Characterisation of admissions and readmissions after 20 days of illness among COVID-19 patients

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ABSTRACT

Introduction: There has been an observed number of readmissions after an index COVID-19 admission, including admissions after an initial home quarantine. The purpose of this study was to identify the clinical characteristics and outcomes of COVID-19 patients who were readmitted or admitted after an initial home quarantine between 21 and 90 days of illness.

Materials and Methods: This was a single-centre retrospective cohort study comprising patients admitted to a state hospital in Selangor, Malaysia, between August and October 2021. The demographic data, clinical characteristics, presenting complaints, laboratory tests, organ dysfunction, use of invasive ventilation, intensive care unit (ICU) admissions, length of hospitalisation and mortality were collected and analysed.

Results: The analysis involved a total of 195 cases. More than a quarter of the cases (52 [26.7%]) were related to the initial COVID-19 infection. Nine cases (4.6%) required mechanical ventilation, while eight cases (4.1%) were admitted to the ICU. The overall mortality was 17 cases (8.7%). Surviving patients were younger (49.5 vs. 58.4 years), less likely to have diabetes mellitus (48.3% vs. 82.4%), or chronic kidney disease (12.9% vs. 41.2%); had higher levels of admission haemoglobin (12.6 vs. 9.1g/dL) and albumin (33.0 vs. 21.0g/L); lower white blood cells (10.2 vs. 13.0 × 10^9/L), creatinine (81.2 vs. 151.9μmol/L) and C-reactive protein (18.2 vs. 135.0mg/L) at admission; less likely to have MI (6.7% vs. 23.5%), sepsis (3.4% vs. 47.1%), or acute kidney injury (3.4% vs. 17.6%) and organ dysfunction (25.3% vs. 94.1%).

Conclusion: Approximately a quarter of patients were admitted or readmitted due to direct COVID-19 complications between 21 and 90 days of illness. The baseline oxygen requirements at admission were independently associated with mortality, invasive mechanical ventilation and ICU admissions. Further research is needed to establish a risk model for patients returning to a hospital to predict their risk of post-COVID complications.

KEYWORDS:
COVID-19, SARS-CoV-2, readmission, mortality, ventilation

INTRODUCTION

Coronavirus disease 2019 (COVID-19) was first reported in late December 2019 in Wuhan City, China.[1] Successively on 25 January 2020, Malaysia reported its first case of COVID-19.[2] On 11 March 2020, the World Health Organisation (WHO) declared COVID-19 a pandemic after more than 118,000 cases were detected in 114 countries and 4,291 people lost their lives.[3] COVID-19 is broken down into five clinical stages in Malaysia. The disease is mild in some people; however, in some, it may progress to pneumonia, acute respiratory distress syndrome and multiorgan dysfunction.[4] It also poses a wide spectrum of devastating complications like organising pneumonia (OP), venous thrombotic events especially pulmonary embolism (PE), myocardial infarction (MI), ischaemic stroke, reduction of estimated glomerular filtration rate (eGFR) and a new term coined as 'Long COVID Syndrome'.[5-11] The emergence of COVID-19 has led to a dramatic loss of human life worldwide, placing huge pressure on the healthcare systems across the world. The COVID-19 Intensive Care Unit (ICU) utilisation rate in Malaysia averaged 49.2% per day in 2021.[12] The Ministry of Health (MOH) Malaysia reported a record of 17,045 new coronavirus cases on 25 July 2021, bringing the total number of infections in the country past one million. The Delta variant was partly responsible for the surge, being more infectious and able to be transmitted more quickly compared with previous strains.[13]

There was an increasing number of readmissions after an index admission for COVID-19, including the admissions after an initial home quarantine, which posed a tremendous challenge to hospitals that were already strained and overwhelmed. The readmission rate ranged from 8% to 24% within the first six months.[14] In a study in New York, the United States of America (USA), 7.9% of patients returned to the emergency department (ED) and 4.5% of patients were readmitted within 30 days of discharge, mainly due to morbidities from COVID-19. The most common primary diagnosis of readmission was hypoxic respiratory failure (68.8%), followed by thromboembolism (12.5%) and sepsis (6.3%), with one in five (22.9%) of readmitted COVID-19 survivors died.[15] Another study from Pennsylvania, USA showed that 21% of readmissions were due to cardiac causes and 9% mortality among the readmissions.[14] A multicentre observational study in Spain reported that 11.7% of patients died during readmission.[16] The distribution of hospital resources may not be optimal due to a lack of understanding regarding the characterisation of readmitted patients. Day 20

This article was accepted: 23 October 2023
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was the cut-off point of interest as any admission within the first 20 days would be managed differently due to the concern of infectious virus shedding and isolation, in accordance with the interim guidance from the Centre for Disease Control and Prevention (CDC).[17] This study aimed to identify the demographic and clinical characteristics of COVID-19 patients who were admitted (or readmitted) between 21 and 90 days of illness, the causes of admission (i.e., the presenting complaints and the diagnoses), the outcomes (i.e., use of invasive ventilation, ICU admission and mortality), and further description of the factors associated with the outcomes.

