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BRIEF COMMUNICATION

Severity of SARS-CoV-2 Omicron variant infection in heart transplant recipients

Fanny Hazan, MD,[a] Constance Verdonk, MD,[b] Guillaume Coutance, MD,[a] Valentine Marie Ferré, MD,[c] Stéphane Marot, MD,[d] Vania Da Dilva Melo, RN,[b] Camille Legeai, MD,[e] Guillaume Lebreton, MD, PhD,[a] Marylou Para, MD,[b] Shaida Varnous, MD,[a] and Richard Dorent, MD[b,e]

From the [a]Département de chirurgie cardiaque, Institut de cardiologie, Hôpital Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris, Sorbonne Université, Paris, France; [b]Département de chirurgie cardiaque, Hôpital Bichat, Assistance Publique-Hôpitaux de Paris, Université Paris Cité, Paris, France; [c]Service de virologie, Hôpital Bichat, Assistance Publique-Hôpitaux de Paris, Université Paris Cité, Paris, France; [d]INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique (iPLESP), Service de virologie, Hôpital Pitié-Salpêtrière Assistance Publique-Hôpitaux de Paris, Sorbonne Université, Paris, France; and the [e]Direction Prélèvement Greffe Organes-Tissus, Agence de la Biomédecine, Saint Denis La Plaine, France.

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SARS-CoV-2 Omicron variant was first detected in France mid-November 2021 in wastewater treatment plants while cases started to increase at the beginning of December. The maximum incidence occurred in mid-January 2022. The Omicron wave spread rapidly throughout France in general population with lower case-fatality rate compared with previous waves. Little is known about infection with Omicron variant in heart transplant (HT) recipients. In this study, we examined incidence and mortality rate of COVID-19 in the general population and among 1,263 HT recipients during the period from June, 2021 to February, 2022, described characteristics of HT recipients infected with SARS-CoV-2 during Omicron (December 1st, 2021-February 7, 2022) and Delta (June 1st- November 30, 2021) periods, and compared hospital course of HT recipients with Omicron and Delta variant infection. Our findings contrast with the reported lower severity for Omicron variant infection compared with Delta variant infection in immunocompetent individuals.

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COVID-19 is associated with worse clinical outcome in heart transplant (HT) recipients than in general population. In addition to chronic immunosuppression, HT recipients commonly present with comorbidities and demonstrate a weaker humoral response to vaccination. A recently published meta-analysis reported hospitalization rate of 80% and mortality rate close to 30% in HT recipients affected by COVID-19 between pandemic's onset and May 2021.[1] The Omicron SARS-CoV-2 variant emerged in French metropolitan area on the beginning of December 2021 and became prevalent during the third week of December.[2] Omicron variant spread much faster than previous variants of concern. Omicron compared with Delta variant exhibited increased transmissibility[2] and lower severity[3,4] in general population. Despite lower vaccine effectiveness against symptomatic disease with Omicron than Delta variant, vaccine protection against hospitalization and mortality remains as high as 90% and

Reprint requests: Richard Dorent, MD, Hôpital Bichat, Assistance Publique-Hôpitaux de Paris, Université Paris Cité, Paris, France. Telephone: +33140256615. Fax: +33140258623.
E-mail address: richard.dorent@aphp.fr

