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Article

Collaborative research for Long Covid Haulers in Greece (characteristics, clinical assessment and rehabilitation). Non-hospitalized and hospitalized long covid patients share similar symptom patterns.

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Abstract: COVID-19 Long Haulers, an estimated 3% to 12% of people infected globally with coronavirus having latter devasting symptoms 12 weeks after the initial infection is on the rise. We conducted a collaborative study with the long covid patient organization in Greece in order to estimate the prevalence, symptoms and problems that adult long haulers experience and then propose a management plan for these patients. Symptoms were obtained from 208 patients using unstructured qualitative free text entries in an anonymized online questionnaire. The majority of respondents (68.8%) were not hospitalized and had been diagnosed more than six months ago with lingering symptoms (66,8%). Eighteen different symptoms (fatigue, tachycardia, shortness of breath, parosmia etc) were mentioned in both hospitalized and community patients. Interestingly, patients with initial mild symptoms suffer from the same persistent symptoms as those who were hospitalized. Awareness of long covid sequelae seems to be low even among medical doctors. Treatment options incorporating targeted rehabilitation programs are either not available or still excluded from the management plan of long covid patients. Since long COVID is a multi-systemic entity, we propose a holistic interventional approach using a multidisciplinary medical team in order to securely and effectively diagnose and treat these specific patients. Academic and medical community must collaborate with long covid patients' organizations so as to provide personalized medicine.

Keywords: Long Covid, post Covid, Post-acute COVID

1. Introduction

The long-term effect of SARS-CoV-2 (COVID-19) is a major concern for stakeholders in the health community as the pandemic which has caused extraordinary morbidity, mortality and global disruption lingers [1],[2]. The emerging patterns and syndromes such as 'Post-acute COVID' fondly called 'long COVID' is phenomenally shifting the

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focus of the global health community to managing the effects in Covid -19 patient survivors [1].

SARS-CoV-2 causes systemic infection and can sustain in the body for months [3]. The occurrence of long-term COVID-19 ailments is presented with various appellations including PASC, Long COVID, Post-Acute COVID-19 Syndrome (PACS), Chronic COVID-19, and Long Haul COVID-19 with slightly varying definitions [1]. Whereas 'Chronic COVID' describes symptoms lasting more than 12 weeks, 'Post-acute COVID' refers to persistent symptoms 3 weeks after COVID-19 infection. The Center for Disease Control (CDC) adopted a description for long covid to include new or persistent symptoms at 4 or more weeks from infection with SARS-CoV-2 [4]. These include a torrent of debilitating symptoms (comprising breathlessness, chest pain, palpitations and orthostatic intolerance) apparently lasting for weeks or more following mild illness [1],[2]. Using corresponding estimated pooled symptom-specific prevalence obtained from the 23 symptoms assessed across 30 studies, Chen et al (2021) pinpoints the five most prevalent symptoms as fatigue at 0.23 (95% CI: 0.13, 0.38), dyspnea at 0.13 (95% CI: 0.09, 0.19), insomnia at 0.13 (95% CI: 0.06, 0.28), joint pain at 0.13 (95% CI: 0.05, 0.29), and memory problems at 0.13 (95% CI: 0.10, 0.18) [2].

The aforementioned endpoint is reflective of the longitudinal severity scores of five symptoms (cough, shortness of breath, fatigue, headaches and anosmia) and general unwellness collected by the National Institute of Health (NIH)-endorsed Protocol and other studies on patient experience of COVID-19 [5]. Conversely, Destin et al (2021) underlines the most common PASC to involve functional mobility impairments, pulmonary abnormalities, and mental health disorders [6]. Harmonizing research for improved understanding of the novel condition erupts newer definitions which incorporate the key effects on both adults and children [7]. The lucidity of the condition using delphi methodology by WHO (2021) as occurring in people with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19, and with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis throws considerable light on the effect in children. Until now, no such definition existed for long COVID in children [8].

More than 200 symptoms have been associated with long COVID to date and the common symptoms include fatigue, shortness of breath, cognitive dysfunction. However, others generally have an impact on everyday functioning [9]. The term long COVID has been conceptually used to identify the presence of any symptoms after COVID infection and consist of two stages: (1) post-acute consequences of SARS CoV-2 infection (PASC) or acute post-COVID infection (from week 5 to week 12 after the onset of symptoms) and, (2) period of COVID (for symptoms lasting more than 12 weeks). Moreover, the recurrence feature of symptoms after COVID, should be incorporated in the definition, as it remains pertinent to determine the pattern (variations) and nature (new onset or worsening) of any symptoms [10]. An estimated 3% to 12% of people infected with coronavirus have symptoms 12 weeks after the initial infection [11].

