalized infants with respiratory syncytial virus infection. *J. Pediatr.* 87, 307–313. doi: 10.2223/JPED.2100

de Souza, W. M., Buss, L. F., Candido, D., Carrera, J.-P., Li, S., Zarebski, A. E., et al. (2020). Epidemiological and clinical characteristics of the COVID-19 epidemic in Brazil. *Nat. Hum. Behav.* 4, 856–865. doi: 10.1038/s41562-020-0928-4

Debiaggi, M., Canducci, F., Ceresola, E. R., and Clementi, M. (2012). The role of infections and coinfections with newly identified and emerging respiratory viruses in children. *Virol. J.* 9:247. doi: 10.1186/1743-422X-9-247

Dias, C. S., Diniz, L. M., Oliveira, M. C. L., Simoes E Silva, A. C., Colosimo, E. A., Mak, R. H., et al. (2024). Outcomes of SARS-CoV-2 and seasonal viruses among children hospitalized in Brazil. *Pediatrics* 153:e2023064326. doi: 10.1542/peds.2023-064326

Diaz, M. H., Cross, K. E., Benitez, A. J., Hicks, L. A., Kutty, P., Bramley, A. M., et al. (2016). Identification of bacterial and viral Codetections with Mycoplasma pneumoniae using the TaqMan Array card in patients hospitalized with community-acquired pneumonia. Open forum. *Infect. Dis.* 3:ofw071. doi: 10.1093/ofid/ofw071

Dyussenbayev, A. (2017). Age periods of human life. *Adv. Soc. Sci. Res. J.* 4:2924. doi: 10.14738/assrj.46.2924

Echenique, I. A., Chan, P. A., Chapin, K. C., Andrea, S. B., Fava, J. L., and Mermel, L. A. (2013). Clinical characteristics and outcomes in hospitalized patients with respiratory viral co-infection during the 2009 H1N1 influenza pandemic. *PLoS One* 8:e60845. doi: 10.1371/journal.pone.0060845

End-to-end integration of SARS-CoV-2 and influenza sentinel surveillance: compendium of country approaches (2024). Available at: https://www.who.int/publications/i/item/9789240056701 (Accessed September 4, 2024).

García-Arroyo, L., Prim, N., Del Cuerpo, M., Marín, P., Roig, M. C., Esteban, M., et al. (2022). Prevalence and seasonality of viral respiratory infections in a temperate climate region: a 24-year study (1997–2020). *Influenza Other Respir. Viruses* 16, 756–766. doi: 10.1111/irv.12972

Gardinassi, L. G., Simas, P. V. M., Salomão, J. B., Durigon, E. L., Trevisan, D. M. Z., Cordeiro, J. A., et al. (2012). Seasonality of viral respiratory infections in southeast of Brazil: the influence of temperature and air humidity. *Braz. J. Microbiol.* 43, 98–108. doi: 10.1590/S1517-838220120001000011

Ginocchio, C. C., and McAdam, A. J. (2011). Current Best practices for respiratory virus testing. *J. Clin. Microbiol.* 49, S44–S48. doi: 10.1128/JCM.00698-11

Godinho, C. A., Yardley, L., Marcu, A., Mowbray, F., Beard, E., and Michie, S. (2016). Increasing the intent to receive a pandemic influenza vaccination: testing the impact of theory-based messages. *Prev. Med.* 89, 104–111. doi: 10.1016/j.ypmed.2016.05.025

Gregianini, T. S., Varella, I. R. S., Fisch, P., Martins, L. G., and Veiga, A. B. G. (2019). Dual and triple infections with influenza A and B viruses: a case-control study in southern Brazil. *J. Infect. Dis.* 220, 961–968. doi: 10.1093/infdis/jiz221

Hall, C. B. (2001). Respiratory syncytial virus and parainfluenza virus. *N. Engl. J. Med.* 344, 1917–1928. doi: 10.1056/NEJM200106213442507

Hashimoto, S., Murakami, Y., Taniguchi, K., and Nagai, M. (2000). Detection of epidemics in their early stage through infectious disease surveillance. *Int. J. Epidemiol.* 29, 905–910. doi: 10.1093/ije/29.5.905

Hermos, C. R., Vargas, S. O., and McAdam, A. J. (2010). Human Metapneumovirus. *Clin. Lab. Med.* 30, 131–148. doi: 10.1016/j.cll.2009.10.002

Hofmann, G. S., Silva, R. C., Weber, E. J., Barbosa, A. A., Oliveira, L. F. B., Alves, R. J. V., et al. (2023). Changes in atmospheric circulation and evapotranspiration are reducing rainfall in the Brazilian Cerrado. *Sci. Rep.* 13:11236. doi: 10.1038/s41598-023-38174-x

Iuliano, A. D., Roguski, K. M., Chang, H. H., Muscatello, D. J., Palekar, R., Tempia, S., et al. (2018). Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. *Lancet* 391, 1285–1300. doi: 10.1016/S0140-6736(17)33293-2

Kim, D., Quinn, J., Pinsky, B., Shah, N. H., and Brown, I. (2020). Rates of co-infection between SARS-CoV-2 and other respiratory pathogens. *JAMA* 323, 2085–2086. doi: 10.1001/jama.2020.6266

Kuitunen, I., Artama, M., Mäkelä, L., Backman, K., Heiskanen-Kosma, T., and Renko, M. (2020). Effect of social distancing due to the COVID-19 pandemic on the incidence of viral respiratory tract infections in children in Finland during early 2020. *Pediatr. Infect. Dis. J.* 39, e423–e427. doi: 10.1097/INF.0000000000002845

Kurskaya, O., Ryabichenko, T., Leonova, N., Shi, W., Bi, H., Sharshov, K., et al. (2018). Viral etiology of acute respiratory infections in hospitalized children in Novosibirsk City, Russia (2013–2017). *PLoS One* 13:e0200117. doi: 10.1371/journal.pone.0200117

Lafond, K. E., Porter, R. M., Whaley, M. J., Suizan, Z., Ran, Z., Aleem, M. A., et al. (2021). Global burden of influenza-associated lower respiratory tract infections and hospitalizations among adults: a systematic review and meta-analysis. *PLoS Med.* 18:e1003550. doi: 10.1371/journal.pmed.1003550

Le Hingrat, Q., Bouzid, D., Choquet, C., Laurent, O., Lescure, F.-X., Timsit, J.-F., et al. (2021). Viral epidemiology and SARS-CoV-2 co-infections with other respiratory viruses during the first COVID-19 wave in Paris, France. *Influenza Other Respir. Viruses* 15, 425–428. doi: 10.1111/irv.12853

Maddah, N., Verma, A., Almashmoum, M., and Ainsworth, J. (2023). Effectiveness of public health digital surveillance Systems for Infectious Disease Prevention and Control at mass gatherings: systematic review. *J. Med. Internet Res.* 25:e44649. doi: 10.2196/44649

Martínez-Roig, A., Salvadó, M., Caballero-Rabasco, M. A., Sánchez-Buenavida, A., López-Segura, N., and Bonet-Alcaina, M. (2015). Viral coinfection in childhood respiratory tract infections. *Arch. Bronconeumol.* 51, 5–9. doi: 10.1016/j.arbres.2014.01.018

