ISSN 1669-9106 MEDICINA (Buenos Aires) 2023: 83: 669-682

Original article

POST COVID-19 SYNDROME. SEVERITY AND EVOLUTION IN 4673 HEALTH CARE WORKERS

CARLOS TAJER[1], MARÍA JOSÉ MARTÍNEZ[1], JAVIER MARIANI[1], MAXIMILIANO DE ABREU[1], LAURA ANTONIETTI[2]

[1]Departamento de Cardiología, Hospital de Alta Complejidad Néstor Carlos Kirchner, Florencio Varela, Provincia de Buenos Aires, Argentina, [2]Departamento de Investigación, Universidad Arturo Jauretche, Florencio Varela, Provincia de Buenos Aires, Argentina

Postal address: Carlos Tajer, Av. Calchaquí 5401, 1888 Florencio Varela, Provincia de Buenos Aires, Argentina
E-mail: ctajer@gmail.com
Received: 10-IV-2023
Accepted: 2-VI-2023

Abstract

Background: The evolution of post COVID syndrome has been variable and we lack information on its impact on healthcare professionals, particularly in Latin America.

Methods: We conducted a survey through a social network in health professionals on post COVID-19 syndrome cases confirmed with PCR. In a web-based questionnaire, we asked about 21 symptoms, their severity, duration, degree of activity impairment and return to work.

Results: 4673 health professionals from 21 countries responded, mean age of 47.8 years, 64.2% women. The initial course was asymptomatic in 9.1%, mild symptoms 36.8%, moderate symptoms without hospitalization 40.8% or with hospitalization 11.7%, and severe symptoms with respiratory assistance 1.6%. The most prevalent symptoms were fatigue (67%), insomnia (44.2%), anxiety (42.3%), myalgia (41.9%) and anosmia (41.2%). Considering only severe symptoms (grades 3-4 on a subjective index from 1 to 4), the most prevalent were slowness (36.3%), impaired concentration (33.1%), anosmia (20.4%), fatigue (19.1%), impaired memory (18.1%) and dyspnea (15.9%). Prevalence dropped by half in the first 5 five months, but in many cases, it lasted for more than a year. In the multivariate analysis, symptoms tended to be grouped into clusters (cognitive, neuropsychiatric, cardiorespiratory, digestive, others). The need to change the work area was 16% and lack of return to work 7.8%, related to older age, number of symptoms and severity of the initial course.

Conclusion: In conclusion, in many cases the persistence of post-COVID symptoms can be prolonged and have an occupational impact on healthcare professionals, requiring the adoption of specific policies to reduce harm.

Key words: post COVID syndrome, long COVID, post-COVID-19, COVID-19

Resumen

Síndrome post COVID-19. Gravedad y evolución en 4673 trabajadores sanitarios

Introducción: La evolución del síndrome post COVID ha sido variable y carecemos de información sobre su impacto en los profesionales de la salud.

Métodos: Realizamos una encuesta a través de una red social en profesionales de la salud sobre casos de síndrome post COVID-19 confirmados con PCR. En un cuestionario web, preguntamos sobre 21 síntomas, su gravedad, duración, grado de afectación de la actividad y reincorporación al trabajo.

Resultados: Respondieron 4673 profesionales sanitarios de 21 países, edad media de 47 años, 64% mujeres. El curso inicial fue asintomático en el 9%, síntomas leves en el 36%, síntomas moderados sin hospitalización en el

40% o con hospitalización en el 11%, y síntomas graves en el 1%. Los síntomas más prevalentes fueron fatiga (67%), insomnio (44%), ansiedad (42%), mialgia (41%) y anosmia (41%). La prevalencia se redujo a la mitad en los primeros 5 cinco meses, pero en muchos casos se prolongó durante más de un año. En el análisis multivariado los síntomas tendieron a agruparse en clusters (cognitivos, neuropsiquiátricos, cardiorrespiratorios, digestivos, otros). La necesidad de cambiar de área de trabajo fue del 16% y la falta de reincorporación al trabajo del 7%, relacionadas con la mayor edad, el número de síntomas y la gravedad del curso inicial.

Conclusión: En muchos casos la persistencia de los síntomas post-COVID puede ser prolongada y tener un impacto laboral en los profesionales sanitarios, requiriendo la adopción de políticas específicas para reducir el daño.

Palabras clave: síndrome post COVID, COVID prolongado, post-COVID-19, COVID-19

KEY POINTS
Current knowledge:

- COVID 19 has generated multiple sequelae, with an impact on quality of life and return to work. A particularly affected sector has been health workers, with a high rate of infections, mortality and sequelae.

Article contribution:

- It analyzes in comparative ways the different definitions of prolonged COVID to make its interpretation more precise. It provides a survey of a large number of health workers in Latin America, with an analysis by symptom and syndrome, its severity and duration, which can support policies for its prevention and containment.

The acute phase of COVID-19 can evolve in a wide variety of ways, from asymptomatic to severe multiorgan involvement. Symptoms can persist for variable periods interfering with return to work and quality of life, with an additional burden on the health care system[1-3]. Several designations for persistent symptoms after the acute stage and different criteria regarding the time of persistence for diagnosis have been postulated. Initially, the National Institutes of Health (NIH) proposed to study cases that persisted with symptoms for more than one month after the initial infection[4].The UK National Institute for Health and Care Excellence (NICE) uses the term Long COVID to define symptoms that continue beyond the first month or appears after the initial infection, in the absence of alternative diagnoses[5]. It considers an acute phase up to the first month, persistence of evolving symptoms from 4 to 12 weeks, and post COVID syndrome after 12 weeks from the initial episode. In turn, the World Health Organization (WHO) has defined post-COVID-19 condition as persistence of symptoms beyond three months, continuing for at least two more months and not explained by other pre-existing illness[6]. Reported symptoms involve various systems and domains, with a higher prevalence of functional mobility problems, respiratory abnormalities and mental health disorders, an incidence of more than 50% in some series, and variable duration, which may extend to more than one year[7-9]. In an analysis of large administrative databases of US Veterans, patients who experienced COVID-19, even without hospitalization compared with a similar control group, had a marked excess of multiple pathologies and medication use during the subsequent six months[10].

The pandemic had a major impact on health care personnel, who were under great strain at work and had a high rate of infection. According to WHO data, infection rates among health care workers exceed those of the general population[11]. Fourteen percent of the positive tests belong to workers in this sector, and in some countries, the figure rises to 35%. Several studies have reported the prevalence of post-COVID-19 syndrome in health care workers and its occupational repercussions in different regions of the world, which are summarized in the Appendix, but we lack information on Latin America. The aim of our study was to evaluate the severity and duration of different post-COVID-19 symptomatology through a survey carried out in a social network of Latin-American health professionals who had suffered a confirmed episode of COVID-19. By obtaining 4673 valid responses, we believe that our study provides relevant information for the interpretation of post-COVID sequelae.

