

The Psychosocial Burden on Liver Transplant Recipients during the COVID-19 Pandemic

Sabine Weber^a Stephanie Rek^{b,c} Daniela Eser-Valeri^b Frank Padberg^b
Florian P. Reiter^{a,d} Enrico De Toni^a Simon Hohenester^a Sebastian Zimny^a
Markus Rehm^e Markus Otto Guba^f Alexander L. Gerbes^a Gerald Denk^{a,g}

^aDepartment of Medicine II, LMU Klinikum, Munich, Germany; ^bDepartment of Psychiatry and Psychotherapy, LMU Klinikum, Munich, Germany; ^cInternational Max Planck Research School for Translational Psychiatry (IMPRS-TP), Munich, Germany; ^dDivision of Hepatology, Department of Medicine II, University Hospital Würzburg, Würzburg, Germany; ^eDepartment of Anesthesiology, LMU Klinikum, Munich, Germany; ^fDepartment of General, Visceral, Transplantation, Vascular, and Thoracic Surgery, LMU Klinikum, Munich, Germany; ^gTransplant Center, LMU Klinikum, Munich, Germany

Keywords

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Abstract

Introduction: Due to the coronavirus disease 19 (COVID-19) pandemic, multiple measures have been implemented including social distancing and curfews. Both the disease and measures might cause stress, particularly in persons at risk, such as liver transplant (LT) recipients. Here, we evaluated the impact on psychosocial well-being of LT recipients. **Methods:** Seventy-nine LT recipients and 83 nontransplanted controls participated in this study. Questionnaires comprising the WHO-five well-being index (WHO-5), the University of California at Los Angeles (UCLA) Loneliness Scale, and the preliminary COVID-19 Pandemic Mental Health Questionnaire (CoPaQ) were distributed among them. For the WHO-5 and UCLA Loneliness Scale, means of sum scores were compared between both groups, while a comparison on item level was conducted for the CoPaQ. **Results:** The general well-being was similar in LT recipients and controls (WHO-5: $64.0 \pm 20.5\%$ vs. $66.4 \pm 17.3\%$), while the UCLA Loneliness Scale indicated a higher level of perceived social isolation (1.90 ± 0.51 vs. 1.65 ± 0.53 , $p = 0.001$). The CoPaQ indi-

cated higher risk perception regarding health issues, in particular concerning the fear of having severe consequences in case of a COVID-19 infection (3.1 ± 1.1 vs. 2.2 ± 1.3 , $p < 0.001$), higher risk-avoiding behavior and stronger adherence to pandemic measures in LT recipients. **Conclusion:** During the COVID-19 pandemic, LT recipients displayed a higher risk perception, a more pronounced risk-avoiding behavior and a higher perception of loneliness, while the overall well-being was comparable to nontransplanted controls.

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Introduction

In order to minimize the simultaneous infection with Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) of large proportions of the population, many countries have implemented strict preventive strategies [1]. It can be hypothesized that people at risk or at least perceiving themselves more at risk might show stronger adherence to pandemic measures and that this behavior could also lead to increased social isolation. However, the psychosocial burden of the pandemic-related measures on liver transplant (LT) recipients has not been evaluated so far.

We therefore analyzed the psychosocial well-being of LT recipients in comparison to nontransplanted controls. To this end, questionnaires from 79 randomly selected patients who had received orthotopic liver transplantation in our transplant center at the Ludwig Maximilian University (LMU) Klinikum, Munich, and from 83 nontransplanted controls were evaluated. The questionnaires included the WHO-five well-being index (WHO-5) [2] and the University of California at Los Angeles (UCLA) Loneliness Scale [3], both of which have been validated in German [4, 5]. In addition, the COVID-19 Pandemic Mental Health Questionnaire (CoPaQ), which has recently been developed to measure personal and social consequences of the COVID-19 pandemic [6], was distributed among the LT recipients and controls.

