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Long-lasting brain fog is related with severity clusters of symptoms in COVID-19 patients

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ABSTRACT

Background: *COVID-19 patients may experience Long-lasting symptoms from weeks to even months.* ***Aim****: To evaluate long-term cognitive impairment based on the severity of symptoms of COVID-19 infection in a primary health system setting.* ***Material and Methods****: From a database of 363 patients, 83 cases aged 47 ± 15 years, (58% females) were selected from June to August 2020. In patients who survived the virus, 24 infection-related symptoms were collected to create three severity clusters (mild, moderate, and severe). The follow-up time was at least seven months. Comparing the first two clusters with the severe cluster, the existence of brain fog and risk factors (obesity, hypertension, diabetes, chronic lung disease, and hypothyroidism) were analyzed.* ***Results:*** *Thirty-one patients (37%) had persistent symptoms lasting up to 240 days. Fifty-one patients (61%) experienced brain fog. Concentration was affected by symptom severity (odds ratio [OR] 3.63, 95% confidence interval [CI] 1.26-10.46, p = 0.02). Short- or long-term memory loss was not affected. Moreover, symptom severity was related to brain fog (OR 3.16, 95% CI 1.05-9.51, p = 0.04). Patients with persistent symptoms had a concentration impairment associated with severity patterns (OR 24.3, 95% CI 1.73-340.11, p = 0.03).* ***Conclusions:*** *Brain fog is associated with symptom severity in COVID-19 survivors and lasts for more than eight months.*

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Key words: *COVID-19; Mental Fatigue; Memory Disorders; Post-Acute COVID-19 Syndrome.*

La niebla cerebral persistente relacionada a la gravedad de síntomas en pacientes con COVID-19

Antecedentes: *Los pacientes que han tenido COVID-19 pueden experimentar síntomas persistentes que duran semanas a meses.* ***Objetivo****: Evaluar el deterioro cognitivo a largo plazo en función de la severidad de los síntomas de la infección por COVID-19, en un escenario de sistema primario de salud.* ***Material y Métodos****: De una base de datos de 363 pacientes se seleccionaron 83 casos de 47 ± 15 años (58% mujeres), de junio-agosto de 2020. Se recopilaron 24 síntomas*

relacionados con la infección, creando tres grupos (leve, moderado y severo), en pacientes que padecieron y sobreviven al virus. El tiempo de seguimiento fue de al menos siete meses. La existencia de niebla cerebral y de factores de riesgo (obesidad, hipertensión, diabetes, enfermedad pulmonar crónica e hipotiroidismo) se comparó los dos grupos de severidad más bajos con el nivel superior. ***Resultados:*** *Treinta y un pacientes (37%) tuvieron síntomas prolongados con una duración de hasta 240 días. Cincuenta y un pacientes (61%) mostraron niebla cerebral. El deterioro de la concentración fue afectado por la severidad (Razón de riesgo (RR) = 3,63, Intervalos de confianza (IC) 95%: 1,26-10,46, p = 0,02). La pérdida de memoria a corto o largo plazo no fue afectada. El grupo con mayor severidad se asoció a niebla cerebral (RR = 3,16, IC95%: 1,05-9,51, p = 0,04). Los portadores de síntomas prolongados tuvieron una alteración de la concentración asociado a severidad (RR: 3,16, IC95%: 1,05-9,51, p= 0,04).* ***Conclusiones:*** *La niebla cerebral está relacionada con la severidad de los síntomas en supervivientes de COVID-19 permaneciendo por más de ocho meses.*

Palabras clave*: Concentración; Fatiga Mental; COVID-19; Trastornos de la Memoria.*

COVID-19 patients may experience lingering symptoms lasting from weeks to even months. These symptoms have already been categorized into six clusters, helping to predict the need for respiratory support[1]. Afterwards, in the recovery period, some neurological challenges appear, cognitive impairment, more likely in patients who required hospitalization[2].

In major studies, other infrequent neurological and psychiatric issues observed include anxiety, psychotic, mood disorders, insomnia and, dementia between others after six months infection[3]. The presence of lasting symptoms defined patients as long-haulers[4].

People at risk of deleterious outcomes are the elderly and those with preexisting conditions like diabetes (DM), hypertension (HT), and heart disease[5-7]. Initial concern had been focused on the elderly, with 71% exhibiting confusion[8], also a common symptom related to aging[9,10]. Furthermore, confusion may indicate neuroinflammation, neuroendocrine abnormalities, and neurotransmitter dysregulation as a result of brain injury[11].

