Performance of the World Health Organization suspected COVID-19 case definition in cluster-associated and sporadic SARS-CoV-2 transmission in Malaysia

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ABSTRACT

Introduction: Cluster-associated transmission has contributed to the majority of COVID-19 cases in Malaysia. Although widely used, the performance of the World Health Organization (WHO) case definition for suspected COVID19 in environments with high numbers of such cases has not been reported.

Materials and Methods: All suspected cases of COVID-19 that self-presented to hospitals or were cluster screened from 1st April to 31st May 2020 were included. Positive SARS-CoV-2 rRT-PCR was used as the diagnostic reference for COVID-19.

Results: 540 individuals with suspected COVID-19 were recruited. Two-third of patients were identified through contact screening, while the rest presented sporadically. Overall COVID-19 positivity rate was 59.4% (321/540) which was higher in the cluster screened group (85.6% vs. 11.6%, p<0.001). Overall, cluster-screened COVID-19 cases were significantly younger, had fewer comorbidities and were less likely to be symptomatic than those present sporadically. Mortality was significantly lower in the cluster-screened COVID-19 cases (0.3% vs. 4.5%, p<0.05). A third of all chest radiographs in confirmed COVID-19 cases were abnormal, with consolidation, ground-glass opacities or both predominating in the peripheral lower zones. The WHO suspected case definition for COVID-19 accurately classified 35.4% of all COVID-19 patients, a rate not improved by the addition of baseline radiographic data. Misclassification rate was higher among the cluster-associated cases (80.6%) compared to sporadic cases (35.3%).

Conclusion: COVID-19 cases in Malaysia identified by active tracing of community cluster outbreaks had lower mortality rate. The WHO suspected COVID-19 performed poorly in this setting even when chest radiographic information was available, a finding that has implications for future spikes of the disease in countries with similar transmission characteristics.

KEYWORDS:
Cluster transmission, case definition, COVID-19, Malaysia, World Health Organization

INTRODUCTION

The rapid spread of COVID-19 from Wuhan, China, in the first two months of 2020 led to the declaration of its pandemic status on 11th March 2020.[1] In Malaysia, outbreaks occurring in clusters have significantly contributed to rising numbers of COVID-19. By June 2020, a total of 53 clusters had been identified, including 17 designated as active as of 28th June 2020.[2] By March 2021, a total of 1250 clusters had been notified to the Malaysian Ministry of Health, including 431 that were still classified as active.[3] In Singapore, 93% of new cases of COVID-19 reported in the first 4 months were linked to a known cluster.[4] In both countries, environmental settings implicated with rapid viral transmission included worker dormitories, schools, social events and mass religious gatherings.[5-9]

In this study, we prospectively evaluated the overall characteristics of suspected COVID-19 cases presenting to four large acute care hospitals in west and east Malaysia during the phase of rising incidence and spanned the peak of the outbreak in April and May 2020. All suspected COVID-19 cases were tested with SARS-CoV-2 real-time reverse transcriptase polymerase chain reaction (rRT-PCR), using that as a diagnostic reference. During the early phase of COVID-19 pandemic, the World Health Organization (WHO) released a case definition for suspected COVID-19 cases that focused on alert symptoms, particularly the presence of fever.[10] In contrast, our local case definition did not require fever as a compulsory symptom, which may have impacted case ascertainment and the identification of individuals with asymptomatic or mild diseases. We thus aim to assess the performance of the WHO case definition for suspected COVID-19 case ascertainment in our region. Since abnormalities on plain chest radiographs are known to accompany the presentation of COVID-19,[11] we further assessed the performance of the same case definition after

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incorporating baseline radiographic information. As a secondary aim, we also aim to evaluate the differences between cluster versus sporadically transmitted COVID-19 patients in Malaysia.

MATERIALS AND METHODS

Study Design and Setting

The regional acute care hospitals involved in this prospective observational cohort study were Hospital Kuala Lumpur (HKL) and Hospital Sungai Buloh (HSB) in West (mainland) Malaysia, and Hospital Umum Sarawak (HUS) as well as Hospital Queen Elizabeth Sabah (HQE) in East (Borneo) Malaysia. The study protocol was approved by the medical research and ethics committee, Ministry of Health Malaysia (NMRR-20-726-54589-IIR). The need for informed consent was waived in the interest of public health exceptionality.

