Long COVID active case detection initiative among COVID-19 patients in Port Dickson, Malaysia: Positive outcomes, the proportion of patients with long COVID and its associated factors (#73808)

First submission

Guidance from your Editor

Please submit by 30 Jul 2022 for the benefit of the authors (and your \$200 publishing discount).



Structure and Criteria

Please read the 'Structure and Criteria' page for general guidance.



Custom checks

Make sure you include the custom checks shown below, in your review.



Author notes

Have you read the author notes on the guidance page?



Raw data check

Review the raw data.



Image check

Check that figures and images have not been inappropriately manipulated.

Privacy reminder: If uploading an annotated PDF, remove identifiable information to remain anonymous.

Files

Download and review all files from the <u>materials page</u>.



4 Table file(s)

Human participant/human tissue checks

- Have you checked the authors ethical approval statement?
- Does the study meet our <u>article requirements</u>?
- Has identifiable info been removed from all files?
- Were the experiments necessary and ethical?

Structure and Criteria



Structure your review

The review form is divided into 5 sections. Please consider these when composing your review:

- 1. BASIC REPORTING
- 2. EXPERIMENTAL DESIGN
- 3. VALIDITY OF THE FINDINGS
- 4. General comments
- 5. Confidential notes to the editor
- You can also annotate this PDF and upload it as part of your review

When ready submit online.

Editorial Criteria

Use these criteria points to structure your review. The full detailed editorial criteria is on your guidance page.

BASIC REPORTING

- Clear, unambiguous, professional English language used throughout.
- Intro & background to show context.
 Literature well referenced & relevant.
- Structure conforms to <u>PeerJ standards</u>, discipline norm, or improved for clarity.
- Figures are relevant, high quality, well labelled & described.
- Raw data supplied (see <u>PeerJ policy</u>).

EXPERIMENTAL DESIGN

- Original primary research within Scope of the journal.
- Research question well defined, relevant & meaningful. It is stated how the research fills an identified knowledge gap.
- Rigorous investigation performed to a high technical & ethical standard.
- Methods described with sufficient detail & information to replicate.

VALIDITY OF THE FINDINGS

- Impact and novelty not assessed.

 Meaningful replication encouraged where rationale & benefit to literature is clearly stated.
- All underlying data have been provided; they are robust, statistically sound, & controlled.



Conclusions are well stated, linked to original research question & limited to supporting results.



Standout reviewing tips



The best reviewers use these techniques

Т	p

Support criticisms with evidence from the text or from other sources

Give specific suggestions on how to improve the manuscript

Comment on language and grammar issues

Organize by importance of the issues, and number your points

Please provide constructive criticism, and avoid personal opinions

Comment on strengths (as well as weaknesses) of the manuscript

Example

Smith et al (J of Methodology, 2005, V3, pp 123) have shown that the analysis you use in Lines 241-250 is not the most appropriate for this situation. Please explain why you used this method.

Your introduction needs more detail. I suggest that you improve the description at lines 57-86 to provide more justification for your study (specifically, you should expand upon the knowledge gap being filled).

The English language should be improved to ensure that an international audience can clearly understand your text. Some examples where the language could be improved include lines 23, 77, 121, 128 – the current phrasing makes comprehension difficult. I suggest you have a colleague who is proficient in English and familiar with the subject matter review your manuscript, or contact a professional editing service.

- 1. Your most important issue
- 2. The next most important item
- 3. ...
- 4. The least important points

I thank you for providing the raw data, however your supplemental files need more descriptive metadata identifiers to be useful to future readers. Although your results are compelling, the data analysis should be improved in the following ways: AA, BB, CC

I commend the authors for their extensive data set, compiled over many years of detailed fieldwork. In addition, the manuscript is clearly written in professional, unambiguous language. If there is a weakness, it is in the statistical analysis (as I have noted above) which should be improved upon before Acceptance.



Long COVID active case detection initiative among COVID-19 patients in Port Dickson, Malaysia: Positive outcomes, the proportion of patients with long COVID and its associated factors

Kim Sui Wan ^{Corresp., 1, 2}, Esther Rishma Sundram ², Ammar Amsyar Abdul Haddi ², Abdul Rahman Dashuki ², Azainorsuzila Mohd Ahad ², Rowena John ², Muhammad Khairul Ridhuan Abdul Wahid ², Ungku Izmin Farah Ungku Halmie ², Farah Edura Ibrahim ², Nachia Banu Abdul Rahim ²

Corresponding Author: Kim Sui Wan Email address: kimsui@moh.gov.my

Background. We aim to determine the proportion and factors associated with long COVID among COVID-19 patients in Port Dickson, Malaysia. The positive outcomes of our long COVID active detection initiative were also described.

Methods. This was a retrospective analysis of long COVID data collected by the Port Dickson District Health Office between 1 September 2021 to 31 October 2021. We called patients to inquire regarding long COVID symptoms in the fifth week post-COVID-19 diagnosis. Long COVID was defined as new or ongoing symptoms lasting more than 28 days from the date of positive SARS-CoV-2 by polymerase chain reaction test. Multivariate logistic regression was conducted to determine factors associated with long COVID.

Results. Among 452 patients, they were predominantly male (54.2%), Malays (68.8%) and aged 18-29 years (58.6%). A total of 27.4% (95% CI: 23.4–31.8) patients experienced long COVID symptoms and were referred to government clinics. The most frequent long COVID symptoms experienced were fatigue (54%), cough (20.2%), muscle pain (18.5%), headache (17.7%) and sleep disturbance (16.1%). Females, patients with underlying cardiovascular disease, asthma and chronic obstructive airway disease, those who received symptomatic care, and patients with myalgia and headaches at COVID-19 diagnosis were more likely to have long COVID. Three patients with suspected severe mental health problems were referred to the district psychologist, and ten patients with no/incomplete vaccination were referred for vaccination.