Other symptoms that address complex cerebral function are memory loss and emotional or cognitive dysfunction, a cytokine release-related phenomenon[12]. Before the actual pandemic, some cohort studies presented gender cognoscitive differences, with a more decline in women[13]. However, in the factual COVID-19 scenario, gender susceptibility indicates a role of women's hormone regulation over de ACE2 receptor, acting as a protector factor[14].

In overview, the most recent interest hotspot of health care is now brain fog, a constellation of symptoms related to memory loss, impaired concentration, and multitask deficits associated with adipocytokine and histamine release[15].

As a result, a need for health care providers to seek cognitive impairment persistence risk associated with severity cluster design only in an outgoing basis setup.

For this reason, we based our work on an epidemiological follow-up study to evaluate mid-term cognitive impairment based on severity cluster, based on a primary health system setting.

Material and Methods

This mid-term retrospective study is from Centro de Salud Familiar (CESFAM) N° 1, an O'Higgins Health Service's primary health care center, in Rancagua, Chile. The results are part of the Rancagua Chilean Study on COVID-19 (RACHIS). The inclusion criteria were any local resident with a positive molecular test and disease-related symptoms between June and August 2020. Initially, 363 patients met the requirements; they were subsequently contacted at least seven months after lab test. We aimed to analyze in them the persistence of memory impairment

(short and long-term memory loss), concentration impairment through a simple questionnaire. To define those with cognoscitive impairment or brain fog[16] we used combinations of loss memory (short or long term) plus concentration loss. All of these variables were checked for a relationship to severity clusters symptoms. Additionally, any symptom that lasted more than four weeks characterized a long hauler case. Patients who could not be contacted, died, did not agree to participate, with mental disabilities (schizophrenia, major depression, bipolar disorder, dissociative disorders, obsessive compulsive disorder, psychosis and paranoia) to avoid confusion bias, asymptomatic, and those who did not answer the questionnaires were excluded. Finally, there were a total of 83 cases, as shown in the flow chart (Figure 1).

All patients were summoned and interviewed between January and April 2021; prior to study entry (at least after seven months of the PCR test), they gave written consent and only thereafter were allowed to complete a questionnaire containing their personal background and initial and persistent symptoms. Height and weight were measured after an overnight fast, and body mass index (BMI) was calculated as each participant's weight in kilograms divided by the square of their height in meters. The preexisting conditions included were: HT, DM, and chronic obstructive pulmonary disease (COPD), all known to worsen the outcome[15,17-19]. HT was defined as a documented history/treatment with antihypertensive medications. DM was based on a physician's diagnosis and/or by the use of medications. Chronic lung disease included patients with COPD and/or asthma. Hypothyroidism (HPT) was also included based on a diagnosis from a previous entry study by a health consultation; these patients were receiving chronic health monitoring.

Survey components

The survey assessed adverse effects that include previous disease(s) and type(s), how long the symptoms lasted after the confirmatory PCR test, short- and long-term memory loss, concentration loss, and the need to access health care. Brain fog presence was included if the patient manifested to have either short- or long-term memory impairment plus altered concentration. In addition, the Goldberg Questionnaire was applied to determine anxiety and depression[20].

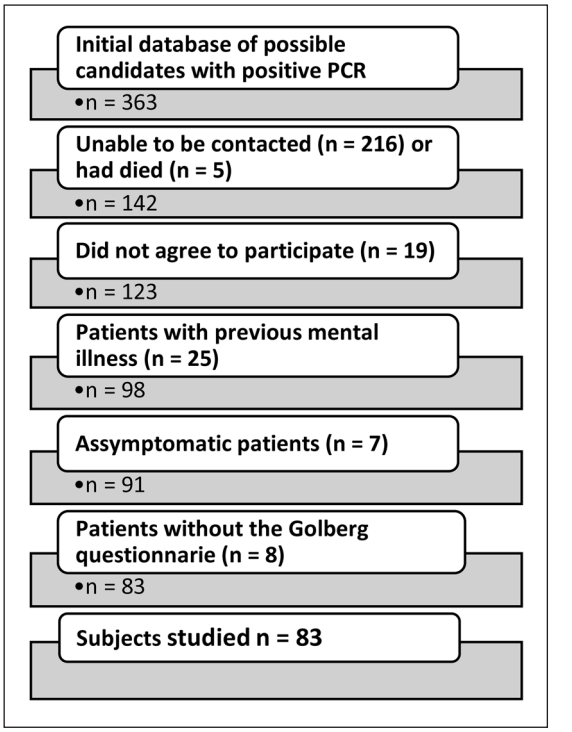

Figure 1. Flow diagram of the study population.