MATERIALS AND METHODS

Research Design

This study involved a single-centre retrospective cohort design based on the medical records of a cohort comprising patients admitted between 1 August and 31 October 2021 in Tengku Ampuan Rahimah Hospital (HTAR), Klang, Selangor, Malaysia, between day-21 and day-90 after the initial confirmed COVID-19 diagnosis. The aim of this study was to analyse the clinical characteristics of patients with COVID-19 who were admitted and those readmitted to the hospital between day-21 and day-90 after being released from home quarantine or discharged from index admission. Readmission referred to patients who were (re-)admitted after being discharged from the index hospital or low-risk quarantine centre admission for COVID-19, while admission referred to patients who were admitted for the first time after initial home quarantine for COVID-19. Only the very first encounter data that fulfilled the inclusion criteria were collected for patients with multiple admissions between days 21 and 90 of illness within the study period.

Study Population

The cohort comprised patients over 18 years old who were admitted into the HTAR medical ward between day-21 and day-90 after initial confirmed COVID-19 diagnosis. Patients who were initially under home quarantine or initially admitted to different healthcare centres and discharged were also included in this study.

Data Collection

The data were collected manually from health records and entered into the database by retrospective review of medical records. An online electronic data capture system was developed using Google Forms to collect and evaluate the patients' demographic data (age, sex, and race), clinical characteristics (comorbidity and initial COVID-19 category), presenting complaints at admission, laboratory tests, final diagnosis, organ dysfunction, use of invasive ventilation, ICU admissions, length of hospitalisation and mortality. Additionally, the patients' identifiable data were pseudonymised for anonymity purposes.

The following are several definitions pertaining to this study:

i. COVID-19 vaccination was complete if the patient had taken a second dose before the admission or readmission and had lapsed more than 14 days. Those who had never taken, only taken one dose, or taken a second dose of COVID-19 vaccine less than 14 days before the admission or readmission were grouped in the incomplete vaccination status.
ii. Initial COVID-19 category was based on the patient's worst COVID-19 clinical stage during the first 20 days.
iii. The PE and OP were diagnosed based on the computed tomography (CT) scan of thorax reported by the radiologist.
iv. Diabetes emergency and hyperglycaemia related to glucocorticosteroids were defined as DKA or hyperosmolar hyperglycaemia state or random blood glucose of more than 11 mmol/l in patients on glucocorticosteroid treatment.
v. Bacterial pneumonia was diagnosed by a physician based on the clinical presentation compatible with acute respiratory infection and consistent radiological findings, with or without a positive microbiological test.
vi. Post-COVID condition: Clinical diagnosis by the attending physician based on the symptoms that developed after acute COVID-19 infection following microbiological recovery, with the exclusion of other diagnoses that could account for the symptoms.
vii. Sepsis was defined as the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3).
viii. AKI was defined as a 50% increase in the baseline creatinine level or a creatinine level greater than 177 umol/L (2 mg/dl) if the previous value was unknown.
ix. The term 'admission related to COVID-19' referred to any admission or readmission with a diagnosis that was either directly (e.g., OP, PE or post-COVID condition) or indirectly (e.g., hyperglycaemia, diabetic ketoacidosis (DKA) or hyperosmolar hyperglycaemic syndrome (HHS) due to steroids administered, or any bleeding due to anticoagulant received as part of COVID-19 treatment) caused by COVID-19. A diagnosis such as MI that could not be entirely attributed to COVID-19 was not considered linked.
x. Organ dysfunction was identified using the score equal to or more than 2 scores in the individual system in the Sequential Organ Failure Assessment (SOFA) score:
    a. Respiratory: PaO2/FiO2 <300 or SaO2/FiO2 ≤220
    b. Coagulation: Platelet $<100 \times 10^3/mm^3$
    c. Liver: Bilirubin is >34 umol/L (2.0mg/dL)
    d. Cardiovascular: use of any inotrope
    e. Central nervous system (CNS): Glasgow Coma Score (GCS) is ≤12
    f. Renal: Creatinine ≥177 umol/L (2.0mg/dL)

Data Analysis

In this study, quantitative variables were expressed as median [interquartile range] or mean [SD] while categorical variables were expressed as absolute frequencies and percentages. The chi-square test and Fisher's exact test were used to compare the categorical variables while Student's t-test and the Mann–Whitney U Test were used to compare the continuous variables. Odds ratios (ORs) and 95% confidence intervals (CIs) were also used where $p<0.05$ was considered statistically significant. All analyses were performed using IBM's SPSS Statistics for Windows version 26.0.

Ethical Aspects

This study was conducted in compliance with ethical principles outlined in the Declaration of Helsinki and the