Materials and methods

An open survey was carried out among health professionals of the Spanish-speaking INTRAMED social network[12]. The survey was anonymous, and the inclusion criterion was to have suffered from COVID-19 confirmed by PCR. The invitation to participate was sent through the network's usual e-mails promoting activities and through the web page. The survey was kept open for one week (October 22 to 29, 2021) and collected sociodemographic data (age, gender, profession, work environment, country), date and clinical course of COVID-19, its impact on work activity (leave, return to work), the persistence of different symptoms more than one month after the initial infection and their severity, the need for consultations, diagnostic studies and new hospitalizations. Questions on a list of 21 symptoms were included: fatigue, dyspnea, cough, chest pains, palpitations or tachycardia, memory impairment, slow reasoning, concentration difficulties, anxiety, depressive symptoms, headaches, insomnia or new sleep disturbances, numbness of limbs, nausea, diarrhea, decreased appetite, joint pain-muscle pain, tinnitus, dizziness-vertigo, loss of taste and/or smell, and skin rashes[13]. For each symptom, the severity, duration and eventual persistence were asked. A subjective scale from 1 to 4 (mild, moderate, severe, very severe) was used to define the severity of most symptoms. For dyspnea, the scheme proposed by the Medical Research Council of the United Kingdom (MRC) was applied[14], and for headache, a severity scale from 1 to 10 was established. The survey also questioned about the studies performed after COVID-19 through a list that included laboratory studies, chest X-ray, electrocardiogram, echocardiogram, Holter monitoring, stress evaluations, cardiac catheterization, functional respiratory study, chest computed tomography, endoscopies, cognitive studies and neurological studies.

Analysis of prevalence according to definitions

Some participants reported that the symptoms had not actually lasted more than one month since the COVID-19 episode, and therefore did not meet the defined long-COVID criteria. For a better interpretation, we summarized in a table the prevalence initially reported by the respondents and then the corrected prevalence, excluding cases that reported symptom duration of less than one month. In a post-hoc analysis, we explored the prevalence of each symptom according to the different definitions described in the introduction (more than one month, more than three months, and more than three months with persistence of at least two months) in a subgroup of 3642 patients with more than 5 months since the episode of COVID-19[5-7].

Ethical considerations

Participants gave their consent by answering the questionnaire. The Hospital El Cruce IRB (resolution 0117) granted ethical approval. Survey responses were anonymous. All study procedures were carried out in accordance with international ethical norms and standards through defined operating procedures to respect the rights of the participants and protect confidentiality. Before starting the questionnaire, the participants were given information about the objectives of the study and the voluntary and anonymous nature of the survey. No records were generated that would allow the personal identification of the participants.

Statistical analysis

Quantitative variables were reported as mean/standard deviation or median/interquartile ranges (IQR) according to their distribution. Discrete variables were reported as number and percentage, with their 95% confidence intervals (95% CI). The analysis of the association between discrete variables was performed with contingency tables, and their p level, odds ratio and confidence intervals were established. The comparative analysis of quantitative variables was performed with parametric or nonparametric methods according to their distribution. For the analysis of variables related to the lack of return to work, a logistic regression analysis was performed selecting those with a significant association in the univariate analysis, with a p level < 0.05. The association of symptoms corrected for age and gender was evaluated in multivariate models. A second multivariate analysis adjusted for symptom severity was performed; for this analysis, level 3-4 of each symptom was considered as severe, and for headaches, an intensity of 6 or more. The R (version 4.2.1)[15] program and R Studio (version R Studio-2022.07.1-554)[16] were used for the analysis.

Results

The survey had 4673 participants from 25 countries with valid responses. Gender distribution was 2998 females (64.2%) and 1675 males (35.8%) and mean age was 47.8 ± 11.8. Most of the professionals were physicians (n = 3080, 67.5%) or nurses (n = 525, 11.5%). A total of 701 participants worked in critical areas (15.3%) and 1332 in emergency services (29%). The initial episode of COVID-19 was asymptomatic in 420 respon-

dents (9.1%), with mild symptoms in 1701 (36.8%), moderate symptoms without hospitalization in 1886 (40.8%), moderate/severe symptoms with hospitalization in 543 (11.7%) and severe symptoms requiring respiratory support in 74 (1.6%).

Need to modify the working area and return to work

Post-COVID-19, 738 respondents out of 4618 (16%) reported requiring a modification of the work area. This change was related to the severity of the initial symptoms: in asymptomatic or with mild symptom cases it was 12% and 11.5% respectively, in moderate cases without hospitalization 18%, and in hospitalized patients 25% ($p < 0.0001$). Total recovery of activity was reported by 3537 patients (76.6%), almost total by 720 (15.6%), only partial by 263 (5.7%) and not recovered by 97 (2.1%), out of a total of 4617 valid responses. We grouped responses indicating no recovery or partial recovery as dichotomous data of lack of recovery, and performed a logistic regression analysis including gender, age, number of symptoms, and severity of the initial episode. Variables independently associated with lack of recovery from work were age with odds ratio (OR) 1.03 (95% CI 1.02-1.04; $p < 0.001$) per year, number of symptoms (OR 1.22, 95% CI 1.19-1.25; $p < 0.001$) per additional symptom, overall hospitalization (OR 1.9, 95% CI 1.1-3.6; $p = 0.025$), and hospitalization with requirement of mechanical ventilation (OR 3.2, 95% CI 1.4-7; $p < 0.001$). Sex was not significantly associated (female OR 0.97; 95% CI 0.74-1.25; $p = 0.802$)).

Frequency and severity of symptoms

Table 1 summarize the frequency of each symptom, its severity and duration in months The first column contains the frequency of each symptom as reported by the respondents, and the last column contains the frequency excluding symptoms with less than one month's duration. In the group that reported appetite disturbance, the weight reduction reported in 530 cases was 5 kg (3-7) (median and interquartile range-IQR). The intensity of headache on a scale from 1 to 10 was 6 (4-7) (median and IQR). Table 1

Considering only severe symptoms (3-4), the most prevalent were slowness (36.3%), impaired concentration (33%), anosmia (20.4%), fatigue (19.1%) and impaired memory (18.1%).

