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Original Research

Clinical Spectrum and Factors Associated to Post Covid Syndrome in Healthcare Workers

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Abstract

Background: Post-COVID Syndrome (PCS) is a newly recognized condition reported by approximately 45% of individuals following COVID-19 infection. This syndrome is estimated to affect the health-related quality of life in 10–30% of affected individuals.

Objective: To examine the characteristics of Post-COVID Syndrome among healthcare workers at Adam Malik Hospital.

Methods: This study employed a cross-sectional descriptive design. Data were collected using structured questionnaires administered to healthcare workers at Adam Malik Hospital who had contracted COVID-19 between 2020 and 2022.

Results: A total of 120 participants were included in the study. The sample was predominantly female (78.3%), with the youngest age group (19–30 years) comprising 37.5% of participants. Most participants had direct exposure to patient care (78.3%) and were confirmed COVID-19 positive in 2021 (42.5%). Notably, 45.0% of participants were unvaccinated, 20.9% had a history of hospitalization, and 78.3% experienced mild COVID-19 infections. Hypertension was identified as the most common comorbidity. Participants were categorized as experiencing Acute PCS (43.9%) or Chronic PCS (56.1%), with both groups exhibiting similar predominant symptoms, including fatigue, persistent cough, memory impairment, and cognitive difficulties. Statistically significant associations were identified between PCS and variables such as sex (p=0.004, OR=0.27), age (p=0.015, OR=4.46), severity of prior COVID-19 infection (p=0.040, OR=1.77), vaccination status (p<0.001, OR=3.82), and the presence of comorbidities (p=0.025, OR=2.53).

Conclusion: Post-COVID Syndrome is characterized by multifactorial etiologies and heterogeneous clinical manifestations. Factors such as gender, age, vaccination status, comorbid conditions, and severity of prior infections were significantly associated with

PCS outcomes. Gender-related differences, potentially influenced by immune response, hormonal mechanisms, and antibody production, appear to contribute to variations in PCS manifestations. These findings underscore the need for further research to elucidate the epidemiology, clinical presentations, and pathological mechanisms underlying this emerging post-viral condition.

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Background

As of September 2023, the novel SARS-CoV-2 had caused more than 770 million cases of coronavirus 2019 (COVID-19) (WHO, 2023). Although recovery is possible within weeks for the most individuals infected, a considerable proportion of people experience a variety of persistent symptoms that continue for months after initial diagnosis, termed post-COVID syndrome (PCS). The global prevalence is estimated 43.0% patients of post SARS-COV-2 infection. Prevalence of hospitalized patient with PCS approximated was higher (54.0%) than non-hospitalized patients (34.0%). This condition was also reported giving significantly impact to 10 – 30% survivor's health-related quality of life (Woodrow et al., 2023). Post COVID syndrome is defined as a condition characterized by respiratory and non-respiratory symptoms or disturbances that develop more than four weeks after the onset of COVID-19 symptoms. Clinical conditions in patients experienced PCS can be: no clinical symptoms but radiologically abnormalities, clinical symptoms with radiological features, and clinical symptoms with radiologically abnormalities (Groff et al., 2021; PDPI, 2021; Djafri et al., 2024). Healthcare workers in particular have endured high rates of COVID-19 infections while working on the frontlines of the pandemic, with some estimates finding over 15% have developed PCS. This vulnerability arises from prolonged occupational exposure, physical and psychological stressors, and, in many cases, inadequate protective measures during the early phases of the pandemic. Furthermore, these persistent symptoms impair healthcare workers' ability to perform their roles, exacerbating existing workforce pressures. Understanding the mechanisms and prevalence of PCS in this group is essential for tailoring interventions to mitigate long-term impacts on their health and professional capacity (Halpin et al., 2021).

In recent study described 79.8% patients observed after SARS-CoV-2 infection have prolonged symptoms about four to seventh months. The study highlighted the variability in PCS presentations, including anosmia (12.4%), ageusia (11.1%), and fatigue (9.7%). These findings underscore the need for a more comprehensive understanding of the implications of these symptoms on prolonged recovery (Augustin et al., 2021). In line to another study was found 56.7% patients after 2 month COVID-19 illness, experienced symptoms related to cognitive or with depressive disorder. For instances, the disruption of essential sensory functions caused by conditions such as anosmia and ageusia, in addition to the hindrance of daily functioning and occupational performance caused by fatigue and neurocognitive impairments, necessitates a comprehensive examination of the prevalence and implications of these symptoms among healthcare workers (Augustin et al., 2021; Jaywant et al., 2024).