Materials and Methods

Study Design and Patient Selection

We performed a cross-sectional study to evaluate the psychosocial burden in LT recipients that are currently receiving medical care after liver transplantation at the LMU Klinikum, Munich. For this purpose, we utilized a questionnaire encompassing the WHO-5, UCLA Loneliness Scale, and the CoPaQ. Inclusion criteria for the LT recipients were age of 18 years or older and at least 1 liver transplantation at our center at the LMU, Munich, between January 1, 2007 and April 30, 2020. Inclusion criteria for the nontransplanted controls were age of 18 years or older. Exclusion criteria for both groups were inability to give informed consent or to read and write in German on a negotiable level. Written informed consent was obtained from each LT recipient and controls. The study protocol conforms to the ethical guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of the Faculty of Medicine, LMU, Munich (Project Number 20-564). Results were blinded; it was therefore not possible to conclude from the questionnaire to which the patient or control had responded. Thus, all the results presented in this study are self-reported, due to ethical reasons more in-depth information on the health status of the participants could therefore not be analyzed.

Measures

WHO-Five Well-Being Index

The WHO-5 is a validated questionnaire that is used as a screening method for psychosocial well-being [7–9]. A complete case analysis was conducted, eliminating 1 subject from each group from this analysis due to missing answers on at least one of the items. The answers were summed up and then means were compared between LT recipients and controls. The raw values range from 0 to 25, with 0 indicating the lowest and 25 the highest well-being/quality of life. Multiplication by 4 gives the 0–100% score that is analog to the Short Form 36 Questionnaire [2].

UCLA Loneliness Scale

The UCLA Loneliness Scale is a 20-item scale measuring subjective feelings of loneliness and social isolation. Each item is rated by the subjects on a scale from 1 (not at all) to 5 (absolutely) [10]. We utilized the revised version that uses reverse scoring for 10 of the 20 items [11]. A complete case analysis was conducted, eliminating 16 subjects (11 LT recipients and 5 nontransplanted controls) from this specific analysis due to missing answers on at

least one of the items. The points the respondents gave to the individual statements were summed up, divided by the number of items, that is, 20, and then means were compared between LT recipients and controls. The overall score ranges from 1 (lowest level of subjective loneliness) to 5 (highest level of subjective loneliness).

COVID-19 Pandemic Mental Health Questionnaire

Additionally, we used the CoPaQ [6] to compare the effects of the COVID-19 pandemic and the pandemic-related measures between LT recipients and nontransplanted controls. Some of the items measuring post-traumatic stress disorder were used from the International Trauma Questionnaire [12]. Respondents rated the single questions according to a 5-point scale in relation to the past 2 weeks with 0 meaning “not at all” and 4 meaning “very much.” Since this questionnaire has not been validated yet and scaling systems are unknown as of yet, it was utilized in its preliminary version and statistical analysis was performed for each item individually. This type of analysis allowed us to evaluate all subjects including those who gave missing answers to one or more questions of the CoPaQ and also those with incomplete answers to the UCLA or WHO-5 questionnaires.

Case Number Estimation and Recruitment

A total sample size of 150 LT recipients and controls were estimated in order to achieve a medium effect for independent sample tests with a power of 90%. From all patients of the database who had received liver transplantation between January 2007 and April 2020, those who had died were excluded, leaving $n = 434$ LT recipients. Out of those, $n = 218$ were randomly selected; $n = 7$ patients were excluded due to an age below 18 years, an inadequate level of knowledge of German or unknown place of residency. Thus, $n = 211$ LT recipients were addressed (see online suppl. Fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000517158), either during routine outpatient controls in our transplant center or via mail. Seventy-nine LT recipients responded (37%). Regarding the controls, a total number of $n = 128$ were approached through personal contact or recruitment on social media platforms. Questionnaires were distributed via mail and $n = 82$ responded (response rate 64%). The recruitment period lasted from August 14, 2020 until October 28, 2020.