Martin-Loeches, I., Lemiale, V., Geoghegan, P., McMahon, M. A., Pickkers, P., Soares, M., et al. (2019). Influenza and associated co-infections in critically ill immunosuppressed patients. *Crit. Care* 23:152. doi: 10.1186/s13054-019-2425-6

Martins Júnior, R. B., Carney, S., Goldemberg, D., Bonine, L., Spano, L. C., Siqueira, M., et al. (2014). Detection of respiratory viruses by real-time polymerase chain reaction in outpatients with acute respiratory infection. *Mem. Inst. Oswaldo Cruz* 109, 716–721. doi: 10.1590/0074-0276140046

Martins, J. P., Siqueira, B. A., Sansone, N. M. S., and Marson, F. A. L. (2023). COVID-19 in Brazil: a three-year update. *Diagn. Microbiol. Infect. Dis.* 2023:116074. doi: 10.1016/j.diagmicrobio.2023.116074

McAdam, A. J., Hasenbein, M. E., Feldman, H. A., Cole, S. E., Offermann, J. T., Riley, A. M., et al. (2004). Human metapneumovirus in children tested at a tertiary-care hospital. *J. Infect. Dis.* 190, 20–26. doi: 10.1086/421120

Ministério da Saúde (2024). Ministério da Saúde. Available at: https://www.gov.br/saude/pt-br/pagina-inicial (Accessed September 3, 2024).

Morales-Jadán, D., Muslin, C., Viteri-Dávila, C., Coronel, B., Castro-Rodríguez, B., Vallejo-Janeta, A. P., et al. (2023). Coinfection of SARS-CoV-2 with other respiratory pathogens in outpatients from Ecuador. *Front. Public Health* 11:1264632. doi: 10.3389/fpubh.2023.1264632

Moreira, A. L. E., da Silva, P. A. N., Assunção, L., Santos, M. O., Ito, C. R. M., de Araújo, K. M., et al. (2023). Profile analysis of emerging respiratory virus in children. *Eur. J. Clin. Microbiol. Infect. Dis.* 42, 873–882. doi: 10.1007/s10096-023-04615-8

Morse, S. S. (2012). Public health surveillance and infectious disease detection. *Biosecur. Bioterror.* 10, 6–16. doi: 10.1089/bsp.2011.0088

Moumbeket Yifomnjou, M. H., Monamele, G. C., Njankouo-Ripa, M., Fatawou Modiyinji, A., Ngoupo, P. A., Boyomo, O., et al. (2023). Viral co-infection with human respiratory syncytial virus in suspected acute and severe respiratory tract infections during COVID-19 pandemic in Yaoundé, Cameroon, 2020–2021. *Influenza Other Respir. Viruses* 17:e13131. doi: 10.1111/irv.13131

Nelson, M. I., and Vincent, A. L. (2015). Reverse zoonosis of influenza to swine: new perspectives on the human-animal interface. *Trends Microbiol.* 23, 142–153. doi: 10.1016/j.tim.2014.12.002

Noyola, D. E., Hunsberger, S., Valdés Salgado, R., Powers, J. H., Galindo-Fraga, A., Ortiz-Hernández, A. A., et al. (2019). Comparison of rates of hospitalization between single and dual virus detection in a Mexican cohort of children and adults with influenza-like illness. *Open Forum Infect. Dis.* 6:ofz424. doi: 10.1093/ofid/ofz424

Palamim, C. V. C., Siqueira, B. A., Boschiero, M. N., and Marson, F. A. L. (2023). Increase in COVID-19 underreporting among 3,282,337 Brazilian hospitalized patients due to SARS: a 3-year report and a major concern for health authorities. *Travel Med. Infect. Dis.* 54:102616. doi: 10.1016/j.tmaid.2023.102616

Pinky, L., and Dobrovolny, H. M. (2016). Coinfections of the respiratory tract: viral competition for resources. *PLoS One* 11:e0155589. doi: 10.1371/journal.pone.0155589

Piret, J., and Boivin, G. (2022). Viral interference between respiratory viruses. *Emerg. Infect. Dis.* 28, 273–281. doi: 10.3201/eid2802.211727

Racial and income inequalities in access to healthcare in Brazilian cities—ScienceDirect (2024). Available at: https://www.sciencedirect.com/science/article/pii/S2214140523001585 (Accessed September 6, 2024).

Rath, B., Conrad, T., Myles, P., Alchikh, M., Ma, X., Hoppe, C., et al. (2017). Influenza and other respiratory viruses: standardizing disease severity in surveillance and clinical trials. *Expert Rev. Anti-Infect. Ther.* 15, 545–568. doi: 10.1080/14787210.2017.1295847

Rice, T. W., Rubinson, L., Uyeki, T. M., Vaughn, F. L., John, B. B., Miller, R. R., et al. (2012). Critical illness from 2009 pandemic influenza a virus and bacterial coinfection in the United States. *Crit. Care Med.* 40, 1487–1498. doi: 10.1097/CCM.0b013e3182416f23

Sansone, N. M. S., Boschiero, M. N., and Marson, F. A. L. (2022b). Epidemiologic profile of severe acute respiratory infection in Brazil during the COVID-19 pandemic: an epidemiological study. *Front. Microbiol.* 13:911036. doi: 10.3389/fmicb.2022.911036

Sansone, N. M., Boschiero, M. N., Valencise, F. E., Palamim, C. V., and Marson, F. A. (2022a). Characterization of demographic data, clinical signs, comorbidities, and outcomes according to the race in hospitalized individuals with COVID-19 in Brazil: an observational study. *J. Glob. Health* 12:5027. doi: 10.7189/jogh.12.05027

Semple, M. G., Cowell, A., Dove, W., Greensill, J., McNamara, P. S., Halfhide, C., et al. (2005). Dual infection of infants by human metapneumovirus and human respiratory syncytial virus is strongly associated with severe bronchiolitis. *J. Infect. Dis.* 191, 382–386. doi: 10.1086/426457

Staadegaard, L., Del Riccio, M., Wiegersma, S., El Guerche-Séblain, C., Dueger, E., Akçay, M., et al. (2023). The impact of the SARS-CoV-2 pandemic on global influenza surveillance: insights from 18 National Influenza Centers based on a survey conducted between November 2021 and march 2022. *Influenza Other Respir. Viruses* 17:e13140. doi: 10.1111/irv.13140

Sullivan, K. M., Dean, A., and Soe, M. M. (2009). OpenEpi: a web-based epidemiologic and statistical calculator for public health. *Public Health Rep.* 124, 471–474

Swets, M. C., Russell, C. D., Harrison, E. M., Docherty, A. B., Lone, N., Girvan, M., et al. (2022). SARS-CoV-2 co-infection with influenza viruses, respiratory syncytial virus, or adenoviruses. *Lancet* 399, 1463–1464. doi: 10.1016/S0140-6736(22)00383-X

Sze, S., Pan, D., Nevill, C. R., Gray, L. J., Martin, C. A., Nazareth, J., et al. (2020). Ethnicity and clinical outcomes in COVID-19: a systematic review and meta-analysis. *EClinicalMedicine* 29:100630. doi: 10.1016/j.eclinm.2020.100630

Szymański, K., Cieślak, K., Kowalczyk, D., and Brydak, L. B. (2017). Co-infection with influenza viruses and influenza-like virus during the 2015/2016 epidemic season. *Adv. Exp. Med. Biol.* 968, 7–12. doi: 10.1007/5584_2016_182

The burden of Influenza (2024). Available at: https://www.who.int/news-room/feature-stories/detail/the-burden-of-influenza (Accessed May 16, 2024).

