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Psychosocial situation, adherence, and utilization of video consultation in young adult long-term pediatric liver transplant recipients during COVID-19 pandemic

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Abstract

Background: Young adults who underwent liver transplantation in childhood (YALTs) are highly vulnerable to non-adherent behavior and psychosocial problems. During the COVID-19 pandemic, special efforts may be necessary to maintain contact with these patients and offer support. This can be achieved through the use of telemedicine. The study's objective was to assess adherence and the psychosocial situation of YALTs during the COVID-19 pandemic in Germany and to evaluate the utilization of video consultations.

Methods: In May 2020, a questionnaire was sent to YALTs treated at the Hamburg University Transplant Center, accompanied by the offer of video appointments with the attending physician. The questionnaire included the Generalized Anxiety Disorder Scale 7, the Patient Health Questionnaire 2, and questions compiled by the authors.

Results: Of 98 YALTs, 12% used the video consultation, while 65% had an in-person appointment. The 56 patients who completed the questionnaire did not report reduced medication adherence during the pandemic, but 40% missed follow-up visits with their primary care physician or check-up laboratory tests. About 70% of YALTs were afraid to visit their physician and the transplant center, and 34% were afraid of a SARS-CoV-2 infection. Mental health and well-being were unimpaired.

Conclusions: During the COVID-19 pandemic, YALTs in our study did not show an increased need for psychosocial support, but a majority were afraid to attend medical appointments, and 40% reported lower appointment adherence. Acceptance of video consultations was lower than expected. The reasons for this need to be further investigated in order to optimize care.

KEYWORDS

adherence, adolescents, COVID-19, liver transplantation, psychosocial, video consultation

Abbreviations: GAD7, Generalized Anxiety Disorder Scale 7; LDT, living donor transplantation; LT, liver transplantation; PHQ2, Patient Health Questionnaire 2; YALTs, Young adults who underwent liver transplantation in childhood.

Kröncke and Lund contributed equally to the study.

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1 | INTRODUCTION

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Young adults who underwent liver transplantation in childhood (YALTs) are regarded as a highly vulnerable group of patients, especially after their transition from pediatric to adult care.^{1,2} There is an increased risk of losing these patients from follow-up care, since YALTs have the highest non-adherence rates of all age groups regarding immunosuppressive medication and post-transplant care.³⁻⁶ Due to the far-reaching impact of non-adherence on the clinical outcome of LT recipients, that is, increased risk of rejection episodes, graft loss, and mortality, improving adherence is a major concern.⁷ In addition to medication and appointment non-adherence, attention should also be paid to increased consumption of alcohol, tobacco, or other addictive drugs.⁸ Furthermore, chronically ill patients advancing to adulthood have a high risk of developing psychosocial problems, especially with regard to their social relationships and occupational situation.^{9,10} Accordingly, the prevalence of mental health problems such as anxiety and depression is found to be higher in young adult transplant recipients than in the general adolescent population.¹¹ The COVID-19 pandemic and its impact on patients' lives can be expected to exacerbate the risks mentioned above. In particular, the restrictions and uncertainties patients face can lead to deterioration of mental health.¹² The impact on adherence is unclear. Although beneficial effects on medication adherence are conceivable due to increased time at home and a more regular daily routine during the pandemic, there is more concern of increased non-adherence, for example, due to impaired mental health or less contact with the transplant center. Especially appointment adherence could be a problem during the pandemic. Thus, special efforts may be necessary to maintain contact with these patients to ensure continuity of care and to offer medical and psychological support.

In Germany, the pandemic first led to severe restrictions on daily life in mid-March 2020. Mandatory measures included shutting down public life, minimizing contact with people from other households, physical distancing, and wearing face masks. Schools and universities were required to switch to home schooling, and employers were encouraged to offer home office where possible. The most severe restrictions were gradually lifted starting in mid-May, but some remained throughout the summer. Severity and handling of the pandemic were the main daily topic in the mass media, especially during the first months.

In this situation, telemedicine applications may be particularly helpful.¹³⁻¹⁶ Since previous studies have shown that younger age is associated with a better acceptance of telemedicine,^{14,16} we assumed that YALTs would benefit from video appointments with their physicians to avoid less-frequent follow-ups and non-adherent behavior during the COVID-19 pandemic. Video consultations offer a resource-saving opportunity to establish regular medical care even over long distances but have not been part of routine care in Germany before the COVID-19 pandemic.

