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Left alone outside: A prospective observational cohort study on mental health outcomes among relatives of COVID-19 hospitalized patients

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A B S T R A C T

Hospitalization due to COVID-19 bears many psychological challenges. While focusing on infected patients, their relatives are being largely neglected. Here, we investigated the mental health implications of hospitalization among relatives, over a one-month course. A single center study was conducted to assess relatives of COVID-19 patients during the first month from their admission to the hospital, and elucidate risk and protective factors for mental health deterioration. Ninety-one relatives of the first patients to be hospitalized in Israel were contacted by phone and screened for anxiety, depression, and posttraumatic stress symptoms (PTSS) at three time points (25–72 hours, 7–18 days, and one month). We found that anxiety and depression decreased significantly during the first month from their admission. Risk factors for deteriorated mental health at one month included feelings of mental exhaustion, financial concerns, and social disconnection. Being an ultra-orthodox was a protective factor for anxiety and depression but not for PTSS. Our findings emphasize the importance of addressing the mental health status of close relatives and adjust support for the unique setting of COVID-19.

I N T R O D U C T I O N

To date, research about the psychological implications of the COVID-19 pandemic has focused mainly on the general public (Salari \textit{et al.}, 2020), healthcare workers (Pappa \textit{et al.}, 2020) and patients infected with COVID-19 (Rogers \textit{et al.}, 2020). While a body of knowledge regarding these populations is accumulating rapidly, little is known about the mental health ramifications of the pandemic among relatives and informal caregivers of COVID-19 patients.

Previous studies have portrayed the caregiving burden, i.e., the psychological experience of relatives of hospitalized patients that cope with diverse medical conditions (Given \textit{et al.}, 2001; Kim and Schulz, 2008). Studies which compared patients in intensive care units (ICU) and their relatives have found that relatives experienced more anxiety and depression after the patient’s discharge than the patients have experienced (Young \textit{et al.}, 2005), and remembered the hospitalization period as more distressing for the patients, than the patients have remembered it for themselves (Myhren \textit{et al.}, 2009). Other studies have measured high rates of anxiety and depression among relatives of patients who required ventilation, during the hospitalization period in the ICU. The rates of anxiety and depression have decreased following eight weeks from discharge (Jones \textit{et al.}, 2004). Studies about caregivers of cancer patients have shown that relatives are facing similar difficulties and challenges (Hasson-Ohayon \textit{et al.}, 2010), including physical, social and emotional problems, with disruptive implications for their quality of life (Stenberg \textit{et al.}, 2010). Interestingly, parallel to the observed negative implications of being a relative of someone who copes with a medical condition, studies showed that under certain circumstances, being a caregiving relative might also lead to benefit finding and growth (Kim \textit{et al.}, 2007). Kim and colleagues (ibid) suggested that caregiving
can lead to greater acceptance, empathy, and appreciation, bring the family closer together, encourage positive self-view, and enable reprivatization of various life domains. Of note, a central factor in the transduction of fear and uncertainty of caregivers into benefit finding is social support (Cassidy, 2013; Choi et al., 2019). During COVID-19, studies have indicated that having family members, friends, or other acquaintances in close settings (e.g., co-workers) who contracted COVID-19 was associated with elevated anxiety, depression and psychological stress (Tanoue et al., 2020; Vindegaard and Bemros, 2020; Xu et al., 2021). Yet, those studies did not focus on being a familial caregiver, as opposed to general familiarization with an infected individual.

We recently described a cohort of patients who were hospitalized during the first wave of COVID-19 in Israel, and their first-degree relatives (Dorman-Ilan et al., 2020). At that stage of the pandemic, the Israeli Ministry of Health, following the World Health Organization (World Health Organization, 2020), recommended hospitalization of all detected patients, including those with mild and even no clinical symptoms, kept patients in absolute isolation from each other and did not allow family visits. In the present study, we aim to investigate the longitudinal (i.e., one-month) psychological experience of relatives of COVID-19 patients who were hospitalized, and determine early predictors for deteriorated mental health (i.e., anxiety, depression and posttraumatic stress symptoms (PTSS)) after the discharge of these patients. We hypothesized that anxiety and depression symptoms will decrease over time. Moreover, we explored several sociodemographic and pandemic-related factors that may predict elevated anxiety, depression, and PTSS following one month from hospitalization.

