Identification of warning signs in Malaysian patients having COVID-19 infection who progress to severe form of the illness

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ABSTRACT

Introduction: Coronavirus disease 2019 (COVID-19) is an infectious disease caused by a novel coronavirus, now widely known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has caused 3 major pandemic waves in Malaysia. We aimed to identify the warning signs as indicators that predict the progression of disease.

Materials and Methods: This is a retrospective cohort study of adult patients more than 12 years of age presenting with laboratory-confirmed COVID-19 admitted in three separate hospitals around the country.

Results: Of the 228 patients initially admitted with mild illness, 47 had progressed requiring oxygen. The median time from admission to deterioration was 3 days (IQR 2 - 5). Age more than ≥50years old (median age = 42.5, IQR = 28.8 – 57.0), higher temperature (mean = 37.3, IQR 36.8 - 38.0), MEWS score >3 (9, 19.1%), Neutrophil-to-lymphocyte ratio (NLR) >3.13 , (18, 38.3%) C-reactive protein (CRP) >5. (12, 27.3%), multiple zonal involvement on the chest radiography on admission (2, IQR 1-3) were more common in the deteriorated group on admission. On multivariate analysis, multiple comorbidities (HR = 7.40, 95 percent CI 2.58–21.2, p0.001), presence of persistent fever (HR = 2.88, 95 percent CI 1.15 – 7.2, p = 0.024), MEWS scoring >3 (HR of 6.72 ;95 percent CI 2.81–16.0, p0.001) were associated with progression to severe illness.

Conclusion: In our cohort, we found that several factors were associated with the severity of COVID19. Early detection of these factors could correctly identify patients who need more intensive monitoring, and early referral for ICU care.

KEYWORDS:
COVID-19, Severe pneumonia, Risk factors, Progression

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the novel coronavirus, which is now widely known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In January 2020, Malaysia had the first family cluster of COVID-19 among travellers arriving from Wuhan, China. Following that, the initial cluster of cases were among Malaysians or foreigners who had strong epidemiological links from affected countries. Reported cases and person-to-person transmission within the community remained relatively low, until large clusters of cases began to emerge in March, with the largest cluster linked to a mass religious gathering. Consequently, a spike in local cases and exportation of cases to neighbouring countries occurred. Since then, Malaysia has seen three waves with the largest being the third wave, and to date, it has recorded 2,699240 cases with a total of 30,956 deaths and a fatality rate of 1.1%.

The search for an antiviral began very early on in the pandemic with studies looking at repurposing drugs with antiviral activity. Evidence has not been very favourable so far, and most of these drugs have yet to be approved for use outside of a clinical trial. WHO Solidarity Trial found that the repurposed drugs had little or no effect on hospitalised patients in terms of reducing overall mortality, initiating ventilation, or reducing hospital stay. Remdesivir, however, has been licenced for use in the European Union for the treatment of COVID-19 in hospitalised patients who require supplementary oxygen following the NIH clinical trial results. In recent times, favourable trial results of novel antiviral agents by two leading pharmaceutical companies have led to a race in procuring these medications by government agencies in the hope to reduce hospitalisation and intensive care unit (ICU) care.

Vaccination efforts offer the best evidence in terms of prevention, reducing hospitalisations and preventing severe disease. However, as primary and booster vaccination efforts

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are being rolled out worldwide, countries are seeing a rapid rise in cases being reported with increasing hospitalisation owing to lack of adherence to preventive measures, such as social distancing and wearing of masks in public, antivaccine drive, and the emergence of variants of concern. Although a large percentage of patients present with mild illness, the risk factor for mortality and severe illnesses is markedly increased in patients greater than 50 years of age and who have more than one non-communicable disease. This was also seen in other studies where older age, smoking, and underlying comorbidities, such as diabetes mellitus, hypertension, and cardiac/lung diseases, were reported as risk factors for severe illness.

