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Article Review

Sars-cov-2 infection in patients undergoing heart transplantation: an integrative review on the new challenge for cardiology

Infecção por sars-cov-2 em pacientes submetidos à transplante cardíaco: uma revisão integrativa sobre o novo desafio para a cardiologia

Bruno Galdino Moreira[1], Andreza Alverga de Lima[2], Maria Alice Vieira Melo de Lima[3], Francisco Guilherme Leite Linhares de Sá[4], Rodolfo de Abreu Carolino[5], Marta Lígia Vieira Melo[6]

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ABSTRACT: Introduction: SARS-CoV-2 is a highly disseminated virus whose main target of infection is the respiratory system, however, by triggering an exacerbated immune response, signaled by the cytokine storm, it can cause damage to multiple organs. Therefore, this study seeks to gather evidence to assess the vulnerability of transplanted patients to the clinical manifestations of COVID-19, considering the management of the immunosuppression regimen and the effects of drug interactions in an attempt to promote adequate therapeutic management strategies. **Development:** This is an integrative literature review, carried out in March 2023, in which 6 articles were selected. Patients submitted to heart transplants, due to immunosuppression, are more likely to have cardiovascular diseases. The contamination by SARS-CoV-2 significantly increases the risk of complications, and sets a challenge: balancing the immunosuppressant regimen with antiviral therapy, in view of drug interactions. **Final considerations:** The use of immunosuppressants seems to be responsible for a milder course of COVID-19 in patients undergoing heart transplantation, by attenuating the cytokine storm. Nevertheless, there is still a serious risk of severity to COVID-19, and it is necessary to prioritize management with antiviral therapies that best adapt to immunosuppressive medications.

KEYWORDS: COVID-19; Cardiac transplant; Immunosuppression therapy.

RESUMO: Introdução: O SARS-CoV-2 é um vírus de alta disseminação cujo principal alvo de infecção é o sistema respiratório, porém, ao desencadear uma resposta imunológica exacerbada, sinalizada pela tempestade de citocinas, pode provocar lesões em múltiplos órgãos. Diante disso, este estudo busca reunir evidências que avaliem a vulnerabilidade de pacientes transplantados às manifestações clínicas do COVID-19, considerando o manejo do regime de imunossupressão e os efeitos das interações medicamentosas, na tentativa de promover estratégias adequadas de gerenciamento terapêutico. **Desenvolvimento:** Trata-se de uma revisão integrativa da literatura, realizada em março de 2023, na qual foram selecionados 6 artigos. Pacientes submetidos a transplantes cardíacos, devido ao quadro de imunossupressão, apresentam maior tendência em apresentar doenças cardiovasculares. A contaminação por SARS-CoV-2 aumenta significativamente o risco de complicações, e estabelece um desafio: equilibrar o regime de imunossupressores com a terapia antiviral, tendo em vista as interações medicamentosas. **Considerações finais:** O uso de imunossupressores parece ser responsável por um curso mais brando da COVID-19 em pacientes submetidos a transplante cardíaco, pela atenuação da tempestade de citocinas. Apesar disso, ainda há risco de gravidade da COVID-19, sendo necessário priorizar o manejo com terapias antivirais que melhor se adaptem às medicações imunossupressoras.

PALAVRAS-CHAVE: COVID-19; Transplante cardíaco; Terapia de imunossupressão.

1. Estudante do Curso de Graduação em Medicina do Centro Universitário Santa Maria – UNFSM – Cajazeiras, PB. https://orcid.org/0000-0002-3145-2195 Email: brunogaldinomoreiracz@gmail.com
2. Estudante do Curso de Graduação em Medicina do Centro Universitário Santa Maria – UNFSM – Cajazeiras, PB. https://orcid.org/0000-0002-0914-2297 Email: andrezaalverga@gmail.com
3. Estudante do Curso de Graduação em Medicina do Centro Universitário Santa Maria – UNFSM – Cajazeiras, PB. https://orcid.org/0000-0002-2393-686X Email: malicevmelo@gmail.com
4. Estudante do Curso de Graduação em Medicina do Centro Universitário Santa Maria – UNFSM - Cajazeiras, PB. https://orcid.org/0000-0001-6388-7508 Email: zuleidelcrispim412@gmail.com
5. Professor do Centro Universitário Santa Maria – UNFSM de Cajazeiras - PB nos cursos de Odontologia e Medicina. https://orcid.org/0000-0002-7962-024X Email: rodolfoorg@yahoo.com.br
6. Professora/orientadora do Centro Universitário Santa Maria – UNFSM de Cajazeiras - PB nos cursos de Bacharelado em Medicina e de Bacharelado em Fisioterapia. https://orcid.org/0000-0002-5882-3291 Email: martaligiafiso@hotmail.com

