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Socio-demographic and clinical predictors of post-acute, mid-and long-term psychological sequelae of COVID-19: a two-year cross-sectional investigation on 1317 patients at the University Hospital of Verona

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Abstract

Background The present paper focuses on socio-demographics, clinical variables, and the distance from the infection in predicting the long-term psycho-social consequences of COVID-19.

Methods Patients were screened with a cross-sectional design at the Psychological Service of the University Hospital of Verona (Italy) at 3, 6, 12, and 18 months after their SARS-CoV-2 infection. The assessment was part of the Horizon 2020-funded ORCHESTRA Project and included the Hospital Anxiety and Depression Scale (HADS), the Short Form Health Survey 36 (SF-36), the Impact of Event Scale-Revised (IES-R), and ad-hoc questions measuring pre-post COVID-19 changes on psycho-social dimensions (sleep quality, nutrition, level of autonomy, work, social relationships, emotional wellbeing).

Results Between June 2021 and June 2023, we evaluated 1317 patients (mean age 56.6 ± 14.8 years; 48% male): 35% at three months, 40% at 6, 20% at 12, and 5% at 18 months after the infection. Thirty-five percent were hospitalized due to COVID-19. Overall, 16% reported some form of clinically significant mental distress following the infection (HADS-TOT), with 13% and 6%, respectively, experiencing anxiety (HADS-Anxiety) and depressive symptoms (HADS-Depression). Four percent testified post-traumatic symptoms. The SF-36 scale revealed that 16% and 17% of subjects had physical or psychological deterioration in quality of life, respectively. The regression analyses showed that females experienced higher levels of anxiety and depression compared to males, along with worse mental and physical quality of life and pre-post infection changes in nearly all the investigated psycho-social dimensions. Younger people felt more anxiety and had a reduced mental quality of life than their older counterparts, who, in turn, had poorer scores in terms of autonomy and physical functioning. Hospitalized patients had lower levels of self-sufficiency, social relationships, and work than non-hospitalized people. The latter were more anxious and reported a lower physical quality of life. Finally, patients evaluated for the first time at 12- and 18 months showed a more significant impairment in mental and physical quality of life than those assessed at three months.

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Conclusions Our data show that COVID-19 psychological sequelae tend to persist over time, still needing clinical attention and intervention planning, especially for females.

Keywords Covid 19, SARS-CoV-2, Anxiety, Depression, Mental distress, Quality of life, Post traumatic symptoms

Text box 1. Contributions to the literature

- Although COVID-19 is no longer a public health emergency, a two-year follow-up showed that there is still a sufficiently large proportion (17%) reporting clinically psychological problems after SARS-CoV-2 infection, without clear changes in time.
- Our data show that post-COVID-19 psychological consequences were different according to gender, age, and hospitalization.
- The findings suggest the existence of a vulnerable part of the population that needs to be monitored over time to manage the long-term psychological consequences of the pandemic and the provision by health services of the appropriate specialized interventions.

Introduction

Physical and psychological symptoms have been extensively described in patients during the post-acute phase of the SARS-CoV-2 infection, with persisting respiratory disorders, along with sensory, neurological, sleep, and physical energy impairment, on the physical side [1–3] and high rates of psychological distress with anxiety, depression, and post-traumatic signs at the mental level [4–9]. As a result, the overall quality of life of people who have experienced COVID-19 was extensively impaired in the short term after the infection [10–13].

With the end of the pandemic officially declared by the World Health Organization (WHO) on May 5, 2023 [14], COVID-19 no longer represents a public health emergency. Despite that announcement, the medium and long-term consequences of the SARS-CoV-2 infections at individual and population levels remain poorly understood, challenging societal organizations and health services worldwide. In this regard, in July 2023, WHO launched a 5-year (2024–2029) action plan to strengthen European health response to face the long-term sequelae of the pandemic [15], making the long COVID issue still worthy of close attention. The scientific literature has gradually introduced the term long COVID (or post-COVID-19 syndrome –PCS-, or post-acute sequelae of COVID-19, or persistent COVID-19) in the last two years. The WHO case definition of long-term COVID-19 (WHO, 2023) describes a syndrome affecting around 10–20% of people" [16], occurring within three months of the SARS-CoV-2 infection and lasting at least two months. The main clinical manifestations are chronic fatigue, diffuse myalgia, respiratory disorders, loss of taste and smell, which come together with cognitive (i.e., difficulty with concentration or brain fog) and psychological (mainly anxiety and depression) symptoms, with the consequence of reducing the overall quality of life [17–25]. Despite such a broad description, clinicians and researchers are far from precisely characterizing the post-COVID-19 syndrome, with the time of symptoms onset, their clinical manifestation, and duration still under debate [26–28]. A recent report including a multinational prospective cohort within the ORCHESTRA project identified four clinical clusters producing a different impact on the quality of life measured with the SF-36 questionnaire and allowing for stratification of post-COVID-19 syndrome severity based on the effect of each cluster and combination of clusters on the physical and mental wellbeing of patients [29]. Furthermore, although the WHO definition considers the three-month term after the infection, some studies have reported the presence of at least one psychological symptom six months after the infection [30, 31], or between six and twelve months [32–38], with some symptoms appearing to show a worsening trend over time [39, 40]. Interestingly, two recent studies suggested the presence of physical (i.e., fatigue, dyspnea, headache, myalgia among the most reported) and psychological (i.e., anxiety, depression, cognitive problems, and sleep disturbance symptoms) consequences of COVID-19 after two years from the infection [41, 42]. Moreover, a meta-analysis [43] on survivors of acute respiratory distress syndrome (ARDS) showed an impaired physical and mental quality of life up to five years after the infection compared to the average population, suggesting the value of monitoring physical and mental consequences even for an extended period. Given such premises, the characterization of the SARS-CoV-2 psychological impact at different time points of the post-acute period appears highly relevant since it can be instrumental in increasing our knowledge of the psycho-social consequences of the disease according to the distance from infection and improving clinical guidelines for patient care accordingly.