Conclusion. Long COVID is prevalent among COVID-19 patients in Port Dickson, Malaysia. Long term surveillance and management of long COVID is needed as we transition to live with COVID-19.

¹ Institute for Public Health, National Institutes of Health, Shah Alam, Selangor, Malaysia

Port Dickson District Health Office, Ministry of Health Malaysia, Port Dickson, Negeri Sembilan, Malaysia



- Long COVID active case detection initiative among
- 2 COVID-19 patients in Port Dickson, Malaysia: Positive
- 3 outcomes, the proportion of patients with long COVID
- 4 and its associated factors

- 6 Wan Kim Sui^{1,2}, Esther Rishma Sundram², Ammar Amsyar Abdul Haddi², Abdul Rahman
- 7 Dashuki², Azainorsuzila Mohd Ahad², Rowena John², Muhammad Khairul Ridhuan Abdul
- 8 Wahid², Ungku Izmin Farah Ungku Halmie², Farah Edura Ibrahim², Nachia Banu Abdul Rahim²

9

- 10 ¹Institute for Public Health, National Institutes of Health, Shah Alam, Selangor, Malaysia
- 11 ²Port Dickson District Health Office, Ministry of Health Malaysia, Port Dickson, Negeri
- 12 Sembilan, Malaysia

13

- 14 Corresponding Author:
- 15 Wan Kim Sui^{1,2}
- 16 ¹Institute for Public Health, National Institutes of Health, Persiaran Setia Murni, Setia Alam,
- 17 40170 Shah Alam, Selangor, Malaysia
- 18 Email address: kimsui@moh.gov.my

19 20

Abstract

- 21 **Background.** We aim to determine the proportion and factors associated with long COVID
- 22 among COVID-19 patients in Port Dickson, Malaysia. The positive outcomes of our long
- 23 COVID active detection initiative were also described.
- 24 Methods. This was a retrospective analysis of long COVID data collected by the Port Dickson
- 25 District Health Office between 1 September 2021 to 31 October 2021. We called patients to
- 26 inquire regarding long COVID symptoms in the fifth week post-COVID-19 diagnosis. Long
- 27 COVID was defined as new or ongoing symptoms lasting more than 28 days from the date of
- 28 positive SARS-CoV-2 by polymerase chain reaction test. Multivariate logistic regression was
- 29 conducted to determine factors associated with long COVID.
- 30 **Results.** Among 452 patients, they were predominantly male (54.2%), Malays (68.8%) and aged
- 31 18-29 years (58.6%). A total of 27.4% (95% CI: 23.4–31.8) patients experienced long COVID
- 32 symptoms and were referred to government clinics. The most frequent long COVID symptoms
- experienced were fatigue (54%), cough (20.2%), muscle pain (18.5%), headache (17.7%) and
- 34 sleep disturbance (16.1%). Females, patients with underlying cardiovascular disease, asthma and
- 35 chronic obstructive airway disease, those who received symptomatic care, and patients with
- 36 myalgia and headaches at COVID-19 diagnosis were more likely to have long COVID. Three
- 37 patients with suspected severe mental health problems were referred to the district psychologist,
- and ten patients with no/incomplete vaccination were referred for vaccination.



- 39 Conclusion. Long COVID is prevalent among COVID-19 patients in Port Dickson, Malaysia.
- 40 Long term surveillance and management of long COVID is needed as we transition to live with
- 41 COVID-19.

58

59

60

61 62

63

64 65

66

67

68 69

70

71

72

73

74

75

76

77

Introduction

- 44 The novel coronavirus SARS-CoV-2 has paved its way into eventually causing the biggest
- 45 pandemic in the 21st century with almost 520 million Coronavirus Disease 19 (COVID-19) cases
- and over 6.1 million deaths worldwide, as of 17 May 2022 (World Health Organization 2022b).
- 47 Evidence has emerged as the pandemic progresses that some patients are experiencing prolonged
- 48 multiorgan symptoms and complications beyond the initial period of acute infection and illness
- 49 (Venkatesan 2021). The new or ongoing symptoms four weeks or more after the start of acute
- 50 COVID-19 are often described as long COVID (National Institute for Health and Care
- 51 Excellence 2020). Long COVID is classified into ongoing symptomatic COVID-19 and post-
- 52 COVID-19 syndrome. Ongoing symptomatic COVID-19 refers to signs and symptoms of
- 53 COVID-19 from four to twelve weeks (Ministry of Health Malaysia 2021c; National Institute for
- Health and Care Excellence 2020). Meanwhile, post-COVID-19 syndrome means signs and
- 55 symptoms that develop during or after an infection consistent with COVID-19, continue for more
- than 12 weeks and are not explained by an alternative diagnosis (Ministry of Health Malaysia
- 57 2021c; National Institute for Health and Care Excellence 2020).

The long COVID symptoms are highly variable and wide-ranging from respiratory, cardiovascular, neurological, gastrointestinal, musculoskeletal, psychological, ear, nose and throat, dermatological and generalised symptoms (Ministry of Health Malaysia 2021c; National Institute for Health and Care Excellence 2020). In the United Kingdom, around one in five people with COVID-19 had symptoms that lasted for ≥5 weeks, and one in ten people had symptoms that lasted for ≥12 weeks (Office for National Statistics United Kingdom 2020). In a prospective cohort study of COVID-19 symptoms, 13.3% of COVID-19 cases had symptoms lasting >28 days, 4.5% for >8 weeks, and 2.3% for >12 weeks (Sudre et al. 2021). The long COVID prevalence equated to an estimated 186,000 individuals (95% CI: 153,000 to 221,000) in England who had symptoms persisting between 5 and 12 weeks (Venkatesan 2021). The high number implied that many resources were needed to help patients and clinicians to understand and manage the long-term effects of COVID-19 (Venkatesan 2021).

