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ORIGINAL ARTICLE

Frailty, psychological well-being, and social isolation in older adults with cognitive impairment during the SARS-CoV-2 pandemic: data from the GeroCovid initiative

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Abstract

Background: The containment measures linked to the COVID-19 pandemic negatively affected the phyco-physical well-being of the population, especially older adults with neurocognitive disorders (NCDs). This study aims to evaluate whether the frailty of NCD patients was associated with different changes in multiple health domains, in particular in relation to loneliness and social isolation, pre- and post-lockdown.

Materials and Methods: Patients were recruited from 10 Italian Centers for Cognitive Disorders and Dementia. Data were collected in the pre-pandemic period (T0), during the pandemic lockdown (T1), and 6–9 months post-lockdown (T2). The UCLA Loneliness Scale-3, Activities of Daily Living (ADL), Instrumental ADL (IADL), Mini-Mental State Examination, and Neuropsychiatric Inventory (NPI) were administered. Caregivers' burden was also tested. Patients were categorized as non-frail, pre-frail, and frail according to the Fatigue, Resistance, Ambulation, Illness, and Loss of Weight scale.

Results: The sample included 165 subjects (61.9% women, mean age 79.5 ± 4.9 years). In the whole sample, the ADL, IADL, and NPI scores significantly declined between T0 and T2. There were no significative variations in functional and cognitive domains between the frail groups. During lockdown we recorded higher Depression Anxiety Stress Scales and Perceived Stress Scale scores in frail people. In multivariable logistic regression, frailty was associated with an increase in social isolation, and a loss of IADL.

Conclusions: We observed a global deterioration in functional and neuropsychiatric domains irrespective of the degree of frailty. Frailty was associated with the worsening of social isolation during lockdown. Frail patients and their caregivers seemed to experience more anxiety and stress disorders during SARS-CoV-2 pandemic.

INTRODUCTION

The COVID-19 pandemic has required important clinical, social and economic interventions in order to limit escalation of the disease and safeguard individuals' health. Considering the well-known impact of lockdown and forced isolation on physical and psychological well-being, particularly in older adults,[1–4] many studies conducted during the COVID-19 pandemic focused on describing the prevalence during this period of frailty, underlying increased vulnerability and compromised ability to cope with everyday or acute stressors.[5–8] Pandemic and containment measures exacerbated self-reported loneliness in a large part of the adult population,[9] increasing the risk of 'social frailty', known as the loss of social resources, social activities, or abilities and general resources that are important for fulfilling basic social needs during one's lifetime.[10] The pandemic's effects on psychological well-being were more intensive in patients with severe cognitive impairment.[11] Although the increased prevalence of loneliness and social isolation in older cognitively compromised adults has already been reported before and after the COVID-19 pandemic,[12,13] studies that considered the trend during the pandemic phases, with particular attention to neurocognitive disorders, are still lacking. In fact, previous findings suggest that the association of frailty and poor global cognition describes the 'frailest among the frail' individuals, who experienced different psychological and/or behavioural effects of COVID-19 and, for these reasons, deserve particular attention.[2,14–17] Given these premises, we could hypothesize an increase of psycho-cognitive and behavioural disorders, with an increasing gradient according to the degree of fragility of the patient. Despite this, to our knowledge no studies have focused on trends of neuropsychiatric disorders according to the degree of frailty during the SARS-CoV-2 pandemic.

The aims of this study were (i) to evaluate the association between frailty and different health domains, particularly in relation to loneliness and social isolation, in a sample of older adults affected by neurocognitive disorders (NCDs) before and after the COVID-19 first wave lockdown; and (ii) to estimate whether the lockdown impacted the psychological and affective well-being of older adults with NCDs and their caregivers' burden differently according to the presence of frailty.

MATERIALS AND METHODS

Study design

The GeroCovid CDCD study ('GeroCovid dementia—psychological health cohort') was part of a multipurpose, multicentre, and multi-setting initiative[11] called the GeroCovid Observational project. The retrospective GeroCovid CDCD study involves 10 Italian Centers for Cognitive Decline and Dementia (CDCDs) and considers three phases during 2020: from January to February (pre-pandemic, T0), from March to May (lockdown, T1), and from July to December (post-lockdown, T2). In Italy lockdown started from March 2020 with the closure of schools and all types of commercial activities, with the exception of basic necessities, and with strict restrictions on moving.

All participants (or their caregivers) gave informed consent to their involvement in the study. The study was approved by the BIO-CAMPUS Ethics Committee, University of Rome—Prot. Number: 22.5 (20).20 OSS ComEtUCBM. Each centre received approval from the local Ethics Committee to perform the study.

Participants

Participants were recruited from Italian CDCDs, using the following inclusion criteria: (i) a last routine cognitive evaluation between January and March 2020, and a next follow-up ambulatory visit expected between September and December 2020; (ii) a diagnosis of Mild Cognitive Impairment (MCI), or of mild-to-moderate dementia (through a complete evaluation that considered DSM-5 criteria, Mini-Mental State Examination [MMSE] score and neuroimaging); and (iii) an MMSE score of >16. Exclusion criteria were the following: (i) inability to undergo psychometrics tests for any reason; and (ii) history of psychiatric illness, according to clinical anamnesis.

