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Psychological burden in patients with COVID-19 and their relatives 90 days after hospitalization: A prospective observational cohort study

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ABSTRACT

Objective: COVID-19 causes psychological distress for patients and their relatives at short term. However, little research addressed the longer-term psychological outcomes in this population. Therefore, we aimed to prospectively assess clinically relevant psychological distress in hospitalized patients with COVID-19 and their relatives 90 days after hospital discharge.

Methods: This exploratory, prospective, observational cohort study included consecutive adult patients hospitalized in two Swiss tertiary-care hospitals between March and June 2020 for confirmed COVID-19 and their relatives. The primary outcome was psychological distress defined as clinically relevant symptoms of anxiety and/or depression measured with the Hospital Anxiety and Depression Scale (HADS) 90 days after discharge.

Results: Clinically relevant psychological distress 90 days after hospital discharge was present in 23/108 patients (21.3%) and 22/120 relatives (18.3%). For patients, risk and protective factors associated with clinically relevant psychological distress included sociodemographic, illness-related, psychosocial, and hospital-related factors. A model including these factors showed good discrimination, with an area under the receiver-operating characteristic curve (AUC) of 0.84. For relatives, relevant risk factors were illness-related, psychosocial, and hospital-related factors. Resilience was negatively associated with anxiety and depression in both patients and relatives and regarding PTSD in relatives only.

Conclusion: COVID-19 is linked to clinically relevant psychological distress in a subgroup of patients and their relatives 90 days after hospitalization. If confirmed in an independent and larger patient cohort, knowledge about these potential risk and protective factors might help to develop preventive strategies.

1. Introduction

The novel Coronavirus disease 2019 (COVID-19) has caused a global pandemic with far-reaching consequences for many aspects of society,

especially for patients diagnosed with COVID-19 and their relatives. While some patients have asymptomatic courses, many patients with COVID-19 experience a variety of symptoms or even develop an acute respiratory distress syndrome [1,2]. Especially vulnerable individuals,

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patients above 65 years, patients with obesity, and people with chronic lung disease or cardiovascular comorbidities [3,4], may experience severe disease courses, requiring intensive care treatment and being linked to increased risk for persisting impairments or even mortality [5–7]. In addition to somatic morbidity, COVID-19 may also cause severe psychological distress. In fact, research during previous similar epidemics has shown that patients are at high risk for mental disorders, including depressive and anxiety disorders, post-traumatic stress disorder (PTSD), and sleep disorders [8]. Further, during previous pandemics, isolation measures similar to the ones currently used to contain COVID-19 have been associated with adverse psychological effects on patients and relatives [9–12].

Still, for COVID-19, there is currently a lack of studies investigating longer-term psychological sequelae of the disease in patients and their relatives. There is growing evidence that COVID-19 is linked to short-term psychological outcomes in patients, relatives as well as the general population [13]. For instance, a large Swiss survey of the general public found an increase in the prevalence of depressive symptoms from 3.4% before the pandemic to 9.1% during confinement and 11.7% during partial deconfinement [14]. Further, studies found prevalence rates of around 50% for psychological morbidities such as depression or anxiety in COVID-19 survivors [13,15]. Again, these outcomes were caused by several factors including isolation of patients and relatives during the initial stage of hospitalization [16]. Still, longer-term psychological outcomes of COVID-19 patients and their relatives remain understudied.

Herein, our aim was to assess risk factors and prevalence of clinically relevant psychological distress in patients and their relatives 90 days after an index hospital stay of patients with COVID-19.

2. Materials and methods

2.1. Study setting

This exploratory, prospective observational two-center cohort study was conducted at the University Hospital Basel and the Kantonsspital Aarau, two tertiary care hospitals in Switzerland, from March until June 2020. The study was approved by the local Ethics Committee (Ethics Committee Northwest and Central Switzerland (Ethikkommission Nordwest- und Zentralschweiz, EKNZ); amendment to reference number 2019–01162). Written informed consent was provided by all participating patients and relatives. This manuscript adheres to the STROBE statement [17].

2.2. Study population

All patients consecutively admitted with COVID-19 and their closest relative were eligible for inclusion into this study. The criteria for hospitalization for COVID-19 were the overall clinical condition of the patient as well as clinical risk factors (e.g., age > 65 years, respiratory rate > 25/min, requirement of oxygen or pulmonary infiltrates observed on a chest imaging). Relatives were chosen according to surrogate decision-making rank (spouse > parents/adult children > others) as indicated in patients' medical records. Patients and relatives with insufficient knowledge of the local languages, cognitive impairment (i.e., a condition where patients were not able to understand and respond to the questions of our interview such as dementia or delirium), or serious psychiatric conditions (e.g., psychosis) were excluded. We did not apply any other exclusion criteria based on patient or COVID-19 related characteristics. We contacted patients and relatives by phone, informed them about our study and asked them to participate. To those who agreed, we sent a letter including the study information and informed consent form which they were asked to sign and return.

2.3. Collection of baseline and follow-up data of patients and relatives

For this study, we conducted telephone interviews with each patients and relatives 30 and 90 days after hospital discharge. In patients, we additionally reviewed medical charts and extracted clinical characteristics related to COVID-19. All other potential risk and protective factors were assessed at the 30-day “baseline” assessment. Primary and secondary outcomes, i.e., symptoms of anxiety, depression, and PTSD were assessed at the 90-day follow-up. To evaluate factors specific to the current pandemic, we used items designed for the purpose of this study. For all other predictive factors and all outcome variables, we conducted well-established clinical risk scores and validated psychometric measures.

