**Study Protocol**

**Retrospective Cohort Follow Up Study on Post Hospitalized Severe COVID-19 Patients**

**Protocol number, version number and date:**

Post COVID-19, Version 1.0, 6 January 2022

**Name and Institution of Principal investigator:**

Dr Hor Chee Peng, Hospital Kepala Batas, Pulau Pinang

**Name and Institution of Co-Investigators:**

Dr Yen Chia How, Clinical Research Centre, Hospital Queen Elizabeth

Teo Ley Khim, Clinical Research Centre, Hospital Pulau Pinang

Teoh Yee Jie, Department of Pharmacy, Hospital Kepala Batas

Dr Chong Tze Lung, Department of Medicine, Hospital Kepala Batas

Dr Wang Hooi Xian, Department of Medicine, Hospital Kepala Batas

Dr Cheng Joo Thye, Department of Medicine, Hospital Kepala Batas

Dr Norhasimawati binti Abdul Mutalib, Hospital Kepala Batas

**Name and address of Sponsor:**

No sponsor

**Study site/s:**

Hospital Kepala Batas

**Contents**

|  |  |
| --- | --- |
| **Topic** | **Page** |
| List of Abbreviations | 1 |
| Research Synopsis | 2 |
| Background and Significance | 3-5 |
| General Objective | 6 |
| Specific Objectives | 6 |
| Risk to Participants | ­­­7 |
| Benefits to Participants | 7 |
| Risk Benefit Assessment | 7 |
| Study Design and Methodology | 7 |
| Study Population | 7 |
| Sample Size | 7 |
| Inclusion Criteria | 7 |
| Exclusion Criteria | 7 |
| Study Duration and Timeline | 7 |
| Study Visits and Procedures | 7 |
| Statistical Analysis Plan | 7 |
| Ethics of Study | 8 |
| Informed Consent/Assent Process | 8 |
| Privacy and Confidentiality | 8 |
| Conflict of Interest | 8 |
| Publication Policy | 8 |
| References | 9 |

**List of Abbreviations**

List commonly used abbreviations/acronyms

|  |  |
| --- | --- |
| WHO | World Health Organization |
| Coronavirus disease 2019 | COVID-19 |
| CDC | Centers for Diseases Control and Prevention |
| NICE | National Institute for Health and Care Excellence |
| PCS | Post COVID-19 Syndrome |

**Research Synopsis**

|  |  |
| --- | --- |
| Study title | Retrospective cohort follow up study on post hospitalized severe and critically ill COVID-19 Patients |
| Study Population | All Category 4 and 5 COVID-19 Patients discharged from Kepala Batas Hospital from January 2021 until August 2021(Discharge home or continue home quarantine or transfer to other facilities for continuation of care) |
| Study Design | A retrospective cohort study. Medical records for the period January 2021 until August 2021 of selected subjects will be reviewed and study data extracted. |
| General Objective | To assess mortality, morbidity and quality of life of patients post severe COVID-19 infection |
| Specific Objectives | -To determine morbidity of post hospitalized severe and critically ill COVID-19 patients  -To determine mortality rate of post hospitalized severe and critically ill COVID-19 patients  -To determine the impact of post COVID-19 condition to bio-psycho-social aspects in life of post hospitalized severe and critically ill COVID-19 patients  -To determine the vaccination status of severe and critically ill COVID-19 patients before and after hospitalization |
| Study endpoints/outcomes | -Mortality as in-patient, 30-day, 60-day, 90-day  -Morbidity as in re-admission, needs for home oxygen  -Quality of life as ability to return to pre-COVID-19 ADL, impact on work (redundant/ change of job), psychosocial (stigmatization/ work/ family/ community/depression/ anxiety) |
| Sample Size | All Category 4 and 5 COVID-19 Patients discharged from Kepala Batas Hospital from January 2021 until August 2021 |
| Study Duration | April- July 2022 |

**1. Background and Significance**

**Introduction**

The recently emerged coronavirus infectious disease (COVID-19) that was caused by the SARS-CoV-2 virus severely affected many countries, including Malaysia. According to WHO, as of 27 December 2021, COVID-19 had infected more than 280 millions people and caused more than 5.4 millions deaths. America is the country with the highest number of COVID-19 cases, as of 4 January, America recorded more than 102 millions cases with 2,404,354 deaths[1]. In Malaysia, according to the Ministry of Health, as of 2 January 2022, Malaysia had recorded 2,764,354 cases of COVID-19 and 31,532 deaths (25170 in patient death, 6362 BID)[2]. While focusing on how to contain its spread and stop the cases surging, the follow-up on the post-hospitalization patients should also be emphasized.

