COVID-19 in heart transplant recipients during February–August 2020: A systematic review

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Abstract
The coronavirus disease 2019 (COVID-19) pandemic represents a major concern in immunosuppressed patients such as heart transplant recipients. Therefore, we performed a systematic review to summarize the clinical features, treatment, and outcomes of heart transplant recipients with COVID-19. We searched electronic databases from inception to January 11, 2021. Thirty-nine articles (22 case reports and 17 cohorts) involving 415 patients were included. The mean age was 59.9 ± 15.7 years and 77% of patients were men. In cohort studies including outpatients and inpatients, the hospitalization rate was 77%. The most common symptoms were fever (70%) and cough (67%). Inflammatory biomarkers (C-reactive protein and procalcitonin) were above the normal range. Forty-eight percent of patients presented with severe or critical COVID-19. Hydroxychloroquine (54%), azithromycin (14%), and lopinavir/ritonavir (14%) were the most commonly used drugs. Forty-nine percent of patients discontinued the baseline regimen of antimetabolites. In contrast, 59% and 73% continued the same regimen of calcineurin inhibitors and corticosteroids, respectively. Short-term mortality among cohorts limited to inpatients was 25%. Our review suggests that heart transplant recipients with COVID-19 exhibited similar demographic and clinical features to the general population. However, the prognosis was poor in these patients.

KEYWORDS
COVID-19, heart transplantation, systematic review

1 INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and was first detected in December 2019 in Wuhan, China.1 Since then, it has spread worldwide, causing significant morbidity and mortality to date.2 Although approved vaccines are increasingly available, many countries are currently facing new waves of cases with even higher transmission rates than the initial peak of the pandemic.3

Heart transplant recipients are a particularly vulnerable population for worse outcomes given the state of immunosuppression and their high prevalence of comorbidities. Moreover, SARS-CoV-2 has proven...
its virulence extends beyond the respiratory system, and as such, cardiovas-
ular involvement of COVID-19, in particular, has been reported by way of myocardial injury,5,6 heart failure,7 and even cardiogenic shock.8

To date, several centers across the world have reported the clinical impact of COVID-19 in these patients. Therefore, we performed a systematic review to summarize the clinical features, treatment, and outcomes of heart transplant recipients with COVID-19.

2 METHODS

This review was reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.9

2.1 Search strategy

An electronic systematic review of the literature was conducted in PubMed, Embase, Scopus, and Web of Science. The keywords used were chosen according to the MESH terminology: “COVID-19” and “heart transplantation”. The search was conducted from inception to October 1, 2020, with an update until January 11, 2021. The complete search strategy is available in Table S1. In addition, we conducted a hand-searching of reference lists of all included studies and relevant reviews to identify further studies.

2.2 Eligibility criteria

The inclusion criteria were the following: (i) studies that included adult patients (≥18 years of age) and (ii) studies that reported data on clinical features, treatment, or outcomes of heart transplant recipients with COVID-19 diagnosed by reverse transcription-polymerase chain reaction (RT-PCR). There were no restrictions on language or publication date. We excluded animal studies, abstracts, editorials, commentaries, systematic reviews, and narrative reviews.

2.3 Study selection

We downloaded all articles from electronic search to EndNote X8 software and duplicate records were removed. Titles and abstracts were independently screened by three review authors (Carlos Diaz-Arocutipa, Darla Carvallo-Castañeda, and Odalis Luis-Ybañez) to identify relevant studies. Likewise, the same review authors independently assessed the full-text of each eligible study and registered reasons for the exclusion. Any disagreement on title/abstract and full-text selection was resolved by consensus.

2.4 Data extraction

The information from each study was independently extracted by two review authors (Darla Carvallo-Castañeda and Odalis Luis-Ybañez) using a standardized data extraction form that was previously piloted. Any disagreement was resolved by a third author (Carlos Diaz-Arocutipa). If additional data was needed, the corresponding author was contacted through e-mail. We extracted the following data: first author name, publication year, country, study design, sample size, age, sex, comorbidities, clinical features, diagnostic methods, treatment, and outcomes.

