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ORIGINAL ARTICLE

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, cardiovascular involvement of COVID-19, in particular, has been reported by way of myocardial injury,[4–6] 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/m^2 (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

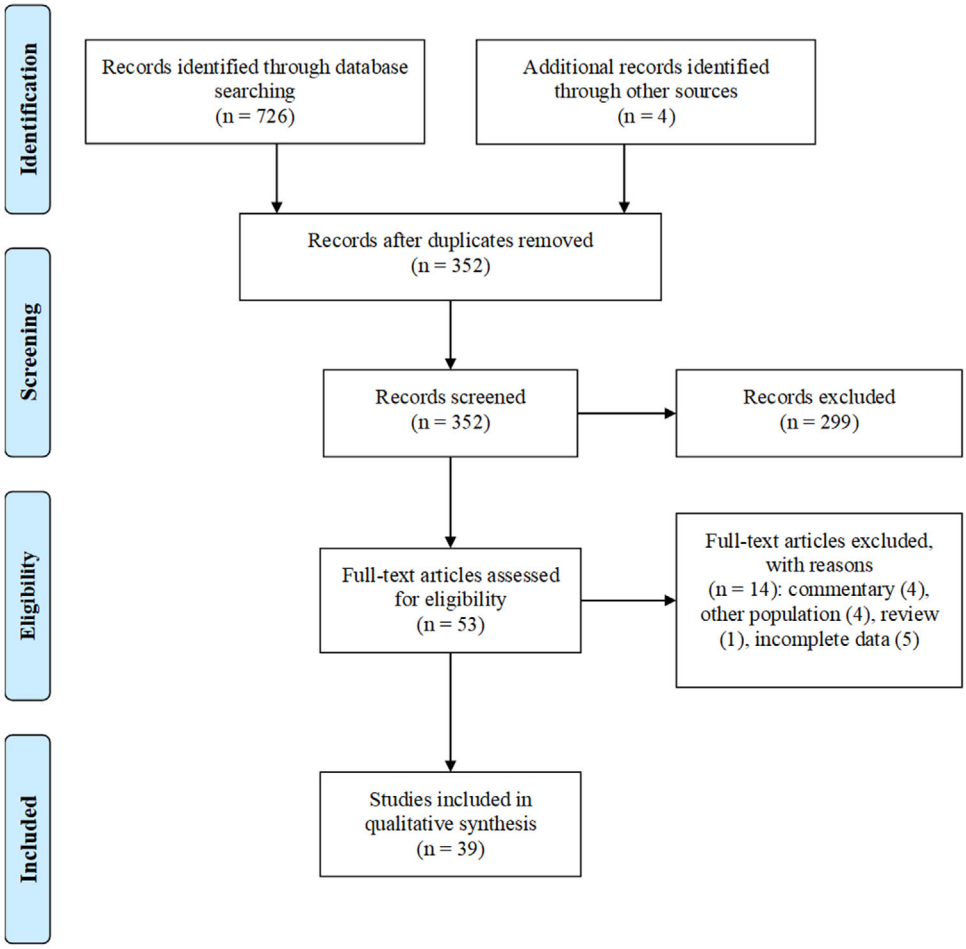

FIGURE 1 Flow diagram of study selection

across eight studies. The most common symptoms included fever (70%), cough (67%), and dyspnea (61%). Six cases were reported as asymptomatic.[13,14] One patient died at home by cardiac arrest and no data on the post-mortem examination was provided.[10] According to the World Health Organization criteria for the classification of COVID-19 severity,[49] 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 S2. 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[22] 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[30,34,41] developed allograft rejection after COVID-19 infection. Of those, only one was re-transplanted.[41] Information about the change of baseline immunosuppressive regimen during COVID-19 infection was only available in one case of rejection. Lima et al.[34] reported that mycophenolate mofetil was discontinued and tacrolimus was reduced. No patients received rituximab for the treatment of rejection. Soquet et al.[41] 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
Cohorts					
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[a]	January–June	23	4%