Statistical Methods

Continuous variables are presented as means \pm standard deviation. Categorical variables are presented as number of subjects (n) and percentage. For WHO-5 and UCLA Loneliness Scale, a reliability analysis was performed with Cronbach's α and minimal criteria (Cronbach's $\alpha > 0.7$) for internal consistency was reached for both questionnaires. Since no dimensions for the CoPaQ have been predefined, an individual comparison of each item was conducted. After testing for normal distribution, χ^2 test and Mann-Whitney U test were applied. $p \leq 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS (version 26; IBM, Armonk, NY, USA).

Results

Baseline Characteristics

The basic characteristics reported by the LT recipients and controls are summarized in Table 1. Mean age and gender distribution were comparable between both

Table 1. Baseline characteristics reported by liver transplant recipients and nontransplanted controls

	Liver transplant recipients (<i>n</i> = 79)	Controls (<i>n</i> = 83)	<i>p</i> value
Age, years [†]	58.2 (±11.1)	52.0 (±19.1)	0.05
Gender, <i>n</i> (%)			
Female	27 (34.2)	40 (48.2)	0.08
Male	51 (64.6)	42 (50.6)	
Risk factors for severe COVID-19 infection, <i>n</i> (%)			
Age >60 years	37 (46.8)	35 (42.2)	0.34
Cardiovascular disease	11 (13.9)	19 (22.9)	0.23
Diabetes	16 (20.3)	6 (7.2)	0.02*
Immunodeficiency, or taking medication that suppresses the immune system (e.g., cortisone)	70 (88.6)	4 (4.8)	<0.001*
Chronic disease of the respiratory system (e.g., asthma, chronic bronchitis)	4 (5.1)	11 (13.3)	0.11
Chronic liver disease	20 (25.3)	1 (1.2)	<0.001*
Chronic kidney disease	17 (21.5)	2 (2.4)	<0.001*
Acute cancer	1 (1.3)	2 (2.4)	>0.99
Cancer during past 5 years	16 (20.3)	8 (9.6)	0.046*
Long-standing heavy cigarette consumption (>20 cigarettes per day in the last 5–10 years)	4 (5.1)	7 (8.4)	0.54
None of the above risk factors	10 (12.7)	35 (42.2)	<0.001*

Continuous variables are presented as means±SD, categorical variable as % (*n*). COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; SD, standard deviation. [†]Four controls did not give any information on age. *Indicates a statistically significant difference (*p* < 0.05).

groups. Significantly more LT recipients indicated that they suffered from diabetes (20.3 vs. 7.2%, *p* = 0.02), chronic kidney disease (21.5 vs. 2.4%, *p* < 0.001), and cancer during the past 5 years (20.3 vs. 9.6%, *p* = 0.046). As expected, the proportions of subjects stating that they were immunodeficient and/or taking immunosuppressants were higher in LT recipients than controls (88.6 vs. 4.8%, *p* < 0.001). The same applied for chronic liver diseases, 25.3% of LT recipients versus 1.2% of nontransplanted controls indicating that they had an underlying liver disease (*p* < 0.001). The details concerning sociodemographic data are summarized in online suppl. Table 1. There were no significant differences regarding reported acute or former SARS-CoV-2 infection rates or COVID-19-related symptoms of the subjects themselves or someone close to them (online suppl. Table 2).

Regarding reporting of previous psychiatric disorders, significantly more LT recipients indicated that they have been diagnosed by a doctor or therapist with substance abuse or addiction disorder (15.2 vs. 0%, *p* < 0.001; online suppl. Table 3). No significant differences were observed for other psychiatric disorders between LT recipients and nontransplanted controls.

WHO-Five Well-Being Index

The WHO-5 did not show a significant difference regarding the overall well-being: The mean score was 64.0 ± 20.5% for LT recipients and 66.4 ± 17.3% for controls (*p* = 0.58). Both groups therefore showed an overall well-being score above 50%, which is the cutoff for tendency toward depression recommended by the WHO [2]. In to-

tal, 27 participants (16.9%) had a score below 50%, with no significant difference between LT recipients and controls (*n* = 14/78, 17.9% vs. *n* = 13/82, 15.9%, *p* = 0.72).