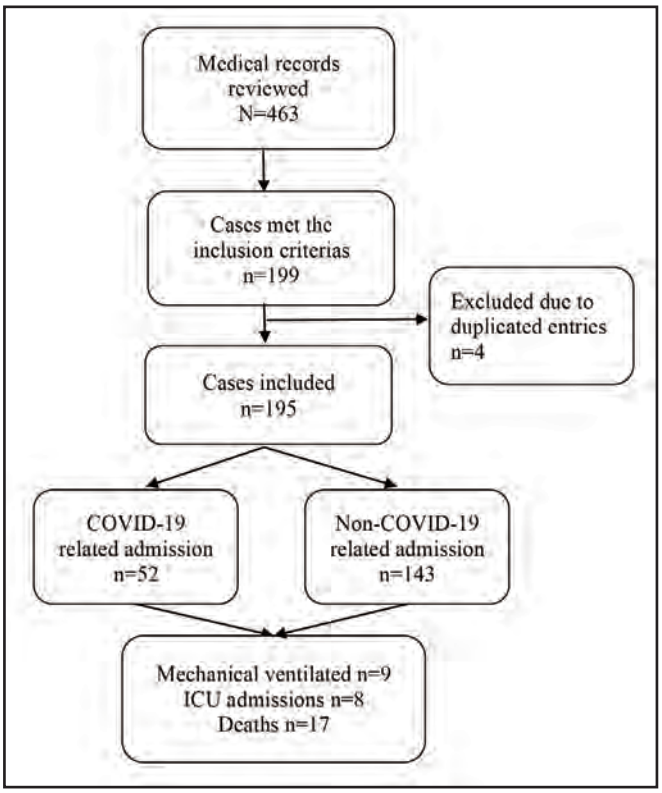

Fig. 1: Study cohort.

Malaysian Good Clinical Practice Guideline. The study had been approved by the Malaysia Medical Research and Ethics Committee (MREC).

RESULTS

From the 463 medical records reviewed, 199 cases met the inclusion criteria. After excluding four cases because of duplicated entries, a total of 195 cases were included in the analysis (Figure 1).

Baseline Characteristics

Table I shows the clinical characteristics of patients who were discharged alive compared to those who did not. The univariate analysis revealed that the surviving patients were younger (49.5 vs. 58.4 years, p=0.004). The majority of patients (153 [78.5%]) had at least one comorbidity, with a mean (SD) of 1.9 (1.4) comorbidities. Diabetes mellitus (DM) (48.3% vs. 82.4%, p=0.007) and chronic kidney disease (12.9% vs. 41.2%, p=0.007) were less prevalent among the survivors. The common symptoms at presentation were shortness of breath (91 [46.7%]), followed by chest pain (38 [19.5%]), fever (37 [19%]), and cough (36 [18.5%]). The symptoms that surviving cases were less likely to present were loss of appetite (29.4% vs. 5.1%, p=0.003) and dizziness (17.6% vs. 3.9%, p=0.045).

The surviving patients required lower baseline oxygen supplementation at admission (p=0.001); those not requiring any oxygen supplementation (65.7% vs. 29.4%), nasal prong (18.0% vs. 23.5%), face mask till high flow nasal cannulation (HFNC) (15.7% vs 35.3%), and mechanical ventilation (0.6% vs. 11.8%). They also had higher levels of admission haemoglobin (median 12.6g/dL [IQR, 10.7-14.3g/dL] vs 9.1 g/dL [IQR, 6.8-12.1g/dL]) and albumin (median 33.0g/L, [IQR, 28.0-37.0g/L] vs 21.0 g/L [IQR, 18.5-24.0g/L]), and lower levels of admission white blood cells (median 10.2 × 10^9/L [IQR, 8.3-13.4 × 10^9/L] vs 13.0 × 10^9/L [IQR, 9.6-17.8 × 10^9/L]), creatinine (median 81.2 µmol/L [IQR, 62.9-119.3µmol/L] vs 151.9 [IQR, 82.3-502.0µmol/L]), and C-reactive protein (CRP) (median 18.2 mg/L (IQR, 4.1-61.2mg/L) vs 135.0 mg/L [IQR, 52.1-202.7mg/L]). Moreover, those who survived were less likely to have MI, sepsis or acute kidney injury (AKI) as the diagnosis. Organ dysfunction was significantly lower (45 [25.3%] vs 16 [94.1%]) among the surviving patients compared to the deceased patients. Respiratory, haematology, cardiovascular (CVS), renal, and central nervous system (CNS) dysfunction was less common in survivors. Furthermore, the surviving cases were less likely to undergo invasive mechanical ventilation at admission (2.8% vs. 23.5%, p=0.004) than mortality cases.

The results further showed that approximately a quarter (52 [26.7%]) of readmission cases were related to previous COVID-19 infection but not associated with mortality. Out of 54 patients discharged with steroids during the initial COVID-19 admission, 19 (35.2%) were readmitted for bacterial pneumonia, thus showing a significant association between steroid use (19 [35.2%] vs. 18 [12.8%]; OR, 3.71; 95% CI, 1.76-7.82; p<0.001) with a diagnosis of bacterial pneumonia.

Outcome

Nine cases (4.6%) required mechanical ventilation during the admission, and eight cases (4.1%) were admitted into the ICU. The median LOS was 6 days (IQR 4-10 days) with a range of 0–64 days. Most cases (134 [68.7%]) did not have any organ dysfunction. As the primary endpoint, the majority of the patients (178 [91.3%]) were discharged alive, while the overall mortality was 17 (8.7%).

DM (8 [88.9%] vs. 92 [49.5%]) and higher initial COVID-19 category severity (categories 4 & 5) (8 [88.9%] vs. 88 [47.3%]) were more likely to have invasive mechanical ventilation (Table II). Higher oxygen requirements at admission were associated with invasive mechanical ventilation. Patients needing invasive mechanical ventilation were also associated with higher creatinine levels (median 169.0µmol/L [IQR, 82.1-367.6µmol/L] vs. 82.4µmol/L [IQR, 62.6-122.9µmol/L]), lower albumin (median 24.0g/L [IQR, 18.5-27.0g/L] vs. 33.0g/L [IQR, 26.0-37.0g/L]), and higher CRP (median 142.0 mg/L [IQR, 38.0-187.1mg/L] vs. 19.5mg/L [IQR, 4.2-67.7mg/L]). Sepsis was found to be significantly related to the need for invasive ventilation (3 [33.3%] vs. 11 [5.9%]). In terms of organ dysfunction, dysfunction in the respiratory (7 [77.8%] vs. 21 [11.3%]), cardiovascular (4 [44.4%] vs. 11 [5.9%]), renal (3 [33.3%] vs. 12 [6.5%]), and central nervous system (3 [33.3%] vs. 9 [4.8%]) required invasive ventilation more frequently.