Prevalence estimates for long COVID specifically in children and young people vary from 1%-51%, with the non-hospitalized Children & young people (CYP) with Long Covid research (The CLoCk Study) estimating that up to 14% experience ongoing symptoms [7]. The CLoCk researchers worked with a panel of more than 100 researchers, experts in health service delivery, and children with long COVID and their parents to score 49 statements on long COVID. These statements were then reviewed by a panel of eight for 11-17 year olds affected by long COVID to reach final agreement.

Their definition of long COVID is a condition in which a child or young person has symptoms (at least one of which is a physical symptom) that: (1) have continued or developed after a diagnosis of COVID-19 (confirmed with one or more positive COVID tests) (2) Impact their physical, mental or social wellbeing. (3) Are interfering with some aspect of daily living (e.g., school, work, home or relationships) and (4) Persist for a minimum duration of 12 weeks after initial testing for COVID-19 (even if symptoms have waxed and waned over that period). The journal of Archives of Disease in Childhood, presented

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definition which closely complements the WHO definition for long COVID in adults. Mount Sinai asserts that there are still not well-established medical causes needed to be explored as seen in the Figure 1.

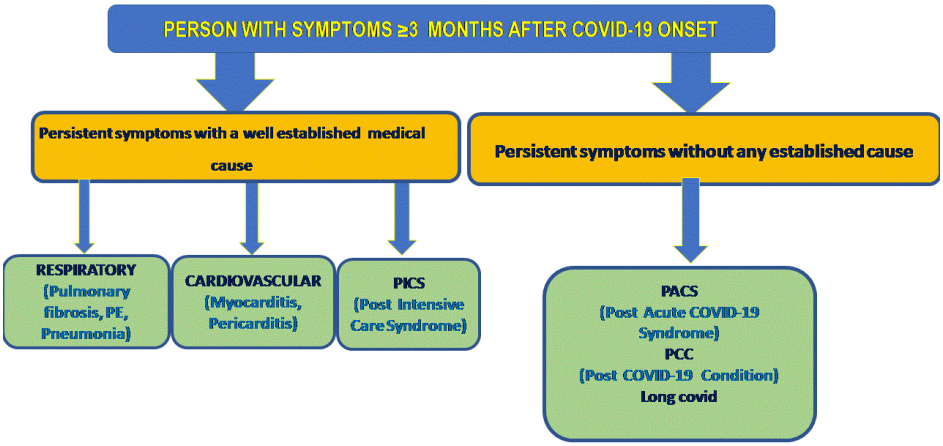

Figure 1. Adjusted algorithm from Mount Sinai 2020 (Tabacof - Rehabilitation management of autonomic dysregulation in Post COVID-19 Condition (who.int))

Reducing the variation in the description is paramount to establishing a common understanding of the prevalence of specific symptoms after COVID-19 [2]. The incidence and evolution of PASC are dependent on time from infection, organ systems and tissue affected, variant of the virus, severity of acute phase and geographic region [6]. Moreover, in a systematic review of short-term and long-term rates of post-acute sequelae of SARS-CoV-2 infection, Destin et al (2021) confirms that more than half of COVID-19 survivors experienced PASC 6 months after recovery. The mechanisms underpinning the Post-acute and chronic manifestations of COVID-19 is only partially comprehended [13]. The patterns may be explained by autonomic instability and may result from deconditioning, hypovolemia or immune- or virus-mediated neuropathy [1]. Nevertheless, these mechanisms can be grouped into the direct effect of the viral infection and the indirect effect on mental health due to posttraumatic stress, social isolation, and economic factors, such as loss of employment [14],[15]. The identification of autonomic dysfunction following COVID-19 infection involves the careful evaluation on the individuals expressing breathlessness, palpitations, fatigue, chest pain, presyncope or syncope. Other symptoms have been identified at varying percentages including low vision, red eyes, vertigo, fatigue, muscle pain, loss of appetite, diarrhea, skin legions, joint pains, headache, rhinitis, loss of smell, Sjogren's syndrome, loss of taste, sore throat, chest pain, cough and shortness of breath. The routine cardiovascular, respiratory and neurological checks with vital signs and pulse oximetry are central to the diagnosis. Further consideration of the utilization of electrocardiogram, blood tests and imaging is essential for identifying other important diagnoses such as organizing pneumonia, pulmonary embolism and myocarditis [1].