Healthcare workers are demonstrably more susceptible to Post-Covid Syndrome (PCS) through a number of evidence-based pathways, with studies revealing a 28% higher incidence compared to matched community controls. This heightened susceptibility can be attributed to the unique occupational exposure to high viral loads (3.2 times higher in nasopharyngeal samples), in conjunction with chronic workplace stress that impairs immune function through sustained elevation of cortisol levels and inflammatory markers (IL-6, TNF-α levels 40% higher than controls). Moreover, the confluence of physical demands from extended work hours, delayed recovery opportunities, and persistent exposure to high-stress environments gives rise to a pathophysiological cascade, resulting in markedly elevated rates of chronic fatigue (OR 2.3), cognitive dysfunction (OR 1.9), and post-exertional malaise (OR 2.1) among healthcare workers with PCS (Gaber, Ashish, & Unsworth, 2021). The prospect of further investigation could facilitate enhanced identification, supportive

care, and rehabilitative approaches for this vulnerable cohort, which is already subjected to considerable pressure in the context of its occupational responsibilities (Halpin et al., 2021).

The objective of this study is to analyze the clinical presentation and the factors associated with the development of post COVID-19 sequelae in healthcare workers at a hospital who previously recovered from COVID-19 infection. Using a cross-sectional analytic design, the research will distribute surveys to characterize current health status in addition to potential predictive indicators like demographics, COVID-19 severity, and occupational roles. Findings can raise awareness regarding long-term ramifications of COVID-19 in this integral workforce while advising institutional policy changes to promote safety and expanded care options for those afflicted. Ultimately, knowledge gained may apply toward reducing lasting morbidity in healthcare personnel critical to maintaining capacity within healthcare systems worldwide continuing to face this protracted pandemic crisis.

Methods

Study design

This study is descriptive study, a cross-sectional design. The dependent and independent variables was collected simultaneously by the authors.

Setting

This cross-sectional study was conducted from August to October 2022 at Adam Malik Hospital in Medan, North Sumatera, Indonesia.

Participants

Study participants were healthcare workers aged ≥18 years and had recovered from COVID-19 infection at least one month. Healthcare workers were grouped as doctors, nurses, ancillary medic (radiologic technician, laboratorians, medical record staff, nutritionist, dietitians, and physiotherapist) and medical support staff (other professions). The target population comprised approximately 250 healthcare professionals who had recovered from Coronavirus Disease 2019 (COVID-19) based on medical records. The sample size required was calculated using the Slovin formula ($n = N / (1 + Ne^2)$), where n represents the required sample size, N is the total population size (250 healthcare workers), and e denotes the margin of error set at 0.05 (5%) with a 95% confidence level. This calculation yielded a minimum required sample size of 96 participants. There were 120 participants who were agreed to be involved in this study. Questionnaire contain about participant's identity, time of COVID-19 confirmed, history of vaccinations, comorbidities, hospitalization details, symptoms in acute phase, and after acute phase.

Instrument

The variables studied included sex, age, symptoms, occupation, work in COVID area, severity of previous COVID-19, history of vaccinations, hospitalization, duration of hospitalization, history of using oxygen, existence of comorbid, and number of comorbid. Age refers to the length of time an individual has been alive. Healthcare workers include medical professionals such as physicians and nurses who are directly involved in clinical practice, but also support staff such as medical assistants, laboratory technicians, or even medical waste handlers who suffered desaturase oxygen (moderate, severe and critical) and without desaturase oxygen (asymptomatic and mild) (PDPI, PERKI, PAPDI, PERDATIN, & IDAI, 2022). Participants who have history of vaccinations defined as received vaccine of COVID-19 one time and getting booster vaccine until three times.
Participants who experienced COVID-19 have reported suffer variety of respiratory or non-respiratory symptoms, it may reveal in 2 to 14 days after virus contact (acute phase). The symptoms that persist more than 4 weeks was define as PCS. PCS classify in to acute PCS (≥ 4 weeks to 12 weeks) and chronic PCS (more than 12 weeks) (PDPI, 2021). Cough, dyspnea, limited activity, sore throat could be common respiratory symptoms. Fatigue, fever, ageusia, anosmia, myalgia, arthralgia, nausea, diarrhea, headache, hyperhidrosis, conjunctivitis,

sleep disorder, confusion, memory disorder are some possible non respiratory symptoms (PDPI, 2021; PDPI et al., 2022; Tleyjeh et al., 2021). Comorbidity is defined as the co-existence of multiple pathological entities in a specific patient. (Klykylo, 2002). Some common comorbid in patients who confirmed COVID-19 are hypertension, diabetes mellitus, COPD, cardiovascular diseases, other endocrine disorder, and immune disorder (PDPI et al., 2022).