2.5 Statistical analysis

Frequencies and proportions were used to summarize categorical variables. Means ± standard deviations or median (interquartile range) were used for continuous variables. Data were presented according to study type (case reports and cohorts) and type of population (inpatients and outpatients/inpatients). All analyses were performed using the statistical software R 3.6.3 (www.r-project.org).

3 RESULTS

3.1 Study selection

Our electronic search retrieved 730 articles. After the removal of duplicates, 352 articles were screened by title and abstract, and of those, 299 articles were excluded. After full-text evaluation of 53 remaining articles, 14 were excluded. The reasons for exclusion were as follows: type of article (commentary [four], other population [four], and review [one]), or incomplete data (five). Finally, 39 articles (22 case reports and 17 cohorts) were selected (Figure 1).10–48 All studies included as cohorts included all known cases of COVID-19 at their heart transplant centers during each study period. Characteristics of the included studies are summarized in Table 1.

3.2 Demographics and clinical features

A total of 415 heart transplant patients with COVID-19 were included. Baseline characteristics of the study population are summarized in Table 2. The mean age was 59.9 ± 15.7 years and 77% of patients were men. Most cases (35%) were from the United States of America. In addition to immunosuppression, hypertension (69%), diabetes (36%), and chronic kidney disease (36%) were the most common comorbidities. The mean body mass index 26.7 ± 5.6 kg/m² (n = 168 patients). The mean time from transplantation to COVID-19 diagnosis was 8.8 ± 9 years (n = 409 patients). In 95% of cases, the only transplanted organ was the heart, while in the rest, it was the heart plus the kidney or lungs. The baseline immunosuppressive regimen was mainly composed by antimetabolites (mycophenolate mofetil, mycophenolic acid, or azathioprine) in 69%, calcineurin inhibitors (tacrolimus or cyclosporine) in 89%, and corticosteroids (prednisone) in 59% of patients. A minority of cases (20%) were managed in the outpatient setting. The median of the average duration of hospitalization was 12.4 (5.7–22.7) days
The most common symptoms included fever (70%), cough (67%), and dyspnea (61%). Six cases were reported as asymptomatic. One patient died at home by cardiac arrest and no data on the post-mortem examination was provided. According to the World Health Organization criteria for the classification of COVID-19 severity, 34% and 14% of patients were classified as severe and critical, respectively. No cases of protracted or relapsing clinical disease were reported. Detailed information about each included study can be found in Table 2. In addition, the results according to study type (case reports and cohorts) and type of population (inpatients and outpatients/inpatients) are presented in Table 2.

### 3.3 Laboratory and imaging findings

The mean white blood cell count was 6100 ± 3500 cells/µl (n = 228 patients), the mean lymphocytes was 958 ± 803 cells/µl (n = 250 patients), the mean C-reactive protein was 82 ± 124 mg/L (n = 180 patients), and the mean procalcitonin was 1.7 ± 2.9 ng/ml (n = 162 patients) (Table 2). In only 28% of patients, the chest imaging (X-ray or computed tomography) was normal.

### 3.4 Management and outcomes

Table 2 shows that the most used drugs for the treatment of COVID-19 were hydroxychloroquine (54%), azithromycin (14%), and lopinavir/ritonavir (14%). One patient who received hydroxychloroquine presented QT interval prolongation on the electrocardiogram but did not develop ventricular arrhythmias. Tocilizumab was given in 8% of cases and other IL-6 inhibitors were not used.

The main changes of the maintenance immunosuppressive regimen during the COVID-19 infection were as follows: discontinuation (49%) or no modification (41%) of antimetabolites, no modification (59%) or reduction (28%) of calcineurin inhibitors, no modification (73%) of corticosteroids, and no modification (80%) of mTOR inhibitors (Figure 2).