Severity clusters

We based our study on the work of Sudre et al.[1], which includes cluster symptoms based on disease severity. However, we include also psychological symptoms that were no described in the previous research. The entire list is: fever, headache, chest pain, odynophagia, cough, dyspnea, tachypnea, cyanosis, myalgia, abdominal pain, prostration, diarrhea, anosmia, ageusia, hoarseness, loss of appetite, fatigue, confusion, (peripheral alterations of nervous injury [PANI] including paresthesia, hemiparesis, and paraplegia), anxiety, panic, and depression.

The symptoms combinations formed three severity groups. The severe group comprise symptoms that could reflect systemic affection and in the opposite direction the mild symptoms included those that did not limit the patients in a general manner and were frequent in the common cold. Finally, the rest of the symptoms constructed the moderate group. Note of point, a similar three levels classification was already previously described[21]. First, the severe group

include a combination of 3-6 symptoms with confusion (myalgia, fatigue, groveling, abdominal pain, dyspnea, tachypnea, diarrhea, and chest pain) plus any combination of mild symptoms (cough, loss of appetite, anosmia, hoarseness, PANI, anxiety, panic, and depression). The moderate cluster comprised patients who exhibited a combination of gastrointestinal symptoms such as ageusia, diarrhea, and odynophagia, plus two mild symptoms. Patients with thoracic pain or myalgia plus any mild symptom were also considered in the moderate group. Finally, mild severity group included those who did not have the aforementioned combinations of symptoms and had any of the following: anosmia, ageusia, paresthesia, hemiparesis, cough, anxiety, panic or depression in combination with headache, cough, sore throat, and fever. Worth stressing that confusion as a symptom is seen in very ill patients and could be part of brain fog. Nonetheless, the symptoms that were evaluated to construct the clusters were those that appears initially. Brain fog was account in the follow up period.

Statistical analysis

G*Power V3 for logistic regression analysis was used for *a priori* sample calculation, considering a power of 80% and an alpha error of 0.05, for a minimum sample size of 75. Demographic characteristics (age and sex), initial symptoms, and long-lasting cognoscitive impairment are presented as the median and standard deviation for continuous variables or absolute values with the percentage for categorical variables. The data normality was evaluated using the Kolmogorov–Smirnov test. Student's t-test compared continuous variables, the chi-square dichotomous variables and Fisher's exact test if required. One-way analysis of variance (ANOVA) was used to compare the three severity groups regarding the duration of symptoms. The Kruskal-Wallis test was used before the logistic regression to identify the variables that were not different among the severity clusters. Binomial logistic regression evaluated the risk of cognoscitive disabilities between the regressors: sex, age, risk factors and severity. In order to have one degree of freedom were compared between the severe group versus the sum of the mild and moderate groups. The procedure for variable selection was enter (all variables in a block and single step). All tests were two-tailed.

Ethical issues

The scientific ethics committee of the Rancagua Municipal Health Corporation approved the study. The research was in accordance with the ethical standards legislated by the Declaration of Helsinki, based on guidance and the principles of the World Medical Association[22]. The study protocol did not interfere with any medical prescription and/or recommendation, or other ongoing protocols.

Results

The population characteristics are summarized in Table 1. Eighty-three patients were evaluated, (age = 47 ± 15, range 19-84 years), included 35 men (42.2%) and 48 women (57.8%). The patients were evaluate for a mean of 8 ± 0.4 months

Table 1. Distribution of patients according to age, sex, and comorbidities

	Total (n = 83)	M (n = 35)	F (n = 48)	p
Age (years)	47 ± 15	47 ± 12	48 ± 17	0.86
Obesity	34 (41.0%)	15 (42.9%)	19 (39.6%)	0.76
HT	28 (33.7%)	10 (28.6%)	18 (37.5%)	0.40
DM	17 (20.5%)	8 (22.9%)	9 (18.8%)	0.65
LD	3 (3.6%)	0 (0%)	3 (6.3%)	0.13
HPT	12 (14.5%)	0 (0%)	12 (25%)	< 0.01

Continuous variables are represented in mean ± standard deviation. Dichotomous variables are represented as number and percentage. M, male; F, female; HT, hypertension; DM, diabetes mellitus; LD, lung disease (chronic obstructive pulmonary disease plus asthma); HPT, hypothyroidism.

after the PCR test (range 7.1-9.7 months). No difference was observed regarding age and most of the comorbidities, with the exception of HPT (absent in males). Obesity (41%) and HT (33.7%) were the more prevalent.