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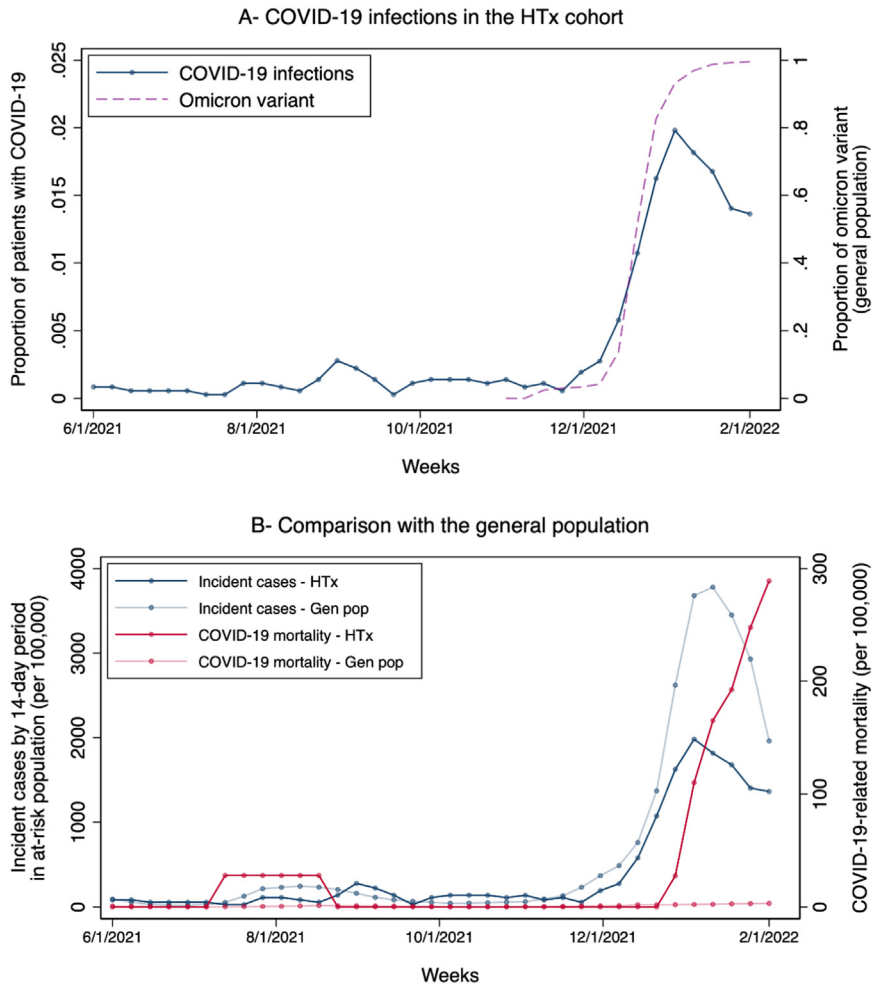

Figure 1 Fourteen-day average new COVID-19 infections in heart transplant recipients (A) and 14-day incidence and mortality rate in heart transplant cohort and general population (B).

95% after a booster dose in general population with Omicron variant infection.[5]

All adult HT recipients from 2 French transplant centers (Pitié-Salpêtrière Hospital and Bichat-Claude Bernard Hospital) with positive reverse transcription-polymerase chain reaction (RT-PCR) or antigen SARS-CoV-2 test from June 1st 2021 to February 7th 2022, were included in this study. The 14-day incidence of COVID-19 was estimated by dividing the number of new COVID-19 cases over 2-week periods by total number of patients followed on the first day of these periods, and 14-day mortality rate was obtained by dividing the number of patients with COVID-19 who died within 2-week periods by total number of patients followed on the beginning of the periods. COVID-19 incidence and mortality rate in the general population were obtained from the weekly reports of Sante publique France Agency.

Delta and Omicron periods (June 1st-November 30, 2021, and December 1st, 2021-February 7, 2022, respectively) corresponded to the first variant case detected in France. From December 2021 to the beginning of February 2022, Omicron wave was driven by Omicron BA.1 sublineage.[2] The variant characterization was performed using specific RT-PCRs, the TaqPath COVID-19 RT-PCR (ThermoFisher) and the VirSNiP assays (TIB Molbiol, Germany) targeting the 69-70del, E484K and L452R spike mutations. Categorical variables were compared using the Fisher's exact test and continuous variables were compared using Wilcoxon test.

Among 1,263 HT recipients, 177 were affected by COVID-19. Their median age [IQR] was 54 [42-65] years and the median time [IQR] between transplantation and COVID-19 diagnosis was 62 months [30-104]. Overall, 89% of the patients were receiving a CNI-based immunosuppressive regimen. Ninety-four percent of the patients had received at least one dose of an mRNA vaccine and 72% had a complete vaccination scheme with 2 doses and a booster at the time of diagnosis. Among 57 (42%) recipients with detectable anti-SARS-CoV-2 spike antibodies, 32 (24%) had antibody titers of 260 BAU/ml or more. Sixty-eight percent (n = 120) of the patients were managed as outpatients. Overall, 146 (82.5%) HT recipients were infected during the Omicron period and 31 (17.5%) during the Delta wave, of which 45 (30.8%) vs 13 (41.9%) required hospitalization.