Another vital issue includes the estimation of the influence of clinical and individual variables, which seem to modulate the psychological impact of the illness in both the short- and long-term. For example, patients who had been admitted to the hospital due to COVID-19 (and especially those requiring a transfer to the intensive care

unit) were more impaired in physical and mental health-related quality of life compared to non-hospitalized people [9]. In addition, anxiety symptoms have been observed in patients admitted to the hospital after the post-acute phase [4, 7, 17], with one study showing fewer anxiety symptoms in patients discharged after COVID-19 compared to those who were not admitted to the hospital [9]. Similarly, individuals hospitalized by COVID-19 were more likely to report persistent symptoms [44, 45] and to develop post-traumatic symptoms disorder (PTSD) compared to those who were not [6, 46].

As regards individual characteristics, being female and older were among the strongest predictors of short and long-term sequelae at both physical and mental levels [3, 25, 47–50], strengthening the importance of considering their role in current research.

The present study reports the experience of a Clinical Psychological Service at a University Hospital in north-eastern Italy over a 2-year period. We aimed to:

1) Investigate the psychological impact of COVID-19 on a cohort of patients with previous SARS-CoV-2 infection who were enrolled in the ORCHESTRA study [51] and underwent a psychological evaluation within the Psychological Service of the University Hospital of Verona from June 2021 to June 2023. Based on what literature showed to be the most relevant variables affecting the psychological impact of COVID-19 [8, 9, 52], we assessed anxiety, depression, post-traumatic symptoms, physical and mental quality of life, along with pre-post Covid19 perceived changes in psycho-social dimensions (autonomy, sleep, nutrition, work, social relationship, emotional well-being) at patients' first psychological evaluation;
2) Given the persistence of symptoms after COVID infection [35, 37, 42, 53], we explored the role of the distance from the SARS-CoV-2 infection on anxiety, depression, physical and mental quality of life, and psycho-social dimensions (autonomy, sleep, nutrition, work, social relationship, emotional well-being), at 3-, 6-, 12-, and 18-month post-acute infection with a cross-sectional design;
3) Evaluate the role of clinical (i.e., hospitalization [46, 54]) and socio-demographic (namely, age and gender [47]) variables in predicting the psychological and psycho-social outcomes of the SARS-CoV-2 infection.

Methods

Study design and participants

In April 2021, the Horizon 2020 multinational prospective research project ORCHESTRA (connecting European cohorts to increase common and effective responses to the SARS-CoV-2 pandemic) was launched, with the aim of generating rigorous and large-scale scientific evidence on the COVID-19 pandemic and deriving recommendations for possible future pandemic events [51]. The ORCHESTRA Work Package 2 (WP2) focused on COVID-19 long-term sequelae, enrolling a cohort of patients with previous COVID-19 from six European and non-European centres, including a cohort of patients recruited at the Verona University Hospital. The patients were followed up at 3-, 6-, 12-, and 18- months post-acute infection through a comprehensive physical and laboratory assessment. In June 2021, the Clinical Psychology Unit of the University Hospital of Verona joined the ORCHESTRA WP2, contributing to collecting psycho-social data during the same time points planned by the follow-up of COVID-19 long-term sequelae study protocol [55].

In- and out-patients with a laboratory-confirmed SARS-CoV-2 infection were included in the study after written informed consent. A psychological screening on the same day of the clinical evaluation at the post-COVID Ambulatory was offered to those aged ≥ 18 years. A team composed of a psychotherapist with the role of supervisor and five residents in psychotherapy handled the psychological consultations and 1-h structured interviews with questionnaires (see paragraph 2.2).

All data were gathered anonymously and managed using the REDCap electronic data capture tool (Research Electronic Data CAPture) hosted at the Interuniversity Consortium CINECA [56].

The study was approved by the Ethical Committee of the Azienda Ospedaliera Universitaria Integrata of Verona (Prog. 3199CESC).

Psychological assessment

Patients were assessed at the time of the first visit performed at the Post-COVID Ambulatory (3, 6, 12, or 18 months after the infection) with the Hospital Anxiety and Depression Scale (HADS) [57, 58], the Impact of Event Scale-Revised (IES-R) [59], and the SF-36 Health Survey (SF-36) [60, 61]. Patients were also asked to evaluate the pre-post COVID-19 perceived changes on some psycho-social dimensions using a study-specific set of questions collected during the clinical interview (for details on assessment measures, see Table 1).