Exercise intolerance is another feature of PASC as exhibited by CPET and cardiopulmonary hemodynamic data in Singh et al (2021) study where patients who have recovered from COVID-19 without cardiopulmonary disease demonstrate a marked reduction in peak oxygen consumption from a peripheral rather than a central cardiac limit, along with an exaggerated hyper ventilatory response during exercise compared with control participants [16]. This could be due to peripheral muscle impairment coming from mitochondrial cellular respiration dysfunction and not necessarily muscle deconditioning. Correlating with this is a recent case report in Rodrigez B. et al., (2021) of a female patient where needle biopsy showed a reduced myosin:actin ratio in regards to previous examination prior to covid and loss of myosin filaments [17]. Reduced peak VO2 is not the only finding in post covid conditions. Some studies have reported mild hyperventilation due to an

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increase in the minute ventilation to carbon dioxide output ratio during exercise, which can de justified due to an increase in central chemosensitivity [16] or by dysfunctional breathing [18]. Small fiber neuropathy as seen in ME/CSF can also be suspected [19].

Nevertheless, performing complete autopsies have been effective in mapping and quantifying SARS-CoV-2, replication, and cell-type specificity across the human body, including brain as reflected in Daniel et al (2021)[3]. Autopsy studies of fatal COVID-19 cases support the ability of SARS-CoV-2 to infect multiple organs extra-pulmonary organs often lack histopathological evidence of direct virally-mediated injury or inflammation [20][21][22][23][24][25][26]. Precisely, autopsies on 44 patients with COVID-19 shows that SARS-CoV-2 is extensively transmitted, even among patients who died with asymptomatic to mild COVID-19, and that virus replication is manifest in multiple pulmonary and extrapulmonary tissues early in infection [3]. Infection with SARS-CoV-2 is also associated with the development of pediatric multisystem inflammatory syndrome (MIS-C), manifestations of which can cause severe organ inflammation and dysfunction in children, with over 10% of cases showing acute kidney injury [27]. Though the burden of infection outside the respiratory tract and time to viral clearance is not well classified, particularly in the brain [28], [29], Daniel et al., (2021) had detected persistent SARS-CoV-2 RNA in multiple anatomic sites, including regions throughout the brain, for up to 230 days following symptoms onset [3].

The pathophysiology of COVID-19 establishes it as a multisystem disease due to in part endothelium damage. SARS-CoV-2 infects the host using the angiotensin-converting enzyme 2 (ACE2) receptors, which are expressed in several organs, including the lung, heart, kidney, intestine, and also expressed by endothelial cells, causing a distinguishable and distinct systemic endotheliitis [30], [31]. In the study by Charfeddine et al (2021) authors showed that persistent symptoms especially chest pain, fatigue, and neurocognitive symptoms (non-respiratory symptoms) during the long COVID-19 period were mainly associated with endothelial dysfunction and that long covid syndrome is frequent [32]. Joshua B. Weschler November 2021 letter to Allergy conveys communication of their group's identified evidence of mast cell activation in sera and lung tissues in patients with acute covid-19 infection which supports the potential role of mast cell activation in a subgroup of patients with PASC [33]. Another implicating factor is immune dysregulation as seen inPhetsouphanh, C. et al (2022). Patients with Long Covid had highly activated innate immune cells, lacked naive T and B cells and showed elevated expression of type I IFN (IFN-β) and type III IFN (IFN-λ1) that remained persistently high at 8 months after infection [34].

YapengSu et al (2022) had recognized 4 anticipating factors for PASC. Amongst them type 2 diabetes, SARS-CoV-2 RNAemia, Epstein-Barr virus viremia, and specific autoantibodies. In patients with gastrointestinal PASC, SARS-CoV-2-specific and CMV-specific CD8+ T cells exhibited unique dynamics during recovery from COVID-19. In that study they found that that immunological associations between PASC factors diminish over time leading to distinct convalescent immune states [35]. Detectability of most PASC factors at COVID-19 diagnosis emphasizes the importance of early disease measurements for understanding emergent chronic conditions and suggests PASC treatment strategies. Notably, an essential consideration while unraveling the pathophysiology of the post-COVID syndrome is a cautious annotation of the clinical symptomatology. Distinguishing enduring symptoms of acute disease site from new symptoms that appear after resolution of the acute disease may help distinguish between potential disease drivers. Confounding variables may, however, include components of PTSD that may blur patients' own evaluation of clinical symptoms and require careful neuropsychiatric evaluations [36]. Long-term PASC intervention must be factored into existing health care systems, especially in low- and middle-income since it effects occur on a scale capable of overwhelming existing health care capacity specifically in the aforementioned geographies [6].

The current study is collaborative research between scientists and long covid patient organization in Greece with the aim to provide an insight on the prevalence of long covid in Greece including symptoms, risk factors, duration, examination of differences in

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prevalence by several other factors including demographic factors, severity of symptoms, initial treatment regimen on adults patients with COVID-19 infections and promote awareness amongst patients and doctors. Awareness includes all aspects of long covid; the economic burden of the disease, the arising socio-economicconditions including employment relations of sufferer, the level of utilization of available resources as well as the depth of disease understanding amongst patient care givers.