ICU admission was noted to have an association with higher baseline oxygen requirements (Table III); no need for oxygen (0 vs. 65.2%]), nasal prong (0 vs. 19.3%), facemask till HFNC (100% vs. 13.9%) and mechanical ventilation (0 vs. 1.6%).

Table I: Baseline characteristics of patients admitted after 20 days of COVID-19 stratified by mortality

Characteristics	Patients, No. (%)			p-value
	Overall	Alive	Death	
Demographic characteristics				
Age, mean (SD), years	50.3 (15.5)	49.5 (15.7)	58.4 (10.2)	0.004**
Age >60 years	59 (20.3)	51 (28.7)	8 (47.1)	0.164
Male gender	114 (58.5)	104 (58.4)	10 (58.8)	0.975
Race				0.213
Malay	117 (60.0)	110 (61.8)	7 (41.2)	
Indian	44 (22.6)	39 (21.9)	5 (29.4)	
Chinese	26 (13.3)	21 (11.8)	5 (29.4)	
Others	2 (1.0)	2 (1.1)	0	
Foreigners	6 (3.1)	6 (3.4)	0	
Comorbidities				
Hypertension	111 (56.9)	99 (55.6)	12 (70.6)	0.234
DM	100 (51.3)	86 (48.3)	14 (82.4)	0.007**
Hyperlipidaemia	28 (14.4)	27 (15.2)	1 (5.9)	0.475
Ischaemic heart disease	33 (16.9)	30 (16.9)	3 (17.6)	1.000
CKD	30 (15.4)	23 (12.9)	7 (41.2)	0.007**
Heart failure	10 (5.1)	9 (5.1)	1 (5.9)	1.000
Cerebrovascular accident	10 (5.1)	9 (5.1)	1 (5.9)	1.000
Asthma	8 (4.1)	8 (4.5)	0	1.000
COPD	8 (4.1)	8 (4.5)	0	1.000
Cancer	5 (2.6)	4 (2.2)	1 (5.9)	1.000
Number of comorbidity				0.336
0	42 (21.5)	41 (23.0)	1 (5.9)	
1	39 (20.0)	35 (19.7)	4 (23.5)	
2	45 (23.1)	42 (23.6)	3 (17.6)	
3	44 (22.6)	38 (21.3)	6 (35.3)	
4 or more	25 (12.8)	22 (12.4)	3 (17.6)	
Smoking	46 (23.6)	45 (25.3)	1 (5.9)	0.080
Vaccination status				0.155
Incomplete	135 (69.2)	121 (68.0)	14 (82.4)	
Complete	59 (30.3)	57 (32.0)	2 (11.8)	
Initial COVID-19 category				0.182
Mild (Categories 1–3)	99 (50.8)	93 (52.2)	6 (35.3)	
Severe (Categories 4–5)	96 (49.2)	85 (47.8)	11 (64.7)	
Symptoms				
Shortness of breath	91 (46.7)	81 (45.5)	10 (58.8)	0.293
Chest pain	38 (19.5)	37 (20.8)	1 (5.9)	0.203
Fever	37 (19.0)	35 (19.7)	2 (11.8)	0.745
Cough	36 (18.5)	33 (18.5)	3 (17.6)	1.000
Reduced appetite	14 (7.2)	9 (5.1)	5 (29.4)	0.003**
Dizziness	10 (5.1)	7 (3.9)	3 (17.6)	0.045**
Day of illness at admission, mean (SD), d	42.7 (16.9)	42.8 (17.3)	41.2 (12.2)	0.612
Day 21-42	111 (56.9)	102 (57.3)	9 (52.9)	0.729
Day 43-90	84 (43.1)	76 (42.7)	8 (47.1)	
Baseline oxygen requirement				0.001**
Nil	122 (62.6)	117 (65.7)	5 (29.4)	
Nasal prong	36 (18.5)	32 (18.0)	4 (23.5)	
Face mask till HFNC	34 (17.4)	28 (15.7)	6 (35.3)	
Mechanical ventilation	3 (1.5)	1 (0.6)	2 (11.8)	
Baseline laboratory values, median (IQR)				
Haemoglobin, g/dL	12.4 (10.4-14.2)	12.6 (10.7-14.3)	9.1 (6.8-12.1)	0.001**
White blood cells, 10^9/L	10.4 (8.3-13.7)	10.2 (8.3-13.4)	13.0 (9.6-17.8)	0.032**
Platelet, 10^9/L	297 (224-370)	297 (230-374)	224 (182-317)	0.057
Creatinine, µmol/L	83.4 (63.3-127.0)	81.2 (62.9-119.3)	151.9 (82.3-502.0)	0.011**
Albumin, g/L	32.0 (26.0-37.0)	33.0 (28.0-37.0)	21.0 (18.5-24.0)	<0.001**
C-reactive protein, mg/L	21.3 (4.4-72.3)	18.2 (4.1-61.2)	135.0 (52.1-202.7)	<0.001**