Of the 496 individuals who met the inclusion criteria and were originally contacted, 275 agreed to participate in the study and were assessed at T0 and T1. At T2, the comprehensive geriatric assessment (CGA) was administered to 214 individuals (35 refused, nine patients were no longer at home with the same caregiver, six were institutionalized, and 11 died). Of the 214 patients who performed both T0 and T2 CGA evaluations, we selected only those evaluated with the Fatigue, Resistance, Ambulation, Illness, and Loss of Weight (FRAIL) scale,

resulting in 165 participants with MMSE score recorded from 18 (the lowest MMSE score recorded) to 30 and aged 70–91 years (Fig. 1).

Procedure

Trained physicians gathered the following information on the patient characteristics for each participant from medical records.

We considered participants' sociodemographic data (age, sex, cohabiting status, years of education), information on risk behaviours (smoking and alcohol consumption), medical history (including diagnosis of cognitive impairment, depressive mood, and other coexisting chronic diseases and comorbidities), and drug treatments.

At T0 and T2, the CGA[18] was performed during ambulatory evaluations and included the following scales: MMSE,[19] Neuropsychiatric Inventory (NPI),[20] Activities of Daily Living (ADL),[21] and Instrumental Activities of Daily Living (IADL).[22] The NPI is used to assess the presence and severity of specific behavioural and psychological symptoms of dementia (BPSD) experienced by each participant, as rated by a reliable study partner. BPSD symptoms assessed

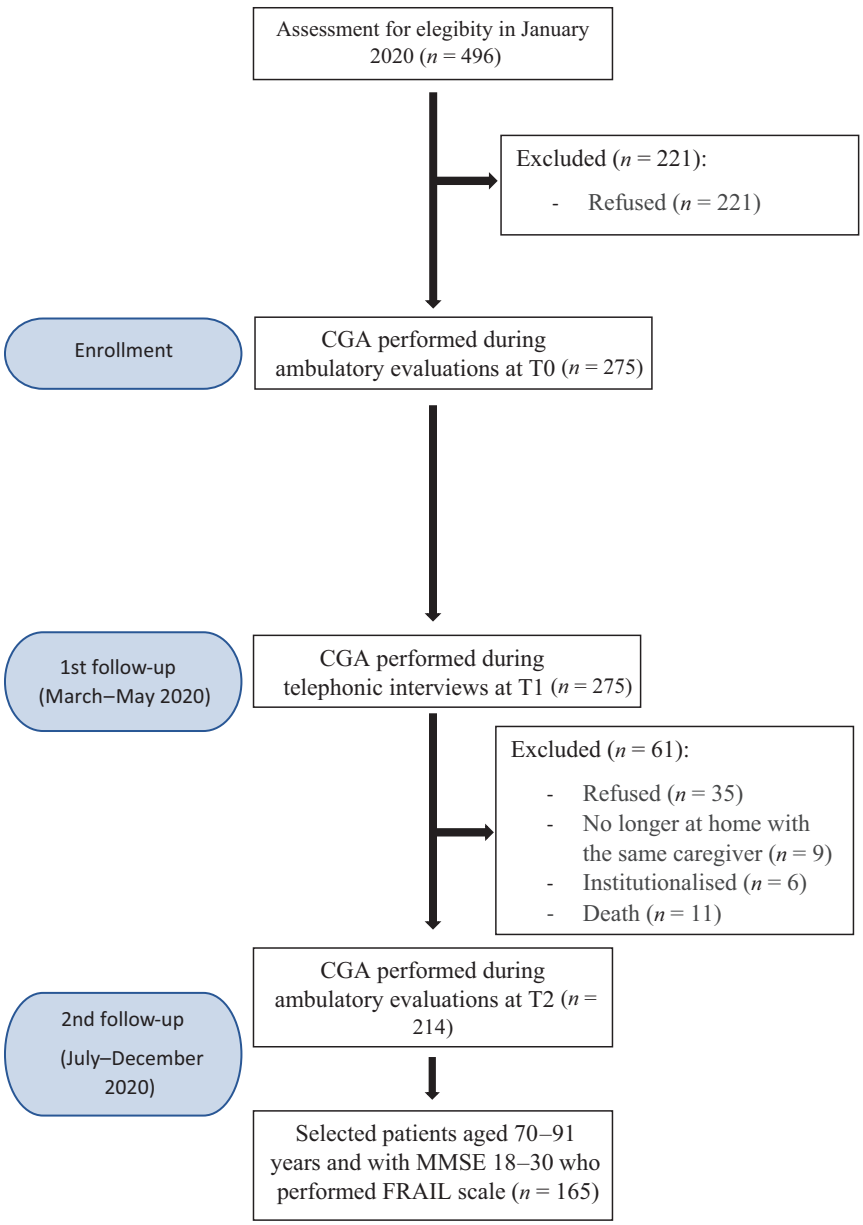

Figure 1 STROBE flowchart of patient selection

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in the NPI questionnaire include delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/lability, aberrant motor activity, night-time behaviour, and appetite disturbance. For each symptom endorsed, the caregiver rated both the severity (1 to 3, for mild, moderate, and marked) and frequency (1 = occasionally, less than once per week; 2 = often, about once per week; 3 = frequently, several times per week but less than every day; 4 = very frequently, once or more per day or continuously) of each symptom. Frequency and severity scores were multiplied to yield an overall severity score (maximum of 12) for each domain, which was summed across all domains to yield a total NPI score.