Malaysia, an upper-middle-income country, was not spared from the pandemic and had over 4.4 million cases and 35,620 deaths as of 17 May 2022 (World Health Organization 2022a). However, the prevalence and factors associated with long COVID symptoms are largely unknown locally. Understanding these knowledge gaps assist public health practitioners and clinicians in planning and managing long COVID symptoms. As a part of our ongoing quality improvement initiative to safeguard the health of residents in Port Dickson, we started monitoring long COVID symptoms among COVID-19 patients. This paper aims to determine the proportion and factors associated with long COVID among COVID-19 patients in Port Dickson,



Malaysia. We further describe the additional positive outcomes of the active detection initiative of long COVID.

Materials & Methods

82 Study design and setting

This was a retrospective analysis of the routine long COVID data collected by the Port Dickson District Health Office between 1 September 2021 to 31 October 2021. Port Dickson district is one of the seven districts situated in Negeri Sembilan state, Malaysia. The district is located about 90 km to the south of Kuala Lumpur, the capital city of Malaysia, with an estimated population of 132,900 people in 2021.

The study population was patients previously diagnosed with COVID-19 who resided in Port Dickson. The inclusion criteria were adults aged 18 years and above, and were in the fifth week (day 29 to 35) post-COVID-19 diagnosis during the data collection period. We excluded those who have died.

Data collection

The Port Dickson District Health Office is responsible for healthcare delivery and public health services in the district alongside with six government healthcare clinics and six smaller rural/community clinics. The critical functional unit during the current COVID-19 pandemic is the Port Dickson Crisis Preparedness and Response Centre that leads and coordinates all prevention and control activities.

The centre continuously received notification of new COVID-19 cases through three main channels: i) State Health Department of Negeri Sembilan via the National Public Health Laboratory Information System; ii) public and private healthcare facilities and iii) COVID-19 Assessment Centre. We defined a COVID-19 patient as a person with a laboratory confirmation for SARS-CoV-2 by reverse transcriptase-polymerase chain reaction (RT-PCR) test (Ministry of Health Malaysia 2021a). It is mandatory in Malaysia for every medical practitioner to notify infectious diseases, including COVID-19 (1988). Our team compiled and collated the notifications in a line-listing format on a daily basis.

The primary triaging officers called all the patients to obtain information that included age, sex, ethnicity, nationality, body weight, past medical history, symptoms and date of onset and vaccination status. Obesity was operationally defined as bodyweight above 90 kg. The vaccine types received by patients during this period were either Comirnaty (Pfizer-BioNTech) or CoronaVac (Sinovac). These data formed the baseline characteristics and independent variables in this analysis. The patients were categorised into three screening categories based on their ages, symptoms and comorbidities. The assigned categories were verified by our trained medical officers and also served as the independent variable. Category one was for patients who fulfilled criteria for home monitoring per Ministry of Health guidelines (Ministry of Health Malaysia 2021b). For adults, they were those below 60 years old with no or only mild symptoms and with or without controlled comorbidities (Ministry of Health Malaysia 2021b). For



paediatric age groups, they were those without symptoms, had no comorbidity and with suitable caregivers; those aged two years and above and with mild symptoms and suitable caregivers could also be considered for home monitoring (Ministry of Health Malaysia 2021b).

Category two was for patients who fulfilled the criteria for admission to the Low-Risk COVID-19 Quarantine and Treatment Centre. The conditions include: a) all confirmed COVID-19 patients who fulfilled home monitoring criteria but without suitable home condition; b) able to ambulate without assistance and self-administer medications and c) do not have ongoing clinical needs such as haemodialysis (Ministry of Health Malaysia 2021b). Meanwhile, category three was for patients that required hospital admission and the criteria were: a) moderate to severe clinical stages; b) age above 60 years; c) all paediatric cases with comorbidity or those below two years old; d) uncontrolled comorbidity such as having unstable angina; e) end-stage renal failure on dialysis and f) pregnant mothers (Ministry of Health Malaysia 2021b).

Our effort to identify patients with long COVID was consistent with the recommendation by National Institute for Health and Care Excellence. We defined long COVID as new or ongoing symptoms lasting more than 28 days from the date of positive SARS-CoV-2 by RT-PCR (National Institute for Health and Care Excellence 2020). Our team called patients to inquire about long COVID symptoms in the fifth week (day 29 to 35) post-COVID-19 diagnosis. If unanswered, we called them up to three times and labelled them as loss of contact. The categories of long COVID symptoms were: a) respiratory symptoms – breathlessness and cough; b) cardiovascular symptoms – chest tightness, chest pain and palpitations; c) generalised symptoms – fatigue and fever; d) neurological symptoms – loss of concentration, memory impairment, headache, sleep disturbance and dizziness; e) gastrointestinal symptoms – abdominal pain, nausea and diarrhoea; f) musculoskeletal symptoms – joint pain and muscle pain; g) psychological symptoms – depression, anxiety and stress symptoms; and h) ear, nose, throat symptoms – tinnitus, earache, sore throat, dizziness, loss of taste and loss of smell (National Institute for Health and Care Excellence 2020).

The primary outcome of this study was to portray the proportion of COVID-19 patients that experienced any long COVID symptoms. When patients were identified to have long COVID, we referred them to the nearest government healthcare clinics. For patients with psychological symptoms, our doctors assessed their clinical history and referred patients to the district psychologist. Besides that, we identified and referred patients with no or incomplete COVID-19 vaccination to the vaccine administration centre.

Statistical analyses

Descriptive analysis was performed for the baseline characteristics and long COVID symptoms. For normally distributed data, the variables were presented in mean \pm standard deviation (SD), while median and inter-quartile range (IQR) were presented for skewed data. Both frequency and percentages were reported for categorical variables.