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Table I: Baseline characteristics of patients admitted after 20 days of COVID-19 stratified by mortality

Characteristics	Patients, No. (%)			p-value
	Overall	Alive	Death	
Final diagnosis				
Bacterial pneumonia	45 (23.1)	40 (22.5)	5 (29.4)	0.549
OP	27 (13.8)	24 (13.5)	3 (17.6)	0.711
PE	32 (16.4)	27 (15.2)	5 (29.4)	0.164
MI	16 (8.2)	12 (6.7)	4 (23.5)	0.038**
Sepsis	14 (7.2)	6 (3.4)	8 (47.1)	<0.001**
Unstable angina	12 (6.2)	12 (6.7)	0	0.605
Heart failure	11 (5.6)	9 (5.1)	2 (11.8)	0.247
AKI	9 (4.6)	6 (3.4)	3 (17.6)	0.033**
COVID-19 relationship				0.399
Yes	52 (26.7)	46 (25.8)	6 (35.3)	
No	143 (73.3)	132 (74.2)	11 (64.7)	
Organ Dysfunction	61 (31.3)	45 (25.3)	16 (94.1)	<0.001**
Respiratory	28 (14.4)	21 (11.8)	7 (41.2)	0.004**
Haematology	16 (8.2)	10 (5.6)	6 (35.3)	0.001**
CVS	15 (7.7)	8 (4.5)	7 (41.2)	<0.001**
Renal	15 (7.7)	8 (4.5)	7 (41.2)	<0.001**
Liver	15 (7.7)	13 (7.3)	2 (11.8)	0.625
CNS	12 (6.2)	2 (1.1)	10 (58.8)	<0.001**
Gastrointestinal	3 (1.5)	2 (1.1)	1 (5.9)	0.241
Length of stay, median (IQR), d	6 (4-10)	6 (4-10)	8 (3-12)	0.877
Mechanical ventilation	9 (4.6)	5 (2.8)	4 (23.5)	0.004**
ICU admission	8 (4.1)	8 (4.5)	0	1.000

Abbreviations: SD, standard deviation; y, years; DM, diabetes mellitus; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; d, day; HFNC, high flow nasal cannulation; IQR, interquartile range; OP, organising pneumonia; PE, pulmonary embolism; MI, myocardial infarction; AKI, acute kidney injury; CVS, cardiovascular system; CNS, central nervous system; ICU, intensive care unit.

Table II: Univariable comparison of patients admitted into the hospital after 20 days of COVID-19 by need for invasive mechanical ventilation

Characteristics	Patients, n (%)		p-value
	No ventilation (n=186)	Ventilation (n=9)	
Demographic characteristics			
Age, mean (SD), years	50.3 (15.7)	50.6 (10.6)	0.957
Age >60 years	57 (30.6)	2 (22.2)	0.726
Male gender	108 (58.1)	6 (66.7)	0.738
Race			0.855
Malay	110 (59.1)	7 (77.8)	
Indian	43 (23.1)	1 (11.1)	
Chinese	25 (13.4)	1 (11.1)	
Others	2 (1.1)	0	
Foreigners	6 (3.2)	0	
Comorbidities			
Hypertension	105 (56.5)	6 (66.7)	0.735
DM	92 (49.5)	8 (88.9)	0.035**
Hyperlipidaemia	26 (14.0)	2 (22.2)	0.620
Ischaemic heart disease	31 (16.7)	2 (22.2)	0.650
CKD	27 (14.5)	3 (33.3)	0.145
Number of comorbidities			0.170
0	42 (22.6)	0	
1	38 (20.4)	1 (11.1)	
2	43 (23.1)	2 (22.2)	
3	41 (22.0)	3 (33.3)	
4 or more	22 (11.8)	3 (33.3)	
Smoking	45 (24.2)	1 (11.1)	0.688
Vaccination status			0.281
Incomplete	127 (68.6)	8 (88.9)	
Complete	58 (31.4)	1 (11.1)	
Initial COVID-19 category			0.017**
Mild (Categories 1-3)	98 (52.7)	1 (11.1)	
Severe (Category 4-5)	88 (47.3)	8 (88.9)	
Symptoms			
Shortness of breath	86 (46.2)	5 (55.6)	0.736
Chest pain	38 (20.4)	0	0.210
Fever	36 (19.4)	1 (11.1)	1.000
Cough	34 (18.3)	2 (22.2)	0.673
Reduced appetite	13 (7.0)	1 (11.1)	0.496
Dizziness	9 (4.8)	1 (11.1)	0.384

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Table II: Univariable comparison of patients admitted into the hospital after 20 days of COVID-19 by need for invasive mechanical ventilation