Trenholme, A. A., Best, E. J., Vogel, A. M., Stewart, J. M., Miller, C. J., and Lennon, D. R. (2017). Respiratory virus detection during hospitalisation for lower respiratory tract infection in children under 2 years in South Auckland, New Zealand. *J. Paediatr. Child Health* 53, 551–555. doi: 10.1111/jpc.13529

Trenholme, A., Webb, R., Lawrence, S., Arrol, S., Taylor, S., Ameratunga, S., et al. (2021). COVID-19 and infant hospitalizations for seasonal respiratory virus infections, New Zealand, 2020. *Emerg. Infect. Dis.* 27, 641–643. doi: 10.3201/eid2702.204041

Vianna, L. A., Siqueira, M. M., Volpini, L. P. B., Louro, I. D., and Resende, P. C. (2021). Seasonality, molecular epidemiology, and virulence of respiratory syncytial virus (RSV): a perspective into the Brazilian influenza surveillance program. *PLoS One* 16:e0251361. doi: 10.1371/journal.pone.0251361

Viegas, M., Barrero, P. R., Maffey, A. F., and Mistchenko, A. S. (2004). Respiratory viruses seasonality in children under five years of age in Buenos Aires, Argentina: a five-year analysis. *J. Infect.* 49, 222–228. doi: 10.1016/j.jinf.2003.10.006

Weigl, J. A. I., Puppe, W., Meyer, C. U., Berner, R., Forster, J., Schmitt, H. J., et al. (2007). Ten years' experience with year-round active surveillance of up to 19 respiratory pathogens in children. *Eur. J. Pediatr.* 166, 957–966. doi: 10.1007/s00431-007-0496-x

Williams, D. R., and Rucker, T. D. (2000). Understanding and addressing racial disparities in health care. *Health Care Financ. Rev.* 21, 75–90

Wishaupt, J. O., van der Ploeg, T., de Groot, R., Versteegh, F. G. A., and Hartwig, N. G. (2017). Single-and multiple viral respiratory infections in children: disease and management cannot be related to a specific pathogen. *BMC Infect. Dis.* 17:62. doi: 10.1186/s12879-016-2118-6

Yan, X., Li, K., Lei, Z., Luo, J., Wang, Q., and Wei, S. (2023). Prevalence and associated outcomes of coinfection between SARS-CoV-2 and influenza: a systematic review and meta-analysis. *Int. J. Infect. Dis.* 136, 29–36. doi: 10.1016/j.ijid.2023.08.021

Zhang, Y., Qiao, L., Yao, J., Yu, N., Mu, X., Huang, S., et al. (2021). Epidemiological and clinical characteristics of respiratory viruses in 4403 pediatric patients from multiple hospitals in Guangdong, China. *BMC Pediatr* 21, 1–10. doi: 10.1186/s12887-021-02759-0

5. CONCLUSÃO

A análise dos dois trabalhos realizados sobre pacientes internados por infecção pelo vírus influenza revelou importantes achados epidemiológicos e clínicos. No primeiro estudo, observou-se que os pacientes internados devido à infecção pelo vírus influenza, predominantemente do tipo A, eram majoritariamente mulheres brancas, com mais de 25 anos e residentes em áreas urbanas. Esses pacientes frequentemente apresentavam sintomas respiratórios e comorbidades pré-existentes, com uma taxa de mortalidade de 14,7%. O risco de morte foi significativamente associado ao tipo A do vírus, especialmente nos casos que necessitaram de internação em UTI e suporte ventilatório. Fatores adicionais como idade avançada, presença de sintomas e sinais clínicos respiratórios, residência em áreas periurbanas e comorbidades específicas também se mostraram relevantes para a predisposição ao óbito.

No segundo estudo, foi destacada a co-detecção do vírus influenza com outros vírus respiratórios, sendo o vírus sincicial respiratório, rinovírus e adenovírus os mais comuns, predominantemente em homens brancos na fase juvenil. A co-detecção do vírus influenza com bocavírus e metapneumovírus esteve associada a um aumento significativo na chance de morte. Além disso, fatores como raça, presença de doenças cardíacas e necessidade de UTI foram igualmente associados a um maior risco de mortalidade.

Em síntese, ambos os estudos enfatizam a complexidade e a gravidade das infecções pelo vírus influenza, particularmente do tipo A, e a influência de comorbidades e fatores demográficos na mortalidade dos pacientes. A necessidade de UTI e suporte ventilatório são indicadores críticos de prognóstico desfavorável. Adicionalmente, a co-detecção de influenza com outros vírus respiratórios, especialmente bocavírus e metapneumovírus, emerge como um fator agravante. Estes achados ressaltam a importância de um monitoramento contínuo e de abordagens terapêuticas específicas para os grupos de maior risco, a fim de reduzir a mortalidade associada a essas infecções virais.

REFERÊNCIAS

AGCA, H.; AKALIN, H.; SAGLIK, I.; HACIMUSTAFAOGLU, M.; CELEBI, S.; ENER, B. Changing epidemiology of influenza and other respiratory viruses in the first year of COVID-19 pandemic. **Journal of Infection and Public Health**, v. 14, n. 9, p. 1186-1190, 2021.

AOKI, F. Y.; PAPENBURG, J.; MUBAREKA, S.; ALLEN, U. D.; HATCHETTE, T. F.; EVANS, G. A. 2021-2022 AMMI Canada guidance on the use of antiviral drugs for influenza in the COVID-19 pandemic setting in Canada. **Journal of the Association of Medical Microbiology and Infectious Disease Canada**, v. *7*, n. 1, p. 1–7, 2022.

BALLEGEER, M.; SAELENS, X. Cell-Mediated Responses to Human Metapneumovirus Infection. **Viruses**, v. 12, n. 5, p. 542, 2020.

BAQUI, P.; BICA, I.; MARRA, V.; ERCOLE, A.; VAN DER SCHAAR, M. Ethnic and regional variations in hospital mortality from COVID-19 in Brazil: a cross-sectional observational study. **The Lancet Global Health**, v. *8*, n. 8, p. 1018–1026, 2020.

BINNS, E.; KOENRAADS, M.; HRISTEVA, L.; FLAMANT, A.; BAIER-GRABNER, S.; LOI, M; LEMPAINEN, J.; OSTERHELD, E.; RAMLY, B.; CHAKAKALA-CHAZIYA, J.; ENAGANTHI, N.; SIMÓ NEBOT, S.; BUONSENSO, D. Influenza and respiratory syncytial virus during the COVID-19 pandemic: Time for a new paradigm. **Pediatric Pulmonology**, v.57, n. 1, p. 38–42, 2022.

BLOUNT, R. E.; MORRIS, J. A.; SAVAGE, R. E. Recovery of cytopathogenic agent from chimpanzees with coryza. **Proceedings of the Society for Experimental Biology and Medicine. Society for Experimental Biology and Medicine**, v. 92, n. 3, p. 544–549, 1956.