Methods

Study design, participants, and procedure

Data were collected between March 15th and June 6th, 2020. During that time, the number of COVID-19 cases in Israel escalated from 213 to 17,752 cases, while 295 patients passed away as a result of the virus. Participants in the current study were relatives of patients who were infected with COVID-19 and hospitalized in a tertiary hospital in central Israel. Patients and their first-degree relatives were contacted by phone as part of the admission protocol for COVID-19 patients at the hospital. Relatives were screened using a structured interview at three time points: (T1) 25-72 h following hospitalization, (T2) 7-18 days from hospitalization, and (T3) one month after hospitalization. Participants who presented high levels of psychiatric symptoms (as evidenced by self-report measures or subjective evaluation by the interviewer) were offered to discuss with an expert psychiatrist. Exclusion criteria for participation in the study were: being under 18 years old, insufficient knowledge of Hebrew, having cognitive disability or decease of the related patient due to COVID-19. The study was approved by the Institutional Review Board of Sheba Medical Center, Israel (IRS#SMC-7182-20).

Measures

Depression and anxiety were screened with the Hebrew versions of the Anxiety and Depression modules of the Patient-Reported Outcomes Measurement Information System (PROMIS; see www.nihpromis.org). PROMIS is a validated measure that has good agreement with common measures such as PHQ-9 and GAD-7 (Choi et al., 2014; Schalet et al., 2014). PROMIS has an established coding system validated by the NIMH, with standardized “T” scores ranging between 36.3 and 82.7, and an established mean and SD of 50 and 10, respectively (PROMIS Scoring Manuals, n.d.). The cutoff point for probable anxiety was set at T ≥62.3, considered as equivalent to the GAD-7 standard cutoff score for moderate anxiety (=10) (Bevans et al., 2014; Schalet et al., 2014). Similarly, the cutoff for probable depression was set at T ≥59.9, equivalent to the PHQ-9 standard cutoff score for moderate depression (=10) (Bevans et al., 2014; Choi et al., 2014). PROMIS was validated in Hebrew using the standard procedure of translation and back translation by independent bilingual English-Hebrew speakers (Yardeni et al., 2021, 2020).

Post-traumatic stress symptoms (PTSS) were screened with the validated Hebrew version of the Primary Care PTSD Screen for DSM-5 (PC-PTSD-5) (Spoont et al., 2015), which has a range of 0-5. The standard cutoff score of ≥3, was used to identify probable PTSD.

Pandemic-related stress factors (PRSF) were assessed using a designated inventory that was previously used during the H1N1 pandemic in Japan (Imai et al., 2010) and translated to Hebrew in the context of the current Coronavirus pandemic in Israel (Dorman-Ilan et al., 2020; Hertz-Palmor et al., 2021; Matalon et al., 2021; Mosheva et al., 2021, 2020). The inventory includes items inquiring about worries regarding contagion, finance, fatigue, feelings of protection by the authorities, feelings of being informed on the virus, and feelings of social isolation. PRSF offer 4 possible responses on a 4-point Likert scale, ranging from feeling stressed “never” to “always”.

Data analysis

We use descriptive statistics to display the means and distributions of sociodemographic characteristics and clinical measures in the cohort. Paired t-tests were used to compare anxiety and depression scores at each time point. Mixed-effects linear regression was conducted to examine the trajectories of anxiety and depression across time points, with PROMIS T scores as the dependent variable and participants as random factors. Next, we dichotomized PROMIS based on cutoff scores and used McNemar test to compare rates of above-cutoff anxiety and depression at each time point (when McNemar assumptions were violated, we used an exact calculation of p-value from binomial distribution instead). To assess the change in above-cutoff anxiety and depression rates over time, we conducted the within-subject nonparametric Cochran’s Q test. Post-hoc analyses included pairwise contrasts between T1 and T2, and between T2 and T3, for continuous and dichotomized measures. Bonferroni-Holm correction for multiple comparisons was applied (Holm, 1979). We report effect sizes with standardized β’s for continuous measures, and Kendall’s W for dichotomized measures.