Assessment questionnaires were selected according to their validation, reliability, and use in previous studies on the Italian population during the COVID-19 pandemic [9]. Psycho-social dimensions were created to facilitate gathering information colloquially during the psychological consultation and to create the opportunity to make the patient feel supported during data collection.

Table 1 Post-COVID-19 Psycho-social assessment of ORCHESTRA Project

Questionnaire	Authors	Brief description of the questionnaire	Scoring and reliability index (Cronbach's alpha) of the questionnaire in our sample
Hospital Anxiety and Depression Scale (HADS)	Zigmond and Snaith, 1983; [57] Costantini et al., 1999 [58]	Self-report scale composed of two 7-item scales developed to measure states of anxiety (HADS-A) and depression (HADS-D) among outpatients in non-psychiatric hospital clinics	Item score 0–3; Cut off indicative of a psychological problem requiring intervention: HADS-TOT ≥ 11 HADS-A ≥ 8 HADS-D ≥ 8 Cronbach's alpha: HADS-A = 0.82; HADS-D = 0.75; HADS-TOT = 0.87
Impact of Event Scale-Revised (IES-R)	Weiss, 2007 [59]	Self-report questionnaire assessing subjective distress for different life events. It includes 22 items, subdivided into three subscales: - Avoidance (the tendency to avoid thoughts or reminders about the incident) - Intrusion (difficulty in staying asleep, dissociative experiencing, similar to flashbacks) - Hyperarousal (irritated feeling, anger, sleep difficulty)	5-point Likert scale (from 0 = not at all, to 4 = extremely) Cut-off indicative of a high risk of PTSD symptomatology IES-R TOT ≥ 33 Cronbach's alpha: IES-R Avoidance = 0.86; IES-R Intrusion = 0.9; IES-R Hyperarousal = 0.82; IES-R TOT = 0.95
SF-36 Health Survey (SF-36)	Ware, 1999 [61], Apolone & Mosconi, 1998 [60]	self-report questionnaire measuring the health-related quality of life (HR-QoL)	Algorithm developed and provided by "The Mario Negri Institute" Cronbach's alpha: SF-36 physical dimension = 0.92; SF-36 psychological dimension = 0.88

Questions on pre-post COVID-19 perceived changes	Possible responses and scoring
Autonomy "Compared to the period preceding the COVID-19 infection, how do you evaluate your present level of autonomy?" (i.e., self-care, daily activities, sport)	0 = not modified, 1 = mildly modified, 2 = significantly modified, and 3 = severely modified
Sleep quality "Compared to the period preceding the COVID-19 infection, how do you evaluate your sleep quality?"	0 = not modified, 1 = mildly modified, 2 = significantly modified, and 3 = severely modified
Nutrition "Compared to the period preceding the COVID-19 infection, how do you evaluate your nutrition?"	0 = not modified, 1 = mildly modified, 2 = significantly modified, and 3 = severely modified
Work "Compared to the period preceding the COVID-19 infection, what is now your work condition?"	0 = went back to working full time, 1 = went back to working part-time, 2 = not working due to COVID-19 infection sequelae, 3 = not working due to reasons different from COVID-19 infection sequelae (i.e. retired and not working anymore, disabled or invalid)
Social relationships "Compared to the period preceding the COVID-19 infection, how do you rate the quality of your relationships? (i.e. couple relation, family, friends)"	0 = not modified, 1 = mildly modified, 2 = significant difficulties, 3 = severe difficulties
Emotional well-being "Compared to the period preceding the COVID-19 infection, how do you evaluate your emotional well-being?"	0 = no changes in emotional well-being, 1 = mild psychological symptoms without an impact on quality of life, 2 = mild psychological symptoms with an effect on quality of life, 3 = severe psychological symptoms

Finally, patients were asked about their availability to be engaged in psychological treatment if they were positive at psychological screening (possible answers: Yes, No).

Statistical analyses

The statistical package Stata 18 [62] was used for all analyses.

Descriptive statistics reported socio-demographic and clinical data.

Multiple regression models were applied to explore a set of potential socio-demographic (age, gender) and clinical (hospitalization, distance from the infection) predictors on the outcome variables (anxiety and depression levels, mental and physical quality of life, changes in specific psycho-social dimensions). The linear or logit function of the models was selected as requested by the dependent variable format. Specifically, linear regressions were applied to screening questionnaires (HADS, SF-36), and logistic regressions to psychosocial dimensions by collapsing responses into binary data (0 = no change vs 1 = at least some change) to compensate for their strongly skewed frequency distributions. Cohen's d and f2 and McKelvey and Zavoina's R2 effect size measures were used to evaluate differences among compared groups.

Results

Aim 1: Impact of SARS-CoV-2 infection on psychological state and psycho-social dimensions

Between June 2021 and June 2023, 1416 patients were assessed for the first time within the ORCHESTRA Project; of these, 1317 (93%) agreed to undergo a psychological assessment. Table 2 shows the socio-demographic and clinical information of the 1317 participants (mean age ± SD: 56.6 ± 14.8).

Psychological outcomes

Of the sample, 1264 (96%) patients completed the HADS and the SF-36 scales. All the patients responded to the IES-R scale.