Frequency of Long-COVID syndrome adjusted to the different definitions

A sub-analysis was performed on 3642 participants who reported having suffered from COVID-19 more than five months prior to the survey. The incidence of long-COVID according to the three definitions discussed in the introduction were applied (NIH: more than one month, NICE more than three months, and WHO more than three months with persistence of at least two months). Table 2.

Number of symptoms per patient and duration

Table 1 reports the duration of each symptom in months as median and interquartile range. Figure 1 summarizes the month-to-month evolution for each symptomatology.

The median number of symptoms reported was 7 (IIC 3-10). The number of symptoms in each of the Latin American countries was variable, with medians between 3 and 9, although most countries ranged from 6 to 8, $p < 0.001$ (Fig. 2).

The number of symptoms was related to gender: female, median and IQR 7 (4-11) and male, 6 (2-9), $p < 0.001$, and to the severity of the initial symptoms: asymptomatic (420 patients), 4 (1-8); mild course (1701 patients), 5 (2- 8); moderate course without hospitalization (1886 patients), 8 (5, 12); hospitalized with (74 patients) or without (542 patients) mechanical respiratory assistance requirements, 9 (6-13), $p<0.001$

Associations between symptoms and other variables. Relationship between the different symptoms

In the univariate analysis, the relationship of each individual symptom with each of the others was statistically significant. The odds of association with its confidence interval are summarized in the Figure 3A.

A multivariate analysis was performed for each symptom as a dichotomous dependent variable, including each of the other symptoms, age and gender. In this analysis the symptoms tended to group into distinct syndromes (Fig. 3B). As examples: lack of appetite was associated with diarrhea, tinnitus, dizziness, anosmia and cough; depression was associated with anxiety and insomnia, slowness, memory problems, younger age and tinnitus; chest pain with palpitations, cough, headache, myalgia; fatigue, the most prevalent symptom, was associated with dyspnea, anxiety, depression, myalgia, memory problems and insomnia, and concentration problems were associated with slowness, memory problems and insomnia.

Relationship with age

In the univariate analysis of the 21 symptoms explored, 7 had no differences by age, 6 were associated with younger ages and 8 with older ages. Although in 15

Table 1 | Frequency and severity of the different symptoms. Corrected frequency: excluding symptoms with persistence of less than one month

Symptom	Frequency n (%)	Duration in months Median (IQR)	With data about severity	n (%)	n (%)	n (%)	n (%)	Corrected frequency n (%)
				0-I	II	III	IV	
Dyspnea	1614 (34.5)	4.5 (2-10)	1599	683 (42.7)	177 (11)	701 (43.8)	38 (2.38)	1433 (30.7)
				1	2	3	4	
Fatigue	3133 (67)	4.0 2-10)	3122	1044 (33.4)	1186 (38)	682 (21.8)	210 (6.73)	2816 (60.3)
Memory issues	2756 (59.2)	9 (4-13)	1703	267 (15.7)	578 (34)	522 (30.6)	336 (19.7)	1530 (32.8)
Anxiety	1968 (42.3)		1960	716 (36.5)	745 (38)	394 (20.1)	105 (5.4)	
Depression	1696 (36.5)	9 (4-13)	1696	611 (36)	636 (37.5)	355 (21)	94 (5.5)	1594 (36.4)
Insomnia	2056 (44.2)	9 (4-14)	2052	531 (25.9)	802 (39)	559 (27.2)	160 (7.8)	1858 (39.8)
Paraesthesia	1339 (28.8)	10 (4-14)	1336	477 (35.7)	546 (40.9)	230 (17.2)	83 (6.2)	1218 (26)
Nausea	437 (9.4)	6 (2-12)	434	202 (46.5)	156 (36)	57 (13.1)	19 (4.4)	369 (7.9)
Diarrhea	625 (13.4)	6 (2-12)	621	257 (41.4)	229 (36.9)	98 (15.8)	37 (6)	491 (10.5)
Decreased appetite	693 (14.9)	3 (1-10)	691	246 (35.6)	289 (41.8)	120 (17.4)	36 (5.2)	579 (12.4)
Myalgia	1946 (41.9)	9 (3-13)	1942	459 (23.6)	816 (42)	508 (26.2)	159 (8.2)	1751 (37.5)
Tinnitus	737 (15.9)	9 (4-14)	737	287 (38.9)	298 (40.4)	114 (15.5)	39 (5.3)	656 (14)
Dizziness	997 (21.5)	8 (3-13)	997	440 (43.8)	383 (38.1)	134 (13.3)	48 (4.8)	850 (18.2)
Anosmia	1916 (41.2)	2 (1-6)	1916	507 (26.4)	465 (24.2)	459 (23.9)	491 (25.6)	1470 (31.5)
Cutaneous eruptions	597 (12.8)	5 (2-12)	597	253 (42)	203 (34)	105 (17.7)	36 (6)	490 (10.5)
Slowness	2450 (52.7)	6 (2-12)	1372	213 (15.5)	214 (15.6)	554 (40.38)	391 (28.5)	1155 (24.8)
Attention disorder	2116 (45.4)	8 (3-13)	1247	153 (12.3)	187 (15)	536 (43)	371 (29.8)	1179 (24)
Cough	1332 (28.5)	2 (1-6)						1076 (23.03)
Chest pain	1378 (29.7)	4 (2-10)						1173 (25.1)
Palpitations	1553 (33.23)	5 (2-12)						1328 (28.4)
Headache	1684 (36.2)	8 (3-13)						1478 (31.6)

symptoms the differences by age were statistically significant, the difference between the presence and absence of the symptom was not greater than 2.5 years between the groups. In the multivariate analysis corrected for gender and symptom severity, four symptoms were associated with younger age and none with older age: headache, OR per year of age 0.97 (95% CI 0.96-0.98); insomnia, OR 0.97 (0.96-0.98); anosmia, OR 0.98 (0.97-0.99) and depression 0.98 (0.96-0.99).

Relationship with gender

The majority of the survey participants were female, 64%. In the univariate analysis, female gender was associated with higher reporting of 19 of the 21 symptoms questioned, with two exceptions: appetite impairment and diarrhea, which were similar in both genders. Age was higher in the male group (51.6 ± 13) than in females (46 ± 11.5), $p < 0.001$.

Requirement for complementary studies

The reported frequency of use of 11 complementary studies was: chest x-ray 860 (18.4%), laboratory tests 1265 (27%), echocardiogram 695 (14.9%), chest CT 622 (13.3%), spirometry 423 (9.1%), ambulatory electrocardiographic monitoring 268 (5.7%), stress evaluations 296 (6.3%), cardiac catheterization 14 (0.3%), digestive endoscopies 88 (1.9%), cognitive studies 126 (2.7%) and neurological studies 214 (4.6%).