Data Collection

Data were collected through structured face-to-face interviews. The interviews were conducted in Bahasa Indonesia. A pre-validated questionnaire was used to collect information on participants' demographic characteristics, COVID-19 history, vaccination status, occupational exposure, and symptoms experienced during and after the acute infection phase.

Data Analysis

Univariate analysis was conducted to describe the demographic and clinical characteristics of participants, with results presented as frequencies and percentages. Bivariate analyses were conducted using chi-squared tests and Fisher's exact tests to explore associations between PCS and independent variables such as age, sex, COVID-19 severity, vaccination history, and comorbidities. The choice of statistical tests was guided by the nature of the data. The chi-squared test was used for categorical data with sufficiently large sample sizes, while Fisher's exact test was applied for small sample sizes or when expected frequencies in any cell were less than five. Assumptions for these tests, such as independence of observations and appropriate cell sizes, were verified prior to analysis. Statistical significance was defined as $p<0.05$. All inferential analyses were carried out using SPSS software version 20.

Ethical Consideration

The institutional ethics review board of Universitas Sumatera Utara, approval number 127/KEP/USU/2021 dated October 18, 2021, provided ethical clearance for implementation of the study protocol

Results

The total of 120 participants, the univariate analysis describes the characteristic in table 1. Most participants were female (78.3%), highest frequency age group was 19–30 years (37.5%), with the largest subgroup occupation is nurse (58.3%) followed by physician (37.5%). 78.3% of participant in this study worked directly to patient COVID-19 in outpatient or inpatient ward. There were 45% of participants without vaccinated COVID-19 during experienced previous COVID-19, but interestingly only 18.3% health workers confirmed COVID-19 in 2020. Then most of participants got caring and treatment by self-isolation (79.2%) at home, but not every participants who experienced COVID-19 using oxygen when treated in hospital because by interview, in this study found that only 15.8% of participants using oxygen. Total of 25 participants who were hospitalized less than 10 days (72.0%). Majority participants experienced mild COVID-19 (94.0%) and had 1 comorbid (31.7%) and just 3 participants had more than 1 comorbid (2.5%).

Base on table 2, the study was found 41 participants had comorbid, and most comorbid are hypertension (34.1%), obesity (17.1%), type 2 diabetes mellitus/T2DM (12.2%), COPD (9.8%) and heart diseases (7.3%). Table 3 described by 71 participant experienced prolonged symptoms after confirmed COVID-19. Base on duration of length symptoms, it classified as acute PCS (25.8%) 2.4±0.7 month, then chronic PCS (33.4%) 9.8±4.9 month. The longest duration of PCS symptoms is about 22 months. In table 4, during the acute phase of SARS-CoV-2 infection, it was revealed most frequent of respiratory symptoms are cough (70.0%), sore throat (38.3%) and dyspnea (26.7%), then non respiratory symptoms fever (63.3%), fatigue (55.8%) and myalgia (52.5%).

Total of participants who had persistent symptoms reported that majority of respiratory symptoms decreased significantly, cough (24.2%), dyspnea (9.2%) and sore throat (3.3%). Then non-respiratory

symptoms are fatigue (49.2%), memory disorder (30%) and confusion (20%). The lowest percentage resolved symptoms are confusion (7.7%), fatigue (11.9%) and memory disorder (12.2%).

Based on the data, the most common acute PCS symptoms reported are fatigue (71.0%), cough (51.6%), memory disorder (32.3%), and confusion (29.0%). Meanwhile, the most prevalent symptoms of chronic PCS are fatigue (90.0%), memory disorder (65.0%), confusion (47.5%), and cough (32.5%).

According to table 5, bivariate analysis indicated significant association between PCS with sex (p=0.004, OR=0.27), age (p=0.015, OR=4.46), severity of previous COVID-19 (p=0.040, OR=1.77), history of vaccination (p= <0.001, OR=3.82) and existence of comorbid (p=0.025, OR=2.53).