Endereço para Correspondência: Rua Santa Cecília, 215. Jardim Oásis. Cajazeiras-PB; brunogaldinomoreiracz@gmail.com

INTRODUCTION

Coronaviruses are a large family of viruses that typically induce mild to moderate illnesses of the upper respiratory tract; however, some can lead to more severe and even fatal diseases, representing significant challenges to global health due to their high rates of lethality and contagion[1].

At the end of the year 2019, in Wuhan, China, a new coronavirus (SARS-CoV-2), responsible for severe acute respiratory disease, was identified[2].

SARS-CoV-2 is a rapidly spreading virus that hijacks the cellular machinery in order to replicate and infect more host cells[3]. The patient's age and the presence of comorbidities are risk factors for the disease[4,5]. The development of the severe form of the disease is associated with a fatality rate of approximately 28.3%, according to Huang et al. (2020)[6].

SARS-CoV-2 primarily targets the respiratory tract; however, the excessive release of cytokines during the severe course of the disease can result in dysfunction and multi-organ failure, including the heart[7]. Thus, the study by Hartmann et al. (2021)[8] describes that SARS-CoV-2 promotes myocardial injury linked to local inflammation, associated with interstitial edema, as elevated levels of TGF-β and interstitial collagen were found. These markers are related to chronic myocardial fibrosis, leading to the assertion that the natural history of the disease is not primarily linked to the involvement of cardiomyocytes.

In a molecular analysis, it is evident that the impact of SARS-CoV-2 on the heart is greater than anticipated. In cardiac tissue, this virus triggers a series of disruptions in the mitochondrial DNA of cardiomyocytes and in the metabolic homeostasis of heart cells. As a result, the patient becomes more susceptible to myocarditis and persistent inflammation, along with thrombocytopenia and coagulopathy, due to the increased presence of anticardiolipin antibodies and the virus's action on toll-like receptor (TLR) signaling pathways, which are expressed in immune cells and cardiac parenchymal cells[9].

Due to the need for lifelong immunosuppressive therapy to prevent rejection episodes, transplant patients appear to be more vulnerable to SARS-CoV-2 contamination. However, the impact of immunosuppressive therapy during the course of infection still remains uncertain[10].

The analysis of the clinical situation of patients undergoing heart transplantation is becoming increasingly urgent in the current context, considering that besides being immunocompromised, these patients have pre-existing comorbidities as risk factors for the severe course of the disease[11, 12].

Physiologically, the virus has the capability to increase the expression of angiotensin-converting enzyme 2 (ACE2), which can potentially lead to serious damage to the cardiovascular system. Regarding patients who have undergone heart transplantation, immunosuppressive drugs, in addition to reducing cells responsible for innate immunity, also result in a reduction of these enzymes, which could, intriguingly, attenuate the inflammatory response. Consequently, there is a possibility that immunocompromised patients may experience a milder clinical course of the disease[13,14].

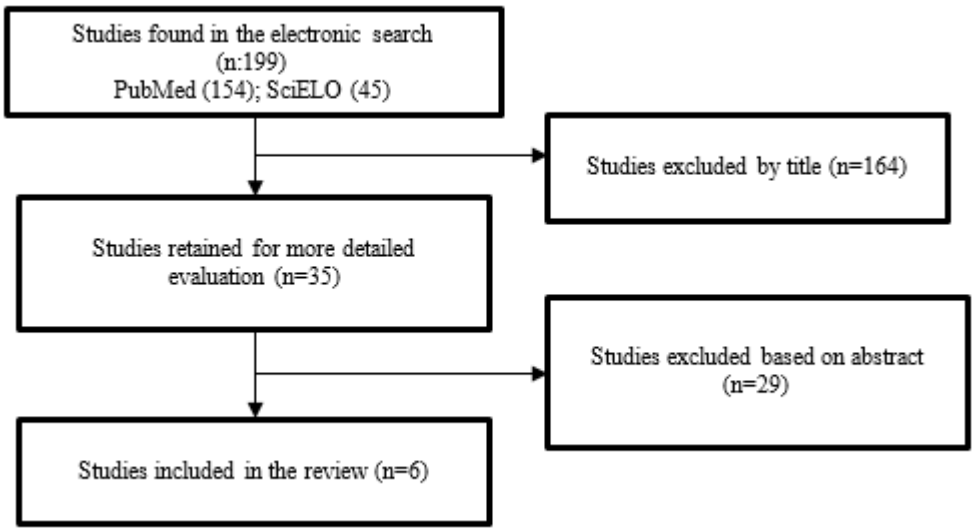
Therefore, COVID-19 presents a unique challenge for heart transplant recipients, as the medical team's lack of knowledge about therapeutic management strategies directly impacts the patients' prognosis[11].