During the Omicron period, incidence (2,917 vs 5,670 per 100,000) peaked lower and mortality (289 vs 3.2 per 100,000) much higher in HT recipients compared with general population (Figure 1). Demographics, comorbidities and immunosuppressive regimens of HT recipients affected

Table 1 Comparison of Demographic and Clinical Characteristics, Immunosuppressive Regimen and Vaccination Status of Transplant Recipients With COVID-19 During Delta and Omicron Waves

	n	Overall *n* = 177	Delta wave *n* = 31 (17.5%)	Omicron wave *n* = 146 (82.5%)	*p* value
Age, median, y	177	54.0 (42.4-64.6)	57.7 (43.2-70.0)	53.7 (42.3-64.6)	.46
Female	177	49 (27.7)	7 (22.6)	42 (28.8)	.66
Primary diagnosis	177				
Dilated cardiomyopathy		79 (44.6)	14 (45.2)	65 (44.5)	
Coronary artery disease		43 (24.3)	8 (25.8)	35 (24.0)	.97
Other		55 (31.1)	9 (29.0)	46 (31.5)	
Time since transplant, median, y	177	5.2 (2.5-8.7)	5.2 (2.7-9.3)	5.2 (2.4-8.7)	.61
Chronic lung disease	174	10 (5.8)	4 (13.3)	6 (4.2)	.07
Body mass index > 30 kg/m^2	170	32 (18.8)	7 (24.1)	25 (17.7)	.44
Diabetes	173	46 (26.6)	9 (30.0)	37 (25.9)	.65
GFR at positive test	169	40.0 (29.6-61.0)	33.4 (22.5-61.2)	41.2 (31.4-61.0)	.12
Dialysis at positive test	176	7 (4.0)	1 (3.3)	6 (4.1)	1.0
COVID-19 reinfection	125	20 (16.0)	1 (5.9)	19 (17.6)	.30
Immunosuppressive regimen	173				
CNI-based		154 (89.0)	23 (79.3)	131 (91.0)	
mTORi-based		17 (9.8)	6 (20.7)	11 (7.6)	.10
Belatacept-based		2 (1.2)	0 (0.0)	2 (1.4)	
Vaccination status at positive test	172				
Unvaccinated		11 (6.4)	2 (6.5)	9 (6.4)	
1-2 doses		38 (22.1)	12 (38.7)	26 (18.4)	.04
≥3 doses		123 (71.5)	17 (54.8)	106 (75.2)	
SARS-CoV-2 IgG >260 BAU at positive test	136	32 (23.5)	2 (10.5)	30 (25.6)	.24

Abbreviations: BAU, binding antibody units; CNI, calcineurin inhibitor; COVID-19, coronavirus disease 2019; GFR, glomerular filtration rate; mTORi, mammalian target of rapamycin inhibitor; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Fisher's exact test and Wilcoxon test were used to calculate *p* values.

by COVID-19 during Omicron and Delta periods were similar (Table 1). As expected, the percentage of cases vaccinated with ≥3 doses was significantly higher during Omicron period. Of the 57 hospitalized cases, 51 (89%) were screened for variant. Information on COVID-19 management was available for almost all the 51 patients (Table 2). Corticosteroids boluses, monoclonal antibodies and antiviral therapies were administered in 71%, 41%, and 4% of patients, respectively, with a similar use in both groups. Overall, 53% of hospitalized patients required intensive care unit (ICU) admission, 38% required mechanical ventilation and/or ECMO and 38% died. Among Omicron hospitalized cases, there were 18 (56%) ICU admissions and 14 (44%) deaths vs 9 (47%) ICU admissions and 5 (26%) deaths among Delta cases (Table 2). The median length of hospital stay was significantly longer in the Omicron cases.

The present study shows substantial differences in SARS-CoV-2 Omicron variant infection between HT recipients and the general population and between Omicron and Delta infection in HT recipients.

