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MANOELA ASTOLFI VIVAN

COMPARAÇÃO DA INCIDÊNCIA E PROGNÓSTICO DA LESÃO MIOCÁRDICA EM PACIENTES COM INSUFICIÊNCIA RESPIRATÓRIA RELACIONADA À COVID-19 E OUTRAS INFECÇÕES PULMONARES: UM ESTUDO DE COORTES CONTEMPORÂNEAS

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Orientador: Dr. Prof Flávio Fuchs

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RESUMO

A pandemia de COVID-19 resultou em mais de 750 milhões de infecções pelo Sars-CoV-2 no mundo, e cerca de 7 milhões de óbitos relacionados à doença. Durante a pandemia, houve mobilização da comunidade científica para a identificação de exames diagnósticos que pudessem auxiliar no manejo e na avaliação da gravidade e de complicações da COVID-19. Alguns desses exames foram utilizados com a finalidade de definir condutas diagnósticas e terapêuticas dos pacientes, antes mesmo de ter sua utilidade demonstrada por estudos clínicos. Estudos observacionais demonstraram uma alta incidência de injúria miocárdica em pacientes internados por COVID-19. Também demonstrou-se haver incremento da incidência dessa complicação conforme maior gravidade da doença, bem como associação da presença dessas complicações com piores desfechos. Este trabalho investiga, em um estudo de coorte retrospectiva, o papel diagnóstico e prognóstico da troponina na avaliação de injúria miocárdica, bem como busca determinar a incidência desta complicação em pacientes internados por COVID-19, comparando com outras infecções pulmonares.

Palavras-chave: COVID-19; Injúria Miocárdica; Pneumonia; Insuficiência respiratória.

ABSTRACT

The COVID-19 pandemic has resulted in more than 750 million infections by SARS-CoV-2 worldwide, and approximately 7 million deaths related to the disease. During the pandemic, the scientific community was mobilized to identify diagnostic tests that could assist in the management and assessment of the severity and complications of COVID-19. Some of these tests were used to define diagnostic and therapeutic approaches for patients, even before their usefulness was demonstrated by clinical studies. Observational studies have demonstrated a high incidence of myocardial injury in patients hospitalized for COVID-19. It has also been demonstrated that there is an increase in the incidence of this complication as the severity of the disease increases, as well as an association between the presence of these complications and worse outcomes. This work investigates, in a retrospective cohort study, the diagnostic and prognostic role of troponin in the evaluation of myocardial injury, as well as seeks to determine the incidence of this complication in patients hospitalized for COVID-19, compared with other pulmonary infections.

Keywords: COVID-19; Myocardial Injury; Pneumonia; Respiratory Failure.

LISTA DE ABREVIATURAS E SIGLAS

COVID-19 = doença por coronavírus 2019

SARS-CoV-2 = coronavírus 2 da síndrome respiratória aguda grave

ECA2 = enzima conversora de angiotensina 2

UTI = unidade de terapia intensiva

SUMÁRIO

3 PANDEMIA DE COVID-19

Os coronavírus são um grupo de vírus de genoma de RNA simples de sentido positivo, pertencentes à subfamília taxonômica Orthocoronavirinae da família Coronaviridae, da ordem Nidovirales, e são importantes patógenos humanos e animais. O primeiro coronavírus foi identificado em 1965, em Londres, pela pesquisadora virologista June Hart [1]. Em dezembro de 2019, um novo coronavírus foi identificado como agente etiológico de casos de pneumonia em Wuhan, uma cidade na província chinesa de Hubei. Em 2020 este novo coronavírus se propagou pelo mundo, atingindo todos os continentes e resultando em uma pandemia global. Em fevereiro de 2020, a Organização Mundial da Saúde designou a doença causada pelo novo coronavírus como COVID-19, que significa "doença por coronavírus 2019", e renomeou o vírus, que era anteriormente conhecido como 2019-nCoV, como coronavírus 2 da síndrome respiratória aguda grave (SARS-CoV-2) [2].

Desde os primeiros relatos de casos em Wuhan, globalmente, foram notificados mais de 750 milhões de casos confirmados de COVID-19, sendo, desses, mais de 37 milhões diagnosticados no Brasil. No que se refere a óbitos, no mundo, foram confirmados cerca de 7 milhões de mortes relacionadas à doença, sendo mais de 700 mil delas no Brasil. No entanto, a contagem de casos notificados subestima os números da COVID-19, uma vez que apenas uma fracção das infecções é diagnosticada e notificada. A Organização Mundial da Saúde declarou o fim da emergência de saúde global da COVID-19 em maio de 2023, mais de três anos após o seu surgimento.

4 INCIDÊNCIA E PROGNÓSTICO DO DANO MIOCÁRDICO NA COVID-19 E EM OUTRAS INFECÇÕES PULMONARES

Injúria miocárdica, definida como um nível de troponina sérica acima do percentil 99 de uma população de referência saudável, é achado comum em pacientes hospitalizados com COVID-19 [5]. Estudos previamente publicados reportaram uma frequência de injúria miocárdica em pacientes com COVID-19 entre 9.2 e 63.5% [6,7,8,9,10], sendo estabelecida a sua associação com piores desfechos e maior mortalidade [6,7,8].

Embora múltiplos mecanismos tenham sido propostos, incluindo hipoxemia, miocardite, chuva de citocinas, inflamação sistêmica, disfunção microvascular, vasculite e doença arterial coronariana, a patogênese da injúria miocárdica na COVID-19 ainda é incerta [11]. Foram publicados relatos de caso que sugerem associação entre infecção por SARS- CoV-2 e miocardite [12-17], mas poucos estudos demonstraram confirmação histológica de miocardite [18-20]. Em apenas um estudo, com dois casos publicados, houve confirmação histológica de miocardite com identificação do genoma viral em células miocárdicas [18]. Adicionalmente, os achados histopatológicos cardíacos observados em autópsias de indivíduos não sobreviventes à COVID-19 não fecharam critérios para miocardite [21].

É importante lembrar que injúria miocárdica não é achado específico da COVID-19 e é frequentemente encontrada em doenças críticas devido a outras causas. Uma revisão sistemática, que incluiu 20 estudos envolvendo 3278 pacientes críticos, reportou incidência de injúria miocárdica de 12% a 85%, com mediana de 43% (IQ 21-59%) [22]. Além disso, esta revisão demonstrou que troponina elevada estava independentemente associada com risco aumentado de morte nesta população (razão de chances 2.5; 95% intervalo de confiança 1.9 a 3.4; P< 0.001) [22].

A enzima conversora de angiotensina 2 (ECA2) tem importante função no sistema cardiovascular, tendo sido identificada como receptor funcional dos coronavírus. O Sars- CoV-2 usa como receptor de entrada na célula a ECA-2, que é expressa em abundância na superfície das células dos pulmões e também do sistema cardiovascular. Assim, foi proposto que o dano pulmonar e cardíaco observado na COVID-19 poderia ser mediado pelo receptor funcional ECA2, o qual é abundantemente expresso na superfície das células dos pulmões e no sistema cardiovascular [23]. Esta hipótese baseou-se em um aparente maior risco de complicações da COVID-19 identificado em pacientes usuários de medicamento bloqueador do receptor da angiotensina [23,24]. A demonstração de que o maior risco para COVID-19 grave não era influenciado pelo uso de bloqueador do receptor da angiotensina, sugerindo que as primeiras observações tiveram como fator confundidor a hipertensão, tornou esta hipótese improvável. [25,26].