Early recognition of patients who are at high risk of developing more severe disease is still very relevant in times of an overwhelmed medical system. Due to the high mortality and morbidity rate, clinicians tend to be very cautious in their management of even mildly symptomatic patients. The lack of access to available antivirals would prompt physicians to overtreat patients in the high-risk groups, even if they present with mild symptoms and show no signs of deterioration leading to overuse of Personal Protective Equipment's (PPE) and exposing patients to drug side effects. The opposite is also true, that these warning signs can guide us to identify the patients who need more intensive monitoring as well as to facilitate early referral for ICU care.

At present, there is an urgent need for us to recognise the warning signs as indicators that predict the progression of disease so that we could correctly identify patients who need more intensive monitoring and early referral for ICU care. The fundamental goal of this research is to reduce mortality and morbidity, provide adequate care, and improve the efficiency of the healthcare system.

MATERIALS AND METHODS

Patient Selection

This is a retrospective cohort study of patients greater than 18 years of age presenting with laboratory-confirmed COVID-19 admitted in three separate hospitals in Malaysia that have been designated to be COVID-19 treating centres – Hospital Sungai Buloh, Selangor; Hospital Lahad Datu, Sabah; and Hospital Melaka, Melaka. The study included patients who were admitted with confirmed COVID-19 illness and did not require oxygen at the time of admission between January 25 and April 30, 2020. Patients requiring oxygen on admission were excluded from the study. Clinical diagnosis and classifications were made according to the Malaysian Management Guidelines for COVID-19, version 5.0. According to the guidelines, COVID-19 patients are classified into five categories: (1) asymptomatic, (2) symptomatic with no pneumonia, (3) pneumonia but not requiring oxygen, (4) pneumonia requiring oxygen, and (5) critically ill patients requiring non-invasive or invasive ventilation or in shock. Laboratory confirmation was based on the presence of SARS-CoV-2 in respiratory specimens using real-time reverse-transcriptase polymerase chain reaction (RT-PCR) assay by the hospital laboratory.

Patients were followed till they reached the outcome of deterioration: Clinically deteriorating to categories 4 and 5 is defined as development of hypoxia with clinical (respiratory rate >20 breath/min and SpO2< 95% or PaO2/FiO2 ratio <300 mmHg) and radiological evidence of worsening pneumonia. For patients who did not deteriorate and remained as mild disease, parameters were collected till day 10 of illness. Patients were followed up till day 10 of illness based on evidence from literature review that suggested the median duration from illness onset to dyspnoea was 7 to 8 days and the current national and WHO guidelines that advocate discharge from COVID-19 care pathway at day 10 of illness., Upon admission, all the patients received standard monitoring and treatment according to the Management Guidelines for COVID-19, version 5.0.

Data Collection

A dedicated team of doctors extracted patient data from the COVID-19 RedCap database (Research Electronic Data Capture) of the three major hospitals. Missing information was traced from hospital electronic records and the patient's manual records. A standardised data collection sheet was used to extract data from RedCap/ manual records, and later, the information was transferred to an excel sheet. Baseline demographic data, clinical symptoms, chronic comorbidities, and vital signs were extracted from the available records using a standardised data collection form. Modified Early Warning Signs (MEWS) scoring was retrieved from the manual notes, which was calculated in real time by skilled nurses during patient review. During the data collection process, this was confirmed by a physician or a trained medical officer to double-check the previously entered numbers. All laboratory and clinical variables were collected at admission, 48 hours before outcome, 24 hours before outcome, and on the day of outcome. Because various patients had a different number of inputs, the poorest vital sign over the previous 24 hours was chosen for analysis.

The chest radiographs were extracted from the hospital picture archiving and communication system (PACS), and reporting was done by a radiologist (with more than nine years of experience), using Digital Imaging and Communications in Medicine (DICOM) images, viewed with a medical-grade monitor system. The findings include the presence or absence of ground-glass opacities, consolidations, reticulations, and/or pleural effusion, as well as the number of total zones involved.