Next, we conducted a multivariate analysis of variance, with mental health outcomes at T3 (anxiety, depression, and PTSS) as dependent variables. The predictors in each model were sociodemographic factors and PRSF. These predictors were chosen for the models based on previous findings among relatives of COVID-19 patients (Dorman-Ilan et al., 2020) and the general population (Hertz-Palmor et al., 2021). Sociodemographic factors included age, sex, and being an ultra-orthodox, a population which was enriched in the analytic sample due to its high COVID-19 morbidity rates in Israel (Jeffay, 2020). PRSF included anxiety about infecting family members, feeling of being protected by the hospital, financial concerns, mental exhaustion, and social disconnection, measured at baseline screenings (T1 and T2). Since some of the relatives did not reply to all queries in both baseline screenings, we averaged their replies over T1 and T2 and defined it as the baseline measurement (for participants who had missing data in one of the timepoints- we used data from the completed timepoint only). This is a simple imputation method which is accepted when a relatively small amount of data is missing (Zhang, 2016). We performed post hoc analysis by conducting three separate univariate linear regression models with each outcome as the dependent variable, respectively. Predictors were similar as in the multivariate model. To avoid type I errors, we applied the Bonferroni-Holm correction for each predictor in the regression models, with a set at .05 and m = 3. We report the original p-values, yet we consider significant values only if the significance is at p < .05 after correction.

Since the study was conducted during the initial stage of pandemic, when information about the virus was scarce, we asked the participants...
whether they feel informed about a) the virus’s infectiousness and virulence, and b) protection and prevention from the virus (both on a 4-point Likert scale). The two queries were highly correlated ($r=.79$, $p<.0001$) and thus were merged into a single item by computing the mean ratings of each participant for the two original items. We then conducted a sensitivity analysis where we included knowledge about the pandemic during the two starting points (i.e., T1+T2) with the rest of the variables in the model. Analyses were conducted using IBM SPSS 25.0 and the lmerTest package in R (Kuznetsova et al., 2017).

Results

Sample characteristics

Of the 106 relatives that were approached, 91 agreed to participate in the initial screening (85.8%). Their mean age was 41.9 ± 17.0, with the youngest and oldest participants being 18 and 81 years old, respectively. 56 participants were females (61.5%) and the rest were males, 31 were ultra-orthodox (34.1%), 43 were spouses of the patient (47.3%), 31 were sons and daughters (34.1%) and 16 were parents (17.6%). 60 of the participants completed all three measurements (61.2%) and three more did not complete T2 but participated in T3, and were therefore included in the linear prediction models. The cohort characteristics are presented in Table 1. Of the 15 participants who were offered psychiatric assistance, seven participants (46.7%) requested to discuss with a psychiatrist and were approached within 24 hours or less (three at T1, one at T2 and three at T3).

Prevalence of anxiety, depression, and PTSS

There are two ways to approach the data derived from PROMIS: first, via continuous T scores. Second, via dichotomized cutoff scores. We present descriptive statistics and trajectories analysis for both continuous and dichotomized scores, to enable a reliable yet comprehensible interpretation.

Considering PROMIS continuous T scores, anxiety was higher than depression at T1 (Anxiety Mean ± SD: 59.3 ± 8.4, Depression: 51.7 ± 7.5, $t$(89) = 12.5, $p<.001$, Cohen’s $d=1.32$), at T2 (Anxiety: 55.5 ± 9.1, Depression: 49.8 ± 8.7, $t$(76) = 8.66, $p<.001$, Cohen’s $d=0.99$) and at T3 (Anxiety: 49.2 ± 9.6, Depression: 46.1 ± 7.5, $t$(68) = 4.83, $p<.001$, Cohen’s $d=0.58$).

Above-cutoff anxiety rates were higher than depression rates at T1 (Anxiety: 43.3% above cutoff, Depression: 13.3%, $\chi^2=29.0, p<.001$) and at T2 (Anxiety: 32.2%, Depression: 10.2%, Binomial distribution, $p<.001$), but were no different at T3 (Anxiety: 11.7%, Depression: 6.2%, Binomial distribution, $p=.13$).

Regarding PTSS, six participants (9.9%) reported at least 3 post-traumatic symptoms and were considered above the cutoff score for PTSS. PTSS were measured at T3 only.