2.3.1. Variables collected during hospitalization and baseline assessment 30 days after discharge

We collected potential predictor variables adhering to four domains, i.e., sociodemographic, illness-related, psychological, and hospital-related. Sociodemographic factors were the same for both samples, but factors in the other three domains partially differed to account for patient- and relative-specific characteristics.

Sociodemographic factors in both patients and relatives included age, gender, citizenship, cultural background, religious affiliation, civil status, children, and current job situation.

2.3.1.1. Patient variables and measures. In patients, illness-related factors included clinical parameters such as medication, i.e., investigational therapy, antibiotics, and anxiolytics during hospitalization, intensive care unit (ICU) stay, intubation, duration of hospitalization, and timepoint of COVID-19 diagnosis. Further, we assessed illness severity by the National Early Warning Score (NEWS) [18], a widely used tool to detect patients at risk of clinical deterioration, and severity of comorbidity by the Charlson Comorbidity Index (CCI) [19]. Self-perceived overall health status was evaluated with the visual analogue scale (VAS) of the EuroQol, ranging from 0 (worst imaginable health) to 100 (best imaginable health) [20,21]. In the domain of psychosocial factors, several psychological factors specific to the current pandemic were evaluated by items designed for the purpose of this study. In patients, these included worries caused by COVID-19 media reports, self-perceived stigma as well as a number of other potential concerning factors, i.e., worries about uncertain prognosis, burden of isolation measures, burden of boredom, worries about health of relatives, burden of missing relatives, worries about job situation, finances and medical care, and other worries as well as coping strategies, i.e., social contacts, distraction, tranquilizers and others. Patients rated each of these variables on a visual analogue scale (VAS) of 0–10. Additionally, we asked patients about pre-existing psychological comorbidities as well as frequency and kind of contact between them and their relatives.

Further, we assessed patients' perceived stress with the Perceived Stress Scale (10-item version; PSS-10), a widely-used tool to evaluate how unforeseeable, uncontrollable and overwhelming respondents perceived their life during the last 30 days. [22,23]. A study evaluating the psychometric properties of the PSS-10 in a representative sample of the German general population showed good internal consistency with a Cronbach alpha of 0.84 and good construct validity [24]. We determined resilience of patients through the 10-item version of the Connor-Davidson Resilience Scale (CD-RISC-10), indicating how well a person can cope with stress [25]. The CD-RISC is commonly used in clinical research and the original 25-item questionnaire as well as the 10-item version showed good validity with a Cronbach alpha of 0.89 and 0.88, respectively [25,26]. Further, the CD-RISC showed high test-retest reliability over a 12-month follow-up period [27–29]. Lastly, through items specifically designed for this study, we evaluated several hospital-related factors by a visual analogue scale of 0–10, i.e., perceived competence of treating physician, contradictory information given by

medical team, burden of having no visitors, missing physical closeness and asked patients if the psychosocial care team was involved.

2.3.1.2. Relative variables and measures. In relatives, in the domain of illness-related factors we assessed if they themselves were quarantined or infected with SARS-CoV-2, self-perceived overall health status (VAS of the EuroQol), the time point of the patient's COVID-19 diagnosis, as well if the patient had died. In alignment with patients' psychosocial variables, for relatives we also evaluated potential risk and protective factors related to the current pandemic evaluated by items designed for this study. Items rated on a VAS of 0–10 included worries and burdens, i. e., worries due to COVID-19 media reports, perceived overall burden due to COVID-19, worries about uncertain prognosis, worries about infection, burden of isolation measures, burden of separation from patient, and other worries as well as helpfulness of coping strategies, i.e., social contacts, distraction, tranquilizers, alcohol consumption, relaxation techniques, sports, and other coping strategies. Additionally, we asked relatives how they were related to the patient, if they lived in the same household, about the frequency of contact with patient, pre-existing psychological comorbidities, psychological help, and intake of psychotropic drugs. Further, we assessed perceived stress (PSS-10) and resilience (CD-RISC-10). Hospital-related factors included contact and satisfaction with the medical team, if the relative received information regarding prognosis, comprehensibility of medical information, if medical care was perceived as sufficient or inadequate, if the relative received recommendations regarding own care, if the psychosocial care team was involved, burden of not being able to visit the patient, and missing physical closeness.

2.3.2. Outcomes

Primary and secondary outcome for both patients and relatives were assessed at 90-day follow-up. The primary endpoint, psychological distress, defined as clinically relevant symptoms of anxiety and/or depression at the time of 90 days after discharge, was measured by the Hospital Anxiety and Depression Scale (HADS) [30]. This self-report measure was developed for patient populations hospitalized with medical conditions and does not contain items on physical symptoms to avoid somatic confounding. A review on psychometric properties of the HADS revealed good reliability and validity with a Cronbach's alpha of 0.83 and 0.82 for the subscales anxiety and depression, respectively, and an optimal balance between sensitivity and specificity of approximately 0.80 when applying a cut-off score of ≥ 8 on both subscales. In line with previous research, a score of ≥ 8 on the depression and/or anxiety subscale (range: 0–21) of the HADS, indicating clinically relevant symptoms of depression and/or anxiety, was defined as clinically relevant psychological distress for the purpose of our study [30,31].