Definitions

Sepsis and septic shock were defined according to the 2016 Third International Consensus Definition for Sepsis and Septic Shock. Fever was defined as an axillary temperature of at least 37.3 degrees Celsius. A lower fever threshold was chosen in order to accommodate for fever threshold in older people as well as to account for the practice of using forehead scanners in wards for detecting temperature.

Modified Early Warning Score (MEWS) is a tool that can be used to detect patients who are clinically deteriorating. The Principle of MEWS is based on the subtle changes in several parameters (Blood Pressure/Pulse Rate/Glasgow Coma Scale/Respiratory Rate) as well as large changes within a

Table I: Clinical presentations of patients with COVID-19 on admission

	Total (n=228)	Stable (n=181)	Deteriorated (n=47)	P-value
Age	42.50 (28.75, 57.00)	38.00 (26.00, 54.00)	57.00 (44.50, 62.50)	< 0.001***
Age ≥ 50	85 (37.3%)	55 (30.4%)	30 (63.8%)	< 0.001***
Male	143 (62.7%)	114 (63.0%)	29 (61.7%)	0.867
Active smoker	24 (11.7%)/23	22 (13.2%)/14	2 (5.3%)/9	0.263
Comorbidity				0.001**
No comorbidity	130 (57.0%)	114 (63.0%)	16 (34.0%)	
1 comorbidity	49 (21.5%)	35 (19.3%)	14 (29.8%)	
≥2 comorbidities	49 (21.5%)	32 (17.7%)	17 (36.2%)	
Days of illness on admission	5.00 (3.00, 8.00)/1	5.00 (3.00, 7.00)/1	6.00 (4.00, 8.00)/0	0.062
Days of illness at outcome	11.00 (10.00, 11.00)/1	11.00 (10.00, 11.00)/1	10.00 (8.00, 12.00)/0	0.036
Days of admission at outcome	5.00 (3.00, 7.00)/1	5.000 (3.000, 8.000)/1	3.00 (2.00, 5.00)/0	< 0.001***
Symptom				
Fever	117 (51.3%)	82 (45.3%)	35 (74.5%)	< 0.001***
Cough	152 (66.7%)	116 (64.1%)	36 (76.6%)	0.120
Sore throat	64 (28.1%)	52 (28.7%)	12 (25.5%)	0.719
Fatigue	19 (8.3%)	12 (6.6%)	7 (14.9%)	0.079
Shortness of breath	21 (9.2%)	12 (6.6%)	9 (19.1%)	0.019*
Haemoptysis	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Anorexia	2 (0.9%)	1 (0.6%)	1 (2.1%)	0.371
Headache	12 (5.3%)	9 (5.0%)	3 (6.4%)	0.716
Diarrhoea	25 (11.0%)	17 (9.4%)	8 (17.0%)	0.186
Nausea	7 (3.1%)	7 (3.9%)	0 (0.0%)	0.350
Vomiting	9 (3.9%)	6 (3.3%)	3 (6.4%)	0.396
Nasal congestion	24 (10.5%)	21 (11.6%)	3 (6.4%)	0.426
Myalgia	17 (7.5%)	8 (4.4%)	9 (19.1%)	0.002**
Signs				
Temperature (°C),	36.80 (36.50, 37.00)	36.80 (36.50, 37.00)	37.30 (36.80, 38.00)	< 0.001***
Respiratory rate (breath per minute)	20.00 (18.00, 20.00)	20.00 (18.00, 20.00)	20.00 (18.00, 20.00)	0.391
MEWS score	0.00 (0.00, 1.00)	0.000 (0.00, 1.00)	1.00 (0.00, 2.00)	< 0.001***
MEWS >3	16 (7.0%)/1	7 (3.9%)/1	9 (19.1%)/0	0.001**
Investigation				
NLR >3.13 cells/μL	50 (22.2%)/3	32 (18.0%)/3	18 (38.3%)/0	0.005**
CRP >5 mg/dL	21 (11.9%)/51	9 (6.8%)/48	12 (27.3%)/3	< 0.001***
Chest radiography: total zone involvement	1.00 (0.00, 2.00)/51	0.00 (0.00, 1.00)/42	2.00 (1.00, 3.00)/9	< 0.001***