From this perspective, the undertaking of this study is justified, aiming to synthesize the most recent information on the topic concerning the influence that COVID-19 has on heart transplant recipients. Specifically, it aims to address the management of the immunosuppression regimen, as well as the effects of interactions between drug therapies.

METHOD

This is an integrative literature review, as it contributes to the process of systematizing and analyzing results, enabling the understanding of a specific theme. It was conducted in March 2023. After formulating the research question, a bibliographic search for scientific articles published in journals indexed in the databases of the Scientific Electronic Library (SciELO) and the National Library of Medicine (PubMed) was conducted. For the research, the following health science descriptors were used: "COVID-19," "Heart Transplant," and "Immunosuppressive Therapy." The boolean operator AND was used to combine these terms. A total of 154 results were found in PubMed and 45 results in SciELO through the search strategy. The inclusion criteria consisted of articles published in the years 2020 and 2023, with English and Portuguese being the accepted languages for the search. Theses, dissertations, editorials, incomplete texts, and non-randomized studies were excluded. After analyzing the results, 6 articles were selected for the development of this study (Figure 1).

Figure 1 - Flowchart of article selection.



Source: Authors' elaboration.

RESULTS

After the search strategy, the following authors were selected (Table 1).

Table 1 - Selection of the chosen authors.

AUTOR/ANO	TIPO DE ESTUDO	OBJETIVO	RESULTADOS
Caraffa et al. (2020)[11]	Cross-sectional study.	Report the experience with heart transplant patients (HT) who contracted COVID-19.	The immunosuppressive therapy was modified with an average reduction involving doses that were 50% cyclosporine and 50% mycophenolate. All patients received a mean dose of corticosteroids as bolus medication, in addition to the therapy. Two patients received ritonavir/lopinavir. Broad-spectrum antibiotics for prophylaxis were administered to all. One patient experienced an ischemic stroke and died from sepsis.
Latif, et al. (2020)[21]	Retrospective cohort study.	Describe the characteristics, treatment, and outcomes of heart transplant recipients with COVID-19.	Heart transplant recipients (HT) may have an increased risk of infection and adverse outcomes with COVID-19 infection due to a range of comorbidities that are common after heart transplantation, including hypertension, diabetes, and cardiac allograft vasculopathy. Additionally, while all require maintenance immunosuppression that predisposes recipients to higher infectious risk, immunosuppression has also been considered protective against the cytokine storm. In this series of confirmed COVID-19 cases among heart transplant recipients, a high fatality rate of 25% was reported, which was much higher than currently reported in other patient populations.
Kanaan et al. (2022)[49]	Retrospective multicenter cohort.	Compare the clinical outcomes of hospitalized heart transplant recipients with COVID-19 with a matched cohort of patients without heart transplantation.	A total of 24 heart transplant cases were matched with 96 non-heart transplant (NHT) controls from 11,481 patients. Five TC patients were within the first year post-transplant. A total of 20 (83.3%) TC patients were on tacrolimus, 23 (95.3%) on mycophenolate mofetil (MMF), 12 (50.0%) on prednisone, 3 (12.5%) on cyclosporine, and 1 (4.0%) on everolimus. TC patients did not show worse outcomes after acquiring COVID-19, whether in the first year post-transplant or following a remote transplant procedure.

