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Long COVID: Association of fear and loneliness with anxiety, depression, and post-traumatic stress disorder: A case-control study

COVID prolongado: asociación entre miedo y aoledad con ansiedad, depresión y trastorno de estrés postraumático: un estudio caso-control

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SUMMARY

Introduction: *Illness-related fear has emerged as a unique mental health concern for individuals with long-standing COVID-19. Our research examined the interplay between fear, feelings of loneliness, depression, anxiety, and post-traumatic stress disorder (PTSD) among COVID-19 patients.*

Methods: *We conducted a population-based case-control study evaluating patients at least eight months post-infection. The study incorporated Goldberg, PHQ-9, and PCL-5 questionnaires, probing how the COVID-19 pandemic impacted various aspects of life, including social, occupational, educational, psychological, and physical aspects. Additionally, we investigated feelings of fear and loneliness. Statistical*

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analysis used was Student t-tests, Chi-Square tests, Fisher's correction, and Kruskal-Wallis tests to ascertain group differences.
Results: *There were no demographic differences among 262 participants, comprising 124 cases and 138 controls. Most patients (94.4 %) were outpatients. COVID-19 survivors exhibited nearly double the risk of psychological trauma compared to controls (OR: 1.857, 95 % CI: 1.123-3.072, P=0.015). Fear was notably more prevalent among them (75 % vs. 63.7 %, p=0.049). While feelings of loneliness were similar across both groups, anxiety and depression were more prevalent among the case group (both, P<0.001). Interestingly, anxiety correlated with an increased risk of fear (OR: 2.474 95 % CI: 1.421-4.308, P=0.001). This fear correlated with higher scores on PCL-5 (P<0.001). Loneliness was significantly linked with anxiety, depression, and PTSD (P<0.001).*
Conclusions: *Fear of reinfection and concurrent loneliness have been verified as significant contributors to the high prevalence of anxiety, depression, and PTSD among outpatients with long-term COVID-19. These symptoms persist even eight months after infection.*

Keywords: *Long COVID, fear, reinfection, loneliness, anxiety, depression, post-traumatic stress disorder.*

RESUMEN

Introducción: *El miedo relacionado con la enfermedad ha surgido como un problema de salud mental para individuos con COVID-19 prolongado. Nuestra investigación examinó la interacción entre el miedo, sentimientos de soledad, depresión, ansiedad y trastorno de estrés postraumático (TEPT) en pacientes con COVID-19.*
Métodos: *Realizamos un estudio casos-controles, evaluados ocho meses después de la infección. Se incorporó los cuestionarios Goldberg, PHQ-9 y PCL-5, se investiga cómo la pandemia afectó aspectos sociales, ocupacionales, educativos, psicológicos y físicos. Además, investigamos los sentimientos de miedo y soledad. El análisis estadístico involucró pruebas t de Student, pruebas de Chi-Cuadrado, corrección de Fisher y pruebas de Kruskal-Wallis para determinar las diferencias entre grupos.*
Resultados: *Se Identificaron 262 participantes sin diferencias demográficas, 124 casos y 138 controles. La mayoría de los pacientes (94,4 %) eran ambulatorios. Los sobrevivientes exhibieron casi el doble de riesgo de trauma psicológico (OR: 1,857, IC del 95 %: 1,123-3,072, P = 0,015). El miedo fue más frecuente entre ellos (75 % vs. 63,7 %, p=0,049). La ansiedad y la depresión fueron más frecuentes en los pacientes (ambos, P < 0,001). La ansiedad estuvo correlacionada con mayor riesgo de miedo (OR: 2,474, IC del 95 %: 1,421-4,308, P = 0,001). El miedo se correlacionó con puntuaciones altas en PCL-5 (p < 0,001). La soledad se relacionó significativamente con ansiedad, depresión y TEPT (p < 0,001).*
Conclusiones: *El miedo a la reinfección y la soledad concurrente contribuyen significativamente a la alta prevalencia de ansiedad, depresión y TEPT entre pacientes con COVID-19 prolongado. Estos síntomas podrían persistir ocho meses después de la infección.*

Palabras clave: *COVID prolongado, miedo, reinfección, soledad, ansiedad, depresión, trastorno de estrés postraumático.*

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has significantly impacted social relationships and mental health worldwide (1). It is crucial to gather data on the mental health of individuals in the post-infection stage to understand these changes better (2). The social upheaval induced by the pandemic has sparked fear, feelings of isolation, and psychiatric disorders in many individuals (3-6). The continuing threat of novel viral strains prompts concerns about adverse health outcomes (3). Fear of COVID-19, modulated by various social, cultural, and religious factors, has been recognized as an adaptive response (7,8). This fear has motivated individuals to adhere to health guidelines, mitigating virus-related mortality (8-10).