Table 1 Characteristic of participants *(n=120)*

Variable (n=120)	**Frequency**	**(%)**
Sex		
Male	26	21.70
Female	94	78.30
Age (years)		
51-60	19	15.80
41-50	20	16.70
31-40	36	30.00
19-30	45	37.50
Occupation		
Phycisian	45	37.50
Nurse	70	58.30
Ancillary Medic	3	2.50
Non Medic	2	1.70
Work in Covid Ward		
Yes	94	78.30
No	26	21.70
History of COVID Vaccination		
3 times	22	18.3
2 times	6	5.0
1 times	38	31.7
Never	54	45.0
Year Confirmed		
2020	22	18.3
2021	51	42.5
2022	47	39.2
History of admision		
Intensive care unit	2	1.7
Ward unit	23	19.2
Self-isolation/Home	95	79.1
History of using oxygen		
High flow nasale canule	1	0.8
Non rebreathing mask	2	1.7
Nasal canule	16	13.3
Never	101	84.2
Duration of hospitalization n= 25 (days)		
>30	1	4.0
21-30	2	8.0

Variable (n=120)	Frequency	(%)
11-20	4	16.0
≤10	18	72.0
Severity of previous COVID-19		
Critical	1	0.8
Severe	1	0.8
Moderate	5	4.2
Mild	94	78.3
Asymptomatic	19	15.8
Number of Comorbid		
≥ 2	3	2.5
1	38	31.7
No	79	65.8

Table 2 Existence of comorbid before confirmed COVID-19 *(n=41)*

Comorbid	Frequency	%
Hypertension	14	34.1
Obesity	7	17.1
Type 2 Diabetes Mellitus (T2DM)	5	12.2
COPD	4	9.8
Heart diseases	3	7.3
Tyroid disease	2	4.9
Sinusitis	2	4.9
Hepatitis	2	4.9
Lipid disorder	2	4.9
Asthma	1	2.4
Migrain	1	2.4
Psoriasis	1	2.4

Table 3 Classification of post COVID syndrome *(n=71)*

Classification	Frequency	%	Duration Mean±SD (month)
Chronic	40	56.1	9.8±4.9
Acute	31	43.9	2.4±0.7

Table 4 Clinical symptoms of PCS

Symptoms	Acute phase (n=120)	%	Persistent ≥1 month	%	Resolved %	Acute PCS (n=31)	%	Chronic PCS (n=40)	%
Cough	84	70.0	29	24.2	65.5	16	51.6	13	32.5
Dyspnea	32	26.7	11	9.2	65.6	2	6.5	9	22.5
Chest pain	9	7.5	0	0.0	100.0	0	0.0	0	0.0
Sore throat	46	38.3	4	3.3	91.3	2	6.5	2	5.0
Fatigue	67	55.8	59	49.2	11.9	22	71.0	32	90.0
Rhinorrhea	7	5.8	0	0.0	100.0	0	0.0	0	0.0
Hoarseness	2	1.7	0	0.0	100.0	0	0.0	0	0.0
Fever	76	63.3	4	3.3	94.7	0	0.0	0	0.0
Headache	58	48.3	4	3.3	93.1	3	9.7	1	2.5
Dizziness	29	24.2	1	0.8	96.6	1	3.2	0	0.0
Tinnitus	3	2.5	0	0.0	100.0	0	0.0	0	0.0
Nausea	26	21.7	0	0.0	100.0	0	0.0	0	0.0
Loss of smell	43	35.8	4	3.3	90.7	1	3.2	3	7.5
Loss of taste	30	25.0	1	0.8	96.7	1	3.2	0	0.0
Myalgia	63	52.5	10	8.3	84.1	7	22.6	3	7.5
Arthralgia	54	45.0	6	5.0	88.9	4	12.9	2	5.0
Diarrhea	16	13.3	0	0.0	100.0	0	0.0	0	0.0

Sleep disorder	34	28.3	14	11.7	58.8	6	19.4	8	20.0
Confusion	26	21.7	24	20.0	7.7	9	29.0	19	47.5
Memory disorder	41	34.2	36	30.0	12.2	10	32.3	26	65.0
Hyperhidrosis	2	1.7	0	0.0	100.0	0	0.0	0	0.0
Conjunctivitis	1	0.8	0	0.0	100.0	0	0.0	0	0.0

Table 5 Analysis factors associated with Post COVID syndrome, (*n=120*)

Variable	Post COVID Syndrome				*p-value*	OR (95%CI)
	Yes		No			
	n	(%)	n	(%)		
Sex					0.004**	0.27(0.11-0.68)
Male	9	7.5	17	14.2		
Female	62	51.7	32	26.7		
Age (years)					0.015**	4.46(1.22-16.27)
> 50	16	13.3	3	2.5		
≤ 50	55	45.8	46	38.3		
Work in COVID area					0.103	0.46(0.18-1.19)
Yes	52	43.3	42	35.0		
No	19	15.8	7	5.8		
Severity of previous COVID-19					0.040*	1.77(1.50-2.08)
Moderate-critical	7	5.8	0	0.0		
Asymptomatic-mild	64	53.3	49	40.8		
History of COVID Vaccination					<0.001*	3.82(1.21-12.12)
Without Vaccination	19	15.8	35	29.2		
With Vaccination	52	43.3	14	11.7		
Hospitalization					0.054	2.62(0.97-7.14)
Yes	19	15.8	6	5.0		
No	52	43.3	43	35.8		
Duration of hospitalization (days)					0.238	4.43(0.52-38.02)
>10	6	5.0	1	0.8		
<=10	65	54.2	48	40.0		
History of using oxygen					0.081	2.76(0.85-8.97)
Yes	14	11.7	4	3.3		
No	57	47.5	45	37.5		
Existence of comorbid					0.025*	2.53(1.14-5.74)
Yes	30	25.0	11	9.2		
No	41	34.2	38	31.7		
Number of comorbid					0.269	1.72(1.48-2.01)
Yes	3	2.5	0	0.0		
No	68	56.7	49	40.8		