BOCHKOV, Y. A.; GERN, J. E. Rhinoviruses and Their Receptors: Implications for Allergic Disease. **Current Allergy and Asthma Reports**, v. 16, n. 4, p. 30, 2016.

BORCHERS, A. T.; CHANG, C.; GERSHWIN, M. E.; GERSHWIN, L. J. Respiratory syncytial virus: a comprehensive review. **Clinical Reviews in Allergy & Immunology**, v. 45, n. 3, p. 331–379, 2013.

BOSCHIERO, M. N.; DUARTE, A.; PALAMIM, C. V. C.; ALVAREZ, A. E.; MAUCH, R. M.; MARSON, F. A. L. Frequency of respiratory pathogens other than SARS-CoV-2 detected during COVID-19 testing. **Diagnostic Microbiology and Infectious Disease**, v. 102, n. 2, p. 115576, 2022.

BRANCHE, A. R.; FALSEY, A. R. Parainfluenza Virus Infection. **Seminars in Respiratory and Critical Care Medicine**, v. 37, n. 4, p. 538–554, 2016.

BRASIL. Ministério da Saúde. **Painel Coronavírus, 2022**. Disponível em: <https://news.google.com/covid19/map?hl=ptBR&mid=%2Fm%2F015fr&gl=BR&ceid=BR%3Apt-419>. Acesso em: 10 de dezembro de 2022.

BRIAN, D. A.; BARIC, R. S. Coronavirus genome structure and replication. **Current Topics in Microbiology and Immunology**, v. 287, n. 1, p. 1–30, 2005.

CALCAGNO, A.; GHISETTI, V.; BURDINO, E.; TRUNFIO, M.; ALLICE, T.; BOGLIONE, L.; BONORA, S.; DI PERRI, G. Co-infection with other respiratory pathogens in COVID-19 patients. **Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases**, v. 27, n. 2, p. 297–298, 2021.

CAO, Y.; LIU, X.; XIONG, L.; CAI, K. Imaging and clinical features of patients with 2019 novel coronavirus SARS-CoV-2: A systematic review and meta-analysis. **Journal of Medical Virology**, v. 92, n. 9, p. 1449–1459, 2020.

CHAN, J. F.; YUAN, S.; KOK, K. H.; TO, K. K.; CHU, H.; YANG, J.; XING, F.; LIU, J.; YIP, C. C.; POON, R. W.; TSOI, H. W.; LO, S. K.; CHAN, K. H.; POON, V. K.; CHAN, W. M.; IP, J. D.; CAI, J. P.; CHENG, V. C.; CHEN, H.; HUI, C. K., YUEN, K. Y. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. **Lancet**, v. 395, n. 10223, p. 514–523, 2020.

CHONG, Y. M.; CHAN, Y. F.; JAMALUDDIN, M. F. H.; HASAN, M. S.; PANG, Y. K.; PONNAMPALAVANAR, S.; SYED OMAR, S. F.; VOON, K. G. L.; SAM, I. C. Detection of respiratory viruses in adults with suspected COVID-19 in Kuala Lumpur, Malaysia. **Journal of Clinical Virology**, v.145, p.105000, 2021.

CHUA, E. X.; ZAHIR, S. M. I. S. M.; NG, K. T.; TEOH, W. Y.; HASAN, M. S.; RUSLAN, S. R. B.; ABOSAMAK, M. F. Effect of prone versus supine position in COVID-19 patients: A systematic review and meta-analysis. **Journal of Clinical Anesthesia**, v. 74, p. 110406, 2021.

COSTANZA, G.; PABA, P.; CIOTTI, M.; OMBRES, D.; DI CARLO, S.; MARCUCCILLI, F.; BERTOLI, A.; DI TRAGLIA, L.; MOZZANI, M.; PIREDDA, L.; PETRONE, V.; FANELLI, M.; PAGANELLI, C.; CORTESE, B.; BALESTRIERI, E.; BERNARDINI, S.; ANDREONI, M.; MATTEUCCI, C.; MINUTOLO, A.; GRELLI, S. Infection Rate of Respiratory Viruses in the Pandemic SARS-CoV-2 Period Considering Symptomatic Patients: Two Years of Ongoing Observations. **Biomolecules**, v.12, n. 7, p. 987, 2022.

COVID-19 Treatment Guidelines Panel. National Institutes of Health; 2021. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. Disponível em: <https://www.Covid19treatmentguidelines.Nih.Gov/>. Acesso em: 08/12/2022.

COVID-19 Weekly Epidemiological Update – World Health Organization. Edition 119 published 23 November 2022, p. 1-26.

DA COSTA, V. G.; SAIVISH, M. V.; SANTOS, D. E. R.; DE LIMA SILVA, R. F.; MORELI, M. L. Comparative epidemiology between the 2009 H1N1 influenza and COVID-19 pandemics**. Journal of Infection and Public Health**, v. 13, n. 12, p. 1797–1804, 2020.

DE FRANCESCO, M. A.; POLLARA, C.; GARGIULO, F.; GIACOMELLI, M.; CARUSO, A. Circulation of Respiratory Viruses in Hospitalized Adults before and during the COVID-19 Pandemic in Brescia, Italy: A Retrospective Study. **International Journal of Environmental Research and Public Health**, v. 18, n. 18, p. 9525, 2021.

DE SOUZA, W. M.; BUSS, L. F.; CANDIDO, D. D. S.; CARRERA, J. P.; LI, S.; ZAREBSKI, A. E.; PEREIRA, R. H. M.; PRETE, C. A.; DE SOUZA-SANTOS, A. A.; PARAG, K. V.; BELOTTI, M. C. T. D.; VINCENTI-GONZALEZ, M. F.; MESSINA, J.; DA SILVA SALES, F. C.; ANDRADE, P. D. S.; NASCIMENTO, V. H.; GHILARDI, F.; ABADE, L.; GUTIERREZ, B.; KRAEMER, M. U. G.; BRAGA, C. K. V.; AGUIAR, R. S.; ALEXANDER, N.; MAYAUD, P.; BRADY, O. J.; MARCILIO, I.; GOUVEIA, N.; LI, G.; TAMI, A.; DE OLIVEIRA, S. B.;

PORTO, V. B. G.; GANEM, F.; DE ALMEIDA, W. A. F.; FANTINATO, F. F. S. T.; MACÁRIO, E. M.; DE OLIVEIRA, W. K.; NOGUEIRA, M. L.; PYBUS, O. G.; WU, C. H.; CRODA, J.; SABINO, E. C.; FARIA, N. R. . Epidemiological and clinical characteristics of the COVID-19 epidemic in Brazil. **Nature Human Behaviour**, v. 4, n. 8, p. 856–865, 2020.

DE VIRGILIO, A.; COSTANTINO, A.; MERCANTE, G.; SPRIANO, G. How to increase the SARS-CoV-2 detection rate through the nasopharyngeal swab?. **Oral Oncology**, v. 106, p. 104802, 2020.

DI SERAFINO, M.; NOTARO, M.; REA, G.; IACOBELLIS, F.; DELLI PAOLI, V.; ACAMPORA, C.; IANNIELLO, S.; BRUNESE, L.; ROMANO, L.;VALLONE, G. The lung ultrasound: facts or artifacts? In the era of COVID-19 outbreak. **La Radiologia medica**, v.125, n. 8, p. 738–753, 2020.