To assess social isolation and loneliness, moreover, the UCLA Loneliness Scale-3[23] was administered. The three items of the UCLA scale were (i) lack of companionship, (ii) feeling left out, and (iii) feeling isolated, in the past 2 weeks. For each question, a 4-point Likert scale (1 = never, 2 = rarely, 3 = sometimes, and 4 = always) was used; scores ranged from 3 to 12, with higher scores indicating higher levels of loneliness. Concerning participants' social environment, we considered the presence of a formal or informal caregiver, and the number of informal visits received on average by each participant before the pandemic period.

T1 evaluations were carried-out by telephonic interviews to the patients, and included the Depression Anxiety Stress Scales-21 (DASS-21),[24] Perceived Stress Scale (PSS),[25] and Coping Orientation to Problems Experienced (COPE),[26] described below.

The DASS-21[24] is composed of a set of three self-report scales designed to measure the emotional states of depression, anxiety, and stress. Each of the three DASS-21 scales contains seven items, divided into subscales with similar content. Cut-off scores for depression, anxiety, and stress were 10, 8, and 15, respectively. The depression scale (including items 3, 5, 10, 13, 16, 17, and 21) assesses dysphoria, hopelessness, devaluation of life, self-deprecation, lack of interest/involvement, anhedonia, and inertia. The anxiety scale (including the items 2, 4, 7, 9, 15, 19, and 20) assesses autonomic arousal, skeletal muscle effects, situational anxiety, and subjective experience of anxious affect. The stress scale is sensitive to levels of chronic non-specific arousal and included the items 1, 6, 8, 11, 12, 14, and 18). It assesses difficulty relaxing, nervous arousal, and being easily upset/agitated, irritable/over-reactive, and impatient. Scores for depression, anxiety, and stress are calculated by summing the scores for the relevant items, then multiplied by two. The cut-offs were used to detect the presence of symptoms of depression.

The PSS[25] is the most frequently used psychological measure to assess perceptions of stress. The degree to which the situations in a person's life are rated as stressful are evaluated by 10 items constructed to capture the level at which respondents perceive their lives as unpredictable, uncontrollable, or overloaded. The scale also contains a series of direct questions about current levels of perceived stress. The PSS was designed to be used in samples drawn from the general population with an educational level at least equal to lower middle school. The items and the response alternatives are easy to understand: for each item, respondents are asked to indicate how often they felt a certain way in the last month (0 = Never, to 4 = Very often). The PSS scores are obtained by reverse-scoring the responses to the four positively formulated items (items 4, 5, 7, and 8), then adding together the scores for all items. A short 4-item scale can be obtained using questions 2, 4, 5, and 10 of the 10 items in the PSS scale.

The COPE[26] is a multidimensional coping inventory to assess the different ways in which people respond to stress. Five scales (of four items each) measure conceptually distinct aspects of problem-focused coping (active coping, planning, suppression of competing activities, restraint coping, seeking of instrumental social support); five scales measure aspects of what might be viewed as emotion-focused coping (seeking of emotional social support, positive reinterpretation, acceptance, denial, turning to religion); and three scales measuring coping responses that arguably are less useful (focus on and venting of emotions, behavioural disengagement, mental disengagement).

The subscales drawn from the COPE for use in the current study are calculated as follows: the subscale 'social support' is indicated by the sum of items 1, 10, 15, 18, and 25; 'positive attitude' is indicated by the sum of items 2, 6, 12, 16, 23, and 24; 'orientation to problem' is indicated by the sum of items 3, 5, 9,13, 20), and 'transcendent orientation' (indicated by the sum of items 8, 11, 14, 19). The sum of the remaining scales refers to "avoidance strategies".

The presence of a caregiver was always required during telephone interviews in order to limit potential biases due to patients' cognitive impairment and their ability to answer questions.[11,27] Finally, the caregivers were evaluated through the Caregiver Burden Inventory (CBI)[28] during the same telephone call. The CBI is a 24-item self-report questionnaire for assessing the burden of caregivers caring for people with chronic disease. The items are rated on a 5-point Likert scale from 0 (Never) to 4 (Nearly always). The questions cover five dimensions of caregiver burden: objective burden; time-dependence, referring to time demands for assistance; psychological burden, understood as the caregiver's feelings of exclusion from expectations and opportunities; physical burden, which describes the caregiver's feelings of fatigue and health problems; social burden, which describes the caregiver's feelings of role conflict; and emotional burden, which describes the caregiver's feelings of shame or embarrassment caused by the patient. Time spent for assistance, social involvement, physical involvement, and relational involvement are represented, respectively by the sum of the items from 1 to 5, from 6 to 10, 11 to 14, and 15 to 19.