Characteristics	Patients, n (%)		p-value
	No ventilation (n=186)	Ventilation (n=9)	
Day of illness at admission, median (IQR), d	39.5 (28.0-56.0)	35.0 (25.0-40.5)	0.198
Baseline oxygen requirement			<0.001**
Nil	122 (65.6)	0	
Nasal prong	35 (18.8)	1 (11.1)	
Face mask till HFNC	29 (15.6)	5 (55.6)	
Mechanical ventilation	0	3 (33.3)	
Baseline laboratory values, median (IQR)			
Haemoglobin, g/dL	12.4 (10.5-14.2)	10.9 (8.2-13.5)	0.168
White Blood cell, 10^9/L	10.4 (8.3-13.9)	12.7 (8.6-13.8)	0.471
Platelet, 10^9/L	297 (224-371)	293 (200-367)	0.695
Creatinine, µmol/L	82.4 (62.6-122.9)	169.0 (82.1-367.6)	0.031**
Albumin, g/L	33.0 (26.0-37.0)	24.0 (18.5-27.0)	0.006**
C-reactive protein, mg/L	19.5 (4.2-67.7)	142.0 (38.0-187.1)	0.013**
Final diagnosis			
Bacterial pneumonia	43 (23.1)	2 (22.2)	1.000
OP	25 (13.4)	2 (22.2)	0.361
PE	29 (15.6)	3 (33.3)	0.168
MI	16 (8.6)	0	1.000
Sepsis	11 (5.9)	3 (33.3)	0.019**
Unstable angina	12 (6.5)	0	1.000
Heart failure	11 (5.9)	0	1.000
AKI	7 (3.8)	2 (22.2)	0.058
Organ dysfunction	52 (28.0)	9 (100.0)	<0.001**
Respiratory	21 (11.3)	7 (77.8)	<0.001**
Haematology	15 (8.1)	1 (11.1)	0.545
CVS	11 (5.9)	4 (44.4)	0.002**
Renal	12 (6.5)	3 (33.3)	0.024**
Liver	13 (7.0)	2 (22.2)	0.145
CNS	9 (4.8)	3 (33.3)	0.012**
Gastrointestinal	2 (1.1)	1 (11.1)	0.133
Length of stay, median (IQR), d	6 (4-10)	10 (6-23)	0.091

Abbreviations: SD, standard deviation; y, years; DM, diabetes mellitus; CKD, chronic kidney disease; COVID-19, coronavirus disease 2019; IQR, interquartile range; d, day; HFNC, high flow nasal cannulation; OP, organising pneumonia; PE, pulmonary embolism; MI, myocardial infarction; AKI, acute kidney injury; CVS, cardiovascualr system; CNS, central nervous system.

Respiratory dysfunction was associated with a higher incidence of ICU admission (87.5% vs. 11.2%). There was a difference in the length of stay between patients admitted into the ICU and those who did not (median, 15 days [IQR, 10-29 days] vs 6 days [IQR, 4-10 days]).

Multivariate analysis was not performed as there were under 20 cases on one side of the event for all outcomes of the study.

DISCUSSION

COVID-19 survivors are still at risk of further complications after the initial acute infectious period. This study provides insight into the clinical presentation and outcomes of COVID-19 survivors when they were admitted on day-21 to day-90 of their illness at a tertiary centre in Malaysia.

As expected, younger age is associated with better survival as older age predisposes patients to complications. Almost 80% of the cohort studied had a burden of at least one comorbidity; notably, a similar picture was seen in multicentre retrospective research done in the United States by Verna et al.[18] Our study found that diabetes is an independent risk factor for both mortality and the need for invasive mechanical ventilation in the univariate analysis, which is in line with other studies.[19-26] Diabetes is commonly associated with a pro-inflammatory state and may contribute to the risk of a more severe course of COVID-19, which may eventually lead to one's demise. However, in our study, DM was not associated with ICU admission as demonstrated in most studies. CKD also showed proportionately higher mortality in COVID-19 survivors.[27] Furthermore, the increased production but decreased clearance of pro-inflammatory cytokines contribute to high mortality in these patients. This suggests that patients with DM or CKD who were hospitalised for COVID-19 might need extra monitoring post-discharge. Initial COVID-19 severity was independently associated with the need for invasive mechanical ventilation. As the initial COVID-19 severity category was based on oxygen requirement and lung involvement, it was not surprising that it was associated with invasive mechanical ventilation for readmitted COVID-19 survivors. Therefore, more severe COVID-19 survivors may need longer inpatient pulmonary rehabilitation or a shorter interval for outpatient review post-discharge. Vaccination against COVID-19 did not confer extra protection on COVID-19 survivors that were readmitted. It was worth noting that at the time of commencement and during the length of the study, the recommended vaccination doses to be considered complete vaccination were two doses, each being 6 months apart.

Table III: Univariable comparison of patients admitted into the hospital after 20 days of COVID-19 by need for ICU admission