Therefore, the objective of this study was to assess YALTs' medication and appointment adherence and their psychosocial situation during the COVID-19 pandemic and to evaluate the preference for and utilization of video consultations.

2 | MATERIALS AND METHODS

2.1 | Patient population and procedure

Young adults who underwent liver transplantation in childhood who were transferred to adult care at the age of 18 are treated in a specialized transition program in the liver transplant outpatient clinic of the Hamburg-Eppendorf University Transplant Center. These patients visit the transplant center at least once a year. Each consultation is usually performed by the same physician, so that patients have a reliable contact person. In May 2020, toward the end of the first wave of the COVID-19 pandemic in Germany, a letter was sent by mail to these patients inviting them to video consultations with their attending physician via a newly established telemedicine tool. An appointment for an in-person visit at the outpatient clinic was offered as an alternative or in addition. Furthermore, patients were asked to complete an attached questionnaire to assess their situation during the COVID-19 pandemic (for detailed information, the questionnaire is provided as supplementary material). As telemedicine tool, the commercially available application CLICKDOC was used, which allows a video contact between the physician and the patient via computer, tablet, or smartphone. In order to get an appointment for a video consultation, patients had to fill out and return multiple forms to comply with the general data protection regulations of the European Union.

The analysis of the data in the context of this study was approved by the local ethics committee (No. WF-005/20).

2.2 | Measures

The patient questionnaire was compiled by the authors (see supplementary material). The following topics were included in the questionnaire: (i) preferences regarding contact with the transplant center, (ii) self-assessment of adherence and health behavior, (iii) sources of information on the subject of COVID-19, and (iv) psychosocial situation. To assess the latter, patients were asked to rate a list of statements about anxiety and psychosocial as well as occupational changes during the pandemic. They also had to rate their mental and somatic well-being. In addition, the Generalized Anxiety Disorder Scale 7 (GAD7)¹⁷ and the Patient Health Questionnaire 2 (PHQ2)¹⁸ were included as screening tools to measure current levels of anxiety and depression. Different response formats were used. Most questions had to be answered on a 4-point Likert scale (yes, very much-not at all) or on a dichotomous scale (yes or no). Mental and somatic well-being were to be rated on a scale from 1 to 10 for the current situation during the COVID-19 pandemic in 2020 and

possible.

retrospectively for the previous year 2019, with 1 representing the worst and 10 the best well-being. It was specified that questions about the COVID-19 pandemic referred to the period since March 16, when severe restrictions were imposed. For some questions, patients were asked to refer to the previous month. Regarding con-

In addition to the self-assessment of the patients' adherence, the attending physicians were asked to categorize the patients' adherence to medication and to appointments into three categories: "non-adherent," "mostly adherent," and "adherent." The assessment was based on the physicians' recollections and/or patient records, and it did not differentiate between the period before and during the COVID-19 pandemic.

tact preferences and sources of information, multiple answers were

2.3 | Statistical analyses

Statements on a 4-point Likert scale were analyzed descriptively by collapsing the response formats "yes, very much" and "rather yes" and "rather not" and "not at all," respectively, into two categories "yes" and "no."

Continuous variables were described as means and standard deviations or median with minimum and maximum. Categorical data are given as absolute and relative frequencies. Fisher's exact test or Chi-square test was performed for comparison of dichotomous or categorical variables, and Mann-Whitney *U* test for ordinal-scaled data. Spearman's rank correlation coefficient (ρ) was calculated to analyze the relationship between ordinal-scaled variables. For two group comparisons of continuous variables, independent samples *t* test and paired samples *t* test were used. Two-sided tests were calculated. The statistical analysis was performed with SPSS version 25.0 (SPSS Inc., Chicago, IL, USA).

3 | RESULTS

3.1 | Patient characteristics

Characteristics of the 98 YALTs who are treated in our adult outpatient transplant clinic after transition from the pediatric clinic are given in Table 1. At the time patients were contacted, their median age was 24 (range: 18–36) years. All patients were long-term LT recipients, who had been transplanted at least 4 years ago (median time since LT: 19 years). Patients came from all over Germany, and 38 patients (39%) lived more than 200 km away from our transplant center.