Furthermore, psychological distress can modify endocrine and immune responses, impacting the progression of the infection (9). Loneliness is often tied to changes in social relationships, which are human needs (11), a social health determinant, and an independent risk factor for anxiety, depression, and dementia (12,13). With mortality rates comparable to smoking, physical inactivity, and obesity, loneliness is now considered a significant public health concern (12,13). In this context, we aimed to investigate the interplay between fear, feelings of loneliness, depression, anxiety, and post-traumatic stress disorder (PTSD) among COVID-19 patients.

METHODS

Recruitment and Sample

This research is part of the larger Chilean Rancagua study (RACHIS), which investigates the neurocognitive after-effects in COVID-19 patients at Family Health Centre No. 1 (CESFAM No. 1). Our study follows a population-based case-control design, comparing COVID-19 patients to controls—individuals with no history of coronavirus infection confirmed by negative polymerase chain reaction (PCR) tests. The COVID-19 patients in our study, with positive PCR results between May 2020 and April 2021, were evaluated at least eight months post-infection. We registered 124 cases from the institutional database and randomly selected 138 age-matched controls (Figure 1). Individuals with mental disabilities (including schizophrenia, bipolar disorder, dissociative disorders, compulsive disorder, psychosis, or paranoia) and those under 18 were excluded. The study authors interviewed all participants between January and August 2021.

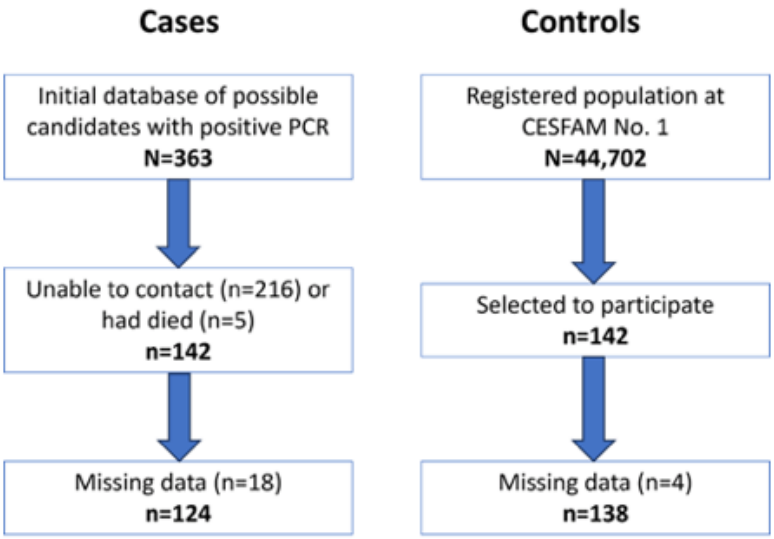

Figure 1. Case/control's sample selection flow diagram
Abbreviations: PCR, polymerase chain reaction; CESFAM No. 1, Family Health Center No. 1.

Ethical issues

The Rancagua Municipal Health Corporation's scientific ethics committee approved the research protocol and adhered to the ethical principles of the Declaration of Helsinki (14). Informed consent was obtained from all study participants, and the study protocol did not interfere with any prescribed medical treatments, recommendations, or other protocols in the health center.

Evaluation

Data collection was facilitated through interviews using a purpose-built questionnaire, which covered demographics, comorbidities, history of illness and mental health treatment, educational level, employment status, psychobiological habits, and the impact of the pandemic on participants.

A questionnaire carried out by the authors asked if, in the last four weeks, they have been afraid of reinfection or infecting others, as well as feelings of general loneliness, was measured on a 5-point Likert scale ranging from 1 ("Not at all") to 5 ("Extremely"). Anxiety and depression were evaluated through two validated questionnaires. The Goldberg questionnaire was used to assess both, defining anxiety with a score above four and depression with a score above three (15).

The Patient Health Questionnaire-9 (PHQ-9) also assessed depression, with severity levels ranging from none/minimal (0-4) to severe (20-27) (16). The PTSD Checklist for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5; PCL-5) evaluated PTSD, employing a cut-off value of 33 (17).