Many patients have survived COVID-19, but little known about both the short- and long-term impacts of COVID-19 after discharge. Majority of the COVID-19 survivors experienced functional limitations especially those with pre-existing comorbidities or with severe diseases, in which the functional impairment ranged from negligible to severe based on Post-COVID-19 Functional Status (PCFS) scale [3]. Among them, readmission after being discharged from hospitalization is not uncommon as proven by multiple evidence and the majority of them were diagnosed with potentially COVID-19-related disorders or complications encompassing respiratory, neurological, gastrointestinal and cardiovascular systems[3, 4]. These considerably contributed to the mortality after the index hospitalization (for COVID-19) which is not recorded as COVID-19 death and hence the actual pandemic mortality might be underestimated.

In research carried out by Ayoubkhani et al., in 2021, 29% of 47,780 COVID-19 patients who were discharged from hospital were readmitted and 12% passed away within 140 days. Patients infected with COVID-19 also increased risk of multiorgan dysfunction, which suggestive of extrapulmonary involvement in COVID-19. The most common complications in post COVID-19 patients are diabetes and cardiovascular events. Patients aged more than 70 years old or patient required ICU admission have higher risk of death, readmission and multiorgan dysfunction compared with patients aged less than 70 years old or patient not required ICU admission. [5]

Based on research done by Pourhoseingholi et. al., (2021) in the UK,out of 1078 patients being studied, in-patient mortality was 25 (2.3%) patients and 97 (9.2%) patients out of 1053 post COVID-19 patients passed away within 365 days of diagnosis. The most common causes of death were vascular and thromboembolic events. In this study, it mentioned that patients with higher age, opacity score and chest X-ray showed ground glass opacity (GGO) or GGO plus crazy paving lesion type have higher mortality rate.  GGO is a sign of the early and active stage of COVID-19 that can progress and worsen patients' health. In contrast, consolidation opacities is a sign of proper activity of the immune system.[6]

A lot of patients who recovered from COVID-19 experience long-term symptoms. Ever since the emergence of COVID-19 pandemic, different terminologies have been proposed such as long COVID, long-haul COVID or the WHO-recommended post COVID-19 condition have been used to describe the condition. Nevertheless, there is still a lack of a globally standardized clinical case definition of this issue.[7]

The most common symptoms are fatigue and breathlessness.[8] The other commonly reported post COVID-19 conditions include headache, attention deficit, hair loss, myalgia, and arthralgia. Some patients reported with more critical manifestations such as stroke, renal failure, myocarditis and pulmonary fibrosis. Majority of post COVID-19 patients suffered from several symptoms and illness while only about 10% of patients recovering from COVID-19 were asymptomatic [9].

The post COVID-19 manifestations were affected by the presence of comorbidities as well as the severity of COVID-19 infection [9]. Most of the individuals with post COVID-19 conditions have underlying comorbidities such as diabetes mellitus, hypertension, obesity, cancer, cardiovascular diseases, and chronic kidney diseases [5, 10]. The severity of the disease is also related to age in which the elderly are more severely affected and with the need for ICU admission. In addition, there is an observed link between the severity of symptoms and its duration. The symptoms for mild cases may last for 2 weeks while for the severe cases, it ranges from 3 to 6 weeks [9].