Definitions

COVID-19 transmission has been classified by the WHO as cluster, sporadic or community-based.[12] A case cluster (also known as cluster outbreak) includes two or more epidemiologically but not necessarily residentially linked cases and who shared temporal, geographic and exposure factors with illness dates that occurred within an overlapping 14-day period.[7,12-15] In Malaysia, the term sporadic (or isolated) transmission was used to describe non-clustered cases that occurred locally or were imported, the latter not linked by association with locally transmitted cases. In March 2021, the WHO classified the principal mode of SARS-CoV-2 transmission in Malaysia in the first pandemic wave as cluster transmission.[12]

Strategy of COVID-19 Case Detection in Malaysia

COVID-19 contact tracing in Malaysia was undertaken by public health authorities through targeted or active screening of identified contacts of SARS-CoV-2-confirmed cases who presented to a hospital or community clinic with an acute respiratory illness.[16] In addition, and in line with the national COVID-19 strategy of "Search, Test, Isolate, Treat and Quarantine", comprehensive testing strategies targeting high-risk groups such as inhabitants of care homes, schools, labour contingents and returned travellers were implemented.[17] The nationwide COVID-19 response was coordinated by the National Crisis Preparedness and Response Center (CPRC). Tracing of close contacts and field investigations were undertaken by local district health officers.[16,18-19] Testing was widely performed and suspected COVID-19 cases identified through tracing, even if asymptomatic, were admitted to respective hospitals and quarantined until their rRT-PCR test result was available during the study period.[18-19]

Participants and Data Collection

All patients aged >12 years presenting with symptoms of an acute respiratory illness to each of the four sites or were identified from contact screening of suspected COVID-19 cluster outbreaks between 1st April 2020 and 31st May 2020 were included. In this study, we adhered to the national COVID-19 practice guidelines issued by the Malaysian Ministry of Health for the management of suspected and confirmed COVID-19 cases in the adult population.[20,21] Case-specific information including demographics, clinical information, laboratory results and plain chest radiographs were collected at the presentation. Routine blood investigations (full blood count with differential count, renal and liver function tests) were performed in all cases.[16,21] Coagulation profile, serum C-reactive protein, lactate dehydrogenase, ferritin and procalcitonin were only performed in symptomatic patients who required supplemental oxygen or higher respiratory support, subject to the availability of these tests at each study site.[16,21] D-dimer testing was not routinely available at all sites.

Confirmation of COVID-19 was defined by a positive rRT-PCR for SARS-CoV-2 viral nucleic acid in naso-pharyngeal swabs. Patients who tested negative remained designated as probable COVID-19 if their clinical presentation was compatible with the disease and no alternative cause was found to account for their symptoms. A non-COVID-19 diagnosis was ultimately concluded if further investigations revealed an alternative clinical explanation for the acute presentation. Patients with confirmed COVID-19 were stratified according to the location of care – medical ward or the intensive care unit (ICU) and method of transmission. Criteria for ICU admission included critical illness with multiorgan dysfunction, symptomatic or objective deterioration and/or increasing oxygen requirement over a 24-hour period despite ward measures.[20,21] All patients were followed until hospital discharge or death.

Acquisition and Scoring of Plain Chest Radiographs

Plain chest radiography was acquired as digital studies in the Emergency or the Radiology Department as part of standard clinical care. All radiographs were collated on a secure DICOM storage driver by a named site radiologist who conveyed the data to a centralised group of four study radiologists to be scored according to a template agreed a priori. The scoring team comprised an experienced thoracic radiologist (ZAH) and three senior thoracic radiology fellows who were blinded to the final clinical diagnosis and outcome.

The presence of radiographic ground-glass, consolidative, reticular and nodular opacities was recorded based on Fleischner society standard definitions.[22] Each hemithorax was divided into three horizontal zones bordered by the 4th and 8th ribs into upper, middle and lower zones; the number of zones affected (0–6) was recorded. The distribution of radiographic abnormalities was categorised by first dividing each hemithorax into three vertical zones; a central distribution was defined by involvement of the two most medial zones while a peripheral distribution was defined by involvement of the lateral third of either or both hemithoraces.

