RESEARCH LETTER

Outcomes of COVID-19 in patients after liver transplantation: a single-center experience

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Introduction SARS-CoV-2 is a novel coronavirus that was first detected in Wuhan, China and caused the first global pandemic in the twenty-first century. The COVID-19 pandemic raised tremendous concern in the liver transplant (LT) community in light of the known impact of comorbidities on the prognosis and high mortality of patients with chronic liver disease and cirrhosis[1] as well as those after LT, as indicated in initial reports.[2,3] Colmenero et al[4] recently presented the epidemiological patterns, incidence, and outcomes of COVID-19 in a multicenter Spanish cohort of 111 LT recipients, pointing to an increased risk of contracting COVID-19 in this group of patients; however, the reported mortality rate was lower than that of a matched general population. A systemic review and meta-analysis of 2772 solid organ transplant recipients (including 505 individuals after LT) presented by Raja et al[5] did not analyze the mortality of patients with COVID-19. Thus, the group of 151 liver-grafted patients from 18 countries, analyzed by Webb et al,[6] represents the largest reported series to date. There were also single-center studies performed in this field, but the analyzed samples were much smaller; for example, a study by Lee et al[7] involved a group of 38 LT individuals treated at the Mount Sinai Hospital in the United States. All these findings indicated a high rate of hospitalization in liver graft recipients, which did not necessarily coincide with a higher COVID-19–related mortality rate.

The aim of this study was to assess the clinical course of COVID-19 in LT recipients from a single liver transplant center in Poland.

Patients and methods A total of 81 White patients who underwent LT at the Liver and Internal Medicine Unit of the Medical University of Warsaw, Poland were prospectively enrolled and evaluated between October 1, 2020 and June 15, 2021. SARS-CoV-2 infection was confirmed by a real-time reverse transcriptase–polymerase chain reaction assay (cobas 6800 System, Roche Diagnostics, Basel, Switzerland) of nasopharyngeal swab specimens. In asymptomatic individuals, tests were performed due to relevant contact with an infected person or obligatory in-hospital testing. Data on the clinical course of the disease were collected in a dedicated database and presented as numbers and percentages to facilitate the comparison with the results of other studies.

Ethics The study protocol was approved by the ethics committee of the Medical University of Warsaw (AKBE/22/2021) and conformed to the ethical guidelines of the 1975 Declaration of Helsinki. Written informed consent to participate was not required due to the nonexperimental design of the study.

Results The study group consisted of 81 patients (34 women and 47 men) at a median age of 55 years (range, 22–73 years). COVID-19 was diagnosed across all indications for LT in a wide time span after the procedure. We noted only 10 COVID-19–related hospital admissions (12.3%), including 2 COVID-19–related deaths (2.5%). The most commonly reported symptom was fatigue (43.2% of patients), followed by dyspnea (26%) and fever (25.9%). In addition, 7.4% of individuals had diarrhea, and 19.7% lost their sense of smell. Pneumonia was present in 13.6% of patients. Nineteen individuals (23.5%) were asymptomatic—9 women and 10 men at a median age of 56.5 years (range, 28–73 years). Of note, 8 of these patients (47.4%) were infected in the direct post-LT period. What is more, in this subgroup we observed the most severe form of pneumonia with the need for mechanical ventilation in 2 individuals who eventually died, representing the only cases of COVID-19–related death in the study cohort. The results are summarized in TABLE 1.

Discussion Based on the presented results, our experience with COVID-19 among LT recipients

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Received: April 13, 2021.
Revision accepted: July 12, 2021.
Published online: October 19, 2021.
Pol Arch Intern Med. 2021; 131 (10): 16090
doi:10.20452/pamw.16090

TABLE 1 Characteristics of patients diagnosed with COVID-19 after liver transplantation

Characteristics			Time of COVID-19 diagnosis			Overall (n = 81)
			≤3 months after LT (n = 15)	4–12 months after LT (n = 7)	>12 months after LT (n = 59)	
Sex	Female		4 (26.7)	4 (57.1)	26 (44.1)	34 (42)
	Male		11 (73.3)	3 (42.9)	33 (55.9)	47 (58)
Age, y, median (range)			55 (22–73)	56 (22–73)	55 (22–73)	55 (22–73)
Etiology of liver disease	Viral hepatitis		2 (13.3)	1 (14.3)	7 (11.9)	10 (12.3)
	Alcohol-related liver disease		3 (20)	2 (28.6)	12 (20.3)	17 (20.9)
	Autoimmune/cholestatic		2 (13.3)	4 (57.1)	27 (45.8)	33 (40.7)
	Other		8 (53.3)	0	13 (22)	21 (25.9)
Immunosuppression	CNI (TAC, CysA)		15 (100)	7 (100)	53 (89.8)	75 (95.6)
	Antimetabolites (MMF, AZA)		10 (66.7)	6 (85.7)	38 (64.4)	54 (66.6)
	Corticosteroids		13 (86.7)	2 (28.6)	14 (23.7)	29 (35.8)
	mTOR (EVE)		0	0	4 (6.8)	4 (4.93)
COVID-19 symptoms	Asymptomatic		8 (53.3)	3 (42.9)	8 (13.6)	19 (23.5)
	Fever >38 °C		3 (20)	0	18 (30.5)	21 (25.9)
	Muscle pain	Mild	0	0	6 (10.2)	6 (7.4)
		Moderate	1 (6.7)	1 (14.3)	13 (22)	15 (18.5)
		Severe	0	1 (14.3)	6 (10.2)	7 (8.6)
	Dyspnea	Mild	1 (6.7)	0	5 (8.8)	8 (9.9)
		Moderate	1 (6.7)	0	7 (11.9)	8 (9.9)
		Severe	2 (13.3)	0	4 (6.8)	5 (6.2)
	Diarrhea	Mild	1 (6.7)	0	2 (3.4)	3 (3.7)
		Moderate	0	0	1 (1.7)	1 (1.2)
		Severe	1 (6.7)	0	1 (1.7)	2 (2.5)
	Fatigue	Mild	4 (26.7)	0	5 (8.8)	9 (11.1)
		Moderate	2 (13.3)	1 (14.3)	12 (20.3)	15 (18.5)
		Severe	0	1 (14.3)	10 (16.9)	11 (13.6)
	Loss of taste		1 (6.7)	1 (14.3)	11 (18.6)	13 (16)
	Loss of smell		2 (13.3)	2 (28.6)	12 (20.3)	16 (19.7)
	Radiologically confirmed pneumonia		4 (26.7)	0	7 (11.9)	11 (13.6)
Hospitalization due to COVID-19			0	0	10 (16.9)	10 (12.3)
Hospitalization due to other causes			11 (73.3)	0	12 (20.3)	23 (28.4)
Death due to COVID-19			2 (13.3)	0	0	2 (2.5)
Death due to other causes			2 (13.3)	0	2 (3.4)	4 (5)