Discussion

Attention has focused on the morbidity and mortality related to the global spread of COVID-19, as a pandemic novel disease, since the outbreak of SARS-CoV-2 infection more than three years ago. However, as time passed, attention turned to squeal symptoms after acute phase infection. The duration of persistence symptoms, risk factor that contributing to protracted sequelae, and patient characteristics are all aspects to be further elucidated (Woodrow et al., 2023).

Our study reveals that gender associated significantly (p=0.004), with value OR 0.273 (0.11-0.68) described as protective factor. This indicates that males may be more likely to experience PCS compared to females. However, the term “protective factor” is complex in this context, as it does not imply immunity from

PCS but rather a lower observed prevalence among females in our sample. Literature data is inconclusive regarding the association between females and long COVID. Female patients experience a higher prevalence of fatigue and related symptoms during the post-recovery period, as shown by several preliminary investigations. It is also worth noting that other studies have found no gender association. The varying results are due to differences in ethnic demographics, country of residence, and potential variations in socioeconomic status among the study populations (Bai et al., 2022). Hormones contribute significantly to the maintenance of the hyper inflammatory state during the acute phase, even after recovery (Lott et al., 2023).

Previous studies have reported conflicting findings regarding gender and long COVID. For instance, Bai et al. (2022) reported that female patients showed a higher prevalence of fatigue and related symptoms during the post-recovery period, while other investigations found no significant association between gender and long COVID outcomes. The differences in these findings may be attributed to variations in ethnic demographics, country of residence, and socioeconomic factors among study populations. For example, socioeconomic status may influence access to healthcare or recovery resources, while ethnic variations in immune response could account for discrepancies in PCS prevalence across genders. Such differences are not explicitly analyzed in our study but are likely relevant to understanding gender-related outcomes (Zeng et al., 2020).

Hormonal influences may also explain some of these gender differences in PCS outcomes. For instance, demonstrated that hormones contribute significantly to maintaining a hyperinflammatory state during the acute phase of COVID-19, with potential long-term impacts on PCS risk. In females, estrogen and progesterone are thought to modulate inflammatory responses, potentially mitigating severe outcomes and reducing PCS risk. In males, androgen hormones, such as testosterone, may exacerbate inflammatory processes, contributing to worse outcomes. Further research is needed to explore these mechanisms more thoroughly in the context of PCS (Lott et al., 2023).

Androgens, which include testosterone and dihydrotestosterone, are steroid hormones that are biosynthesized in both male and female individuals. Research indicates that androgen levels increase during puberty, with males having higher levels than females. This is an indication that men may be more vulnerable to COVID-19 due to their higher levels of androgens. Theoretically, while stimulating up-regulation of androgenic transcriptional signaling cascades, these male steroids potentiate TMPRSS2 expression to facilitate anchorage-mediated viral cellular invasion. States of androgen depletion and androgen receptor inactivation do not conform to postulated risk reduction models for COVID-19 critical illness. The relationship between hormonal influences and genomic activation pathways (Mohamed, Moulin, & Schiöth, 2021). However, this may also contribute to the perpetuation of disease manifestations. Female patients exhibit increased attention to interoceptive awareness and associated somatic dysfunction (Bai et al., 2022).

Additionally, studies have shown that male and female patients with mild, moderate, and recovering symptoms exhibit similar levels of serum SARS-CoV-2 IgG antibodies during recovery. However, in severe cases, females tend to have significantly higher antibody titers compared to males (Zeng et al., 2020). This finding suggests that females may mount a more vigorous antibody response during the early phase of COVID-19, potentially reducing viral persistence and the risk of chronic PCS symptoms. However, the relationship between antibody titers and long-term outcomes remains unclear, necessitating further investigation. Gender-related differences in PCS outcomes likely arise from a combination of hormonal influences, variations in immune responses, and social determinants of health. These findings underscore the importance of considering gender as a critical variable in PCS research and tailoring interventions to address the unique needs of different demographic groups.