The questionnaire was filled out by 56 (57%) patients (questionnaire responders, Table 1). To estimate a possible selection bias, we investigated whether questionnaire responders differed systematically from questionnaire non-responders by comparing both groups. The comparison revealed no significant differences, except that questionnaire responders lived closer to the transplant center (t = 2.3, p = .03).

3.2 | Video consultation and contact preferences

Of the 56 patients who completed the questionnaire, 16.1% (n = 9) replied that they wanted to have a video consultation, while 48.2% (n = 27) preferred an in-person appointment. In addition, 35.7% (n = 20) of the patients chose to be contacted via telephone and 12.5% (n = 7) via e-mail.

These preferences stated in the questionnaire are in accordance with the appointments in the outpatient clinic that actually took place during 2020. Overall, 76 (77.6%) of the 98 patients who received a letter had a consultation with their physician at the transplant center in the year 2020, either via in-person contact or via video. A total of 12 (12.2%) patients used the video consultation, 9 of them in addition to in-person visits and 3 patients as the only way of contact. The majority of patients (n = 64) chose solely an in-person appointment (Table 1). A comparison between patients with video consultation versus those with only in-person contact revealed that patients using the telemedicine tool lived significantly further away from the clinic (t = -2.6, p = .01) and more of them had experienced at least one late rejection episode ($X^2 = 5.1$, p = .04).

3.3 | Adherence and health behavior during the COVID-19 pandemic

The attending physicians were able to assess medication and appointment adherence in 83 and 77 of the 98 patients, respectively. In total, 72% were considered as medication adherent and 78% as appointment adherent. Of the questionnaire responders, most were rated as adherent to intake of medications (74%) and keeping appointments (81%), opposed to about 10% being rated as medication and appointment non-adherent (Figure 1A and B). Also, the majority of the patients who did not respond to the questionnaire were rated as medication (69%) and appointment (73%) adherent (Figure 1A and B). Overall, there was no significant difference between the group of patients answering to the questionnaire and those who did not, neither regarding medication (U = 813.0, Z = -4, p = .7) nor appointment (U = 645.5, Z = -.9, p = .4) adherence.

Also, there were no statistically significant differences with regard to adherence between patients who did not present for an appointment in 2020 and those who did (medication adherence: n = 12vs. n = 71, U = 423.5, Z = -.04, p = .97; appointment adherence: n = 7 vs. n = 70, U = 185.5, Z = -1.5, p = .15).

By self-assessment in the questionnaire, 21 of 53 patients (39.6%) stated that they had missed follow-up appointments with their primary care physician or check-up laboratory tests during the COVID-19 pandemic. On the other hand, patients reported good medication adherence during the pandemic, with 88% having missed no dose of their immunosuppressive drugs within the previous month (Figure 2). Regarding individual changes, only 3 (6%) patients had missed more doses of their immunosuppressive drugs within the previous month than usual, while 9 (18%) patients had missed less doses and thus showed better adherence than usual. None of the patients had considered discontinuing their immunosuppressive drugs.

