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Impact of the COVID-19 lockdown on liver transplant recipients. A single center observational study

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Authorship

All authors contributed to and have approved the final manuscript.

All authors had access to the study data and critically reviewed, revised, and approved the final manuscript. All the authors fulfil the four ICMJE authorship criteria (substantial contributions to conception or design of the work, or the acquisition, analysis, or interpretation of data for the work; drafting of the work or revising it).


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The authors declare no conflicts of interest.

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Keywords

Abbreviations
LT, Liver Transplant; GAD, Generalized Anxiety Disorder; COVID-19, CORonaVIrus Disease 2019; CVD, cardiovascular disease; PSWQ, Penn State Worry Questionnaire; BRS, Brief Resilience Scale; ISI, Insomnia Severity Index, LTE, List of Threatening Experiences; PHQ-9, Patient Health Questionnaire 9; IQR, interquartile range; CKD, Chronic Kidney Disease

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ABSTRACT

**Background:** The impact of the COVID-19 outbreak and lockdown on liver transplant (LT) patients remains unknown. The aim of this cross-sectional study was to assess the consequences of the COVID-19 pandemic on the physical and mental health of LT patients during the lockdown period.

**Methods:** Between August and October 2020 a web-based questionnaire was emailed to 238 LT patients undergoing regular follow-up at our unit. This pseudonymized survey explored demographic and lifestyle variables (i.e. eating and physical habits), disruptions in routine medical care, and different dimensions of mental health, COVID-19-related mood and coping (worries/anxiety, depression, insomnia, fear of Covid, resilience, etc.), and health perception using different validated instruments.

**Results:** 48.7% (116 of 238) LT recipients accepted to participate, 104 of whom gave their consent to publish the data. The median age was 63 years. Up to 39.4% presented worrying scores indicating moderate/severe generalized anxiety disorder (GAD), whereas 25.5% exhibited moderate/severe insomnia and only 10.5% moderate/severe depression. Forty patients (38.5%) gained weight, 24% experienced a worsening in their eating habits and 63.4% referred to practice less or much less exercise during the lockdown. Only 25% perceived a worsening in the control of their chronic comorbidities. Missed medical appointments (0.9%) or worsening adherence to therapy (1.9%) were exceptional.

**Conclusions:** COVID-19 lockdown has negatively impacted the mental and physical health of LT patients. Long-term consequences remain unclear.
INTRODUCTION

On January 30, 2020, World Health Organization declared the global 2019 COronaVirus Disease outbreak (COVID-19) a public health emergency.(1) The Spanish Government decreed a lockdown on March 14 as a result of the pandemic that lasted almost two months.(2) As a result, the Spanish population was placed in social isolation with permission to leave the house limited to buying food or medicine. These measures greatly disrupted people's lives and had implications for health and wellbeing in the general population.(3)

Previous studies on subjects who had been quarantined for acute infectious diseases, like SARS or MERS, reported a high prevalence of symptoms of psychological distress.(4, 5) These included anxiety, depression, insomnia, and fear of getting sick or dying. Fear is an adaptive defense mechanism that is fundamental for survival and involves several biological processes of preparation for a response to potentially threatening events. However, when it is disproportionate, as in a pandemic, it becomes harmful. Thus, it has been associated with increasing degrees of anxiety, stress and insomnia in healthy individuals and with more intense symptoms in those with pre-existing psychiatric disorders.(6)

There are indications of increased levels of post-traumatic stress disorder and depression following SARS-CoV-2 infection.(7) Quarantine and the isolation associated with the pandemic are additional risk factors for psychological impact. Other reported consequences of quarantine stress are the onset and continuation of tobacco consumption and alcohol abuse,(8) and a change in lifestyle and eating habits leading to unhealthy diet.(6, 7) All of them carry an increased risk of obesity, diabetes and cardiovascular disease (CVD).

