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Research paper

Clinical characteristics and risk factors for severe COVID-19 infections in Malaysia: A nationwide observational study

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ABSTRACT

Background: COVID-19 emerged as a major public health outbreak in late 2019. Malaysia reported its first imported case on 25th January 2020, and adopted a policy of extensive contact tracing and hospitalising of all cases. We describe the clinical characteristics of COVID-19 cases nationwide and determine the risk factors associated with disease severity.

Method: Clinical records of all RT-PCR confirmed COVID-19 cases aged ≥12 years admitted to 18 designated hospitals in Malaysia between 1st February and 30th May 2020 with complete outcomes were retrieved. Epidemiological history, co-morbidities, clinical features, investigations, management and complications were captured using REDCap database. Variables were compared between mild and severe diseases. Univariate and multivariate regression were used to identify determinants for disease severity.

Findings: The sample comprised of 5889 cases (median age 34 years, male 71.7%). Majority were mild (92%), and 3.3% required intensive care, with 80% admitted within the first five days. Older age (≥51 years), underlying chronic kidney disease and chronic pulmonary disease, fever, cough, diarrhoea, breathlessness, tachypnoea, abnormal chest radiographs and high serum CRP (≥5 mg/dL) on admission were significant determinants for severity ($p<0.05$). The case fatality rate was 1.2%, and the three commonest complications were liver injuries (6.7%), kidney injuries (4%), and acute respiratory distress syndrome (2.3%).

Interpretations: Lower case fatality rate was possibly contributed by young cases with mild diseases and early hospitalisation. Abnormal chest radiographic findings in elderly with tachypnoea require close monitoring in the first five days to detect early deterioration.

1. Research in context

1.1. Evidence before this study

Up to 80% of COVID-19 cases had mild to moderate diseases, with 15% having severe diseases, and 5% became critically ill. The case fatality ratio by countries ranges between 1% and 12%, with various public health response mechanisms. Abnormality in pulmonary CT scan was predictive of severe disease together with clinical presentation and blood investigations. Pulmonary complications were commoner than other organ dysfunctions.

1.2. Added value of this study

We reported clinical characteristics of COVID-19 cases with more than 90% of cases had mild diseases and low fatality rates in Malaysia which implemented early, compulsory hospitalisation, regardless of disease stage upon diagnosis. Progression to severe diseases requiring intensive care occurred within five days of admission. Abnormal plain chest X-ray predicted severe diseases, apart from the symptomatic presentation and abnormal biochemical pa-

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rameters. Occurrence of acute liver and kidney injuries were more common than acute respiratory distress syndrome.

1.3. Implications of all the available evidence

Early compulsory hospitalisation of cases upon COVID-19 diagnosis allows close monitoring for deterioration and may prevent deaths. Abnormal plain chest X-ray findings could be a useful predictor for severe disease in a resource-limited setting.

2. Introduction

The coronavirus disease 2019 (COVID-19) pandemic caused by the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has infected more than 16 million people with over 600,000 deaths worldwide [1]. Malaysia, a multi-racial tropical country in Southeast Asia, first reported its cases involving three Chinese tourists on 25th January 2020. By the end of February, a total of 29 cases were reported, mostly overseas travellers. In early March, Malaysia had a large cluster linked to a three-day religious gathering attended by approximately 16,000 participants, including 1500 non-Malaysians [2]. This cluster was also linked to other cases in at least six other Southeast Asian countries.

In response to the large cluster outbreak, Malaysia implemented "Movement Control Order 2020" under the Prevention and Control of Infectious Diseases Act 1988 and the Police Act 1967 on 18th March [3]. Major government hospitals in the country were designated as facilities for managing COVID-19 cases, and triaging centres for suspected individuals categorised as Person Under Investigation were established. As of 20th May, there were 3347 cases linked to the religious cluster contributing to nearly 50% of reported cases in Malaysia. Continuous intensive public health efforts resulted in the reduction of confirmed cases from a peak of about 200 new cases from middle of March to less than 50 per day in April [3].

COVID-19 infections can be symptomless or mildly symptomatic but remain contagious [4,5]. From the beginning of the outbreak, Malaysia escalated its national preparedness response by implementing contact tracing, early identification of cases and compulsory hospital admission regardless of disease severity strategies, aiming to break the cycle of transmission.

As of 8th July 2020, COVID-19 cases in Malaysia numbered 8674 with 8481 recoveries and 121 fatalities, giving CFR of 1.39% and a crude mortality rate of 0.037 deaths per 100,000 populations with Malaysia population currently around 32.6 million [3].

Reports on case fatality rate vary between geographical regions with studies reporting different outcomes and risk factors [6-8]. This disparity has raised a few postulations including the effectiveness of government policies, epidemic preparedness and response, and bias in reporting of the actual number of cases [7]. Most papers reported clinical characteristics and mortality rates based on data from single or selected centres. At the time of this write-up, there are limited studies describing a whole country experience during this COVID-19 pandemic from its onset until flattening of the epidemiological curve. This study aimed to characterise the clinical features, management and outcomes of the first 5889 COVID-19 cases nationwide in Malaysia. We also examined the factors associated with severe disease.