The mean symptom duration was 31 ± 42 days (range 2-240 days). Ten patients required hospitalization, six of them intensive care, but without needing mechanical ventilation. During follow-up, two patients needed to be re-hospitalized with a mean duration of 2.5 days and without a deleterious outcome.

Headache (85.5%) and myalgia (72.3%) comprised the most observed symptoms in all patients. Among the gastrointestinal symptoms, ageusia was the most observed (65.1%) and diarrhea the least (32.5%). Hemiparesis and paraplegia were absent from all patients. Psychological symptoms (anxiety, depression, and panic) were in general less observed (Table 2). No gender differences were observed concerning the severity cluster. Nonetheless, female patients had milder symptoms than males (Table 2).

Fifty-one patients (61.4%) had at least one of the cognoscitive impairment studied. The incidence of each was: short-memory loss (36.1%, n = 30), long-memory loss (38.6%, n = 32), concentration impairment (48.2%, n = 40), and brain fog (61.4%, n = 51). The COVID-19 symptoms lasted a mean of 31 ± 34 days (range 2-180 days).

Risk factors and severity

The presence of risk factors studied failed to had significative association with the severe cluster. Obesity (10/34 [29.4%] vs 16/49 [32.7%], p = 0.754), HT (7/28[25%] vs 19/55[34.5%], p = 0.375), DM (6/17[30.3%] vs 20/66[30.3%], p = 0.692, LD:0/3 [0%] vs 26/80 [32.5%], p = 0.233 and HPT (3/12 [25%] vs 23/71 [32.4%], p = 0.610).

Concentration and memory impairment

Regarding concentration impairment, the model provided good sensitivity (72.1%) but lower specificity (60%), for an overall 66.3% capacity to predict cases and an odds ratio (OR) of 3.631 (95% CI 1.260-10.464) if severe cases are present (Table 3). Memory loss and severity cluster was absent (Table 4). Of note, the male gender was a protective factor for short-term memory impairment, but no influence in the brain fog analysis (Table 5).

Although memory impairment and concentration could be related to age, none of them were true in this population. No difference was found between mean age in those who had long-term memory (47 ± 16 vs. 48 ± 14 years), short-term memory impairment (45 ± 14 vs 49 ± 15 years, p = 0.303) or concentration deficit (47 ± 14 vs. 48 ± 16 years, p = 0.794) compared with those who not presented the variable. Additionally, we

Table 2. Frequency of symptoms observed in patients and distribution by severity groups

Fever	66.3%	Headache	85.5%	Thoracic pain	37.3%
Odynophagia	49.4%	Cough	51.8%	Dyspnea	57.8%
Tachypnea	30.1%	Cyanosis	6%	Myalgia	72.3%
Abdominal pain	27.7%	Prostration	16.9%	Diarrhea	32.5%
Anosmia	66.3%	Ageusia	65.1%	Hoarseness	14.5%
Loss of appetite	44.6%	Fatigue	38.6%	Confusion	14.5%
PANI	18.1%	Anxiety	12%	Panic	9.6%
Depression	6.2%				
	Cluster distributions				
	Total	**M (n = 35)**	**F (n = 48)**	**p**	
Mild	31 (37.3%)	9 (25.7%)	22 (45.8%)	0.06	
Moderate	26 (31.3%)	13 (37.1%)	13 (27.1%)	0.33	
Severe	26 (31.3%)	13 (37.1)	13 (27.1%)	0.33	

PANI, peripheral alterations of nervous injury.

Table 3. Concentration impairment and severity cluster

Concentration impairment	p	Exp(β)	95% C.I.	
			Lower	Upper
Age	0.70	0.99	0.96	1.03
Sex (male)	0.14	0.48	0.18	1.27
Obesity	0.95	0.97	0.37	2.57
HT	0.07	3.10	0.93	10.41
DM	0.09	0.31	0.08	1.22
LD	0.39	0.32	0.02	4.33
Severity	0.02*	3.63	1.26	10.46
Constant	0.94	1.07		

*p < 0.05; Exp(β): beta exponential; HT, hypertension; DM, diabetes mellitus; LD, lung disease; HPT, hypothyroidism. For gender, male was used as the reference variable, and for the cases of the risk factor if they were present.