Three patients developed allograft rejection after COVID-19 infection. Of those, only one was re-transplanted. Information about the change of baseline immunosuppressive regimen during COVID-19 infection was only available in one case of rejection. Lima et al. reported that mycophenolate mofetil was discontinued and tacrolimus was reduced. No patients received rituximab for the treatment of rejection. Soquet et al. reported a patient who developed lymphoma and was treated with four cycles of rituximab two months prior to
### TABLE 1
Comparison of case series of heart transplant recipients with COVID-19

| Study | Year | Country | Date of inclusion | Sample size | Mortality |
|-------|------|---------|------------------|-------------|-----------|
| Ahluwalia et al. | 2020 | USA | March 10–May 15 | 5 | 20% |
| Al-Darzi et al. | 2020 | USA | March 13–May 1 | 6 | 0% |
| Bottio 1 et al. | 2020 | Italy | February 21–June 30 | 47 | 30% |
| Bottio 2 et al. | 2020 | Italy | July 1–August 30 | 6 | 0% |
| Caraffa et al. | 2020 | Italy | Not reported | 6 | 33% |
| Cavagna et al. | 2020 | Italy | February | 5 | 40% |
| Coll et al. | 2020 | Spain | February 20–July 13 | 69 | 22% |
| Felldin et al. | 2020 | Sweden | February 21–June 22 | 6 | 33% |
| Garcia-Cosio et al. | 2020 | Spain | February 28–April 28 | 13 | 23% |
| Hoek et al. | 2020 | The Netherlands | Not reported | 4 | 25% |
| Iacovoni et al. | 2020 | Italy | February–March | 26 | 27% |
| Kates et al. | 2020 | USA | March 7–May 14 | 57 | 14% |
| Ketcham et al. | 2020 | USA | March 21–April 22 | 13 | 15% |
| Latif et al. | 2020 | USA | March 1–April 24 | 28 | 25% |
| Lima et al. | 2020 | USA | March 14–April 19 | 5 | 0% |
| Rivinius et al. | 2020 | Germany | March–June | 21 | 33% |
| Singhvi et al. | 2020 | USA | March 1–May 15 | 22 | 23% |
| Trapani et al. | 2020 | Italy | February 21–June 22 | 53 | 36% |

| Case reports | 2020 | Several countries | January–June | 23 | 4% |

**Abbreviations:** USA, United States of America.

*Italy, Germany, USA, China, France, Switzerland, Russia, and Turkey.

SARS-CoV-2 infection. This patient presented with critical COVID-19 and required heart re-transplantation due to allograft dysfunction. We found four cases of prolonged positive RT-PCR testing.4,34,41,42,46 Twenty-one percent of patients developed acute respiratory distress syndrome, 16% required invasive mechanical ventilation, and 23% were admitted to the intensive care unit. Overall, 23% of patients died during hospitalization. The mortality rate based on cohorts that included only inpatients was 25%. In addition, the mortality rate of cohorts that included outpatients and inpatients was 24% (Table 2).

4 | DISCUSSION

4.1 | Main findings

To our knowledge, this is the first systematic review that summarizes clinical data from the largest international series of heart transplant recipients with COVID-19. The mean age was nearly 60 years and most cases were men. The majority of cases were managed in the inpatient setting and almost half of the patients had mild or moderate COVID-19. The regimen of calcineurin inhibitors, corticosteroids, and mammalian target of rapamycin (mTOR) inhibitors were not modified in more than half of the patients. In contrast, antimetabolites were discontinued in half of the cases. One-fifth of the patients required admission to the intensive care unit. Overall, the short-term mortality was 23%.

4.2 | Clinical profile of heart transplant patients with COVID-19

We found that COVID-19 in heart transplant recipients shares some demographic and clinical characteristics with the general population in terms of male predominance, type of comorbidities, and clinical presentation. Whether heart transplant recipients are more vulnerable to acquiring COVID-19 due to their chronic immunosuppression state remains unclear. However, the prevalence of SARS-CoV-2 infection may be underestimated because asymptomatic transplant recipients are not routinely tested.

As occurs in non-transplanted patients with COVID-19, our results show that heart transplant recipients exhibited an elevation of C-reactive protein and procalcitonin. These inflammatory biomarkers have proven to be useful as prognostic factors for poor outcomes in COVID-19.50 Furthermore, most cases presented absolute lymphopenia. This is a common finding during COVID-19 and has been independently associated with increased mortality.50 While this finding may be explained by the SARS-CoV-2 infection itself, the myelotoxicity related to the immunosuppressive therapy in transplant recipients may also be involved. Although the role of these biomarkers in heart transplant recipients with COVID-19 remains to be determined, it could be considered during the risk stratification of hospitalized patients with COVID-19.
## TABLE 2  Characteristics of heart transplant recipients with COVID-19