TABLE 1 Patient characteristics

nor median (range or %) Age at time of study 24.0 (18-36) 23.0 (18-36) 25.5 (19-30) 23.5 (18-36) Time since LT (years) 19.0 (4-28) 19.0 (5-28) 17.0 (5-26) 19.0 (6-28) Sex: fenale 45 (45.9%) 26.9 (46.4%) 5 (41.7%) 31 (48.4%) Age at LT (days/years) 2.4 y (12 d-18 y) 10.0 y (73 d-15 y) 2.3 y (12 d-18 y) Primary LT indication University 2 (16.7%) 2 (50.0%) Metabolic liver disease 15 (15.3%) 9 (16.1%) 2 (16.7%) 9 (14.1%) Cholestatic liver disease 12 (12.2%) 7 (12.5%) 1 (8.3%) 6 (9.4%) Autoimmune liver disease 12 (12.2%) 7 (15.5%) 1 (8.3%) 7 (12.8%) Other 9 (9.2%) 5 (8.9%) 3 (25.0%) 5 (7.8%) Other 9 (9.2%) 10 (17.6%) 1 (23.3%) 2 (25.0%) Immunosuppression 11 (12.6%) 1 (23.3%) 2 (5.6%) 3 (20.6%) Immunosuppression 14 (3.0%)		Total sample n = 98	Questionnaire responders n = 56	Video consultation n = 12	Only in-person consultation n = 64
Time since LT (years) 19.0 (4–28) 19.0 (5–28) 17.0 (5–26) 19.0 (6–28) Sex: female 45 (45.9%) 26 (46.4%) 5 (41.7%) 31 (48.4%) Age at LT (days/years) 2.4 y (12 d–18 y) 2.9 y (12 d–18 y) 10.0 y (73 d–15 y) 2.9 y (12 d–18 y) Primary LT indication		<i>n</i> or median (range or %)	<i>n</i> or median (range or %)	<i>n</i> or median (range or %)	n or median (range or %)
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Distance to transplant center146.0 km (3-838 km)102.5 km (3-838 km)226.5 km (23-756 km)101.0 km (3-624 km)Living situation(3-838 km)(23-756 km)(3-624 km)With family/partner35 (62.5%)(3-624 km)With roommates11 (19.6%)11 (19.6%)Alone10 (17.9%)(3-624 km)Occupation27 (48.2%)11 (19.6%)Job training8 (14.3%)5chool/UniversityJob training3 (5.4%)	Dual therapy	36 (36.7%)	23 (41.1%)	3 (25.0%)	25 (39.1%)
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	School/University		7 (12.5%)		
No occupation 11 (19.6%)	Unspecified education		3 (5.4%)		
	No occupation		11 (19.6%)		

Abbreviations: LT, liver transplantation; LDT, living donor transplantation.

There was a moderate correlation between patients' self-reported medication adherence and the physicians' proxy-reported medication adherence (n = 47, $\rho = .29$, p = .04).

Furthermore, no patient reported more alcohol consumption than usual, and only 2 of 54 patients (3.6%) indicated more tobacco consumption.

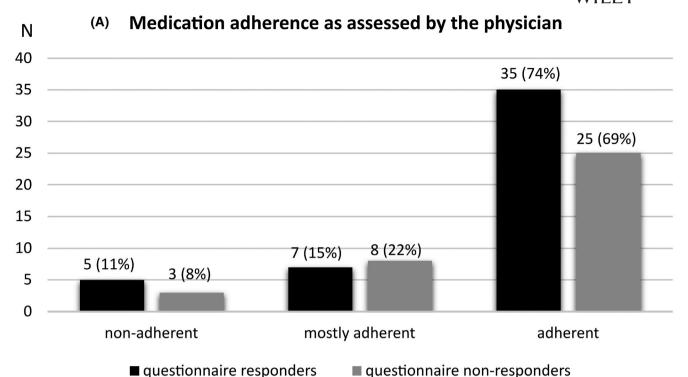
3.4 | Sources of information regarding the COVID-19 pandemic

Of the patients who completed the questionnaire, 63% named the media as a source of information about their risk in the COVID-19

pandemic, while 30% of the patients stated that the transplant center was their source of information (Figure 3).

3.5 | Patients' psychosocial situation during the COVID-19 pandemic

Regarding symptoms of anxiety and depression during the COVID-19 pandemic, questionnaire responders (n = 56) showed a mean GAD7 score of 4.68 (SD = 3.99) and a mean PHQ2 score of 1.20 (SD = 1.39). Symptom scores above critical cutoff values of \geq 10 for the GAD7 and \geq 3 for the PHQ2 were reported by 10.7% (n = 6) and 8.9% (n = 5) of the patients, respectively.



N (B) Appointment adherence as assessed by the physician

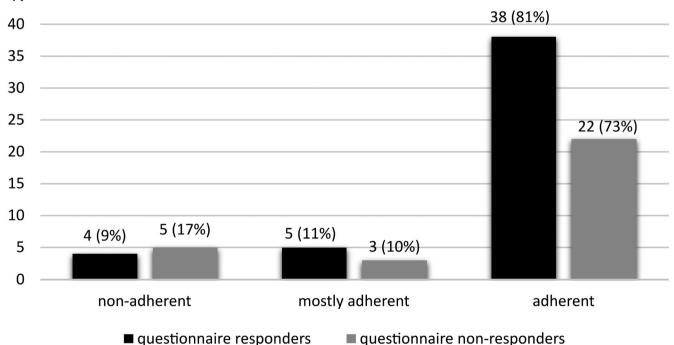


FIGURE 1 (A) Medication adherence as assessed by the physicians of patients who responded to the questionnaire (n = 47) and those who did not (n = 36). (B) Appointment adherence as assessed by the physicians of patients who responded to the questionnaire (n = 47) and those who did not (n = 30)