As regards HADS, 193 (17%) patients reported some form of clinically significant mental distress (HADS-TOT ≥ 11). The analysis of the subscales HADS-A and HADS-D revealed that 148 (13%) and 71 (6%) patients, respectively, experienced anxiety (HADS-A ≥ 8) and depressive symptoms (HADS-D ≥ 8).

The SF-36 scale showed a deterioration in quality of life in both the physical and the mental dimensions, which interested 16% and 17% of the sample, respectively. According to the HADS scale, cut-score patients who were significantly distressed (HADS-TOT ≥ 11) had lower scores (that is, more significant impairment) at the SF-36 subscales (SF36 physical: $t = 16$; $p < 0.01$; Cohen's d = 0.51; SF36 mental: $t = 17.8$; $p < 0.01$; Cohen's d = 1.94).

Four percent reported post-traumatic symptoms (IES-R score ≥ 24). Among them, 2% scored 24–32, and 2% scored > 33, which is compatible with a diagnosis of post-traumatic stress disorder (PTSD). All IES-R subscale scores were higher in distressed patients (HADS-TOT ≥ 11) compared to those with HADS-TOT < 11 (avoidance: $t = 8.73$, $p < 0.01$; Cohen's d = 0.62; intrusion: $t = 10.15$; $p < 0.01$; Cohen's d = 0.75; hyper-arousal: $t = 10.1$; $p < 0.01$; Cohen's d = 0.76).

Psychosocial dimensions

Among the participants, 1301 (99%) patients answered the questions on the psycho-social changes they perceived compared to before the SARS-CoV-2 infection. Overall, up to 28% of the sample reported at least one mild change compared to the pre-COVID-19 infection period, with the sleep dimension being the most impaired. Table 3 summarizes the frequencies and percentages of answers.

Finally, 1266 (96%) patients answered the question regarding their availability to undergo a psychological intervention eventually. Of these, ninety-five percent expressed a positive attitude towards psychological treatment.

Aims 2 and 3: Role of distance from the infection and socio-demographical and clinical predictors concerning the psychological and psycho-social outcomes

Psychological outcomes

Psychological outcomes were assessed with the HADS and SF-36 questionnaires. Given the low percentage of patients who reported an IES-R score > 24 (4%, of which only 2% had a score > 33, suggesting the presence of PTSD), we decided not to include the IES-R scale in the regression analyses.

Both socio-demographic and clinical factors predicted the HADS-A scores.

Females experienced more anxiety than males (21% vs. 7.8%, respectively, has HADS-A > 8), as did younger than older patients (21% in the age range 18–39, 21% aged 40–55, 9.7% aged 56–69, and 8.3% aged over 70 years had HADS-A > 8). The level of anxiety was lower in people who were hospitalized (8% of hospitalized patients had HADS-A > 8) compared to those who were not (18.3% of non-hospitalized patients had HADS-A > 8). The distance from the infection did not affect the HADS-A score (12.5% at three, 15.6% at six, 16% at 12, and 10.7% at 18 months had HADS-A > 8).

As regards HADS-D, scores were explained partially by gender only (see Table 4), with females experiencing higher scores for depression symptoms compared

to males (8.3% of females and 4.6% of males have HADS-D > 8).

Socio-demographic factors predictive of impaired SF-36 psychological dimension (SF-36 mental score) were age and gender (see Table 5). Younger patients showed lower scores than their older counterparts (meaning that they felt worse), with 10.9% of patients in the age range 18–66 having SF-36 scores minus two standard deviations (SD) under the mean of the population, compared to the 7.4% of those aged more than 56 years. Females were psychologically more impaired than males, with 6.3% of females and 2.6% of males having an SF-36 mental score under the mean (< 2 SD). The distance from the infection showed a predictive role too: patients assessed at 12 months felt worse than those evaluated at three months (7.1% vs. 3.4% at 12 and three months, respectively).

The SF-36 physical dimension scores were predicted by age, gender, hospitalization, and distance from the infection (see Table 5). Older and female patients, including those who had not been hospitalized, felt more impaired physically than those who were younger, male and had been hospitalized. Patients assessed for the first time at 18 months were the most impaired (14.7% with SF-36 physical score < 2SD at 18 months, compared to 7.1% at 12, and 5.8% at six months).

Psychosocial dimensions

Table 6 reports socio-demographic and clinical predictors of the psycho-social dimensions.

The level of autonomy (in self-care, daily activities, and sports) was predicted by age, with older patients scoring worse than younger counterparts (5.6% with more than 56 years had at least mildly modified autonomy compared to 3% in the age range 18–55). Also, patients hospitalized for COVID-19 were three times as likely to perceive an adverse change in autonomy compared to non-hospitalized patients (8.6% in the hospitalized and 2.2% in the non-hospitalized group).

Being female represents a risk factor for bad sleep quality (32.5% of females compared to 22.8% of males) and nutrition (12.9% of females versus 8.7% of males).

The variable 'work' was predicted by gender and hospitalization. In particular, being female and hospitalized for COVID-19 predicted a more difficult return to work following the infection. Specifically, 9.9% of the female group, compared to 7.3% of males, experienced difficulties returning to full-time work, as did hospitalized patients (12%) compared to those who were not (7.2%).