Characteristics	Patients, n (%)		p-value
	No ICU admission (n=187)	ICU admission (n=8)	
Demographic characteristics			
Age, mean (SD), y	50.6 (15.4)	44.0 (18.2)	0.243
Age>60y	57 (30.5)	2 (25.0)	1.000
Male gender	107 (57.2)	7 (87.5)	0.143
Race			0.762
Malay	113 (60.4)	4 (50.0)	
Indian	41 (21.9)	3 (37.5)	
Chinese	25 (13.4)	1 (12.5)	
Others	2 (1.1)	0	
Foreigners	6 (3.2)	0	
Comorbidities			
Hypertension	106 (56.7)	5 (62.5)	1.000
DM	94 (50.3)	6 (75.0)	0.280
Hyperlipidaemia	26 (13.9)	2 (25.0)	0.322
Ischaemic heart disease	31 (16.6)	2 (25.0)	0.625
CKD	29 (15.5)	1 (12.5)	1.000
Number of comorbidities			0.344
0	41 (21.9)	1 (12.5)	
1	39 (20.9)	0	
2	43 (23.0)	2 (25.0)	
3	40 (21.4)	4 (50.0)	
4 or more	24 (12.8)	1 (12.5)	
Smoking	43 (23.0)	3 (37.5)	0.395
Vaccination status			1.000
Incomplete	129 (69.4)	6 (75.0)	
Complete	57 (30.6)	2 (25.0)	
Initial COVID-19 category			0.493
Mild (Categories 1-3)	96 (51.3)	3 (37.5)	
Severe (Categories 4-5)	91 (48.7)	5 (62.5)	
Symptoms			
Shortness of breath	85 (45.5)	6 (75.0)	0.149
Chest pain	37 (19.8)	1 (12.5)	1.000
Fever	36 (19.3)	1 (12.5)	1.000
Cough	35 (18.7)	1 (12.5)	1.000
Reduced appetite	14 (7.5)	0	1.000
Dizziness	10 (5.3)	0	1.000
Day of illness at admission, median (IQR), d	39.0 (28.0-55.0)	38.5 (25.3-69.5)	0.774
Baseline oxygen requirement			<0.001**
Nil	122 (65.2)	0	
Nasal prong	36 (19.3)	0	
Face mask till HFNC	26 (13.9)	8 (100.0)	
Mechanical ventilation	3 (1.6)	0	
Baseline laboratory values, median (IQR)			
Haemoglobin, g/dL	12.4 (10.3-14.1)	13.5 (10.8-15.4)	0.489
White Blood cell, 10^9/L	10.4 (8.3-13.4)	13.8 (8.9-17.0)	0.234
Platelet, 10^9/L	298 (226-371)	236 (202-284)	0.121
Creatinine, µmol/L	81.9 (62.7-124.5)	115.8 (89.0-432.5)	0.071
Albumin, g/L	33.0 (26.0-37.0)	30.5 (19.0-41.3)	0.780
C-reactive protein, mg/L	20.3 (4.4-68.4)	87.5 (12.6-137.0)	0.206
Final diagnosis			
Bacterial pneumonia	44 (23.5)	1 (12.5)	0.684
OP	25 (13.4)	2 (25.0)	0.306
PE	30 (16.0)	2 (25.0)	0.620
MI	16 (8.6)	0	1.000
Sepsis	14 (7.5)	0	1.000
Unstable angina	12 (6.4)	0	1.000
Heart failure	11 (5.9)	0	1.000
AKI	8 (4.3)	1 (12.5)	0.320
Organ dysfunction	53 (28.3)	8 (100.0)	<0.001**
Respiratory	21 (11.2)	7 (87.5)	<0.001**
Haematology	15 (8.0)	1 (12.5)	0.502
CVS	13 (7.0)	2 (25.0)	0.118
Renal	15 (8.0)	0	1.000
Liver	14 (7.5)	1 (12.5)	0.479
CNS	12 (6.4)	0	1.000
Gastrointestinal	3 (1.6)	0	1.000
Length of stay, median (IQR), d	6.0 (4.0-10.0)	15 (10-29)	0.001**

Abbreviations: SD, standard deviation; y, years; DM, diabetes mellitus; CKD, chronic kidney disease; COVID-19, coronavirus disease 2019; IQR, interquartile range; d, day; HFNC, high flow nasal cannulation; OP, organising pneumonia; PE, pulmonary embolism; MI, myocardial infarction; AKI, acute kidney injury; CVS, cardiovascular; CNS, central nervous system.

Complete vaccination was shown to confer protection in the multivariate analyses in Taib et al.,[28] however, the multivariate analysis was unable to proceed in our study due to low numbers on one side of the event, i.e., mortality.

Shortness of breath was the highest reported symptom at presentation (46.7%) in our study, which was comparable to previous literature that showed 50% of patients reported respiratory distress as a presenting complaint.[29] This study demonstrated that the presenting complaint of loss of appetite was one of the main symptoms associated with mortality; further analysis showed that this was especially significant in the elderly cohort, which was consistent as they were generally presented with atypical symptoms rather than typical infectious or respiratory symptoms. Dizziness was another significant symptom among non-survivors in our study, although the number was small yet still statistically significant. However, further analysis showed that the symptom was not associated with the elderly population or hypotension. Those readmitted early (between days 21 and 42 of illness) were not shown to be associated with mortality. Nonetheless, this group of early readmitted patients was more likely to have a final diagnosis related to COVID-19 illness compared to those who were readmitted later (between days 43 and 90 of illness). This is in line with past research, which reported that COVID-19 survivors who were readmitted within 30 days of discharge mostly had the condition directly associated with COVID-19.[15]