Abbreviations: USA, United States of America.
[a]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.[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		Cohorts (inpatients)		Cohorts (outpatients and inpatients)	
	n/*N*[b]	%	*n*/*N*[b]	%	*n*/*N*[b]	%	*n*/*N*[b]	%	*n*/*N*[b]	%
Age (years)[a]	59.9 ± 15.7, *n* = 415		53.3 ± 14.4, *n* = 23		60.3 ± 15.8, *n* = 392		58.9 ± 18.5, *n* = 48		60.6 ± 15.4, *n* = 344	
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%	118/344	34%
Germany	24/415	6%	3/23	13%	21/392	5%	21/48	44%	0/344	0%
China	2/415	.5%	2/23	9%	0/392	0%	0/48	0%	0/344	0%
Italy	145/415	35%	2/23	9%	143/392	36%	5/48	10%	138/344	40%
France	2/415	.5%	2/23	9%	0/392	0%	0/48	0%	0/344	0%
Switzerland	1/415	.2%	1/23	4%	0/392	0%	0/48	0%	0/344	0%
Russia	1/415	.2%	1/23	4%	0/392	0%	0/48	0%	0/344	0%
Turkey	1/415	.2%	1/23	4%	0/392	0%	0/48	0%	0/344	0%
Spain	82/415	20%	0/23	0%	82/392	21%	0/48	0%	82/344	24%
Sweden	6/415	1.5%	0/23	0%	6/392	2%	0/48	0%	6/344	2%
The Netherlands	4/415	1%	0/23	0%	4/392	1%	4/48	8%	0/344	0%
Comorbidities										
Immunosuppression	272/272	100%	16/16	100%	256/256	100%	39/39	100%	217/217	100%
Hypertension	189/272	69%	10/16	62%	179/256	70%	31/39	79%	148/217	68%
Diabetes	99/272	36%	7/16	44%	92/256	36%	17/39	43%	75/217	34%
Chronic kidney disease	99/272	36%	8/16	50%	91/256	35%	19/39	49%	72/217	33%
Chronic lung disease	22/272	8%	1/16	6%	21/256	8%	4/39	10%	17/189	6%
BMI (kg/m^2)[a]	26.7 ± 5.6, *n* = 168		38.2 ± 11.2, *n* = 3		26.5 ± 5.5, *n* = 165		26.9 ± 6.9, *n* = 39		26.4 ± 5, *n* = 126	
Time since heart transplantation (years)[a]	8.8 ± 9, *n* = 409		6.3 ± 6.8, *n* = 22		9 ± 9.2, *n* = 387		8.3 ± 9.4, *n* = 43		9.1 ± 9.3, *n* = 344	
Transplanted organ										
Heart	395/415	95%	18/23	78%	377/392	96%	44/48	91%	333/344	97%
Heart + kidney	18/415	4%	5/23	22%	13/392	3%	3/48	6%	10/344	3%
Heart + lung	2/415	.5%	0/23	0%	2/392	.5%	1/48	2%	1/344	.3%
Baseline immunosuppressive regimen										
Antimetabolites	238/346	69%	17/21	81%	221/325	68%	32/43	74%	189/282	67%
Calcineurin inhibitors	314/351	89%	21/21	100%	293/330	89%	41/48	85%	252/282	89%
Corticosteroids	203/346	59%	13/21	62%	190/325	58%	27/43	56%	163/282	58%
mTOR inhibitors	73/346	21%	4/21	19%	69/325	21%	10/43	23%	59/282	21%
Clinical setting										
Inpatient	304/382	79%	19/21	90%	285/361	79%	27/27	100%	258/334	77%
Outpatient	78/382	20%	2/21	9%	76/361	21%	0/27	0%	76/334	23%
Symptoms										
Fever	193/276	70%	15/21	71%	178/255	70%	29/39	74%	149/216	69%
Cough	163/242	67%	12/21	57%	151/221	68%	31/39	79%	120/182	66%
Dyspnea	138/226	61%	13/21	62%	125/205	61%	31/39	79%	94/166	57%
Gastrointestinal	105/276	38%	8/21	38%	97/255	38%	16/39	41%	81/216	37%
Myalgias	53/166	32%	6/21	28%	47/145	32%	0/5	0%	47/140	33%

(Continues)

TABLE 2 (Continued)