UCLA Loneliness Scale

The UCLA Loneliness Scale revealed that a higher subjective perception of loneliness was reported by LT recipients than controls (1.90 ± 0.51 vs. 1.65 ± 0.53, *p* = 0.001). If the responses were compared on an item level, LT recipients indicated more often than that when they were alone too much and that they were lacking a group of friends. LT recipients did not consider themselves as outgoing as controls. However, LT recipients also indicated that they had people they could talk or turn to (online suppl. Table 4).

CoPaQ – Risk Perception

LT recipients were more worried about being infected with COVID-19 and about being affected by the COVID-19 pandemic personally (Table 2). In particular, they indicated that they were significantly more worried about having severe consequences for their own health in case of infection (3.1 ± 1.1 vs. 2.2 ± 1.3, *p* < 0.001) or about dying of COVID-19 (2.2 ± 1.3 vs. 1.4 ± 1.3, *p* < 0.001). Controls on the other hand were more worried that they could infect others.

CoPaQ – Adherence to Pandemic Measures and Perception of the Usefulness of the Implementation of Those Measures

LT recipients showed a significantly higher adherence to pandemic measures overall (3.2 ± 0.8 vs. 2.8 ± 0.9, *p* <

Table 2. Perception of risk and adherence to pandemic measures reported by LT recipients and controls regarding the COVID-19 pandemic

	LT recipients (n = 79)	Controls (n = 83)	p value
“I am worried that ...”			
I have no means of control over the COVID-19 pandemic	1.7±1.4	1.7±1.2	0.91
I will infect myself with COVID-19	2.2±1.2	1.8±1.0	0.02*
Please indicate how likely you think it is that you will be infected with COVID-19	1.8±0.9	1.9±1.0	0.59
People close to me are infected with COVID-19	2.0±1.1	2.2±1.0	0.35
I will infect other people with COVID-19	1.5±1.2	1.9±1.2	0.02*
The consequences of the COVID-19 pandemic will greatly affect me personally	2.3±1.3	1.8±1.2	0.01*
In case of infection with COVID-19, the consequences for my health will be severe	3.1±1.1	2.2±1.3	<0.001*
I will die of COVID-19	2.2±1.3	1.4±1.3	<0.001*
People close to me will die of COVID-19	2.2±1.3	2.3±1.2	0.63
Adherence to the pandemic measures†	3.2±0.8	2.8±0.9	<0.001*
Hygiene measure	3.7±0.6	3.5±0.8	0.02*
Reduction of social contacts	3.1±1.0	2.6±1.1	0.001*
Curfew	2.9±1.2	2.2±1.4	0.004*

Demonstrated are means (±SD). Respondents could rate their answers according to a 5-point scale with 0 meaning “not at all” and 4 meaning “very much.” COVID-19, coronavirus disease 2019; LT, liver transplant. *Indicates a statistically significant difference ($p < 0.05$). †Respondents answered to questions starting with “To what extent have you adhered to the following COVID-19, pandemic measures over the past 2 weeks?” and demonstrated are the answers to the composite item “adherence to pandemic measures” and to the individual items, respectively. Cronbach’s $\alpha > 0.7$ indicated an adequate internal consistency overall items.

Table 3. Behavioral changes and negative sensations caused by the COVID-19 pandemic reported by LT recipients and nontransplanted controls