Composite endpoints of mortality, use of invasive ventilation, and mortality were associated with those with higher baseline oxygen requirements. Baseline oxygen requirement and respiratory dysfunction were the only factors associated with ICU admission, subsequently explaining the fact that the primary criterion for ICU admission was respiratory dysfunction in that overwhelming period. Past studies showed that there is a high proportion of COVID-19 survivors with diffusing capacity for carbon monoxide (DLCO) impairment and lung injury 3 months after discharge [30] and these symptoms remain highly prevalent even 1 year after discharge.[31] The laboratory findings of higher creatinine, higher CRP, and lower albumin were found to be related to both mortality and the use of invasive mechanical ventilation. Furthermore, elevated CRP and creatinine levels as well as higher IL-6, tumour necrosis factor-α (TNF-α) and ferritin levels were found in non-survivors as compared to the survivors of COVID-19 infection.[32] Increased production and decreased clearance of pro-inflammatory cytokines by the kidney also contribute to high mortality in these patients. Hypoalbuminaemia had long been associated with poor outcomes in clinical settings.[16] As an 'inverse acute phase reactant', albumin may serve as a protective factor against cytokine storms as a result of COVID-19 pathologic sequelae. This study found that the end point of mortality was associated with the final diagnosis of sepsis, MI, or AKI. COVID-19 may cause sepsis similar to bacterial infections[33], may potentially be associated with myocardial injury leading to a type II MI,[16] linked to coronary thrombosis,[7-8] and cause eGFR reduction;[27] however, we cannot conclude a direct causal relationship. Furthermore, the cardiovascular background risks were high in our cohort, i.e., hypertension (56.9%), DM (51.3%) and ischaemic heart disease (16.9%). There was an increased risk of secondary bacterial infection in patients treated with steroids for the initial COVID-19 phase. The finding is consistent with Obata et al. who reported a higher rate of bacterial and fungal infections associated with steroid use among patients with COVID-19 infection.[34] More than a quarter of the readmitted cases were discharged with steroids, while more than one-third of these cases had bacterial pneumonia – both recorded a statistically significant association. Nonetheless, the diagnosis of bacterial pneumonia captured in our study was based on suggestive clinical and imaging features that did not necessarily yield a positive culture.

Our findings further indicated that respiratory, CVS, renal, and CNS dysfunctions were associated with mortality and the need for invasive mechanical ventilation. Haematology dysfunction was also associated with mortality. The association between respiratory, CVS, and renal dysfunction with invasive mechanical ventilation can happen in either direction. Sepsis was most likely to establish the link between haematological dysfunction and mortality. The effects of COVID-19 effects on the respiratory and renal systems had been discussed earlier, with previous research suggesting cardiovascular reactivity as a post-acute sequela of COVID-19 infection with a pronounced incidence of postural hypotension,[35] which could be the mechanism of the CVS dysfunction. Although COVID-19 also causes neurological complications, including depressed levels of consciousness, the neurological symptoms of post-acute COVID-19 are usually mild. Furthermore, the CNS dysfunction observed in our cohort could likely be influenced by numerous other factors not related to COVID-19; however, this was not further examined due to its complexity. The overall mortality rate from this study stood at 8.7%, which was comparatively lower than other studies.[15-16,18] This could owe to the possibility that the most fragile patients did not survive during the index admission.

STRENGTHS AND LIMITATIONS

This study was based on a local population and hence the characteristics compiled may stand as the predictors for local Malaysian populations. The identification of predictors and patterns of readmission will allow for the development of targeted interventions for hospitalised COVID-19 patients in their index admission as well as readmission.

There were several limitations in this study. First, we did not have the benefit of readmission rate data as the number of admission upon initial diagnosis of COVID-19 illness is unavailable. The lack of patient registry in a well-developed computerised system further made this data very difficult to compute. Second, this was a single-centre study; thus, extrapolation of the results should be done with caution. Third, the small sample size prevented multivariable analysis.

CONCLUSION

This study showed that approximately a quarter of patients were readmitted into the hospital due to direct COVID-19 complications. Age, DM and CKD were the baseline characteristics independently associated with mortality for patients who were readmitted between 20 and 90 days after

the initial COVID illness. Whereas, DM and the initial highest COVID-19 category were independently associated with invasive mechanical ventilation for this cohort of patients. Baseline oxygen requirements at admission were independently associated with all three outcomes: mortality, invasive mechanical ventilation and ICU admission. Furthermore, the laboratory findings of low haemoglobin, low albumin, high white blood cells, high creatinine, and high CRP; final diagnosis of MI, sepsis and AKI; as well as organ dysfunction of respiratory, haematology, CVS, renal and CNS were associated with poorer outcomes.

Currently, there is no established guideline on the guidance and prioritisation of care for patients with morbidity after recovering from initial discharge or home quarantine of COVID-19. Further research is needed to analyse the effect of COVID-19 on morbidity and mortality within the first 90 days of illness and beyond in local settings and to establish a risk model for patients returning to a hospital to predict their risk of post-COVID-19 complications.

ACKNOWLEDGEMENTS

All authors contributed to the conceptualisation, data collection, interpretation, analysis and writing of this paper. We would like to thank the Director General of Health Malaysia for the permission to publish this paper. Our deepest appreciation to our Head of Internal Medicine Department, Dr Eashwary Mageswaren for the opportunity to conduct this study. We also extend our gratitude to Dr Vijayan A/L P. Panirselvam for his ideas and guidance as well as to the HTAR medical records office and the HTAR CRC team for their assistance in tracing the medical records and data analysis respectively.

DECLARATION

This study has no conflict of interest and is not funded by any organisation.

ETHICAL APPROVAL

This study was registered with the National Medical Research Register (NMRR) and approved by the Medical Research and Ethics Committee (MREC) and the Ministry of Health (MOH). MREC Approval Letter 21-02279-AUO (1) dated 15 December 2021. NMRR ID 21-02279-AUO (IIR)

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