Statistical analysis

Data were recorded in a structured database. The sample size was determined through contingency table tests, assuming a statistical power of 95 % and an alpha error of 0.05. The Kolmogorov-Smirnov test examined data normality, identifying and eliminating outlier records to maintain age homogeneity between groups. Continuous variables were analyzed with the Student's t-test and dichotomous variables with the Chi-Square test, incorporating Fisher's adjustment when necessary. The Kruskal-Walli's test was used for variables involving the Likert scale. All tests were two-tailed.

RESULTS

Our study involved 262 individuals, including 124 COVID-19 cases and 138 controls. No significant differences were found between groups concerning age, sex, educational level, comorbidities, or psychobiological habits. The mean age for the COVID-19 cases was 45 ± 13 years, while that of the controls was 45.9 ± 9 years (Table 1). Of the COVID-19 cases, 117 (94.4 %) did not require hospitalization during the acute infection phase, with only seven (5.6 %) needing critical care for a brief period.

Table 1. Demographic characteristics of the sample.

	Cases n=124	%	Controls n=138	%	p-value
Gender					0.529
Female	68	54.8	81	58.7	
Male	56	45.2	57	41.3	
Comorbidities					0.171
Hypertension	40	32.3	34	24.6	0.158
Diabetes	22	17.7	16	11.6	0.265
Hypothyroidism	15	12.1	11	7.9	0.370
Cancer *	4	3.2	1	0.7	0.684
Heart disease *	4	3.2	2	1.4	0.622
CKD*	3	2.4	1	0.8	0.555
Mental health history	27	21.8	26	17.4	
Education level					0.237
Basic	38	30.6	33	23.9	
Middle	56	45.2	80	57.9	
University	30	24.2	25	18.2	
Psychobiological habits					0.580
Alcohol	76	61.2	81	58.6	0.200
Tobacco	29	23.4	42	30.4	0.466
Marijuana	6	4.8	8	4.9	0.150
Employment	78	63.9	77	55.7	

*Fisher's correction.
Abbreviation: CKD, Chronic renal failure

While the prevalence of mental disorders was comparable between the groups, the distribution of specific issues varied. The most frequent diagnoses in the COVID-19 group were depression (12.9 %) and anxiety (5.6 %), while controls primarily exhibited depression (6.2 %), anxiety (3.6 %), and mixed anxiety-depression disorders (3.6 %).

Impact of the pandemic

The pandemic's effects (spanning social, occupational, educational, psychological, and physical aspects) were distributed differently among the groups. A significantly higher proportion of the COVID-19 group (42.8 %) reported being affected than the controls (29.7 %; Figure 2). The psychological and physical aspects of life were most disrupted among the COVID-19 group, whereas the control group was more impacted socio-economically (Figure 3). COVID-19 patients were nearly twice as likely to be psychologically affected as controls (Odds Ratio [OR]: 1.857, 95 % Confidence Interval [CI]: 1.123-3.072, P = 0.015).

Prevalence of fear of reinfection and feelings of loneliness

We observed a difference between the cases and controls regarding fear of reinfection or infection, with the COVID-19 patients reporting more intense fear based on the scale. However, the prevalence and intensity of loneliness were similar in both groups (Table 2).

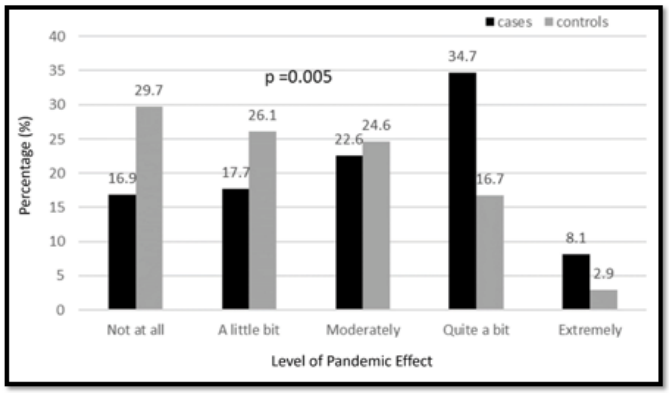

Figure 2. The degree to which individuals are affected by the pandemic in both groups.