Characteristics	Total		Case reports		Cohorts		Cohorts (inpatients)		Cohorts (outpatients and inpatients)	
	n/*N*[b]	%	*n*/*N*[b]	%	*n*/*N*[b]	%	*n*/*N*[b]	%	*n*/*N*[b]	%
Laboratory										
White blood cells (cells/μL)[a]	6100 ± 3500, *n* = 228		5200 ± 200, *n* = 11		6200 ± 3600, *n* = 217		9200 ± 4800, *n* = 39		5500 ± 3300, *n* = 178	
Lymphocytes (cells/μL)[a]	958.1 ± 803.5, *n* = 250		939 ± 427, *n* = 11		959 ± 820.9, *n* = 239		1018 ± 618, *n* = 39		989 ± 886, *n* = 200	
C-reactive protein (mg/L)[a]	81.7 ± 124, *n* = 180		119 ± 213, *n* = 17		77.8 ± 115, *n* = 163		110 ± 90, *n* = 26		86 ± 120, *n* = 137	
Procalcitonin (ng/ml)[a]	1.7 ± 2.9, *n* = 162		2.3 ± 6, *n* = 8		1.7 ± 2.8, *n* = 154		4.4 ± 6.7, *n* = 39		.7 ± 1.55, *n* = 115	
Abnormal chest X-ray or CT	176/243	72%	15/17	88%	161/226	71%	37/43	86%	124/183	68%
Treatment										
Hydroxychloroquine	175/323	54%	13/21	62%	162/302	54%	22/48	46%	140/254	55%
Azythromycin	47/323	14%	4/21	19%	43/302	14%	9/48	19%	34/254	13%
Lopinavir/ritonavir	44/323	14%	3/21	14%	41/302	13%	0/48	0%	41/254	16%
Remdesivir	4/323	1%	1/21	5%	3/302	1%	1/48	2%	2/201	1%
Tocilizumab	26/323	8%	4/21	19%	22/302	7%	4/48	8%	18/201	9%
Modification of immunosuppressive regimen										
Antimetabolites										
No modification	40/98	41%	5/15	33%	35/83	42%	8/30	27%	27/53	51%
Reduction	29/127	23%	1/15	7%	28/112	25%	0/30	0%	28/82	34%
Discontinuation	48/98	49%	8/15	53%	40/83	48%	22/30	73%	18/53	34%
Increase	1/98	1%	1/15	7%	0/83	0%	0/30	0%	0/53	0%
Calcineurin inhibitors										
No modification	47/79	59%	11/19	58%	36/60	60%	7/17	41%	29/43	67%
Reduction	42/152	28%	5/19	26%	37/133	28%	10/17	59%	27/116	23%
Discontinuation	5/79	6%	1/19	5%	4/60	7%	0/17	0%	4/43	9%
Increase	1/79	1%	1/19	5%	0/60	0%	0/17	0%	0/43	0%
Initiation	1/79	1%	1/19	5%	0/60	0%	0/17	0%	0/43	0%
Corticosteroids										
No modification	50/68	73%	5/11	45%	45/57	79%	16/25	64%	29/32	91%
Discontinuation	1/68	1%	1/11	9%	0/57	0%	0/25	0%	0/32	0%
Increase	4/68	6%	2/11	18%	2/57	3%	1/25	4%	1/32	3%
Reduction	1/68	1%	1/11	9%	0/57	0%	0/25	0%	0/32	0%
Change from oral to intravenous	12/68	18%	2/11	18%	10/57	17%	8/25	32%	2/32	6%
mTOR inhibitors										
No modification	20/25	80%	1/3	33%	19/22	86%	8/9	89%	11/13	85%
Discontinuation	5/25	20%	2/3	67%	3/22	14%	1/9	11%	2/13	15%
Reduction	3/37	8%	0/3	0%	3/34	9%	0/9	0%	3/25	12%
COVID-19 severity										
Mild	28/91	31%	8/23	35%	20/68	29%	4/10	40%	16/58	27%
Moderate	30/91	33%	4/23	17%	26/68	38%	4/10	40%	22/58	38%
Severe	49/144	34%	6/23	26%	43/121	35%	0/10	0%	43/111	39%
Critical	20/144	14%	5/23	22%	15/121	12%	2/10	20%	13/111	12%

(Continues)

TABLE 2 (Continued)

Characteristics	Total		Case reports		Cohorts		Cohorts (inpatients)		Cohorts (outpatients and inpatients)	
	n/*N*[b]	%	*n*/*N*[b]	%	*n*/*N*[b]	%	*n*/*N*[b]	%	*n*/*N*[b]	%
Acute respiratoty distress syndrome	42/196	21%	5/23	22%	37/173	21%	2/10	20%	35/163	21%
Non-invasive oxygen supplementation	100/212	47%	11/23	48%	89/189	47%	11/31	35%	78/158	49%
Mechanical ventilation	50/315	16%	4/23	17%	46/292	16%	15/44	34%	31/248	12%
Intensive care unit admission	86/374	23%	7/23	30%	79/351	22%	23/44	52%	56/307	18%
Outcome										
Discharged	256/405	63%	18/23	78%	238/382	62%	26/48	54%	212/334	63%
Remained hospitalized	20/405	5%	2/23	9%	18/382	5%	8/48	47%	10/334	3%
Ambulatory	35/405	9%	2/23	9%	33/382	9%	2/48	4%	31/334	9%
Dead	94/405	23%	1/23	4%	93/382	24%	12/48	25%	81/334	24%