We categorized participants according to the FRAIL scale,[29] which consists in a brief assessment of five items: fatigue, resistance, ambulation, illnesses, and loss of weight. For this study, 'fatigue' was measured by asking respondents how much time during the past 4 weeks they felt tired, 'resistance' was assessed by asking participants if they had any difficulty walking up 10 steps alone without resting and without aids, and 'ambulation' by asking if they had any difficulty walking several hundred yards alone and without aids; yes responses were each scored as 1 point. 'Illness' was scored 1 for respondents who reported five or more illnesses in their pathological anamnesis. Loss of weight was scored 1 for respondents with a weight decline of 5% or greater within the past 12 months based on self-report. We performed frailty evaluations with patients and their caregivers, so that the caregiver could help to reconstruct the response when the patient was unable to provide an answer or provided it uncertainly. Each FRAIL scale characteristic was scored 0–1, and scores ranged from 0 (best) to 5 (worst). According to the FRAIL scale, participants were categorized as frail (score $\geq$3), pre-frail (score = 1–2) and non-frail (score = 0). The FRAIL scale was administrated at both T0 and T2.

Analyses

Descriptive characteristics of the sample are expressed as means $\pm$ standard deviations (SDs) or as count (%), as appropriate.

The comparison of the sociodemographic and health-related characteristics of non-frail, pre-frail, and frail participants was performed by using chi-squared or Fisher exact tests for categorical variables and generalized linear model testing for homoscedasticity through the Levene's test for quantitative ones. Post hoc analyses with Bonferroni adjustment for multiple comparisons were applied. The comparison of quantitative variables between T0 and T2 was performed through paired-samples *t*-tests. Delta (Δ) values for functional and psycho-cognitive variables were obtained from the difference of T2 and T0 values of the same items. In particular, Δ values for ADL and IADL tests were considered as 'loss of functional autonomy', 'loss of ADL', or 'loss of IADL' when there was a loss of at least 1 point in the final score compared to the previous evaluation.

A multivariable logistic regression was performed to test the association between frailty and changes in social isolation feeling, functional and cognitive status, and depressive or behavioural symptoms after T2. The model was corrected for age, sex, and education status. Analyses were performed in IBM SPSS version 28.0.1.0 (IBM Corp., Armonk, NY).

RESULTS

We evaluated 165 individuals (61.9% women), including 47 individuals who were not frail, 92 who were pre-frail, and 26 who were frail. The most common cognitive disorders observed were Alzheimer's disease (28.7%), vascular dementia (24.7%), MCI (24.3%), and mixed dementia (14.9%).

Table 1 and Fig. 2 show the participants' functional, cognitive, and neuropsychiatric characteristics, expressed as variations between T0 and T2, and as single scores at T0 and T2. The sample's mean age was 79.49 $\pm$ 4.89 years and the frail patients were the oldest group (82.08 $\pm$ 4.17 vs 78.21 $\pm$ 4.65 for no-frail and 79.96 $\pm$ 4.87 for pre-frail, $P = 0.004$). Subjects were stable in functional and psycho-cognitive domains during the observational period

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between frailty groups (Table 1). In pre-frail patients we observed significant reductions of functional autonomy parameters during the 6 months of follow-up (Fig. 2, $P < 0.01$). Differences in the MMSE and NPI total scores between the frailty groups before and after the lockdown were not observed, while

Table 1 Descriptive functional and psycho-cognitive characteristic as variations between T0 and T2 in the total sample and sorted by frailty levels (FRAIL scale)

N item (18)	All patients ($n = 165$)	Not frail (FRAIL = 0) ($n = 47$)	Pre-frail (FRAIL = 1–2) ($n = 92$)	Frail (FRAIL >2) ($n = 26$)	*P*-value
Age (years)	79.59 ± 4.89	78.21 ± 4.65	79.96 ± 4.87	82.08 ± 4.17	**0.01**
Sex (F)	61.9%	55.3%	65.2%	65.4%	0.49
Education (years)	7.36 ± 3.74	7.23 ± 3.98	7.04 ± 3.380	7.00 ± 3.55	0.94
Lived alone: yes	22.4%	27.7%	17.4%	30.8%	0.16
Caregiver: yes	78.5%	80.9%	76.1%	92.3%	0.18
Smoking habit					0.69
Never	76.4%	76.0%	74.2%	84.6%	
Former	17.6%	18.0%	20.2%	7.7%	
Current	6.0%	6.0%	5.6%	7.7%	
Use of antipsychotics	15.7%	14.9%	14.1%	23.8%	0.54
Depressive mood	19.4%	20.0%	14.3%	34.6%	0.72
Hearing deficits	12.5%	8.0%	15.5%	19.2%	0.36
Vision deficits	11.3%	4.0%	13.1%	11.5%	0.12
Diabetes mellitus	17.6%	12.2%	17.9%	26.9%	0.28
Hypertension	68.9%	46.0%	81.2%	73.1%	**<0.001**
Atrial fibrillation	13.1%	8.0%	13.1%	23.1%	0.18
COPD	4.4%	0	6.0%	7.7%	0.17
Number of chronic diseases	3.28 ± 1.72	2.35 ± 1.02	3.49 ± 1.73	4.30 ± 1.95	**<0.001**
Functional domains					
ΔADL	−0.23 ± 1.01	−0.04 ± 0.59	−0.27 ± 0.98	−0.36 ± 1.75	0.35
ΔIADL	−0.49 ± 1.37	−0.40 ± 1.09	−0.71 ± 1.48	−0.31 ± 1.49	0.27
Psycho-cognitive domains					
ΔMMSE	−0.17 ± 2.35	−0.32 ± 1.91	−0.07 ± 2.46	−0.92 ± 2.79	0.27
ΔUCLA	0.49 ± 0.21	0.61 ± 1.50	0.45 ± 1.18	0.70 ± 1.14	0.65
ΔNPI	2.35 ± 11.28	1.42 ± 8.04	2.86 ± 12.02	1.92 ± 15.12	0.87