Univariate binary logistic regression was first conducted to determine individual factors associated with long COVID symptoms. Multivariate logistic regression analysis was carried out



- 158 for variables with P < 0.25 and clinically essential variables. The Omnibus test of model
- 159 coefficients was used to check the model against the baseline model. The coefficient of
- determination, R^2 , represented the amount of variation in the outcome that the model explained.
- 161 The Hosmer & Lemeshow test indicated if the model was a good fit for the data. The model's
- predictive power was assessed using the classification table and area under the Receiver
- Operating Characteristic (ROC) curve. All analyses were carried out using the IBM SPSS
- 164 Statistical Software, version 23.

Ethical approval

- 167 This paper utilised anonymized secondary data from Port Dickson District Health Office. All
- patients' identifiers such as name, identity card numbers, contact numbers, and addresses were
- 169 first removed. The Medical Research Ethics Committee (MREC) Ministry of Health Malaysia
- approved this study (NMRR ID-22-01103-GRF). Written informed consent was waived by the
- MREC in accordance with local legislation and national guidelines as this was a retrospective
- analysis of secondary anonymised dataset.

173174

187

188

189 190

191 192

193

194

195196

197

Results

- 175 A total of 452 COVID-19 cases were analysed and patients were predominantly male (54.2%),
- Malays (68.8%) and were in the 18-29-year age category (58.6%) (Table 1). It was observed that
- 177 28.3% of patients were smokers and the majority of cases (73.2%) did not have comorbidities.
- 178 Among those with comorbidities, the most common comorbidities reported were obesity
- 179 (45.5%), followed by hypertension (36.3%) and diabetes (26.4%). Additionally, 77.2% of cases
- 180 reported having COVID-19 symptoms at the time of diagnosis. The most common symptoms
- experienced were fever (73.6%) followed by cough (63.3%) and loss of taste or ageusia (57.9%).
- More than half of the patients (55%) received two doses of COVID-19 vaccines at the time of
- 183 COVID-19 diagnosis, whereas only 20% did not receive any vaccination dose. Meantime, most
- patients were treated at the Low-risk Quarantine and Treatment Centre (63%) after diagnosis,
- and the maximum care received by patients were mainly symptomatic treatment and did not
- require oxygen supplementation (73.2%).

Table 2 exhibits the descriptive characteristics of long COVID symptoms reported on the fifth week post diagnosis. It was discovered that 124 or 27.4% (95% CI: 23.4–31.8) patients experienced long COVID symptoms. The most frequent symptoms experienced were fatigue (54%), cough (20.2%), muscle pain (18.5%), headache (17.7%) and sleep disturbance (16.1%).

Simple logistic regression was performed and variables with P values <0.25 were selected to be included in the final model. These variables were age group, sex, ethnicity, smoking status, obesity, cardiovascular disease, asthma and COAD, fever, cough, fatigue, headache, myalgia, sore throat, coryza, dyspnoea, anorexia, nausea, or vomiting, diarrhoea, loss of taste and loss of smell (Table S1).

In the final multiple logistic regression model, six independent factors were associated with long COVID: females, underlying cardiovascular disease, asthma/COAD, headaches,



myalgia and receiving symptomatic treatment but not oxygen (Table 3). Underlying cardiovascular disease yielded the highest odds (aOR: 20.8, 95% CI: 3.84–113.2). The second strongest associated factor was asthma and COAD (aOR:3.39, 95% CI: 1.09–10.58). This was followed by patients receiving symptomatic care but without oxygen treatment (aOR:2.28, 95% CI: 1.15–4.51). Meanwhile, being females, having myalgia and headache at COVID-19 diagnosis were twice as likely to develop long COVID compared to the respective counterparts.

We referred all 124 patients with long COVID to the nearest government clinics for further assessment by medical doctors. Three patients with suspected severe mental health problems were referred to the district psychologist for further intervention. In addition, ten patients were identified to have no/incomplete COVID-19 vaccination during our surveillance calls and were referred to the vaccine administration centre for vaccination.

Discussion

The proportion of our patients with long COVID (27.4%) was within the range of 4.7% to 80% reported in a systematic review (Cabrera Martimbianco et al. 2021). The prevalence varied widely due to differences in population, the accuracy of diagnosis, the capability of the healthcare system, the duration of follow up, the reporting systems and symptoms examined (Cabrera Martimbianco et al. 2021). Our top five long COVID symptoms had similarities with preliminary findings from the Ministry of Health, Malaysia research on long COVID patients: lethargy (78.9%), breathing difficulties when performing certain tasks (52.9%), coughing (18.1%), insomnia (14.5%) and anxiety (10.4%) (Carvalho 2021).

Our most common long COVID symptom of fatigue is similar to many studies (Cabrera Martimbianco et al. 2021; Crook et al. 2021; D'Cruz et al. 2021). Evidence shows that miscommunication in the inflammatory response pathways may result in chronic fatigue (Islam et al. 2020). Olfactory neuron damage leads to increased resistance to cerebrospinal fluid drainage through the cribriform plate, and this indirectly affects the central nervous system by congesting the glymphatic system (Jessen et al. 2015). When the glymphatic system is congested, toxin accumulation may lead to post COVID-19 fatigue (Wostyn 2021).

The frequency of cough among our long COVID patients was consistent with prevalence range reported in a systematic review (Cabrera Martimbianco et al. 2021). The pathophysiology of cough is hypothesised to be due to neuroinflammatory response or SARS-CoV-2 invasion to vagal sensory nerves causing hypersensitivity of the cough pathways (Song et al. 2021). Besides that, the neuroinflammatory response also affects various regions in the brain to induce symptoms like pain, headache, sleep disturbance and others (Song et al. 2021). This mechanism may explain the long COVID symptoms among our patients.

Our analysis revealed that patients with underlying cardiovascular disease (CVD) is the strongest factor associated with long COVID. This is a new finding as limited studies show direct associations between underlying CVD with long COVID. Pre-existing CVD did not show an association with long COVID (Crook et al. 2021). Nevertheless, this result should be



interpreted with caution due to the small sample size of patients with underlying CVDs and the wide 95% confidence intervals.