	LT recipients (n = 79)	Controls (n = 83)	p value
“Because of the COVID-19 pandemic, over the past 14 days I have ...”			
Avoided internal reminders of the experience of the COVID-19 pandemic (e.g., thoughts, feeling, or physical sensations)	0.5±0.9	0.2±0.5	0.02*
Avoided external reminders of the experience of the COVID-19 pandemic (e.g., people, places, conversations, objects, activities, or situations)	0.6±1.1	0.3±0.7	0.03*
Been “super-alert,” watchful, or on guard	1.5±1.3	1.1±1.2	0.03*
Suffered from sleep problems, such as early morning awakening	0.7±1.2	0.4±0.8	0.044*
“Over the past 14 days I ...”			
Have consumed substantially more alcohol than usual	0.04±0.2	0.4±0.9	<0.001*
Have not been able to control my use of addictive substances (alcohol, cigarettes, and drugs)	0.0±0.0	0.1±0.4	0.049*
Have had the excessive urge to wash and/or disinfect my hands again and again so that I do not become ill from germs or contamination	0.9±1.2	0.6±1.0	0.04*
Have visited my GP more often	0.2±0.7	0.02±0.2	0.01*
Have avoided visits to my GP	0.8±1.3	0.3±0.9	0.001*
Have increased social distancing	1.6±1.4	0.9±1.2	0.002*
Have reduced any contact with fellow human beings	1.7±1.2	1.2±1.1	0.003*

Demonstrated are means (±SD) of the reported behavioral changes by LT recipients and controls. Respondents could rate their answers according to a 5-point scale with 0 meaning “not at all” and 4 meaning “very much.” COVID-19, Coronavirus disease 2019; LT, liver transplant; GP, general practitioner; SD, standard deviation. *Indicates a statistically significant difference ($p < 0.05$).

0.001) as well as to the subitems hygiene measures, reduction of social contacts, and curfew (Table 2). When asked about the usefulness of pandemic measures, there was no difference between LT recipients and controls (online suppl. Table 5): both LT recipients and controls perceived hygiene measures (3.7 ± 0.4 and 3.6 ± 0.5 , $p > 0.05$) and solitary-based behavior (3.0 ± 0.9 and 3.2 ± 0.7 , $p > 0.05$) as highly useful.

CoPaQ – Behavioral Changes and Negative Sensations Caused by the COVID-19 Pandemic

LT recipients were more likely to avoid internal and external reminders of the experience of the COVID-19 pandemic, to be more watchful and to suffer from early morning awakening (Table 3). Regarding other negative sensations or sleeping disorders, no significant difference was observed between LT recipients and controls (online suppl. Table 6).

Table 4. Stress factors and insecurities during the COVID-19 pandemic reported by LT recipients and nontransplanted controls

	LT recipients (n = 79)	Controls (n = 83)	p value
“Because of the COVID-19 pandemic, over the past 14 days I have felt stressed or burdened a lot by ...”			
Worries about my health	1.6±1.4	0.8±1.1	<0.001*
Worries of not being able to get medical care	1.0±1.3	0.4±0.8	<0.001*
Financial worries	0.7±1.2	0.2±0.6	0.004*
Concerns for my own personal safety	1.4±1.4	0.7±1.0	0.001*
“Over the past 14 days, I have been able to distance myself well from stress/burden due to ...”			
Worries of not being able to get medical care	2.1±1.5	2.8±1.6	0.003*
Childcare	1.5±1.8	2.5±1.7	0.02*
Uncertainties regarding my job, training place, studies, or school	1.5±1.7	2.5±1.8	0.01*
“Over the past 14 days I ...”			
Have tried to avoid COVID-19 news and notifications as far as possible	1.2±1.3	0.7±1.1	0.01*
Have had the feeling that the political leadership was standing up for me	2.0±1.3	2.6±1.2	0.01*
Have perceived democracy as an effective form of government	2.8±1.2	3.2±1.1	0.01*
Have had the feeling that public institutions (e.g., police and judiciary) can be relied upon	2.5±1.1	3.0±0.9	0.002*
Have had the feeling that news and reports on the COVID-19 pandemic are being deliberately withheld	1.4±1.3	0.7±1.0	<0.001*
Have had the feeling that false reports or untruths about the COVID-19 pandemic are being deliberately disseminated on public broadcasting (e.g., radio and television stations)	0.7±1.0	0.3±0.8	0.01*
Have had the belief that what is happening here is the effect of a struggle or competition between different superpowers	0.7±1.3	0.2±0.6	0.02*
Have had the belief that this infection serves to deliberately reduce the world population, since there are no longer enough resources for everyone	0.5±1.0	0.2±0.6	0.03*

Demonstrated are means (\pm SD) of the stress factors and insecurities reported by LT recipients and controls. Respondents could rate their answers according to a 5-point scale with 0 meaning “not at all” and 4 meaning “very much.” COVID-19, coronavirus disease 2019; LT, liver transplant; SD, standard deviation. *Indicates a statistically significant difference ($p < 0.05$).