Table 2 | Frequency of symptoms corrected according to different symptom persistence criteria*. N (%)

Criteria n	NIH 3642	NICE 3642	WHO 3642
	≥ 1 mes	≥ 3 meses	≥ 5 meses
Dyspnea	1241 (34.1)	959 (26.3)	726 (19.9)
Chest pain	968 (26.6)	725 (19.9)	566 (15.5)
Fatigue	2344 (64.4)	1798 (49.4)	1380 (37.9)
Cough	861 (23.6)	504 (13.8)	381 (10.5)
Anosmia	1178 (32.3)	646 (17.7)	529 (14.5)
Palpitations	1105 (30.3)	863 (23.7)	712 (19.5)
Insomnia	1535 (42.1)	1420 (39.0)	1323 (36.3)
Headache	1258 (34.5)	1127 (30.9)	1018 (28.0)
Tinnitus	547 (15.0)	503 (13.8)	481 (13.2)
Decreased appetite	459 (12.6)	306 (8.4)	252 (6.9)
Paraesthesia	1006 (27.6)	945 (25.9)	909 (25.0)
Attention disorder	1335 (36.7)	1238 (34.0)	1119 (30.7)
Myialgia	1439 (39.5)	1288 (35.4)	1189 (32.6)
Slowness	1478 (40.6)	1227 (33.7)	1057 (29.0)
Memory issues	1848 (50.7)	1590 (43.7)	1398 (38.4)
Depression	1254 (34.4)	1164 (32.0)	1083 (29.7)
Nausea	235 (6.5)	209 (5.7)	162 (4.5)
Diarrhea	402 (11.0)	320 (8.8)	282 (7.7)
Dizziness	698 (19.2)	613 (16.8)	555 (15.2)
Cutaneous eruptions	413 (11.3)	318 (8.7)	279 (7.7)

** Respondents with at least 5 months since acute episode of COVID-19*

Figure 1 | Reported duration in months for each symptomatology

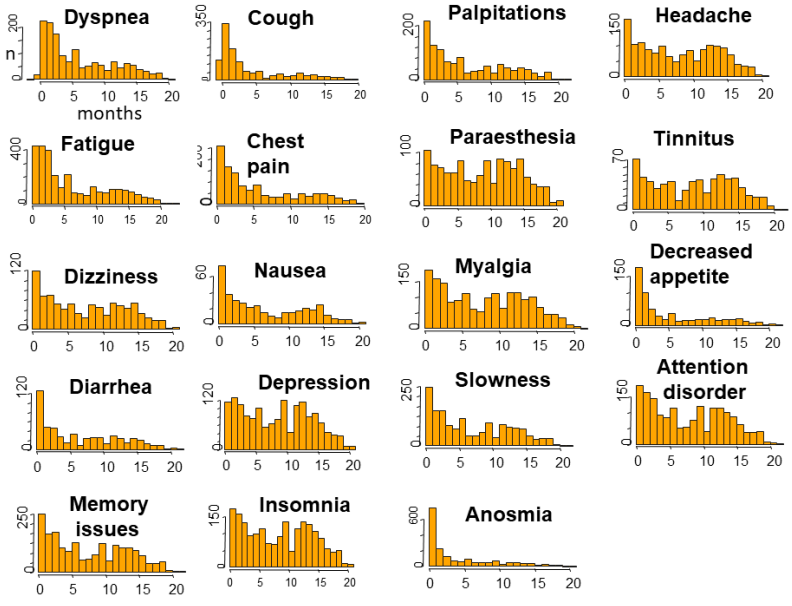
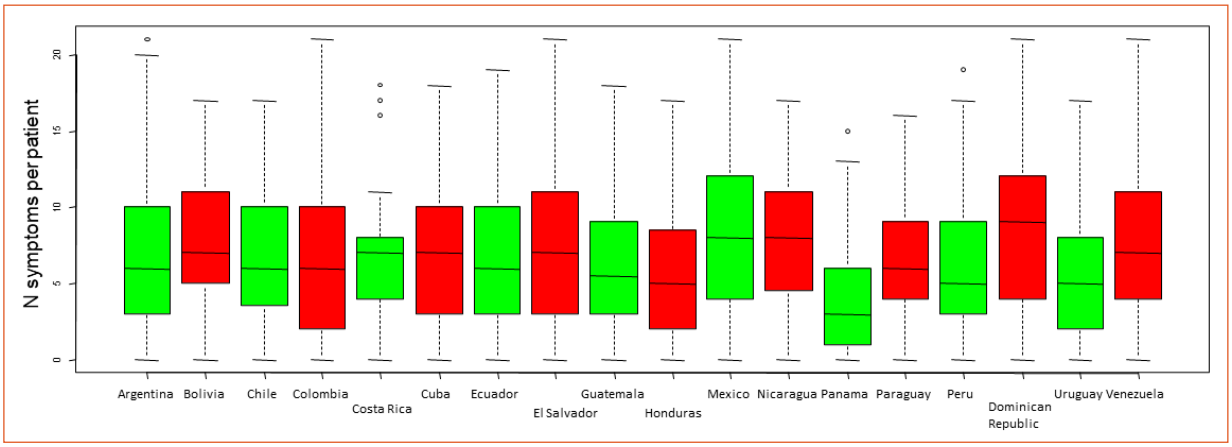


Figure 2 | Distribution of the number of symptoms according to countries (excluding countries with less than 10 participants)



Requirement for consultations, new medications, leave of absence and rehabilitation

The relationship between each symptom and the requirement for consultations, new medications, rehabilitation, new hospitalizations and the initial COVID-19 course was analyzed. Each symptom was associated with a higher severity course of the initial COVID-19 episode, with the requirement for new consultations, rehabilitation, psychotherapy and new hospitalizations, with the use of new medications and tranquilizers in particular. Table 3 summarizes as an example the relationship between dyspnea and the variables discussed.

Discussion

The perception of post-COVID-19 sequelae has implications for quality of life, work capacity and demand on the health care system. In this survey of health professionals in Latin America, the frequency of the different conditions reported was high, with frequent overlapping of symptoms (median of 7). In a survey of 6504 patients with confirmed or suspected COVID-19, 203 different symptoms were reported and the number of symptoms per patient was 55.9 ± 25[17]. Although without an exact reference to the number of symptoms, other series have had similar results[18]. In our series, the prevalence of the number of symptoms per country was variable, which could be expected due to the epidemiological differences by region and their multiple conditioning factors[19]. Although this variability was statistically significant, most countries reported 6 to 8 symptoms per participant. As in other series, this multiplicity of symptoms was statistically associated with greater severity of the initial episode of COVID-19 and female gender[9,17,18]. Post-COVID-19 sequelae decrease with evolution, so that the prevalence of "Long- COVID" will vary according to the adopted cut-off point in months.