In addition, patients rated their mental and somatic well-being as quite good (M = 7 on a scale of 1-10). There were no significant changes in either mental (t = .3, p = .8) or somatic (t = 1.9, p = .06) well-being between the time of the pandemic 2020 as compared to 2019 (Figure 4). A minority of patients (12.5%) thought that a COVID-19 disease is likely to be more severe for transplanted as compared to non-transplanted persons, while a third stated to be afraid to get infected with SARS-CoV-2. More than half of the patients were afraid to use public transportation or go shopping, and even more



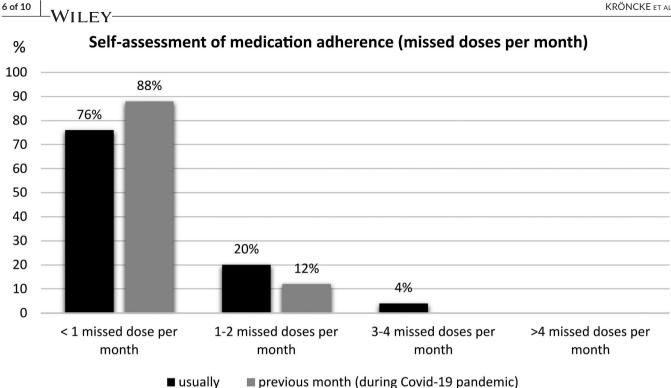


FIGURE 2 Medication adherence according to patients' self-assessments, usually (n = 54) and during the COVID-19 pandemic (previous month, n = 49)

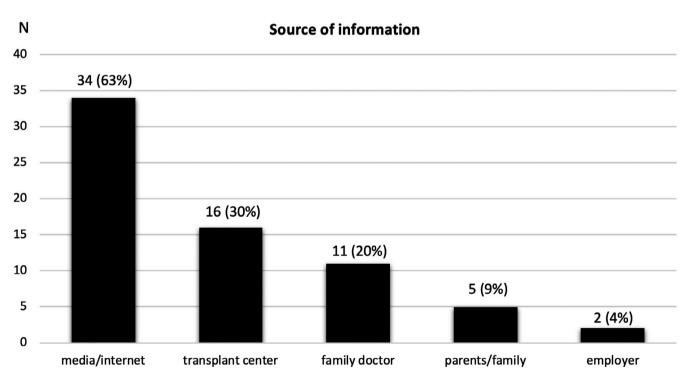


FIGURE 3 Sources of information on personal impact of the COVID-19 pandemic (n = 54, multiple answers possible)

were afraid to visit their transplant center and their primary care physician during the COVID-19 pandemic. A third continued meeting their friends, while almost the same proportion often felt lonely (Table 2).

A fifth of the 45 patients who were employed or in education reported no changes of their occupational situation during the COVID-19 pandemic. Most of the others were on sick leave at least part of the time (27%) or worked in home office (6.7% part of the

Mental and somatic well-being

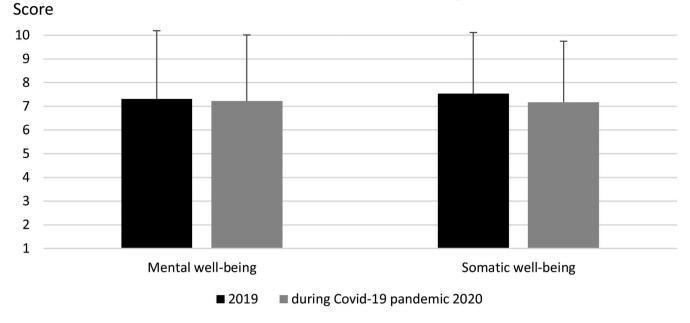


FIGURE 4 Mean and standard deviation of mental and somatic well-being during the COVID-19 pandemic in 2020 (n = 55) compared with the previous year of 2019 (n = 55). 10 = best, 1 = worst