The secondary outcome, i.e., symptoms of post-traumatic stress disorder, was assessed through a German translation of the Impact of Event Scale-revised (IES-R), which measures symptoms of emotional distress caused by traumatic events [32]. The IES-R is a 22-item questionnaire containing three subscales covering the three symptom domains intrusion, avoidance and hyperarousal. The IES-R has been shown to have high internal consistency with a Cronbach's alpha of 0.96 and good diagnostic accuracy when applying a cut-off score of 1.5 [33], which we used to categorize participants regarding symptoms of PTSD.

2.4. Statistical analyses

Descriptive statistics, i.e. frequencies as well as means and standard deviations were used to present characteristics of the study population. Data from the patient and relative sample were analyzed separately. To investigate the associations of potential risk and protective factors assessed at 30-day follow-up and clinically relevant psychological distress at 90-day follow-up, we conducted univariable logistic regression models. We further conducted multivariable logistic regression

models within the four domains, each including all significantly associated variables of the respective domain as well as the pre-defined variables age and gender in the patient sample and age, gender and death of patient in the relative sample. To investigate which variables might be independently associated, we additionally calculated a combined regression model including the pre-defined as well as all risk and protective factors associated with the outcome in univariable analyses. We show odds ratios (OR) and 95% confidence intervals (CI) as a measure of association and the area under the receiver operating characteristic curve (AUC) as a measure of discrimination. A p -value of < 0.05 (two-tailed) was considered statistically significant. All statistical analyses were conducted using Stata 15 (Stata Corp, College Station, Texas, USA).

3. Results

3.1. Study sample and baseline demographics

Between March and June 2020, 301 patients with COVID-19 were hospitalized at the University Hospital of Basel ($n = 198$) and Kantonsspital Aarau ($n = 103$). Fig. 1 shows the flowchart of patients and relatives regarding study inclusion. Forty patients (13.3%) had died until 30-day follow-up assessment, 86 (28.9%) met exclusion criteria such as insufficient knowledge of the local language (17.9%), cognitive impairment or severe underlying psychiatric conditions (10.6%), 47 (15.6%) were not reachable by phone and 20 (6.6%) did not give informed consent. Twelve (4%) patients did not indicate any relatives. Of the 289 remaining relatives, 15.9% did not speak the local language and 8.3% did not give informed consent. Seventy-eight (27%) of eligible relatives were not reachable by phone for the either the 30- or 90-day assessment. The final samples therefore consisted of 108 patients and 120 relatives.

Sociodemographic and clinical characteristics of the patient and relative cohorts are shown in Table 1. Patients were on average 58 years old and 41.1% were female. The mean duration of hospitalization was 9 days and 18 (16.8%) patients were transferred to the ICU with 11 (10.4%) requiring intubation. Relatives' mean age was 58 years, 79% were female, and they were mainly patients' spouses (52.1%).

3.2. Primary endpoint of patients: clinically relevant psychological distress 90 days after discharge

First, we focused on the patient cohort. Twenty-three patients (21.3%) showed clinically relevant psychological distress, i.e., symptoms of depression and/or anxiety defined by a score of ≥ 8 on the depression and/or anxiety subscale of the HADS. Of those, 20 (18.5%) showed symptoms of anxiety and ten (9.3%) symptoms of depression, with seven patients (6.5%) showing both.

Several factors were associated with clinically relevant psychological distress in univariable analyses (see Supplemental Table S1), including sociodemographic, i.e., female gender, illness-related, i.e., lower perceived health status, psychosocial, i.e., lower resilience, higher level of perceived stress, increased worries due to COVID-19 media reports, worries by isolation measures, burden by boredom, worries about job situation, worries about medical care, and hospital-related factors, i.e., burden of having no visitors and missing physical contact. The psychosocial domain model yielded an AUC of 0.82, the highest AUC of all domain models which is only slightly lower than the AUC of the overall model (Table 2).

3.3. Primary endpoint of relatives: clinically relevant psychological distress 90 days after discharge

Second, we focused on the cohort of relatives. Twenty-two relatives (18.3%) showed clinically relevant psychological distress, i.e., symptoms of depression and/or anxiety 90 days after patients' discharge. Of