As manifestações clínicas em pacientes com COVID-19 e com evidência de dano miocárdico são diversas. A maior parte dos pacientes apresenta sintomas típicos da infecção por Sars-CoV-2, como dispneia, tosse, febre, mialgia e cefaleia, sem sintomas típicos de doença cardíaca, como dor torácica ou palpitações. A dispneia é um sintoma inespecífico que pode estar relacionado a causas cardíacas ou não cardíacas em pacientes com COVID-19.

A comparação direta da incidência de dano miocárdico em pacientes com COVID-19 e pacientes com outras doenças foi abordada por 2 estudos. Um estudo retrospectivo, realizado em cinco hospitais do Johns Hopkins Healthcare System, incluiu 243 pacientes de terapia intensiva em ventilação mecânica com COVID-19 e comparou com pacientes de um estudo de coorte prospectivo publicado em 2017 que havia avaliado prevalência de dano miocárdico em 506 doentes críticos com síndrome respiratória aguda grave atribuível a pneumonia primária. Neste estudo, mais de um tipo de troponina foi utilizado, com alguns pacientes tendo realizado teste com troponina I e outros com troponina T. A incidência de dano miocárdico foi similar entre os dois grupos, sendo 51% entre os pacientes com COVID- 19 e 49.6% em pacientes com síndrome do desconforto respiratório agudo secundária a pneumonia [95% IC 0,78-1,44 P=0,37] [9]. Um outro estudo multicêntrico que incluiu prospectivamente pacientes de centros na Áustria e Alemanha avaliou a frequência de troponina T e troponina I elevadas em 156 pacientes de terapia intensiva e em ventilação mecânica com COVID-19, comparando com uma coorte retrospectiva que incluiu pacientes internados em centros de terapia intensiva entre 2016 e 2020 por insuficiência respiratória aguda por pneumonia grave. Este estudo encontrou uma incidência de dano miocárdico de 96.4% em pacientes com pneumonia grave e 78.1% em pacientes com COVID-19 [P=0,002] [10].

4.1 JUSTIFICATIVA

Embora diversos mecanismos tenham sido propostos de forma e explicar a alta frequência de injúria miocárdica em pacientes com COVID-19, a causa deste reiterado achado ainda não está esclarecida. Ainda não há estudo que, no contexto de terapia intensiva, em uma coorte única e com único tipo de troponina tenha investigado a prevalência de dano miocárdico em pacientes com COVID-19 e comparado com aqueles internados por insuficiência respiratória secundária a outras infecções pulmonares. Tal comparação pode contribuir para o estudo do padrão de acometimento cardíaco da COVID-19.

4.2 HIPÓTESE CONCEITUAL

A injúria miocárdica observada em pacientes com COVID-19 não se deve, exclusivamente, ao dano viral direto às células miocárdicas, mas também a mecanismos fisiopatológicos associados à doença crítica, à insuficiência respiratória e às infecções pulmonares graves.

4.3 OBJETIVOS

Objetivo Primário

Comparar a prevalência de injúria miocárdica em pacientes com insuficiência respiratória aguda por COVID-19 com a decorrente de outras infecções pulmonares.

Objetivos secundários:

- Identificar fatores de risco associados ao desenvolvimento de dano miocárdico em pacientes internados em UTI por COVID-19;
- Avaliar a troponina I ultrassensível como preditora de mortalidade intra-hospitalar em pacientes de terapia intensiva com COVID-19 e em outras infecções pulmonares;
- Comparar a incidência de insuficiência renal aguda, necessidade de terapia renal substitutiva, eventos trombóticos em pacientes com COVID-19 e com outras infecções pulmonares.
- Comparar níveis de marcadores inflamatórios, necessidade de emprego de cateter nasal de alto fluxo/ventilação mecânica não invasiva/ventilação mecânica invasiva, tempo de ventilação mecânica, tempo de internação em UTI, tempo total de internação, e mortalidade em pacientes com COVID-19 e com outras infecções pulmonares.

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Comparison of incidence and prognosis of myocardial injury in patients with COVID-19-related respiratory failure and other pulmonary infections: a contemporary cohort study

Manoela Astolfi Vivan, MD a,b,c

Vania Naomi Hirakata, Msc a,d

Maria Antônia Torres Arteche c

Débora Marques de Araujo c

Sandra Costa Fuchs, Professor, MD, PhD a,c

Flávio Danni Fuchs, Professor, MD, PhD a,c,e

a Graduate Program in Cardiology, Federal University of Rio Grande do Sul (UFRGS), Porto Alegre, RS, Brazil

b Divison of Intensive Care Medicine, Hospital de Clínicas de Porto Alegre (HCPA), Porto Alegre, RS, Brazil

c Federal University of Rio Grande do Sul (UFRGS), Porto Alegre, RS, Brazil

d Division of Statistics, Hospital de Clínicas de Porto Alegre (HCPA), Porto Alegre, RS, Brazil

e Division of Cardiology, Hospital de Clínicas de Porto Alegre (HCPA), Porto Alegre, RS, Brazil

Corresponding author: Manoela Astolfi Vivan

Hospital de Clínicas de Porto Alegre. Rua Ramiro Barcelos, 2350 – Santa Cecília. Porto Alegre- RS, Brazil - 90035007.

Email: manoelavivan@gmail.com

Fone: 55 51 997390415

ABSTRACT

Myocardial injury (MI) is frequent in critically ill patients with COVID-19, but its pathogenesis remains unclear. We hypothesized that MI is not solely due to viral infection by SARS-CoV-2, but rather due to the common pathophysiological mechanisms associated with severe pulmonary infections and respiratory failure. This contemporary cohort study was designed to compare the incidence of MI in patients with acute respiratory failure caused by COVID-19 to that of patients with other pulmonary infections. In addition, we aimed to investigate whether MI was a distinct risk factor for in-hospital mortality in patients with COVID-19 compared to those with non-COVID-19 infections. The study included 1444 patients with COVID-19 [55.5% men; age 58 (46;68) years] and 182 patients with other pulmonary infections [46.9% men; age 62 (44;73) years]. The incidence of MI at ICU admission was lower in COVID-19 patients (36.4%) compared to non-COVID-19 patients (56%), and this difference persisted after adjusting for age, sex, coronary artery disease, heart failure, SOFA score, lactate, and C-reactive protein [RR 0.84 (95% CI, 0.71-0.99)]. MI at ICU admission was associated with a 59% increase in mortality [RR 1.59 (1.36-1.86); P<0.001], and there was no significant difference in the mortality between patients with COVID-19 and those with other pulmonary infections (P=0.271). We concluded that MI is less frequent in patients with critical COVID-19 pneumonia and respiratory failure compared to those with other types of pneumonia. The occurrence of MI is a significant risk factor for in-hospital mortality, regardless of the etiology of the pulmonary infection.

Keywords: COVID-19, myocardial Injury, SARS-CoV-2, myocarditis

Comparison of incidence and prognosis of myocardial injury in patients with COVID-19-related respiratory failure and other pulmonary infections: a contemporary cohort study

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has resulted in over 500 million SARS-CoV-2 infections globally, with more than 6 million deaths reported. Myocardial injury, defined as an elevated serum troponin level higher than the 99th percentile of a reference population, is a common finding in hospitalized COVID-19 patients [1]. Previous studies have reported the frequency of myocardial injury in COVID-19 patients to range from 9.2 to 63.5% [2,3,4,5,6], with a well-established association with worse outcomes and increased mortality [2,3,4].

