LETTER TO THE EDITORS

Solid organ transplantation is not a risk factor for COVID-19 disease outcome

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To the Editor

Reports indicate an increased mortality risk for solid organ transplant recipients with COVID-19 [1,2], which may have been influenced by clinical decision making (triage) during the early phase of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. In Germany, relatively few transplant recipients were infected, and the capacity of the healthcare system was at no point in time overwhelmed. Hereby, high capacity PCR testing including all potential organ donors, symptomatic organ recipients or other patients, as well as a relatively high number of hospitals with intensive care units (1248) and transplant centers (40) with high capacities allowed a completely unimpaired organ procurement and transplantation situation throughout the first wave of the pandemic despite having SARS-CoV-2 infection rates of app. 2200 per million persons at the end of May 2020. Our data lead to a different assessment of the risk associated with COVID-19 after organ transplantation.

In organ recipients, transplantation was performed more than 1 year ago in over 80%. Calcineurin inhibitor-based immunosuppression was administered in 71.7%, mycophenolate acid/mofetil was given in 63.4%, mTOR inhibitors were given in 10.9%, and corticosteroid maintenance therapy was given in 63%. No transplant recipient received a T-cell depleting treatment, and B-cell depleting agents were administered in one patient. Two patients received a steroid bolus within the last six months before COVID-19 diagnosis. None of the patients were treated with remdesivir or with reconvalescent patient plasma.

A matched-pair analysis (1:30) of 46 transplant recipients with 1380 controls without transplantation within one registry (LEOSS) was performed. With the exception of chronic kidney disease, which was more frequent in the transplant patient group, known COVID-19 risk factors such as age, gender and comorbidities [3–5] were closely matched with controls (Table 1). Multivariable conditional logistic regression failed to identify organ transplantation as a risk factor for mortality (OR 0.27, 95% CI 0.12–1.25); the proportion of people who survived was comparable in transplant recipients (91.3%) and the control population (82.5%). Similarly, immunosuppressant administration was also not associated with an increased mortality risk in this combined cohort of transplant and control patients with COVID-19. To expand on this observation, sensitivity analyses were performed on 153 immunosuppressed patients, excluding individuals with organ transplantation, and compared to

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Table 1. Shows the patient data from Germany from the Lean European Open Survey on SARS-CoV-2-infected patients (LEOSS).

	Patient characteristics		Univariate analysis		Multivariable analysis	
	Transplant patients, 46 *n* (%)	Controls, 1380 *n* (%)	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Transplant patients	46 (100)		0.47 (0.16–1.39)	0.174	0.27 (0.12–1.25)	0.992
Immunosuppressive medication[†]	46 (100)	93 (7.8)	1.31 (0.75–2.28)	0.347	0.71 (0.28–1.79)	0.472
Sex						
Female	18 (39.1)	578 (41.9)	*			
Male	28 (60.9)	802 (58.1)				
Age						
<45	11 (23.9)	264 (19.1)	*			
46–55	11 (23.9)	185 (13.4)				
56–65	13 (28.3)	275 (19.9)				
>65	11 (23.9)	656 (47.5)				
Comorbidities						
Chronic kidney disease	28 (60.8)	241 (17.5)	*			
COPD/Asthma	2 (4.4)	116 (8.5)	*			
On dialysis	2 (4.4)	31 (2.3)	*			
Diabetes mellitus	12 (26.1)	313 (22.7)	*			
Hypertension	33 (71.7)	842 (61.0)	*			
Coronary artery disease	9 (19.6)	219 (15.9)	*			
Chronic heart failure	9 (19.6)	149 (10.8)	*			
Peripheral vascular disease	4 (8.7)	71 (5.1)	*			
Myocardial infarction	1 (2.2)	95 (6.9)	*			
Cerebrovascular diseases	2 (4.7)	149 (10.8)	0.69 (0.45–10.8)	0.104	0.63 (0.29–1.31)	0.216
Ethnicity						
Caucasian	34 (87.2)	1113 (96.1)	Ref.			
Non-Caucasian	5 (12.8)	45 (3.9)	1.22 (0.38–2.61)	0.997		
Smoking status						
Nonsmoker	19 (79.2)	471 (70.5)	Ref.			
Smoker	/	84 (12.6)	0.75 (0.36–1.56)	0.438		
Former smoker	5 (20.8)	113 (16.9)	0.85 (0.46–1.57)	0.599		
Days from contact until diagnosis						
(median IQR)	1 (1–1)	1 (1–1)	1.02 (0.93–1.12)	0.625		
(mean, min-max)	2 (1–6)	2 (0–6)				
Clinical phase at diagnosis[‡]						
Uncomplicated phase	33 (71.7)	859 (62.9)	Ref.		Ref.	
Complicated phase	11 (23.9)	399 (29.5)	2.88 (2.04–4.07)	<0.001	3.11 (1.72–5.62)	<0.001
Critical phase	2 (4.4)	102 (8.6)	6.69 (3.90–11.12)	<0.001	3.83 (1.59–9.19)	0.003
Overall inpatient stay						
(median, IQR)	13 (6–22)	10 (6–19)	0.99 (0.97–0.99)	0.021	0.92 (0.89–9.67)	<0.001
(mean, min–max)	13 (0–68)	14 (6–121				

Table 1. Continued.