3. Methods

3.1. Study design

This study is a multi-centre observational study supported by National Institutes of Health, Malaysia, together with Infectious Diseases teams from 18 COVID-19 designated hospitals in Malaysia.

3.2. Data source

All reverse-transcriptase-polymerase chain reaction (RT-PCR) confirmed COVID-19 cases aged 12 years and above were consecutively recruited from 18 designated COVID-19 hospitals between 1st February 2020 and 30th May 2020. They were followed up until achieving complete outcome at discharge. Hospital admission and isolation were compulsory to all COVID-19 cases according to the Acts. Cases aged below 12 years of age had their data captured separately for further analysis. A national ClinData_COVID-19 registry using Research Electronic Data Capture (REDCap) system adapted from International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) - WHO Case Report Form was used for data entry [9,10]. Individual case data were extracted and entered into REDCap database by trained research assistants in respective hospitals with a standardised data definition dictionary as reference. Data verification was performed with standardised protocol prior to submission into the ClinData_COVID-19 registry. The data management performed quality assurance check on data entry, prior to extraction of data for analysis by independent data analysts.

3.3. Study ethics

The study was registered with the National Medical Research Register (NMRR-20-580-54339) and approved by the Medical Research and Ethics Committee, Ministry of Health, Malaysia (KKM/NIHSEC/P20–706).

3.4. Laboratory confirmation

Nasopharyngeal and/or oropharyngeal swabs, tracheal aspirates, sputum or serum samples were used for reverse-transcriptase-polymerase chain reaction (RT-PCR) analysis at designated National Public Health Laboratories, Institute for Medical Research, and accredited hospital laboratories.

3.5. Disease staging and clinical management

Cases admitted at designated hospitals were managed by infectious diseases teams according to COVID-19 Management Guideline in Malaysia by the Ministry of Health [3]. This national guideline was developed based on expert panel consensus from Ministry of Health, with reference to interim guidelines from China and Singapore [11,12].

Each case was staged according to clinical severity; stage I: asymptomatic case, stage II: symptomatic without pneumonia, stage III: pneumonia without hypoxia, stage IV: pneumonia with hypoxia requiring oxygen supplementation therapy and stage V: critically ill. Close monitoring for signs of early deterioration and appropriate aggressive interventions were instituted. As per guideline, all cases were admitted for 14 days, or until free of SARS-CoV-2 carriage on repeated nasopharyngeal/oropharyngeal swabs, or death ensued.

3.6. Study variables and outcomes of interest

Variables related to sociodemographic data, admission characteristics, clinical progression, laboratory and radiographic investigations, management and clinical outcome were analysed for its association with disease severity. For this study, we focused on disease severity with worst clinical progression (worst disease severity experienced by each case) throughout hospitalisation and concluded upon discharge. We classified stages I to III diseases as mild diseases, whilst stages IV and V as severe diseases. We defined disease complication according to ISARIC - WHO Case Report Form.

Table 1
Sociodemographic, clinical histories and disease staging of COVID-19 cases upon admission.