However, little is known about the long-term impact of COVID-19 lockdown on the global health (physical and mental) of liver transplant (LT) patients. The disruption of routine medical care is especially problematic for patients with chronic conditions that require regular follow-up such as LT recipients. They require continuous medical surveillance due to polypharmacy, comorbidities, and the risk of allograft rejection. Therefore, the aim of the present study was to evaluate the impact of COVID-19 lockdown in Spain on the overall health of LT recipients.
MATERIAL AND METHODS

Study Design and Participants

We conducted a web-based cross-sectional pseudonymized survey based on SurveyMonkey™. This study was approved on July 19, 2020 by the Ethics Committee of Cantabria (act 19/2020).

The online survey was developed by members of the LT Unit and Psychiatric Department of the University Hospital Marqués de Valdecilla (Spain). It covered five sections about health habits and physical and mental repercussions during the period of home confinement established by the Spanish authorities from March 15 to May 4, 2020 (Figure 1). The online survey was piloted with the research team prior to being sent to all LT patients undergoing regular follow-up at the LT unit of our hospital. Exclusion criteria were the patient’s refusal to participate, active cancer, an estimated life expectancy of less than one year, severe psychiatric disease, inability to participate due to either technological barriers or impossibility to attend to the outpatient clinic to complete the survey. All participants were requested to sign the informed consent either online or at the hospital. The data were collected electronically between August and October 2020.

Survey sections

The first section included sociodemographic data (Table 1), and medical comorbidities. The second section comprised items related to lifestyle, sources of information about COVID-19 and self-care during the lockdown. Participants were also required to answer different questions about weight gain and eating and exercise habits.

In the third section, participants were invited to fill out different validated questionnaires on reactions and coping strategies to the COVID-19 pandemic, and other general questionnaires to evaluate mental health. The Fear of COVID-19 Scale was used to measure the fear of suffering COVID-19. This scale ranges from 7 to 35 points, the latter indicating a maximum level of fear.(9) Pathological worry was addressed by using the Spanish abbreviated version of the Penn State Worry Questionnaire (PSWQ-11), the gold standard measure of the unspecific worry that
characterizes generalized anxiety disorder (GAD). On this scale, the highest possible score indicating a state of maximal concern is 55 and the cutoff points to identify a moderate and severe GAD are 33 and 38 points, respectively. The ability to recover from stress was evaluated through the Spanish version of the brief resilience scale (BRS-6). The BRS-6 was coded as low (1.00-2.99), normal (3.00-4.30), and high (4.31-5.00). Insomnia severity was evaluated using the Spanish version of the 7-item insomnia severity index (ISI), the cutoffs for moderate and severe insomnia being 15 and 22 points, respectively. To assess recent stressful events we used the Spanish version of the List of Threatening Experiences (LTE), a subset of 12 life event categories with considerable long-term contextual threat (LTE-12). Finally, depression was evaluated through the patient health questionnaire 9 (PHQ-9). The PHQ-9 classed the level of depression severity as minimal (0-4), mild (5-9), moderate (10-14), and severe (≥ 15).

The fourth section was designed to identify self-reported changes in LT treatment and adherence to treatment, and to evaluate the perception of health surveillance during the lockdown. Participants were also asked if they had experienced a SARS-CoV-2 infection. In the fifth section, the patients were asked about their health-related quality of life by EuroQol-5D-3L. A descriptive evaluation of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) was performed. Each dimension has three possible levels scored from 1 (no problems) to 3 (extreme problems); “1” in all the five items was considered full health. In a second part, patients had to complete the EQ-5D visual analogue scale (VAS), a 0-100 scale where they were asked to indicate overall health perception, 0 being the worst and 100 the best imaginable health condition respectively.

**Statistical analyses**

Quantitative variables were expressed as mean (standard deviation) or median (range or interquartile range -IQR-), and qualitative variables as absolute value and proportions. Statistical analysis was performed with IBM SPSS Statistics v22.0 for Mac (IBM Corp, Armonk, NY).
RESULTS

Of 315 LT patients undergoing regular follow-up at our LT unit, 238 were eligible to participate in the study. 116 (48.8%) accepted and completed the survey (Figure 2). Finally, 104 LT participants gave their consent to publish the data. None of the participants reported current or past COVID-19 disease.