Note: Numbers are mean ± standard deviation, or count (%), as appropriate. *P*-values refer to the comparisons between FRAIL groups. Post hoc analyses with Bonferroni adjustment for multiple comparisons were applied. Abbreviations: FRAIL, Fatigue, Resistance, Ambulation, Illness, and Loss of Weight scale; COPD, chronic obstructive pulmonary disease; ADL, Activities of Daily Living; IADL, Instrumental ADL; MMSE, Mini-Mental State Examination; UCLA, UCLA Loneliness Scale-3; NPI, Neuropsychiatric Inventory. The values of $p < 0.05$ are in bold.

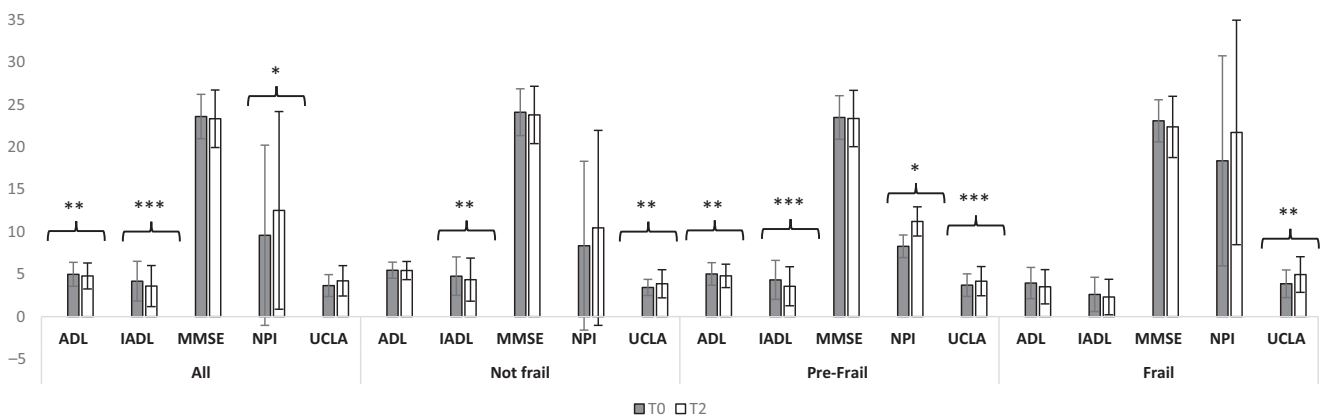

Figure 2 T0 and T2 descriptive cognitive, functional, neuropsychiatric, and social characteristics sorted by frailty levels (FRAIL scale). ADL, Activities of Daily Living; IADL, Instrumental ADL; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; NPI, Neuropsychiatric Inventory; UCLA, UCLA Loneliness Scale-3. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

Table 2 T0 and T2 descriptive neuropsychiatric characteristics in the total sample and sorted by frailty levels