2. Materials and Methods

Online questionnaire was distributed to a cohort of long covid patients who are members of Long Covid Greece patient society's Facebook, named Long Covid Greek supported group who are members of a patient organization. The survey effected with the use of google forms specifically designed to collect such data with anonymized IP. Participants started answering the questionnaire after were well informed that all anonymized and de-identified data will be used from Long Covid Greece Patient Society for scientific reasons Participant's consent were obtained in line with EUGDPR and ICH GCP recommendation. (Good Clinical Practice Network https://ichgcp.net/publications/informed-consent-of-trial-subjects). Symptoms were obtained from patients using free text entries as we aimed to capture information of important research interest. The free text has been analyzed by identifying term frequencies and common bigrams (sequence of two adjacent terms) and trigrams (sequence of three adjacent terms).

Incorrect entries and misspellings have been identified using the Levenshtein distance algorithm [37] (with distance setting =1). Subsequently, we used Information Extraction to automatically identify symptom entries and generate true/false features in the case that a specific symptom was either present or absent on a patient level, in order to minimize the time required for feature generation. These entries were then checked for their validity by two investigators and corrected where applicable. The use of decision tree model has been handy in the precise classification of patients into specific groups based on demographic, time of disease, hospitalization and expressed symptoms. For data hypothesis a decision tree algorithm (KNIME FRAMEWORK) has been used [38], [39], [40]. The method used is "Decision Tree Learner", using "Gini" to split data [41], "class column" and "minimum number entries per node" was set to 30. Since we focus to create hypotheses rather than evaluate the predictive capabilities of our algorithm, no train, test, and validation data subsets were used, and the decision tree analysis was performed using our entire dataset. Interactions between symptoms revealed with network analysis [42].

3. Results

The sample constitute of 208 patients, 77.9% female and male 22.15%. Participants' response wereanonymized. Only adults 18 years above were included in the survey. Majority of respondents fall within the age range of 41—50 years. The duration since diagnosis with long covid; <1 month (3.9%), 7 to 12 months (44.7%), 1-6 months (29.3%), > 12 months (22.1%). Regarding hospitalizations and admissions, 68.8% have not been hospitalized, 26.9% have been hospitalized outside ICU while 1.3% hospitalized at the ICU. Interestingly 68,5% of the patients that were not hospitalized still suffered from fatigue and 16,8 from dyspnea, 28,7% from difficulty in concentration and 28% from tachycardia.

Response on awareness and utilization of long covid rehabilitation resource, 26.9% reported they have undergone post covid rehabilitation, 51% have not, while 22.1% are oblivious of such rehabilitation. On vaccination status, 73.6% are vaccinated, 26.4% are unvaccinated. Among the vaccinated 20.4% reported improved symptoms after vaccination, 34% reports no change in symptoms, 34% are unsure of improvement or worsening while 11.6% reports worsened situation. On availability for research, 69.2% are willing to participate in a long covid research irrespective of drug related or not, 26.9 opted to be part of a non-pharmacological intervention/study while 3.9% are unwilling. The preference for health settings for diagnosis and therapy 78.4% prefers to visit a large organized

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health setting for their diagnoses while 21.6% prefer health centers within their neighborhood.

3.1. Persistent symptoms

Eighteen different symptoms were mostly mentioned by the Greek group of long covid haulers (figure 2).

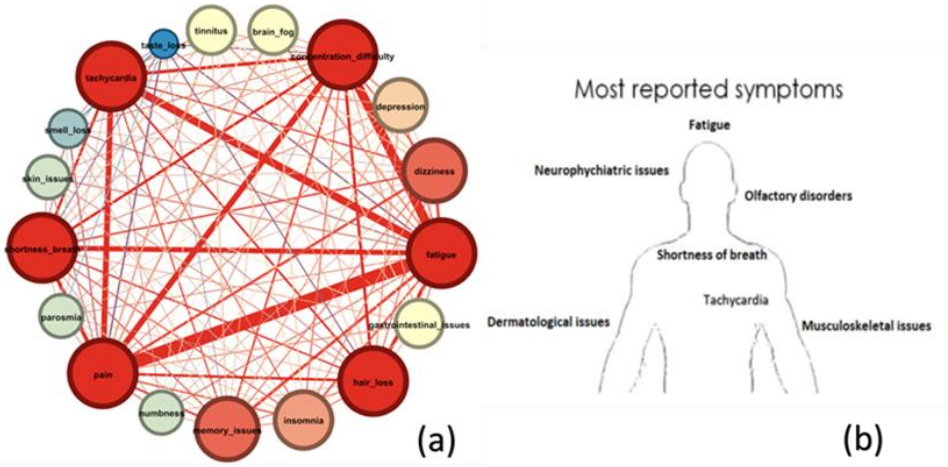

Figure 2. (a) Network Analysis graph of persistent symptoms. Larger nodes imply higher degree centrality. (b) Most reported symptoms in Greek Long Covid society (LCGr).