	Total (N = 5889)	Mild disease (n = 5418)	Severe disease (n = 471)	p-value
Age, years	34.0 (24.00, 51.00)	32.0 (24.00, 48.00)	58.0 (49.00, 66.00)	< 0.001
Age group, n (%)				< 0.001
<30-y	2486 (42.2)	2472 (45.6)	14 (3.0)	
31–50y	1919 (32.6)	1803 (33.3)	116 (24.6)	
51–70y	1315 (22.3)	1051 (19.4)	264 (56.1)	
71+y	169 (2.9)	92 (1.7)	77 (16.3)	
Male gender, n (%)	4221 (71.7)	3884 (71.7)	337 (71.5)	0.957
Ethnicity*, n (%)				< 0.001
Malay	3433 (58.4)	3104 (57.4)	329 (70.0)	
Chinese	391 (6.7)	334 (6.2)	57 (12.1)	
Indian	135 (2.3)	114 (2.1)	21 (4.5)	
Other Malaysian ethnics[γ]	521 (8.9)	481 (8.9)	40 (8.5)	
Other nationality	1396 (23.8)	1373 (25.4)	23 (4.9)	
Contact history with COVID-19 cases*, n (%)	3374 (62.7)	3135 (63.4)	239 (54.7)	< 0.001
Status as healthcare worker*, n (%)	343 (5.8)	327 (6.0)	16 (3.4)	0.018
Presence of comorbidity, n (%)				
Hypertension	931 (15.8)	702 (13.0)	229 (48.6)	< 0.001
Diabetes mellitus	578 (9.8)	394 (7.3)	184 (39.1)	< 0.001
Asthma	196 (3.3)	176 (3.2)	20 (4.2)	0.230
Chronic cardiac disease	190 (3.2)	124 (2.3)	66 (14.0)	< 0.001
Obesity	94 (1.6)	74 (1.4)	20 (4.2)	< 0.001
Chronic kidney disease	92 (1.6)	39 (0.7)	53 (11.3)	< 0.001
Chronic pulmonary disease (except asthma)	32 (0.5%)	15 (0.3%)	17 (3.6%)	< 0.001
Active smoker, n (%)	529 (9.0)	496 (9.2)	33 (7.0)	0.130
Presenting symptoms, n (%)				
Cough	1897 (32.2)	1568 (28.9)	329 (69.9)	< 0.001
Dry cough	1118 (19.0)	942 (17.4)	176 (37.4)	< 0.001
Wet cough	779 (13.2)	626 (11.6)	153 (32.5)	< 0.001
Fever	1737 (29.5)	1388 (25.6)	349 (74.1)	< 0.001
Sore throat	841 (14.3)	735 (13.6)	106 (22.5)	< 0.001
Runny nose	608 (10.3)	550 (10.2)	58 (12.3)	0.155
Shortness of breath	312 (5.3)	147 (2.7)	165 (35.0)	< 0.001
Diarrhoea	298 (5.1)	200 (3.7)	98 (20.8)	< 0.001
Anosmia	163 (2.8)	160 (3.0)	3 (0.6)	0.001
Nausea and/or vomiting	108 (1.8)	67 (1.2)	41 (8.7)	< 0.001
Ageusia	42 (0.7)	42 (0.8)	0	0.046
Days of illness at presentation*, median (IQR)	3.0 (0.00, 7.00)	2.0 (0.00, 7.00)	6.00 (3.00, 9.00)	< 0.001
Case severity upon admission, n (%)				< 0.001
Stage I: Asymptomatic	2956 (50.2)	2926 (54.0)	30 (6.4)	
Stage II: Symptomatic without pneumonia	1859 (31.6)	1775 (32.8)	84 (17.8)	
Stage III: Pneumonia without hypoxia	801 (13.6)	717 (13.2)	84 (17.8)	
Stage IV: Pneumonia with hypoxia	210 (3.6)	0	210 (44.6)	
Stage V: Critically ill	63 (1.1)	0	63 (13.4)	

Data are median (IQR) or n (%). P values were calculated by Mann-Whitney U test or Fisher's exact test, as appropriate.
* There were missing data for this variable with details reported in Table S1.
[γ] Other ethnics in Sabah and Sarawak, and indigenous people from Peninsular Malaysia.

3.7. Statistical analyses

Cases' data were de-identified and analysed as a cohort. Cases aged below 12 years were excluded from the analyses for this study. Variables with missing data are reported in Supplementary Table S1. Missing data were treated with listwise deletion in subsequent analyses. Continuous measurements were presented as median and interquartile range, while categorical variables were described using frequency and percentage. Mann-Whitney U test and Fisher's exact test were used respectively to compare differences between the severity of COVID-19 cases. Univariate and multivariate logistic regressions were used to analyse risk factors associated with disease severity upon discharge. We selected variables from demographics, clinical histories and assessment, laboratory and imaging investigation to be included in the multivariate logistic regressions, based on clinical justification and statistical reasoning from univariate analyses. Variables from univariate analyses with $p<0.05$ were recruited for the multivariate logistic regression model. Multivariate logistic regressions were performed in a stepwise approach with results from the final model reported in this study. The two-sided statistical significance level, p-value, was set at 0.05 for all analyses in this study. R version 3.6.3 used for all analyses.

3.8. Role of funding source

None.

4. Results

4.1. Sociodemographic, clinical histories and disease staging

During the study period, 5889 COVID-19 cases were admitted to hospitals nationwide. On admission, 4815 (81.8%) COVID-19 cases presented with stages I and II, followed by 801 (13.6%) at stage III, 210 (3.6%) at stage IV while 63 (1.1%) presented at stage V (Table 1). Overall, 95% presented with a mild disease on admission, and 3.5% subsequently progressed to severe disease. About 70% were male, whilst the median age was 34 years (24,51) with more than half of the severe cases aged ≥ 51 years. Nearly 23% of the cases were non-Malaysians either visiting or employed in the country, and about 6% were healthcare workers. A significant number of cases (62.7%) had a history of contact with known COVID-19 cases within the past 14 days of diagnosis and/or symptoms onset.

There were 71 COVID-19 infected pregnant women with 23 being in the first trimester, 18 in the second trimester and 29 in the third trimester. Among them, six cases underwent lower segment

Table 2
Clinical assessment, imaging findings and laboratory parameters of cases with COVID-19 cases upon admission.