Controls indicated to a higher extend that they consumed more alcohol than usual or that they were not able to control the use of addictive substances (Table 3). However, means were below 1 on a 5-point scale from 0 to 5 indicating a general low level of substance abuse. Furthermore, no significant differences were observed regarding nicotine or other drug abuse (online suppl. Table 7). LT recipients were more likely to have an excessive urge for handwashing, to visit their general practitioner more often or to avoid visits to the general practitioner (Table 3). Yet, also regarding those items means were below 1 for both groups.

Regarding social interactions and daily routines, LT recipients indicated that they were more likely to increase social distancing (1.6 ± 1.4 vs. 0.9 ± 1.2 , $p = 0.002$) and to reduce any contact with fellow human beings (1.7 ± 1.2 vs. 1.2 ± 1.1 , $p = 0.003$; Table 3). However, LT recipients maintained social contacts, for example, via telephone or video chats similar to the controls (online suppl. Table 8). Other than that, there was no difference in the daily routine of LT recipients when compared to controls. Increases in verbal and/or physical conflicts were overall rare with no relevant difference between LT recipients and controls (online suppl. Table 8).

CoPaQ – Stress Factors and Insecurities during the COVID-19 Pandemic

Regarding pandemic-related stress, differences between LT recipients and controls were mainly observed

for health-related questions (Table 4). LT recipients were more worried about their health (1.6 ± 1.4 vs. 0.8 ± 1.1 , $p < 0.001$), about not being able to get medical care (1.0 ± 1.3 vs. 0.4 ± 0.8 , $p < 0.001$), and about their personal safety (1.4 ± 1.4 vs. 0.7 ± 1.0 , $p = 0.004$). In addition, LT recipients reported higher financial concerns. No significant differences were observed for other factors that could cause stress (online suppl. Table 9).

Subjects from both groups were likely to distance themselves from worries about their own health and personal safety in a similar manner ($p > 0.05$; online suppl. Table 10). However, LT recipients could distance themselves less from worries about not being able to receive medical care when needed (2.1 ± 1.5 vs. 2.8 ± 1.6 , $p = 0.003$), about childcare and job insecurities (Table 4).

CoPaQ – Media Consumption and Trust in Political Institutions during the COVID-19 Pandemic

LT recipients indicated to a greater extend that they tried to avoid news and notifications about COVID-19 (1.2 ± 1.3 vs. 0.7 ± 1.1 , $p = 0.01$; Table 4), while there was no difference in the number of hours of media consumption regarding COVID-19, the burden caused by the media images, or the ability to distance oneself from COVID-19-related news (online suppl. Table 11).

Furthermore, LT recipients indicated a lower level of trust in political institutions. They were less likely to feel that the political leadership was standing up for them (2.0 ± 1.3 vs. 2.6 ± 1.2 , $p = 0.01$) to perceive de-

mocracy as an effective form of government (2.8 ± 1.2 vs. 3.2 ± 1.1 , $p = 0.01$) or to feel that the public institutions could be relied upon (2.5 ± 1.1 vs. 3.0 ± 0.9 , $p = 0.002$; Table 4). LT recipients were also more likely to have the feeling that the news on the COVID-19 pandemic were deliberately being withheld (1.4 ± 1.3 vs. 0.7 ± 1.0 , $p < 0.001$) or that false reports or untruths about the COVID-19 pandemic were being disseminated (0.7 ± 1.0 vs. 0.3 ± 0.8 , $p = 0.01$; Table 4). In addition, there were differences observed regarding conspiracy theories behind the COVID-19 pandemic. However, the mean scores regarding those statements were generally low (Table 4; online suppl. Table 12). Further, no differences were observed regarding the perception of social cohesion (online suppl. Table 13).