Despite multiple proposed mechanisms, including hypoxemia, myocarditis, cytokine storm, systemic inflammation, microvascular dysfunction, vasculitis, and coronary heart disease, the pathogenesis of myocardial injury in COVID-19 patients remains unclear [7]. While some case reports have suggested an association between SARS-CoV-2 infection and myocarditis [8-13], few studies have provided histological confirmation of myocarditis [14-16]. In only one study with two reported cases, histological examination confirmed myocarditis with the identification of viral genome in myocardial cells [14]. The histopathologic heart findings observed during autopsies of COVID-19 non-survivors do not meet the criteria for myocarditis [17].

It is important to note that myocardial injury is not specific to COVID-19 and is frequently observed in critically ill patients due to other causes as well. A systematic review of 20 studies involving 3278 patients reported incidences of myocardial injury ranging from 12% to 85%, with a median of 43% (IQ 21-59%) among intensive care patients [18]. Furthermore, the review demonstrated that elevated troponin was independently associated with an increased risk of death in this population (OR 2.5; 95% confidence interval 1.9 to 3.4; P< 0.001) [18]. Thus, we postulated that myocardial injury observed in COVID-19 patients was not solely due to viral infection by SARS-CoV-2, but rather due to the common pathophysiological mechanisms associated with severe pulmonary infections and respiratory failure.

There is currently no comparative study examining the frequency of myocardial injury in contemporary cohorts of critically ill patients with respiratory failure caused by COVID-19 and those with respiratory failure caused by non-COVID-19 etiologies. Therefore, the primary objective of this study is to compare the incidence of myocardial injury in patients with acute respiratory failure due to COVID-19 with that of patients with respiratory failure caused by other pulmonary infections. It is also unclear if the occurrence of myocardial injury has a distinct influence on the prognosis of patients with pulmonary COVID-19 compared to those with non-COVID-19 infections. Thus, we have addressed this issue as a secondary objective of our study.

MATERIAL AND METHODS

We conducted a retrospective contemporary cohort study that included all patients admitted to the intensive care units of Hospital de Clínicas de Porto Alegre (HCPA), a tertiary care university-affiliated hospital, from March 2020 to June 2021, with respiratory failure attributed to pulmonary infection. The HCPA Research Ethics Committee approved the study (number 48398721700005327; approval on June 10, 2021), and the patient’s informed consent was waived due to the retrospective nature of data collection.

The electronic medical records of all adult patients admitted to the intensive care units of HCPA with respiratory failure attributed to pulmonary infection were reviewed. Acute respiratory failure was defined by the presence of one of the following criteria: $PaO_2 < 60$mm/Hg or $SpO_2 \leq 90\%$ with 0.21 FiO_2. COVID-19 diagnosis was established based on positive results of nasopharyngeal swabs tested by RT-PCR or antigen testing. All patients included in the study had either RT-PCR or antigen testing for Sars-CoV-2 performed. Patients were either discharged or had died at the time of data collection and analysis.

We collected and recorded clinical data, demographic characteristics, medical history, laboratory tests, and outcomes during hospitalization. Data related to laboratory results and clinical data at ICU admission were considered only if the interval between admission and processing of laboratory data was less than 48 hours. We used a chemiluminescence microparticle immunoassay (Alinity i STAT High Sensitive Troponin-I Reagent Kit, Abbott Laboratories, Lake Forest, IL, USA) for the quantitative determination of cardiac troponin I. For patients who had more than one troponin measurement within 48 hours of admission, we used the highest value recorded.

The primary objective was to determine the proportion of patients with myocardial injury upon ICU admission, as indicated by a high-sensitivity cardiac troponin I value greater than the 99th percentile of a healthy reference population (34.2 pg/mL for men; 15.6 pg/mL for women). The extent of myocardial injury was also evaluated based on the degree of troponin elevation, which was categorized as less than the upper limit of normal (ULN), between 1 and 5 times ULN, between 5 and 10 times ULN, and greater than 10 times ULN, and also assessed as a continuous variable. Patients who had type 1 or type 2 myocardial infarction or did not undergo troponin testing were excluded from the analysis. We compared the association between myocardial injury and in-hospital mortality as well as a composite outcome (in-hospital death, pulmonary embolism, or renal replacement therapy) among patients with respiratory failure due to COVID-19 pneumonia and those with pneumonia caused by non-COVID-19 etiologies, both overall and within each group.

Statistical analysis

The Statistical Package for the Social Sciences, version 20.0® (Cary, USA) was used to perform statistical analyses. Patients were classified into subgroups based on their COVID-19 diagnosis or other pulmonary infections. The normal distribution of continuous variables was assessed using a histogram and the Shapiro-Wilk test. Descriptive statistics were presented as frequencies (%) for categorical data, means and standard deviations (SD) for continuous data with normal distribution, and median and interquartile range (IQR) for continuous data without normal distribution. Student's t-test or Mann-Whitney's test was used for continuous variables, and the chi-square test or Fisher's exact test was used for categorical variables to compare between groups when appropriate.

A Poisson regression model with robust variance was used to analyze factors associated with myocardial injury, while a Gamma regression model was employed to examine factors associated with troponin as a continuous variable. The linearity of continuous variables was assessed, and the linearity assumption criteria were met. To evaluate the association of myocardial injury with mortality and the composite outcome, Cox proportional hazard models were used, and the proportional hazard assumption was assessed, with the assumption of proportionality criteria being met. Additionally, a Cox proportional hazard model was utilized to evaluate the interaction between COVID-19 and myocardial injury with in-hospital mortality. Confounding variables were selected based on their association with the dependent variable in the univariate analysis ($P < 0.1$) and their presumed causal association with the outcome. Receiver operating characteristic curves were created to assess the ability of high-sensitivity cardiac troponin I to predict in-hospital mortality in patients with COVID-19 or other pulmonary infections. The area under the ROC curves for each group was compared to test for significant differences. Statistical significance was accepted at $P < 0.05$.

RESULTS

Out of the 1615 COVID-19 patients admitted to the ICU during the study period, troponin was assessed within 48 hours of admission for 1444 patients (89.4%) who were included in the study. Similarly, troponin was assessed for 182 (90.1%) of the 202 patients admitted to the ICU with other pulmonary infections within 48 hours of admission and included in the study (Figure 1). No significant differences were observed in demographics, comorbidities, or outcomes between patients who had troponin checked and those who did not, as indicated in Supplements 1 and 2. Furthermore, in the sensitivity analysis, including or excluding patients without troponin checked did not alter the comparison of demographics, comorbidities, laboratory and clinical findings at ICU admission or outcomes between COVID-19 and non-COVID-19 patients (Supplement 3).

The median age of COVID-19 patients included in the study was 58 years [interquartile range (IQR): 46-68], and 802 patients (55.5%) were male. Among non-COVID-19 patients, the median age was 62 years (IQR: 44-73), and 85 patients (46.7%) were male. Patients admitted due to non-COVID-19 pulmonary infections had a lower body mass index [30.4 (IQR: 26.5-35.7) vs. 26.5 (IQR: 22.3-31.3); $P<0.001$] and a higher prevalence of comorbidities such as cerebrovascular disease, heart failure, coronary artery disease, chronic lung disease, and chronic HIV infection, as shown in Table 1. Non-COVID-19 patients had higher Sequential Organ Failure Assessment (SOFA) scores, a greater need for invasive mechanical ventilation, and a higher need for vasopressors at ICU admission, as demonstrated in Table 1. Conversely, non-COVID-19 patients had higher PaO_2/FiO_2 ratios, indicating better gas exchange compared to COVID-19 patients (Table 1).