	Total (N = 5889)	Mild disease (n = 5418)	Severe disease (n = 471)	p-value
Clinical assessment upon admission*				
Systolic BP (mmHg), median (IQR)	128.0 (118.00, 139.00)	128.0 (118.00, 138.00)	132.5 (121.00, 146.25)	< 0.001
Diastolic BP (mmHg), median (IQR)	78.0 (70.00, 86.00)	78.0 (70.00, 86.00)	78.0 (70.00, 86.00)	0.524
Pulse rate (beats per min), median (IQR)	84.0 (75.00, 93.00)	84.0 (75.0, 93.0)	89.0 (80.00, 100.0)	< 0.001
Tachycardia (≥100 bpm), n (%)	764 (13.0%)	642 (11.9%)	122 (26.1%)	< 0.001
Temperature (°C), median (IQR)	36.8 (36.50, 37.00)	36.8 (36.50, 37.00)	37.0 (36.80, 37.90)	< 0.001
Fever (≥37.5%), n (%)	525 (9.0%)	350 (6.5%)	175 (37.5%)	< 0.001
Respiratory rate (breath per min), median (IQR)	19.0 (18.00, 20.0)	19.00 (18.00, 20.00)	20.0 (20.00, 24.00)	<0.001
Tachypnoea(≥21 bpm), n (%)	376 (6.7%)	195 (3.8%)	181 (41.3%)	< 0.001
Chest X-ray findingsγ				< 0.001
Normal	3118 (69.0%)	3077 (73.4)	41 (12.6)	
Abnormal	1399 (31.0%)	1115 (26.6)	284 (87.4)	
Ground glass opacities	733 (16.2%)	601 (14.3)	132 (40.6)	< 0.001
Consolidation	379 (8.4%)	260 (6.2)	119 (36.6)	< 0.001
Interstitial opacities	336 (7.4%)	243 (5.8)	93 (28.6)	< 0.001
Nodular opacities	101 (2.2%)	82 (2.0)	19 (5.8)	< 0.001
Hyperinflation	6 (0.1%)	5 (0.1)	1 (0.3)	0.361
Laboratory parameters*, mean (SD)				
White cell count (x10^9/L)	7.8 (2.44)	7.7 (2.25)	8.0 (4.14)	0.003
Absolute neutrophil count (cells/uL)	4.7 (2.03)	4.6 (1.85)	5.6 (3.47)	0.009
Absolute lymphocyte count (cells/uL)	2.2 (0.86)	2.3 (0.84)	1.4 (0.74)	< 0.001
Lymphocyte level <1 cells/uL, n (%)	157 (4.5)	85 (2.6)	72 (28.8)	< 0.001
Haemoglobin (g/dl)	14.4 (4.39)	14.5 (4.50)	13.4 (2.22)	< 0.001
Haematocrit (%)	42.5 (8.96)	42.7 (9.04)	39.9 (7.36)	< 0.001
Platelet (x10^9/L)	270.0 (80.45)	273.1 (78.68)	231.1 (91.88)	< 0.001
Alanine transaminase (U/L)	35.5 (32.96)	34.9 (33.07)	43.0 (30.65)	< 0.001
Aspartate transaminase (U/L)	30.9 (25.99)	29.0 (20.40)	56.2 (58.26)	< 0.001
Serum urea (mmol/L)	4.1 (2.50)	3.9 (1.48)	7.2 (6.94)	< 0.001
Serum sodium (mmol/L)	139.3 (2.87)	139.5 (2.46)	136.0 (4.95)	< 0.001
Serum potassium (mmol/L)	3.8 (0.47)	3.8 (0.45)	3.9 (0.64)	0.245
Serum creatinine (μmol/L)	86.4 (84.49)	79.9 (41.88)	167.5 (260.42)	< 0.001
C-reactive protein (mg/dL)	15.1 (41.07)	9.9 (28.55)	85.6 (91.46)	< 0.001
CRP level >5 mg/dL, n (%)	859 (27.7)	670 (23.2)	189 (90.0)	< 0.001
Lactate dehydrogenase (U/L)	246.0 (99.61)	233.3 (66.24)	420 (231.88)	< 0.001

* There were missing data for all laboratory parameters, ranging between 40.3% and 59.2% with details reported in Table S1.
γ Only a total of 4517 chest X-ray being done.

caesarean section with no reported vertical transmission, whereas six had severe COVID-19 with two requiring ICU care.

About 25% of admitted cases had at least one comorbidity, and 1053 (20.0%) had history of medication for chronic diseases. Hypertension was the most common comorbidity (931, 15.8%) followed by diabetes mellitus (578, 9.8%) and asthma (196, 3.3%). About 496 (9.2%) active smokers had mild disease, while 33 (7.0%) had severe COVID-19 disease.