| Characteristics                        | Total                  | Case reports | Cohorts (inpatients) | Cohorts (outpatients and inpatients) |
|----------------------------------------|------------------------|--------------|-----------------------|---------------------------------------|
|                                        | n/Nb (%)               | n/Nb (%)     | n/Nb (%)              | n/Nb (%)                              |
| Age (years)                            | 59.9 ± 15.7, n = 415  | 53.3 ± 14.4, n = 23 | 60.3 ± 15.8, n = 392 | 58.9 ± 15.5, n = 48                   |
|                                        | 77%                    | 78%          | 77%                   | 83%                                   |
| Male                                   | 278/362 77%            | 18/23 78%    | 260/339 77%           | 40/48 83%                             |
|                                        |                        |              | 220/291 76%           |                                       |
| Country                                |                        |              |                       |                                       |
| USA                                    | 147/415 35%            | 11/23 48%    | 136/392 35%           | 18/48 37%                             |
| Germany                                | 24/415 6%              | 3/23 13%     | 21/392 5%             | 21/48 44%                             |
| China                                  | 2/415 .5%              | 0/392 0%     | 0/48 0%               | 0/344 0%                              |
| Italy                                  | 145/415 35%            | 2/23 9%      | 143/392 36%           | 5/48 10%                              |
| France                                 | 2/415 .5%              | 0/392 0%     | 0/48 0%               | 0/344 0%                              |
| Switzerland                            | 1/415 .2%              | 0/392 0%     | 0/48 0%               | 0/344 0%                              |
| Russia                                 | 1/415 .2%              | 0/392 0%     | 0/48 0%               | 0/344 0%                              |
| Turkey                                 | 1/415 .2%              | 0/392 0%     | 0/48 0%               | 0/344 0%                              |
| Spain                                   | 82/415 20%             | 0/23 0%      | 82/392 21%            | 0/48 0%                               |
| Sweden                                 | 6/415 1.5%             | 0/23 0%      | 6/392 2%              | 0/48 0%                               |
| The Netherlands                         | 4/415 1%               | 0/23 0%      | 4/392 1%              | 0/48 0%                               |
| Comorbidities                          |                        |              |                       |                                       |
| Immunosuppression                      | 272/272 100%           | 16/16 100%   | 256/256 100%          | 39/39 100%                            |
| Hypertension                           | 189/272 69%            | 10/16 62%    | 179/256 70%           | 31/39 79%                             |
| Diabetes                               | 99/272 36%             | 7/16 44%     | 92/256 36%            | 17/39 43%                             |
| Chronic kidney disease                 | 99/272 36%             | 8/16 50%     | 91/256 35%            | 19/39 49%                             |
| Chronic lung disease                   | 22/272 8%              | 1/16 6%      | 21/256 8%             | 4/39 10%                              |
| Time since heart transplantation       | 8.8 ± 9, n = 409       | 6.3 ± 6.8, n = 22 | 9 ± 9.2, n = 387    | 8.3 ± 9.4, n = 43                     |
| Transplanted organ                     |                        |              |                       |                                       |
| Heart                                  | 395/415 95%            | 18/23 78%    | 377/392 96%           | 44/48 91%                             |
| Heart + kidney                         | 18/415 4%              | 5/23 22%     | 13/392 3%             | 3/48 6%                               |
| Heart + lung                           | 2/415 .5%              | 0/23 0%      | 2/392 .5%             | 1/48 2%                               |
| Baseline immunosuppressive regimen     |                        |              |                       |                                       |
| Antimetabolites                         | 238/346 69%            | 17/21 81%    | 221/325 68%           | 32/43 74%                             |
| Calcineurin inhibitors                 | 314/351 89%            | 21/21 100%   | 293/330 89%           | 41/48 85%                             |
| Corticosteroids                        | 203/346 59%            | 13/21 62%    | 190/325 58%           | 27/43 56%                             |
| mTOR inhibitors                        | 73/346 21%             | 4/21 19%     | 69/325 21%            | 10/43 23%                             |
| Clinical setting                       |                        |              |                       |                                       |
| Inpatient                              | 304/382 79%            | 19/21 90%    | 285/361 79%           | 27/27 100%                            |
| Outpatient                             | 78/382 20%             | 2/21 9%      | 76/361 21%            | 0/27 0%                               |
| Symptoms                               |                        |              |                       |                                       |
| Fever                                  | 193/276 70%            | 15/21 71%    | 178/255 70%           | 29/39 74%                             |
| Cough                                  | 163/242 67%            | 12/21 57%    | 151/221 68%           | 31/39 79%                             |
| Dyspnea                                | 138/226 61%            | 13/21 62%    | 125/205 61%           | 31/39 79%                             |
| Gastrointestinal                       | 105/276 38%            | 8/21 38%     | 97/255 38%            | 16/39 41%                             |
| Myalgias                               | 53/166 32%             | 6/21 28%     | 47/145 32%            | 0/5 0%                                |
(Continues)
### Table 2 (Continued)