Regarding social relationships, patients with a history of hospitalization due to SARS-CoV-2 showed more difficulties (in such dimension of quality of life) compared to

Table 2 Socio-demographic and clinical characteristics of the patients who underwent psycho-social evaluation (Total sample *N* = 1317 patients)

Socio-demographic characteristics of the sample	
Gender, N (%)	
Male	630 (48.0%)
Female	687 (52.0%)
Age range, N (%)	
18–39	166 (13.0%)
40–55	441 (33.0%)
56–69	426 (32.0%)
> 70	284 (22.0%)
Education, N (%)	
Primary school	100 (8.2%)
Middle school	290 (23.8%)
High school	531 (43.6%)
Bachelor's or Master's degree	279 (22.9%)
Post-graduate degree	11 (0.9%)
Employment, N (%)	
Employed	766 (58.2%)
Unemployed	37 (2.8%)
Housewife	67 (5.1%)
Student	27 (2.1%)
Retired	375 (28.5%)
Missing	45 (3.4%)
Marital status, N (%)	
Single	172 (13.3%)
Married	868 (67.2%)
Cohabitant	97 (7.5%)
Separated/Divorced	88 (6.8%)
Widowed	66 (5.1%)
Missing	26 (2.0%)
Clinical characteristics of the sample	
Pre-existent pathologies, N (%)	
Yes	431 (33.0%)
No	885 (67.0%)
Hospitalization, N (%)	
Yes	461 (35.0%)
No	850 (65.0%)
Distance of the first assessment from COVID-19 infection, N (%)	
3 months	461 (35.0%)
6 months	532 (40.0%)
12 months	261 (20.0%)
18 months	63 (5.0%)
COVID-19 waves, N (%)[a]	
1 (February 2020-May 2020)	59 (4.5%)
2 (June 2020-December 2020)	308 (23.4%)
3 (January 2021-June 2021)	444 (33.7%)
4 (July 2021-March 2022)	470 (35.7%)
5 (April 2022-May 2023)	36 (2.7%)
Early treatment for SARS-CoV-2 infection with monoclonal antibody, N (%)	
Yes	173 (13.0%)
No	1140 (87.0%)

In the whole table, where the percentages do not reach 100%, less than 1% of the missing data is missing

[a] COVID-19 waves have been set according to (https://nextstrain.org/sars-cov-2/)

non-hospitalized patients (15.6% versus 9.9%); the same was true for females (14.1%) compared to males (9.5%).

Emotional well-being was predicted by gender, with females having twice the likelihood of being impaired after the illness (24.1% of females compared to 12.6% of males), and distance from the infection. As for the latter, people assessed for the first time 18 months after the SARS-CoV-2 infection were more compromised at the psychological-emotional level compared to those who completed the evaluation at three months (27.9% at 18 months versus 17.3% at three months).

Discussion

The overall aim of the present study was to assess the role of socio-demographic and clinical variables and the distance from the infection in predicting the COVID-19 short-(three months), mid-(6-months), and long-term (more than 12 months) psycho-social sequelae after SARS-CoV-2 infection.

As regards the first aim of the study (assessing the presence of psychological conditions deserving clinical attention and measuring the pre-post-COVID-19 changes in a series of psychosocial variables with a study-specific set of questions), we observed the presence of clinically significant psychological distress in 17% of our total sample (regardless of the distance from the infection) being a substantial percentage lower compared to other Italian studies published in a very short time after the beginning of the pandemic [4, 7, 9], but similar to those of articles published subsequently, also covering different geographical contexts [25, 63–65]. It should be noted that by starting our assessment in June 2021, we could not measure the levels of psychological distress in the early stages of the pandemic; on the other hand, the length of the follow-up allowed us to detect the presence of persistent psychological symptoms over a two years-period. Such observation is consistent with data coming from the literature worldwide, showing an overall deterioration in the level of mental health conditions after the COVID-19 pandemic in both people who were infected [19, 43, 66–68] and in the general population [69–71], including healthcare workers [72, 73]. This boosts the need to maintain vigilance towards specific psychological dimensions, resulting in impairment after the pandemic.

Results related to the subscales HADS-A and HADS-D showed that anxiety symptoms appear to be more diffuse compared to depressive ones in our sample. This is understandable if we consider the psychological impact of the COVID-19 pandemic and its consequences (lockdown, shortage of personal protective equipment), which included feelings of uncertainty, isolation, fear of infecting family members, and fear of death, as the most frequently reported [74]. In our sample, people with higher levels of distress were also those who reported a deterioration in physical (16%) and mental (17%) quality of life, along with symptoms of PTSD in terms of higher levels of avoidance, intrusion, and hyper-arousal (2% clinical PTSD; 2% sub-clinical PTSD threshold), suggesting the presence of a minor, albeit significant, sample sub-group requiring prudent clinical attention over time and needing focused interventions [75].

