

Incidence and prognosis of COVID-19 amongst heart transplant recipients: a systematic review and meta-analysis

Furqan Ahmed¹, Minaam Abid¹, Talha Maniya², Muhammad Shariq Usman ^{3*}, and Marat Fudim^{4,5}

¹Department of Medicine, Dow University of Health Sciences, Mission Rd, Saddar, 74200 Karachi, Pakistan; ²Department of Medicine, Ziauddin University, Shahrah-e-Ghalib Rd, Block 6 Clifton, 74200 Karachi, Pakistan; ³Department of Medicine, University of Mississippi Medical Center, 2500 North State Street, Jackson, MS 39216, USA; ⁴Division of Cardiology, Duke University Medical Center, 2301 Ervin Rd, NC 27710, Durham, USA; and ⁵Duke Clinical Research Institute, NC 27701, Durham, USA

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Several studies have highlighted the cardiovascular effects of Coronavirus Disease 2019 (COVID-19), including an increased risk of arteriovenous thrombosis, myocarditis, and myocardial infarction.¹ In addition, it is well-established that patients with pre-existing cardiovascular diseases have an increased susceptibility to COVID-19, and a worse prognosis.² These concerns also extend to heart transplant (HT) recipients, who are often on chronic immunosuppression and have an increased burden of comorbidities.^{3,4} However, the incidence and prognosis of COVID-19 in HT recipients have not been well-characterized, primarily due to studies with small sample sizes. Thus, we conducted a systematic review and meta-analysis of published studies in an effort to provide a well-powered comprehensive assessment of the risk and prognosis of COVID-19 in recipients of HT.

This study was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions.⁵ We performed an electronic search of databases PubMed and Scopus from inception to the first week of May 2021 using the following search string: (Heart transplant OR Cardiac transplant) AND (COVID-19 OR SARS-Cov-2 OR coronavirus disease 19). Additionally, we hand-searched reference lists of relevant articles to identify any missed articles. The search and data extraction were conducted independently by two reviewers (M.A. and F.A.). For our analysis, we only included articles with at least 10 HT recipients. The COVID-19 infection rate in the HT cohort in each study was calculated or extracted from the study. For each HT cohort, the COVID-19 infection rate in the region (during the study period) was used as control; this information was retrieved from official government sources or published research articles. In a similar manner, the mortality rate in the HT recipients with COVID-19 was also compared with the general population. The OpenMetaAnalyst software was used for all analyses. Mortality and hospitalizations rates in the HT population were arcsine transformed and pooled using a random-effects model in order to derive summary estimates.

To compare infection and mortality rates with the general population, odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated and pooled using a random-effects model. The data underlying this article are available in the article and in its online supplementary material.

Our initial search yielded 397 studies. After applying inclusion and exclusion criteria, 18 studies were included in the study. References for all included studies are given in [Supplementary material online, Table S1](#). The detailed literature search is highlighted in the PRISMA flow chart ([Supplementary material online, Figure S1](#)). Ten studies reported the COVID-19 infection rate amongst HT patients. Amongst a total of 5588 HT patients, 2.54% contracted COVID-19. The likelihood of COVID-19 infection was significantly higher in the HT population compared with the general population (OR 5.47; 95% CI 3.03–9.89, $I^2 = 90.6%$, $P < 0.001$; [Figure 1A](#)). Twelve studies reported outcomes in HT recipients who contracted COVID-19 ($n = 424$ patients). Characteristics of participants in the included studies are shown in [Table 1](#), of whom 75% were male, 35% had diabetes mellitus and 65% had hypertension. The pooled mortality rate was 27.6% (95% CI 23.2–32.2%; $n = 107/384$; [Figure 1B](#)) and the pooled hospitalization rate was 82.9% (95% CI 77.1–87.9%; $n = 242/298$; [Figure 1C](#)). Compared with the general population, the mortality rate due to COVID-19 was significantly higher in the HT population (OR 3.37; 95% CI 2.25–5.05, $I^2 = 64.5%$, $P < 0.001$; [Figure 1D](#)).