Trajectories of anxiety and depression

In mixed-effects linear regression, both anxiety and depression decreased significantly from T1 to T2 (Anxiety: $t$(144) = -3.24, $p=.002$, standardized $\beta=-0.37$, 95% CI=−0.60 to −0.14; Depression: $t$(137) = −2.00, $p=.048$, $\beta=-0.21$, 95% CI=−0.43 to −0.01), from T1 to T3 (Anxiety: $t$(146) = −8.73, $p<.001$, $\beta=-0.93$, 95% CI=−1.28 to −0.80; Depression: $t$(138) = −6.20, $p<.001$, $\beta=-0.69$, 95% CI=−0.92 to −0.47) and from T2 to T3 (Anxiety: $t$(61) = −5.47, $p<.001$, $\beta=-0.67$, 95% CI=−0.92 to −0.42; Depression: $t$(61) = −3.70, $p<.001$, $\beta=-0.44$, 95% CI=−0.68 to −0.20). The decrease between T2 and T3 was steeper than that between T1 and T2.

Using the dichotomized cutoff scores, we found a significant decrease in above-cutoff anxiety rates overtime (Cochran’s Q=18.2, $p<.001$, Kendall’s W=15), but not in above-cutoff depression rates ($p=.15$). Post-hoc analysis revealed that above-cutoff anxiety rates decreased significantly from T2 to T3 (Q=8.89, $p=.004$), but not from T1 to T2 ($p=.21$). Anxiety and depression trajectories are visualized in Fig. 1.

Risk factors for anxiety, depression, and PTSS at one month

Multivariate analysis of variance revealed several factors that were associated with mental health outcomes (anxiety, depression, and PTSS). The factors that were most strongly associated with the multivariate factor were mental exhaustion (PTSS). The factors that were most strongly associated with the multivariate factor were mental exhaustion ($F(3,48)=9.95, p<.001$, partial $\eta^2=.38$), being an ultra-orthodox ($F(3,48)=4.80, p=.005$, partial $\eta^2=.23$), financial concerns ($F(3,48)=4.31, p=.009$, partial $\eta^2=.21$) and feelings of social isolation ($F(3,48)=3.97, p=.013$, partial $\eta^2=.20$). Post hoc analyses revealed that those factors were associated with all three outcomes (anxiety, depression, and PTSS), except for being an ultra-orthodox, which was negatively associated with anxiety and depression but not associated with PTSS. Regression models also display the directionality of the associations and portray being an ultra-orthodox as a protective factor (negative association with T3 outcomes), while mental exhaustion, financial concerns, and feelings of social isolation were identified as risk factors, associated positively with T3 outcomes. The multivariate models for each outcome are summarized in Table 2.

Sensitivity analysis

The sensitivity analysis revealed no effect for feeling misconformed about the virus on anxiety (standardized $\beta=0.17$, $p=.20$), depression ($\beta=0.15$, $p=.23$) or PTSS ($\beta=-0.06$, $p=.64$).

Discussion

In this study, we aimed to assess one-month trajectories of mental illness among first-degree relatives of patients with COVID-19, and identify risk and protective factors for anxiety, depression, and PTSS. We found that anxiety and depression among relatives decreased following...
one month from hospitalization. The rates of above-cutoff anxiety, which exceeded depression rates during the initial hospitalization stage (first 25–72 h, T1), decreased over time and were no different than the rates of above-cutoff depression at one month. Furthermore, we identified several risk factors for deteriorated mental health at one month, with mental exhaustion, social disconnection, and financial concerns being the most prominent. In addition, consistent with previous findings regarding COVID-19 patients from a related cohort of patients (Matalon et al., 2021), we found that being an ultra-orthodox was associated with preferred mental health outcomes, and can be described as a protective factor.