Our survey was designed considering the persistence of symptomatology beyond the first month and we reported additionally the prevalence according to different cut point's criteria. From this analysis it can be inferred that: a) half of the reported symptoms disappear within the first five months and b) a significant percentage of the surveyed population persists with symptoms, whose reported duration can also be very long, in many cases over one year, which is in agreement with other series[8,9] In the univariate analysis each symptom was statistically linked to each of the other 21, but in the multivariate analysis corrected for gender and age, symptomatic "clusters" emerged: digestive, cognitive, cardiorespiratory and neuropsychiatric, which in turn implied differentiated complementary studies. In the referenced survey by Davis et al.[17] which contemplated 203 symptoms, three clusters of symptom grouping were defined, although without a clear cut-off point by organic systems as those observed in our study. The most prevalent symptom in our series is fatigue, coincident with reports available in the literature. This symptom has been

Figure 3A | Association between symptoms expressed as odds ratio (colored boxes) and 95% confidence intervals (boxes below). The colors mark the intensity of the association in red, yellow to green grading. All associations were significant

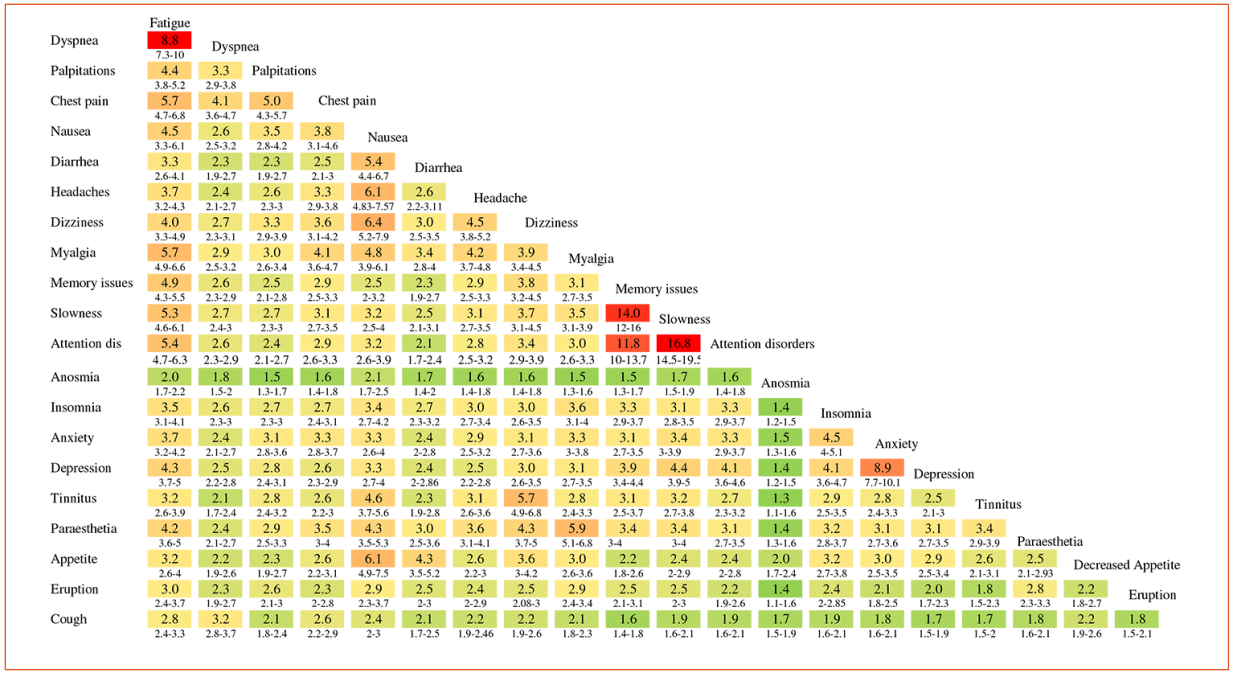


Figure 3B | Association between symptoms in multivariate analysis. The colored boxes indicate the odds ratio and the boxes below its confidence interval. The color grading is as in the previous figure. Only significant odds ratios were included