To the best of our knowledge, this is the first meta-analysis studying the risk and prognosis of COVID-19 amongst HT patients. Our findings show that the odds of being diagnosed with COVID-19 are more than five times higher in HT recipients. Our findings also show that the chances of hospitalization in HT recipients with COVID-19 are approximately 80%; and the mortality rate approaches 30%. The most likely contributor to susceptibility and poor prognosis of COVID-19 in HT recipients is the use of immunosuppressants, which increase the likelihood of symptomatic disease and unchecked progression.

* Corresponding author. Tel: +1 601 666 2525, Email: shariqusman@outlook.com

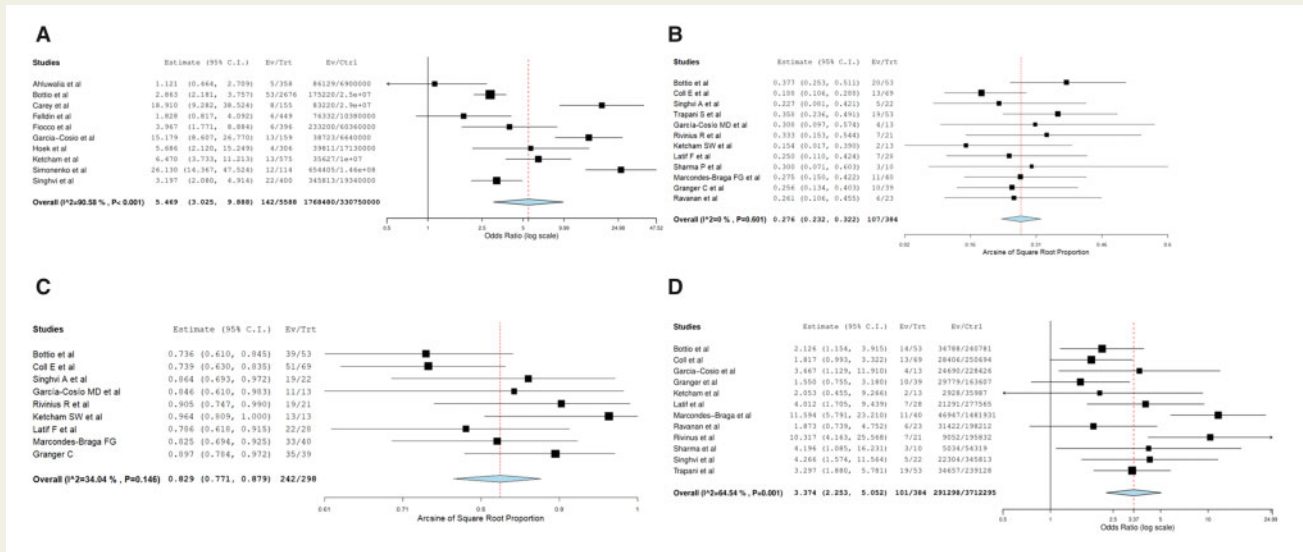


Figure 1 Forest plots displaying. (A) The odds of COVID-19 infection in heart transplant recipients compared with general population. (B) Mortality rate amongst heart transplant recipients infected with COVID-19. (C) Hospitalization rate amongst heart transplant recipients infected with COVID-19. (D) Mortality rate amongst heart transplant recipients infected with COVID-19 compared to general population infected with COVID-19.

Table 1 Baseline characteristics of heart transplant patients infected with COVID-19