Despite the variation in the initial severity of acute phase, patient with initial mild symptoms suffer from the same persistent symptoms as those who were hospitalized. No significant differences were found in most symptoms between the two groups (hospitalized and non-hospitalized) as shown in table 1.

Table 1. Comparison results between hospitalized and non-hospitalized long covid haulers.

	Post hospitalization (n=64)	**Post mild acute phase (n=144)**	**Pvalue**
Male	33.84% (22/64)	17,34% (25/144)	**0.00677**
Female	*64,61% (42/64)*	*82.6% (119/144)*	***0.00677***
Fatigue	71,87% (46/64)	69,44% (100/144)	0.72356
Musculoskeletal	*64,06 %(41/64)*	*45,80% (66/144)*	***0.01519***
Neurophychiatric	50,00 %(32/64)	40,27 (58/144)	0.19148
Tachycardia	26,56% (17/64)	28,4%(41/144)	0.77681
Parosmia	*1,56% (1/64)*	*13.19%(19/144)*	***0.00862***
Olfactory disorders (incl.parosmia)	*3,13% (2/64)*	*22.22% (32/144)*	***0.00058***
At least one neurological (excl. fatigue)	75,00%(48/64)	77.77%(112/144)	0.66076
Shortness of breath	23,43% (15/64)	15,27% (22/144)	0.15552
Dermatological	18,75% (12/64)	18,05% (26/144)	0.90478

3.1.1. Neurological

The majority of symptoms as described by the patients seem to be related to the nervous system. More than 70% of long covid haulers reported fatigue as the main symptom. Ad-additionally, 75% of participants had at least one neurological problem

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(except fatigue) months after infection. Long covid haulers also reported neuropsychiatric issues- mainly cognitive in 50%.

Interestingly, parosmia and other olfactory disorders were presented mostly in mild acute phase group of patients (table 1). This is in accordance with Kathrin Ohla et data that fount that olfactory dysfunction appears to be a component of long-COVID, with parosmia as a prominent symptom in almost half of those with smell loss [43].

3.1.2. Musculoskeletal

In patients experiencing long term effects of covid-19, almost 78% reported musculoskeletal problems. Following comparison between those who were severely ill and those with mild illness, musculoskeletal symptoms were 8.7 times more frequent in post-hospitalized patients

3.1.3 Tachycardia

Tachycardia is a common symptom in both groups. However, our research does not allow the attribution of tachycardia to the underlying cause. Namely, tachycardia could be caused from hypoxemia, hyperthyroidism, a cardiovascular disease, or neurological disease such as Postural Orthostatic Tachycardia Syndrome (POTS) or dysautonomia.

3.1.4 Shortness of breath

Shortness if breath is a symptom mainly attributed to respiratory disorders. Since covid-19 is a virus that primarily affects the respiratory system residual dyspnea is usually attributed from both patients and health care professionals to a pneumonia or fibrosis caused from covid. However, dyspnea could be caused additionally from cardiovascular disorders and deconditioning. Therefore, a careful differential diagnostic algorithm should be followed before treatment of dyspneic long covid patients.

3.1.3 Dermatological

In relation to dermatological symptoms the most commonly reported was prolonged hair loss. Other dermatological problems like acne, psoriasis and rashes have also been reported in this study group.

3.2. Socioeconomic Impact

On effect of covid ailment on employment relations, about 58.2% are faced with problems at work for prolonged ailment. Also, while asked if there is common understanding of the ailment situation at work, 29.8% responded “yes”, 20.2% “No”, 39.4% are self-employed while 10.6 % have not returned back to work. Moreover, 12% of the respondents are attended to by public hospital while 88% are not. 53.4% are not being rightly attended to medically, 30.8% have been attended to by private doctors, 13.5% are attended to by a mix of public and private doctors, 2.3 % are being attended to by doctors from public hospitals. With respect to the number of medical resources used while having the ailment, 11.5% affirmed they have not visited different doctors to resolve their symptoms, 42.3% have visited at most 2 different doctors, 42.3% have visited up to 10 different doctors, while 3.9 % have visited more than 10 different doctors to find solution to symptoms. Similarly, when asked if they’ve encountered doctors with awareness of the ailment, 46.6% responded in the affirmative of having encountered doctors who are unaware of Long Covid, 25% responded in negation, 28.4% believes doctors they encountered are aware but without any active engagement. On economic expenditure