Socio-demographic and medical characteristics of the participants.

The median age of the participants was 63 years (range 30-83) with a median time since LT of 99 months (6-320) (Table 1). Overall, 75% of the patients were men, and most were of Spanish nationality (97%). More than half of the participants (53.8%) had basic studies and most participants (86.5%) were confined at home and unemployed. Participant characteristics and comorbidities are shown in Table 1.

Lifestyle, information seeking on COVID-19 and self-care

Most patients (75%) acknowledged living with someone during the confinement and one quarter did not have a garden, terrace or outside access. Most frequent causes for going out during the COVID-19 lockdown were shopping (supermarket, pharmacy) and waste disposal (80%). The majority of patients felt sufficiently informed about the coronavirus pandemic.

The vast majority of patients (90%) reported washing hands and wearing masks more frequently than before the COVID-19 lockdown. Only 7.7% required medical assistance or testing for SARS-CoV-2 infection with no positive cases. Moreover, less than 1% of the patients started or increased their alcohol or tobacco consumption, and none started using other substances such as cannabis, cocaine or other drugs.

Mental health, mood and coping during COVID-19 lockdown

Participants showed intermediate levels of fear on the Fear of COVID-19 Scale (median 18; IQR, 7-28). When COVID-19-related worries were addressed using the Spanish version of the PSWQ-11, the median score was 30 (11-47). According to the PSWQ-11, 60.6% of the patients did not present GAD (95%CI = 50.5-69.9), whereas 18.1% (11.6-27.1) and 21.3% (14.2-30.6) had moderate and severe GAD, respectively (Table
2. Most participants had no insomnia or only subclinical insomnia (74.5%; 64.8-82.2) on the ISI scale. However, up to 23.4% (16.0-32.9) revealed moderate clinical insomnia and 2.1% (0.6-7.4) severe insomnia. Eleven participants (10.5%; 6.0-17.9) reported at least a moderate degree of depression defined as a PHQ9 ≥ 10, whereas only four patients (3.8%; 1.5-9.5) had major depression (PHQ9 ≥ 15). Finally, most participants suffered no additional stressful events (60.6%; 50.9-69.4) in the LTE scale, and showed normal or high levels of resilience (79.6%; 70.3-86.5).

**Physical health, well-being and medical care**
Forty participants (38.5%) experienced weight gain. Twenty-five patients (24%) reported worsening eating habits (eating extra, more often, unhealthily or erratically) and 63.4% practiced less or much less physical activity than before. A minority of patients (1%) referred missing medical consultations because of fear of SARS-CoV-2 infection, and most participants had their face-to-face consultations changed to telephone consultations (75%). Missed medication doses or drug schedule changes were exceptional (1.9%). Moreover, no patient reported problems in collecting their medication during confinement. No patient experienced rejection or other liver-related complications. Twenty-six patients (25%) perceived the control of their chronic medical comorbidities as worse or much worse, while the remaining patients perceived the same control as before lockdown. Participants who perceived a poorer control attributed it to worse eating and exercise habits (42.3%), higher levels of anxiety, fear or stress (37.5%), and/or to greater difficulties in obtaining adequate medical assistance (20.2%) during the COVID-19 lockdown.