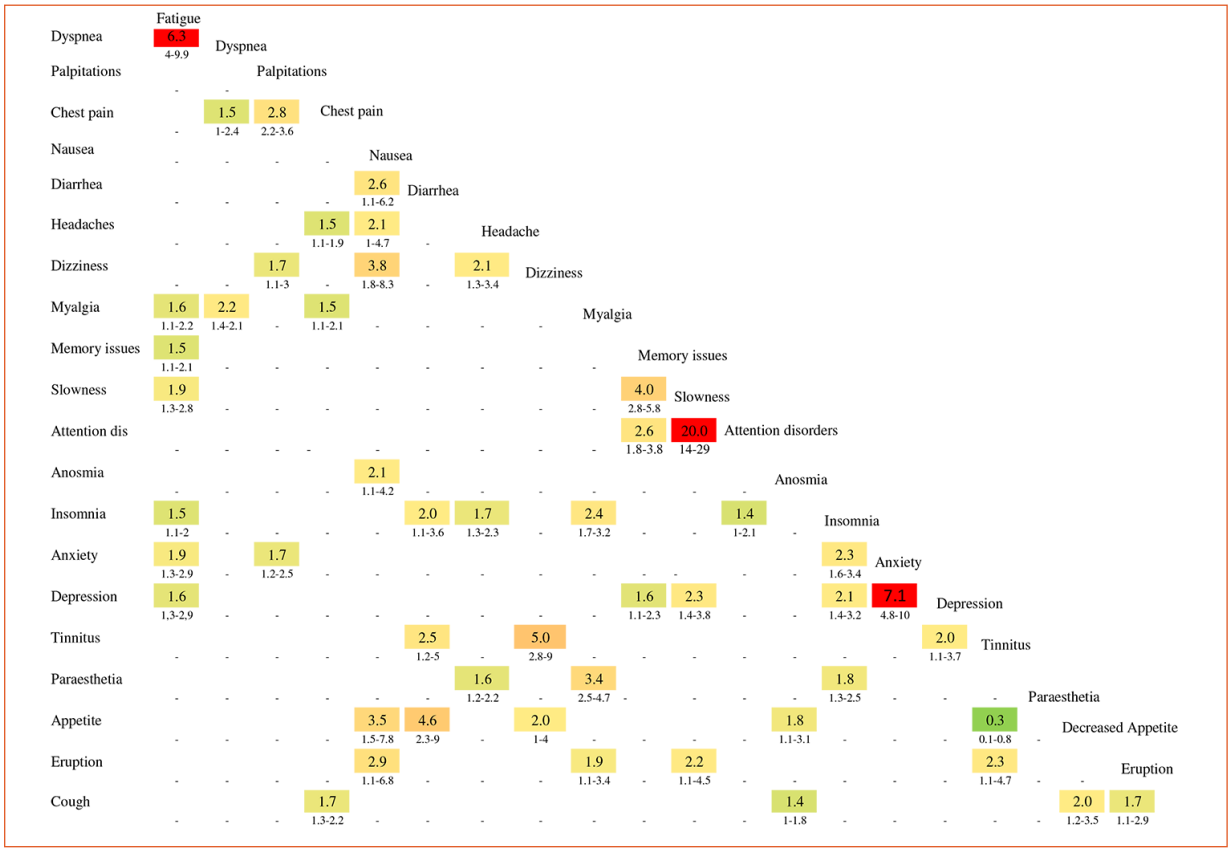


Table 3 | Persistent dyspnea and its relationship to initial COVID course, duration of leave, re-interventions and new medications. N(%)

	Total	Dyspnea Yes	Disnea No	p
n	4673	1614	3057	
New physician consultations	1857 (39.9)	980 (60.9)	877 (28.9)	< 0.001
New medications	1211 (26.2)	626 (39.1)	585 (19.3)	< 0.001
Rehabilitation	518 (11.2)	360 (22.5)	158 (5.2)	< 0.001
Psychotherapy	672 (14.5)	343 (21.4)	329 (10.9)	< 0.001
New psychotropic medication	730 (15.8)	372 (23.2)	358 (11.8)	< 0.001
Hospitalization	95 (2.1)	60 (3.7)	35 (1.2)	< 0.001
Leave days (median [IQR])	15 (10.21)	20 (14.30)	14 (10.18)	< 0.001
Course of initial episode of COVID-19				< 0.001
No Symptoms	420 (9.1)	61 (3.8)	359 (11.9)	
Mild symptoms	1701 (36.8)	277 (17.2)	1423 (47.2)	
Moderate symptoms/no hospitalization	1886 (40.8)	892 (55.4)	994 (33.0)	
Moderate symptoms/severe symptoms with hospitalization	542 (11.7)	338 (21.0)	204 (6.8)	
Severe symptoms/mechanical ventilation	74 (1.6)	41 (2.5)	33 (1.1)	

associated with that of chronic fatigue syndrome[20]. In this condition, also called myalgic encephalomyelitis[21], a distinct clinical feature is the so-called PEM (post-exertional malaise), an intense malaise of exhaustion after activity, a post-COVID aspect that has not been thoroughly addressed. Chronic fatigue syndrome has no clear etiopathogenesis, and a randomized study has reported that both psychotherapy and exercise have an influence on the improvement of symptomatology[22], although the validity of their results is still questioned[23]. Nevertheless, rehabilitation has been proposed as a strategy for the improvement of post-COVID syndrome[24]. The prevalence of symptoms that could be grouped as neuropsychiatric in our series was high. For reference, we compared the reported incidence of at least three-month duration with a recent meta-analysis that explored this domain in 10 530 patients[25]. Five of the symptoms considered in our series had percentages above the 95% confidence interval of the meta-analysis (memory disturbances, headache, myalgia, depression and fatigue) and three were somewhat higher but within the 95% CI: (concentration-attention, anosmia and insomnia). This higher incidence in our population is more striking considering that 55% of the patients included in the meta-analysis were hospitalized during the acute phase vs. only 12.3% in our series, and the severity of the initial condition is related to a higher incidence of all symptoms both in the meta-analysis as in our experience. It is difficult to infer whether this greater involvement is associated with the condition of health professionals in our population and their particular vulnerability in this pandemic, given that there are multiple biases and confounders that we cannot rule out. Previous studies have reported the frequency of psychological involvement in health care workers and its relationship with multiple symptoms[26], which coincides with the frequency reported in our survey. In a study of patients who reported having suffered from COVID-19 and a control group, it was observed that the symptomatology was not related to the plasma confirmation of having had the disease, but to the belief of having suffered from it[27]. This observation is more related to a subjective-emotional explanation than to an "organic" sequela. Return to work has been a major challenge during the pandemic, and has required specific policies to improve the safety of workers and prevent infection[28,29]. In Huang et al.[18], it is reported that

12% of those who were employed before the disease had not returned to work after 12 months. The difficulty in returning to work in our series was conditioned by the greater severity of the initial symptoms, age and higher number of symptoms. This is only a modest approximation to the evaluation of the problem, since we lacked a personal history of other pathologies and other relevant subjective dimensions[30]. Different reviews have discussed the complexity of the etiological interpretation of symptoms. In the case of cardiorespiratory symptoms (dyspnea, fatigue, precordial pain, palpitations), they may imply persistent pulmonary involvement, myocardial aggression[31], autonomic dysfunction[32], classic or microvascular angina pectoris[33], or peripheral detraining[34]. In our series-although multiple studies were used (chest computed tomography, electrocardiogram, chest x-ray, ambulatory electrocardiographic monitoring, stress tests, and even cardiac catheterization) their application was restricted, indicating that the population that responded to the survey possibly did not consider that they needed supplementary evaluations. Women participated more frequently than men in this survey and reported greater symptomatology. In an analysis of a cohort of 1969 patients, female gender was associated in an adjusted manner with many more symptoms than in our series[35], although the population differed from ours, since they were 15 years older and in all cases had been discharged from hospital. We do not have thorough studies on gender perspective in this syndrome.

This study is a survey performed through a social network, where the participating health professionals decide whether to answer or not. Frequently, in this type of survey, those who have symptomatology are more likely to answer, which biases towards a higher prevalence. The INTRAMED network has registered hundreds of thousands of members distributed in different countries, so that although we have a large number of responses it implies an important bias and limits the possibility of establishing the real prevalence of the syndrome. Even so, the detailed report has allowed us to analyze its severity and evolution. Although COVID-19 affects both genders indistinctly, two-thirds of the survey participants were women. The duration of symptoms may not be accurate since many participants had suffered from COVID-19 more than a year earlier. Vaccination status was not asked in order to simplify the otherwise rather lengthy questionnaire. During 2020, no vaccines were available, but in 2021, most countries in the region developed mass vaccination projects starting with the groups at greater risk, prioritizing health personnel. Although there is agreement on the ability of vaccination to prevent infections and their serious complications, the data on the prevention of post-COVID-19 syndrome are not yet consistent.