In our study indicates that age (cut point 50 years) associated significantly (*p=0.015*) with existence of PCS, elder age increased 4.46 times (95% CI 1.22-16.27). Age-related decline in organ function and physiological reserve results in reduced cardiorespiratory performance, musculoskeletal deterioration, neural degeneration with diminished healing capacity, prolonged recovery times and increased risk of complications (Xiong et al., 2021). Accumulation of age-associated degenerative-immune, inflammation and cellular damage that promotes aberrant immune responses to initial SARS-CoV-2 infection and post-viral autoimmunity. Ageing involves several elements of the immune system (Moreno-Pérez et al., 2021).

Superimposed upon direct viral pathogenic sequelae (as exemplified by age-related alterations in angiotensin converting enzyme 2 (ACE2) expression modulating SARS-CoV-2 infectivity), senescence confers

multifarious effects upon auxiliary innate immune factors, further exacerbating COVID-19 morbidity. Specifically, immune encompasses heightened baseline inflammation with excessive cytokine production alongside attenuated phagocyte-mediated microbe clearance – factors independently correlated with critical coronavirus illness. In parallel, the adaptive immune compartment exhibits equally pronounced senescent deterioration as evidenced by exhausted, poorly responsive T-lymphocyte pools, thus furnishing additional substrate for disease severity in geriatric groups. Consequently, severe COVID-19 morbidity stands as a product of multiple discrete immunologic facets independently disrupted by the aging phenotype. Comprehensive science of geriatric approaches robustly probing each pathogenic contributor will prove essential to fully elucidate the intersection of immunosenescence and augmented COVID-19 susceptibility with age (Grifoni et al., 2023).

The immune dysregulation seen with aging, including increased baseline inflammation, cytokine production, and reduced T-cell responses, mirrors much of the immune pathology noted in those with long-lasting PCS. The parallel immune phenotypes suggest overlapping mechanisms driving prolonged viral recovery in elderly populations specifically. direct viral sequalae, dysregulated inflammation and loss of immune control perpetuates incremental lung, heart, brain and end-organ damage for months following acute COVID-19. Persistent tissue injury and accelerated aging from uncontrolled immune pathways likely precipitate the fatigue, headaches, neurocognitive dysfunction and loss of stamina defining PCS in older survivors (Bajaj et al., 2021).

Age-related immune degeneration impairs viral clearance both during the acute phase of SARS-CoV-2 infection and for months after the infection. Those allow viral persistence in reservoir niches to continuously stimulate inflammatory cascades. The resultant chronic immune activation state and inability to fully eradicate virus align closely with hypotheses around post-COVID symptom chronicity, particularly in elderly populations where baseline immunosenescence is more prominent (Maltezou, Pavli, & Tsakris, 2021).

According to the data found severity of previous COVID-19 was significantly associated (p=0.040), indicating that more severe of previous COVID-19 increased 1.77 time (95%CI 1.50-2.07) as risk of PCS. However, current study shows that mild COVID-19 could be develop PCS. While the risk and severity of post-COVID conditions like long COVID do rise with more critical initial illness, patients with milder acute COVID can still experience prolonged recovery marked by fatigue, headaches, dyspnea, "brain fog", and activity intolerance. Even with mild infection, evidence now suggests SARS-CoV-2 virus may persist in various bodily reservoirs either through evasion of immune control, replication in immune privileged sites, or integration of viral fragments into host cell DNA. These viral remnants spark continual inflammation through molecular mimicry and macrophage activation. Mild COVID has been found to trigger autoantibody production that can enduringly attack host cells like neurons and cardiolipin months later, seeding autoimmunity reactions that flare in cycles. Nerve damage from direct viral injury may also disrupt autonomic function regulating stamina, temperature control, blood pressure, and sleep cycles (Van Kessel, Olde Hartman, Lucassen, & Van Jaarsveld, 2022).

Mechanistically, a more severe infection corresponds to high viral replication, extensive inflammation, and end-organ cellular damage from both the virus and resulting immune activity early in the disease course. In patients that survive, the resultant tissue injury, especially to lungs and the vascular endothelium, are slow to fully repair - leaving survivors vulnerable to dysfunction like blood micro clots, oxygen exchange abnormalities, fibrotic scarring that impairs gas transfer, and loss of lung volume or reserve capacity. The greater loss of cardiorespiratory function means activities requiring exertion are much more difficult to tolerate months later, manifesting as fatigue, exercise intolerance, and shortness of breath (Chau et al., 2021). Emerging evidence links severe COVID severity to epigenetic shifts, chronic immune activation, and heightened inflammation months later - providing substrate for autoimmunity disorders as well as symptoms like "brain fog", headaches, pain and fatigue. In summary, the initial severity of critical COVID illness leaves a "scar" upon multiple biological systems that heal slowly and increase risks of delayed, chronic, or even permanent symptoms (Proal & VanElzakker, 2021).

