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Brief communication

COVID-19 in orthotopic heart transplant recipients and association with donor specific antibodies

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ABSTRACT

De novo donor-specific antibodies (DSAs) are associated with increased risk of antibody-mediated rejection and worse clinical outcomes after orthotopic heart transplant (OHT). No study has reported the production of DSAs after infection by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in an OHT population.

In this retrospective study, we described coronavirus disease 2019 (COVID-19) incidence and clinical course in a large, contemporary OHT cohort. We showed that the case-fatality rate has significantly decreased since the early days of the pandemic, although remains higher than that of the general population. In addition, we found that 10% of OHT recipients developed *de novo* DSAs or experienced an increase in pre-existing DSAs after COVID-19, with the majority occurring in unvaccinated patients (15% *vs* 2%). Further studies are necessary to substantiate our findings in an external cohort.

1. Introduction

De novo donor-specific antibodies (DSAs) are associated with increased risk of antibody-mediated rejection (AMR) and graft loss after orthotopic heart transplant (OHT) [1]. Viral infections have the potential to induce or reactivate the production of DSAs, yet the development of DSAs after infection by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has not been reported. In addition, early studies of coronavirus disease 2019 (COVID-19) in the OHT population were limited to smaller series that suggested poor clinical outcomes [2,3]. Therefore, we sought to describe COVID-19 clinical course and post-infectious DSAs in a large, contemporary cohort.

2. Methods

We retrospectively analyzed adult OHT recipients followed at Washington University School of Medicine in St. Louis between April 1, 2020 and December 31, 2021. COVID-19 infection was defined by positive antigen or PCR test in setting of exposure or symptoms. Patients were considered fully vaccinated 2 weeks after 2 doses of the BNT162b (Pfizer-BioNTech) or mRNA-1273 (Moderna) vaccines or after a single dose of the AD26.COV2·S (Johnson & Johnson) vaccine. Our institutional protocol is to check DSAs at 3 and 12 months post-transplant or for clinical concern of AMR. Starting in mid-2021, DSAs were reassessed 4–6 weeks after infection with SARS-CoV-2. *De novo* DSAs were defined as newly detected antibodies against donor MHC alleles with mean fluorescence intensity (MFI) >2000 or angiotensin-II type 1 receptor (AT1R). In patients with pre-existing DSAs, a significant increase was defined as an MFI value that was 20% or more higher compared to the most recent DSA checked prior to COVID-19. All statistical analyses were performed using GraphPad Prism 9.3.0 (GraphPad Software, San Diego, CA). This study was approved by the Washington University Institutional Review Board and was conducted in compliance with the ISHLT ethics statement.

Abbreviations: DSA, donor specific antibody; AMR, antibody-mediated rejection; OHT, orthotopic heart transplant; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; COVID-19, coronavirus disease 2019; MFI, mean fluorescence intensity; AT1R, angiotensin-II type 1 receptor; SOT, solid organ transplant.

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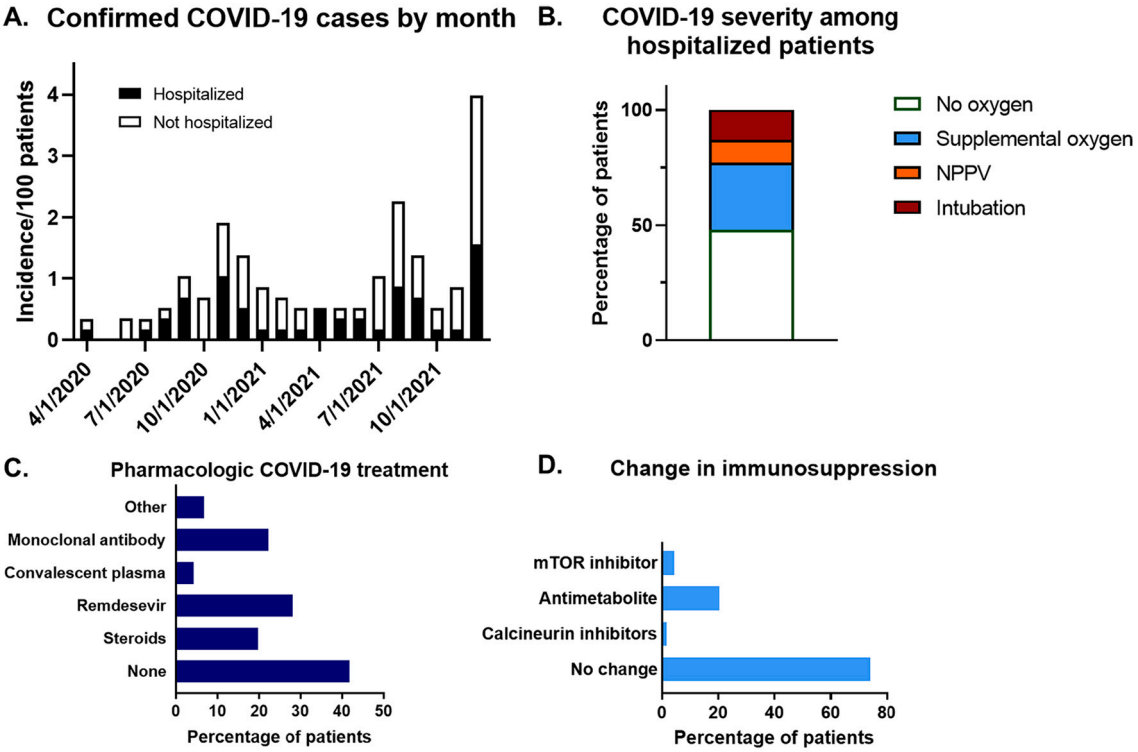