A week prior to commencement of the study, 50 randomly selected plain chest radiographs from COVID-19 patients were scored independently by members of the radiology panel. Moderate to good interobserver agreement was achieved for the presence of ground-glass opacity (κ=0.931, 95% CI 0.725-1.138), consolidation (κ=1.000, 95% CI 0.793-1.207) and reticulation (κ = 0.754, 95% CI 0.547-0.960). Good interobserver agreement was also observed for zonal involvement (κ = 0.751, 95% CI 0.643-0.858) as well as the distribution of abnormalities (κ=0.744, 95% CI 0.616-0.871).

Table I: Baseline clinical, laboratory and plain radiographic characteristic of confirmed COVID-19 cases stratified to a mode of transmission

		Overall N=321	Transmission		*p* value
			Cluster N=299	Sporadic N=22	
Clinical					
Age, median (IQR), years		34.0 (26.0-50.0)	33.0 (25.0-47.0)	50.0 (36.5-58.7)	<0.05
Gender, n (%)	Male	213 (66.4)	201 (67.2)	12 (54.5)	0.246
	Female	108 (33.6)	98 (32.8)	10 (45.5)	
Ethnicity, n (%)	Malay	180 (72.3)	174 (75.7)	6 (31.6)	<0.001
	Chinese	30 (12.0)	23 (10.0)	7 (36.8)	
	Indian	6 (2.4)	5 (2.2)	1 (5.3)	
	Native	33 (13.3)	28 (12.2)	5 (26.3)	
Current Smoker, n (%)		41 (13.4)	36 (12.7)	5 (22.7)	0.194
Presence of Co-morbidities, n (%)		70 (21.8)	58 (19.4)	12 (54.5)	<0.001
Co-morbidities, n (%)	Hypertension	49 (15.3)	42 (14.0)	7 (31.8)	<0.05
	Cardiovascular	11 (3.4)	9 (3.0)	2 (9.1)	0.130
	Diabetes mellitus	27 (8.4)	21 (7.0)	6 (27.3)	<0.05
	Malignancy	5 (1.6)	3 (1.0)	2 (9.1)	<0.05
	COPD	5 (1.6)	4 (1.3)	1 (4.5)	0.241
	Chronic kidney disease	7 (2.2)	6 (2.0)	1 (4.5)	0.431
Symptomatic, n (%)		122 (38.0)	105 (35.1)	17 (77.3)	<0.001
Symptoms	Fever	63 (19.6)	51 (17.1)	12 (54.5)	<0.001
	Cough	67 (20.9)	58 (19.4)	9 (40.9)	<0.05
	Sore throat	34 (10.6)	33 (11.0)	1 (4.5)	0.490
	Dyspnoea	22 (6.9)	16 (5.4)	6 (27.3)	<0.05
Temperature, median (IQR), °C		36.7 (36.5-37.0)	36.7 (36.5-37.0)	36.6 (36.4-36.9)	0.282
SpO_2, median (IQR), %		98.0 (97.0-99.0)	98.0 (97.0-99.0)	97.5 (96.0-99.0)	0.062
Heart rate, median (IQR), *beats/m*		86.0 (77/2-97.0)	86.0 (18.0-20.0)	90.0 (76.5-99.0)	0.383
Respiratory rate, median (IQR), *breathe/m*		20.0 (18.0-20.0)	20.0 (18.0-20.0)	20.0 (19.0-21.5)	0.069
Systolic blood pressure, median (IQR), mmHg		130.0 (121.0-140.0)	131.0 (122.0-140.0)	124.0 (114.0-142.0)	0.295
Laboratory					
Haemoglobin, median (IQR), g/dL		14.30 (13.10-15.40)	14.30 (13.20-15.40)	12.40 (11.30-15.05)	<0.05
Total white blood cell, median (IQR), × 10^9/L		8.00 (6.60-9.40)	8.00 (6.60 9.24)	8.00 (7.60-12.33)	<0.05
Absolute lymphocyte count, median (IQR), × 10^9/L		2.20 (1.70-2.78)	2.20 (1.78-2.79)	1.56 (0.88-2.79)	<0.05
Platelet, median (IQR), × 10^9/L		267 (222-311)	267 (222-314)	266 (198-294)	0.601
Blood urea nitrogen, median (IQR), *mmol/L*		3.80 (3.00-4.55)	3.70 (2.92-4.40)	4.60 (3.60-7.35)	<0.05
Alanine aminotransferase, median (IQR), *mmol/L*		25.0 (16.0-43.0)	25.0 (16.0-43.0)	32.0 (18.0-97.0)	0.294
C-reactive protein, median (IQR), *mg/dL*		0.40 (0.40-1.00)	0.40 (0.40-0.80)	6.00 (1.55-182.50)	<0.001
Radiographic					
Chest X-Ray Available, n (%)		316 (98.4)	295 (98.7)	21 (95.5)	0.241
Chest X-Ray Abnormal, n (%)		109 (34.5)	97 (32.9)	12 (57.1)	<0.05
Ground Glass Opacities, n (%)		90 (28.5)	80 (27.1)	10 (47.6)	<0.05
Consolidation, n (%)		34 (10.8)	29 (9.8)	5 (23.8)	<0.05
Reticulation, n (%)		29 (9.2)	23 (7.8)	6 (28.6)	<0.05
Bilaterality, n (%)		51 (16.1)	42 (14.2)	9 (42.9)	<0.05
Zone, n (%)	Upper	4 (3.7)	3 (3.1)	1 (9.1)	0.604
	Mid-Lower	80 (74.8)	72 (75.0)	8 (72.7)	
	No zonal predilection	23 (21.5)	21 (21.9)	2 (18.2)	
Distribution, n (%)	Central	27 (25.2)	26 (27.1)	1 (9.1)	0.179
	Peripheral	43 (40.2)	40 (41.7)	3 (27.3)	
	Mixed	28 (26.2)	23 (24.0)	5 (45.5)	
	Diffuse	9 (8.4)	7 (7.3)	2 (18.2)	
Outcomes					
ICU admission, n (%)		16 (5.0)	11 (3.7)	5 (22.7)	<0.001
Death, n (%)		2 (0.6)	1 (0.3)	1 (4.5)	<0.05