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on doctors' visitation, 47.6% have spent at least 500 euro on doctors, 31.3% have spent over 500 euro while 21.2% have spent nothing. (Figure 3)

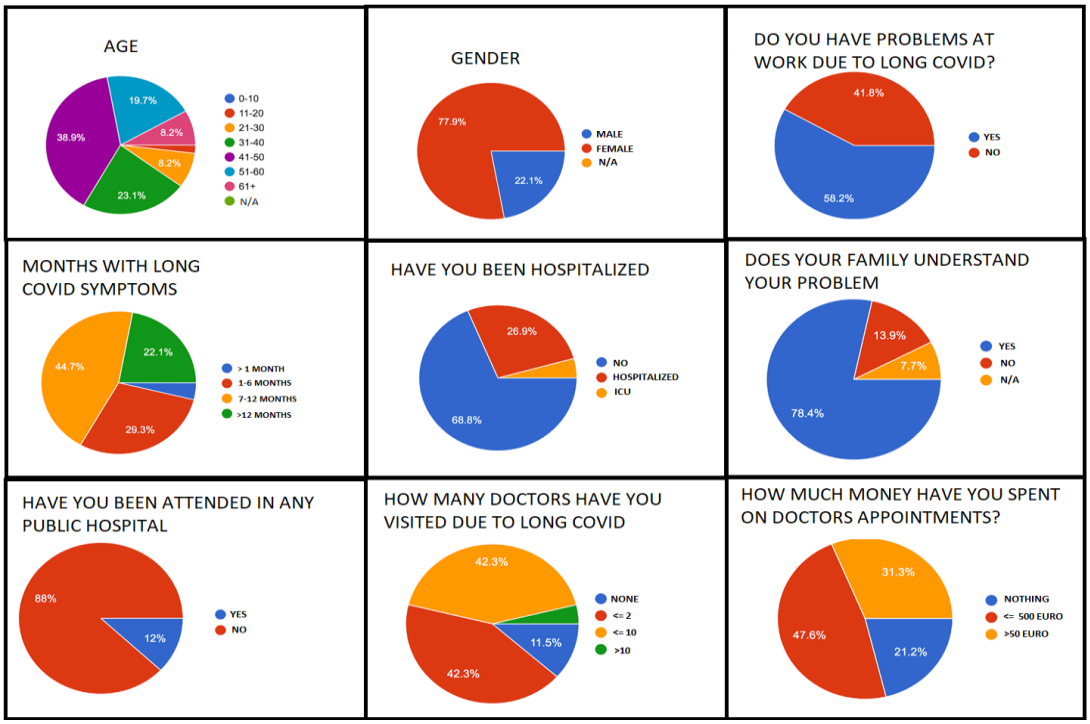

Figure 3. Socioeconomic impact of long covid

The decision tree analysis shows clearly that fatigue is a key factor which is positively related to work issues. Patients who report occupational issues show higher rates of fatigue and visited many doctors in order to be diagnosed and treated (figure 4).

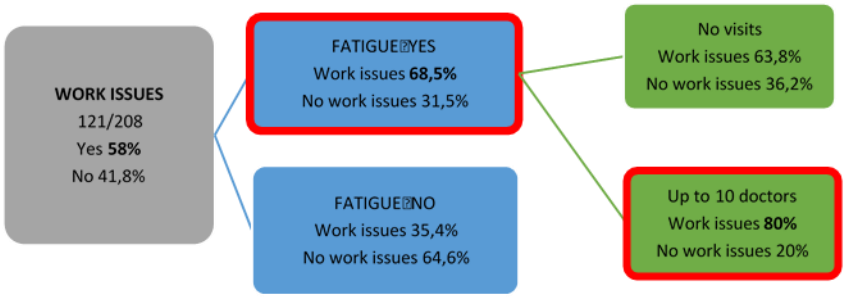

Figure 4. Decision tree reveals that fatigue appears to be extremely higher in patients with work problems

4. Discussion

Following an initial period of distrust and psychiatric approach of the patients who continued to complain of symptoms or develop new symptoms long after their COVID-19 disease, a post covid syndrome seems to be documented in the literature.

Despite the heterogeneity and methodological problems of related studies for post or long covid syndrome, a number of symptoms and signs have been identified as components of the syndrome [9].

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Although the approach to the post covid consists only of descriptive references, the first attempts to highlight a causal mechanism suggest a heterogeneous and multifactorial syndrome. Pathogenetic mechanisms such as systemic inflammation, immediate involvement of the nervous system, the effects of hypoxia and hypovolemia, endothelitis, the effects of the cytokine cascade, post ICU syndrome, the remaining of the virus in the body in an undetectable state, a late immune response, autonomic neuropathy e.t.c. have been proposed in the literature.