N item (26)	All patients evaluated with FRAIL scale ($n = 165$)	Non-frail (FRAIL = 0) ($n = 47$)	Pre-frail (FRAIL = 1–2) ($n = 92$)	Frail (FRAIL >2) ($n = 26$)	*P*-value
NPI T0	9.59 ± 10.62	8.36 ± 9.95	8.29 ± 9.75	18.36 ± 12.38	**0.01**
NPI T2	12.52 ± 11.65*	10.46 ± 11.49	11.22 ± 10.42*	21.71 ± 13.23	**0.01**
Delusions					
NPI T0 Delusions F × S	0.38 ± 1.78	0.47 ± 1.52	0.21 ± 1.49	0.93 ± 3.19	0.37
NPI T2 Delusions F × S	0.51 ± 1.98*	0.43 ± 1.73	0.53 ± 2.02	0.60 ± 2.32	0.95
Hallucination					
NPI T0 Hallucination F × S	0.09 ± 0.46	0.19 ± 0.74	0.05 ± 0.27	0.00 ± 0.00	0.23
NPI T2 Hallucination F × S	0.10 ± 0.57	0.14 ± 0.75	0.10 ± 0.53	0.07 ± 0.25	0.90
Agitation/aggression					
NPI T0 Agitation/aggression F × S	0.50 ± 1.28	0.61 ± 1.29	0.48 ± 1.37	0.36 ± 0.74	0.79
NPI T2 Agitation/aggression F × S	1.27 ± 2.35**	1.29 ± 2.29*	1.44 ± 2.59*	0.53 ± 1.12	0.41
Depression/dysphoria					
NPI T0 Depression/dysphoria F × S	2.06 ± 3.32	1.97 ± 3.59	1.75 ± 2.70	3.79 ± 4.75	0.11
NPI T2 Depression/dysphoria F × S	3.01 ± 3.78	2.79 ± 3.95	2.49 ± 3.20*	5.56 ± 4.84	**0.01**
Anxiety					
NPI T0 Anxiety F × S	1.60 ± 2.74	1.26 ± 1.97	1.24 ± 2.45	4.14 ± 4.24	**<0.001**
NPI T2 Anxiety F × S	1.86 ± 2.75	1.45 ± 2.37	1.67 ± 2.16	3.50 ± 4.73	**0.03**
Euphoria/elation					
NPI T0 Euphoria/elation F × S	0.16 ± 0.84	0.31 ± 1.34	0.11 ± 0.50	0.00 ± 0.00	0.39
NPI T2 Euphoria/elation F × S	0.10 ± 0.57*	0.18 ± 0.77	0.10 ± 0.53*	0.00 ± 0.00	0.61
Apathy/indifference					
NPI T0 Apathy/indifference F × S	1.58 ± 2.83	1.03 ± 2.23	1.40 ± 2.43	3.86 ± 4.65	**0.01**
NPI T2 Apathy/indifference F × S	1.62 ± 2.76	1.23 ± 2.17	1.44 ± 2.56	3.06 ± 4.02	0.07
Disinhibition					
NPI T0 Disinhibition F × S	0.23 ± 1.29	0.14 ± 0.68	0.33 ± 1.63	0.00 ± 0.00	0.60
NPI T2 Disinhibition F × S	0.31 ± 1.21	0.43 ± 1.37	0.27 ± 1.23	0.27 ± 0.79	0.84
Irritability/lability					
NPI T0 Irritability/lability F × S	1.03 ± 2.38	0.61 ± 1.55	1.03 ± 2.35	2.14 ± 3.75	0.12
NPI T2 Irritability/lability F × S	1.22 ± 1.93	1.04 ± 2.13	1.36 ± 1.91	0.93 ± 1.62	0.62
Aberrant motor behaviour					
NPI T0 Aberrant motor behaviour F × S	0.22 ± 1.03	0.22 ± 0.76	0.27 ± 1.25	0.00 ± 0.00	0.68
NPI T2 Aberrant motor behaviour F × S	0.20 ± 0.93	0.36 ± 1.33	0.16 ± 0.81	0.07 ± 0.25	0.55
Nighttime behaviours					
NPI T0 Nighttime behaviours F × S	1.44 ± 2.53	0.97 ± 2.45	1.55 ± 2.28	2.14 ± 3.61	0.30
NPI T2 Nighttime behaviours F × S	2.41 ± 3.23**	1.72 ± 3.25	2.33 ± 2.87*	4.13 ± 4.29*	0.05
Appetite/eating					
NPI T0 Appetite/eating F × S	0.41 ± 1.46	0.37 ± 2.03	0.30 ± 0.75	1.00 ± 2.18	0.26
NPI T2 Appetite/eating F × S	0.61 ± 1.66	0.32 ± 0.81	0.33 ± 0.86	2.33 ± 3.57	**<0.001**

Note: Numbers are mean ± standard deviation, or count (%), as appropriate. *P*-values refer to the comparisons between FRAIL groups. Frequencies do not sum to 100% due to missing values. Post-hoc analyses with Bonferroni adjustment for multiple comparisons were applied. Abbreviations: FRAIL, Fatigue, Resistance, Ambulation, Illness, and Loss of Weight scale; NPI, Neuropsychiatric Inventory; F, frequency; S, severity. The values of $p < 0.05$ are in bold. * < 0.05; ** < 0.01.

UCLA scores increased from T0 to T2 in all groups ($P < 0.01$).

The analysis of the descriptive items of the NPI scale sorted by frailty levels at T0 and T2 is reported in Table 2. Frail people had higher depression (5.56 ± 4.84 vs 2.79 ± 3.95 in not frail and 2.49 ± 3.20 in pre-frail, $P = 0.01$), anxiety (3.50 ± 4.73 vs 1.45 ± 2.37 in not frail and 1.67 ± 2.16 in pre-frail, $P = 0.03$), and eating disorders (2.33 ± 3.57 vs 0.32 ± 0.81 in not frail and 0.33 ± 0.86 in pre-frail, $P < 0.001$) scores at T2. Between T0 and T2, there was an increase in scores for agitation (0.48 ± 1.37 vs 1.44 ± 2.59, $P < 0.05$), depression (1.75 ± 2.70 vs 2.49 ± 3.20, $P < 0.05$), and sleep disorders (1.55 ± 2.28 vs 2.33 ± 2.87, $P < 0.05$) in the pre-frail group.

The evaluation during the lockdown period (T1) showed that frail individuals had higher total DASS (19.76 ± 13.99 vs 11.53 ± 11.57 in not frail and 14.99 ± 10.90 in pre-frail, $P = 0.02$) and PSS (18.88 ± 7.72 vs 14.07 ± 7.41 in not frail and 15.93 ± 6.74 in pre-frail, $P = 0.02$) scores (Table 3), and worse 'positive attitude' coping strategies compared to the other groups (13.77 ± 3.07 vs 16.98 ± 4.12 in not frail and 15.87 ± 4.09 in pre-frail). Higher caregiving burden, in particular for social and relational involvement (items 15–19 and items 6–10, respectively) were observed in caregivers of frail subjects.