The proportion of patients with myocardial injury at ICU admission was lower among COVID-19 patients (36.4%) compared to non-COVID-19 patients (56%) [Figure 2; relative risk (RR) 0.64; 95% confidence interval (CI) 0.56–0.75)]. Although this association weakened with covariate adjustment, it remained statistically significant after controlling for age, sex, coronary artery disease, heart failure, Sequential Organ Failure Assessment (SOFA) score (creatinine, total bilirubin, PaO_2/FiO_2 ratio, mean arterial pressure/vasopressor, Glasgow Coma Scale, platelets), lactate, and C-reactive protein [RR 0.84 (95% CI, 0.71-0.99)]. When troponin levels were assessed as a continuous variable, they were also lower in COVID-19 patients compared to non-COVID-19 patients [Table 2; median (interquartile range) 11.6 (9.9-53.7) vs. 35.5 (9.9-218), $p < 0.001$], and this difference remained statistically significant after adjusting in a gamma regression model a gamma regression model for age, sex, coronary artery disease, heart failure, SOFA score (creatinine, total bilirubin, PaO_2/FiO_2 ratio, mean arterial pressure/vasopressor, Glasgow Coma Scale, platelets), lactate, and C-reactive protein using ($P=0.042$).

COVID-19 patients had higher rates of in-hospital death, the composite outcome (in-hospital death, pulmonary embolism or renal replacement therapy), longer hospital stays, longer ICU stays, and longer mechanical ventilation duration compared to non-COVID-19 patients (Table 3; $P<0.001$). Although pulmonary embolism was more frequently diagnosed among COVID-19 patients (20.6% vs 5.5%), it is worth noting that 822/1615 (50.9%) of these patients underwent a computed tomography pulmonary angiogram (CTPA), while only 47/202 (23.3%) of non-COVID-19 patients underwent a CTPA. The in-hospital mortality rate was 41% among COVID-19 patients and 26.4% among patients with other pulmonary infections.

The mortality rate was significantly higher in COVID-19 patients with troponin levels >5x ULN (49.8%) compared to those with troponin levels under the ULN (26.4%; $P<0.001$; Figure 3). Similarly, non-COVID-19 patients with higher troponin levels had a higher mortality rate (31.7%) compared to those with troponin levels under the ULN (16.3%; P=0.032; Figure 3).

The presence of myocardial injury at ICU admission was associated with a 59% increase in mortality [RR 1.59 (95% CI, 1.36-1.86), P<0.001]. This association attenuated but remained statistically significant after adjusting for age, sex, and SOFA score [RR 1.21 (95% CI, 1.01-1.44), P=0.034]. The association between myocardial injury and mortality was also present when troponin was evaluated as a continuous variable (P = 0.026). There was no significant interaction effect between COVID-19 and non-COVID-19 infections regarding the association of myocardial injury with in-hospital death (P=0.271). The AUC for high-sensitivity cardiac troponin I to predict in-hospital mortality was 0.66 (95% CI, 0.63-0.69) for COVID-19 patients and 0.63 (95% CI, 0.53-0.72) for other pulmonary infections (Figure 4). There was no statistically significant difference in the C-statistic for the AUC calculated for high-sensitivity cardiac troponin I to predict in-hospital mortality in COVID-19 patients compared to other pulmonary infections (P=0.572).

DISCUSSION

In this retrospective contemporary cohort study of critically ill patients with respiratory failure, the incidence of myocardial injury was less common in patients with COVID-19 pneumonia than in patients with other pulmonary infections. The occurrence of myocardial injury was a risk factor for in-hospital mortality, regardless of whether the infection was caused by COVID-19 or other agents. These findings highlight the additional risk posed by myocardial injury in patients with severe pneumonia and respiratory failure, and suggest that it is not directly caused by the infectious agent but rather is more likely due to the multisystem organ dysfunction secondary to Severe Acute Respiratory Syndrome.

During the early stages of the pandemic, an alarming incidence of myocardial injury was detected among critically ill COVID-19 patients [2,3,4,5,6], leading to the elaboration of hypotheses to explain this incidence. Among them, it was proposed that the pulmonary and cardiovascular damage could be mediated by a functional cell entry receptor of Sars-CoV-2, a type 2 Angiotensin Converting Enzyme receptor (ACE2), which is abundantly expressed on the surface of cells in the lungs and cardiovascular system [19]. This hypothesis was based on an apparent higher risk of complications by COVID-19 infection identified in patients taking Angiotensin Receptor Blockers (ARB) [19,20]. The demonstration that a higher risk for severe COVID-19 infection was not influenced by the use of ARB, suggesting that first observations were confounded by hypertension, turned this hypothesis unlikely [21,22]. The hypothesis that myocardial injury could be caused by myocarditis by COVID-19 was also unlikely. The genome of the virus has been identified in the myocardium in a few studies [13], and the histopathologic findings observed described in autopsies of COVID-19 non-survivors are not suggestive of myocarditis. [7]. Myocardial injury seen in patients with severe COVID-19 infection, particularly with severe pneumonia and respiratory failure, could be secondary to unspecific supply-demand mismatch, cytokine storm, systemic inflammation, microvascular dysfunction, vasculitis, and coronary thrombosis, described in patents with Acute Respiratory Distress Syndrome [23]. Our findings are in accordance with this hypothesis.

To date, only two studies have compared the incidence of myocardial injury in cohorts of patients with respiratory failure caused by Sars-CoV-2 and other agents [5,6]. However, these studies had limitations, including smaller sample sizes of patients with COVID-19 and the use of historical controls. In the study conducted at the hospitals of the Johns Hopkins Healthcare System, the incidence of myocardial injury was found to be similar (around 50%) in patients with COVID-19 and non-COVID-19 pneumonia [5]. The 2-fold increased hazard for mortality was no longer statistically significant after adjusting for covariates. The study conducted in

Austria and Germany found higher incidences of myocardial injury and a higher incidence in patients with other types of pneumonia (96.4%) compared to those with COVID-19 (78.1%) [6], but did not report the association of myocardial injury with the risk of mortality.

Non-comparative studies that included only patients with respiratory failure due to Sars-CoV-2 found an incidence of myocardial injury that was similar to that observed in our study [2,3,4]. Similarly, cohorts of patients with respiratory failure caused by other infectious agents, as well as those with critical illness from other causes, have shown an incidence of myocardial injury that is approximately similar to our findings [18,24,25].

Due to the retrospective nature of our study, it was not possible to obtain and analyze data on ventricular function. However, in the literature there are published studies by other authors who investigated this topic, finding a considerably high incidence of right ventricular dysfunction. A small single center study conducted in patients with COVID-19 admitted to ICU found that almost half of patients had left ventricular diastolic dysfunction (46%), and it was associated with a trend toward higher mortality, even though the study was underpowered [26]. In accordance, a post-hoc analysis of a cohort of ICU patients who underwent at least two echocardiography examinations, found that 67% of patients had at least 1 type of right ventricle involvement (acute cor pulmonale, right ventricle failure or right ventricle dysfunction) [27].