| Characteristics | Total | Case reports | Cohorts (inpatients) | Cohorts (outpatients and inpatients) |
|-----------------|-------|--------------|----------------------|--------------------------------------|
|                 | n/N 6 | n/N 7        | n/N 5               | n/N 7                                |
| Laboratory      |       |              |                      |                                      |
| White blood cells (cells/µL)<sup>a</sup> | 6100 ± 3500, n = 228 | 5200 ± 200, n = 11 | 6200 ± 3600, n = 217 | 9200 ± 4800, n = 39 |
| Lymphocytes (cells/µL)<sup>a</sup> | 958.1 ± 803.5, n = 250 | 939 ± 427, n = 11 | 959 ± 820.9, n = 239 | 1018 ± 618, n = 39 |
| C-reactive protein (mg/L)<sup>a</sup> | 81.7 ± 124, n = 180 | 119 ± 213, n = 17 | 77.8 ± 115, n = 163 | 110 ± 90, n = 26 |
| Procalcitonin (ng/ml)<sup>a</sup> | 1.7 ± 2.9, n = 162 | 1.7 ± 2.8, n = 154 | 1.7 ± 2.8, n = 154 | 4.4 ± 6.7, n = 39 |
| Abnormal chest X-ray or CT | 176/243 | 15/17 | 161/226 | 37/43 |
| Treatment       |       |              |                      |                                      |
| Hydroxychloroquine | 175/323 | 13/21 | 162/302 | 22/48 |
| Azythromycin    | 47/323 | 4/21 | 43/302 | 9/48 |
| Lopinavir/ritonavir | 44/323 | 4/21 | 41/302 | 0/48 |
| Remdesivir      | 4/323 | 1/21 | 3/302 | 1/48 |
| Tocilizumab     | 26/323 | 4/21 | 22/302 | 4/48 |
| Modification of    |       |              |                      |                                      |
| immunosuppressive regimen | | | | |
| Antimetabolites  |       |              |                      |                                      |
| No modification  | 40/98 | 5/15 | 35/83 | 8/30 |
| Reduction        | 29/127 | 1/15 | 28/112 | 0/30 |
| Discontinuation  | 48/98 | 8/15 | 40/83 | 22/30 |
| Increase         | 1/98 | 1/15 | 0/83 | 0/30 |
| Calcineurin inhibitors   | | | | |
| No modification  | 47/79 | 11/19 | 36/60 | 7/17 |
| Reduction        | 42/152 | 5/19 | 37/133 | 10/17 |
| Discontinuation  | 5/79 | 1/19 | 4/60 | 0/17 |
| Increase         | 1/79 | 1/19 | 0/60 | 0/17 |
| Corticosteroids  | | | | |
| No modification  | 50/68 | 5/11 | 45/57 | 16/25 |
| Discontinuation  | 1/68 | 1/11 | 0/57 | 0/25 |
| Increase         | 4/68 | 2/11 | 2/57 | 1/25 |
| Reduction        | 1/68 | 1/11 | 0/57 | 0/25 |
| Change from oral to intravenous | 12/68 | 2/11 | 10/57 | 8/25 |
| mTOR inhibitors  | | | | |
| No modification  | 20/25 | 1/3 | 19/22 | 8/9 |
| Discontinuation  | 5/25 | 2/3 | 3/22 | 1/9 |
| Reduction        | 3/37 | 0/3 | 3/34 | 0/9 |
| COVID-19 severity | | | | |
| Mild       | 28/91 | 8/23 | 20/68 | 20/68 |
| Moderate     | 30/91 | 4/23 | 26/68 | 26/68 |
| Severe       | 49/144 | 6/23 | 43/121 | 43/121 |
| Critical     | 20/144 | 5/23 | 15/121 | 15/121 |