DINA, J.; VABRET, A.; GOUARIN, S.; PETITJEAN, J.; LECOQ, J.; BROUARD, J.; ARION, A.; LAFAY-DELAIRE, F.; FREYMUTH, F. Detection of human bocavirus in hospitalised children. **Journal of Paediatrics and Child Health**, v. 45, n. 3, p. 149–153, 2009.

DING, L.; WANG, L.; MA, W.; HE, H. Efficacy and safety of early prone positioning combined with HFNC or NIV in moderate to severe ARDS: a multi-center prospective cohort study. **Critical Care**, v. 24, n. 1, p. 28, 2020.

DROŻDŻAL, S.; ROSIK, J.; LECHOWICZ, K.; MACHAJ, F., SZOSTAK, B.; PRZYBYCIŃSKI, J.; LORZADEH, S.; KOTFIS, K.; GHAVAMI, S.; ŁOS, M. J. An update on drugs with therapeutic potential for SARS-CoV-2 (COVID-19) treatment. **Drug Resistance Updates**, v. 59, p. 100794, 2021.

ESPOSITO, A.; PALMISANO A.; SCOTTI, G. M.; MORELLI, M. J.; VIGNALE, D.; DE COBELLI, F.; TONON, G.; TACCHETTI, C. Why is chest CT important for early diagnosis of COVID-19? Prevalence matters. **MedRxiv: The Preprint Server For Health Science,** 2020

FEDELE, F.; ARIA, M.; ESPOSITO, V.; MICILLO, M.; CECERE, G.; SPANO, M.; DE MARCO, G. COVID-19 vaccine hesitancy: a survey in a population highly compliant to common vaccinations. **Human Vaccines & Immunotherapeutics**, v. 17, n. 10, p. 3348–3354, 2021.

FERNANDES, L. L.; PACHECO, V. B.; BORGES, L.; ATHWAL, H. K.; de PAULA EDUARDO, F.; BEZINELLI, L.; CORREA, L.; JIMENEZ, M.; DAME-TEIXEIRA, N.; LOMBAERT, I. M. A.; HELLER, D. Saliva in the Diagnosis of COVID-19: A Review and New Research Directions. **Journal of dental research**, v. 99, n. 13,p. 1435–1443, 2020.

FICHTNER, F.; MOERER, O.; LAUDI, S.; WEBER-CARSTENS, S.; NOTHACKER, M.; KAISERS, U.; Investigators and the Guideline Group on Mechanical Ventilation and Extracorporeal Membrane Oxygenation in Acute Respiratory Insufficiency. Mechanical Ventilation and Extracorporeal Membrane Oxygenation in Acute Respiratory Insufficiency. **Deutsches Arzteblatt International**, v. 115, n. 50, p. 840–847, 2018.

FIELDS, B. K. K.; DEMIRJIAN, N. L.; GHOLAMREZANEZHAD, A. Coronavirus Disease 2019 (COVID-19) diagnostic technologies: A country-based retrospective analysis of screening and containment procedures during the first wave of the pandemic. **Clinical Imaging**, v. 67, p. 219–225, 2020.

Food and Drug Administration. 2020. Fact Sheet for Healthcare Providers: Emergency Use Authorization (EUA) of REGEN-COV (Casirivimab and Imdevimab).

FRY, A. M.; LU, X.; CHITTAGANPITCH, M.; PERET, T.; FISCHER, J.; DOWELL, S. F.; ANDERSON, L. J.; ERDMAN, D.; OLSEN, S. J. Human bocavirus: a novel parvovirus epidemiologically associated with pneumonia requiring hospitalization in Thailand. **The Journal of Infectious Diseases**, v. 195, n. 7, p. 1038–1045, 2007.

GAITONDE, D. Y.; MOORE, F. C.; MORGAN, M. K. Influenza: Diagnosis and Treatment. **American Family Physician**, v. 100, n. 12, p. 751–758, 2019.

GAMBLIN, S. J.; VACHIERI, S. G.; XIONG, X.; ZHANG, J.; MARTIN, S. R.; SKEHEL, J. J. Hemagglutinin Structure and Activities. **Cold Spring Harbor Perspectives in Medicine**, v. 11, n. 10, p. 038638, 2021.

GAREGNANI, L.; STYRMISDÓTTIR, L.; ROSON RODRIGUEZ, P.; ESCOBAR LIQUITAY, C. M.; ESTEBAN, I.; FRANCO, J. V. Palivizumab for preventing severe respiratory syncytial virus (RSV) infection in children. **The Cochrane database of systematic reviews**, v.11, n. 11, p.13757, 2021.

GILCA, R.; DE SERRES, G.; TREMBLAY, M.; VACHON, M. L.; LEBLANC, E.; BERGERON, M. G.; DERY, P.; BOIVIN, G. Distribution and clinical impact of human respiratory syncytial virus genotypes in hospitalized children over 2 winter seasons. **The Journal of Infectious Diseases**, v. 193, n. 1, p. 54–58, 2006.

GRIFFITHS C, DREWS SJ, MARCHANT DJ. Respiratory Syncytial Virus: Infection, Detection, and New Options for Prevention and Treatment. **Clin Microbiol Ver**, v. 30, n.1, p.277-319, 2017.

GUAN, W. J.; NI, Z. Y.; HU, Y.; LIANG, W. H.; OU, C. Q.; HE, J. X.; LIU, L.; SHAN, H.; LEI, C. L.; HUI, D. S. C.; DU, B.; LI, L. J.; ZENG, G.; YUEN, K. Y.; CHEN, R. C.; TANG, C. L.; WANG, T.; CHEN, P. Y.; XIANG, J.; LI, S. Y. China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. **The New England journal of medicine**, v. 382, n. 18, p. 1708–1720, 2020.

GUIDO, M.; TUMOLO, M. R.; VERRI, T.; ROMANO, A.; SERIO, F.; DE GIORGI, M.; DE DONNO, A.; BAGORDO, F.; ZIZZA, A. Human bocavirus: Current knowledge and future challenges. **World journal of Gastroenterology**, v. 22, n. 39, p. 8684–8697, 2016.

HERMOS, C. R.; VARGAS, S. O.; MCADAM, A. J. Human metapneumovirus. **Clinics in Laboratory Medicine**, v. 30, n. 1, p. 131–148, 2010.

HU, W.; FRIES, A. C.; DEMARCUS, L. S.; THERVIL, J. W.; KWAAH, B.; BROWN, K. N.; SJOBERG, P. A.; ROBBINS, A. S. Circulating Trends of Influenza and Other Seasonal Respiratory Viruses among the US Department of Defense Personnel in the United States: Impact of the COVID-19 Pandemic. **International Journal of Environmental Research and Public Health**, v. 19, n. 10, p. 5942, 2022.

JARTTI, T.; HEDMAN, K.; JARTTI, L.; RUUSKANEN, O.; ALLANDER, T.; SÖDERLUND-VENERMO, M. Human bocavirus-the first 5 years**. Reviews in Medical Virology**, v. 22, n. 1, p. 46–64, 2012.

KANGABAM, R.; SAHOO, S.; GHOSH, A.; ROY, R.; SILLA, Y.; MISRA, N.; SUAR, M. Next-generation computational tools and resources for coronavirus research: From detection to vaccine discovery. **Computers in Biology and Medicine**, v. 128, p. 104158, 2021.