	Patient characteristics		Univariate analysis		Multivariable analysis	
	Transplant patients, 46 *n* (%)	Controls, 1380 *n* (%)	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Overall ICU stay						
(median, IQR)	0 (0–5)	0 (0–6)	1.03 (1.02–1.05)	<0.001	0.95 (0.86–1.04)	0.253
(mean, min–max)	4 (0–28)	5 (0–68)				
Overall mechanical ventilation						
(median, IQR)	0 (0–3)	0 (0–0)	1.05 (1.03–1.07)	<0.001	1.11 (1.00–1.23)	0.040
(mean, min–max)	3 (0–28)	3 (0–28)				
CRP at baseline						
<3	7 (15.2)	136 (9.9)	Ref.		Ref.	
3–29	7 (15.2)	362 (26.2)	2.67 (0.99–7.14)	0.051	1.69 (0.48–6.01)	0.412
30–120	14 (30.4)	353 (25.6)	4.77 (1.82–12.47)	0.001	1.59 (0.45–5.53)	0.463
>249	11 (23.9)	206 (14.9)	10.65 (3.99–28.39)	<0.001	1.95 (0.53–7.16)	0.315
Ferritin at baseline						
<300	10 (21.7)	125 (9.1)	Ref.			
300–1000	8 (17.4)	161 (11.6)	2.82 (0.97–8.22)	0.057	1.09 (0.02–58.92)	0.968
>1000	2 (4.4)	133 (9.6)	8.33 (2.86–24.3)	>0.001	10.54 (0.33–34.09)	0.184
Leukocytes at baseline						
<1000	/	8 (0.58)	2.49 (0.42–14.99)	0.318	n.a.	
1000–8000	28 (60.9)	762 (55.2)	Ref.		Ref.	
>8000	11 (23.9)	303 (21.9)	1.76 (1.22–2.54)	0.002	1.62 (0.83–3.14)	0.157
Lymphocytes at baseline						
<500	8 (17.4)	148 (10.7)	3.24 (1.97–5.35)	<0.001	2.62 (1.24–5.55)	0.012
500–800	5 (10.9)	190 (13.8)	1.73 (1.05–2.84)	0.031	1.63 (0.81–3.26)	0.172
>800	8 (17.4)	510 (36.9)	Ref.		Ref.	

n.a., not applicable; ref., reference category.

Univariable conditional logistic regression and multivariable conditional logistic regression were performed to identify factors associated with COVID-19-related mortality. Results from the uni- and multivariable conditional logistic regression models are displayed with odds ratio (OR) and 95% confidence intervals (CI); all variables with a *P*-value >0.2 in the univariate analysis were fitted simultaneously in the multivariable model. All statistical analyses were performed with STATA (Stata Statistical Software: Release 14. StataCorp LP, College Station, TX, USA). Forty-six transplanted patients (73.3% kidney, 13.3% heart, 8.9% liver, 2.2% lung, 6.6% combined) with COVID-19 disease were matched 1:30 with controls comprising COVID-19 affected individuals without transplantation (A). Critical clinical phase: defined by need for catecholamines, life-threatening cardiac arrhythmia, need for unplanned mechanical ventilation, prolongation (>24 h) of planned mechanical ventilation, liver failure with Quick <50%, qSOFA ≥2, acute renal failure in need of dialysis.

*Matching included age, gender and coexisting conditions at the time of diagnosis using nearest neighbor matching.

†In the past 3 months.

‡Complicated clinical phase: defined by need for new or increased oxygen supplementation, PaO_2 at room air <70 mmHg, SO_2 at room air <90%, GOT or GPT >5x ULN, new cardiac arrhythmia, new pericardial effusion >1 cm, new heart failure with pulmonary edema, congestive hepatopathy or peripheral edema.

a cohort matched at a ratio of 1:10 characterized by the identical risk factors. Mortality was found to be independent of the chronic use of immunosuppressive therapy at the time of COVID-19 diagnosis. While the relatively small number of transplant patients is a limitation of this study, the major result appeared to be robust also with other matching ratios (1:10 or 1:20).

Expectedly, the overall need for mechanical ventilation, late presentation in complicated or critical clinical phase, and lymphocyte counts below 500/µl were identified as risk factors for increased mortality.

In conclusion, while clinical condition and severe lymphopenia at the time of COVID-19 diagnosis were confirmed as relevant risk factors for an unfavorable outcome, prior solid organ transplantation was not shown to have an adverse effect on mortality in comparison with a matched COVID-19 reference population.

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