* P-value < 0.05
** P-value < 0.01
*** P-value < 0.001
Mann–Whitney U test for all continuous data [median, (Q1, Q2)]; Fisher's exact test for all categorical data [count (%)]

Table II: COVID-19 patient clinical parameters at 48 hours prior to severe illness outcome

	Total (n=228)	Stable† (n=181)	Deteriorated (n=47)	P-value
Signs				
Temperature (°C)	36.90 (36.60, 37.00)/57	36.80 (36.50, 37.00)/38	37.25 (37.00, 37.85)/19	<0.001***
Respiratory rate (breath per minute)	20.00 (18.00, 20.00)/55	20.00 (18.00, 20.00)/36	20.00 (18.75, 20.00)/19	0.462
Investigation				
NLR >3.13 cells/μL	17 (25.4%)/161	11 (22.4%)/132	6 (33.3%)/29	0.364
CRP >5 mg/dL	11 (19.6%)/172	6 (14.6%)/140	5 (33.3%)/32	0.142
Chest radiography: total zone involvement‡	1.00 (0.00, 2.00)/200	0.500 (0.00, 2.00)/161	2.00 (1.00, 3.00)/39	0.035*
MEWS score‡	1.00 (0.00, 2.00)/200	0.50 (0.00, 2.00)/161	2.00 (1.00, 3.00)/39	0.035

* P-value < 0.05
*** P-value < 0.001
†Day 10 of disease as outcome
‡Missing data more than 85%
Mann–Whitney U test for all continuous data [median, (Q1, Q2)]; Fisher's exact test for all categorical data [count (%)]

single variable during clinical deterioration. An increasing score or a score of more than three is associated with an increased likelihood of death or ICU care.

Statistical Analysis

Patients aged above 18 years and presented with mild illness (less than stage 4) on presentation in the designated COVID-19 treating hospitals were included and de-identified for this analysis. No imputation was done on missing data, and the numbers were reported after slash in the table. Continuous variables were reported as median with interquartile range, and categorical variables were reported as frequency and percentages. Mann–Whitney U test and Fisher's exact test were used respectively to compare differences between the

Table III: COVID-19 patient clinical parameters at 24 hours prior to severe illness outcome

	Total (n=228)	Stable† (n=181)	Deteriorated (n=47)	P-value
Signs				
Temperature (°C)	36.90 (36.60, 37.00)/110	36.80 (36.50, 37.00)/95	37.15 (36.98, 37.88)/15	<0.001***
Respiratory rate (breath per minute)	20.00 (18.00, 20.00)/28	19.00 (18.00, 20.00)/14	20.00 (19.00, 20.00)/14	<0.001***
Investigation				
NLR >3.13 cells/μL	23 (29.9%)/151	15 (25.0%)/121	8 (47.1%)/30	0.131
CRP >5 mg/dL	13 (19.1%)/160	7 (13.5%)/129	6 (37.5%)/31	0.063
Chest radiography: total zone involvement‡	1.00 (0.00, 3.00)/199	1.00 (0.00, 1.25)/161	3.00 (2.00, 4.00)/38	0.002**

** Pvalue <0.01
*** P-value < 0.001
†Day 10 of disease as outcome
‡Missing data more than 85%
Mann–Whitney U test for all continuous data [median, (Q1, Q2)]; Fisher's exact test for all categorical data [count (%)]

Table IV: COVID-19 patient clinical parameters on the day of developing severe illness outcome