	Ν	%
I believe that for transplant recipients, infection with the coronavirus would be worse than for other people	7	12.5
I am afraid to get infected with the coronavirus	19	33.9
During the corona pandemic, I was afraid to use public transportation or go shopping	30	53.6
During the corona pandemic, I was afraid to go to the transplant center	40	71.4
During the corona pandemic, I was afraid to go to my family doctor	39	69.6
During the corona pandemic, I continued to meet with friends ^a	18	32.7
During the corona pandemic, I often felt lonely ^a	17	30.9
a 		

TABLE 2 Patients' anxiety regarding the COVID-19 pandemic and related psychosocial changes (n = 56)

an = 55.

time, 6.7% most of the time, and 8.8% full-time home office). Other changes were mostly due to closed educational facilities. More than half of the patients stated that their employer was considerate of their situation as a transplant recipient (Table 3).

4 | DISCUSSION

This study is the first to assess YALTs' psychosocial situation and their use of telemedicine during the COVID-19 pandemic.

TABLE 3 Occupational changes during the COVID-19 pandemic (*n* = 45 working/in education)

	Ν	%			
No changes regarding occupational situation	9	20.0			
On sick leave (3-12 weeks)	12	26.6			
Home office	10	22.2			
Other changes	7	15.6			
No answer	7	15.6			
My employer was considerate regarding my situation as a transplant recipient					
Yes	25	55.6			
No	10	22.2			
No answer	10	22.2			

With 12%, less patients than expected accepted the newly established offer of a video appointment with the attending physician. The reasons for the rather low interest in this telemedicine tool are unclear. A previous study from Los Angeles, USA,¹⁹ found an overall high satisfaction rate with telemedicine appointments in a small group of 21 adult LT patients. Video consultation reduced commute and waiting time and did not compromise patient-physician interaction compared to a control group of patients with regular in-person appointments. In our sample, 39% of patients lived in a distance of more than 200 km from the transplant center, but perhaps, distance is not such an obstacle for patients of a younger age. On the other hand, the required, relatively complicated consent process for receiving a telemedicine appointment may have deterred YALTs. Furthermore, it is conceivable that patients preferred a complete WILEY

check-up at the transplant center, including laboratory and diagnostic tests, which are not regularly done by their primary care physician. But it is also possible that the young patients felt insecure and too shy to communicate with a doctor via video, in particular since many had visited the adult clinic only a few times before. Thus, a strong personal patient-doctor relationship may not have been established yet. Results showed that more patients who used video consultations had experienced rejection episodes, and 9 of the 12 patients used video appointments in addition to in-person appointments and not as a substitute. Therefore, video consultations could not fully replace in-person appointments in our study. However, they can be used to reduce in-person contacts, as they provide a viable alternative for patients who require closer follow-up care. Also, it might take some time to achieve a higher acceptance of this new contact option.

It is also remarkable, that more than 60% of the patients used the mass media as their primary source of information regarding their personal situation in the COVID-19 pandemic. Only 30% sought information from the transplant center. This is more than in another German study, in which only 15% of the transplant recipients used the center as their source of information.²⁰ These data, however, show that patients may not be accustomed to communicating with their transplant center via telemedicine tools and receive important information in this way. At our institution, information regarding the COVID-19 pandemic was provided on the center's website, but more frequent updates might be necessary. Also, better accessibility of specialized staff by phone could help to provide reliable information. In the future, an interactive telemedicine application may be helpful, which offers educational units, a platform for exchange between medical staff and patients as well as a patient forum.^{21,22} This may also be useful in maintaining patients' adherence and wellbeing. Hanke et al.,²³ who reported on a telemedicine-based aftercare program for kidney transplant recipients, concluded that this program was effective in maintaining physical activity and quality of life during the first wave of the COVID-19 pandemic. The pandemic highlights the advantages of such telemedicine and eHealth tools and could facilitate their broader implementation.^{24,25}

Regarding their psychosocial situation, YALTs in our study reported no differences in mental and somatic well-being compared with the year before. Anxiety and depression scores above critical cutoff values were found in 11% and 9% of patients, respectively. In a British study¹¹ examining 51 young LT recipients (mean age: 18.1 years) before the COVID-19 pandemic, the percentage of patients with critical depression levels was comparable (10%), while more patients than in our study showed critical anxiety levels (18%). It should be kept in mind that the screening tools used in our and other studies do not provide a clinical diagnosis of anxiety or depressive disorder. However, they are useful for identifying patients with relevant symptom burden. Thus, it appears that the large majority of patients in our study were able to cope with the initial stress caused by the first wave of the pandemic and retain good mental health. Nonetheless, the patients with critical scores were contacted by their attending physician and offered psychological care.