With Omicron variant emergence, COVID-19 spread rapidly in the French population as well as in our cohort (Figure 1). It is established that the high number of mutations in the Omicron spike protein facilitate SARS-CoV-2 entry into human cells and contribute to its increased transmissibility.[6] In addition, these mutations are also associated with an evasion from neutralization by natural or therapeutic antibodies.[7] Notably, incidence of infection remained at a lower level in our cohort than in the general population. This contrasts with reports published before the emergence of Omicron.[1] The reasons for these findings are unclear.

Surprisingly, Omicron variant was associated with a high risk of death in our cohort. This differs from the results of several national cohort studies reporting a lower risk of severe outcomes following Omicron infection compared with Delta variant.[3,4] This discrepancy could be explained by the lower antibody response following vaccination associated with a waning over time of vaccine-induced immunity in HT recipients.[8,9] Indeed, only 24% of the patients from our cohort displayed antibody titers above the threshold of 260 BAU/ml at the time of COVID-19 diagnosis. On the other hand, the great excess mortality in our cohort during the Omicron wave vs the Delta wave could be due to the substantial reduction in neutralizing activity of antibodies against Omicron.[7,10] Overall, the increased immune escape from Omicron seems to prevail on the reduced intrinsic severity. The dramatic increase in the number of new COVID-19 cases after Omicron variant emerged played also a role on mortality directly and through its impact on the health care system.

In conclusion, our findings underline the importance of specifically characterizing severity of new SARS-CoV-2 variants in HT recipients, and support the use of adapted bivalent mRNA vaccines targeting Omicron subvariants in addition to SARS-CoV-2 original strain.

Table 2 Characteristics and Outcomes of Hospitalized Transplant Recipients With SARS-CoV-2 Delta and Omicron Infection

	n	Delta cases *n* = 19 (37.2%)	Omicron cases *n* = 32 (62.8%)	*p* value
Age, median, y	51	57.7 (46.1-66.2)	61.5 (57.7-65.9)	.37
Time since transplant, median, y	51	5.4 (3.4-6.8)	5.1 (1.9-7.4)	.42
Chronic lung disease	50	3 (16.7)	4 (12.5)	.69
GFR at positive test	49	30.7 (22.5-39.6)	34.7 (16.0-49.0)	.69
Dialysis at positive test	50	1 (5.6)	4 (12.5)	.64
COVID-19 reinfection	37	1 (11.1)	3 (10.7)	1.0
Immunosuppressive regimen	50			
CNI-based		16 (88.9)	29 (90.6)	
mTORi-based		2 (11.1)	3 (9.4)	1.0
Belatacept-based		0 (0.0)	0 (0.0)	
Vaccination status at positive test	51			
Unvaccinated		1 (5.2)	0 (0.0)	
1-2 doses		9 (47.4)	9 (28.1)	.10
≥3 doses		9 (47.4)	23 (71.9)	
Chest CT imaging involvement (%)	27	37.5 (25-50)	35.0 (22.5-65.0)	.82
Dexamethasone use	48	13 (72.2)	21 (70.0)	1.0
Monoclonal antibody treatment	49	7 (38.9)	13 (41.9)	1.0
Remdesivir/nirmatrelvir-ritonavir use	49	0 (0.0)	2 (6.3)	.78
Oxygen treatment	50	12 (66.7)	24 (75.0)	.53
Mechanical ventilation or ECMO	50	5 (27.8)	14 (43.8)	.37
ICU admission	51	9 (47.4)	18 (56.3)	.58
Length of stay in hospital	48	8.5 (5.0-18.0)	18.5 (10.0-27.5)	.03
Death	50	5 (26.3)	14 (45.2)	.24

Abbreviations: CNI, calcineurin inhibitor; COVID-19, coronavirus disease 2019; CT, computed tomography; ECMO, extracorporeal membrane oxygenation; GFR, glomerular filtration rate; ICU, intensive care unit; mTORi, mammalian target of rapamycin inhibitor.

Fisher's exact test and Wilcoxon test were used to calculate *p* values.

Disclosure statement

The authors have no disclosure regarding the present study.

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