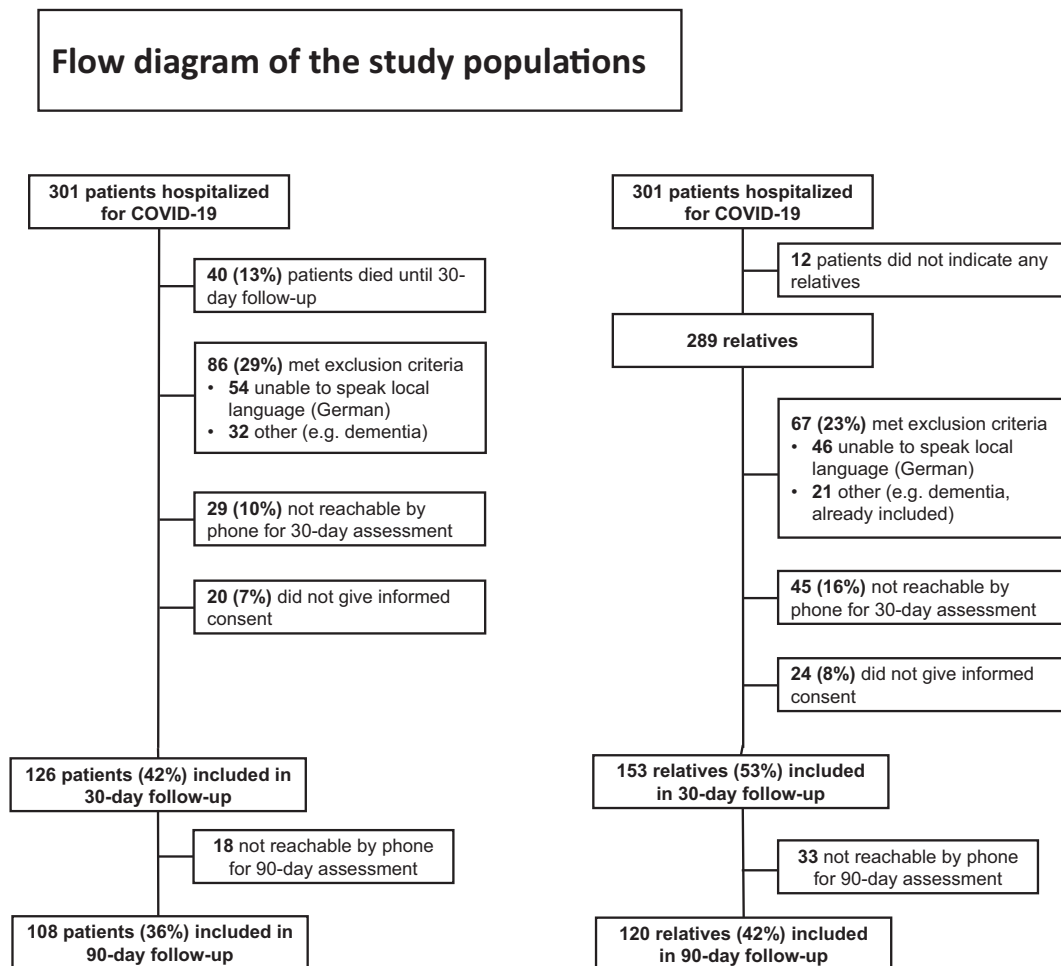


Fig. 1. Flow diagram of the study population. Flow diagram illustrating inclusion and exclusion of eligible participants.

those, 17 (14.2%) relatives displayed symptoms of anxiety and 13 (10.8%) symptoms of depression with eight relatives (6.7%) having both.

Several factors were associated with clinically relevant psychological distress in univariable analyses, including illness-related, i.e., lower perceived health status, psychosocial, i.e., lower resilience, higher level of perceived stress, type of communication between relatives and patients, higher perceived overall burden, increased worries due to uncertain prognosis, higher burden of isolation measures, helpfulness of sport and other coping strategies, and hospital-related factors, i.e., higher burden due to not being able to visit the patient and missing physical closeness (see Supplemental Table S2). Self-perceived overall health status, perceived stress, perceived overall burden due to COVID-19, and sport as a helpful coping strategy were independently associated with clinically relevant psychological distress within the four domain models (Table 3). The psychosocial domain model showed the same discriminative value as the overall multivariable model with an AUC of 0.95.

3.4. Secondary endpoints: PTSD in patients and relatives 90 days after discharge

Third, we focused on PTSD in the patient and the relative cohorts as a secondary outcome. A total of 8 patients (7.8%) showed symptoms of PTSD. In univariable analyses, factors that were associated with symptoms of PTSD in patients were sociodemographic factors, i.e., female gender, non-central/western European background, being widowed,

separated or single, illness-related factors, i.e., lower perceived health status, and psychosocial factors, i.e., higher perceived stress, increased worries due to COVID-19 media reports, and being worried about job situation or finances (see Supplemental Table S3). Cultural background and civil status were independently associated within the sociodemographic domain. The sociodemographic and psychosocial model each yielded an AUC of 0.86 while the overall multivariable model including all statistically significant variables as well as age and gender showed an AUC of 0.69 (Table 4).

Eight of the 113 relatives (7.1%) with available information suffered from considerable PTSD symptoms. Illness-related, i.e., lower perceived health status, psychosocial, i.e., intake of psychotropic drugs, lower resilience, higher perceived stress, increased worries due to COVID-19 media reports, and higher burden of isolation measures and hospital-related factors, i.e., not being able to visit the patient were associated with relatives' PTSD symptoms (see Supplemental Table S4). Resilience emerged as an independently associated factor within the psychosocial domain. The psychosocial domain model and the overall multivariable model showed an AUC of 0.95 (Table 5).

4. Discussion

Within this two-center, exploratory, prospective observational cohort study assessing the prevalence of clinically relevant psychological distress and associated factors in patients with COVID-19 and their relatives 90 days after hospitalization, we found that a quarter of patients and relatives suffered from psychological distress 90 days after

Table 1
Sociodemographic and clinical characteristics of the study populations.