*Data are presented in median (IQR) and n (%). ICU = Intensive care unit.

Table II: Chest radiographic profile of confirmed COVID-19 patients stratified to ICU admission (n=316)

		Non-ICU Admission	ICU Admission	*p* value
Number of cases available for analysis, n (%), N=321		300 (98.3)	16 (100.0)	-
Abnormal CXR, n (%), N=316		93 (31.0)	16 (100.0)	<0.001
Ground Glass Opacities, n (%), N=109		76 (81.7)	14 (87.5)	0.574
Consolidation, n (%), N=109	19 (20.4)	14 (87.5)	<0.001	
Reticulation, n (%), N=109	16 (17.2)	12 (75.0)	<0.001	
Bilateral Changes, n (%), N=109		36 (38.7)	15 (93.8)	<0.001
Zone, n (%), N=107	Upper	4 (4.4)	0 (0.0)	<0.05
	Mid-Lower	73 (80.2)	7 (43.8)	
	No Zonal Predilection	14 (15.4)	9 (56.2)	
Distribution, n (%), N=107	Central	26 (28.6)	1 (6.2)	<0.001
	Peripheral	42 (46.1)	1 (6.2)	
	Mixed	17 (18.7)	11 (68.8)	
	Diffuse	6 (6.6)	3 (18.8)	
Total Zonal Involvement, median (IQR), N=109		2.0 (1.0-2.5)	4.0 (3.2-5.0)	<0.001

*Data are presented in median (IQR) and n (%). N is the total number of patients with available data. p-values were calculated by Kruskall Wallis Test, X2 test or Fisher's exact test as appropriate. CXR = chest radiograph, ICU = Intensive care unit