In this study describe that hospitalization and using oxygenation did not associate significantly with existence of PCS. These former ICU patients commonly face neurocognitive deficits as well that disrupt function. The physical, cognitive, emotional, and functional declines layered upon cellular damage from severe initial COVID synergize into persisting sequalae that define post-COVID disability (Weidman et al., 2022). Oxygen

toxicity Prolonged high levels of supplemental oxygen during COVID-19 hospitalization may contribute to oxygen toxicity - resulting in acute lung damage as well as chronic lung function impairment. This can manifest later as dyspnea, cough, and exercise intolerance (Kjellberg et al., 2023). Hyperoxia results in increased generation of reactive oxygen intermediates that promote inflammation and aggravate pulmonary contusion. The resulting inflammation and scarring may endure after COVID-19 and perpetuate respiratory symptoms (Cuervo, 2022). Endothelial dysfunction Higher oxygen saturation levels have also been linked with endothelial dysfunction and elevated thrombotic markers - which may feed into the microvascular and clotting sequalae thought to occur in PCS (Xu, Ilyas, & Weng, 2023).

Existence of comorbid reveal significant association (p=0.025) with prevalence PCS, that increase 2.5-fold (95%CI 1.11-5.73) than without comorbid. Although, based on bivariate analysis number of comorbid showed there are not significantly associated with post COVID-syndrome but value OR 1.72 (95%CI 1.48-2.01) indicate more than 1 comorbid could increase risk of PCS. Hypertension is the most frequent comorbid, then followed by obesity and T2DM. Several pre-existing comorbidities have been associated with increased risks of developing PCS, as well as worse resulting disability. Some of the key associations and proposed mechanisms linking common comorbidities to post-COVID sequalae (Russell, Lone, & Baillie, 2023). Cardiovascular diseases as a common existence comorbid. Hypertension inflicts chronic oxidative stress and vascular inflammation - damaging endothelium lining and reducing vascular reactivity. COVID also targets endothelial cells, further disrupting fragile vasculature. This synergy may worsen microvascular injury, ischemia, and inefficient oxygen delivery to tissues that manifest in long COVID symptoms (Matsumoto et al., 2023).

Obesity associated with the above conditions, adipose chronic inflammation cascades and metabolic abnormalities may directly perpetuate long COVID symptomology including fatigue, pots-like presentations, and cardio-pulmonary complications (Vimercati et al., 2021). Significantly higher levels of pro-inflammatory factors such as IL-6, TNF-alpha and CRP are secreted from the adipose tissue of obese patients. These factors are strongly linked to chronic inflammation and a wide range of health issues. This creates a systemic inflammatory state even pre-COVID. Added on top of COVID-induced inflammation, the cumulative impact may continue to perpetuate fatigue, pain, and other symptoms after acute infection resolves. Obesity is tied to metabolic comorbidities like diabetes, dyslipidemia and insulin resistance which synergize with COVID's acute impacts on glucose control, vascular injury, and hypercoagulability (Loosen et al., 2022; Mal, Mukherjee, Upadhyay, Mohanty, & Pattnaik, 2022).

Diabetes causes chronic endothelial inflammation and microvascular damage. COVID also targets the endothelium, further disrupting vascular integrity. Diabetic angiopathy causes cumulative organ damage to kidneys, eyes, nerves over time via ischemia and atherosclerosis. By enabling further acute tissue injury, COVID delays healing of end-organ damage needed for full symptom recovery. Disrupted glucoregulation and insulin resistance promote hypercoagulability and systemic inflammation - both thought to drive prolonged post-COVID sequalae (Rizvi et al., 2022).

Comorbid conditions like obesity, diabetes, cardiovascular disease, and depression all involve some element of systemic inflammation. Added together with COVID-induced cytokine cascades, this can result in heightened, uncontrolled inflammation even months after the acute infection - perpetuating symptoms. When superimposed with acute COVID damage, healing is much harder given cumulative burden across multiple organ systems. Having multiple comorbid illnesses correlates with more advanced biological aging and "exhausted" dysregulated immune function at baseline (Barh et al., 2021).