Our study has limitations, mainly related to retrospective data collection. Nonetheless, the criteria for the selection of participants with and without COVID-19 respiratory failure were similar, and the cohorts were contemporary and managed in an ICU with equal resources and medical expertise. Although not all patients had myocardial injury assessed in the first 48 hours from ICU admission (10% of missing troponin I US at ICU admission), the baseline characteristics and outcomes of the patients who did and did not have troponin checked were comparable. Additionally, myocardial injury was diagnosed solely by cardiac markers, without including further cardiac evaluation tests like echocardiography, magnetic resonance imaging, or biopsy. Nevertheless, it is unlikely that the groups differed regarding the findings of these examinations. The strengths of our study include the comparison of contemporary cohorts, the thorough control for a comprehensive set of potential confounders, and the relatively large sample size.

CONCLUSIONS

In conclusion, our study provides evidence that myocardial injury is less common in patients with COVID-19 pneumonia and respiratory failure compared to those with other severe pulmonary infections. This finding supports the hypothesis that the occurrence of myocardial injury is secondary to pathophysiological mechanisms associated with serious pulmonary infection and respiratory failure. Additionally, our study found that the presence of myocardial injury is a risk factor for in-hospital mortality, irrespective of the etiology of the pulmonary infection.

The practical implication of these findings is that the key to reducing the risk of myocardial injury and its consequences may be to institute adequate intensive care and support to optimize organ dysfunction. Further prospective studies are needed to confirm these findings.

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Data Sharing Statement

The data that support the findings of this study are available from the corresponding author, MAV, upon reasonable request.

Data Access, Responsibility, and Analysis Statement

MAV had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of Interest Statement

The authors declare that they have no conflict of interest.

Ethical Approval Statement

All procedures performed in this study were in accordance with the ethical standards of the HCPA Research Ethics Committee and with the Helsinki declaration and its later amendments. The HCPA Research Ethics Committee approved the study (number 48398721700005327).

Informed consent Statement

Not applicable

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Author Contribution Statement

MAV, FF and SF: conceptualization, methodology, investigation, formal analysis, writing. MATA and DMA: investigation and critical review. VNH: statistical analysis and critical review. All the authors reviewed and approved the final manuscript.

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Table 1. Characteristics of patients admitted to the ICU with respiratory failure attributed to COVID-19 or other pulmonary infections

Features	COVID-19 n = 1444	Other pulmonary infections n = 182	P value
Demographics			
Age (years)	58 (46;68)	62 (44;73)	0.103
Gender			0.027
Male	802 (55.5)	85 (46.7)	
Female	642 (44.5)	97 (53.3)	
Body Mass Index (kg/m²)	30.4 (26.5;35.7)	26.5 (22.3;31.3)	<0.001
Comorbidities			
Hypertension	821 (56.9)	98 (53.8)	0.475
Diabetes mellitus	494 (34.2)	59 (32.4)	0.678
Renal replacement therapy	32 (2.2)	6 (3.3)	0.429
Cerebrovascular disease	78 (5.4)	25 (13.7)	<0.001
Heart disease	193 (13.4)	49 (26.9)	<0.001
Coronary artery disease	126 (8.7)	29 (15.9)	0.003
Heart failure	147 (10.2)	37 (20.3)	<0.001
Valvopathy	80 (5.5)	33 (18.1)	<0.001
COPD	75 (5.2)	49 (26.9)	<0.001
Smoking (present or past)	314 (21.7)	83 (45.6)	<0.001
Malignancy	87 (6)	21 (11.5)	0.010
HIV	30 (2.1)	15 (8.2)	<0.001
Laboratory findings at ICU admission			
D-dimer (µg/mL)	1.5 (0.8; 4.5)	2.3 (1.1; 4.7)	0.009
White blood cell count (103/µL)	9.9 (7.3;13.7)	12 (8.9; 15.7)	<0.001
Lactate (mmol/L)	1.5 (1.2; 2.1)	1.8 (1.2; 3.2)	<0.001
Prothrombin time (seconds)	13.8 (13.1;14.8)	14.8 (13.9;16.4)	<0.001
Creatinine (mg/dL)	0.9 (0.8; 1.6)	1.2 (0.8;2)	0.015
Fibrinogen (mg/L)	652 (549;751)	538 (374;658)	<0.001
CRP (mg/L)	162 (100;241)	109 (35;213)	<0.001
Clinical data at ICU admission			
SOFA score	4 (3;6)	5 (3;8)	0.035
Ventilatory Support			<0.001
Non-invasive or HFNC	352 (24.4)	18 (9.9)	
Invasive mechanical ventilation	503 (34.8)	75 (41.2)	
Vasopressor	334 (23.1)	67 (36.8)	<0.001
PaO2/FiO2 ratio	122 (86;194)	203 (131;292)	0.000

Data expressed as median (p25;p75) or n (%). HFNC = high-flow nasal cannula. ICU = intensive care unit. COPD = chronic obstructive pulmonary disease. HFNC = high flow nasal catheter.

Table 2. Myocardial injury among patients admitted to the ICU with respiratory failure attributed to COVID-19 or other pulmonary infections

	All patients	COVID-19 n = 1444	Other pulmonary infections n = 182	P value
Troponin	13.2 (9.9;62.8)	11.6 (9.9;53.7)	35.5 (9.9;218)	<0.001
Myocardial injury	627(38.5)	525 (36.4)	102 (56)	<0.001
Troponin positive <5x ULN	314 (50)	272 (51.8)	42 (41.2)	
Troponin positive ≥ 5x ULN	106 (16.9)	86 (16.4)	20 (19.6)	
Troponin positive ≥ 10x ULN	207 (33.1)	167 (31.8)	40 (39.2)	

Data expressed as median (p25;p75) or n (%). *ULN = upper limit of normal; COVID-19 = coronavirus disease 19.*

Table 3. Outcomes in patients admitted to the ICU with respiratory failure attributed to COVID-19 or other pulmonary infections

	COVID-19 n = 1444	Other pulmonary infections n = 182	P value
Outcomes			
Renal replacement therapy (new)	339 (23.5)	21 (11.5)	< 0.001
Pulmonary embolism	298 (20.6)	10 (5.5)	<0.001
Non survivor	592 (41)	48 (26.4)	<0.001
Composite	838 (58)	66 (36.3)	<0.001
Length of hospital stay	19 (11;32)	14 (10;22)	<0.001
Length of ICU stay	10 (6;21)	4 (1;12)	<0.001
Length of mechanical ventilation	13 (7;24)	6 (4;11)	< 0.001

Data expressed as median (p25;p75) or n (%). Composite outcome = in-hospital death, pulmonary embolism, renal replacement therapy (new). ICU = intensive care unit.