At presentation, it was observed that almost 70% remained afebrile up to admission. Only a quarter of cases with mild disease reported fever as compared to three-quarters of those with severe diseases. The pattern was similar for cough. Out of 329 severe COVID-19 cases with cough, 153 (32.5%) had sputum. Other upper respiratory tract symptoms included sore throat (841, 14.3%) and rhinorrhoea (608, 10.3%). Only less than 3% of cases presented with anosmia. For gastrointestinal symptoms, 298 (5.1%) of cases reported diarrhoea, and diarrhoea was one of the earliest symptoms among severe cases (21%).

The median of illness onset to admission was 3 days (0, 7). Those who had severe COVID-19 were admitted later at day 6 (IQR 3, 9) as compared to those with mild disease.

4.2. Clinical assessment, imaging findings and laboratory parameters

Higher systolic blood pressure, pulse rate, respiratory rate and temperature upon initial assessment during admission, were observed among those with severe diseases (Table 2).

Among 5053 (85.8%) cases underwent chest X-ray imaging, 4517 (72.9%) were reported by independent radiologists. Up 26.6% of cases with mild diseases had abnormal features on their chest X-rays. The main abnormalities reported were ground-glass opacities (733, 16.2%), followed by consolidation (379, 8.4%), interstitial opacities (336, 7.4%), and nodular opacities (101, 2.2%).

Lymphopenia, coupled with raised inflammatory markers, were observed in the severe disease group, apart from increased liver transaminases levels and serum creatinine.

4.3. Clinical use of medications, complications and clinical outcomes of COVID-19 cases

Hydroxychloroquine was prescribed for more than 37% of cases, mainly those with severe disease (Table 3). Antiviral agents, especially lopinavir/ritonavir, were initiated for 77% of severe disease. Steroids and tocilizumab were prescribed sparingly, mostly to cases with severe diseases.

Acute liver (6.7%) and kidney (4%) injuries, and acute respiratory distress syndrome (ARDS) (2.3%) were the three most common complications seen in our COVID-19 cases. Among those severe cases, 7.7% developed secondary bacteraemia. For cardiac complications, 39 (8.3%) of severe COVID-19 cases developed cardiac arrhythmia. Deep vein thrombosis and pulmonary embolism affected 10 (2.1%) severe COVID-19 cases.

A total of 193 (3.3%) ICU admissions were reported in this cohort, with 51 cases admitted for at least 14 days in ICU (Table 4). Almost all cases admitted longer than 13 days were on invasive ventilation. Almost 80% of all ICU admissions occurred within the first five days of hospitalisation.

For all severe cases, around 40% were admitted into an intensive care unit with 29% requiring invasive ventilation. Duration of hospitalisation was significantly longer among severe cases with a median of 14 (9, 23) days. Our cohort recorded 73 in-hospital deaths with a case fatality rate (CFR) of 1.2%. All mortality occurred

Table 3
Clinical use of medications, complications and clinical outcomes of COVID-19 cases.

	Total (N = 5889)	Mild disease (n = 5418)	Severe disease (n = 471)	p-value
Clinical use of medications*, n (%)				
Hydroxychloroquine	2211 (37.5)	1810 (33.4)	401 (85.1)	< 0.001
Antiviral drugs	1091 (18.5)	654 (12.1)	437 (92.8)	< 0.001
Ribavirin	25 (0.4)	1 (<0.01)	24 (5.1)	< 0.001
Lopinavir/ritonavir	848 (14.4)	483 (8.9)	365 (77.5)	< 0.001
Interferon alpha	9 (0.2)	0	9 (1.9)	< 0.001
Interferon beta	133 (2.3)	3 (0.1)	130 (27.6)	< 0.001
Neuraminidase inhibitor	103 (1.7)	63 (1.2)	40 (8.5)	< 0.001
Ritonavir	148 (2.5)	65 (1.2)	83 (17.6)	< 0.001
Favipiravir	12 (0.2)	6 (0.1)	6 (1.3)	< 0.001
Atazanavir	152 (2.6)	66 (1.2)	86 (18.3)	< 0.001
Antibiotic	748 (12.7)	407 (7.5)	341 (72.6)	< 0.001
Chloroquine	134 (2.3)	120 (2.2)	14 (3.0)	0.262
Steroid	128 (2.2)	19 (0.4)	109 (23.6)	< 0.001
Antifungal agent	59 (1.0)	20 (0.4)	39 (8.4)	< 0.001
Tocilizumab	25 (0.4)	1 (<0.01)	24 (5.1)	< 0.001
Complications				
Liver injuries	393 (6.7)	249 (4.6)	144 (30.6)	< 0.001
Acute renal injury	236 (4.0)	89 (1.6)	147 (31.3)	< 0.001
Acute respiratory distress syndrome	136 (2.3)	1 (<0.00)	135 (28.8)	< 0.001
Bacteraemia	39 (0.7)	3 (0.1)	36 (7.7)	< 0.001
Arrhythmia	41 (0.7)	2 (<0.01)	39 (8.3)	< 0.001
Cardiac arrest	38 (0.6)	0	38 (8.1)	< 0.001
Heart failure	19 (0.3)	3 (0.1)	16 (3.4)	< 0.001
Endocarditis/myocarditis	12 (0.2)	2 (<0.01)	10 (2.1)	< 0.001
Cardiac ischemia	12 (0.2)	2 (<0.01)	10 (2.1)	< 0.001
Coagulopathy	12 (0.2)	0	12 (2.6)	< 0.001
Stroke	3 (0.1)	1 (<0.01)	2 (0.4)	0.018
Gastrointestinal haemorrhage	12 (0.2)	1 (<0.01)	11 (2.3)	< 0.001
Venous thromboembolism	10 (0.2)	0	10(2.1)	< 0.001
Duration of hospitalisation, days	11.0 (8.00, 15.00)	10.0 (7.00, 14.00)	14.0 (9.00, 23.00)	< 0.001
Admission to Intensive Care Unit	193 (3.3)	5 (0.1)	188 (39.9)	< 0.001
Mechanical ventilation	138 (2.3)	1 (<0.01)	137 (29.1)	< 0.001
Death	73 (1.2)	1 (<0.01)	72 (15.3)	< 0.001