Discussion/Conclusion

The COVID-19 pandemic has caused high disturbances of health-care systems, which led to political measures aiming to shelter patients at risk. Here we analyzed the psychological impact of the COVID-19 pandemic and those pandemic-related measures on LT recipients in comparison to nontransplanted controls by applying the standardized questionnaires WHO-5 and UCLA Loneliness Scale, as well as the recently developed CoPaQ.

Regarding baseline characteristics, we observed significantly higher rates of reported chronic kidney disease and diabetes mellitus in LT recipients, which can be explained by the side effects of immunosuppression [13–15]. As expected, LT recipients reported more often to be under immunosuppression and to suffer from chronic liver disease. Interestingly; however, 6 LT recipients (8%) stated that they were not under immunosuppression, although the question explicitly included “taking medication that suppresses the immune system.” It remains unclear whether those patients indeed did not take their immunosuppression or whether this answer indicates that immunosuppressants were not perceived as such. Furthermore, 66% of LT recipients stated that they did not suffer from chronic liver disease. This probably reflects the adaption toward their chronic disease and indicates that these organ recipients perceive themselves as cured. Cancer in the past 5 years was reported more often by LT recipients (20.3 vs. 9.6%), most likely owing to the fact that the majority of those patients underwent transplantation for hepatocellular carcinoma. Regarding underlying psychiatric disorders, a significantly higher proportion of LT recipients stated that they had been formerly diagnosed with substance abuse, which most likely reflects the rate of patients with former alcoholic liver disease as the cause for liver cirrhosis and consequently liver

transplantation. Conversely, the proportion of underlying alcoholic liver disease in around 16% of all LT recipients is within the range of the expected [16].

Interestingly, no significant differences regarding psychosocial well-being were observed between LT recipients and controls. Both groups showed a comparable level of well-being with similar rates of participants being at risk for mental vulnerability. This finding might indicate that the COVID-19 pandemic and pandemic-related measures do not have a higher impact on the psychosocial well-being of LT recipients compared to nontransplanted controls.

By applying the UCLA Loneliness Scale, a higher level of subjectively perceived loneliness and social isolation were observed in LT recipients. However, it needs to be noted that LT recipients were more likely to not feel part of a group of friends, to feel like they do not have much in common with people around them, and to feel like their ideas and interests are not shared by people surrounding them. Those feelings could be due to their situation independently from the pandemic, since in the majority of cases they have suffered from chronic liver disease for years before transplantation and with the liver transplantation have undergone a drastic change in their lives. It is therefore unclear if those feelings were triggered by the COVID-19 pandemic or by the chronic disease and liver transplantation itself. Conversely, LT recipients did not indicate that they felt more alone or that they had less people to turn to.

The CoPaQ revealed that LT recipients and controls perceived the implemented pandemic-related measures as similarly useful. However, a trend toward a more risk-avoiding behavior in LT recipients was observed. They were more likely to adhere to pandemic-related measures, such as hygiene, social distancing, and curfew. It can be speculated that LT recipients showed higher adherence to the measures due to a higher risk perception. In line with this, LT recipients were more worried about getting infected with SARS-CoV-2 or having a more severe course of disease.

LT recipients were also more likely to suffer from negative sensations caused by the pandemic and pandemic-related stress when compared to controls, in particular regarding worries about their own health and about not being able to seek medical help when needed. On the other hand, no difference was observed for items such as worries about being in quarantine, curfews, and uncertainties neither about the professional situation nor about being infected with COVID-19 when possible COVID-19-related symptoms occur. Regarding the maintenance of daily routines or social contacts via telephone or video calls, we did not observe a difference either. LT recipients found it harder to distance themselves from worries about receiving the medical help when needed, childcare, and

their job positions. Yet, no difference was reported regarding the ability to distance themselves from worries about their own health and safety.

