Hospital de Clínicas de Porto Alegre
Programa de Residência Médica em Medicina Interna

Arthur Zaro
Guilherme Jorge Semmelmann Pereira Lima
Miriam Richartz Rosa

MORTALIDADE EM PACIENTES COM HIV INTERNADOS POR COVID-19

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Trabalho de Conclusão de Residência apresentado ao Programa de Residência Médica do Hospital de Clínicas de Porto Alegre como requisito parcial para a obtenção do título de especialista em Medicina Interna

Orientador: Renato Seligman

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LIST OF ACRONYMS

ICU	Intensive care unit
PLWH	People living with HIV
APTT	Activated Partial Thromboplastin time
COPD	Chronic obstructive pulmonary disease
ART	Antiretroviral therapy
TGO/AST	Aspartate aminotransferase
TGP/ALT	Alanine aminotransferase

RESUMO

Introdução:A pandemia pelo COVID 19 assolou o Brasil e o mundo nos últimos anos. Objetivo de muitos estudos, a população com HIV esteve particularmente exposta neste período. **Métodos:** Nosso estudo objetivou estudar os desfechos clínicos e comparar a mortalidade por COVID entre portadores de HIV e pacientes sem HIV. Foi realizado um estudo de coorte unicêntrico. Dados foram obtidos por meio de análise retrospectiva de prontuários médicos. O desfecho primário foi mortalidade hospitalar. Além disso, admissão em centro de tratamento intensivo (CTI), tempo de internação hospitalar e tempo de internação em CTI foram os desfechos secundários estudados. A comparação entre as características dos grupos e as proporções entre os desfechos foi realizada por meio do teste qui-quadrado para variáveis categóricas e teste t de Student ou teste U de Mann-Whitney para variáveis contínuas. Foi realizada uma regressão multivariada de Poisson com variâncias robustas para avaliar a associação entre pacientes HIV positivos e outros preditores no risco de mortalidade. **Resultados:** De 16 de março de 2020 a 30 de novembro de 2022, um total de 6.559 internações hospitalares por COVID-19 - confirmadas laboratorialmente - foram identificadas. Em comparação com pacientes HIV negativos, as pessoas vivendo com HIV (PVHIV) eram significativamente mais jovens (idade média de 48 vs. 58 anos, p<0,001) e apresentavam taxas mais altas de tuberculose (7,1% vs. 0,4%, p<0,000), diabetes (7,1% vs. 2,6%, p=0,003) e doença renal crônica (11,5% vs. 6,0%, p=0,016). Entre as PVHIV, a taxa de mortalidade foi ligeiramente inferior à dos pacientes não HIV, embora esta diferença não tenha sido estatisticamente significativa (19,5% vs 21,2% p= 0,658). A mediana do tempo de internação hospitalar foi significativamente maior para PVHIV em 25,0 dias (IQR 14,25 - 41,25), em comparação com 18,0 dias (IQR 10,0 - 31,0) para o grupo não-HIV (p=0,008). A despeito disso, admissões em CTI não apresentaram diferença estatística entre os grupos (35,4% vs 44,4%, p=0,056). Na análise de regressão multivariada, a presença de doença pulmonar obstrutiva crônica foi associada a uma diminuição do risco de mortalidade, com um RR de 0,52 (IC 95%: 0,35-0,77, p = 0,001). **Conclusão:** Em nosso estudo retrospectivo, pessoas vivendo com HIV não demonstraram uma maior taxa de mortalidade por COVID-19. No entanto, foram identificados diversos fatores independentemente associados ao risco de mortalidade por COVID-19 em pacientes hospitalizados, como idade avançada, sexo masculino, doença renal crônica e hepatopatia crônica.

SUMMARY

1. INTRODUCTION

The COVID-19 pandemic has ravaged Brazil and the world in recent years. An estimated 700 million cases occurred worldwide, with nearly 700.000 deaths in Brazil **(1)**. Despite the majority of patients leading a favorable course, around 5% had critical presentations, such as respiratory failure, septic shock, and/or multiple organ dysfunction **(2)**, which made the identification of priority groups at higher risk of adverse outcomes essential.