Previous evidence has indicated that underlying health conditions, including CVD and its risk factors, may lead to severe COVID-19 and mortality (Matsushita et al. 2020; Yang et al. 2020). CVD as a risk factor of severe COVID-19 may partially explain the association between underlying CVD with long COVID. Patients recovering from severe COVID-19 may require an extended period to recover, contributing to the persistence of symptoms beyond 28 days. The severity of long COVID was correlated with the severity of acute COVID-19 infection (Kamal et al. 2021). Besides that, COVID-19 is linked with the new onset of cardiovascular complications (Harrison et al. 2021). Long-term effects of myocardial inflammation in recovered COVID-19 patients has also been reported (Puntmann et al. 2020). We hypothesise that cardiac damages following COVID-19 may worsen in the patients with CVD who later developed long COVID.

Our result that females were more likely to have long COVID was consistent with other studies (Bai et al.; Torjesen 2021). Middle-aged women have a higher risk of experiencing a range of debilitating ongoing symptoms, such as fatigue, breathlessness, muscle pain, anxiety, depression, and 'brain fog' after hospital treatment for COVID-19 (Torjesen 2021). Hormonal differences may result in hyperinflammatory status among females in the early phase of the disease (Bienvenu et al. 2020). A stronger IgG antibodies production among females at the beginning of COVID-19 could lead to different disease outcomes between sexes (Zeng et al. 2020).

The primary target organ for COVID-19 is the respiratory tract. Hence, our finding of an association between underlying asthma with long COVID symptoms is not surprising and has been similarly reported (Michelen et al. 2021; Sudre et al. 2021). Substantial damage to the lungs and respiratory tract can occur as SARS-CoV-2 replicates inside endothelial cells, resulting in endothelial damage and intense immune and inflammatory reaction (Kempuraj et al. 2020). Patients with pre-existing lung abnormalities are more likely to develop fibrotic-like changes to lung tissue (Han et al. 2021). Thus, underlying asthma and COAD may be a precipitating factor in long COVID symptoms.

We found that patients who presented with headaches at the onset of COVID-19 diagnosis are three times more likely to develop long COVID symptoms. Although headaches are among the most frequent neurological symptoms in long COVID, the exact causes of headaches in long COVID remain uncertain (Martelletti et al. 2021). Possible mechanisms are direct neuro-invasion with damage on the neuronal pathway and indirect effects mediated by hypoxia, hypertension, coagulopathy and cytokine storm on the central nervous system (Martelletti et al. 2021). The worsening of pre-existing brain diseases and the development of new ones such as cerebrovascular events, infectious and toxic encephalopathy and meningoencephalitis may also explain the symptom (Martelletti et al. 2021).

Patients with any viral infections commonly experience myalgia. However, myalgia caused by COVID-19 infection persists longer and is more severe than the usual myalgia of other viral infections. Generalised inflammation and cytokine response inside the musculoskeletal



system can cause myalgia (Henry et al. 2020). In COVID-19, SARS-CoV-2 can penetrate ACE2 receptors, causing infection and damage to the muscle (Kucuk et al. 2020). Myalgia will be persistent and long COVID symptoms will develop due to the increased lactate levels, low pH, and low oxygen levels (Kucuk et al. 2020). The evidence supported the results of our analysis that patients with myalgia at the time of diagnosis were more prone to develop long COVID symptoms.

Our symptomatic patients at disease onset were more likely to develop long COVID than asymptomatic ones. Symptomatic disease is a proxy for more severe COVID-19 and can explain its association with long COVID. Previous studies reported that patients hospitalised for severe COVID-19 frequently suffer long-term symptoms (Bellan et al. 2021; Huang et al. 2021). For instance, patients who were more severely ill during their hospital stay had worse pulmonary functions six months after the acute infection (Huang et al. 2021).

Our initiative to actively detect long COVID has yielded some positive outcomes. Since the natural progression of long COVID remains uncertain, there is a need to investigate, treat and follow up patients (Ministry of Health Malaysia 2021c). Hence, we referred all patients with long COVID symptoms to the nearest government clinics for multidisciplinary team management (Ministry of Health Malaysia 2021c). Besides that, evidence has shown that patients with COVID-19 have higher risk of mental health problems several months post initial infection (Huang et al. 2021; Taquet et al. 2021). After elaborate phone call conversations with patients, our medical doctors identified and referred three patients suspected of severe mental health problems to the psychologist. At the time of our initiative, the COVID-19 vaccination coverage in Port Dickson had achieved around 90%, and we had observed a decrease in daily vaccine uptake. Through our long COVID active case detection, we managed to identify and refer ex-COVID-19 patients who were yet to be vaccinated.

The main strength of this analysis is the use of real-world data to determine the proportion of COVID-19 patients with long COVID and its associated factors. We believe our findings can add new knowledge into the pool of existing information on long COVID, especially in Malaysia. Implementing this long COVID surveillance initiative helped improve the quality of public health service and may reduce the long-term disease burden posed by long COVID among COVID-19 patients in our district.

We acknowledge several limitations. Firstly, the demographic characteristics of our COVID patients were not representative of the general population in Port Dickson and Malaysia. These differences were not unexpected as higher proportions of COVID-19 patients were reported during the period among younger adults in higher education institutions and workplaces. Thus, our results may not be externally generalised to the whole population. Secondly, the small sample size for some associated factors was small, and this could cause insufficient study power and wide confidence intervals. Thirdly, our long COVID surveillance by telephone call might not have adequately excluded the alternative explanations for some symptoms and mistakenly assigned them as long COVID. This was unavoidable as our medical doctors could not examine them physically and perform relevant investigations. Nevertheless, we



referred them all to the government clinics for further management. Finally, we could not follow up with patients further to observe the persistence of long COVID symptoms beyond twelve weeks and the outcomes of our referrals.