Table III: Performance of WHO suspected COVID-19 case definition with or without abnormal baseline plain chest radiograph (n=540)

	rRT-PCR Positive Rate, % (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	Diagnostic Accuracy, % (95% CI)
Overall (N=540)						
Fulfilled WHO Criteria	59.4 (55.1-63.6)	11.8 (8.5-15.9)	69.8 (63.3-75.8)	36.5 (28.6-45.2)	35.1 (32.9-37.3)	35.4 (32.9-43.9)
Fulfilled WHO Criteria and/*or* Abnormal CXR*	61.12 (56.7-65.3)	38.3 (32.9-43.9)	28.8 (22.7-35.6)	45.8 (41.7-49.9)	22.9 (19.1-27.3)	34.6 (30.5-38.9)
Cluster-associated Transmission (N=350)						
Fulfilled WHO Criteria	85.4 (81.2-88.9)	10.0 (6.8-14.0)	74.5 (60.3-85.6)	69.7 (56.3-80.4)	12.3 (10.7-14.2)	19.4 (15.4-23.9)
Fulfilled WHO Criteria and/*or* Abnormal CXR*	85.2 (81.0-88.8)	36.2 (30.7-42.0)	58.8 (44.1-72.4)	83.5 (78.0-87.9)	13.7 (11.1-16.9)	39.6 (34.4-44.9)
Sporadic Transmission (N=190)						
Fulfilled WHO Criteria	11.5 (7.4-17.0)	36.3 (17.2-59.3)	68.4 (60.8-75.3)	13.1 (7.6-21.5)	89.1 (85.4-91.9)	64.7 (57.4-71.5)
Fulfilled WHO Criteria and/*or* Abnormal CXR*	12.2 (7.7-18.1)	66.6 (43.0-85.4)	18.6 (12.7-25.8)	10.2 (7.7-13.5)	80.0 (66.7-88.8)	24.5 (18.3-31.7)

CXR = Chest radiograph, rRT-PCR = real time reverse transcriptase polymerase chain reaction, WHO = World Health Organization

Statistical Analysis

Data analysis was performed using SPSS, version 21 (Chicago, IL, USA). Normality of distribution was assessed by the Shapiro–Wilk test. Categorical data were expressed as frequency (percentage), with significance determined by the Pearson Chi-square or Fisher's exact test. Continuous parametric variables were expressed as mean (standard deviation) or median (interquartile range, IQR), with differences analysed by the independent t-test or Mann–Whitney U test. Interobserver agreement in relation to chest radiographic findings was evaluated by Fleiss' kappa coefficient. Sensitivity, specificity, positive predictive and negative predictive values were calculated using standard definitions via 2 × 2 contingency tables using SARS-CoV-2 rRT-PCR as the reference standard for COVID-19 diagnosis. Diagnostic accuracy was defined by the proportion of patients correctly classified by the screening criteria. For all analyses, $p<0.05$ was considered statistically significant.

RESULTS

Characteristics of the Study Population

A total of 540 individuals were recruited during the 8.5-week study period, comprising those who presented acutely to the study hospitals with symptoms suggestive of COVID-19 (190; 35.2%) and those who were contact-traced from cluster outbreaks of COVID-19 (350; 64.8%). The positive SARS-CoV-2 rRT-PCR test rate of the whole cohort was 59.4% (321/540). The remaining 40.6% (219/540) who tested negative included 19 cases ultimately labelled as probable COVID-19 due to COVID-19-compatible symptoms and 200 non-COVID-19 cases where an alternative diagnosis was identified to explain their clinical presentation.

The median age of the study cohort was 40 (IQR 28-58) with male gender accounting for almost two-thirds (63.1%) of all cases. The baseline demographic, clinical and radiographic characteristics of the cohort are summarised in Table I.