Table 4
Characteristics of COVID-19 cases admitted to intensive care unit.

		ICU Duration		
	Total (N = 193)	< 14 days (N = 142)	>= 14 days (N = 51)	p-value
Admission diagnosis, n (%)				0.237
Mild (Stage I, II, and III)	62 (32.1)	49 (34.5)	13 (25.5)	
Severe (Stage IV and V)	131 (67.9)	93 (65.5)	38 (74.5)	
Duration between ward and ICU admission, n (%)				0.017
On admission	64 (33.2)	38 (26.8)	26 (51.0)	
1–5 days	100 (51.8)	80 (56.3)	20 (39.2)	
6–10 days	21 (10.9)	17 (12.0)	4 (7.8)	
≥ 11 days	8 (4.1)	7 (4.9)	1 (2.0)	
Duration of ICU stay, days, median (IQR)	7.0 (3.00, 15.00)	5.0 (2.25, 9.00)	21.0 (18.00, 33.00)	
Diabetes, n (%)	82 (42.5)	53 (37.3)	29 (56.9)	0.015
Laboratory parameters*, mean (SD)				
C-reactive protein (mg/dL)	120.0 (106.15)	95.0 (95.91)	171.7 (109.35)	0.001
Lactate dehydrogenase (U/L)	526.3 (315.31)	512.7 (370.01)	553.5 (160.81)	0.023
Absolute Lymphocyte count (cells/uL)	1.2 (0.56)	1.2 (0.58)	1.1 (0.51)	0.768

among the severe disease group, except one case with mild disease, succumbed to perforated gastric ulcer.

4.4. Factors associated with severe COVID-19 disease

From univariate regression analyses, several factors were associated with severe disease (Table 5). Adjusting these variables in the multivariate complete case analysis model (n = 2427), severe disease (5.32%) was associated with older age ≥51 years, underlying comorbidities such as chronic kidney disease and chronic pulmonary disease, presenting symptoms such as fever, cough, diarrhoea, shortness of breath, clinically assessed tachypnoea and chest X-ray abnormality as well as high CRP, but not lymphopenia. The odds of an abnormal chest x-ray on admission were five times more in severe COVID-19 cases.

5. Discussion

This study is the first national study in Southeast Asia for all laboratory-confirmed COVID-19 cases representing a whole country's experience with definite outcome showing low mortality. Malaysia implemented serial policies including extensive contact tracing, expedited laboratory testing, compulsory hospital quarantine for those suspected for COVID-19, and instituted movement control order for the public which were made possible by the normative legal acts: Prevention and Control of Infectious Diseases Act 1988 and the Police Act 1967 [13]. We reported up to 92% having mild diseases with a low case fatality rate of 1.2%. These findings were similar to other reports [1,14,15]. Older groups were mostly symptomatic, and for those with comorbidities, the likelihood of progressing to poorer outcomes was high [16,17]. In Malaysia, hy-

Table 5
Risk factors associated with COVID-19 severity.