In conclusion, our study shows the evolution of symptoms compatible with post-COVID-19 syndrome among health personnel in our region, which in many cases reached enough severity to interfere with quality of life, implying a change of job or the impossibility of recovering it. The prevalence of symptoms decreases over the months but in many cases it persists for more than a year and has required complementary studies, new medication, psychotherapy, rehabilitation and new hospitalizations. In the multivariate examination, symptoms could be grouped by "clusters", which allowed discriminating cognitive, neuropsychiatric, cardiorespiratory, digestive and other conditions, which required differentiated studies and may have specific pathogenesis. Health care workers have been exposed to an extraordinary demand from the community in this pandemic, with very significant personal repercussions on their health- related quality of life and their ability to work, which require long-term care and protection strategies in both medical and occupational aspects.

Conflict of interest: None to declare

References

1. Carfì A, Bernabei R, Landi F; Gemelli. Against COVID-19 Post-Acute Care Study Group. Persistent symptoms in patients after acute COVID-19. *JAMA* 2020; 324: 603-5.
2. Tenforde MW, Kim SS, Lindsell CJ, et al. Symptom duration and risk factors for delayed return to usual health among outpatients with COVID-19 in a multistate health care systems network - United States, March-June 2020. *MMWR Morb Mortal Wkly Rep* 2020; 69: 993-8.
3. Raman B, Bluemke D, Lüscher T, Neubauer S. Long COVID: post-acute sequelae of COVID-19 with a cardiovascular focus. *Eur Heart J* 2022; 43: 1157-72
4. Datta SD, Talwar A, Lee JT. A proposed framework and timeline of the spectrum of disease due to SARS-CoV-2 infection: illness beyond acute infection and public health implications. *JAMA* 2020; 324: 2251-2.
5. National Institute for Health and Care Excellence. COVID-19 rapid guideline: managing the long-term effects of COVID-19. In: *https://www.nice.org.uk/guidance/ng188*; accessed February 2023.
6. World Health Organization. A clinical case definition of post COVID-19 condition by a Delphi consensus. In: *https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021*; accessed October 2021.
7. Crook H, Raza S, Nowel J, Young M, Edison P. Long covid-mechanisms, risk factors and management. *BMJ* 2021; 374; 1648
8. Groff D, Sun A, Ssentongo A, et al. Short-term and long-term rates of postacute sequelae of SARS-CoV-2 infection: a systematic review. *JAMA Netw Open* 2021; 4: e2128568.
9. Han Q, Zheng B, Daines L, Sheikh A. Long-term sequelae of COVID-19: a systematic review and meta-analysis of one-year follow-up studies on post-COVID symptoms. *Pathogens* 2022; 11: 269.
10. Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. *Nature* 2021; 594: 259-64.
11. COVID-19: occupational health and safety for health workers: interim guidance. In: *https://www.who.int/publications/i/item/WHO-2019-nCoV-HCW_advice-2021-1*; accessed February 2023.
12. In: *https://www.intramed.net*; accessed February 2023.
13. In: *https://www.who.int/covid-19/post-covid*; accessed February 2023.
14. Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. *Chest* 1988; 93: 580-6.
15. R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. In: *https://www.eea.europa.eu/data-and-maps/indicators/oxygen-consuming-substances-in-rivers/r-development-core-team-2006*; accessed February 2023.
16. RStudio Team (2020). RStudio: integrated development for R. RStudio, PBC, Boston, MA URL. In: *http://www.rstudio.com/*; accessed February 2023.
17. Davis H, Assaf G, McCorkell L, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. *E Clinical Medicine* 2021; 38: 101019
18. Huang L, Yao Q, Gu X, et al. 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study. *Lancet* 2021; 398: 747–58.
19. COVID-19 National Preparedness Collaborators. Pandemic preparedness and COVID-19: an exploratory analysis of infection and fatality rates, and contextual factors associated with preparedness in 177 countries, from Jan 1, 2020, to Sept 30, 2021. *Lancet* 2022; 399: 1489-512
20. Newman M. Chronic fatigue syndrome and long covid: moving beyond the controversy. *BMJ* 2021; 373: n1559
21. Carruthers BM, van de Sande MI, De Meirleir KL, et al. Myalgic encephalomyelitis: international consensus criteria. *J Intern Med* 2011; 270: 327-38.
22. White PD, Goldsmith KA, Johnson AL, et al. Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomized trial. *Lancet* 2011; 377: 823-36.
23. Shepherd CB. PACE trial claims for recovery in myalgic encephalomyelitis/chronic fatigue syndrome - true or false? It's time for an independent review of the methodology and results. *J Health Psychol* 2017; 22: 1187-91
24. Singh SJ, Barradell AC, Greening NJ, et al. British Thoracic Society survey of rehabilitation to support recovery of the post-COVID-19 population. *BMJ Open* 2020; 10: e040213.
25. Premraj L, Kannapadi N, Briggs J, et al. Mid and long-term neurological and neuropsychiatric manifestations of post-COVID-19 syndrome: a meta-analysis. *J Neurol Sci* 2022; 434: 120162.

26. Chew NWS, Lee GKH, Tan BYQ, et al. A multinational, multicentre study on the psychological outcomes and associated physical symptoms amongst healthcare workers during COVID-19 outbreak. *Brain Behav Immun* 2020; 88: 559-65.
27. Matta J, Wiernik E, Robineau O, et al. Association of self-reported COVID-19 infection and SARS-CoV-2 serology test results with persistent physical symptoms among french adults during the COVID-19 pandemic. *JAMA Intern Med* 2022; 182: 19–25.
28. Zhang JC, Findlater A, Cram P, Adisesh A. Return to work for healthcare workers with confirmed COVID-19 infection. *Occup Med (Lond)* 2020; 70: 345-6.
29. CDC: Interim guidance for managing healthcare personnel with SARS-CoV infection or exposure to SARS-CoV-2. In: *https://www.cdc.gov/coronavirus/2019-ncov/hcp/guidance-risk-assesment-hcp.html*; accessed February 2023.
30. Lai R, Tan L, Lai X, Zhang X, Zhou Q. Help-seeking behavior of returning to work in healthcare workers and its influencing factors during COVID-19 subsiding. *J Occup Environ Med* 2020; 62: 898-903.
31. Puntmann VO, Carerj ML, Wieters I, et al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). *JAMA Cardiol* 2020; 5: 1265-73.
32. Blitshteyn S, Whitelaw S. Postural orthostatic tachycardia syndrome (POTS) and other autonomic disorders after COVID-19 infection: a case series of 20 patients. *Immunol Res* 2021; 69: 205-11.
33. Vallejo N, Teis A, Mateu L, Bayés-Genís A. Persistent chest pain after recovery of COVID-19: microvascular disease-related angina? *Eur Heart J Case Rep* 2021; 5: ytab105.
34. Fernández de Las Peñas C, Martín Guerrero J, Pellicer Valero Ó, et al. Female sex is a risk factor associated with long-term post-COVID related-symptoms but not with COVID-19 symptoms: the LONG-COVID-EXP-CM multicenter study. *J Clin Med* 2022; 11: 413.
35. Ledford H. How vaccination affects the risk of long COVID. *Nature* 2021; 599: 546-8.