	Total (n=228)	Stable† (n=181)	Deteriorated (n=47)	P-value
Signs				
Temperature (°C)	36.90 (36.70, 37.00)/108	36.80 (36.60, 37.00)/95	37.10 (36.83, 38.08)/13	<0.001***
Respiratory rate (breath per minute)	20.00 (18.00, 20.00)/8	19.00 (18.00, 20.00)/8	22.00 (20.00, 26.00)/0	<0.001***
Investigation				
NLR >3.13 cells/μL	39 (34.5%)/115	19 (27.1%)/111	20 (46.5%)/4	0.035
CRP >5 mg/dL	26 (24.1%)/120	7 (10.9%)/117	19 (43.2%)/3	<0.001***
Chest radiography: total zone involvement‡	1.50 (0.00, 3.00)/166	0.00 (0.00, 1.00)/155	2.00 (1.00, 4.00)/11	<0.001***
MEWS score	0.00 (0.00, 2.00)/8	0.00 (0.00, 1.00)/8	3.00 (2.00, 5.00)/0	
MEWS >3	38 (16.7%)/1	4 (2.2%)/0	34 (72.3%)/1	<0.001***

*** P-value < 0.001
†Day 10 of disease as outcome
‡Missing data more than 85%
Mann–Whitney U test for all continuous data [median, (Q1, Q2)]; Fisher's exact test for all categorical data [count (%)]

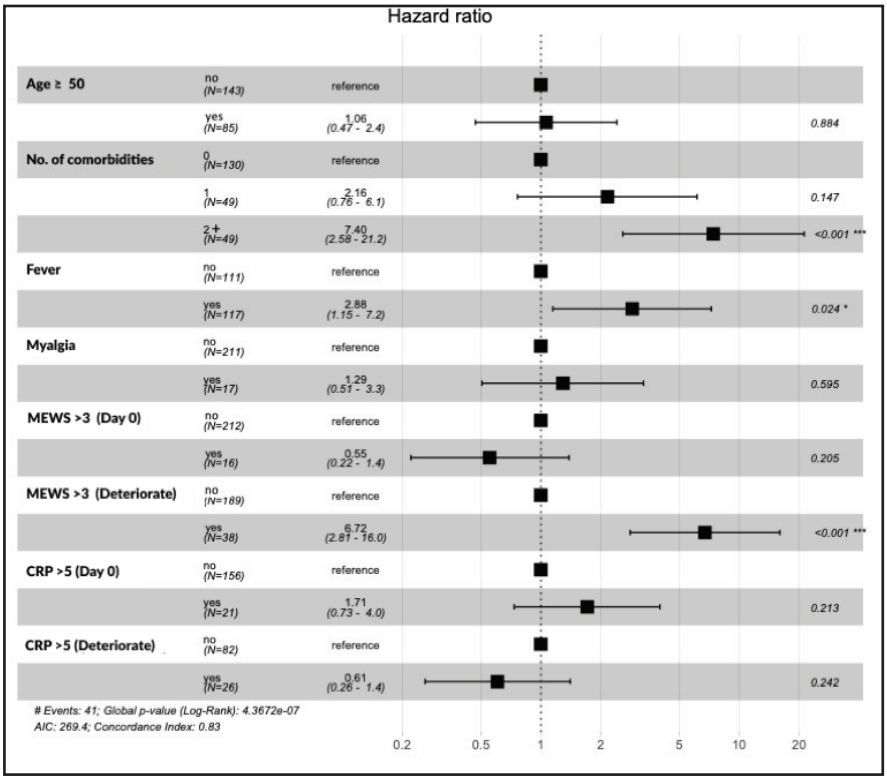

Fig. 1: Forest plot of the hazard ratio for the predictors associated with deterioration of COVID-19 patients.

stable and deteriorated group. Time specified data point analysed at 48 hours, 24 hours before and on the day of deterioration, or day 10 of illness for stable patients. The Kaplan–Meier survival curves were plotted with the purpose of comparing variables, which can be found at Appendix 1. Cox regression model was done for hazard ratio of different risk factors. The two-sided statistical significance level, P-value, was set at 0.05 for all analyses in this study. All were performed using R version 3.6.3.