Characteristics	Patients	Relatives
	n = 108	n = 120
Age, years	58.4 (15.8)	57.6 (14.7)
<40 years	12 (11.2%)	13 (10.9%)
40–64 years	56 (52.3%)	66 (55.5%)
65–80 years	33 (30.8%)	31 (26.1%)
>80 years	6 (5.6%)	9 (7.6%)
Gender, female	44 (41.1%)	94 (79.0%)
Citizenship		
Switzerland	73 (68.9%)	99 (83.2%)
Germany	14 (13.2%)	5 (4.2%)
France	5 (4.7%)	6 (5.0%)
Other	14 (13.2%)	9 (7.6%)
Cultural background		
Central Europe	78 (73.6%)	90 (75.6%)
Western Europe	7 (6.6%)	7 (5.9%)
Eastern Europe	4 (3.8%)	6 (5.0%)
Southern Europe	7 (6.6%)	9 (7.6%)
Northern Europe	2 (1.9%)	0
Asia	1 (0.9%)	0
Africa	4 (3.8%)	0
Religious affiliation		
Catholic	28 (26.7%)	35 (29.4%)
Protestant	25 (23.8%)	39 (32.8%)
Other Christian denomination	6 (5.7%)	9 (7.6%)
Jewish	2 (1.9%)	2 (1.7%)
Muslim	8 (7.6%)	5 (4.2%)
Other religion	2 (1.9%)	3 (2.5%)
No religious affiliation	34 (32.4%)	26 (21.8%)
Civil status		
Married/in partnership	67 (63.2%)	92 (77.3%)
Divorced	19 (17.9%)	9 (7.6%)
Widowed	6 (5.7%)	6 (5.0%)
Single	14 (13.2%)	12 (10.1%)
Children, yes	71 (69.6%)	88 (73.9%)
Education		
High School	9 (8.8%)	4 (3.4%)
Apprenticeship	70 (68.6%)	76 (64.4%)
College/University	23 (22.5%)	38 (32.2%)
Current job situation		
Employed	63 (60.0%)	57 (50.0%)
Unemployed	0	4 (3.5%)
Retired	37 (35.2%)	43 (37.7%)
Disability benefits	2 (1.9%)	3 (2.6%)
Homemaker	2 (1.9%)	5 (4.4%)
Other	1 (1.0%)	2 (1.8%)
Previous psychotherapy	6 (5.8%)	8 (7.1%)
Pre-existing psychological comorbidities	15 (14.6%)	14 (12.6%)
Follow-up duration: hospital discharge to 30 day-assessment, days	33.6 (5.7)	36.8 (7.5)
Follow-up duration: 30- to 90 day-assessment, days	66.3 (14.4)	61.7 (13.1)
Patient characteristics		

Table 1 (continued)

Characteristics	Patients	Relatives
	n = 108	n = 120
Duration of hospitalization (days), mean (SD)	8.95 (6.63)	
Severity of illness (NEWS score), mean (SD)	6.16 (3.58)	
Comorbidity (CCI), mean (SD)	2.36 (2.09)	
Antibiotics during hospitalization	36 (34.3%)	
Oxygen supply		
No oxygen supply	39 (36.8%)	
Nasal cannula/NIV	56 (52.8%)	
Intubation	11 (10.4%)	
Anxiolytics during hospitalization	20 (19.2%)	
Investigational treatment ^a	74 (70.5%)	
ICU stay (yes/no)	18 (16.8%)	
Relatives' characteristics		
Relationship to patient		
Patient is spouse		62 (52.1%)
Patient is child		7 (5.9%)
Patient is sibling		11 (9.2%)
Patient is parent		27 (22.7%)
Other		12 (10.1%)
Relative living in same household with patient		64 (53.8%)
Relative quarantined		46 (44.2%)
Relative also infected with COVID-19		37 (32.7%)

Data are presented as n (%) or mean (standard deviation).

Abbreviations: SD, standard deviation; NEWS, National Early Warning Score; NIV, Non-invasive ventilation; ICU, Intensive Care Unit; CCI, Charlson Comorbidity Index;

^a Investigational treatment: Hydroxychloroquine, Lopinavir/Ritonavir, Remdesivir, Tocilizumab, Convalescent Plasma.

hospital discharge. Several sociodemographic, illness-related, psychosocial and hospital-related risk factors and protective factors associated with clinically relevant psychological distress in patients and relatives were identified with each only moderate discrimination in ROC analyses and few independently associated. When combining all psychosocial factors that showed a statistically significant association, however, there was high prognostic accuracy to identify these patients and relatives. The same was true for the combination of age and gender and the significantly associated factors from all four domains in patients, as well as age, gender, death of patient and the significantly associated factors from all four domains in relatives. This is a relevant finding, because some of the factors may be at least partially modifiable during routine hospital care.

Several points of our results are worth discussing. First, the rates of clinically relevant psychological distress found in this study are in line with findings from recent short-term follow-up studies: Early studies on the psychological consequences of COVID-19 showed prevalence rates among newly recovered patients from 14% and 11% to 21% and 29% of anxiety and depression symptoms, respectively [34,35]. Mazza et al. evaluated Italian adults surviving COVID-19 one month after hospital discharge of which 31% reported clinically relevant depression and 42% anxiety symptoms [15]. In our follow-up, we found 21.3% of patients and 18.3% of relatives suffering from clinically relevant psychological distress. These short-term findings are comparable with our findings at

Table 2

Multivariable associations of predictor variables and clinically relevant psychological distress at 90-day follow-up in patients.