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AUTOR/ANO	TIPO DE ESTUDO	OBJETIVO	RESULTADOS
Peters et al. (2022)[51]	Case-control study.	Evaluate the safety and efficacy of COVID-19 vaccination and its associations with SARS-CoV-2 infection and clinical outcomes in a large population of adult heart transplant recipients.	A total of 436 heart transplant recipients were included in the study, of which 106 patients were infected with COVID-19. COVID-19 vaccination was associated with a lower risk of COVID-19 infection (risk ratio [RR], 0.41; 95% CI, 0.30-0.56), hospitalization (RR, 0.29; 95% CI, 0.14-0.61), and death (RR, 0.19; 95% CI, 0.05-0.82). Among the 366 vaccinated heart transplant recipients, there was no echocardiographic evidence of graft dysfunction. COVID-19 vaccination was linked to fewer COVID-19 infections, hospitalizations, and deaths, without specific adverse events related to heart transplantation. COVID-19 vaccination for all heart transplant recipients is of paramount importance.
Tschopp et al. (2020)[3]	Retrospective multicenter cohort.	Provide a comprehensive overview of the epidemiology, clinical presentation, treatment, and outcomes of the early microbiologically documented SARS-CoV-2 infections among adult recipients of solid organ transplantation (SOT).	The clinical manifestations of SARS-CoV-2 infection in middle-aged solid organ transplant (SOT) recipients appear to be similar to those of the general population, without an apparent higher rate of complications. The most common presenting symptoms were fever (76%), dry cough (57%), nausea (33%), and diarrhea (33%). Ninety-five percent and 24% of patients required hospitalization and ICU admission, respectively, and 19% were intubated. After a median follow-up of 33 days, 16 patients were discharged, 3 remained hospitalized, and 2 patients died.
Lima, Brian et al. (2021)[17]	Cross-sectional study.	Evaluate the impact of COVID-19 on heart transplant recipients.	All five patients experienced moderate (requiring hospitalization, n=3) or severe disease (requiring ICU and/or mechanical ventilation, n=2). Both severe cases were transplanted approximately 6 weeks prior to presentation and acquired COVID-19 through community spread. All five patients were on immunosuppressive therapy with mycophenolate mofetil (MMF) and tacrolimus, and three who were transplanted within the previous 2 months were additionally on prednisone. The two severe cases had profound lymphopenia along with markedly elevated C-reactive protein, procalcitonin, and ferritin levels. All had bilateral ground-glass opacities on chest imaging. MMF was discontinued in all five, and both severe cases received convalescent plasma. All three recent transplants underwent routine endomyocardial biopsies, revealing mild (n=1) or no acute cellular rejection (n=2), and no visible viral particles on electron microscopy. Within 30 days of admission, the two severe cases remained hospitalized but improved clinically, while the other three were discharged.

Source: Authors' elaboration.

DISCUSSION

SARS-CoV-2 is a positive-sense, non-segmented, single-stranded RNA virus. It contains four main structural proteins: the spike protein (S), the nucleocapsid protein (N), the membrane protein (M), and the envelope protein (E)[3].

The virus enters the host cell through the binding between the spike protein (S) and the angiotensin-converting enzyme 2 (ACE2) receptor. By inhibiting the conversion of the enzyme to its active form, the parasite increases ACE2, favoring lung injury and causing severe damage, particularly in the cardiovascular system[15].

In transplant patients, the specific characteristics of COVID-19 still remain uncertain regarding the impact of immunosuppressive therapy during the infection phase[10]. According to some authors such as Molnar et al. (2020)[16] and Tschopp et al. (2020)[3], initially, transplant-related immunosuppression appears to increase the risk of contagion. However, after the infection sets in, clinical manifestations in transplant recipients seem to be similar to those of the general population, with no apparent higher rate of complications and a similar risk of mortality.

Especially about patients who have undergone heart transplantation, in addition to the immunosuppressive regimen, it must be considered that these patients have cardiovascular diseases, which elevate the fatality rate by 10.5%. This constitutes one of the major complicating factors in the clinical picture of COVID-19, along with chronic respiratory diseases (6.3%), diabetes (7.3%), and hypertension (6%)[4,11,12].

When evaluating heart transplant recipients, it might seem initially that they are more likely to experience a severe course of COVID-19. Therefore, the medical community follows a treatment approach that faces the main challenge of balancing immunosuppressive regimens with antiviral therapy. Consequently, two key points are essential for the management of these patients[17,18].

a) The challenges for managing immunosuppressive therapy;

b) Possible drug interactions;

The challenges for managing immunosuppressive therapy

The rapid emergence and spread of SARS-CoV-2 have generated doubts and controversies regarding the established protocols for managing the immunosuppression regimen in COVID-19 patients[19].