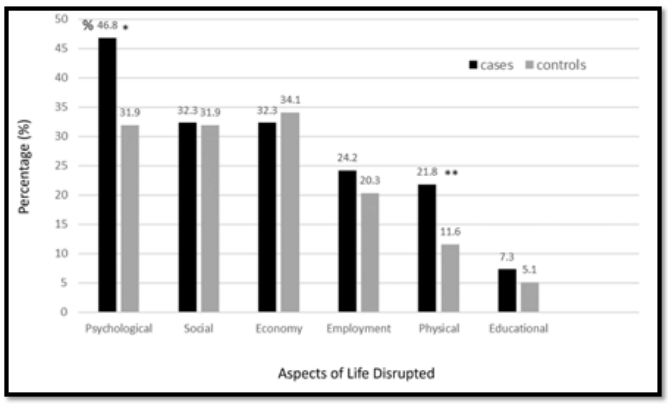

Figure 3. Aspects affected by the pandemic in percentages of cases and controls.
*p=0.015, **p=0.028

Table 2. Fear, loneliness, anxiety, depression, and post-traumatic stress disorder

	Cases n=124	%	Controls n=138	%	p-value
Fear of Reinfection/infection	93	75.0	88	63.7	0.049
Scale					<0.001
Not at all	31	25.0	50	36.2	
A Little bit	13	10.5	23	16.7	
Moderately	19	15.3	34	24.6	
Quite a bit	44	35.5	25	18.1	
Extremely	17	13.7	6	4.3	
Loneliness	56	45.2	65	47.1	0.753
Scale					0.185
Not at all	68	54.8	73	52.9	
A Little bit	23	18.5	40	29.0	
Moderately	9	7.3	12	8.7	
Quite a bit	18	14.5	9	6.5	
Extremely	6	4.8	4	2.9	
Anxiety	81	65.3	39	28.3	<0.001
Depression	77	62.1	32	23.2	<0.001
Depression severity (PHQ-9)					<0.001
Nonminimum	47	37.9	92	66.7	
Mild	24	19.4	31	22.4	
Moderate	29	23.4	7	5.1	
Moderately severe	16	12.9	5	3.6	
Severe	8	6.4	3	2.2	
Post-traumatic stress disorder	27	21.8	NA	NA	NA

Prevalence of anxiety, depression, and post-traumatic stress disorder

The Goldberg questionnaire indicated a higher prevalence and risk of anxiety in COVID-19 patients than in controls (OR: 4.782, 95 % CI: 2.833-8.071, P < 0.001; Table 2). We also observed a higher prevalence of depression in COVID-19 patients than in controls (OR: 5.427, 95 % CI:3.173-9.281, P<0.001). Depression and anxiety were more prevalent in female patients (50/77, 64.9 %; OR: 2.984, CI95 %: 1.407-6.327, P=0.004) and (52/81, 64.2 %; OR: 3.026, CI95 %: 1.405-6.517, P=0.004), respectively. The PHQ-9 further confirmed that COVID-19 patients had higher depression scores than controls (8.39 ± 6.57 vs. 4.11 ± 4.95; p < 0.001), with most cases being moderate or severe depression.

PTSD, assessed using the PCL-5, was present in 27 cases (21.8 %), with a mean score of 21.8 ± 17.6 (range: 0 – 72), of which 17 (62.9 %) were women. Among these, 11 (40.7 %) had a history of previously diagnosed mental health problems, suggesting an increased risk of PTSD (OR: 3.480, 95 % CI: 1.364-8.878, P = 0.007).

Relationship between fear of reinfection or infection, anxiety, depression, and PTSD

A correlation was observed between the fear of reinfection or infection and anxiety in 66 (53.2 %) cases and 25 (18.1 %) controls (OR: 2.474 95 % CI: 1.421-4.308, P = 0.001). Fear of reinfection or infection was linked to depression

in 61 (49.2 %) cases and 21 (15.2 %) controls (OR: 1.940 95 % CI: 1.14-3.378 P = 0.018). A strong association was also identified between fear of reinfection and PTSD in 25 of 27 patients (92.5 %), with an elevated risk (OR: 5.331 95 % CI: 1.184-23.998, P = 0.017).

Relationship between feelings of loneliness, anxiety, depression, and PTSD

Among individuals who reported anxiety (n=81), 54 % also reported loneliness (OR: 3.072, CI 95 %: 1.385 - 6.816, P = 0.005). In the control group, 74.4 % reported both anxiety and loneliness (OR: 5.075, CI 95 %: 2.219-11.606, P < 0.001). Similarly, a link was found between depression and loneliness: of the 77 depression cases, 43 (55.8 %) also reported feelings of loneliness (OR: 3.308, CI 95 %: 1.414-7.227, P = 0.02). Among the controls, 26 of the 32 depression cases (81.5 %) also reported loneliness (OR: 7.444, CI 95 %: 2.818 – 19.668, P < 0.001). Notably, PTSD and loneliness were highly correlated. Of the 27 cases of PTSD, 21 (77.7 %) also reported feelings of loneliness (OR: 6.200, CI 95 %: 2.287-16.810, P < 0.001).