Table 4. Memory loss and Severity cluster

	P value	Exp(β)	95% C.I.	
			Lower	Upper
Short-term memory loss				
Age	0.08	0.97	0.93	1.00
Sex (male)	0.03*	0.32	0.11	0.88
Obesity	0.69	0.82	0.30	2.23
HT	0.15	2.40	0.72	7.94
DM	0.46	1.63	0.44	6.05
LD	0.77	0.68	0.05	9.20
Severity	0.40	1.57	0.55	4.49
Constant	0.26	2.95		
Long-term memory loss				
Age	0.59	0.99	0.95	1.03
Sex (male)	0.17	0.52	0.20	1.33
Obesity	0.84	0.91	0.35	2.34
HT	0.56	1.40	0.46	4.30
DM	0.91	0.93	0.27	3.22
LD	0.52	2.33	0.18	29.60
Severity	0.79	0.87	0.32	2.39
Constant	0.81	1.25		

*p < 0.05, Exp(β), beta exponential; HT, hypertension; DM, diabetes mellitus; LD, lung disease; HPT, hypothyroidism. For gender, male was used as reference variable, and for the cases of the risk factor if they were present.

separate those older adults (> 60 years), n = 18 and without finding statistical difference with the rest of the population: 6/18 vs. 26/64, p = 0.785 for long-term memory, 3/18 vs 27/64, p = 0.056 for short-term memory, and 7/18 vs 33/64, p = 0.427.

Brain fog

Regarding brain fog and age; those who had the variable and those who did not had similar age (48.9 ± 16 years vs. 46 ± 14 years, p = 0.458). Noteworthy, brain fog was slightly higher in women (66.7%) than men (54.3%, p = 0.252). More patients with brain fog had significantly more anxiety (70.6%) than those without brain fog (29.4%, p = 0.015; OR 3.086, 95% CI 1.227-7.761). Similarly, more patients with brain fog had depression than those without brain fog (78.4% vs. 21.6%, p < 0.001, OR 6.942, 95% CI 2.583-18.658). In the multivariate analysis, brain fog presence was also related to the severity cluster (Table 5). The model exhibited a very low sensitivity of 31.3%, a higher specificity of 88.2% and a 66.3% capacity to detect cases.

Long-hauler patients

Overall, 37.3% of patients (n = 31), nine men and twenty-two women, had persistent symptoms after four weeks. These patients were also related to severity cluster and concentration impairment (OR 24.271, 95% CI 1.732–340.105, p = 0.018). Neither memory loss nor brain fog presence was

Table 5. Brain fog risk

Brain fog	p	Exp (β)	95% C.I.	
			Lower	Upper
Age	0.40	0.98	0.95	1.02
Sex (male)	0.22	0.55	0.21	1.44
Obesity	0.37	0.64	0.24	1.68
HT	0.33	1.79	0.56	5.71
DM	0.49	0.64	0.18	2.25
LD	0.87	1.24	0.10	15.89
Severity	0.04*	3.16	1.05	9.50
Constant	0.19	3.46		

*p < 0.05, Exp(β), beta exponential; HT, hypertension; DM, diabetes mellitus; LD, lung disease; HPT, hypothyroidism. For gender, male was used as reference variable, and for the cases of the risk factor if they were present.