Based on the literature, there are still no in-depth studies on COVID-19 in heart transplant patients. At first glance, it might be possible to conclude that immunosuppression is unfavorable for the course of the disease; however, some studies such as Decker et al. (2020)[20], Huang et al. (2020)[6], and Latif et al. (2020)[21] point to immunosuppression as a protective factor against the cytokine storm generated by COVID-19.

Regarding the pharmacodynamics of drugs used in immunosuppressive therapy, studies indicate that, in addition to their immunosuppressive activity, these drugs activate the renin-angiotensin-aldosterone system (RAAS) and therefore have a certain capacity to modulate the expression of pulmonary receptors of angiotensin-converting enzyme 2 (ACE2), which are the same binding sites for viral particles of SARS-CoV-2[14].

The study by Bösch et al. (2020)[13] observed a decrease in interleukin 6 (IL-6) values in the blood, raising the hypothesis that the inflammatory response would be more attenuated in transplant patients. However, according to Ren et al. (2020)[23], it is necessary to highlight that in transplant patients, there is a possibility of inaccuracies in laboratory data since even before the infection, some patients already exhibit lymphopenia, possibly due to the use of immunosuppressants that hinder the development of lymphocytes and the expression of pro-inflammatory cytokine genes such as IL-2, IL-3, IL-4, interferon-gamma, and tumor necrosis factor-alpha (TNF-α).

Despite some discrepancies, the studies by Defilippis et al. (2020)[24] and Huang et al. (2020)[6] agree on the need for reduction or even temporary suspension of immunosuppressants, so that antiviral therapy can take effect, provided there is regular patient monitoring due to the high risk to which patients are exposed.

Additionally, for the clinical management of COVID-19 in post-heart transplant patients, healthcare professionals should be vigilant regarding elevated cardiac biomarkers, the risk of right ventricular dysfunction, arrhythmias, and thromboembolic events[25].

Interactions between drug therapies

The care of heart transplant patients requires greater attention in cases of COVID-19 contamination, since it is necessary to consider the effects of drug interactions and adverse reactions that can be caused by the medications used, such as electrocardiographic changes caused by some drugs[18].

Lopinavir and ritonavir have attracted attention as potential forms of treatment against COVID-19 in vitro studies, given that positive results were seen in studies on SARS and MERS. It is noted that lopinavir inhibits the CYP450 enzyme, which degrades tacrolimus, an immunosuppressant of the calcineurin inhibitor class, increasing its plasma concentration[26]. Due to the hypothesis that tacrolimus has the ability to reduce the viral load of SARS-CoV-2 by increasing its plasma availability, these drugs have potential in fighting the virus, although there is still no proof or in-depth studies regarding these medications[20].

By analyzing lopinavir and ritonavir in clinical practice without correlation with other medications, the literature describes that these drugs did not show efficacy in treating severe COVID-19 patients. The study by Cao et al. (2020)[27] demonstrated in a cohort of 199 individuals that patients did not respond to treatment with these drugs and remained with an unchanged clinical condition. Corroborating these results, the studies by Horby et al. (2020)[28] and Shafiekhani et al. (2021)[29] reached similar conclusions, as these studies found unchanged mortality rates among the studied groups and no reduction in hospitalization days.

Ribavirin also constitutes a promising pharmacological agent against COVID-19 due to its effectiveness against a wide range of DNA and RNA viruses. However, this medication can worsen the clinical condition of patients with cardiovascular comorbidities, such as transplant patients, as it can cause hemolytic anemia, as well as thrombocytopenia and pancytopenia[18].

Still, despite this medication seemingly being promising, combined with post-transplant immunomodulatory therapy, the studies by Tong et al. (2020)[30] and Hung et al. (2020)[31] have already demonstrated that this medication is not recommended for COVID-19-infected patients, as there is no evidence of improvement in clinical conditions, reduction in hospitalization days, mortality, and various side effects.

The pharmacological agent tocilizumab, an interleukin-6 (IL-6) inhibitor, combats the hyperinflammatory syndrome characterized by hypercytokinemia, mentioned as the pathogenesis of severe COVID-19[22].