DISCUSSION

Long COVID is characterized by a high prevalence of anxiety, depression, and PTSD, often linked to heightened fear of reinfection and feelings of loneliness. In some studies, this fear has been reported in two-thirds of the population (18). Persisting symptoms may have a biological basis in neuroinflammation and immunological dysfunction, detectable up to eight months post-COVID-19 infection (19-21). The psychological impact increases the risk of long-term COVID-19, as supported by our findings. Chronic and disproportionate fear of reinfection, a negative emotion, can catalyze the development of psychiatric disorders and exacerbate symptoms in individuals with pre-existing mental health issues (22,23). The heightened fear of reinfection in our study may arise from the experience of a life-threatening illness, compounded by media influence and lack of information about low reinfection rates (23-25). Fear of infection and death can result in dysphoric states, leading to anxiety, depression, and severe PTSD (22,26).

Loneliness, a significant side effect of the COVID-19 pandemic, is prevalent, with rates ranging from 27 % to 49 %, according to a systematic review (27). In Chile, loneliness increased between November and April 2021, reaching 22 % in the general population. Our patient group demonstrated a higher loneliness rate than this national average, aligning with reports from other regions (27,28).

In the present study, the psychological and economic impacts of the pandemic were the most significant concerns among respondents, with women being disproportionately affected. A recent study revealed how the pandemic-induced economic downturn led to increased loneliness, isolation, personal, family, and community tensions, and concerns about access to basic necessities, especially among women (5). In Chile, as in other parts of Latin America, women traditionally juggle child-rearing and domestic activities with paid work, and reductions in family income threaten their independence and autonomy (5,29,30).

Before the pandemic, Chile had one of the highest burdens of psychiatric diseases worldwide, with 23.2 % of the population affected (31). As of April 2021, 32.8 % of the population had suspected or diagnosed mental health issues, and 46.7 % showed symptoms of mild to severe depression (28). International studies have reported high rates of clinically significant anxiety (59 %) and moderate depression symptoms (39 %) (32). Various studies have also noted depression rates between 43.3 % and 50.3 %, anxiety between 45.4 % and 47 %, and PTSD between 28 % and 31.8 %, depending on the age group (32-34). This study, conducted eight months post-infection, found high rates of anxiety and depression and a lower rate of PTSD among individuals with mental health issues. Notably, having a prior psychiatric diagnosis increases the risk of COVID-19 infection by 65 % (35).

Up to 40.5 % of patients can experience long COVID symptoms, including fear, depression, confusion, and insomnia, up to a year after infection (36). Although vaccines have reduced the prevalence of ongoing symptoms (37),

mental health remains a significant issue for Chile. Extrapolating our findings to the recovery population suggests potential economic losses and reduced quality of life. Before the pandemic, despite a higher rate of mental health problems per capita than in neighboring countries, Chile still had insufficient mental health services to meet demand. Only 38.5 % of patients received treatment in institutions (31). It is estimated that 24 % of Chileans had mental health problems during the pandemic, with 75 % yet to be seen by specialists (28). The current model of waiting for patients to seek treatment is inadequate in addressing the pandemic's consequences. Health personnel must proactively identify patients in their communities, involving other community members and employing strategies for mental health promotion, particularly at the municipal level (38,39). In addition to pharmacological and cognitive-behavioral therapy interventions, community education using emerging technology tools can help promote resilience techniques, mindfulness training, and the PERMA model of positive psychology (Positive Emotion, Engagement, Relationships, Meaning, and Accomplishment) (38-42).

CONCLUSIONS

Our study demonstrates that after COVID-19 infection, fear of reinfection and perceptions of loneliness are independent risk factors contributing to the prevalence of anxiety, depression, and PTSD in patients with persistent mild symptoms for up to eight months. We observed a high prevalence of fear in the Chilean population, exacerbated by pre-existing mental illnesses. Psychological factors play a significant role in the sequelae of infection and contribute to symptom persistence. Future analyses should consider economic and social contexts in conjunction with clinical data. Comprehensive strategies for addressing these issues are needed, including identifying sustainable funding sources, developing on-site identification and treatment protocols, and promoting community-based mental health resources.

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Conflicts of Interest

The authors declare that they have no conflicts of interest. The financial entity did not influence the preparation, methodology, data collection, analysis, or final manuscript.

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