Table 6. Gender distribution by symptom and severity cluster in long haulers

	M	F	p		M	F	p
Headache	4 (44.4%)	12 (54.5%)	0.70	Myalgia*	0 (0.0%)	9 (40.9%)	0.03
Thoracic pain*	6 (27.3%)	3 (33.3%)	1.00	Abd. Pain*	0 (0.0%)	3 (13.6%)	0.54
Odynophagia*	2 (9.1%)	1 (11.1%)	1.00	Prostration*	0 (0.0%)	1 (4.5%)	1.00
Cough*	5 (22.7%)	3 (33.3%)	0.66	Anosmia*	3 (33.3%)	8 (36.4%)	1.00
Dyspnea*	3 (33.3%)	7 (31.8%)	1.00	Ageusia*	1 (11.1%)	7 (31.8%)	0.38
Tachypnea*	0 (0.0%)	3 (13.6%)	0.54	Diarrhea*	0 (0.0%)	1 (4.5%)	1.00
Cyanosis*	0 (0.0*)	1 (4.5%)	1.00	Hoarseness*	1 (11.1%)	1 (4.5%)	0.50
Anorexia*	4 (44.4%)	5 (22.7%)	0.39	Fatigue*	2 (22.2%)	8 (36.4%)	0.68
Confusion*	1 (11.1%)	2 (9.1%)	1.00	PANI*	2 (22.2%)	3 (33.3%)	0.61
Panic*	0 (0.0*)	1 (4.5%)	1.00	Depression*	2 (22.2%)	2 (9.1%)	0.56
Anxiety*	1 (11.1%)	1 (4.5%)	0.50				

	Severity		
	Mild	Moderate	Severe
M	2 (22.2%)	4 (44.4%)	6 (66.7%)
F	8 (36.4%)	7 (31.8%)	15 (68.2%)
p	*0.68	*0.68	*1.00

M; male, F; female, F* Fisher test correction, Abd Pain; abdominal pain, PANI; peripheral alterations of nervous injury.

associated with this group in regression analysis (data not shown). Long hauler patients regarding severity clusters lack relationship. However, only myalgia was related to women as an isolated symptom (Table 6).

Discussion

Symptoms persistence after Covid-19 already have been observed in hospitalized patients, with a follow up of 12 weeks in a three-severity level (mild, moderate and severe). Arnold et al.[23] found that severe patients had an elevated percentage of lingering symptoms after outpatient 8-12 weeks follow-up, a result consonant with our study. Most of the symptoms that stayed were shortness of breath and myalgia, interestingly, no cognoscitive issues were reported. Although different in symptom prevalence, we had a high percentage of at least one of the characterized symptoms.

In contrast to specific symptom, our focus was over the patients' mental health influence. Nowadays, the new term for this patient could be neuro-Covid from chronic Covid syndrome where multiple organ sigs and symptom are observed[24]. These can explain the relationship with severity cluster. No relationship with age was observed, as well concerning risk factors as we originally expected.

Regarding symptoms and comorbidities of COVID-19 vary from populations. For example, an Egyptian study noticed a high prevalence of fatigue (72.8%) and low prevalence in HT (7.7%) and DM (5.2%)[25]. Differently we had high prevalence in Obesity, HT and DM, and myalgia, thoracic pain and dyspnea. Interestingly, we found no relationship in long term symptoms between gender. However, anxiety and depression were more observed in men. On the contrary, a large study in Chile, evaluating psychological distress, observed the opposite[26], leaving to our results prejudicated by the small sample.

Of note that a very few of our patients required hospitalization, and we did not observe more severe lesions as others describe in a similar time-frame, like stroke, intracranial hemorrhage, Guillain-Barré syndrome, encephalitis, or myo-

neural junction and/or muscle disease[3]. In spite of this fact, brain fog seems to be present in less life-threatening conditions

While authors have discussed the pathophysiological mechanism and incidence of brain lesions, most of them included only severe hospitalized patients[27,28]. Nevertheless, we can envision that future treatment directions should include treating brain fog with proper nutrition requirements[29], which must exceed the standard levels recommended to deal with neural inflammation and oxidative stress[30] and slow the progression of cognoscitive decline[31]. Moreover, a worrisome topic is that the target population unexpectedly increased after observing long-haul symptoms in patients already vaccinated[32]. Some authors reported no changes in persistent symptoms in 55%, and worsened in 18% of the cases[33].

Study strength and limitations

This study is a novel in the region and serve as pilot research. Nonetheless, it is limited because it has an observational design and represents a small portion of central Chile, as well as age groups representation. Additionally, the data was retrospectively collected, and can collide with different literature definitions of brain fog[16] where the concept is present at the beginning of the infection[34], or is late presentation associated phenomenon[35]. Fortunately, some authors have raised the problem to form an international consortium in a prospective design to assess the problem including Chile[36].

Worthy to point out, the results can be assembled in equations to calculate the individual risk of presenting persistent cognitive impairment, with the beneficial base to reduce long-term morbidity.

Finally, we conclude that brain fog is related to initial symptom severity in COVID-19 survivors from a primary care setup, and this phenomenon can last for more than eight months.

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