	Univariate		Multivariate (n = 2427)	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age, years*	1.08 (1.08 - 1.09)	<0.001		
Age group *vs* <31 years	reference		reference	
31–50y	11.36 (6.50 - 19.84)	<0.001	8.53 (2.45–43.99)	0.003
51–70y	44.35 (25.79 - 76.27)	<0.001	21.95(6.30–114.51)	<0.001
71+*y*	147.78 (80.61 - 270.93)	<0.001	73.36 (14.56–484.90)	<0.001
Female (*vs* Male)	1.01 (0.82 - 1.24)	0.95	–	–
Malay (*vs* Non-Malay)	0.83 (0.67 - 1.05)	0.111	–	–
History of contact	0.71 (0.57 - 0.90)	0.003	0.89(0.48–1.67)	0.712
Days of illness before admission*	1.04 (1.02 - 1.05)	<0.001	0.97 (0.92–1.02)	0.270
Co-morbidities				
History of chronic cardiac diseases	6.96 (5.05 - 9.50)	<0.001	1.48 (0.59–3.51)	0.390
History of hypertension	6.36 (5.22 - 7.75)	<0.001	0.98 (0.51–1.84)	0.953
History of chronic kidney disease	17.49 (11.46 - 26.91)	<0.001	3.31 (1.12–9.64)	0.029
History of diabetes mellitus	8.18 (6.61 - 10.10)	<0.001	1.04 (0.53–2.01)	0.912
History of chronic pulmonary disease	12.44 (5.87 - 27.06)	<0.001	14.06 (2.46–69.29)	0.001
Obese	3.20 (1.89 - 5.19)	<0.001	4.28 (0.32–47.67)	0.281
Active smoking	0.75 (0.51 - 1.06)	0.119	–	–
Presenting symptoms				
Fever	8.31 (6.72 - 10.33)	<0.001	2.94 (1.55–5.70)	0.001
Cough	5.69 (4.64 - 7.00)	<0.001	1.84 (1.02–3.34)	0.044
Runny nose	1.24 (0.92 - 1.65)	0.14	–	–
Sore throat	1.85 (1.47 - 2.32)	<0.001	1.57 (0.80–3.03)	0.184
Nausea and vomiting	7.62 (5.07 - 11.32)	<0.001	0.38 (0.07–1.78)	0.244
Diarrhoea	6.86 (5.25 - 8.90)	<0.001	4.01 (1.76–9.05)	0.001
Shortness of breath	19.34 (15.06 - 24.86)	<0.001	6.57 (2.89–15.15)	<0.001
Vital signs				
Tachycardia (≥100 bpm)	2.61 (2.09 - 3.26)	<0.001	1.00 (0.47–2.04)	0.999
Tachypnoea (≥21 bpm)	17.90(14.11 - 22.71)	<0.001	6.26 (3.18–12.46)	<0.001
Temperature ≥37.5°C	8.64 (6.95 - 10.72)	<0.001	1.77 (0.91–3.40)	0.087
Chest radiography				
Abnormalities detected	19.122 (13.85 - 27.09)	<0.001	5.60 (2.95 - 11.25)	<0.001
Laboratory parameters*				
High CRP level (≥5 mg/dL)	29.81 (18.84 - 47.17)	<0.001	3.32 (1.66 - 7.00)	0.001
Lymphopenia (<1 cell/uL)	14.98 (10.57 - 21.22)	<0.001	1.96 (0.87 - 4.34)	0.101

* Per 1 unit increase. Malays *versus* non-Malays comparison among Malaysians.

pertension (15.1%), diabetes mellitus (9.8%), cardiovascular disease (3.2%), asthma (3.3%) and chronic kidney disease (1.6%) were the most prevalent comorbidities [18]. The prevalence of chronic diseases amongst COVID-19 cases was below the national average, which suggests that public health preventive measures might have a role in reducing the risk of transmission to this vulnerable population. Our distribution of comorbidities was similar, as reported by Fu et al. in a systematic review of 26 studies in China [19]. The review showed that the median proportion for hypertension was 16.0%, diabetes was 10.1%. In our cohort, underlying comorbidities such as chronic kidney disease and chronic pulmonary disease were associated with severe COVID-19 disease.

The CFR for COVID-19 in Malaysia was low as compared to other coronavirus epidemics such as SARS-CoV (9.5%) and MERS-CoV (34.4%) [20]. Presentation of COVID-19 was milder despite high virological similarity with SARS-CoV causing higher transmissibility than the other two. This could lead to underestimation of CFR due to underreporting of the asymptomatic infected population in the community [21].

Early hospitalisation leads to enforced separation from the greater community, especially those in vulnerable groups. In Malaysia, the strategy of hospital isolation of all suspected and confirmed individuals contributed to the reduction of local transmission. Our approach was similar to countries demonstrated lower CFR such as Singapore (0.05%) and Republic of Korea (2.10%) where "trace, test and treat" was practised [22-24]. In countries where selective hospitalisation was implemented, the CFR was much higher in Italy (14.24%), Iran (5.47%), United States (3.44%) and United Kingdom (15.25%) [16,24,25]. This stringent hospital containment has helped Malaysia in identifying individuals at risk of deterioration and allows for early intervention when they do deteriorate.

The majority of affected individuals in Malaysia were of younger age group, with a median age of our sample at 34 years with a male preponderance. In contrast, New York, China, Korea and Singapore reported a much older group of cases between 40 and 63 years. This skewed age distribution could be related to the cluster effect from 3-days religious gathering where more younger males were involved [2]. As asymptomatic transmission and pre-symptomatic transmission of SARS-CoV2 happens, clustering effects among young males can contribute to a higher transmission rate [26,27]. In addition, effective contact tracing, early confinement and stringent social distancing limited the spread of disease from younger, mobile population to the elderly, as compared to overseas study [28]. This religious clustering effect was similarly noted in countries like Korea, where a sudden spike of cases occurred after a religious congregation with about 5200 followers tested positive [29]. The number of clusters reduced once mass gatherings were suspended in these countries [2].