Our results are mostly in line with observations made for other diseases, for which immunosuppression is used, for example, inflammatory bowel disease (IBD). As demonstrated by a Portuguese study that relied on self-reporting of a total of 124 IBD patients, for instance, increased anxiety was observed in IBD patients [17]. Moreover, in line with our results, levels of depressive symptoms were mostly within the range of the expected in that study [17]. Similarly, high levels of concern regarding their own health were reported by 2 studies conducted in IBD patients in Australia, in particular driven by the fear of being infected with COVID-19 [18, 19]. In contrast to our findings, 1 study observed higher rates of depression in comparison to the rates reported for the general population [19]. However, no comparison to non-IBD patients was made in neither of those studies, which limits the comparability with our findings.

This study has limitations. For instance, a selection bias needs to be considered, since subjects who are more active and socially open might have participated in higher numbers in the study. It can also be speculated that persons with psychological problems are more reluctant to participate in a study on mental issues. Another limitation is the relatively low response rate of LT recipients of only 37%, possibly due to the postal invitation. In addition, nontransplanted controls were contacted via personal enquiry or through social media platforms and only received the questionnaires after they had indicated interest in being recruited for the study. This could explain the differences in response rates between LT recipients and controls. Furthermore, the CoPaQ has not been independently validated yet and therefore results are preliminary. Being an exploratory study, the results will require replication in larger cohorts. Since no pre-defined scoring system has been established for the CoPaQ so far, individual item testing was applied, which could lead to a multiple-testing bias and an overestimation of statistically relevant differences. The latter might also apply for the comparison of responses to the UCLA on the item level. In addition, this study was only cross-sectional, and longitudinal data were not available since the baseline psychological well-being has not been evaluated neither for LT recipients nor controls. Finally, the results were only obtained through self-reporting. Since the questionnaires were blinded and pseudonymized, clinical data, in particular regarding the etiology of liver disease, time from transplantation, or medically recorded comorbidities were not available for analysis.

Nevertheless, to the best of our knowledge, we here present the first prospective study on the psychosocial burden on LT recipients during the COVID-19 pan-

dem. In conclusion, we observed a more risk-avoiding behavior and a higher risk perception concerning own health and safety in LT recipient. There was also a trend toward a higher perception of loneliness, which might be due to the transplantation and the consecutive changes in life rather than the pandemic itself. The general well-being, however, was not significantly different when compared to nontransplanted controls. These findings have high implications, since they could also apply to patients with immunosuppressive therapy due to other reasons, which should be evaluated in further studies.

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Statement of Ethics

The study protocol conforms to the ethical guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of the Faculty of Medicine, LMU, Munich (Project Number 20-564). Written informed consent was obtained from each participant.

Conflict of Interest Statement

G.D. discloses that he has received honoraria for lectures, teaching, advisory activities, and travel support from AbbVie, Alexion, Falk Foundation, Gilead, GMP Orphan, Intercept, and Novartis. E.D.T. has received honoraria for lectures, teaching, advisory activities, and travel support from AstraZeneca, Bayer, BMS, Eisai, Eli Lilly & Co., Pfizer, IPSEN, Roche, Falk, research funding from Arqule, AstraZeneca, BMS, Bayer, Eli Lilly, and Roche and other reimbursements from Arqule, AstraZeneca, BMS, Bayer, Celsion, and Roche. S.W. declares that she has received travel support from AbbVie and Gilead. The other authors have no conflicts of interest to declare.

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Author Contributions

S.W. and G.D.: participated in research design, in the writing of the paper, in the performance of the research, and in the data analysis. S.R., D.E.-V., and F.P.: participated in research design, the performance of the research, and the data analysis. F.R., E.D.T., S.H., S.Z., M.R., M.O.G., and A.L.G.: participated in research design and in the revision of the manuscript.

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