(Continues)
### TABLE 2 (Continued)

| Characteristics                        | Total | Case reports | Cohorts (inpatients) | Cohorts (outpatients and inpatients) |
|----------------------------------------|-------|--------------|----------------------|--------------------------------------|
|                                        | n/N   | n/N          | n/N                  | n/N                                  |
|                                        | %     | %            | %                    | %                                    |
| Acute respiratory distress syndrome    | 42/196| 5/23         | 37/173               | 35/163                                |
|                                        | 21%   | 22%          | 21%                  | 21%                                  |
| Non-invasive oxygen supplementation    | 100/212| 11/23       | 11/31                | 78/158                                |
|                                        | 47%   | 48%          | 35%                  | 49%                                  |
| Mechanical ventilation                 | 50/315| 4/23         | 15/44                | 31/248                                |
|                                        | 16%   | 17%          | 34%                  | 12%                                  |
| Intensive care unit admission          | 86/374| 7/23         | 23/44                | 56/307                                |
|                                        | 23%   | 30%          | 52%                  | 18%                                  |
| Outcome                                |       |              |                      |                                      |
| Discharged                             | 256/405| 18/23        | 26/48                | 212/334                               |
|                                        | 63%   | 78%          | 54%                  | 63%                                  |
| Remained hospitalized                  | 20/405| 2/23         | 8/48                 | 10/334                                |
|                                        | 5%    | 9%           | 47%                  | 3%                                   |
| Ambulatory                             | 35/405| 2/23         | 2/48                 | 31/334                                |
|                                        | 9%    | 9%           | 4%                   | 9%                                   |
| Dead                                   | 94/405| 1/23         | 12/48                | 81/334                                |
|                                        | 23%   | 4%           | 25%                  | 24%                                  |

Abbreviations: USA, United States of America; COVID-19, coronavirus disease 2019; CT, computed tomography; mTOR, mammalian target of rapamycin.

aMean ± standard deviation.
bData are n/total (denominator varies among variables according to available information).

### 4.3 Management

In our study, nearly half of the patients received hydroxychloroquine, azithromycin, or lopinavir/ritonavir as pharmacological therapy for COVID-19. These drugs were initially recommended for COVID-19 management due to the evidence of in vitro inhibition of SARS-CoV-2 replication and to the positive results from some observational studies. However, recent large randomized controlled trials have shown that none of these drugs have a clinically beneficial effect on COVID-19 patients; thus, they are not currently used. In addition, the use of hydroxychloroquine and azithromycin has been associated with an increased risk of QT interval prolongation predisposing to ventricular arrhythmias. Overall, only a few patients received remdesivir as part of COVID-19 treatment. Of note, none of the trials on drugs for COVID-19 included immunocompromised individuals.

Our review shows that the modification of the baseline immunosuppressive regimen varied across studies. Overall, 72% of antimetabolites, 34% of calcineurin inhibitors, 2% of corticosteroids, and 88% of mTOR inhibitors were reduced or discontinued during COVID-19 infection. Without supporting clinical data to guide decision-making, the appropriate approach to immunosuppression management is unknown. Currently, several international transplant societies have provided some mixed recommendations to guide the management of immunosuppression during COVID-19. The International Society of Heart and Lung Transplantation recommends holding antimetabolites and mTOR inhibitors in COVID-19 patients with moderate or severe disease. In contrast, the British Transplantation Society proposes discontinuing antimetabolites in all cases and, in patients requiring hospitalization, recommends reducing or stopping calcineurin inhibitors and increasing corticosteroids. The American Society of Transplantation only suggests that reduction of immunosuppressive therapy (with the maintenance of corticosteroids) should be considered in infected patients who have not had recent episodes of rejection, especially, in severe cases. This disparity in the recommendations reflects the need for more studies to clarify what is the best approach to immunosuppressive therapy for these patients.