KEILMAN L. J. Seasonal Influenza (Flu). **The Nursing Clinics of North America**, v. 54, n. 2, p. 227–243, 2019.

KERR, S. L.; MATHEW, C.; GHILDYAL, R. Rhinovirus and Cell Death. **Viruses**, v. 13, n. 4, p. 629, 2021.

KESEBIR, D.; VAZQUEZ, M.; WEIBEL, C.; SHAPIRO, E. D.; FERGUSON, D.; LANDRY, M. L.; KAHN, J. S. Human bocavirus infection in young children in the United States: molecular epidemiological profile and clinical characteristics of a newly emerging respiratory virus. **The Journal of Infectious Diseases**, v. 194, n. 9, p. 1276–1282, 2006.

KIM, D.; QUINN, J.; PINSKY, B.; SHAH, N. H.; BROWN, I. Rates of Co-infection Between SARS-CoV-2 and Other Respiratory Pathogens. **JAMA**, v. 323, n. 20, p. 2085–2086, 2020.

KLUGE, S.; JANSSENS, U.; WELTE, T.; WEBER-CARSTENS, S.; MARX, G.; KARAGIANNIDIS, C. German recommendations for critically ill patients with COVID-19. **Medizinische Klinik, Intensivmedizin und Notfallmedizin**, v. 115, n. 3, p. 111–114, 2020.

KNOLL, M. D.; WONODI, C. Oxford-AstraZeneca COVID-19 vaccine efficacy. **Lancet**, v. 397, n. 10269, p. 72–74, 2021.

LARICI, A. R.; CICCHETTI, G.; MARANO, R.; MERLINO, B.; ELIA, L.; CALANDRIELLO, L.; DEL CIELLO, A.; FARCHIONE, A.; SAVINO, G.; INFANTE, A.; LAROSA, L.; COLOSIMO, C.; MANFREDI, R.; Natale, L. Multimodality imaging of COVID-19 pneumonia: from diagnosis to follow-up. A comprehensive review. **European Journal of Radiology**, v. 131, p. 109217, 2020.

LEE, J.; CHOI, E. H.; LEE, H. J. Comprehensive serotyping and epidemiology of human adenovirus isolated from the respiratory tract of Korean children over 17 consecutive years (1991-2007). **Journal of Medical Virology**, v. 82, n. 4, p. 624–631, 2010.

LEVINE-TIEFENBRUN, M.; YELIN, I.; KATZ, R.; HERZEL, E.; GOLAN, Z.; SCHREIBER, L.; WOLF, T.; NADLER, V.; BEN-TOV, A.; KUINT, J.; GAZIT, S.; PATALON, T.; CHODICK, G.; KISHONY, R. Initial report of decreased SARS-CoV-2 viral load after inoculation with the BNT162b2 vaccine. **Nature Medicine**, v. 27, n. 5, p. 790–792, 2021.

LIMA, S. T.; VERGUEIRO, M. V. B.; SOUZA JR, E.C.; FERREIRA, D. L.; SOUZA, E. M. A.; MELLO, W. A.; SOUSA, R. C. M.; SANTOS, M. C. Epidemiologia molecular de cepas de rinovírus humano circulantes na Cidade de Belém. **Revista Pan-Amazônica de Saúde**, v. 7, p. 159-165, 2016.

LION. T. Adenovirus infections in immunocompetent and immunocompromised patients. **Clinical Microbiology Reviews**, v. 27, n. 3, p. 441–462, 2014.

LIPPI, G.; SIMUNDIC, A. M.; PLEBANI, M. Potential preanalytical and analytical vulnerabilities in the laboratory diagnosis of coronavirus disease 2019 (COVID-19). **Clinical Chemistry and Laboratory Medicine**, v. 58, n. 7, p. 1070–1076, 2020.

LIU, J.; LIU, S. The management of coronavirus disease 2019 (COVID-19). **Journal of Medical Virology**, v. 92, n. 9, p. 1484–1490, 2020.

LIU, R.; HAN, H.; LIU, F.; LV, Z.; WU, K.; LIU, Y.; FENG, Y.; ZHU, C. Positive rate of RT-PCR detection of SARS-CoV-2 infection in 4880 cases from one hospital in Wuhan. **Clinica Chimica Acta**, v. 505, p.172–175, 2020.

LOEVINSOHN, G.; HAMAHUWA, M.; HARDICK, J.; SINYWIMAANZI, P.; FENSTERMACHER, K. Z. J.; MUNACHOONGA, P.; WEYNAND, A.; MONZE, M.; MANABE, Y. C.; GAYDOS, C. A.; ROTHMAN, R. E.; PEKOSZ, A.; THUMA, P. E.; SIMULUNDU, E.; SUTCLIFFE, C. G. Respiratory viruses in rural Zambia before and during the COVID-19 pandemic. **Tropical Medicine & International Health**, v. 27, n. 7, p. 647–654, 2022.

LUO M. Influenza virus entry. **Advances in Experimental Medicine and Biology**, v. 726, p. 201–221, 2012.

LYNCH, J. P.; KAJON, A. E. Adenovirus: Epidemiology, Global Spread of Novel Serotypes, and Advances in Treatment and Prevention. **Seminars in Respiratory and Critical Care Medicine**, v. 37, n. 4, p. 586–602, 2016.

LYNCH, J. P.; FISHBEIN, M.; ECHAVARRIA, M. Adenovirus. **Seminars in Respiratory and Critical Care Medicine**, v. 32, n. 4, p. 494–511, 2011.

MAJUMDER, J.; MINKO, T. Recent Developments on Therapeutic and Diagnostic Approaches for COVID-19. **The AAPS Journal**, v. 23, n. 1, p.14, 2021.

MANIRUZZAMAN, M.; ISLAM, M. M.; ALI, M. H.; MUKERJEE, N.; MAITRA, S.; KAMAL, M. A.; GHOSH, A.; CASTROSANTO, M. A.; ALEXIOU, A.; ASHRAF, G. M.; TAGDE, P.; RAHMAN, M. H. COVID-19 diagnostic methods in developing countries. **Environmental Science and Pollution Research International**, v. 29, n. 34, p. 51384–51397, 2022.

MCARDLE, A.; WASHINGTON, K. E.; CHAZARIN ORGEL, B.; Binek, A.; MANALO, D. M.; RIVAS, A.; AYRES, M.; PANDEY, R.; PHEBUS, C.; RAEDSCHELDERS, K.; FERT-BOBER, J.; VAN EYK, J. E. Discovery Proteomics for COVID-19: Where We Are Now. **Journal of Proteome Research**, v. 20, n. 10, p. 4627–4639, 2021.

MENG, L.; QIU, H.; WAN, L.; AI, Y.; XUE, Z.; GUO, Q.; DESHPANDE, R.; ZHANG, L.; MENG, J.; TONG, C.; LIU, H.; XIONG, L. Intubation and Ventilation amid the COVID-19 Outbreak: Wuhan's Experience. **Anesthesiology**, v. 132, n. 6, p. 1317–1332, 2020.

MORIYAMA, M.; HUGENTOBLER, W. J.; IWASAKI, A. Seasonality of Respiratory Viral Infections. **Annual review of virology**, v. 7, n. 1, p. 83–101, 2020.