The low anxiety levels in 89% of the patients are in line with the finding that about the same percentage of patients (87.5%) did not consider themselves more susceptible to a severe course of a COVID-19 disease compared with the general population. Still, one third of the YALTs were afraid to get infected with the virus. In another study, conducted at two German transplant centers in April 2020,²⁰ a much higher percentage (65%) of organ transplant recipients with a mean age of 62 years were afraid to become infected with SARS-CoV-2. Also, in a study on German kidney transplant recipients (median age: 57 years), life satisfaction and perceived action competence were significantly lower in April 2020 compared with 6 months previously.²⁶ It is conceivable that the markedly younger age and therefore the lack of known risk factors for a severe COVID-19 disease course explain the lower anxiety levels in our study sample. In addition, the time of the assessment during the COVID-19 pandemic may have an important impact on the results. Here, the guestionnaire was sent out in mid-May, when restrictions were already beginning to be gradually lifted. So far, there are no other studies investigating the psychosocial impact of COVID-19 on YALTs. Therefore, a repeated assessment during the more severe second wave of the pandemic seems advisable.

Even though the vast majority of patients did not exhibit elevated anxiety or depression levels, 49% reported that they took sick leave or worked in home office during the pandemic, 54% stated being afraid to use public transportation, and about 70% were afraid to visit the transplant center as well as their primary care physician. While the first can be interpreted as reasonable protective behavior in the face of the actual dangers of the pandemic, the latter gives cause for concern. Indeed, patients reported that they actually missed follow-up appointments with their primary care physician and check-up laboratory tests during the pandemic. On the other hand, medication adherence was not worse during the pandemic. On the contrary, more patients reported better medication adherence. This might be due to the restrictions requiring them to stay at home more. Therefore, non-adherence due to forgetting the medication during an eventful day or leaving it at home when going out of the house was less likely. Also, there was no relevant increase in alcohol and tobacco use according to patients' self-assessments, which contrasts with a German general population survey that found younger age groups at risk of increased alcohol consumption during the first shutdown.27

There are some limitations of this study. First, the response rate to the questionnaire was only 57%. It is conceivable that patients with better adherence and lower anxiety and depression scores might be more prone to fill out the questionnaire. Furthermore, patients' answers might have been biased by social desirability. However, the physicians' rating of patients' adherence did not differ significantly between patients who filled out the questionnaire and those who did not, and neither did the self-reported adherence and the proxy-reported adherence. Nevertheless, it should be noted that physicians were not able to assess the adherence of all YALTs, since some were not yet well enough known to them. In addition, the results of a rather higher medication adherence suggest possible beneficial changes during the pandemic. Also, fewer infections due to the increased preventive measures might have had a positive impact on patients' well-being. These aspects were not assessed in the study. Neither could a more in-depth analysis of the characteristics of the group using video consultations be conducted, because the small size of this subsample made statistical comparisons difficult. Finally, it should be taken into account that the COVID-19 pandemic in Northern Germany in spring 2020 was less severe compared with the second wave and compared with other countries.

In conclusion, there was generally no increased need for psychosocial support for the YALTs during the first wave of the COVID-19 pandemic. However, this should be reassessed as the pandemic continues. Also, the use of video consultations was lower than expected considering the patients' young age, their long distance from the transplant center, and their fear of visiting the transplant center as well as their local physician. To improve appointment adherence and optimize care, the reasons for this should be further investigated, and efforts to implement telemedicine care should be expedited, since it offers many advantages, not only during a pandemic.

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CONFLICT OF INTEREST

The authors of this manuscript have no conflicts of interest to disclose.

AUTHOR CONTRIBUTION

Sylvia Kröncke contributed to research design, data analysis, and the writing of the paper. Louisa Katharina Lund and Martina Sterneck contributed to research design, performance of the research, data analysis, and the writing of the paper. Angela Buchholz contributed to data analysis and the writing of the paper. Melanie Lang contributed to research design, performance of the research, and the revision of the paper. Andrea Briem-Richter and Enke Freya Grabhorn revised the paper.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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