Conclusions

- In conclusion, more than a quarter of our COVID-19 patients in Port Dickson, Malaysia, experienced long COVID symptoms. Females, underlying CVD, asthma and COAD, symptomatic care, myalgia, and headaches at COVID-19 diagnosis were independent factors associated with long COVID. Long term surveillance and management of long COVID should be considered by policymakers, public health practitioners and clinicians as we transition to live with COVID-19. Sufficient monetary, material and human resources are needed to implement such initiative. We recommend prospective cohort studies to understand the natural progression
- such initiative. We recommend prospective cohort studies to understand the natural progress of long COVID while monitoring patients' outcomes or responses to treatment in Malaysia.

Acknowledgements

The authors would like to thank the Director-General of Health Malaysia for permission to publish this paper. We applaud all Port Dickson District Health Office staff for their support and dedication during this unprecedented COVID-19 pandemic.

References

- 337 1988. Prevention and Control of Infectious Diseases Act 342. Malaysia.
- Bai F, Tomasoni D, Falcinella C, Barbanotti D, Castoldi R, Mulè G, Augello M, Mondatore D,
 Allegrini M, Cona A, Tesoro D, Tagliaferri G, Viganò O, Suardi E, Tincati C, Beringheli
 T, Varisco B, Battistini CL, Piscopo K, Vegni E, Tavelli A, Terzoni S, Marchetti G, and
 Monforte AdA. Female gender is associated with long COVID syndrome: a prospective
 cohort study. *Clinical Microbiology and Infection*. 10.1016/j.cmi.2021.11.002
 - Bellan M, Soddu D, Balbo PE, Baricich A, Zeppegno P, Avanzi GC, Baldon G, Bartolomei G, Battaglia M, Battistini S, Binda V, Borg M, Cantaluppi V, Castello LM, Clivati E, Cisari C, Costanzo M, Croce A, Cuneo D, De Benedittis C, De Vecchi S, Feggi A, Gai M, Gambaro E, Gattoni E, Gramaglia C, Grisafi L, Guerriero C, Hayden E, Jona A, Invernizzi M, Lorenzini L, Loreti L, Martelli M, Marzullo P, Matino E, Panero A, Parachini E, Patrucco F, Patti G, Pirovano A, Prosperini P, Quaglino R, Rigamonti C, Sainaghi PP, Vecchi C, Zecca E, and Pirisi M. 2021. Respiratory and Psychophysical Sequelae Among Patients With COVID-19 Four Months After Hospital Discharge. *JAMA Network Open* 4:e2036142-e2036142. 10.1001/jamanetworkopen.2020.36142
 - Bienvenu LA, Noonan J, Wang X, and Peter K. 2020. Higher mortality of COVID-19 in males: sex differences in immune response and cardiovascular comorbidities. *Cardiovascular Research* 116:2197-2206. 10.1093/cvr/cvaa284
 - Cabrera Martimbianco AL, Pacheco RL, Bagattini ÂM, and Riera R. 2021. Frequency, signs and symptoms, and criteria adopted for long COVID-19: A systematic review. *International Journal of Clinical Practice* 75:e14357. https://doi.org/10.1111/ijcp.14357
 - Carvalho M. 2021. Covid-19: Nearly 20,000 in M'sia suffering from long Covid, says Deputy Health Minister. *Available at https://www.thestar.com.my/news/nation/2021/12/08/covid-*



389

- 360 <u>19-nearly-20000-in-m039sia-suffering-from-long-covid-says-deputy-health-minister</u> 361 (accessed 8 January 2022.
- Crook H, Raza S, Nowell J, Young M, and Edison P. 2021. Long covid—mechanisms, risk factors, and management. *BMJ* 374:n1648. 10.1136/bmj.n1648
- D'Cruz RF, Waller MD, Perrin F, Periselneris J, Norton S, Smith L-J, Patrick T, Walder D,
 Heitmann A, Lee K, Madula R, McNulty W, Macedo P, Lyall R, Warwick G, Galloway
 JB, Birring SS, Patel A, Patel I, and Jolley CJ. 2021. Chest radiography is a poor
 predictor of respiratory symptoms and functional impairment in survivors of severe
 COVID-19 pneumonia. *ERJ Open Research* 7:00655-02020. 10.1183/23120541.00655 2020
- Han X, Fan Y, Alwalid O, Li N, Jia X, Yuan M, Li Y, Cao Y, Gu J, Wu H, and Shi H. 2021. Six month Follow-up Chest CT Findings after Severe COVID-19 Pneumonia. *Radiology* 299:E177-E186. 10.1148/radiol.2021203153
- Harrison SL, Buckley BJR, Rivera-Caravaca JM, Zhang J, and Lip GYH. 2021. Cardiovascular risk factors, cardiovascular disease, and COVID-19: an umbrella review of systematic reviews. *European Heart Journal Quality of Care and Clinical Outcomes* 7:330-339.
 10.1093/ehjqcco/qcab029
- Henry BM, Lippi G, and Wong J. 2020. Myalgia may not be associated with severity of coronavirus disease 2019 (COVID-19). *World Journal of Emergency Medicine* 11:193-194. 10.5847/wjem.j.1920-8642.2020.03.013
- Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, Kang L, Guo L, Liu M, Zhou X, Luo J, Huang
 Z, Tu S, Zhao Y, Chen L, Xu D, Li Y, Li C, Peng L, Li Y, Xie W, Cui D, Shang L, Fan
 G, Xu J, Wang G, Wang Y, Zhong J, Wang C, Wang J, Zhang D, and Cao B. 2021. 6month consequences of COVID-19 in patients discharged from hospital: a cohort study.
 The Lancet 397:220-232. 10.1016/S0140-6736(20)32656-8
- Islam MF, Cotler J, and Jason LA. 2020. Post-viral fatigue and COVID-19: lessons from past
 epidemics. Fatigue: Biomedicine, Health & Behavior 8:61-69.
 10.1080/21641846.2020.1778227
 - Jessen NA, Munk AS, Lundgaard I, and Nedergaard M. 2015. The Glymphatic System: A Beginner's Guide. *Neurochem Res* 40:2583-2599. 10.1007/s11064-015-1581-6
- Kamal M, Abo Omirah M, Hussein A, and Saeed H. 2021. Assessment and characterisation of
 post-COVID-19 manifestations. *International Journal of Clinical Practice* 75:e13746.
 https://doi.org/10.1111/ijcp.13746
- Kempuraj D, Selvakumar GP, Ahmed ME, Raikwar SP, Thangavel R, Khan A, Zaheer SA, Iyer
 SS, Burton C, James D, and Zaheer A. 2020. COVID-19, Mast Cells, Cytokine Storm,
 Psychological Stress, and Neuroinflammation. *The Neuroscientist* 26:402-414.
 10.1177/1073858420941476
- Kucuk A, Cumhur Cure M, and Cure E. 2020. Can COVID-19 cause myalgia with a completely
 different mechanism? A hypothesis. *Clinical Rheumatology* 39:2103-2104.
 10.1007/s10067-020-05178-1
- Martelletti P, Bentivegna E, Spuntarelli V, and Luciani M. 2021. Long-COVID Headache. SN
 Comprehensive Clinical Medicine 3:1704-1706. 10.1007/s42399-021-00964-7
- Matsushita K, Ding N, Kou M, Hu X, Chen M, Gao Y, Honda Y, Zhao D, Dowdy D, Mok Y,
 Ishigami J, and Appel LJ. 2020. The Relationship of COVID-19 Severity with
- 404 Cardiovascular Disease and Its Traditional Risk Factors: A Systematic Review and Meta-405 Analysis. *Global heart* 15:64-64. 10.5334/gh.814