Figure 1. Flow chart of the study.
Abbreviations: ICU = intensive care unit. MI = myocardial infarction. COVID-19 = coronavirus disease 19

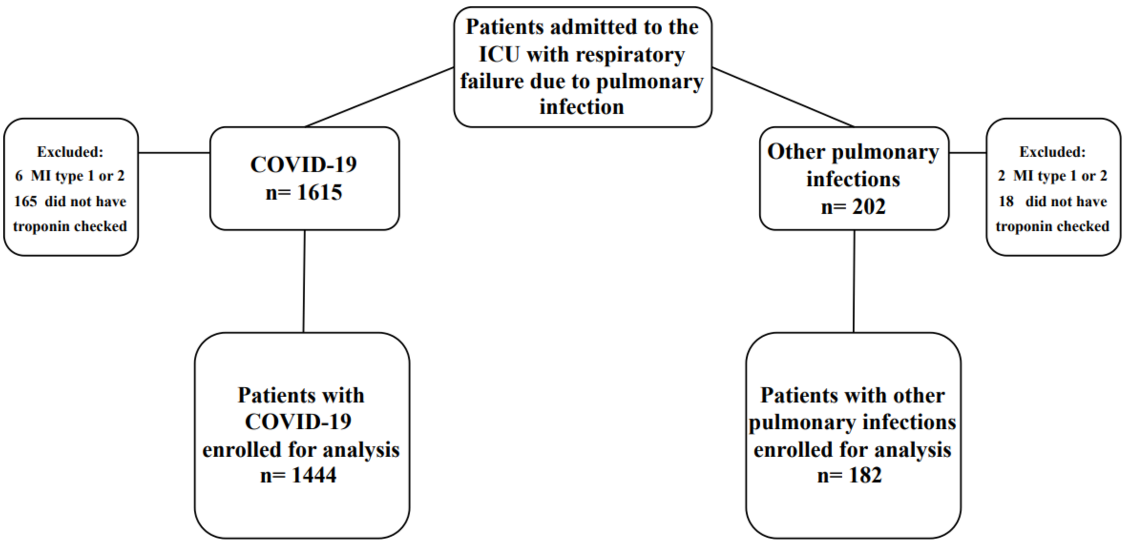


Figure 2. Myocardial injury relative risk (CI 95%) for COVID-19 *vs* non COVID-19 patients. Adjusted by robust Poisson regression model for age, sex, coronary artery disease, heart failure, SOFA score (creatinine, total bilirubin, PaO2/FiO2 ratio, mean arterial pressure/vasopressor, Glasgow Coma Scale, platelets), lactate and C-reactive protein.

Legend: COVID-19 = coronavirus disease 19

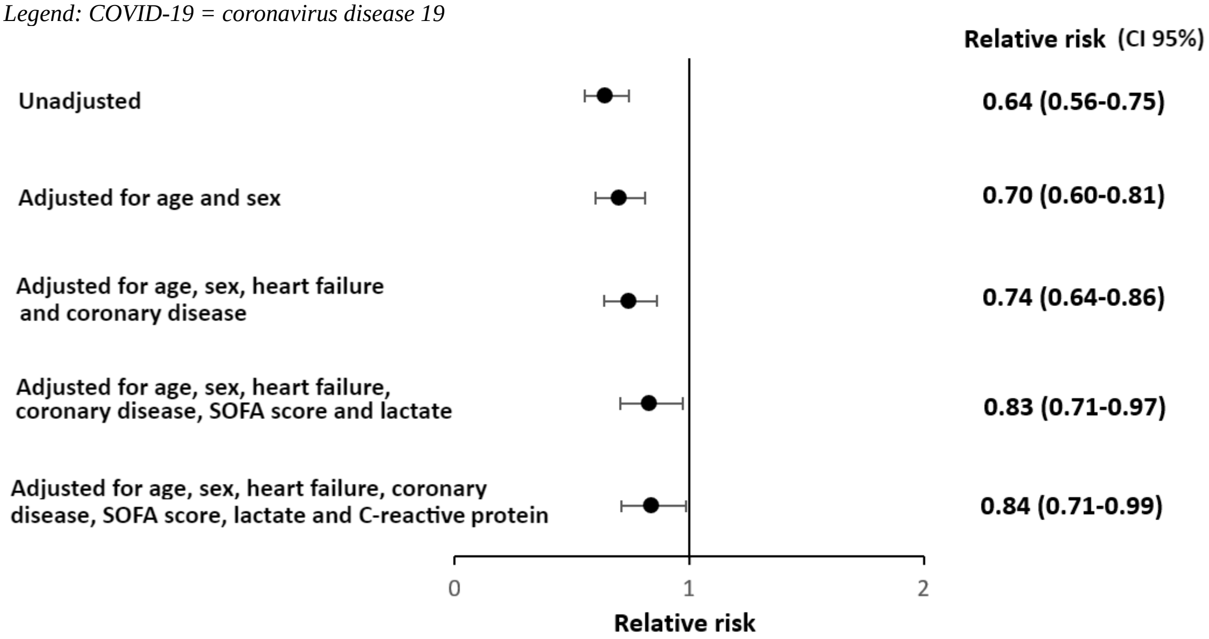


Figure 3. 30-day mortality by category of troponin level at ICU admission

(A) Patients admitted to the ICU with respiratory failure attributed to COVID-19. P<0.001 for difference in proportions. (B) Patients admitted to the ICU with respiratory failure attributed to non COVID-19 pulmonary infections. P=0.032 for difference in proportions.