RESULTS

Table I shows that out of the 228 patients initially admitted with mild illness, 47 had progressed into severe pneumonia requiring oxygen. Overall, 37.3% of patients was ≥50 years old (median age = 42.5, IQR = 28.8–57.0) with more than half of deteriorated patients were ≥50 years old. The median day of illness at time of admission was six days (IQR= 4–8), whereas the median day at deterioration was at day 10 of illness (IQR = 8–12). The median time from admission to deterioration was three days (IQR= 2–5).

For the deteriorated group, 66% had ≥1 comorbidities compared to only 37% in the stable group. On admission, the majority of the deteriorated group ($p < 0.001$) had a fever. Symptoms such as shortness of breath and myalgia were also recorded with significant differences between the two groups, with 19% of deteriorating patients exhibiting these symptoms.

Higher temperature (37.3, IQR = 36.8–38.0), MEWS score >3 (9, 19.1%), neutrophil-to-lymphocyte ratio (NLR) >3.13 (18, 38.3%), C-reactive protein (CRP) >5mg/dL (12, 27.3%), and multiple zone involvement on the chest radiography on admission (2, IQR= 1–3) were significantly different between the two groups.

In the days leading up to outcome, the deteriorated group had higher temperatures and higher respiratory rate, with more than one zone of lung field involvement, as indicated in Tables II–IV. When compared the groups, CRP >5 was significantly different at 24 hours and on the day of deterioration.

As evident from Figure 1, ≥2 comorbidities, presence of fever on admission, and MEWS score >3 (HR of 6.72 ,95% CI: 2.81–16.0, $p < 0.001$). were associated with patients' deterioration. Multiple comorbidities (HR = 7.40, 95%: CI 2.58–21.2, $p < 0.001$) and the presence of persistent fever was associated with progression to severe COVID-19 (HR = 2.88, 95% CI: 1.15–7.2, $p = 0.024$).

DISCUSSION

The COVID-19 pandemic in Malaysia is currently seeing its largest yet challenging wave of infections., The pandemic has imposed a strain in the major designated hospitals and led to the opening of low-risk treatment centres especially in areas of high surges such as cities and the rural areas of the east coast. Front liners and healthcare workers from various levels of training and background have been mobilised to assist in the clinical care and management of these patients in the low-risk treatment centres, while the sicker patients were hospitalised in the designated hospitals for more intensive monitoring. Sim et al. reported that up to 92% were admitted with mild disease and the overall mortality rates in Malaysia were low (1.2%), which is somewhat similar to other reports. However, in low-risk treatment centres where monitoring may not be as intensive as the hospital settings, identification of warning signs and patients who are at higher risk of further deterioration will improve the efficiency of the health system.

We identified patients greater than 50 years old and those with two or more comorbidities as having a higher risk of deterioration. A previous nationwide report[15] showed that having a history of chronic kidney disease and chronic pulmonary disease had the highest risk of developing severe disease. A closer look at the analysis indicates that patients with most chronic conditions, including obesity, were at risk of severe disease. Globally, various reports highlighted a clear and strong age-related gradient of 50–60 years of age and the presence of comorbidities as risk factors of mortality associated with COVID-19. It is not fully known why the presence of advanced age and comorbidities are important risk factors for severe covid infection. Several theories have been postulated such as a disturbed metabolism with high levels of insulin circulating, prothrombotic tendencies due to drugs or even predisposing medical conditions, increased circulating cytokine response, dysregulated gut microbiome, and a defective macrophage-neutrophil function. Studies have shown that age alone is the most significant risk factor for severe disease, and generally, this has also been documented with other coronaviruses and influenza viruses that affect the elderly. A declining immune function or immune senescence and a reduced cell-mediated immunity together with the increased likelihood that an elderly person will have one or more comorbidities that itself can lead to the risk of severe illness.