Fever and cough were the commonest symptoms on admission. We found that less than 30% of cases had a fever on admission, and this finding was similar to large cohort studies in China and New York [1,14]. In other coronavirus epidemics such as MERS and SARS, about 98–100% presented with fever on admission [20]. The difference in presentation among these coronavirus diseases is still being investigated, but viral tropism may be a factor [30]. When clinical endpoints were considered, there were no differences in severity of COVID-19 based on gender and ethnicity. This observation was different from the UK and US, where ethnicity was linked to disease severity [31,32]. The Malaysian public healthcare system

is subsidised with good accessibility for both citizens and foreigners according to geographical coverage. On the contrary, even with The Families First Coronavirus Response Act (FFCRA) and numerous policies in the US to relieve public health burden, health disparities still prominent as evident by more African Americans had poorer COVID-19 outcomes [31,33-35].

Majority of severe cases (87.4%) had abnormalities on baseline CXR. These non-specific radiographical changes like ground-glass opacity, bilateral lower zone involvements were consistent with computed tomography (CT) findings as described in other studies [36,37]. China utilised CT scan with an artificial intelligent solution and was found to be useful for early detection, but our study showed CXR alone sufficed for COVID-19 management. Furthermore, CXR is low cost, easily performed with a less complex disinfectant protocol as compared to CT scan [38].

Various risk factors have been associated with the worst prognosis throughout the illness [16,17,39,40]. In our sample, those with higher C-reactive protein had greater disease severity [41]. Other predictors such as older age group, tachypnoea, abnormal CXR findings are also significantly associated with disease severity. These findings were similar to Chang et al. in a sample of 211 cases [42].

Clinical decisions on the use of medications were made by physicians in-charge with reference to national guideline. Steroid usage in our cohort (2.2%) was very low as compared to four studies from China, ranging from 7.6 to 44.9% [41,43-45]. Although one study indicated steroid may have a beneficial effect by reducing mortality in ARDS, it is not conclusive for routine use of steroid in COVID-19 treatment [46]. The number of cases developed ARDS was low (136, 2.3%) which is comparable with cohort reported by Guan et al. [1]. However, some studies showed a higher prevalence of ARDS (10–40%) presumably due to delay in hospitalisation [43,44].

The most common extra-pulmonary manifestations were deranged liver function (6.7%) and acute kidney injury (4.0%). Cheng et al. reported that elevated creatinine (>132 umol/L) at baseline and acute kidney injury above stage 2 (KDIGO criteria) were associated with higher mortality. The aetiology of kidney involvement is multifactorial with possible direct cytopathic effects on kidney tissues [47]. A review on liver injuries by Cha et al. postulated that this complication could be due to direct viral attack on hepatocyte, cytokine storm or hypoxic injury secondary to severe acute respiratory syndrome [48]. Lower incidence of ARDS compared to acute kidney and liver injuries possibly due to the nature of milder disease occurred in our young cohort [41].

First five days of hospitalisation was vital in COVID-19 management as 85% of ICU admission in the sample occurred at this period. Similarly, Gupta et al. found in a study of 2215 ICU cases in the US, the median time from onset to ICU admission was 7 days [49]. This observation is crucial as close observation for deterioration of COVID-19 cases can be implemented. Beyond this critical period, cases with lesser risk factors can be placed at a quarantine centre with less intensive care facility. Cases with higher CRP level on admission had longer ICU stay, possibly due to its correlation with the level of inflammation reflecting severe COVID-19 disease in early stage [44].

There were several limitations to this study. We were unable to have standardised laboratory investigations for all cases as these were based on available data according to the study sites. This had led to selective and limited analyses which shall be interpreted with cautions. We also acknowledged recall and documentation biases on clinical histories involving presenting symptoms, duration of illness and exposure history. Hence, we evaluated risk factors for disease severity based on the context of present evidence. Nonetheless, our study recruited a large sample whereby all cases admitted consecutively from 18 hospitals.

6. Conclusion

In Malaysia, our COVID-19 cohort was younger, with the majority having a mild disease and low mortality. Identification of factors associated with severe disease and early hospitalisation allows risk stratification and monitoring of cases for timely interventions.

Contributors

All authors contributed equally to this paper.

Data sharing statement

All data used within the study belongs to *ClinData_COVID-19* Research Team. Please contact the corresponding author for the data extraction procedure.

Declaration of Competing Interest

The authors declare no competing interests.

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Supplementary materials

Supplementary materials associated with this article can be found, in the online version, at doi:10.1016/j.lanwpc.2020.100055.

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