MUNSHI, L.; DEL SORBO, L.; ADHIKARI, N. K. J.; HODGSON, C. L.; WUNSCH, H.; MEADE, M. O.; ULERYK, E.; MANCEBO, J.; PESENTI, A.; RANIERI, V. M.; FAN, E. Prone Position for Acute Respiratory Distress Syndrome. A Systematic Review and Meta-Analysis. **Annals of the American Thoracic Society**, v. 14, n. 4, p. S280–S288, 2017.

MURPHY K. SARS CoV-2 Detection From Upper and Lower Respiratory Tract Specimens: Diagnostic and Infection Control Implications. **Chest**, v. 158, n. 5, p. 1804–1805, 2020.

NYPAVER, C.; DEHLINGER, C.; CARTER, C. Influenza and Influenza Vaccine: A Review. **Journal of Midwifery & Women's Health**, v. 66, n. 1, p. 45–53, 2021.

O'DRISCOLL, B. R.; HOWARD, L. S.; EARIS, J.; MAK, V.; British Thoracic Society Emergency Oxygen Guideline Group.; BTS Emergency Oxygen Guideline Development Group. BTS guideline for oxygen use in adults in healthcare and emergency settings. **Thorax**, v. 72, n. 1, p. ii1–ii90, 2017.

O'SHEA, P. M.; LEE, G. R.; GRIFFIN, T. P.; TORMEY, V.; HAYAT, A.; COSTELLOE, S. J.; GRIFFIN, D. G.; SRINIVASAN, S.; O'KANE, M.; BURKE, C. M.; FAUL, J.; THOMPSON, C. J.; CURLEY, G.; TORMEY, W. P. COVID-19 in adults: test menu for hospital blood science laboratories. **Irish Journal of Medical Science**, v. 189, n. 4, p. 1147–1152, 2020.

PALAMIM, C. V. C.; BOSCHIERO, M. N.; VALENCISE, F. E.; MARSON, F. A. L. Human Development Index Is Associated with COVID-19 Case Fatality Rate in Brazil: An Ecological Study**. International Journal of Environmental Research and Public Health**, v. 19, n. 9, p. 5306, 2022.

PARK, J. Y.; KIM, H. I.; KIM, J. H.; PARK, S.; HWANG, Y. I.; JANG, S. H.; KIM, Y. K.; JUNG, K. S. Changes in respiratory virus infection trends during the COVID-19 pandemic in South Korea: the effectiveness of public health measures. **The Korean Journal of Internal Medicine**, v. 36, n. 5, p. 1157–1168, 2021.

PERK, O.; OZCAN, S.; EMEKSIZ, S.; UYAR, E.; Gulhan, B. Comparison of Clinical Findings in SARS-CoV-2 with Other Respiratory Viruses in Critically Ill Children during the COVID-19 Pandemic. **Journal of Tropical Pediatrics**, v. 67, n. 6, p. 102, 2021.

PETTER, E.; MOR, O.; ZUCKERMAN, N.; OZ-LEVI, D.; YOUNGER, A.; ARAN, D.; ERLICH, Y. Evidência inicial do mundo real para menor carga viral de indivíduos que foram vacinados por BNT162b2. **MedRxiv: The Preprint Server For Health Sciences**, 2021.

PFEIFER, M.; EWIG, S.; VOSHAAR, T.; RANDERATH, W.; BAUER, T.; GEISELER, J.; DELLWEG, D.; WESTHOFF, M.; WINDISCH, W.; SCHÖNHOFER, B.; KLUGE, S.; LEPPER, P. M. Position Paper for the State-of-the-Art Application of Respiratory Support in Patients with COVID-19 - German Respiratory Society. **Pneumologie**, v. 74, n. 6, p. 337–357, 2020.

PIEDIMONTE, G.; PEREZ, M. K. Respiratory syncytial virus infection and bronchiolitis. **Pediatrics in Review**, v. 35, n. 12, p. 519–530, 2014.

POLACK, F. P.; THOMAS, S. J.; KITCHIN, N.; ABSALON, J.; GURTMAN, A.; LOCKHART, S.; PEREZ, J. L.; PÉREZ MARC, G.; MOREIRA, E. D.; ZERBINI, C.; BAILEY, R.; SWANSON, K. A.; ROYCHOUDHURY, S.; KOURY, K.; LI, P.; KALINA, W. V.; COOPER, D.; FRENCK, R. W.; JR, HAMMITT, L. L.; TÜRECI, Ö.; NELL, H.; SCHAEFER, A.; ÜNAL, S.; TRESNAN, D.B.; MATHER, S.; DORMITZER, P. R.;SAHIN, U.; JANSEN, K. U.; GRUBER, W. C.; C4591001 Clinical Trial Group. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. **The New England Journal of Medicine**, v. 383, n. 27, p. 2603–2615, 2020.

SADOFF, J.; LE GARS, M.; SHUKAREV, G.; HEERWEGH, D.; TRUYERS, C.; DE GROOT, A. M.; STOOP, J.; TETE, S.; VAN DAMME, W.; LEROUX-ROELS, I.; BERGHMANS, P. J.; KIMMEL, M.; VAN DAMME, P.; DE HOON, J.; SMITH, W.; STEPHENSON, K. E.; DE

ROSA, S. C.; COHEN, K. W.; MCELRATH, M. J.; CORMIER, E.; HENDRIKS, J.; STRUYF, F.; DOUOGUIH, M.; VAN HOOF, J.; SCHUITEMAKER, H. Interim Results of a Phase 1-2a Trial of Ad26.COV2.S Covid-19 Vaccine. **The New England Journal of Medicine**, v. 384, n. 19, p. 1824–1835, 2021.

SAFIABADI TALI, S. H.; LEBLANC, J. J.; SADIQ, Z.; OYEWUNMI, O. D.; CAMARGO, C.; NIKPOUR, B.; ARMANFARD, N.; SAGAN, S. M.; JAHANSHAHI-ANBUHI, S. Tools and Techniques for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)/COVID-19 Detection. **Clinical Microbiology Reviews**, v. 34, n. 3, p. e00228-20, 2021.

SAINT-PIERRE CONTRERAS, G.; MUÑOZ GOMEZ, G.; SILVA OJEDA, F. In search of other respiratory viruses during the COVID-19 pandemic. **Revista Clinica Espanola**, v. 221, n. 4, p. 247–248, 2021.

SANSONE, N. M. S.; BOSCHIERO, M. N.; ORTEGA, M. M.; RIBEIRO, I. A.; PEIXOTO, A. O.; MENDES, R. T.; MARSON, F. A. L. Severe Acute Respiratory Syndrome by SARS-CoV-2 Infection or Other Etiologic Agents Among Brazilian Indigenous Population: An Observational Study from the First Year of Coronavirus Disease (COVID)-19 Pandemic. **Lancet Regional Health**, v. 8, p. 100177, 2022.

SANSONE, N. M.; BOSCHIERO, M. N.; VALENCISE, F. E.; PALAMIM, C. V.; MARSON, F. A. L. Characterization of demographic data, clinical signs, comorbidities, and outcomes according to the race in hospitalized individuals with COVID-19 in Brazil: An observational study. **Journal of Global Health**, v. 12, p. 05027, 2022.