Fig. 1. COVID-19 incidence, severity, and treatment. A, COVID-19 incidence and hospitalization by month. B, COVID-19 severity among hospitalized patients. C/D, Pharmacologic treatment and change in immunosuppression after COVID-19 diagnosis, respectively.

A. Clinical characteristics	Unvaccinated	Vaccinated	p
Age (years)	53	59	0.06
Sex (%male)	71	55	0.12
Race (%Caucasian)	75	71	0.68
Cardiomyopathy etiology (%ischemic)	22	22	0.99
Hypertension (%)	56	45	0.27
Diabetes (%)	28	31	0.84
Chronic kidney disease (%)	34	31	0.84
Median time between OHT and COVID-19 diagnosis (days)	3465	2620	0.05
Allosensitized (%PRA>50)	6	6	0.99
Crossmatch (%positive)	10	6	0.52

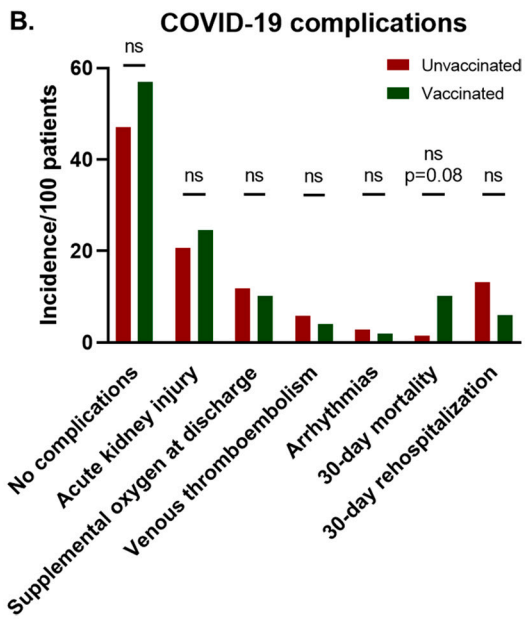

Fig. 2. COVID-19 complications. A, Baseline characteristics of heart transplant patients with COVID-19. B, Complications after COVID-19 infection.

3. Results

3.1. COVID-19 incidence and severity

A total of 577 patients were followed during the study period and 117 cases of SARS-CoV-2 infection were identified. COVID-19 incidence and hospitalizations are shown in Fig. 1A. Among hospitalized patients, 51% received supplemental oxygen and 23% required either non-invasive positive pressure ventilation or intubation (Fig. 1B). For patients who received pharmacologic treatment, the most common regimen was some combination of dexamethasone, remdesivir, and/or monoclonal antibody (Fig. 1C). During acute infection, most patients had either no change to their immunosuppression (72%) or a dose-reduction/discontinuation of their antimetabolite (20%, Fig. 1D).