	Multivariable models within domains			Overall multivariable model, adjusted for age & gender	
	OR (95% CI)	p	AUC	OR (95% CI)	p
Sociodemographic factors					
Age (years)	0.98 (0.95, 1.01)	0.227	0.67	1.01 (0.97, 1.06)	0.653
Gender (female)	3.51 (1.32, 9.3)	0.012		1.59 (0.49, 5.16)	0.438
Illness-related factors					
Self-perceived overall health status (Euroqol VAS 0–100), mean (SD)	0.97 (0.94, 0.99)	0.014	0.63	0.98 (0.94, 1.01)	0.215
Psychosocial factors					
Resilience (CD-RISC), mean (SD)	0.92 (0.83, 1.03)	0.140	0.82	0.92 (0.83, 1.03)	0.154
Perceived Stress (PSS-10), mean (SD)	1.09 (0.99, 1.2)	0.068		1.09 (0.98, 1.21)	0.126
Worries due to COVID-19 media reports, mean (SD)	1.19 (0.98, 1.44)	0.085		1.17 (0.96, 1.42)	0.131
Burden of isolation measures, mean (SD)	1.02 (0.85, 1.23)	0.841		1.03 (0.8, 1.33)	0.825
Burden of boredom, mean (SD)	1.06 (0.89, 1.26)	0.500		1.08 (0.9, 1.3)	0.389
Worried about job situation, mean (SD)	1.02 (0.84, 1.23)	0.880		1.03 (0.81, 1.29)	0.831
Worried about medical care, mean (SD)	1.33 (0.96, 1.86)	0.089		1.35 (0.94, 1.95)	0.107
Hospital-related factors (VAS 0–10)					
Burden of having no visitors, mean (SD)	1.13 (0.91, 1.4)	0.264	0.66	0.92 (0.67, 1.27)	0.621
Missing physical contact/closeness, mean (SD)	1.06 (0.86, 1.3)	0.604		1.04 (0.8, 1.35)	0.783

Note. SD, standard deviation; OR, odds ratio; 95%CI, 95% Confidence Interval; COVID-19, Coronavirus disease 2019; CD-RISC, Connor-Davidson Resilience Scale; PSS-10, Perceived Stress Scale; VAS, visual analogue scale. P-values < 0.05 were considered statistically significant.

three-months follow-up, which highlights the need to reduce these sequelae by better caring for patients and relatives [36]. Herein, we identified several potential targets. Whether preventive strategies help to reduce these risks, however, remains unclear and needs further research.

Interestingly, in our study the proportion of patients and relatives with clinically relevant psychological distress was similar to the proportion of patients reporting symptoms of anxiety. This is in line with a recent study reporting also high levels of anxiety and depression in both, isolated patients with COVID-19 and their relatives, during the initial stage of hospitalization [16]. Anxiety was also predominant in their analysis. Similarly, also other studies investigating relatives of patients with COVID-19 or other infections in the context of previous epidemics suggest that they suffer from higher levels of distress as compared to individuals of the general population [35,37–41]. Importantly, we have learned that also the non-infected Swiss general population have an increase in depressive symptoms to up to 11.7% [14]. This suggests, that

Table 3

Multivariable associations of predictor variables and psychological distress at 90-day follow-up in relatives.

	Multivariable model within domains			Overall multivariable model, adjusted for age & gender	
	OR (95% CI)	p	AUC	OR (95% CI)	p
Socio-demographic factors					
Age (years)	1.01 (0.98, 1.04)	0.656	0.55	1.02 (0.97, 1.07)	0.501
Gender (female)	1.82 (0.49, 6.76)	0.368		0.54 (0.06, 4.88)	0.587
Illness-related factors					
Self-perceived overall health status (Euroqol VAS 0–100), mean (SD)	0.93 (0.9, 0.96)	<0.001	0.78	0.96 (0.91, 1.01)	0.142
Death of patient	2.12 (0.54, 8.25)	0.280		0.94 (0.05, 19.05)	0.968
Psychosocial factors					
Resilience (CD-RISC), mean (SD)	0.87 (0.74, 1.03)	0.113	0.95	0.87 (0.72, 1.06)	0.163
Perceived Stress (PSS), mean (SD)	1.25 (1.04, 1.51)	0.020		1.22 (1.00, 1.50)	0.052
Type of communication between relatives and patients					
Telephone, text and other	1 (Ref)			1 (Ref)	
Video calls & visits	0.56 (0.10, 3.02)	0.501		0.83 (0.11, 6.07)	0.853
Burdening factors (VAS 0–10)					
Perceived overall burden, mean (SD)	1.86 (1.22, 2.82)	0.004		1.77 (1.13, 2.76)	0.012
Worries by uncertain prognosis, mean (SD)	0.92 (0.73, 1.16)	0.495		0.88 (0.68, 1.15)	0.353
Burden of isolation measures, mean (SD)	0.86 (0.66, 1.13)	0.282		0.84 (0.63, 1.12)	0.245
Helpfulness of coping strategies (VAS 0–10)					
Sport, mean (SD)	0.80 (0.64, 1.00)	0.047		0.86 (0.67, 1.11)	0.249
Other, mean (SD)	0.91 (0.75, 1.10)	0.304		0.92 (0.74, 1.15)	0.462
Hospital-related factors (VAS 0–10)					
Burden of not being able to visit patient (VAS 0–10), mean (SD)	1.15 (0.93, 1.43)	0.198	0.76	1.05 (0.67, 1.65)	0.821
Missing physical contact/closeness (VAS 0–10), mean (SD)	1.2 (0.99, 1.45)	0.064		1.18 (0.85, 1.64)	0.329

Note. SD, standard deviation; OR, odds ratio; 95%CI, 95% Confidence Interval; CD-RISC, Connor-Davidson Resilience Scale; PSS-10, Perceived Stress Scale; VAS, visual analogue scale. P-values < 0.05 were considered statistically significant.

even though the pandemic has taken a toll on the mental well-being of all [39–41], more attention should be paid to patients with COVID-19 and their relatives in order to develop strategies to prevent persistent adverse psychological outcomes [38,42,43].