As severe hospitalization with traumatic scenes from the ICUs has been a recurrent decimal in the description of the SARS-CoV-2 effect on its human host [44]. All post ICU symptoms should be seen under the light of the traumatic experience of a life-threatening illness, the psychological impact of the illness, the experience of hospitalization and recovery, posttraumatic stress, social isolation, and economic factors, such as loss of employment [12],[13].

However, it has been shown that an important percentage of patients that contacted the virus without resulting to serious illness have later remaining symptoms and became 'long covid`' patients. This is corroborated with report published in NIHR (2022) where hyperpolarized xenon MRI scans were utilized to investigate possible lung damage in long COVID patients who experience breathlessness and were not hospitalized during COVID-19. The early findings suggest that COVID-19 may result in persistent impairment in gas transfer and underlying lung abnormalities. However, the extent to which these abnormalities contribute to breathlessness is currently unclear. In our cohort 68.8%% of long covid patients have not been hospitalized. Only 26.9% have been hospitalized and 4.3% were in the ICU. The description of persisting long covid symptoms are similar in all aforementioned categories.

As observed in our sample, symptoms correlated to neural system dysfunction in 'long-COVID patients' are common, including fatigue, headache, 'brain fog' and cognitive impairment, smell, or taste problems, sleep and mood disorders, myalgias, and dysautonomia, thereby representing core aspects of 'long-COVID' [45].

The number and the severity of acute COVID-19 symptoms and need for hospitalization and/or ICU [46] admission have been associated with an increased risk of developing long COVID syndrome [47].

However, non-hospitalized and patients with milder forms of the illness have been also found to frequently develop neuropsychiatric sequelae. In our study there was no significant difference between the two groups (hospitalized vs non hospitalized) in frequency of neurological and mental health complaints. In fact, a large retrospective cohort study including 236,379 patient records by Taquet et al. found that the incidence of neurological or psychiatric diagnoses at 6 months post-COVID-19 infection was 33%, with an increased risk even for patients who were not hospitalized [46]. Similarly, in a study in patients with post-Covid syndrome in Brazil 39.8% of individuals reported memory problems, 36.9% anxiety, 44.9% depressed, and 45.8% had sleep problems [49]. However, prevalence rates vary considerably across studies and estimates for mental health symptoms appeared to be lower in Covid-19 survivors in Greece post-hospitalization (depression 19%, anxiety 27%, traumatic stress 39%, insomnia 33%) [50].

Summarizing evidence to date, a recently published systematic review and meta-analysis, including data from 47,910 patients, showed that up to 80% of infected patients developed one or more long-lasting symptoms, including fatigue (58%), headache (44%), attention disorder (27%), ageusia (23%), anosmia (21%), memory loss (16%), anxiety (13%) and depression (12%) [46]

Chen et al (2021) had described a handful of individuals with symptoms of 'long COVID', positing that long covid condition may be related to a virus- or immune-mediated disruption of the autonomic nervous system resulting in orthostatic intolerance syndromes. The onward suggestion that all physicians should be well armed with knowledge

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for the accurate recognition of such cases, appreciate the symptom burden and provide supportive management shows the proclivity of physicians to addressing such health concern. They had presented a rationale for an underlying impaired autonomic physiology post-COVID-19 and recommended means of management.

It is also important to note that most of our patients faced skepticism and disbelief from their families or professional environment even from health professional because of the ignorance of the post COVID symptoms.

Therefore, both awareness campaigns for the public and educational programs for health care professionals should be designed. Nevertheless, further research is necessary in order to reveal the nature of the post covid syndrome or syndromes.

Patient rehabilitation is one of the highlighted means recommended in line with the above study and it is essential to avert re-hospitalizations and readmission due to the aforementioned and other long covid related symptoms, as well as improve patients' post-covid quality of life. However, it is instructive to note that the seriousness of hospitalization seems to be a factor related to rehabilitation in a hospital/clinical setting. Namely, almost all patients that were admitted to an ICU followed a rehabilitation program after being discharged. In the contrary most of the non-hospitalized patients not only have not followed any rehabilitation program but even ignore the possibility of being offered such treatment. 52% of of patients holds for having tried rehabilitation during and post disease condition. The age bracket of the subset both for male and females fall within 41 to 60 years+ with majority of them being within the 51-60 years bracket. It should be mentioned as a limitation of our study that since all patients were recruited from a Facebook group, possibly older patients not familiar with FB, have not been included to the study.

Our study is the first study in Greece that records data for non-hospitalized long covid patients. It is difficult to establish any serious correlation between non hospitalization and other symptoms categories due to the small sample size involved.