Abbreviations: USA, United States of America; COVID-19, coronavirus disease 2019; CT, computed tomography; mTOR, mammalian target of rapamycin.
[a]Mean ± standard deviation.
[b]Data 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.[51,52] 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.[53,54] In addition, the use of hydroxychloroquine and azithromycin has been associated with an increased risk of QT interval prolongation predisposing to ventricular arrhythmias.[55] 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[56] recommends holding antimetabolites and mTOR inhibitors in COVID-19 patients with moderate or severe disease. In contrast, the British Transplantation Society[57] 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[58] 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.[34] 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.[41] 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.[30]; 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.[59] Whether the allograft rejection is due to SARS-CoV-2 infection through direct and/or indirect mechanisms,[60] 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%.[61] Among the possible causes that may explain this increased

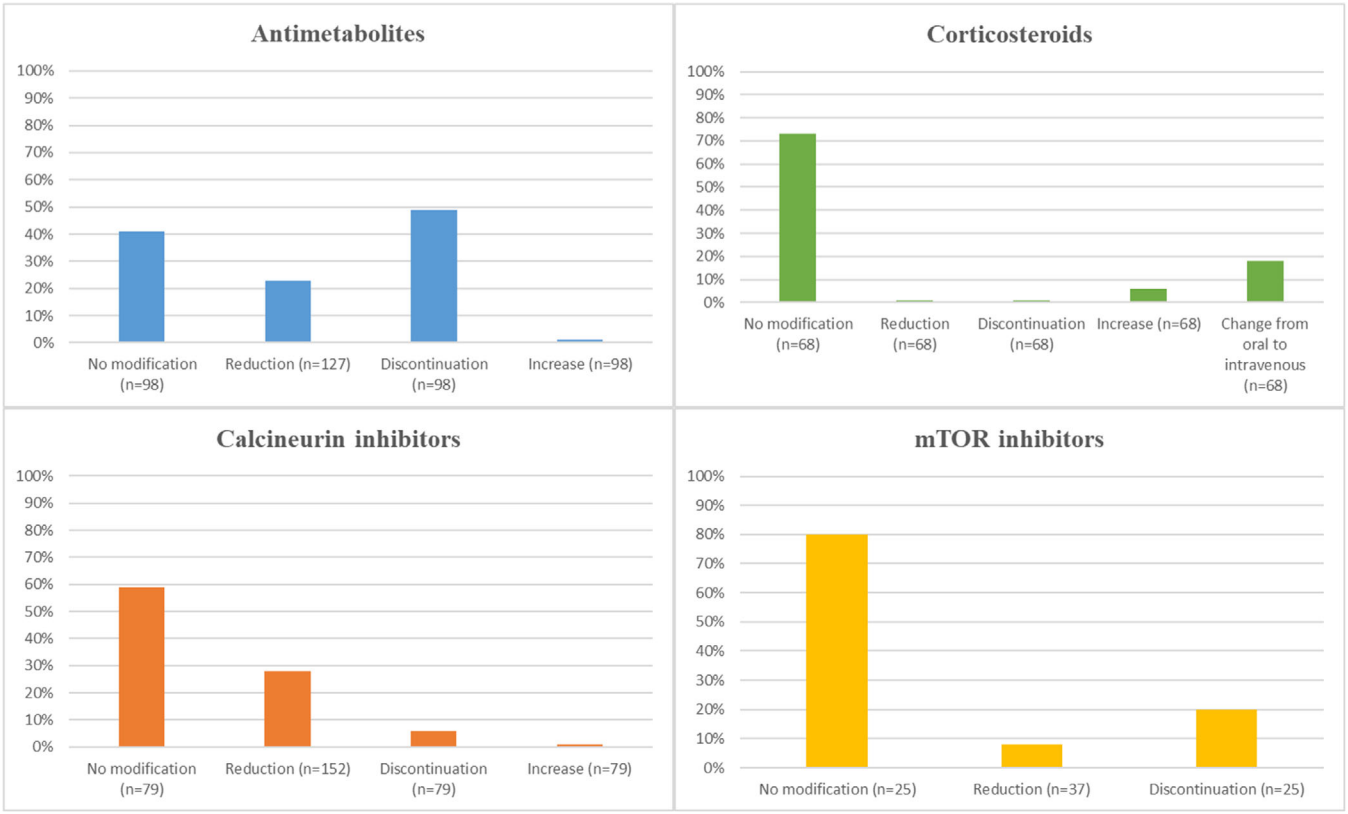

FIGURE 2 Modification of baseline immunosuppression treatment in heart transplant recipients with COVID-19. mTOR, mammalian target of rapamycin; COVID-19, coronavirus disease 2019

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. In contrast, 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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