Appendix - Post-COVID syndrome in health care workers

Several series of post-COVID syndrome in health care workers have been reported.

Out of 932 cases in the UK they obtained 138 surveys, of which 32% had persistent symptoms for 4 months[1]. The major problem was fatigue and a distinctive feature was the low rate of medical consultation (16%) and leave request (2%). In another series also from the UK they surveyed 139 healthcare workers who had suffered from COVID-19 at least three months previously, with a persistent symptom rate of 71%[2]. In Ireland, members of the Irish Hospital Consultants Association were surveyed. Of the 114 workers who agreed to participate, 25% reported prolonged COVID[3]. Three studies were published in Germany. One survey reported 4315 health care workers who had experienced COVID in 2020 and explored in 2021[4]. The prevalence of severe fatigue was 10.7%, with a negative impact on recovery from work. In a survey of 2053 health workers, almost 73% experienced persistent symptoms for more than three months[5]. The most frequently reported symptoms were fatigue/exhaustion, concentration/memory problems and shortness of breath, with impact on quality of life. In a longitudinal study, of 165 health care workers who had suffered from COVID-19, responses were obtained in 73, of whom 31.5% persisted with symptoms (most frequently fatigue and memory disturbances) that affected their quality of life for several months[6].

In a survey in India, 163 health workers were surveyed and reported multiple symptomatologies[7]. The most common symptom was fatigue (42.9%), followed by anosmia and ageusia (21.5%), headache and myalgia. In a tertiary hospital in South India, they explored through questionnaires the prevalence of psychological disorders post-COVID-19 in 107 health workers[8]. The prevalence of depression, anxiety, and post-traumatic stress disorder was 26.2%%, 12.1%, and 3.7%, respectively, which was associated with the persistence of physical symptoms.

A series from South Africa surveyed 60 workers who had experienced COVID-19 two months earlier. The most frequent symptoms were by fatigue, anxiety, and sleep disorders[9]. A French study evaluated the persistence of alterations in taste and olfactory chemosensors in 366 health care workers, with a follow-up of 11 months[10]. Chemosensory dysfunctions persist in a third of COVID-19 patients 11 months after COVID-19. In Saudi Arabia, an online questionnaire was administered to 316 workers and students of a dental hospital. The mean age of the participants was 28.8 +/-8.7 and 54.7% were female[11]. Of the respondents, 19.6% suffered from COVID-19. Persistent COVID was reported by 38.7% of infected staff and 58.3% of infected students.

A Swedish cohort study surveyed 393 healthcare workers 8 months after COVID-19 via smartphone about the presence and severity of 23 symptoms[12]. Eight percent reported persistence of symptoms moderately to severely affecting their work life. In 15%, this problem moderately to severely hinders their social life and in 12%, their family life. In a Danish longitudinal study, which included 210 HIV-positive participants, 30% reported alterations in taste and smell at 3 months[13]. The variables associated with persistent COVID were older age and female sex.

References

1. Gaber T, Ashish A, Unsworth A. Persistent post-covid symptoms in healthcare workers. *Occup Med (Lond)* 2021; 71: 144-6.
2. Tempany M, Leonard A, Prior R, et al. The potential impact of post-COVID symptoms in the healthcare sector. *Occup Med (Lond)* 2021; 71: 284-9.
3. Doherty AM, Colleran GC, Durcan L, Irvine AD, Barret E. A pilot study of burnout and long covid in senior specialist doctors. *Ir J Med Sci* 2022; 191: 133-7.
4. Haller J, Kocalevent R, Nienhaus A, Peters C, Bergelt C, Koch-Gromus U. Persistent fatigue symptoms following COVID-19 infection in healthcare workers: risk factors and impact on quality of life. *Bundesgesundheitsblatt* 2022; 65: 471-80.
5. Peters C, Dulon M, Westermann C, Kozak A, Nienhaus A. Long-term effects of COVID-19 on workers in health and social services in Germany. *Int J Environ Res Public Health* 2022; 19: 6983.

6. Platten M, Nienhaus A, Peters C, et al. Cumulative incidence of SARS-CoV-2 in healthcare workers at a general hospital in Germany during the pandemic-A longitudinal analysis. *Int J Environ Res Public Health* 2022; 19: 2429.
7. Rao S, Amara V, Chaudhuri S, Krishna B, Todur P. "Post-COVID-19 syndrome:" the new pandemic affecting healthcare workers and how the frontline warriors are battling it. *Indian J Palliat Care* 2021; 27: 313-8.
8. Uvais N, Moideen S, Rajagopal S, Maheshwari V, Gafoor T. Psychological morbidity among COVID-19 survivors: a cross-sectional study among health care workers. *Prim Care Companion CNS Disord* 2022; 24: 21m03177.
9. Wose Kinge C, Hanekom S, Lupton-Smith A, et al. Persistent symptoms among frontline health workers post-acute COVID-19 infection. *Int J Environ Res Public Health* 2022; 19: 5933.
10. Bussiere N, Mei J, Levesque-Boissonneault C, et al. Persisting chemosensory impairments in 366 healthcare workers following COVID-19: an 11-month follow-up. *Chem Senses* 2022; 47: bjac010.
11. Abu-Hammad O, Alnazzawi A, Babkair H, et al. COVID-19 infection in academic dental hospital personnel; a cross-sectional survey in Saudi Arabia. *Int J Environ Res Public Health* 2021; 18: 10911.
12. Havervall S, Rosell A, Phillipson M, et al. Symptoms and functional impairment assessed 8 months after mild COVID-19 among health care workers. *JAMA* 2021; 325: 2015-16
13. Nielsen KJ, Vestergaard JM, Schlünssen V, et al. Day-by-day symptoms following positive and negative PCR tests for SARS-CoV-2 in non-hospitalized healthcare workers: A 90-day follow-up study. *Int J Infect Dis* 2021; 108: 382-90.