In Malaysia, all COVID-19 patients were categorised into 5 stages:

|  |  |  |
| --- | --- | --- |
| Clinical Stage | Clinical condition | Severity |
| 1 | Asymptomatic | Mild |
| 2 | Symptomatic, no pneumonia |
| 3 | Symptomatic, pneumonia | Moderate |
| 4 | Symptomatic, pneumonia, requiring supplemental oxygen | Severe |
| 5 | Critically ill with multi-organ involvement | Critically ill |

Source: Ministry of Health Malaysia, August 2021

Sousa (2020) stated that, elderly (age > 60 years old) had 3.7 times higher risk of mortality compared to younger patients. Besides, the mortality risks are 32.6 times higher in people with neurological disease, 14.3 times higher in patients with diabetes and 19.3 times higher in people with cardiovascular diseases. Mortality risk was 3 times higher in hospitalized patients and 3.5 times higher in those patients admitted to ICU[11]. Another study carried out by Tian W. et. Al. (2020) also stated that, older age, hypertension, diabetes, cardiovascular disease, cerebrovascular disease and chronic renal disease were associated with higher risk of mortality in COVID-19 [12].

It is anticipated that COVID-19 not only exert a major impact on physical health, but also on psychosocial aspects. There has been concern that the COVID-19 patients might develop psychiatric sequelae, in which the arising of this concern was initially based on established fact from other coronaviruses and later by the emerging evidence from other countries.  Symptoms of post-traumatic stress, depression and anxiety were commonly reported by COVID-19 survivors, and these symptoms were reported to persist up to 6 months after the infection [13]. COVID-related stigma is also one of the issues that is encountered by the patients that potentially complicates their recovery. Apart from affecting their mental health, stigmatization may cause the COVID-19 patients to develop negative changes in their health behaviour (e.g., avoid or delay seeking help) and this eventually compromise their physical health outcome [14].

Reduced working hours, changed job types or inability to return to work is common among COVID-19 patients after hospitalization [15]. The enormous huge economic burden from healthcare costs and restrictions of economic activities will be further increased by these undocumented productivity losses.

Despite numerous researches on outcomes of COVID-19 patients globally, there is still relatively paucity of the data regarding survivors of COVID-19 in Malaysia. The burden of these consequences is yet to be studied and an efficient outpatient follow-up is important. By doing the follow-up of patients who have survived the COVID-19, data and information can be collected and analysed, and hence to define the clinical and healthcare needs for post-acute care of COVID-19 survivors.

**2. Objective**

**General Objective:**

To assess mortality, morbidity and quality of life of patients post severe COVID-19 infection

**Specific objective:**

1. To determine morbidity of post hospitalized severe and critically ill COVID-19 patients
2. To determine mortality rate of post hospitalized severe and critically ill COVID-19 patients
3. To determine the impact of post COVID-19 condition to bio-psycho-social aspects in life of post hospitalized severe and critically ill COVID-19 patients
4. To determine the vaccination status of severe and critically ill COVID-19 patients before and after hospitalization

**3. Methodology**

This is the retrospective study using secondary data from Kepala Batas Hospital COVID-19 patient Registry.

**3.1 Study Type and Design**

This is an observational cohort study using Kepala Batas Hospital COVID-19 patients registry database.

**3.2 Study Population**

All Category 4 and 5 COVID-19 Patients during hospitalization in Kepala Batas Hospital from January 2021 until August 2021.

**3.3 Inclusion Criteria**

1. Age > 18 years old
2. All patients diagnosed COVID-19 with Category 4 & 5 during the period of  hospitalization in Kepala Batas Hospital from January 2021 until August 2021.

**3.4 Exclusion Criteria**

1. Patients unable to contact or defaulted follow up in the registry.
2. Excluded cases diagnosed COVID-19 with category 1-3.
3. Patients with incomplete follow up details in the registry

**3.5 Sample Size**

All Category 4 and 5 patients admitted to Kepala Batas Hospital for COVID-19 from 1st January 2021 until 31st August 2021.

**3.6 Study Duration and Timeline**

This study started from January 2022 to December 2022.

Stage 1: Protocol development (1 month) - 1 January 2022- 31 January 2022

Stage 2: Ethic Approval (1 month) - 1 February 2022 - 1 march 2022

Stage 3: Data cleaning (3 months)- 1 march 2022- 31 May 2022

Stage 3: Data analysis (3 months)- 1 June 2022- 31 August 2022

Stage 3: Manuscript writing & publication (4 months) -1 september 2022- 31 December 2022

**3.7 Study Visits and Procedures**

This is study using the secondary database and no study visits or extra procedures required.