Chang et al. showed that fever > 37.5°C and chest X-ray (CXR) on arrival were risk factors in predicting progression of COVID-19. Sim et al.[19] showed that the presence of fever of ≥ 37.5°C, diarrhoea, tachypnoea with RR ≥ 21, and an abnormal CXR on presentation were significant risk factors associated with COVID-19 severity. Deborah et al. also showed that persistent prolonged fever beyond seven days from disease onset had a higher risk of ICU admission (11.1% vs. 0.9; $p=0.05$). Additionally, in our study, we showed that symptoms of fever, shortness of breath, myalgia, increased respiratory rate, and increased infiltrates on the CXR were significantly more common in the group that deteriorated.

MEWS is widely used to identify patients at risk of deterioration by triggering an escalated response in an overwhelmed clinical environment. Sylvian et al. studied whether the use of a modified version of the Early Warning Scoring (EWS) could contribute to an early pick up of patients who require ICU admissions. They looked at 36 patients in a 12-hour interval over 36-hour time period and showed median EWS was higher in the group that required ICU care ($p<0.001$). Anna et al. showed that, in the 68 patients who

were retrospectively reviewed, national early warning signs were a good predictor of ICU admission. In their multivariate analysis, MEWS threshold of 5–7 was significantly related to ICU admissions. In our study, we similarly looked at MEWS on admission and at 6-hour intervals till the desired outcome. Additionally, we also evaluated a MEWS threshold of more than 3 predicting deterioration. A lower MEWS score chosen as our aim was to pick up patients who are more likely to require oxygen rather than ICU admission, thus triggering an increased monitoring and clinical review. In the group of patients who deteriorated in our study, the MEWS score was considerably greater on the days of presentation and outcome compared to the stable group. However, a major limitation to MEWS scoring was the accuracy of respiratory rate being estimated. It was done manually and extremely operator dependent and thus may influence the outcome of the study.

Beyond demographics and clinical characteristics, a clear and strong correlation between laboratory parameters such as CRP, neutrophilia, lymphopenia, and elevated levels of D-dimer were often observed in patients who deteriorated or required ICU care. In our study, both CRP and NLR were significant predictors of deterioration. The other laboratory parameters such as ferritin, D-dimer levels were not analysed as there were missing data in some patients. We strongly recommend tracking the rate of change of CRP rather than a single value and correlate it with NLR values to predict patients who are likely to progress. CRP can be a useful surrogate marker of increased Interleukin-6 activity and other relevant cytokine mediated hyperinflammation pathways, which have been implicated in COVID-19 severe lung damage.

The study answers a very relevant clinical question and involves multiple treatment sites, and thus, the findings of this study can be generalised to all treatment sites. However, the study does have several limitations. First and foremost was the retrospective nature of the study. The documentation was based on manual and electronic records and thus may not be accurate/complete. Second, we did not have standardised laboratory investigations in all the three sites, and this led to selective analysis and missing data.

CONCLUSION

We found that in patients presenting with mild illness, factors such as age greater than 50 years, presence of more than two comorbidities, fever, shortness of breath, increased CXR infiltrates, a raised MEWS score of more than 3, CRP values more than 5 mg/dL, and NLR > 3.13 were significantly associated with progress to more severe disease. Thus, in patients who present with the above risk factors, close monitoring in a high-risk centre is recommended with more frequent reviews and escalating treatment where necessary. However, future research is still needed to determine the factors that cause individuals to deteriorate but do not mount a hyperinflammatory response.

ETHICAL APPROVAL

Ethical approval for this study was obtained from the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia (NMRR 20-1237-55360).

CONFLICT OF INTEREST

The authors state that there is no conflict of interest to declare.

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