In the multivariable logistic regression, after adjusting for age, sex, and schooling, we found that frailty at T2 was associated with the worsening of social isolation during lockdown (odds ratio (OR): 1.24, 95% confidence interval (CI) 1.060–1.950,

Table 4 Logistic multivariable regression: association between frailty at T2 and covariates

		95% CI		
Variable	OR	Lower	Upper	*P*-value
Age	0.84	0.55	1.29	0.43
Sex M	0.19	0.01	6.09	0.36
Schooling	1.45	0.88	2.37	0.14
ΔIADL	5.72	1.03	1.89	**0.04**
ΔMMSE	0.48	0.20	1.15	0.10
ΔNPI	0.87	0.65	1.15	0.31
ΔUCLA	1.24	1.06	1.95	**0.04**

Abbreviations: OR, odds ratio; CI, confidence interval; IADL, Instrumental Activities of Daily Living; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; UCLA, UCLA Loneliness Scale-3. The values of $p < 0.05$ are in bold.

Table 3 Results of the evaluation through DASS, COPE and CBI scales at T1

N Item (15)	All patients ($n = 165$)	Non-frail (FRAIL = 0) ($n = 47$)	Pre-frail (FRAIL = 1–2) ($n = 92$)	Frail (FRAIL >2) ($n = 26$)	*P*-value
DASS total (sum of all items)	14.73 ± 11.83	11.53 ± 11.57	14.99 ± 10.90	19.76 ± 13.99	**0.02**
DASS stress	11.41 ± 9.33	8.77 ± 8.58	12.11 ± 9.26	13.69 ± 10.19	0.05
DASS anxiety	6.04 ± 7.21	4.60 ± 6.83	5.63 ± 6.58	10.08 ± 8.73	**0.01**
DASS depression	12.11 ± 9.77	9.70 ± 9.24	12.24 ± 9.29	16.16 ± 11.35	**0.01**
PSS total	15.89 ± 7.21	14.07 ± 7.41	15.93 ± 6.74	18.88 ± 7.72	**0.02**
COPE					
COPE social support	11.68 ± 3.94	12.16 ± 3.69	11.60 ± 3.95	11.15 ± 4.36	0.56
COPE avoidance strategies	8.35 ± 2.66	7.96 ± 2.83	8.45 ± 2.47	8.69 ± 3.01	0.46
COPE positive attitude	15.85 ± 4.07	16.98 ± 4.12	15.87 ± 4.09	13.77 ± 3.07	**0.01**
COPE orientations to problem	12.55 ± 3.47	13.20 ± 3.33	12.30 ± 3.54	12.23 ± 3.45	0.32
COPE transcendent orientation	10.52 ± 4.26	10.44 ± 4.48	10.44 ± 4.20	10.92 ± 4.22	0.87
CBI					
CBI time-dependence	7.09 ± 5.29	5.97 ± 5.62	6.88 ± 4.62	9.33 ± 6.12	**0.04**
CBI psychological burden	4.83 ± 4.91	4.71 ± 5.20	3.96 ± 3.82	7.48 ± 6.35	**0.01**
CBI physical burden	3.57 ± 3.70	3.26 ± 3.39	3.18 ± 3.37	5.08 ± 4.68	0.07
CBI social burden	2.40 ± 3.28	2.88 ± 3.43	1.54 ± 2.39	4.13 ± 4.40	**0.01**
CBI emotional burden	1.45 ± 2.22	1.51 ± 2.10	1.21 ± 2.07	2.00 ± 2.72	0.31

Note: Numbers are mean ± standard deviation, or count (%), as appropriate. *P*-values refer to the comparisons between FRAIL groups. Frequencies do not sum to 100% due to missing values. Post hoc analyses with Bonferroni adjustment for multiple comparisons were applied. Abbreviations: FRAIL, Fatigue, Resistance, Ambulation, Illness, and Loss of Weight scale; DASS, Depression Anxiety Stress Scales; PSS, Perceived Stress Scale; COPE, Coping Orientation to Problems Experienced; CBI, Caregiver Burden Inventory. The values of $p < 0.05$ are in bold.

$P = 0.042$), and loss of IADL (OR: 5.72, 95% CI 1.025–1.889, $P = 0.047$) (Table 4).

DISCUSSION

In our study, we observed more anxiety and stress symptoms in frail patients and their caregivers during lockdown; frailty was associated with increased feelings of social isolation and loneliness after the first wave of the COVID-19 pandemic. Nevertheless, the worsening in functional and psycho-cognitive domains was not exacerbated in frail individuals, but occurred similarly in all involved individuals. Pre-frail patients seemed to experience more neuropsychiatric disorders (especially agitation, aggression, and sleep disorder domains) during lockdown.