**Health-related Quality of life**
The proportion of patients in full health was 48.07% (50/104). Figure 3 shows the level of reported problems on each of the five dimensions of the EQ-5D-3L questionnaire. Although most of the patients did not present problems in the different dimensions evaluated, up to 30% of the patients presented moderate/high levels of pain/discomfort and anxiety/depression. The median EQ-5D-3L VAS score was 78 points (IQR, 21).
DISCUSSION
The COVID-19 confinement period resulted in poorer diet and physical exercise habits leading to poor weight control, and by a perception of worse control of their medical conditions in up to 25% of the LT patients surveyed. Remarkably, up to 40% exhibited moderate or severe levels of anxiety and up to one quarter referred moderate or severe insomnia. However, high rates of resilience were detected.
Our LT population felt well informed about the development of the pandemic and also had intermediate levels of concern and fear of COVID-19 infection, as recently reported.(19) There were no cases of infection in the study period. Health authorities during this period reported a mean and maximum incidence of 110 and 263 cases per 100,000 inhabitants, respectively. In contrast with previous studies(8, 19, 20), most participants showed a high adherence to immunosuppressive and other prescribed drugs with no changes in their tobacco or alcohol habits, likely related to the short period of confinement. Given the potential risk of infection in hospitals, soon after lockdown most participants had their face-to-face consultations changed to telephone consultations. As shown by other studies (21-23), change seemed to have no impact on the medical surveillance of our LT recipients.
Up to 39% of participants showed moderate or severe GAD, which had an impact on their perception of quality of life. Previous reports about COVID-19 and psycho-emotional distress have also reported moderate and severe depressive or anxious symptoms in about one third of patients.(24-29) The lower percentage of moderate-severe depression (10.5%) in our study appears to correlate with the high degree of resilience shown by our patients. Indeed, only a few respondents reported loss of confidence and interest in things or poorer decision making, all of which represent coping mechanisms to overcome a crisis. In line with previous reports, the most common symptoms of our patients were related to sleeping disorders.(30, 31) Up to 72.3% of the patients showed some degree of insomnia during the lockdown, with 25% referring moderate-severe insomnia. These changes are probably related to changes in sense of time, sedentary lifestyle, prolonged television viewing time, and increased use of electronic devices.
Since the start of the lockdown almost 40% of the patients reported weight gain mainly related to changes in eating habits and a reduction in physical activity. These changes in short periods of time can become permanent and lead to substantial weight gain.\(^{32}\) In fact, up to 40% of the patients who perceived poorer control of their chronic comorbidities attributed it to diet and exercise. Regardless, given their well-known association with deleterious health outcomes,\(^{33-35}\) our study highlights the need to implement strategies to further increase home-based physical activity and to encourage adherence to a healthy diet during periods of confinement.

Some of the limitations of our study are related to the cross-sectional design that evaluates a short period of time. The absence of baseline records for some of the instruments used, the single-center nature of the study, and a possible selection bias related to low participation may also constitute certain limitations. However, the extraordinary nature of the situation makes the findings relevant to foresee and face future similar situations.

In conclusion, there is a negative impact of confinement on both physical and mental health of LT patients. It is likely that longer periods of confinement and observation may show a greater impact. Therefore, it is necessary to develop psychological and nutritional support measures and enhance physical exercise to minimize these negative effects.

**ACKNOWLEDGMENTS**

We wish to express our gratitude and respect to the patients and parents, for sharing their experiences with us.
REFERENCES


Table 1. General characteristics of the study population

<table>
<thead>
<tr>
<th>Variable</th>
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<th>Variable</th>
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<td>Gender (men)</td>
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<td>Aetiology of liver disease</td>
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<td>Advanced vocational Training</td>
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<td>University degree</td>
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<td>Married/living with a partner</td>
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<td>Months from LT</td>
<td>99 (6-320)</td>
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<td>Single</td>
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Qualitative variables are expressed as number and percentage (n; %); quantitative variables are expressed as median and range (median; range). HCC: Hepatocellular carcinoma; CVD: Cardiovascular disease; CKD: Chronic kidney disease.
Figure 1. Impact of COVID-19 lockdown on physical and mental health. Study diagram.

PSWQ-11: Spanish abbreviated version of the Penn State Worry Questionnaire (PSWQ); ISI: insomnia severity index; LTE-12: List of Threatening Experiences (12 categories); PHQ-9: patient health questionnaire 9; BRS-6: brief resilience scale; EQ.5D-3L VAS: EuroQol-5D-3L visual analogue scale.

Figure 2. Flow-chart of the study
Figure 3. Health-related quality of life (EuroQoL-5D-3L)

Descriptive evaluation of each of the five dimensions of the EuroQoL-5D-3L in levels:
Level 1: absence of problems; Level 2: some degree of problems or moderate feeling;
Level 3: impossibility of doing different actions or severe discomfort