Legend: ULN = upper limit of normal; COVID-19 = coronavírus disease 19

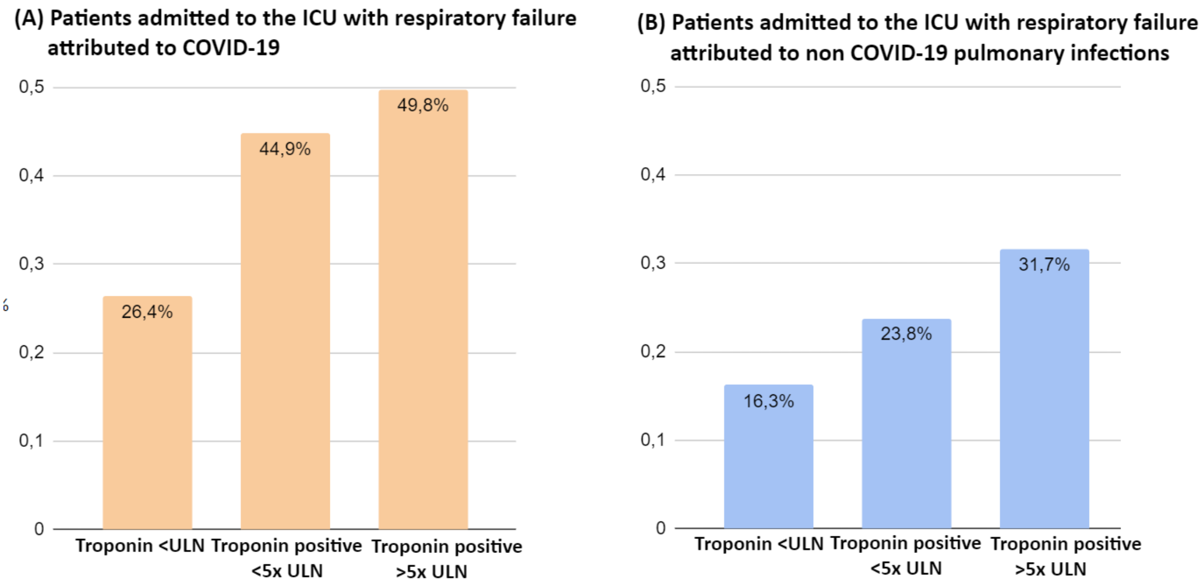
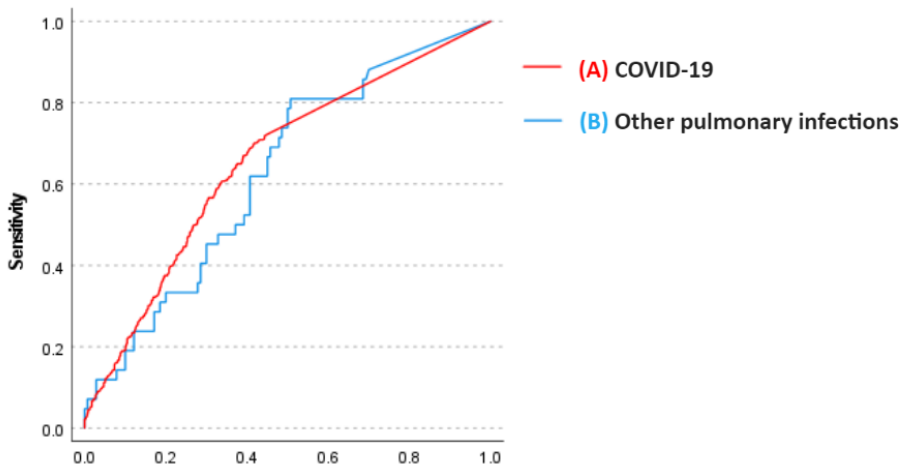
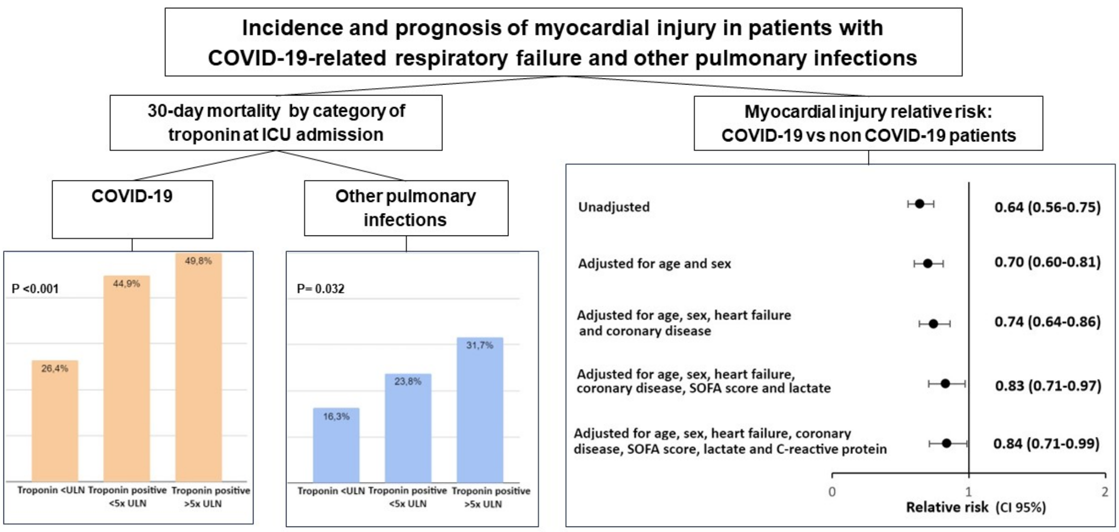


Figure 4. Receiver operating characteristics curves calculated for high-sensitivity cardiac troponin I to predict in-hospital mortality. (A) COVID-19 patients. Area under de curve(AUC) 0,656(95% CI 0.626-0.685). (B) Other pulmonary infections. Area under de curve(AUC) 0,628 (95% CI 0.535-0.720). There was no statistically significant difference in C-statistic for AUC calculated for high-sensitivity cardiac troponin I to predict in-hospital mortality in COVID-19 patients compared to other pulmonary infections (p=0.572).



GRAPHICAL ABSTRACT



Supplement 1. Comparison of non-COVID-19 patients with versus without troponin checked

Features	Total	No troponin checked n = 18	Troponin checked n = 182	P value
Demographics				
Age (years)	60.5 (42;72)	54.5 (29.8;65.5)	62(44.8;73)	0.070
Gender				0.624
Male	92 (46)	7 (38.9)	85 (46.7)	
Female	108 (54)	11 (61.1)	97 (53.3)	
Body Mass Index (kg/m²)	25.9 (21.6; 31.3)	21.6(19.2;28.3)	26.6(22.3;31.3)	0.022
Comorbidities				
Hypertension	104 (52)	6 (33.3)	98 (53.8)	0.139
Diabetes mellitus	62 (31)	3 (16.7)	59 (32.4)	0.194
Chronic kidney disease	25 (12.5)	4 (22.2)	21 (11.5)	0.252
Cerebrovascular disease	26 (13)	1 (5.6)	25 (13.7)	0.478
Heart disease	51 (25.5)	2 (11.1)	49 (26.9)	0.168
Coronary artery disease	31 (15.5)	2 (11.1)	29 (15.9)	0.745
Heart failure	38 (19)	1 (5.6)	37 (20.3)	0.206
Valvulopathy	34 (17)	1 (5.6)	33 (18.1)	0.320
COPD	53 (26.5)	4 (22.2)	49 (26.9)	0.785
Smoking (present or past)	93 (46.5)	10 (55.6)	83(45.6)	0.465
Malignancy	26 (13)	5 (27.8)	21 (11.5)	0.065
HIV	17 (8.5)	2(11.1)	15 (8.2)	0.655
Laboratorial findings at ICU admission				
P/F ratio	206.7 (131;299)	234 (143;343)	203 (131;293)	0.350
White blood cell count (103/µL)	12 (8.8;16)	11.5 (7.5; 17.6)	12 (8.9;15.7)	0.752
Lactate (mmol/L)	1.7 (1.2; 3.4)	1.5 (1.1; 4.5)	1.8 (1.2; 3.2)	0.703
Creatinine (mg/dL)	1.2 (0.8;2)	0.8 (0.6; 1.8)	1.2 (0.8;2)	0.082
CRP (mg/L)	109 (36;212)	111 (52;211)	109 (35;213)	0.894
Outcome				
Death	54 (27)	6 (33.3)	48 (26.4)	0.580
Renal replacement therapy	22 (11)	1 (5.6)	21 (11.5)	0.699
Length of mechanical ventilation	6 (4;10.8)	6 (6;6)	6 (4; 11)	0.929

Data expressed as median (p25;p75) or n (%).

Supplement 2. Comparison of COVID-19 patients with versus without troponin checked