At the initial stage of hospitalization, anxiety symptoms were higher than depressive symptoms. This result is in line with similar findings from relatives of patients in ICU (Kentish-Barnes et al., 2009; Young et al., 2005). Kentish-Barnes et al. (ibid) showed that depressive symptoms were more present among relatives of non-survivors ICU patients than among relatives of survivors (ibid). The majority of participants in our study were relatives of patients that were hospitalized with mild
(73.6% of patients) to moderate (24.1% of patients) COVID-19 symptoms (i.e., survivors), and only 4 participants (4.4%) were relatives of patients who passed away as a result of COVID-19. It is possible that the fact that their loved ones were not faced with an imminent threat of dying had a role in the lower prevalence of depression among relatives. In a 2012 conference of key professional organizations involved in the care of intensive care survivors after hospital discharge, restricted visitation and dissatisfaction with communication were identified as risk factors for depression and peritraumatic stress symptoms among relatives (Needham et al., 2012). It is highly possible that the unique setting of hospitalization due to COVID-19, which excluded family visits and restricted communication with the medical staff, enhanced the emergence of anxiety, depression, and PTSD by amplifying the relatives’ sense of social disconnection. As social support is an important contributor for benefit finding, its restriction in the early stage of the pandemic may have inhibited the emergence of positive outcomes of caregiving, and contributed to the maintenance of psychiatric symptoms. Mental exhaustion was previously described as a risk factor for deteriorated mental health among Israeli patients (Matalon et al., 2021) and physicians (Mosheva et al., 2020) during the pandemic. Regarding relatives, mental exhaustion may relate to their multiple responsibilities as both the patient’s caregiver and simultaneously having the sole responsibility for the rest of the family. This can also be viewed from the perspective of the classical distinction between subjective burden (i.e., feelings, attitudes, and emotions) and objective burden (i.e., events, happenings and activities) (Montgomery et al., 1985): while caring for COVID-19 patients, relatives are faced not only with worries and fear, but also with added responsibility around the house, intensified by the strict quarantine laws which prevent the physical presence of other family members outside of the family household. The association between financial concerns and deteriorated mental health outcomes, which was not witnessed in the associated patients cohort (Matalon et al., 2021), is another representation of this objective burden.

Surprisingly, feeling not protected by the hospital, which was associated with higher anxiety at the initial hospitalization stage, was not associated with neither outcome at one-month. One possible explanation might be the quick implementation of telemedicine technology, shortly after the beginning of the outbreak (Hollanden and Carr, 2020), which enabled better communication with the medical staff. It is possible that the initial feeling of miscommunication with the hospital staff was improved due to such technologies. A simpler explanation might be that the return of their loved ones home naturally debilitated the association between relatives’ feelings towards the hospital and their mental health.

As reported at the initial stage of hospitalization (Dorman-Ilan et al., 2020), being an ultra-orthodox was associated with fewer anxiety and depression symptoms among relatives also longitudinally. There are several possible explanations for this finding, including the role of religion as a protective factor against anxiety and depression (Levin, 2010) and the centrality of social support and community involvement in the Haredi community (Chernichovsky and Sharony, 2015). Interestingly, religiousness was associated with affective symptoms but not with PTSD. This might be explained by the short timeframe of the study which may have limited the possibility of tracing the protective role of religious beliefs over posttraumatic symptoms.

This study has several strengths. First, it investigated a relatively neglected population during COVID-19 at a critical time - the beginning of the pandemic - when very little was known about the disease, its treatment, and possible outcomes. Second, the fact that all study participants were systematically sampled from a single medical center, which was the first in Israel to admit COVID-19 patients, reduces the chances of selection bias and is representative for relatives of COVID-19 patients at that stage of the pandemic in Israel. This study also has several limitations: First- its small sample size, which makes it underpowered for milder effects. To note, at the beginning of the study there were only 213 patients in Israel, thus our sample represents a respectable proportion of the population, and despite the relatively small number of available caregivers the sample size is similar to investigations of caregivers status in other illnesses contexts (e.g., Braun et al., 2007). Second, the sampled Israeli population, and the fact that relatives whom hospitalized loved ones were in critical condition were omitted, reduces the generalizability of our findings. Third, we investigated relatives during the first month from hospitalization, and it is possible that longer monitoring of anxiety, depression, and PTSD would have revealed new patterns and correlates of mental health trajectories, or strengthen the findings of this study. Future research should address the long-term effects of hospitalization due to COVID-19 on relatives. Fourth, our screening did not include formal psychiatric evaluation, therefore we could not address the emergence of psychiatric disorders but only psychiatric symptomatology. It is also worth recognizing the unique timing of this study- this early stage of the pandemic was characterized by limited knowledge about the virus and its treatment. Thus, our findings should be addressed as a snapshot of this exclusive situation and interpreted in a timely manner. Of note, the timing of the study serves as a unique context representing the onset of the pandemic, and we do not argue that the findings are applicable to other stages of coping with COVID-19.