422

423

424

425

440 441

- Michelen M, Manoharan L, Elkheir N, Cheng V, Dagens A, Hastie C, O'Hara M, Suett J,
 Dahmash D, Bugaeva P, Rigby I, Munblit D, Harriss E, Burls A, Foote C, Scott J, Carson
 G, Olliaro P, Sigfrid L, and Stavropoulou C. 2021. Characterising long COVID: a living
 systematic review. *BMJ Global Health* 6:e005427. 10.1136/bmjgh-2021-005427
- Ministry of Health Malaysia. 2021a. COVID-19 Management Guidelines in Malaysia No.5/2020
 (latest update on 3 September 2021).
- 412 Ministry of Health Malaysia. 2021b. Management of suspected, probable and confirmed 413 COVID-19 case (updated 4 June 2021).
- 414 Ministry of Health Malaysia. 2021c. Post Covid-19 Management Protocol 1st edition 2021.
- National Institute for Health and Care Excellence. 2020. NICE guideline. COVID-19 rapid guideline: managing the long-term effects of COVID-19.
- Office for National Statistics United Kingdom. 2020. The prevalence of long COVID symptoms and COVID-19 complications. *Available at https://www.ons.gov.uk/news/statementsandletters/theprevalenceoflongcovidsymptomsan*

420 *dcovid19complications* (accessed 4 September 2021.

- Puntmann VO, Carerj ML, Wieters I, Fahim M, Arendt C, Hoffmann J, Shchendrygina A, Escher F, Vasa-Nicotera M, Zeiher AM, Vehreschild M, and Nagel E. 2020. Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). *JAMA Cardiology* 5:1265-1273. 10.1001/jamacardio.2020.3557
- Song W-J, Hui CKM, Hull JH, Birring SS, McGarvey L, Mazzone SB, and Chung KF. 2021.
 Confronting COVID-19-associated cough and the post-COVID syndrome: role of viral neurotropism, neuroinflammation, and neuroimmune responses. *The Lancet Respiratory Medicine* 9:533-544. https://doi.org/10.1016/S2213-2600(21)00125-9
- Sudre CH, Murray B, Varsavsky T, Graham MS, Penfold RS, Bowyer RC, Pujol JC, Klaser K,
 Antonelli M, Canas LS, Molteni E, Modat M, Jorge Cardoso M, May A, Ganesh S,
 Davies R, Nguyen LH, Drew DA, Astley CM, Joshi AD, Merino J, Tsereteli N, Fall T,
 Gomez MF, Duncan EL, Menni C, Williams FMK, Franks PW, Chan AT, Wolf J,
 Ourselin S, Spector T, and Steves CJ. 2021. Attributes and predictors of long COVID.
 Nature Medicine 27:626-631. 10.1038/s41591-021-01292-y
- Taquet M, Geddes JR, Husain M, Luciano S, and Harrison PJ. 2021. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. *The Lancet Psychiatry* 8:416-427. 10.1016/S2215-0366(21)00084-5
 - Torjesen I. 2021. Covid-19: Middle aged women face greater risk of debilitating long term symptoms. *BMJ* 372:n829. 10.1136/bmj.n829
- Venkatesan P. 2021. NICE guideline on long COVID. *The Lancet Respiratory Medicine* 9:129.
- World Health Organization. 2022a. Malaysia situation. WHO Coronavirus Disease (COVID-19)
 Dashboard. Available at https://covid19.who.int/region/wpro/country/my (accessed 18
 May 2022.
- World Health Organization. 2022b. WHO Coronavirus (COVID-19) Dashboard. *Available at* https://covid19.who.int/ (accessed 18 May 2022.
- Wostyn P. 2021. COVID-19 and chronic fatigue syndrome: Is the worst yet to come? *Medical Hypotheses* 146:110469. https://doi.org/10.1016/j.mehy.2020.110469
- Yang X, Yu Y, Xu J, Shu H, Xia Ja, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan
 S, Zou X, Yuan S, and Shang Y. 2020. Clinical course and outcomes of critically ill