However the descriptive outlook of the probable tendencies of vital health stakeholders towards embracing rehabilitation as captured in the data for this class of patients, send a warning signal regarding responsive approach to therapy. This is crucial specifically for those non-hospitalized patients with little or no symptoms considering what has been known of the disease from the covid-19 autopsy study of Daniel et al (2021). Further, an extensive documentation of described symptoms prevalent in different age group including fogged brain and other none respiratory symptom has been made. This is appropriate for the current time as most symptoms to look out for do not fall under the conventional ones attributed to covid-19. Notably, extensive distribution of SARS-CoV-2 in the body, have been observed through scanty inflammation or direct viral cytopathology outside of the lungs [3]. This corroborates with findings from the results of our present study which emphasizes similar symptoms are reported across different age groups as well as vaccination status.

We acknowledge that Long COVID is a multi-systemic entity that requires multiple partners to care for patients. Given the characteristics of the individuals and the duration of the disease as they were first recorded in the Greek population, an algorithm is proposed (Figure 5) . Namely, we adapted already used algorithms by adding data from the Greek long covid cohort in order to target the Greek population and its characteristics.

Our proposal for an holistic interventional approach using a multidisciplinary medical team is in fact using personalized medicine for our long covid patients. However, its effectiveness in securely diagnosing the underlying cause of long covid symptoms remain to be proved.

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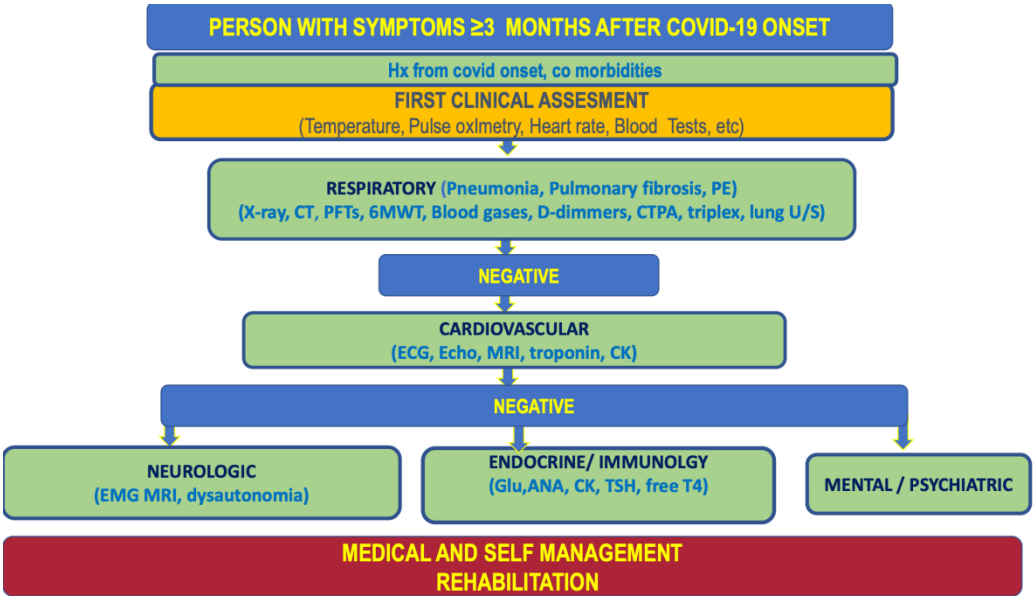

Figure 5. Proposed holistic approach diagnostic algorithm

Employing a clinical framework that ensures that all initial appointments are based on predominant symptoms, and evaluations and treatment are determined on a case-by-case basis is highly desired. Furthermore, psychological and neuropsychiatric complications are commonly encountered and should be proactively screened for and differentiated from other overlapping physical complaints as well assertively managed in a multidisciplinary manner.

5. Conclusions

Since non-hospitalized and hospitalized long covid patients share similar symptom pattern, long covid may rather be genetically driven than acute phase severity dependent. It is well known that there are significant genetics variations between populations [51][52] and this can explain different outcomes between studies mentioned above [49][50]. Studies with larger sample and genetic analysis must be conducted in order to identify the pathophysiologic pathway of this new medical entity.

Institutional Review Board Statement: The study was approved by the Ethics Committee of Evangelismos Hospital Athens, protocol code 173 /24-4-2020

Informed Consent Statement: Patients of these study cannot be identified in any way. Google forms did not ask any participant for personal data neither asked for their IPs. However, all Participants started answering the questionnaire after were well informed that all anonymized and de-identified data will be used from Long Covid Greece Patient Society for scientific reasons.

Conflicts of Interest: The authors declare no conflict of interest

Data Availability Statement : The data presented in this study are available on request from the corresponding author.

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