Several potential risk and protective factors could be identified in this study, although not all of them are modifiable, but still may help to

Table 4
Multivariable associations of predictor variables and PTSD symptoms at 90-day follow-up in patients.

	Multivariable models within domains			Overall multivariable model, adjusted for age & gender	
	OR (95% CI)	p	AUC	OR (95% CI)	p
Sociodemographic factors					
Age (years)	0.99 (0.94, 1.04)	0.761	0.86	1.05 (0.96, 1.15)	0.297
Gender (female)	5.84 (0.73, 46.58)	0.096		2.89 (0.09, 91.82)	0.548
Cultural background					
Central/Western Europe	1 (Ref)			1 (Ref)	
Other	13.82 (1.33, 143.3)	0.028		20.82 (0.18, 2473.88)	0.213
Civil status					
Married/partnership	1 (Ref)			1 (Ref)	
Widowed/separated/single	7.09 (0.98, 51.36)	0.052		34.08 (0.36, 3209.94)	0.128
Illness-related factors					
Self-perceived overall health status (Euroqol VAS 0–100), mean (SD)	0.95 (0.91, 1.00)	0.030	0.65	1.01 (0.95, 1.08)	0.695
Psychosocial factors					
Perceived Stress (PSS-10), mean (SD)	1.14 (0.99, 1.31)	0.072	0.86	1.12 (0.90, 1.39)	0.328
Worries due to COVID-19 media reports, mean (SD)	1.37 (0.97, 1.91)	0.070		1.39 (0.89, 2.18)	0.146
Worried about job situation, mean (SD)	1.02 (0.71, 1.46)	0.915		1.29 (0.75, 2.20)	0.360
Worried about finances, mean (SD)	1.45 (0.98, 2.13)	0.060		1.25 (0.77, 2.04)	0.369

Note. SD, standard deviation; COVID-19, Coronavirus disease 2019; PSS, Perceived Stress Scale; VAS, Visual Analogue Scale. *P*-values < 0.05 were considered statistically significant.

identify high risk subjects. Some of these factors are known to be associated with psychological distress in general such as female gender, subjective health and resilience, while other factors such as the burden due to isolation measures or COVID-19 media reports are specific to the current pandemic.

Regarding the former category, we found that female patients were significantly more likely than males to suffer from clinically relevant psychological distress. In the general population, women are known to be more prone to depression and anxiety disorders [44]. Previous research also reported increased risk for anxiety and depression in women affected by COVID-19 [15,16,45]. Interestingly, gender of relatives and being in a relationship were not associated with psychological distress in relatives in our sample. Possibly, the current pandemic poses specific challenges on these relationships. Social support is a well-known protective factor regarding mental health, which has been affected by contact restrictions in COVID-19 patients. A review on the effects of quarantine measures during previous epidemics indicated a negative impact on psychological well-being of patients and relatives especially due to separation from partners and relatives [9], which is in line with the findings of our study. While the majority of women tend to feel most emotionally supported by their friends, men usually report to mainly turn to their partner for emotional support [46,47]. Thus, particularly male relatives may experience distress due to fear about the course of disease of the partner and the lack of emotional support. Still, further research re-evaluating our findings and conducting external validation

Table 5
Multivariable associations of predictor variables and PTSD symptoms at 90-day follow-up in relatives.

	Multivariable models within domains			Overall multivariable model, adjusted for age & gender	
	OR (95% CI)	p	AUC	OR (95% CI)	p
Sociodemographic factors					
Age (years)	0.98 (0.93, 1.03)	0.408	0.58	0.98 (0.91, 1.05)	0.602
Illness-related factors					
Self-perceived overall health status (VAS 0–100), mean (SD)	0.95 (0.91, 0.99)	0.009	0.78	0.99 (0.93, 1.06)	0.864
Psychosocial factors					
Psychotropic drugs	2.65 (0.20, 34.87)	0.459	0.95	2.95 (0.20, 43.04)	0.429
Resilience (CD-RISC), mean (SD)	0.77 (0.61, 0.97)	0.024		0.78 (0.62, 0.97)	0.027
Perceived Stress (PSS), mean (SD)	1.11 (0.94, 1.32)	0.218		1.09 (0.88, 1.36)	0.429
Worried due to COVID-19 media reports, mean (SD)	1.71 (0.90, 3.24)	0.099		1.70 (0.81, 3.56)	0.161
Burden of isolation measures, mean (SD)	1.20 (0.81, 1.79)	0.353		1.23 (0.79, 1.92)	0.367
Hospital-related factors					
Burden of not being able to visit patient (VAS 0–10), mean (SD)	1.46 (1.03, 2.09)	0.035	0.76	1.00 (0.57, 1.76)	0.995

Note. SD, standard deviation; COVID-19, Coronavirus disease 2019; CD-RISC, Connor-Davidson Resilience Scale; PSS, Perceived Stress Scale; VAS, Visual Analogue Scale. *P*-values < 0.05 were considered statistically significant.

of prediction models is needed. Also, rates of psychological distress often decline with increasing age overall [48], and in COVID-19 [37,49]. Still, there was no association of age and distress in our sample. As we focused our study to older, hospitalized patients, our study might have been biased in this regard.