PeerJ

152	patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective,
153	observational study. The Lancet Respiratory Medicine 8:475-481. 10.1016/S2213-
154	2600(20)30079-5
155	Zeng F, Dai C, Cai P, Wang J, Xu L, Li J, Hu G, Wang Z, Zheng F, and Wang L. 2020. A
156	comparison study of SARS-CoV-2 IgG antibody between male and female COVID-19
ŀ57	patients: A possible reason underlying different outcome between sex. Journal of
ŀ58	Medical Virology 92:2050-2054. https://doi.org/10.1002/jmv.25989



Table 1(on next page)

Baseline characteristics of COVID-19 patients

COAD: Chronic obstructive airway disease



1 Table 1: Baseline characteristics of COVID-19 patients

Baseline characteristics	n = 452	% (100.0)
Age		
Years, median (IQR)	28.0 (11.0)	
18 - 29	265	58.6
30 - 39	101	22.3
40 - 49	36	8.0
50 – 59	24	5.3
≥ 60	26	5.8
Sex		
Male	245	54.2
Female	207	45.8
Pregnancy	11	5.3
Ethnicity		0.0
Malay	311	68.8
Chinese	46	10.2
Indian	82	18.1
Others	13	2.9
Smoking	13	2.9
9	128	28.3
Comorbidities	221	72.2
No	331	73.2
Yes	121	26.8
Weight >90 kg	55	45.5
Diabetes	32	26.4
Hypertension	44	36.3
Cardiovascular disease	9	7.4
Asthma and COAD	14	11.6
Neoplasm	2	1.7
Thyroid disease	3	2.5
Others: anaemia, gastritis, spondylitis	13	10.7
COVID-19 symptoms at onset		
No	103	22.8
Yes	349	77.2
Fever	257	73.6
Cough	221	63.3
General weakness or fatigue	151	43.3
Headache	128	36.7
Myalgia	132	37.8
Sore throat	109	31.2
Coryza	161	46.1
Dyspnoea	45	12.9
Anorexia, nausea or vomiting	24	6.9
Diarrhoea	53	
		15.2
Loss of taste	170	48.7
Loss of smell	202	57.9
COVID-19 vaccination status during diagnosis	250	
Two doses of Comirnaty or CoronaVac	250	55.3
Only one dose of Comirnaty or CoronaVac	111	24.6



Baseline characteristics	n = 452	% (100.0)
Not vaccinated	91	20.1
Management settings		
Home	109	24.1
Low-risk Quarantine and Treatment Centre	286	63.3
Hospital	57	12.6
Maximum care received		
Asymptomatic	104	23.0
Symptomatic, not requiring oxygen supplement	331	73.2
Symptomatic, requiring oxygen supplement	16	3.5
Intubation	1	0.2

⁻COAD: Chronic obstructive airway disease



Table 2(on next page)

Long COVID symptoms at fifth week post diagnosis (n = 452)

The cumulative total for all symptoms could exceed the total number of patients as each patient might have multiple long COVID symptoms.



1 Table 2: Long COVID symptoms at fifth week post diagnosis (n = 452)

Long COVID symptoms	n	%
Asymptomatic	328	72.6
Symptomatic	124	27.4
Respiratory symptoms		
Cough	25	20.2
Breathlessness	18	14.5
Cardiovascular symptoms		
Chest tightness/pain	12	9.7
Palpitation	7	5.6
Generalised symptoms		
Fatigue	67	54.0
Fever	2	1.6
Neurological symptoms		
Loss of concentration	13	10.5
Memory impairment	16	12.9
Headache	22	17.7
Sleep disturbance	20	16.1
Dizziness	14	11.3
Gastrointestinal symptoms		
Abdominal pain	2	1.6
Nausea	3	2.4
Diarrhoea	0	0.0
Musculoskeletal symptoms		
Joint pain	14	11.3
Muscle pain	23	18.5
Psychological symptoms		
Depression symptoms	3	2.4
Anxiety symptoms	8	6.5
Stress symptoms	5	4.0
Ear, nose, and throat symptoms		
Tinnitus	6	4.8
Earache	1	0.8
Sore throat	8	6.5
Loss of taste	3	2.4
Loss of smell	7	5.6

² The cumulative total for all symptoms could exceed the total number of patients as each patient

³ might have multiple long COVID symptoms.



Table 3(on next page)

Independent factors associated with long COVID

-COAD: Chronic obstructive airway disease -Omnibus tests of model coefficients (P <0.001) - Hosmer-Lemeshow goodness of fit test (P = 0.930), classification table (overall correct percentage: 75.7%), -2 log likelihood (466.5), Nagelkerke R square (0.19) -Area under receiving operating characteristics, ROC curve: 0.73, standard error 0.03, P<0.001 and 95% CI: 0.68-0.78.



1 Table 3: Independent factors associated with long COVID

Baseline characteristics	Adjusted OR	95% CI for	P values
		adjusted OR	
Female	2.09	1.33 - 3.29	0.001
Cardiovascular disease	20.84	3.84 - 113.2	< 0.001
Asthma and COAD	3.39	1.09 - 10.58	0.035
Headache	1.97	1.20 - 3.24	0.008
Myalgia	1.98	1.20 - 3.27	0.007
Maximum care received			
- Asymptomatic	1.00		
- Symptomatic, not requiring oxygen	2.28	1.15 - 4.51	0.019
- Symptomatic, requiring oxygen / intubation	1.30	0.34 - 4.92	0.705

^{2 -}COAD: Chronic obstructive airway disease

8

^{3 -}Omnibus tests of model coefficients (P < 0.001)

^{4 -}Hosmer-Lemeshow goodness of fit test (P = 0.930), classification table (overall correct

⁵ percentage: 75.7%), -2 log likelihood (466.5), Nagelkerke R square (0.19)

^{6 -}Area under receiving operating characteristics, ROC curve: 0.73, standard error 0.03, P<0.001

⁷ and 95% CI: 0.68–0.78.