**3.8 Statistical Analysis Plan**

The data analysis will be done using the SPSS version 23. Descriptive data will be expressed as mean ± standard deviation (SD) unless otherwise stated. Categorical data will be analysed using Chi-square or Fisher‘s exact test. A value of P < 0.05 is considered statistically significant.

**3.9Risk and benefit to study participants**

This study does not present any direct benefit to the participants. However, the study does provide a better understanding of the disease/condition studied

**3.10 Risk Benefit Assessment**

This study does not present any risk benefit to the participants. Study findings shall potentially greatly improve treatment outcomes.

**3.11 Ethics of Study**

Study team got approval from the Kepala Batas Hospital director for using the COVID-19 patient registry data and the data kept under the Microsoft Excel. The study will also be conducted in compliance with the protocol. Approval from the MREC (Medical Research and Ethics Committee) will be received before conducting the study.

**3.12 Informed Consent/Assent Process**

No informed consent needed as this is a retrospective study.

**3.13 Privacy and Confidentiality**

Subject’s names will be kept on a password-protected database and will be linked only with a study identification number for this research. The identification number instead of patient identifiers will be used on subject data sheets. All data will be entered into a computer that is password protected. On completion of study, data in the computer will be copied to CDs and the data in the computer erased. CDs and any hardcopy data will be stored in a locked office of the investigators and maintained for a minimum of three years after the completion of the study. The CDs and data will be destroyed after that period of storage. Subjects will not be allowed to view their personal study data, as the data will be consolidated into a database.

**3.14 Conflict of Interest**

The investigator declares there is no conflict of interest.

**3.15 Publication Policy**

No personal information will be disclosed and subjects will not be identified when the findings of the study are published. Approval from the Director General of Health Malaysia will be received before publication.

**References**

1. Organisation, W.H. WHO Coronavirus (COVID-19) Dashboard. 2022; Available from: https://covid19.who.int/.

2. Malaysia, M.o.H. COVID-19 Cases in Malaysia. 2022; Available from: https://covidnow.moh.gov.my/cases/.

3. Huang, C., et al., 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. The Lancet, 2021. 397(10270): p. 220-232.

4. UYAROGLU, O.A., et al., Thirty-day readmission rate of COVID-19 patients discharged from a tertiary care university hospital in Turkey: an observational, single-center study. 2020.

5. Ayoubkhani, D., et al., Post-covid syndrome in individuals admitted to hospital with covid-19: retrospective cohort study. bmj, 2021. 372.

6. Pourhoseingholi, M.A., et al., Predicting 1‐year post‐COVID‐19 mortality based on chest computed tomography scan. Journal of Medical Virology, 2021. 93(10): p. 5694.

7. Soriano, J.B., et al., A clinical case definition of post-COVID-19 condition by a Delphi consensus. The Lancet Infectious Diseases, 2021.

8. guideline, N. COVID-19 rapid guideline: managing the long-term effects of COVID-19. 18 December 2020

9. Kamal, M., et al., Assessment and characterisation of post‐COVID‐19 manifestations. International journal of clinical practice, 2021. 75(3): p. e13746.

10. Giannis, D., et al., Postdischarge thromboembolic outcomes and mortality of hospitalized patients with COVID-19: the CORE-19 registry. Blood, The Journal of the American Society of Hematology, 2021. 137(20): p. 2838-2847.

11. Sousa, G., et al., Mortality and survival of COVID-19. Epidemiology & Infection, 2020. 148.

12. Tian, W., et al., Predictors of mortality in hospitalized COVID‐19 patients: a systematic review and meta‐analysis. Journal of medical virology, 2020. 92(10): p. 1875-1883.

13. Taquet, M., et al., 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. The Lancet Psychiatry, 2021. 8(5): p. 416-427.

14. Schnyder, N., et al., Association between mental health-related stigma and active help-seeking: systematic review and meta-analysis. The British Journal of Psychiatry, 2017. 210(4): p. 261-268.

15. Chopra, V., et al., Sixty-day outcomes among patients hospitalized with COVID-19. Annals of Internal Medicine, 2021. 174(4): p. 576-578.