The 71 of total participants diagnosed experiencing PCS, it was classified acute PCS (43.9%) and chronic PCS (56.1%). The study reveals predominantly unresolved in subgroup non-respiratory symptoms: confusion, fatigue and memory disorder, compared with respiratory symptoms: cough and dyspnea that it still remain about one-third. According to most frequent of PCS, indicate fatigue, memory disorder and confusion. Indeed, both acute PCS and chronic PCS showed that vary of symptoms is almost similar. This is consistent with the current study that reported prolonged fatigue, dyspnea and neurological impairment as the most common PCS symptoms. SARS-CoV-2 is highly neuro-invasive compared to known coronaviruses, leading to multiple prolonged sequelae including headache, chemosensory dysfunction and neurocognitive problems. Interestingly, in marked differences from SARS and MERS, anosmia and ageusia are commonly reported at acute onset and persist in approximately 10% of patients with PCS. (Del Rio, Collins, & Malani, 2020; Peghin et al.,

2021). Post-COVID presentation may be explained through potential pathways such as a low level of antibodies to SARS-CoV-2, a prolonged inflammatory response to SARS-CoV-2, deconditioning, and repeated infection with SARS-CoV-2, as suggested by previous studies (Outhoff, 2020).

Alterations in neuronal function associated with significant upregulation levels of circulating cytokines, particularly IL-6, which can penetrate the blood-brain barrier, may arise and potentially induce central nervous system (CNS) complications, including changes in mental state, and neuro-cognitive dysfunction. GABAergic dysfunction may underlie both neuromotor and cognitive fatigue, explaining the occurrence of apathy and impaired executive function. Further research is needed to confirm that IL-6-induced hyper-inflammation decreases GABA receptor density (Maltezou et al., 2021). Symptoms such as fatigue can be challenging to evaluate due to their complex and multifactorial causes. An earlier study reported that typical ME/CFS symptoms, such as post-exertional fatigue, were perceived after COVID-19 in a large comparative study. In this respect, 21 studies included in a systematic review found that a high percentage of patients enrolled in long-term COVID-19 studies had cardinal features of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), such as fatigue, post-exertional malaise, and reduced daily activity (Davis et al., 2021).

Conclusion

This study emphasized the multifactorial approach to PCS, demonstrating significant associations with gender, age, disease severity, vaccination status, and comorbid conditions. Key findings include the protective effect of female gender and the influence of comorbidities such as hypertension and diabetes on the risk of PCS. Therapeutic management approaches should include personalized, evidence-based strategies that address persistent symptoms, including fatigue, cognitive dysfunction, and respiratory problems. Recovery outcomes could be significantly improved by interventions such as multidisciplinary rehabilitation programs, mental health support, and comorbidity management. However, identifying the most effective interventions for specific PCS subgroups requires further study. Future studies should consider addressing gaps in our current knowledge of the pathogenesis of PCS, particularly the role of immune dysregulation, hormonal influences, and viral persistence. Studies should also explore the impact of socioeconomic and regional disparities on PCS outcomes, as these factors are likely to contribute to the variability observed in different populations. Patient databases are essential to the development of our findings on PCS, but challenges such as resource limitations, data inconsistencies, and varying clinical practices across regions must be addressed. While guidelines for the diagnosis and management of PCS have been developed, significant gaps remain. The development of standardized definitions and evidence-based guidelines will facilitate earlier detection, improve care, and support the global response to PCS. In conclusion, this study provides a foundation for improving PCS diagnosis, treatment, and prevention efforts. By addressing existing knowledge gaps and overcoming practical barriers, future research can guide the development of comprehensive, patient-centered care strategies for PCS.

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Author contribution
Joshua Princeman Sinaga (JPS) responsible for provided the original idea, gathering data, wrote, the draft of the manuscript or performed significant (> 50%) revision, substantial contributions to the conception or design of the work; or the acquisition, analysis, interpretation of data for the work and contributed to discussion of the manuscript content; **Bintang Yinke Magdalena Sinaga (BYMS)** responsible for provided the original idea, gathering data, wrote, the draft of the manuscript or performed significant (> 50%) revision, substantial contributions to the conception or design of the work; or the acquisition, analysis, interpretation of data for the work and contributed to discussion of the manuscript content; **Parluhutan Siagian (PS)** responsible for provided the original idea, gathering data, wrote, the draft of the manuscript or performed significant (> 50%) revision, substantial contributions to the conception or design of the work; or the acquisition, analysis, interpretation of data for the work and contributed to discussion of the manuscript content; **Putri Chairani**

Eyanoer (PCE) responsible for statistical analysis, interpretation of data for the work and contributed to discussion of the manuscript content; **Yoseph Leonardo Samodra (YLS)** responsible for statistical analysis, interpretation of data for the work and contributed to discussion of the manuscript content.

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