Within the domain of illness-related factors, patients and relatives with lower subjective overall health status experienced increased psychological distress. Objective clinical parameters usually concomitant with psychological sequelae, e.g., high illness severity and hospitalization in the ICU [50–52], however, were not associated. This might potentially be explained by the comparably small number of patients with severe illness course who needed intensive care treatment, i.e. 18 patients (16%) in our sample vs. 26% in a recent meta-analysis [53]. Several psychosocial factors were associated with clinically relevant psychological distress as expected and a combination of those showed high predictive value. Resilience, which can be defined as a person's emotional and mental capacity to adapt well when experiencing critical life events [54–56], was negatively associated with anxiety and depression in both patients and relatives and with PTSD in relatives only. Resilience was not independently associated though and its association might be explained by other psychosocial characteristics and circumstances. Based on our findings, availability of coping strategies such as exercise or social support through telephone and video calls as well as risk factors such as perceived stress or the overall burden due to COVID-19 might mediate the association between resilience and symptoms of anxiety, depression and PTSD. There is evidence indicating that resilience might be associated with poor mental health, e.g.,

symptoms of depression and anxiety in general [57]. Further, a review on resilience as a protective factor regarding symptoms of anxiety, depression and post-traumatic stress during the current pandemic found that many people use “resilient” coping strategies to handle COVID-19-related distress [58]. Exercise, which has a well-known positive effect on symptoms of depression and anxiety, emerged as a helpful coping strategy in relatives in our study. Perceived stress, a widely-researched risk factor for symptoms of anxiety, depression and PTSD was associated with clinically relevant psychological distress in both patients and relatives. Future studies are needed to better understand how these factors are connected.

Further, we identified several potential risk and protective factors specific to COVID-19 that were associated with clinically relevant psychological distress in patients and relatives. Similar to other studies, overall burden due to COVID-19 was a relevant factor [14]. In addition, social connectedness did not significantly affect psychological distress in multivariable analyses beyond other psychosocial factors and its effect might therefore significantly vary depending on other characteristics and circumstances. The perceived burden of isolation measures, the burden of having no visitors or not being able to visit and missing physical contact were associated with clinically relevant psychological distress in patients and relatives. This again is in line with older studies showing adverse psychological effects of quarantine and isolation [9,16,37]. Particularly, physical distancing seems to be an important factor for psychological distress [59]. Bridging this gap between physical distancing and social connection might be possible with the help of digital technologies and more such interventions are urgently needed. However, our findings suggest that social connectedness may be considered in a larger context of several relevant interacting psychosocial factors.

Overall, of the factors associated with clinically relevant distress in our study, many are well-known risk and protective factors and some are specific to COVID-19. This emphasizes the importance of not solely focusing on the negative impact of the COVID-19 pandemic and associated restrictions specifically but additionally considering the known characteristics that pose individuals at increased risk of developing significant psychological distress as well as the known protective factors and interventions that buffer the negative impact of stressful life events. Future research should further evaluate the role and interactions of known predictive factors and potential COVID-19 related risk factors. Insight into these dynamics might help to identify individuals who are at increased risk early on and to provide adequate support with the aim to prevent or mitigate mental health problems. Considering PTSD, one short-term follow-up study found a majority of inpatients with COVID-19 to report PTSD symptoms [60], while another found a third of patients showing clinically relevant symptoms [15]. In our population, the lower rates of 7.8% and 7.1% for PTSD symptoms in patients and relatives, respectively, might be reflected by the later timepoint of our assessment. The higher rates found in the other studies [15,60] might therefore display symptoms of acute stress remitting within 1 month after a traumatic event, of which only a minority develop a full PTSD [61].

4.1. Limitations

This study has some limitations. This two-center Swiss study was rather small and did not allow for rigorous statistical adjustment. Also, the observational design does not allow to draw any conclusions regarding preventive effects and the study is thus rather hypothesis generating. Due to the limited sample size, we did not have separate derivation and validation samples. External validation in independent and larger cohorts is therefore warranted. Further, the follow-up period of 3 months may have led to other factors leading to psychological distress and may confound findings as we did not have an unaffected control cohort at hand. Further, as the aim of this study was to assess a broad scope of potential risk and protective factors, multiple tests were

conducted without statistical correction, to aid in an exploratory hypothesis generation. However, a type I error cannot be ruled out and findings must, therefore, be considered exploratory and need validation.

4.2. Conclusions

A quarter of hospitalized patients with COVID-19 and their relatives experience clinically relevant psychological distress 90 days after hospital discharge. Psychosocial and isolation-related factors associated with psychological distress are at least partially modifiable during routine hospital care. External validation of these exploratory findings in a larger patient cohort is warranted.

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Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jpsychores.2021.110526>.

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