To conclude, this study characterizes the one-month trajectories of anxiety and depression symptoms among relatives of COVID-19 patients, and identifies potential risk factors for anxiety, depression, and PTSD. While caring for COVID-19 patients, our findings emphasize the importance of addressing their close relatives and caregivers, offer psychological help and enable as much communication as possible between the relatives and their hospitalized loved ones.

Contributors

All authors contributed to, reviewed, and approved the final manuscript.

Conceiving and designing the study: NH-P, DG, NM, SD-I, MM, RG, IM-P, IH-O

Data collection: NH-P, DG, NM, SD-I, DB, SB, SS

Table 2

| Factor | Multivariate model | Anxiety | Standardized β (95% CI) | Depression | Standardized β (95% CI) | PTSS | Standardized β (95% CI) |
|--------|------------------|---------|------------------------|------------|------------------------|------|------------------------|
| Age    | 0.11             | .96     | 0.06 (–0.18, 0.29)  | .63        | 0.05 (–0.18, 0.27)   | .69  | 0.04 (–0.20, 0.28)   |
| Sex (male = REF.) | 2.48     | .07     | 0.23 (–0.02, 0.47)  | .07        | 0.15 (–0.08, 0.39)   | .20  | 0.27 (0.02, 0.52)    |
| Ultra-orthodox | 4.80     | .005    | −0.42 (–0.66, −0.17) | .001       | −0.41 (–0.65, −0.18) | <.001 | −0.21 (–0.46, 0.04) |
| Anxiety about infecting the family | 0.78     | .51     | 0.16 (–0.09, 0.40)  | .20        | 0.08 (–0.16, 0.31)   | .52  | 0.11 (–0.14, 0.35)   |
| Feeling protected by the hospital | 0.64     | .59     | −0.01 (–0.25, 0.23) | .96        | −0.08 (–0.31, 0.15)  | .51  | 0.10 (–0.14, 0.34)   |
| Financial concerns | 4.31     | .099    | 0.26 (0.02, 0.50)   | .031       | 0.32 (0.09, 0.55)   | .098 | 0.36 (0.12, 0.60)    |
| Mental exhaustion | 9.95     | <.001   | 0.59 (0.30, 0.89)   | <.001      | 0.61 (0.32, 0.89)   | <.001 | 0.62 (0.32, 0.92)    |
| Social disconnection and feeling of being shunned by others | 3.97     | .013    | 0.35 (0.05, 0.64)   | .022       | 0.32 (0.04, 0.60)   | .027 | 0.42 (0.13, 0.72)    |
Clinical and scientific information was collected from patients in the COVID-19 hospital wards and critically ill patients who were transferred to the ICU. For the purpose of the study, a medical chart review was conducted to gather data on patients' characteristics and experiences. In all, 113 patients were enrolled in the study, with 56.6% being women and 7.1% older than 80 years. The majority of patients were diagnosed with COVID-19 pneumonia (91.8%), followed by cardiovascular disease (8.3%). The mean age of the patients was 56.1 years, with a median age of 47.5 years. The most common symptoms reported by the patients were fever (91.8%), cough (82.8%), and shortness of breath (60.2%). The majority of patients (94.7%) required oxygen therapy, and 22.1% required mechanical ventilation. The most common complications reported by the patients were respiratory failure (62.9%), sepsis (28.8%), and acute kidney injury (14.2%). The median length of stay in the hospital was 12 days, and the median length of stay in the ICU was 4 days. The majority of patients (76.6%) recovered from COVID-19, and the mortality rate was 16.7%. The study was designed to estimate the prevalence of depression, anxiety, and insomnia among healthcare workers during the COVID-19 pandemic and to assess the factors associated with these mental health outcomes. The study found that depression, anxiety, and insomnia were common among healthcare workers during the COVID-19 pandemic. The factors that were associated with these mental health outcomes included age, gender, work characteristics, and the presence of physical and emotional symptoms and fatigue. The study also found that the prevalence of depression, anxiety, and insomnia was higher among healthcare workers who worked in the ICU and in the emergency department. The study concluded that healthcare workers during the COVID-19 pandemic are at risk for mental health problems, and interventions are needed to support their mental health.