In a study, Fontana et al. (2020)[32] indicated an improvement in the condition of transplant recipients with COVID-19 using monotherapy or combined therapy with tocilizumab. However, the role of tocilizumab remains undefined due to adverse effects such as upper respiratory tract infections, cardiovascular complications, and liver failure[33]. In another study, Shafiekhani et al. (2021)[29] also demonstrated the effectiveness of tocilizumab combined with remdesivir and indicated it as a safe therapeutic option for post-transplant patients, considering the clinical specificities of each patient.

Baricitinib, a selective Janus kinase inhibitor (JAK1/JAK2), has demonstrated great effectiveness in treating COVID-19 thanks to its anti-inflammatory action, directly affecting the cytokine cascade, and its antiviral mechanism[34]. Besides its effect on reducing biomarkers and cytokines, when combined with remdesivir, baricitinib is associated with a lower rate of severe adverse events, overall clinical improvement, especially in patients requiring high-flow oxygen or non-invasive ventilation (NIV), and a 1-day reduction in recovery time[35].

Tofacitinib, another class of medications that acts specifically on JAK1 and JAK3, also has a reducing effect on the inflammation cascade[36]. With a blocking effect on interleukin signaling, this drug showed high efficacy and safety, especially in hospitalized patients with COVID-19 pneumonia. In the randomized STOP-COVID study involving 289 patients, tofacitinib led to a lower risk of death or respiratory failure by day 28 compared to the placebo group. Moreover, this drug demonstrated promising clinical effects in patients with moderate SARS-CoV-2 infection, thus being indicated when baricitinib is unavailable[36].

In contrast to the previous study, in 2022 the World Health Organization (WHO) contraindicated the use of tofacitinib in critically or severely ill COVID-19 patients. This decision is based on limited evidence regarding the decrease in mortality rate or duration of mechanical ventilation, as well as indications of increased serious side effects associated with the medication[37].

Formed by the combination of nirmatrelvir, a protease inhibitor with antiviral action against the coronavirus, and ritonavir, an HIV-1 protease inhibitor and inhibitor of cytochrome P450 3A (CYP3A) necessary for maintaining nirmatrelvir, nirmatrelvir-ritonavir is one of the newest drugs in COVID-19 treatment[38]. Its efficacy has been proven in studies by Mahase (2021)[39] and Vangeel et al. (2022)[40], showing a reduction in the risk of hospitalization or death within 28 days compared to a placebo in vaccinated patients.

Because of its prominence in COVID-19 treatment and its specificities with post-transplant immunosuppressive therapy, nirmatrelvir-ritonavir has become the subject of study to validate its clinical use[41]. In this context, the studies by Devresse et al. (2022)[42], Hedvat et al. (2022)[43], Salerno et al. (2022)[44], Stawiarski et al. (2023)[45] indicated that nirmatrelvir/ritonavir could be a promising therapeutic option for transplant patients with COVID-19. However, adjustments and careful monitoring of the drug are necessary to minimize the risk of adverse effects and graft damage.

The literature also makes important considerations regarding molnupiravir, an antiviral that acts as a substrate for the SARS-CoV-2 RNA polymerase, impairing virus replication and infection[46]. Thus, the study by Dhand et al. (2023)[47] shows positive results regarding a decrease in mortality, a reduction in hospitalization days, and minimal drug interaction with immunosuppressive therapy.

In Table 2, some pharmacological interactions are presented, with a focus on changes in the QT interval, which are most influential on cardiac receptors, recommending not to discontinue heart medications and to maintain strict cardiac monitoring[48].

Table 2 - Antiviral Drugs and Their Interactions with Immunosuppressive Drugs.

Fármacos	Side Effects	Drug Interactions
lopinavir /ritonavir	Hipercolesterolemia; Increased serum TGs; Elevated liver enzymes.	May increase serum concentrations of everolimus, ciclosporin, and tacrolimus. Can also increase sirolimus levels.
ribavirin	Neutropenia; Lymphocytopenia; Hemolytic anemia; Elevated serum bilirubin.	Can increase serum concentrations of active azathioprine metabolites.
remdesivir	Skin rash; Diarrhea; Hypotension; Increased liver enzymes.	Can induce CYP enzymes including CYP1A2, CYP2B6, and CYP3A4.
tocilizumabe	Hepatotoxicity; Increased ALT and AST levels; Increased risk of upper respiratory tract infections; Neutropenia; Leukopenia; Thrombocytopenia.	May decrease serum concentration of tacrolimus.