Table 3 Distribution of psycho-social changes compared to before the Sars-Cov2 infection (Responders *N* = 1301 patients)

Psychosocial dimensions	
Autonomy, N (%)	
Not modified	1239 (95.2%)
Mildly modified	40 (3.1%)
Significantly modified	13 (1.0%)
Severely modified	7 (0.5%)
Missing	2 (0.2%)
Sleep quality, N (%)	
Not modified	935 (71.9%)
Mildly modified	301 (23.1%)
Significantly modified	58 (4.5%)
Severely modified	6 (0.5%)
Missing	1 (0.1%)
Nutrition, N (%)	
Not modified	1158 (89.0%)
Mildly modified	121 (9.3%)
Significantly modified	21 (1.6%)
Severely modified	1 (0.1%)
Work, N (%)	
Went back to working full-time	869 (66.8%)
Went back to working part-time	54 (4.1%)
Not working due to COVID-19 infection sequelae	29 (2.2%)
Not working due to reasons different from Covid-19 infection sequelae	338 (26.0%)
Missing	11 (0.9%)
Social relationships, N (%)	
Not modified	1144 (87.9%)
Mildly modified	130 (10.0%)
Significant difficulties	23 (1.7%)
Severe difficulties	2 (0.2%)
Missing	2 (0.2%)
Emotional well-being, N (%)	
No psychological symptoms	1053 (81.0%)
Mild psychological symptoms without an impact on quality of life	176 (13.5%)
Mild psychological symptoms with an impact on quality of life	55 (4.2%)
Severe psychological symptoms	10 (0.8%)
Missing	7 (0.5%)

Table 4 Predictors of the HADS scores

Predictors	HADS-Anxiety				HADS-Depression			
	b	Standard error	95% Confidence interval		b	Standard error	95% Confidence interval	
			lower	upper			lower	upper
Socio-demographic								
Age	**-0.02**	0.01	-0.04	-0.01	-0.00	0.01	-0.01	0.01
Gender	**1.23**	0.21	0.82	1.64	**0.73**	0.16	0.41	1.04
Clinical								
Hospitalization	**-0.73**	0.23	-1.18	-0.28	-0.02	0.18	-0.37	0.32
Distance from the infection								
3 months	(base)				(base)			
6 months	0.38	0.23	-0.08	0.84	0.33	0.18	-0.02	0.83
12 months	0.54	0.29	-0.03	1.11	0.39	0.22	-0.05	0.83
18 months	0.40	0.50	-0.57	1.37	0.61	0.38	-0.14	1.36

Statistically significant results are in bold

Cohen's f^2: HADS-A = 0.07; HADS-D = 0.02

Table 5 Predictors of the SF-36 scores

Predictors	SF-36 Physical				SF-36 Mental			
	b	Standard error	95% Confidence interval		b	Standard error	95% Confidence interval	
			lower	upper			lower	Upper
Socio-demographic								
Age	**-0.16**	0.02	-0.19	-0.13	**0.07**	0.02	0.03	0.11
Gender	**-2.79**	0.47	-3.72	-1.86	**-3.62**	0.56	-4.71	-2.53
Clinical								
Hospitalization	**-1.76**	0.52	-2.78	-0.75	-0.98	0.61	-2.17	0.21
Distance from the infection								
3 months	(base)				(base)			
6 months	**-1.26**	0.53	-2.31	-0.21	-0.31	0.62	-1.53	0.92
12 months	**-1.39**	0.66	-2.68	-0.11	**-1.78**	0.77	-3.29	-0.28
18 months	**-3.06**	1.13	-5.28	-0.84	1.91	1.32	-0.69	4.51

Statistically significant results are in bold

Cohen's f^2: SF-36 Physical = 0.13; SF-36 Mental = 0.06

To assess a series of psychosocial dimensions of possible pre-COVID-19 alterations, we also administered a study-specific set of questions related to pre-post-COVID-19 changes in autonomy, sleep, nutrition, work, social relationships, and emotional well-being. Results showed that up to 28% of the sample reported at least one mild change compared to the pre-COVID-19 infection period, with the quality of sleep as the most impaired, followed by emotional well-being and social relationships. Compared to the use of standardized questionnaires assessing the presence of symptomatology in the present moment or on a time range, it is worth employing ad-hoc open questions specifically designed to detect pre-post infection changes. This clinical research approach also represented a first response to the patient's socio-emotional needs to be heard and understood in a time of emergency for the health services.

Regarding our second aim, we explored how the distance from the infection and the first psychological evaluation have impacted the psychological (anxiety, depression, physical and mental quality of life) and psycho-social (autonomy, sleep, nutrition, work, social

Table 6 Predictors of the psycho-social dimensions: autonomy, sleep quality, nutrition work, social relationships, emotional well-being