Male sex, hypertension, obesity, cerebrovascular disease, diabetes, older age and unspecified immunosuppression states have been established as some of the predictors to poor clinical outcomes **(3) (4)**. People living with HIV (PLWH) were early on designated as an at-risk population **(5)(6)** and were particularly affected by reduced access to routine care **(7)**. Supporting this recommendations was the evident T-cell–mediated immune responses dysfunction in PLWH with undetermined consequences in the response to SARS-CoV-2 co-infection **(8)**, on top of the already established higher prevalence of some comorbidities in this population **(9-10-11).** However, the impact of HIV on COVID-19 mortality is not straightforward, and a noticeable number of earlier studies **(12, 13)** supported that PLWH had similar COVID clinical outcomes to people without HIV (PWOH). This could be hypothesized as secondary to its role in downplaying the intensity of immune response such as in the cytokine-storm characteristic of more severe COVID-19 presentations **(14).** To date, the exact extent to which the many causes of immunodeficiency, such as in solid organ transplant recipients, diabetics and, more frequently, HIV, interact with COVID-19 immune response and impact clinical outcomes is subject of debate in the literature. Even more recent papers **(15, 16)** still describe heterogeneous results in hospitalizations, ICU admissions and mortality rates among PLWH during the COVID pandemic.

This study aims to evaluate the clinical characteristics and outcomes of hospitalized COVID-19 patients among PLWH and PWOH individuals, as well as investigate admission risk factors associated with critical illness and in-hospital mortality among patients coinfected with COVID-19 and HIV.

2. METHODS

A retrospective cohort study was conducted at Hospital de Clínicas de Porto Alegre (HCPA), a large (937-bed) tertiary-care university hospital located in Porto Alegre, southern Brazil.

We included all consecutive adult patients (age ≥ 18 years) admitted to HCPA from March 16, 2020, to November 30, 2022 with laboratory-confirmed COVID-19, determined by a positive real-time reverse transcriptase polymerase chain reaction (RT-PCR) or antigen testing on naso/oropharyngeal swabs. Patients were followed up from admission date until discharge or in-hospital death. If a patient had more than one admission during the study period, only the most recent hospitalization was considered.

Data was collected from electronic health records (EHRs) regarding demographics, medical history, clinical parameters and laboratory results, including diagnostic codes and hospitalization outcomes. Additional data on HIV-specific variables such as antiretroviral (ARV) therapy, CD4 count, and viral load was extracted via chart review.

The primary outcome was in-hospital death. Secondary outcomes were ICU admission, hospital length of stay and ICU length of stay.

The main exposure of interest was HIV-positive status. PLWH were identified using HIV-specific ICD-10 codes. Additional patients were identified using positive laboratory results (HIV-1 RNA viral load or antigen assays). Medical records were reviewed for all PLWH in order to confirm HIV-status.

Demographics variables were age and sex. Baseline comorbidities associated with a worse prognosis (hypertension, diabetes, chronic pulmonary diseases, cardiovascular diseases, chronic liver diseases, cerebrovascular disease, obesity, chronic kidney disease, tuberculosis) were defined using ICD-10 codes at admission.

Baseline laboratory values included: complete blood count, creatinine, urea, total bilirubin, aspartate aminotransferase, C-reactive protein, d-dimer, ferritin, lactate, creatine phosphokinase and fibrinogen. Tests were ordered according to attending physician criteria and were defined as the first results available upon admission.

Variables related to the PLWH group were: current ARV use at time of hospital admission; most recent CD4 (cells/uL) presented as absolute count and categorized into >200 and <= 200 cells/uL; viral suppression, defined as a HIV-RNA viral load of <50 copies/mL within the last 12 months before admission.

Statistical analysis

Descriptive statistics was conducted to summarize baseline characteristics of the study participants, including demographics, comorbidities and laboratory values. Categorical variables were reported as frequencies and percentages. Continuous variables were presented as means with standard deviations or medians with interquartile ranges. The Kolmogorov-Smirnov test was used to assess data normality.

Comparison between groups characteristics and proportions across outcomes were conducted using Chi-square test for categorical variables and Student's t-test or Mann-Whitney U test for continuous variables. A multivariate poisson regression with robust variances was performed to evaluate the association of HIV status and other predictors on mortality risk, while also accounting for confounders. Age, sex and HIV-status were included in the model a priori. Other factors were considered for inclusion in the model if independently associated with the outcome at a p <0,1 in bivariate analysis. Variables with missing data above 10% were not included.

The results obtained from the model are expressed as Relative Risks (RR), with 95% confidence intervals. Among PLWH, the same approach was used to evaluate the impact of ARV use, CD4 count, and viral load on mortality.

All tests were two-tailed, and a p-value <0.05 was considered statistically significant. The absolute totality of statistical analyzes were performed in IBM SPSS version 27.0.

Ethics

The study was approved by the institutional Research Ethics Committee (CAAE: 27559019.3.0000.5327) and due to its retrospective nature, patient's informed consent was waived. This research was conducted in accordance with the Declaration of Helsinki and all data was maintained with full confidentiality. Research project number 2019-0651.