3.2. COVID-19 complications

In our cohort, 58% of COVID-19 cases occurred in unvaccinated

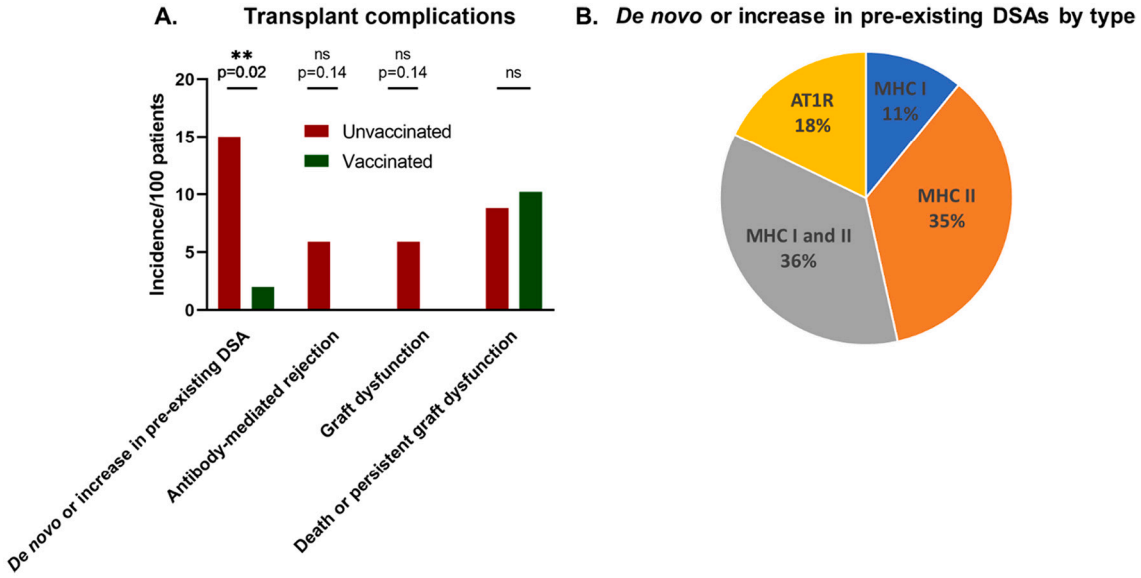

Fig. 3. Transplant complications and change in donor specific antibodies (DSAs) after COVID-19 infection. A, Transplant-specific complications after COVID-19 infection. B, Type of antibody detected in patients with development of *de novo* or increase in pre-existing DSAs.

patients and their baseline characteristics are shown in Fig. 2A. The most common complication was acute kidney injury, occurring in 21% of patients. Overall case-fatality after SARS-CoV-2 infection was 5% and case-fatality among hospitalized patients was 13% (Fig. 2B).

3.3. *De novo* DSAs and transplant complications

Unvaccinated OHT recipients had higher incidence of developing either *de novo* or an increase in pre-existing DSAs compared to vaccinated patients (15% *vs.* 2%, $p = 0.02$, Fig. 3A). There was also a non-significant increase in the incidence of AMR in unvaccinated patients, although long-term graft dysfunction and mortality did not differ. Among patients who developed *de novo* or increase in pre-existing DSAs, antibodies targeting MHC II antigens were the most common (Fig. 3B).

4. Discussion

In this study, we describe the clinical course of COVID-19 in a large, single-center population. Moreover, we provide information about the relationship between COVID-19 and the development of new or worsening DSAs. We found that COVID-19 incidence in OHT recipients mirrored that of the general population; however, the case-fatality rate remained higher (5% *vs.* 1.2%) [4]. To our knowledge, this is the largest published experience analyzing the incidence and outcomes of COVID-19 in OHT patients and the first to describe association between SARS-CoV-2 infection and DSAs.

Genuardi et al. and Bottio et al. analyzed 99 and 47 cases of COVID-19 in OHT recipients in the United States and Northern Italy respectively, showing case-fatality rates of 24–37% among hospitalized patients [2,3]. Contrary to these studies, we found a lower 13% case-fatality rate among hospitalized patients in our cohort. This observation is consistent with improving clinical outcomes in other solid organ transplant (SOT) recipients infected with SARS-CoV-2 [5]. Advances in clinical care, advent of vaccines, and less severe variants likely contribute to this phenomenon. Interestingly, we noted a trend towards higher 30-day mortality among fully vaccinated patients. We suspect this is due to vaccines eliciting variable humoral immunity in OHT recipients [6].

In addition, we also found that 10% of patients developed *de novo* or increase in pre-existing DSAs after COVID-19. The majority of DSAs were against MHC II antigens and occurred in unvaccinated patients. Based on prior data, the cumulative lifetime incidence of DSAs in OHT recipients ranges from 25 to 35%, with greatest risk in the first year after transplant and annualized risk of <5% thereafter [7–9]. Of note, it was recently shown that SARS-CoV-2 infection is associated with disruption of B cell tolerance, which could explain this association [10]. As *de novo* DSAs are known to be associated with AMR, coronary artery vasculopathy, and graft loss, our findings suggest that more frequent surveillance of DSAs after COVID-19 infection should be considered.

Our study has several important limitations. First, while we describe an association between COVID-19 and development of *de novo* DSAs in unvaccinated patients, we cannot establish causality. Second, vaccination guidelines changed throughout the study period. To maintain consistency, we defined fully vaccinated patients according to CDC guidelines after emergency use authorization of the vaccines. However, we recognize that additional doses of the mRNA vaccines may be necessary to elicit an appropriate immune response in the SOT population. Lastly, findings from our single-centered study may not be generalizable to all transplant recipients. Nevertheless, this report represents the largest COVID-19 study in the OHT population to date and offers important insight into disease trajectory and the potential concern for DSA production.

In conclusion, COVID-19 incidence in OHT patients mirrors that of the general population, although case-fatality has significantly decreased since the beginning of the pandemic. We found an association between COVID-19 and development of new or worsening DSAs in unvaccinated patients. Future studies are needed to confirm our findings and to ascertain whether these DSAs are transient or persistent.

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Authors' contributions

Study conception and design: BQY, JMV, JDS, AKV.
Acquisition of data: BQY, DL, RP.
Analysis and interpretation of data: BQY, JMV, JDS, AKV.
Drafting of manuscript: BQY.
Critical revision: JMV, JDS, AKV.

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