Predictors	Autonomy				Sleep Quality				Nutrition			
	OR[a]	Standard error	95% Confidence interval		OR	Standard error	95% Confidence interval		OR	Standard error	95% Confidence interval	
			lower	upper			lower	upper			lower	upper
Socio-demographic												
Age	**1.04**	0.01	1.02	1.06	1.00	0.00	1.00	1.01	1.00	0.01	0.99	1.01
Gender	1.31	0.37	0.76	2.27	**1.58**	0.21	1.23	2.04	**1.56**	0.29	1.08	2.26
Clinical												
Hospitalization	**3.36**	1.03	1.84	6.11	0.77	0.11	0.58	1.02	1.18	0.23	0.80	1.74
Distance from the infection												
3 months	(base)				(base)				(base)			
6 months	1.02	0.34	0.52	1.98	0.98	0.14	0.73	1.31	1.29	0.27	0.86	1.94
12 months	1.10	0.42	0.52	2.33	1.35	0.24	0.96	1.91	1.07	0.28	0.64	1.79
18 months	1.88	0.97	0.68	5.17	1.61	0.48	0.90	2.87	1.36	0.57	0.60	3.08
	Work				**Social Relationships**				**Emotional Well-Being**			
	OR[a]	**Standard error**	**95% Confidence interval**		**OR**	**Standard error**	**95% Confidence interval**		**OR**	**Standard error**	**95% Confidence interval**	
			lower	**upper**			**lower**	**upper**			**lower**	**upper**
Socio-demographic												
Age	1.00	0.01	0.98	1.02	1.01	0.01	1.00	1.02	1.00	0.01	0.99	1.01
Gender	**1.64**	0.40	1.02	2.66	**1.88**	0.35	1.32	2.70	**2.24**	0.35	1.65	3.05
Clinical												
Hospitalization	**1.83**	0.46	1.12	3.00	**1.75**	0.33	1.21	2.53	0.98	0.16	0.71	1.36
Distance from the infection												
3 months	(base)				(base)				(base)			
6 months	0.72	0.20	0.42	1.24	1.10	0.23	0.73	1.66	0.94	0.16	0.67	1.32
12 months	0.92	0.29	0.50	1.69	1.40	0.34	0.88	2.24	1.37	0.28	0.92	2.04
18 months	1.58	0.73	0.63	3.92	1.10	0.46	0.48	2.49	**1.98**	0.64	1.05	3.73

McKelvey and Zavoina's R^2: Autonomy = 0.2; Sleep Quality = 0.03; Nutrition = 0.02; Work = 0.05; Social Relationships = 0.05; Emotional Well-Being = 0.06

[a] Statistically significant results are in bold

relationship, emotional well-being) outcomes. We evaluated patients for the first time at 3, 6, 12, and 18 months after the COVID-19 infection, obtaining two important conclusions: on the one hand, the distance from the infection had no role in predicting the levels of anxiety (HADS-A score) and depression (HADS-D score), which ranged between 10.7 and 16% in patients evaluated at different time points; on the other hand, we observed a deterioration in both physical (6, 12, and 18 months) and mental (12 months) quality of life over time, as revealed by SF-36 scores, together with the dimension 'emotional well-being,' which resulted in patients evaluated at 18 months as worse than in those assessed at a shorter distance from the infection. Taken together, these findings suggest that some symptoms (specifically, anxiety and depressive ones), if not treated, tend not to disappear with time but instead remain stable, while other COVID-19 consequences (on the mental and physical quality of life) would deteriorate over time. Although counterintuitive at first sight, this observation becomes more understandable if we consider that the pandemic has tested public health services, which have not been able to guarantee the psychological and psychiatric support necessary for situations of mild or modest severity, as the resources necessarily had to be allocated towards the more critical conditions. Arguably, this means that COVID-19 survivors who suffered from mild to moderate anxious or depressive symptoms, that were not adequately addressed, continued to manifest these symptoms even many months later, as suggested elsewhere [40, 62, 75].

As for the third aim of our study, which investigated the role of clinical (i.e., hospitalization) and socio-demographic (namely, age and gender) variables in predicting the psychological and psycho-social dimensions outcomes of the COVID-19 infection, we observed a significant impact of gender and age in predicting psychological and psychosocial outcomes. In particular, in our sample, females seem to have felt the consequences of the infection to a greater extent than their male counterparts, as they reported more anxiety, depressive symptoms, and a more impaired mental and physical quality of life compared to males. Also, women had worse sleep quality, more significant problems in nutrition, and more difficulties in returning to work full time, as such in social relationships and emotional well-being after the infection compared to males, in line with most of the existing literature showing that the female gender was the most disadvantaged by the pandemic [3, 25, 47–50, 76]. This disparity can be due to both the direct consequences of the infection. Indeed, fatigue and sleep quality impairment are among the most reported symptoms in females, being related to COVID-19 severity [77] and usually associated with anxiety and depression [78], along with the greater prevalence of eating disorders in females than males [79–81]. Also, as a secondary effect of the pandemic, the most general condition of women in family, work, and society, at least in Italy, contributed to a higher number of women, compared to men, being forced to permanently abandon their jobs due to the need to take care of their children because of schools' closures. This led to an exacerbation of gender-based pre-existing differences [82].

Unlike gender, the age variable has a different trend depending on the variables considered. In particular, younger patients experienced more psychological distress than the older ones, with greater levels of anxiety and lower mental quality of life. By contrast, older people were more impaired in autonomy in everyday life and had a lower physical quality of life than the youngest. This difference (more significant psychological impact in young people and greater physical impact in the elderly) can be interpreted in light of greater resilience and adaptation processes in older adults [83] and the change of perspective in different phases of life: a young person who got the infection experienced a more remarkable impact on occupational, family and life perspectives, compared to an older person. Older people were more prone to physical disorders and comorbidities which were exacerbated by COVID-19, with the consequence of higher limitations in their autonomy [84–86].

As for the role of hospitalization, hospitalized (that is the most severe) patients manifested fewer anxious symptoms in the HADS-A sub-scale and felt better in terms of mental quality of life compared to the non-hospitalized group, having a less severe COVID-19 infection, possibly the first group having received the more medical assistance compared to the second one who therefore received less intensive care at home and had to rely only on their resources to deal with the consequences of the stressful event [9]. Moreover, hospitalized patients had lower autonomy and impaired social life compared to the non-hospitalized ones [87].