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Fármacos	Side Effects	Drug Interactions
baracitinibe	Elevated LDL cholesterol levels; Upper respiratory tract infections; Headaches; Herpes infections; Urinary tract infections; Neutropenia; Thrombocytosis.	Risk of additive immunosuppression when combined with potent immunosuppressive drugs like azathioprine, tacrolimus, or ciclosporin.
tofacitinibe	Anemia, Abdominal pain, Diarrhea, Dyspepsia, Gastritis, Nausea, Vomiting, Fatigue, Peripheral edema, Fever, Headache, Dyslipidemia, Joint pain, Bronchitis, Herpes zoster, Influenza, Nasopharyngitis, Pharyngitis, Pneumonia, Sinusitis, Urinary tract infection, Cough, Hypertension.	Increased exposure when co-administered with strong CYP3A4 inhibitors and decreased exposure with strong CYP inducers.
nirmatrelvir-ritonavir	Nausea, vomiting, tremors, hyperkalemia, weakness, confusion, acute respiratory failure, cough, dyspnea.	Increases serum concentrations of immunosuppressants, especially tacrolimus. Caution needed due to potential tacrolimus toxicity.
molnupiravir	Nausea, diarrhea, headache reported.	Alters serum levels of immunosuppressants depending on the administered dose of molnupiravir.

Source: Authors' elaboration.

Immunosuppressive therapy in patients who have undergone heart transplantation is complex and stringent. Aimed at preventing organ rejection, immunosuppression targets the body's defenses, which can predispose patients to more severe forms of opportunistic diseases[49]. In the context of COVID-19, the study by Mendoza et al. (2023)[50] indicates that there is no difference between severe and non-severe forms of the disease in transplant patients, and there is no increased risk of secondary infection for these patients.

With the advent of COVID-19 vaccination, other dilemmas have arisen in the management of these patients, with potential clinical implications. Studies show that vaccination reduces mortality and infection rates in the general population. Not unexpectedly, transplant patients also exhibit similar rates of vaccine effectiveness, which implies that there is no need to alter immunosuppressive therapy and that this group should be prioritized for vaccination[51].

CONCLUSION

The management of heart transplant patients in the context of COVID-19 presents multifaceted challenges. The intricate balance between immunosuppressive therapy and the susceptibility to severe infections requires careful consideration. Studies have shed light on the potential interactions between antiviral medications and immunosuppressants, underlining the need for vigilant monitoring and tailored approaches for each patient.

In combating SARS-CoV-2 in heart transplant patients, it's essential to maintain a balance between antiviral drugs and immunosuppressive therapy, taking into account the clinical condition, comorbidities, and the preservation of the transplanted organ.

It has been observed that transplant patients may experience a milder clinical course of the disease, considering that immunosuppressive drugs lead to a reduction in the inflammatory response by attenuating the cytokine storm caused by COVID-19.

As highlighted in this discussion, antiviral drugs like lopinavir/ritonavir, ribavirin, tocilizumab, baricitinib, tofacitinib, nirmatrelvir-ritonavir, and molnupiravir have shown varying interactions with immunosuppressive regimens. These interactions should be thoroughly evaluated to mitigate potential risks and optimize therapeutic outcomes.

However, the risk of a severe course of COVID-19 remains considerable for these patients. Therefore, the prescription of antiviral therapy should adhere to protocols that take into account the effects of drug interactions, in order to avoid exacerbating the patient's condition further. Despite the existing studies, further research on this topic is needed, with larger cohorts, to develop comprehensive and up-to-date protocols.

In conclusion, the intricate interplay between immunosuppression, antiviral treatments, and vaccination underscores the need for a multidisciplinary approach in the management of heart transplant recipients during the COVID-19 pandemic. Clinicians should carefully evaluate each patient's medical history, medication regimen, and clinical status to make informed decisions that prioritize both organ graft survival and the mitigation of COVID-19-related risks. Ongoing research and collaboration within the medical community will continue to shape the best practices for the care of these vulnerable patients.

Author contributions: Authors Bruno Galdino Moreira, Andreza Alverga de Lima, Maria Alice Vieira Melo de Lima, and Francisco Guilherme Leite Linhares de Sá played active roles in selecting the articles and crafting the main body of the text. Meanwhile, Rodolfo de Abreu Carolino and Marta Lígia Vieira Melo participated as reviewers of the final manuscript.

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