Features	Total	No troponin checked n = 165	Troponin checked n = 1444	P value
Demographics				
Age (years)	59 (46;68)	60 (47.5;68)	58(46;68)	0.346
Gender				0.741
Male	891 (55.4)	89 (53.9)	802 (55.5)	
Female	718 (44.6)	76 (46.1)	642 (44.5)	
Body Mass Index (kg/m²)	30.4 (26.4; 35.6)	29.1(25.2;34.4)	30.4(26.5;35.7)	0.051
Comorbidities				
Hypertension	910 (56.6)	89 (53.9)	821 (56.9)	0.507
Diabetes mellitus	554 (34.4)	60 (36.4)	494 (34.2)	0.604
Chronic kidney disease	127 (7.9)	18 (10.9)	109 (7.5)	0.129
Cerebrovascular disease	85 (5.3)	7 (4.2)	78 (5.4)	0.712
Heart disease	215 (13.4)	22 (13.3)	193 (13.4)	1.000
Coronary artery disease	142 (8.8)	16 (9.7)	126 (8.7)	0.664
Heart failure	162 (10.1)	15 (9.1)	147 (10.2)	0.785
Valvulopathy	86 (5.3)	6 (3.6)	80 (5.5)	0.364
COPD	88 (5.5)	13 (7.9)	75 (5.2)	0.149
Smoking (present or past)	356 (22.1)	42 (25.5)	314 (21.7)	0.277
Malignancy	94 (5.8)	7 (4.2)	87 (6)	0.482
HIV	33 (2.1)	3(1.8)	30 (2.1)	1.000
Laboratorial findings at ICU admission				
P/F ratio	122 (86;194)	124 (84;191)	122 (87;195)	0.862
White blood cell count (103/µL)	9.9 (7.3;13.7)	9.9 (7.2; 13.7)	10 (7.3;13.7)	0.523
Lactate (mmol/L)	1.5 (1.2; 2)	1.4 (1.1; 1.9)	1.5 (1.2; 2.1)	0.119
Creatinine (mg/dL)	1.0 (0.8;1.6)	0.9 (0.7; 1.6)	1.0 (0.8;1.6)	0.106
CRP (mg/L)	162 (97;242)	152 (83;238)	163 (100;242)	0.129
Outcome				
Death	666 (41.4)	74 (44.8)	592 (41)	0.359
Renal replacement therapy	372 (23.1)	33 (20)	339 (23.5)	0.332
Length of mechanical ventilation	13 (7;24)	11 (7;23)	13 (7; 24)	0.617

Data expressed as median (p25;p75) or n (%).

Supplement 3. Characteristics of patients admitted to the ICU with respiratory failure attributed to COVID-19 or other pulmonary infections (sensitivity analysis including patients without troponin checked)

Features	**COVID-19 n = 1609**	**Other pulmonary infections n = 200**	**P value**
Demographics			
Age (years)	59 (46;68)	60.5 (42;72)	0.315
Gender			0.013
Male	891 (55.4)	92 (46)	
Female	718 (44.6)	108 (54)	
Body Mass Index (kg/m²)	30.4 (26.4;35.6)	25.9 (21.6;31.2)	<0.001
Comorbidities			
Hypertension	910 (56.6)	104 (52)	0.227
Diabetes mellitus	554 (34.4)	62 (31)	0.344
Renal replacement therapy	36 (2.2)	9 (4.5)	0.085
Cerebrovascular disease	85 (5.3)	26 (13)	<0.001
Heart disease	215 (13.4)	51 (25.5)	<0.001
Coronary artery disease	142 (8.8)	31 (15.5)	0.005
Heart failure	162 (10.1)	38 (19)	<0.001
Valvulopathy	86 (5.3)	34 (17)	<0.001
COPD	88 (5.5)	53 (26.5)	<0.001
Smoking (present or past)	356 (22.1)	93 (46.5)	<0.001
Malignancy	94 (5.8)	26 (13)	<0.001
HIV	33(2.1)	17 (8.5)	<0.001
Laboratory findings at ICU admission			
D-dimer (µg/mL)	1.5 (0.8; 4.5)	2.4 (1; 5)	0.012
White blood cell count (103/µL)	9.9 (7.3;13.7)	12 (8.8; 15.9)	<0.001
Lactate (mmol/L)	1.5 (1.2; 2)	1.7 (1.2; 3.4)	<0.001
Prothrombin time (seconds)	13.8 (13.1;14.9)	15 (13.8;16.7)	<0.001
Creatinine (mg/dL)	0.9 (0.8; 1.6)	1.2 (0.8;2)	0.045
Fibrinogen (mg/L)	648 (546;748)	541 (375;656)	<0.001
CRP (mg/L)	162 (97;242)	109 (36;213)	<0.001
Clinical data at ICU admission			
SOFA score	4 (3;6)	5 (3;8)	0.039
Ventilatory Support			<0.001
Non-invasive or HFNC	402 (25)	21 (10.5)	
Invasive mechanical ventilation	534 (33.2)	83 (41.5)	
Vasopressor	357 (22.2)	75 (37.5)	<0.001
PaO2/FiO2 ratio	122 (86;193)	206 (131;298)	0.000
Outcomes			
Renal replacement therapy (new)	372 (23.1)	22 (11)	< 0.001
Pulmonary embolism	334 (20.8)	10 (5)	<0.001
Non survivor	666 (41.4)	54 (27)	<0.001
Composite	930 (57.8)	72 (36)	<0.001
Length of hospital stay	19 (11;31)	13 (9;22)	<0.001
Length of ICU stay	10 (5;20)	4 (1;11)	<0.001
Length of mechanical ventilation	13 (7;24)	6 (4;10.8)	< 0.001

7 CONSIDERAÇÕES FINAIS

A pandemia de COVID-19 resultou em mais de 7 milhões de óbitos entre 2020 e 2023, representando uma emergência de saúde sem precedentes na história. Durante a pandemia, a comunidade científica empenhou-se de maneira rápida para a identificação de exames diagnósticos que pudessem auxiliar no manejo, avaliação da gravidade e de complicações da COVID-19. Alguns testes laboratoriais precocemente identificados como marcadores de gravidade da COVID-19 e utilizados também na avaliação de outras doenças conhecidas, foram utilizados durante a pandemia com a finalidade de definir condutas diagnósticas e terapêuticas antes de a sua utilidade e performance ter sido demonstrada por estudos clínicos, em pacientes internados por COVID-19.

Ainda no início da pandemia, estudos observacionais demonstraram uma alta incidência de injúria miocárdica em pacientes internados por COVID-19, e a incidência desta complicação estava associada a uma maior gravidade da COVID-19. Adicionalmente, demonstrou-se que a ocorrência dessa complicação se associava a piores desfechos. Nesse contexto, os testes laboratorial troponina passou a integrar rotineiramente a avaliação de pacientes com COVID-19, muitas vezes com objetivo de rastrear injúria miocárdica. Este trabalho investigou, em um estudo de coorte retrospectivo, o papel diagnóstico e prognóstico da troponina na avaliação de injúria miocárdica, bem como buscou determinar a sua incidência em pacientes internados por COVID-19.

Em uma coorte comparativa e contemporânea, demonstrou-se que a incidência de injúria miocárdica foi menor em pacientes com pneumonia por COVID-19 do que a encontrada em outras infecções pulmonares. A ocorrência de injúria miocárdica associou-se com maior risco para mortalidade intra-hospitalar, independente da etiologia da infecção pulmonar. Esses achados destacam o risco adicional representado pela lesão miocárdica em pacientes com pneumonia grave e insuficiência respiratória, e sugerem que não é causada diretamente pelo agente infeccioso, sendo mais provavelmente decorrente da disfunção multissistêmica de órgãos com instalação secundária à Síndrome Respiratória Aguda Grave. A implicação prática é a de privilegiar cuidados intensivos adequados para fins de reduzir o risco de injúria miocárdica e as suas consequências.

Este trabalho evidencia a necessidade de solicitarmos e interpretarmos exames laboratoriais com cautela, sempre considerando o contexto clínico e a população no qual está sendo utilizado, pois tais variáveis são determinantes para a performance e utilidade dos testes diagnósticos. Adicionalmente, uma implicação prática deste trabalho é a de demonstrar que a utilização de dados médicos adequadamente coletados no contexto assistencial pode ser muito útil para o avanço do conhecimento, independentemente do planejamento a priori de projetos de pesquisa. Essa nuance foi obviamente importante para doença que era até então desconhecida e demonstrou que o sistema de registro de dados disponibilizado pelo Hospital de Clínicas de Porto Alegre é muito eficiente para atingir esses objetivos.