The present study has both strengths and limitations. Regarding the former, we collected data on a large sample of patients from Verona and its countryside for 2 years, using different time points and several instruments. Such an approach allowed us to observe the impact of the distance from the infection on a wide range of psychological and psychosocial outcomes at 3, 6, 12, and 18 months and suggests the feasibility of collecting clinical data useful for research purposes and, at the same time, providing a prompt psychological counseling service to the population. As for the psychosocial

variables (autonomy, sleep, nutrition, work, social relationship, and emotional well-being), we specifically explored the pre-post changes with a study specific set of questions, with the advantage of having explored the actual impact of the infection on the variables under study, net of previous situations. As a further strength point, it is important to mention the fact of having managed to activate a close and effective collaboration between different hospital departments (namely, the Infectious Disease and the Clinical Psychology departments), which resulted in an ad-hoc post-COVID-19 clinic having the patient's integrated physical and psychological health as the primary focus. Our clinical-based research experience suggests the importance of promoting in the future and in other clinical contexts the close integration of Services, adopting a bio-psycho-social, multidisciplinary and a patient-centered perspective [88, 89].

As a limitation of our study, it is important to mention that we collected data from June 2021 to June 2023, being such an interval of time characterized by different SARS-CoV-2 variants and by the introduction of vaccination in Italy in December 2020. Therefore, we cannot know if and how those variables may have affected our results. In the same way, we did not include other variables in our study that may have played the role of moderators/mediators concerning the investigated outcomes. For example, spirituality can be related to the levels of depression and anxiety [90], and cognitive reserve can represent a protective factor against the cognitive and psychological sequelae derived from the illness [91]. Second, we cannot exclude a biased (but still based on a clinical request) selection (i.e., patients who were admitted to the screening at 12- and 18-months were those who experienced more psychological symptoms) nor fail to take into account the fact that older patients were also those who generally (and regardless of having contracted the SARS-CoV-2) are vulnerable to physical symptoms and comorbidities, together with lower levels of autonomy than the younger counterpart of the population, with consequent difficulty in discriminating the effects of older age from those of the infection. Another point of view is to consider these effects as a sum rather than necessarily wanting to distinguish them. We explicitly asked what changes were found following the infection to offset this bias. Third, the sample of people evaluated at 18 months was small; therefore, our conclusions need to be confirmed in a larger sample of patients. Finally, since we know that COVID-19 has impacted the Italian regions differently, the generalization of our results outside our geographical area can be limited.

Conclusion

The present study showed the presence of psychological and psychosocial sequelae of COVID-19 in a sub-group of patients with a previous laboratory-confirmed SARS-CoV-2 infection, with such consequences differently predicted by sociodemographic and clinical factors. Overall, our findings suggest the existence of a vulnerable part of the population, mainly composed of women, who appear to have paid the highest psychological and social debt following COVID-19 and who, therefore, should be monitored over time and offered specialistic interventions, even after many months after the COVID-19 infection [92]. From a preventive perspective of planning health services and carefully allocating resources, with a view to possible future new health emergencies, part of the health budget should be therefore intended to manage the long-term consequences of the pandemic in this part of the population, with ad hoc trained personnel and focused interventions [93, 94] (https://nextstrain.org/sars-cov-2/). Based on the percentage of people in our sample (95%) who expressed the need for additional psychological support, since December 2022 we have been implementing the 'Cognitive Therapy Focused on Post-Traumatic Stress Disorder delivered via telemedicine to groups of patients after Sars-Cov2 infection' project (TELEGIFTT; approved by the Ethical Committee of the Azienda Ospedaliera Universitaria Integrata of Verona-Prog. 4015CESC, and partly funded by the Brain Research Foundation, BRF Verona) to provide an e-health, group-based and specialist psychotherapeutic intervention focused on the psychological consequences of the SARS-CoV-2 infection. The trajectory that led us from data collection to the creation of a personalized and specialized intervention highlights the feasibility of public psychology services of providing a specialized clinical service and, at the same time, collecting data for research purposes.

Authors' contributions

LDP, MM, and ET conceptualized the study, critically reviewed it, and revised the manuscript for important intellectual content. CP contributed substantially to manuscript writing and revision. MPZ, AM; MA, DC, MF, CB, STN, GM, EG conducted clinical consultations and collected data. GH revised the manuscript for language and important intellectual content. EG conducted clinical consultations, collected data and revised the manuscript for important intellectual content. MM provided statistical analysis and critically reviewed and revised the manuscript for important intellectual content. All authors reviewed the manuscript.

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Data availability
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and the Helsinki Declaration of 1975, as revised in 2000. The study was approved by the Ethical Committee of the Azienda Ospedaliera Universitaria Integrata of Verona (Prog. 3199CESC).
Patients were free to participate or not participate, and no remuneration was offered to respondents. Participation was voluntary and anonymous; no demographic or personal information able to identify the responder was collected. Each participant was asked for consent before the consultation. At any time, participants were allowed to terminate the study if they desired.

Consent for publication
All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of this work. All authors consent to the publication of this work.

Competing interests
The authors declare no competing interests.

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