SCHUSTER, J. E.; Williams, J. V. Human Metapneumovirus. **Microbiology Spectrum**, v. 2, n. 5, p. 1110.1128, 2014.

SEYED HOSSEINI, E.; RIAHI KASHANI, N.; NIKZAD, H.; AZADBAKHT, J.; HASSANI BAFRANI, H.; HADDAD KASHANI, H. The novel coronavirus Disease-2019 (COVID-19): Mechanism of action, detection and recent therapeutic strategies. **Virology,** v. 551, p. 1–9, 2020.

SHARMA, A.; AHMAD FAROUK, I.; LAL, S. K. COVID-19: A Review on the Novel Coronavirus Disease Evolution, Transmission, Detection, Control and Prevention. **Viruses**, v. 13, n. 2, p. 202, 2021.

SILVA, A. K.; SANTOS, M. C.; MELLO, W. A.; SOUSA, R. C. M. Ocorrência de Bocavírus Humano associado às infecções respiratórias agudas em crianças de 0 a 2 anos de idade na Cidade de Belém, Pará, Brasil. **Revista Pan-Amazônica de Saúde**, v. 1, n. 1, p. 87-92, 2010.

SMEDBERG, J. R.; DIBIASE, L. M.; HAWKEN, S. E.; ALLEN, A.; MOHAN, S.; SANTOS, C.; SMEDBERG, T.; BARZIN, A. H.; WOHL, D. A.; MILLER, M. B. Reduction and persistence of co-circulating respiratory viruses during the SARS-CoV-2 pandemic. **American Journal of Infection Control**, v. 50, n. 9, p. 1064–1066, 2022.

SOLOMON, D. A.; SHERMAN, A. C.; KANJILAL, S. Influenza in the COVID-19 Era. **JAMA**, v. 324, n. 13, p. 1342–1343, 2020.

STASI, C.; FALLANI, S.; VOLLER, F., SILVESTRI, C. Treatment for COVID-19: An overview. **European Journal of Pharmacology**, v. 889, p. 173644, 2020.

STEGEMAN, I.; OCHODO, E. A.; GULEID, F.; HOLTMAN, G. A.; YANG, B.; DAVENPORT, C.; DEEKS, J. J.; DINNES, J.; DITTRICH, S.; EMPERADOR, D.; HOOFT, L.; SPIJKER, R.; TAKWOINGI, Y.; VAN DEN BRUEL, A.; WANG, J.; LANGENDAM, M.; VERBAKEL, J. Y.; LEEFLANG, M. M.; Cochrane COVID-19 Diagnostic Test Accuracy Group. Routine laboratory testing to determine if a patient has COVID-19. **The Cochrane Database of Systematic Reviews**, v. 111 n. 11, p. CD013787, 2020.

TABATABAEIZADEH, S. A. Airborne transmission of COVID-19 and the role of face mask to prevent it: a systematic review and meta-analysis. **European Journal of Medical Research**, v. 26, n. 1, p. 1, 2021.

TAO, Y.; ZHANG, X.; QIU, G.; SPILLMANN, M.; JI, Z.; WANG, J. SARS-CoV-2 and other airborne respiratory viruses in outdoor aerosols in three Swiss cities before and during the first wave of the COVID-19 pandemic. **Environment International**, v. 164, p. 107266, 2022.

TRISTRAM, D. A.; HICKS, W. JR.; HARD, R. Respiratory syncytial virus and human bronchial epithelium. **Archives of Otolaryngology-Head & Neck Surgery**, v. 124, n. 7, p. 777–783, 1998.

UJIIE, M.; TSUZUKI, S.; NAKAMOTO, T.; IWAMOTO, N. Resurgence of Respiratory Syncytial Virus Infections during COVID-19 Pandemic. **Emerging Infectious Diseases**, v. 27, n. 11, p. 2969–2970, 2021.

VAN DOREMALEN, N.; BUSHMAKER, T.; MORRIS, D. H.; HOLBROOK, M. G.; GAMBLE, A.; WILLIAMSON, B. N.; TAMIN, A.; HARCOURT, J. L.; THORNBURG, N. J.; GERBER, S. I.; LLOYD-SMITH, J. O.; DE WIT, E.; MUNSTER, V. J. Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1. **The New England journal of medicine**, v. 382, n. 16, p. 1564–1567, 2020.

VANDENBERG, O.; MARTINY, D.; ROCHAS, O.; VAN BELKUM, A.; KOZLAKIDIS, Z. Considerations for diagnostic COVID-19 tests. **Nature reviews Microbiology**, v. 19, n. 3, p. 171–183, 2021.

VERGARA, R. J. D.; SARMIENTO, P. J. D.; LAGMAN, J. D. N. Building public trust: a response to COVID-19 vaccine hesitancy predicament. **Journal of Public Health**, v. 43, n. 2, p e291–e292, 2021.

VILLENAVE, R.; THAVAGNANAM, S.; SARLANG, S.; PARKER, J.; DOUGLAS, I.; SKIBINSKI, G.; HEANEY, L. G.; MCKAIGUE, J. P.; COYLE, P. V.; SHIELDS, M. D.; POWER, U. F. In vitro modeling of respiratory syncytial virus infection of pediatric bronchial epithelium, the primary target of infection in vivo. **Proceedings of the National Academy of Sciences of the United States of America**, v. 109, n. 13, p. 5040–5045, 2012.

VITIELLO, A.; FERRARA, F.; TROIANO, V.; LA PORTA, R. COVID-19 vaccines and decreased transmission of SARS-CoV-2. **Inflammopharmacology**, v. 29, n. 5, p. 1357–1360, 2021.

WANG, D.; HU, B.; HU, C.; ZHU, F.; LIU, X.; ZHANG, J.; WANG, B.; XIANG, H.; CHENG, Z.; XIONG, Y.; ZHAO, Y.; LI, Y.; WANG, X.; PENG, Z. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. **JAMA**, v. 32, n. 11, p. 1061–1069, 2020.

WHO. Weekly epidemiological update on COVID-19 - 23 November 2022. Disponível em: <https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---23-november-2022>-OMS. Acesso em: 23 de novembro de 2022.

WINDISCH, W.; WEBER-CARSTENS, S.; KLUGE, S.; ROSSAINT, R.; WELTE, T.; KARAGIANNIDIS, C. Invasive and Non-Invasive Ventilation in Patients With COVID-19. **Deutsches Arzteblatt International**, v. 117, n. 31-32, p. 528–533, 2020.

WU, J.; LIU, J.; LI, S.; PENG, Z.; XIAO, Z.; WANG, X.; YAN, R.; LUO, J. Detection and analysis of nucleic acid in various biological samples of COVID-19 patients. **Travel Medicine and Infectious Disease**, v. 37, p. 101673, 2020.

YUAN, H.; YEUNG, A.; YANG, W. Interactions among common non-SARS-CoV-2 respiratory viruses and influence of the COVID-19 pandemic on their circulation in New York City. **Influenza and Other Respiratory Viruses**, v. 16, n. 4, p. 653–661, 2022.

YUM, S.; HONG, K.; SOHN, S.; KIM, J.; CHUN, B. C. Trends in Viral Respiratory Infections During COVID-19 Pandemic, South Korea. **Emerging Infectious Diseases**, v. 27, n. 6, p. 1685–1688, 2021.