Study	Total cases of HT	Median age (years)	Male, n (%)	Median time since transplant (years)	Diabetes, n (%)	Hypertension, n (%)	CKD, n (%)	Mortality, n (%)	Hospitalization, n (%)	ICU admission, n (%)	Invasive ventilation, n (%)
Bottio et al. (Cohort 1)	47	61.84	37 (79)	10.46 ± 8.70 ^a	8 (17)	30 (64)	NA	14 (37)	38 (81)	4 (9)	2 (4)
Bottio et al. (Cohort 2)	6	59	4 (67)	7.8 ^a	2 (33)	4 (67)	NA	6 (100)	1 (17)	0 (0)	0 (0)
Coll et al.	69	64	54 (79)	10.17	NA	NA	NA	13 (22)	51 (86)	7 (12)	3 (6)
Singhi et al.	22	58.6	14 (63.6)	4.6	12 (54.5)	21 (95.5)	14 (63.6)	5 (22.7%)	19 (86.4)	4 (18.2)	4 (21.1)
Trapani et al.	53	59.8 ^a	NA	6.1	NA	NA	NA	19 (35.8)	NA	NA	NA
García-Cosío et al.	13	63	10 (76.9)	17	2 (15.4)	7 (53.8)	6 (46.2)	4 (31)	11 (84.6)	1 (8.3)	1 (8.3)
Fellain et al.	6	55 ^a	5 (83.3)	11.7	1 (16.7)	2 (33.3)	2 (33.3)	1 (16.7)	3 (50)	NA	NA
Rivinius et al.	21	58.6	17 (81.0)	7.83 ± 6.89 ^a	7 (33.3)	15 (71.4)	6 (28.6)	7 (33.3)	19 (90.5)	17 (71.4)	8 (38.1)
Ketcham et al.	13	61 ^a	13 (100)	8	9 (69)	11 (85)	11 (85)	2 (15)	13 (100)	13 (46)	5/13 (38)
Latif et al.	28	64	22 (79)	8.6	17 (61)	20 (71)	10 (36)	7 (25)	22 (79)	7 (25)	7 (25)
Sharma et al.	10	NA	NA	NA	NA	NA	NA	3 (33.3)	NA	NA	NA
Hoek et al.	4	51	3 (100)	10	NA	NA	NA	0 (0)	NA	NA	NA
Fiocco et al.	6	NA	NA	NA	NA	NA	NA	2 (33.3)	NA	NA	NA
Ahluwalia et al.	5	50	4 (80)	21	5 (100)	5 (100)	5 (100)	1 (20)	3 (60)	NA	NA
Marcondes-Braga et al.	40	53	24 (60)	2.8	10 (25)	14 (35)	15 (37.5)	11 (27.5)	33 (82.5)	17 (42.5)	9 (22.5)
Granger et al.	39	54.4	26 (66.7)	4.9	16 (40)	28 (71.8)	21 (53.8)	10 (25.6)	35 (89.7)	14 (35.9)	8 (20.5)
Simonenko et al.	12	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Ravanan et al.	23	NA	NA	NA	NA	NA	NA	6 (26.1)	NA	NA	NA
Carey et al.	8	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

CKD, chronic kidney disease; HT, heart transplant; NA, not available.
^aMean.

Early in the COVID-19 pandemic, it was hypothesized that immunosuppressed patients may be less likely to contract a severe form of COVID-19, due to a lower risk of immune-mediated cytokine storms.^{6,7} Recent, more comprehensive, data refute this and suggest a poorer prognosis in COVID-19 patients who have been on immunosuppressive therapy.⁸ Findings from our study corroborate these recent data. Studies assessing mortality in kidney transplant recipients with COVID-19 have confirmed the same.⁹ Another major contributor to a poor COVID-19 prognosis is the high burden of comorbidities in HT patients, as seen in our study population.¹⁰ The direct effects of COVID-19 on the cardiovascular system may also play a role in the poorer prognosis.²

Certain limitations must be kept in mind when interpreting the results of this study. There is possibility of confounding bias given that this is a meta-analysis of case series and observational studies. Differences in COVID-19 infection rate, management protocols, differences in heart transplantation protocols and immunosuppressive treatments between countries may limit the interpretation of our findings. Predictors of increased susceptibility and poor prognosis of COVID-19 in HT recipients may be better delineated by large scale cohort studies running multivariate adjusted analyses; however, such studies are unlikely to emerge soon given that relatively small number of HT cases. The current analysis provides evidence supporting the use of increased protective measures and close monitoring of HT recipients during the pandemic.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology* online.

Conflict of interest: none declared.

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