During containment measures, we observed a slight increase in anxiety, depression, and stress symptoms in frail patients. Looking at caregiver burden, in the context of the COVID-19 pandemic we confirmed increases in especially social and relational involvement, and less but still significant in time spent for assistance and physical involvement, for caregivers of frail individuals, in line with previous studies.[30–32] Moreover, our data confirmed the association between social isolation and frailty in patients affected by cognitive impairment in the post-pandemic phase.[17,33] High prevalence of loneliness and social isolation in older adults have already been reported before the COVID-19 pandemic, with loss of social partners,[34] reduction of social contacts,[35] and physical limitations as some of the mechanisms involved.[12] The mobility limitations induced by the lockdown could both limit communication with family and friends, and could erase the routine, confusing the circadian rhythm and flattening the days of older people, resulting in reduced cognitive stimulation. All of these may impact negatively on cognitive and affective well-being.[13] We hope that in the future greater attention will be given to early detection of social isolation as a modifiable risk factor for frailty, especially considering patients affected by NCDs; part of primary care may involve taking charge of the psychological well-being of the patient and his or her caregiver, an aspect of attention that today is unfortunately reserved only for cases where required.

Regarding the health domains analysed, surprisingly persons affected by NCDs remained broadly stable, save for some expected minimal within-group variation in functional and neuro-psychiatric areas. The UCLA scores were higher after lockdown in all subjects, regardless of frailty, while there was a deterioration especially in the not frail and pre-frail patients in terms of the IADL scores. A possible explanation could be that, while frail patients were more impaired even before the start of the pandemic, the reduction in mobility due to the lockdown could have significantly compromised the residual autonomy of the remaining two groups of subjects; physical limitations could be responsible for an exacerbation of joint pain, which translates into greater stiffening and increasing difficulty in performing even the simplest movements.[36] In our sample we did not observe significant changes in the MMSE scores, in contrast with previous studies[37–39]; however, the methodological strategies were different, i.e. the follow-up periods and the way in which the MMSE scale was administered. Our evaluations at T0 and T2 were both performed during ambulatory visits, in contrast with other studies, in which the first clinic appointment was followed by a telephone interview. Moreover, our last evaluation was at 69 months, suggesting that minimal cognitive changes could not be highlighted with the MMSE. This is supported also in the study of Sardella *et al*., in which no MMSE change between baseline and the first follow-up was reported.

An interesting result was the NPI trend, in which scores increased in all groups from T0 to T2, but no significative variations between the three type of patients considered were reported. There was a further worsening of agitation/aggression in the pre-frail and not frail groups, and of night-time behaviour in frail and pre-frail individuals, supporting the hypothesis that restrictive measures adopted during the COVID-19 lockdown could increase BPSD even in older adults with cognitive impairment despite of their frailty status.[40] Previous studies conducted both in the periods before and during COVID-19 showed a substantially stability of the NPI, showing an increase only in specific sub-categories[41–43]; however, they were conducted with different scales and covering shorter periods than our study.[2,44] Although not perfectly comparable to other papers actually in the literature, due to different methods or timing of evaluation, we support the hypothesis that the restrictive measures adopted during the COVID-19 waves and the pandemic itself could increase

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especially the agitation, anxiety, and depression of patients due to social isolation and concern for their own health status and that of their families, perhaps explaining our results. The unique value of our results lies in the longer observation time of the patients, which was more able to highlight the pandemic lockdown's effect in subjects with NCDs. To our knowledge, this is the first study that considered variations of functional, psycho-cognitive, and behavioural disorders based on the degree of frailty. Overall, we can say that pre-frail patients were apparently the most vulnerable to minimal changes during the pandemic, as if the lockdown had somehow moved the threshold for defining a frail subject. In line with this, the impairment of coping ability inherent in the concept of fragility[7,45] fails, as no significant differences were detected in the COPE scale during the lockdown.

Some limitations should be acknowledged. First, the scales used for the psycho-affective evaluation at T1 have not been validated for remote administration. However, these tools have been previously administered remotely,[46] although originally not designed in this format. Second, we do not know the psycho-affective profile of the patients with cognitive impairment before the pandemic; we only have reference population data. Another limit is that our study did not consider a control group of individuals without cognitive impairment. Also, due to the strict criteria of our study, the sample size was small, limiting the statistical power of analyses, especially considering the inter-group and intra-group comparisons that were conducted.

Our study also has some strengths. It was in fact a multicentre study that investigated the topic of cognitive-behavioural changes during the COVID-19 pandemic on a specific population of elderly people affected by cognitive impairment revaluated at different time points. Finally, we evaluated multiple health domains, considering different aspects of psychological well-being, including the caregiver's point of view.

CONCLUSIONS

This study found that during the Covid-19 pandemic, people affected by NCDs with a frail status seemed to experience more anxiety and stress disorders than pre-frail and not frail individuals, although a worsening of BPSDs was observed in all patients regardless of their degree of frailty. Also, frail patients' caregivers seem to have suffered the effects of the pandemic the most. Our study points out the role of social isolation in worsening the feeling of loneliness of frail patients with cognitive impairment.

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STUDY APPROVAL STATEMENT

The study protocol was conducted according to good clinical practice guidelines and the ethical standards of the 1964 Declaration of Helsinki as revised in 2000 and was reviewed and approved by the BIO-CAMPUS Ethics Committee, University of Rome—Prot. Number: 22.5 (20).20 OSS ComEtUCBM.

CONSENT TO PARTICIPATE STATEMENT

The subjects participating in this study received a thorough explanation of the risks and benefits of inclusion and gave their oral and written informed consent to publish the data.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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