Data are presented as number (percentage) of patients unless otherwise indicated.

Abbreviations: AZA, azathioprine; CNI, calcineurin inhibitors; CysA, cyclosporine A; EVE, everolimus; LT, liver transplantation; MMF, mycophenolate mofetil; mTOR, mammalian target of rapamycin; TAC, tacrolimus

appeared to be promising so far, with a generally mild clinical course of the disease as well as a low percentage of patients in need of advanced oxygen supplementation and low number of deaths in this group.

The higher proportion of men in the study cohort confirms the previously reported male predominance among the infected patients, resulting from a higher frequency of chronic liver disease and greater number of LTs in men. The median age of patients in our study (55 years) seemed to be lower than in other reports (60, 65, and 66 years as reported by Webb et al,[6] Colmenero et al,[4] and Lee et al,[7] respectively). This may be due to the sampling bias; in our center, approximately 30% of LTs are performed in young or middle-aged patients with autoimmune diseases, without a high number of advanced comorbidities.

The clinical course of SARS-CoV-2 infection in our cohort was mild, in contrast to the results presented by Lee et al,[7] who reported mild course of the disease in only 8% of patients, whereas 46% had a severe course of infection. Similarly, Pereira et al[2] and Fernandez-Ruiz et al[3] reported high mortality rates among LT recipients, regardless of the need for hospitalization, suggesting a high risk of death in this group of patients. However, according to Webb et al,[6] LT was not

associated with an increased risk of death among the recipients infected with SARS-CoV-2. They reported hospitalization and mortality rates of 82% and 19%, respectively. Our results were also corroborated by the initial report on the clinical course of COVID-19 from Italy, which showed mild disease with a mortality rate of only 3% in long-term LT survivors.

The Mount Sinai group studied by Lee et al[7] showed an overall reduction of immunosuppression of 79%, with a 100% reduction of mycophenolate mofetil in hospitalized patients with SARS--CoV-2; Webb et al[6] found no impact of the time from LT to COVID-19 diagnosis and the type of immunosuppressant on the outcome. Immunosuppression might attenuate the initial inflammatory response, increasing cell injury caused by the virus and promoting bacterial or fungal superinfection; however, the protective role of a weaker immune response in determining a milder disease presentation in immunosuppressed LT recipients has also been hypothesized.[8-10] The early phase of COVID-19 is associated with viral clearance that occurs as a result of the immune response, whereas in the second phase, a deregulation of $CD4^+$ T cells and activation of $CD8^+$ T cells and macrophages may occur, accompanied by a cytokine storm in the most severe forms of the disease.[11]

In the study by Colmenero et al,[4] calcineurin inhibitors were not associated with worse COVID-19 outcomes, but mycophenolate mofetil therapy, with a cytostatic potential on activated lymphocytes, was an independent predictor of a severe course of infection in a dose-dependent manner. COVID-19 has a direct cytotoxic effect on $CD8^+$ lymphocytes, exerting a synergic and deleterious effect on depleting peripheral lymphocytes with further aberrant immune reconstitution. Thus, the fact that the vast majority of our cohort had mild COVID-19 might be linked with routinely used lower dosages of mycophenolate mofetil (usually 500–1000 mg vs 2000 mg in the Spanish cohort[5]). The immunosuppressive regimen was not withdrawn in any of our patients; in 11.9% of LT recipients, immunosuppression was reduced, with mycophenolate mofetil temporarily discontinued. This finding, together with the government advice regarding social distancing, disinfection, and mask wearing might be the explanation for good outcomes in our group of patients after LT infected with SARS-CoV-2.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

HOW TO CITE Raszeja-Wyszomirska J, Wójcicki M, Milkiewicz P. Outcomes of COVID-19 in patients after liver transplantation: a single-center experience. Pol Arch Intern Med. 2021; 131: 16090. doi:10.20452/pamw.16090

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