Interestingly, three patients developed allograft rejection after SARS-CoV-2 infection. Lima et al. reported one case of mild acute cellular rejection (at two weeks after COVID-19 diagnosis) based on the preponderance of lymphocytic infiltrate without evidence of myocardial injury. Soquet et al. reported another case of severe allograft dysfunction leading to heart retransplantation, although it was ultimately considered as chronic rejection. The last case of acute cellular rejection was reported by Kates et al.; however, further details were not provided. The actual incidence of allograft rejection in solid-organ recipients with COVID-19 is currently unknown because endomyocardial biopsy is not routinely performed in these patients. Nevertheless, an unusually high rate of acute allograft rejection after COVID-19 in kidney transplant recipients was reported in a small case series. Whether the allograft rejection is due to SARS-CoV-2 infection through direct and/or indirect mechanisms, or is related to the change in immunosuppressive therapy is still largely unclear.

### 4.4 Prognosis of heart transplant patients with COVID-19

The short-term mortality of heart transplant recipients with COVID-19 was 23% considering ambulatory and hospitalized patients. Our results were similar to those reported in solid-organ transplant recipients as shown in a recent meta-analysis, which found an all-cause mortality of 18.6%. Among the possible causes that may explain this increased
mortality are older age, male predominance, high prevalence of comorbidities, and the use of chronic immunosuppressive therapy.

4.5 | Limitations

Our systematic review has some limitations. First, we included 22 case reports in our study. Although publication and selection bias may arise because only data from patients with unusual characteristics and poor outcomes may have been published, we have also included cohort studies. Second, while the majority of cases were from the in-hospital setting, others were from a surveillance program of COVID-19 in cohorts of solid-organ transplant recipients. Therefore, our pool of patients may not represent the entire population of heart transplant recipients with SARS-CoV-2 infection, since asymptomatic and mild cases could be underestimated leading to overestimation of morbidity and mortality. Third, most of the studies were from the "first wave" and the drugs used for the treatment of COVID-19 (hydroxychloroquine, azithromycin, and lopinavir/ritonavir) are no longer recommended. Fourth, information about patients was incomplete in a high proportion of studies, especially concerning COVID19 severity and modification on immunosuppressive regimen. Fifth, we were unable to compare our findings to the general population because, only transplant recipients were evaluated in the included studies. Finally, since only aggregated data were available, it was not possible to assess the impact of changes in immunosuppressive therapy on clinical outcomes.

5 | CONCLUSION

Our review shows that heart transplant recipients with COVID-19 presented demographic and clinical features similar to the general population. The immunosuppressive regimen of calcineurin inhibitors, corticosteroids, and mTOR inhibitors was not modified in more than half of the patients. Antimetabolites were discontinued in half of the cases. Overall, we found a high short-term mortality in these patients. Nevertheless, given that our results were from case reports and cohorts, further prospective multicenter studies with larger samples are required to guide the clinical care of this population.

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CONFLICT OF INTEREST

None of the authors reported any conflicts of interest.

AUTHOR CONTRIBUTIONS

Carlos Diaz-Arocutipa, Darla Carvallo-Castañeda, and Odalis Luis-Ybañez involved in concept/design. Carlos Diaz-Arocutipa, Darla
Carvallo-Castañeda, and Odalis Luis-Ybañez involved in data acquisition. Carlos Diaz-Arocutipa, Darla Carvallo-Castañeda, Odalis Luis-Ybañez, Marcos Pariona, Mercedes Rivas-Lasarte, and Jesús Álvarez-García involved in data analysis/interpretation. Carlos Diaz-Arocutipa, Darla Carvallo-Castañeda, and Odalis Luis-Ybañez drafted the article. Carlos Diaz-Arocutipa, Darla Carvallo-Castañeda, Odalis Luis-Ybañez, Marcos Pariona, Mercedes Rivas-Lasarte, and Jesús Álvarez-García critically revised the article. Carlos Diaz-Arocutipa, Darla Carvallo-Castañeda, Odalis Luis-Ybañez, Marcos Pariona, Mercedes Rivas-Lasarte, and Jesús Álvarez-García approved the article.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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