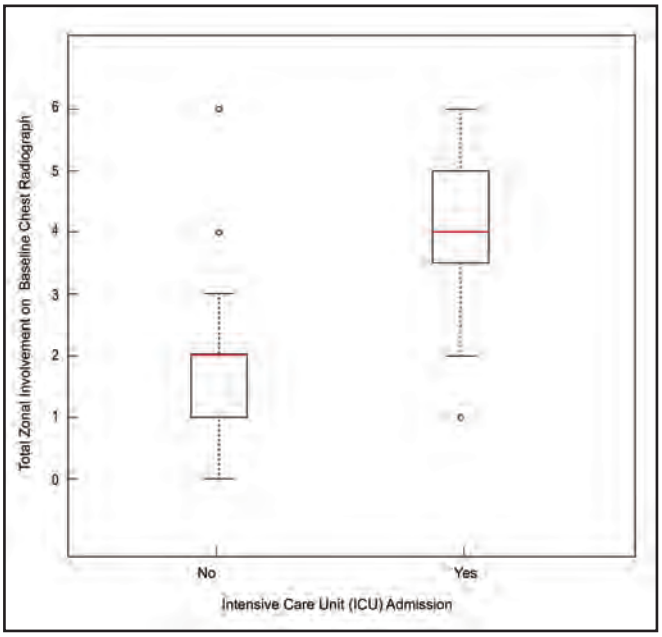

Fig. 1: Box and whisker plot demonstrating total zonal involvement on COVID-19's baseline chest radiograph in patients managed in medical ward versus patients requiring intensive care unit admission.

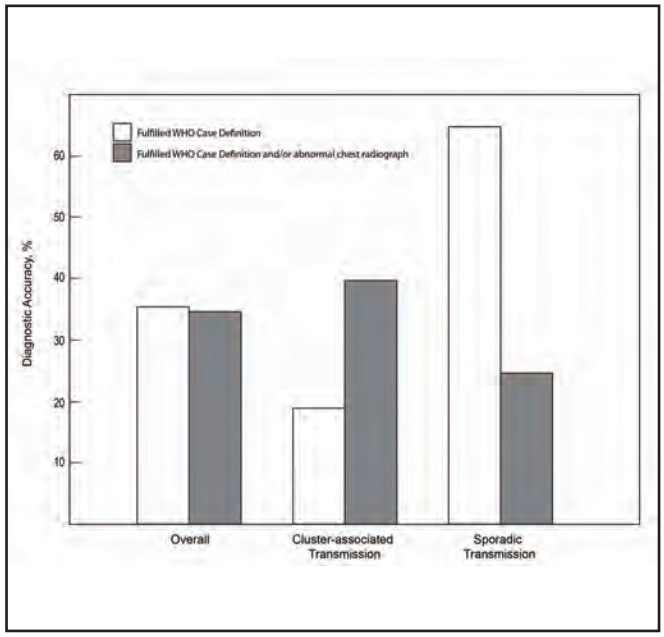

Fig. 2: Performance of WHO suspected COVID-19 case definition with or without abnormal baseline chest radiograph in overall, cluster-associated and sporadic transmission cohort.

Differences Between Sporadically Transmitted and Cluster-Associated COVID-19 Cases

93.1% (299/321) of cases that tested positive for SARS-CoV-2 were identified through the investigation of cluster outbreaks compared to only 6.9% occurring as sporadic COVID-19 cases with no epidemiologic link to a cluster. As most of the cluster outbreaks occurred in the Klang Valley urban conurbation around the capital Kuala Lumpur, the majority of COVID-19-positive patients recruited at HKL (86.2%; 43/50) and HSB (96.2%; 200/208) were identified through cluster contact tracing.[2]

COVID-19 patients detected through the screening of clusters were significantly younger (33 [IQR 25-47] vs. 50 [IQR 36-58], $p<0.05$), had significantly fewer comorbidities (19.4% vs. 54.5%, $p<0.001$) and were less likely to be symptomatic (35.1%; 105/299 vs. 77.3%; 17/22; $p<0.001$). The baseline vital indices (temperature, saturation, respiratory rate and systolic blood pressure) did not differ among the cluster or sporadic transmission groups. Malay ethnicity was associated with a higher proportion of COVID-19 cases from the cluster-screened group than non-Malay ethnicities (75.7%; 174/299 vs. 54.5%; 6/22, $p<0.001$). Hypertension, the commonest reported co-morbidity was more prevalent in the sporadic transmission group (14.0% and 31.8% respectively, $p<0.05$), as well as diabetes mellitus and underlying malignancy ($p<0.05$ for both).

The majority (95%) of patients with COVID-19 received ward-based care. 5% (16/321) of these patients were transferred to the ICU after a median of 6 (IQR 3.2-9.5) days on the medical ward; of these, 62.5% (10/16) were intubated and received invasive mechanical ventilation. Overall, the mortality rate for confirmed COVID-19 cases was very low at 0.6%, significantly lower still in the cluster-screened compared to sporadically transmitted cases (0.3% vs. 4.5%, $p<0.05$). These findings are summarised in Table I.

Baseline Radiographic Findings in Confirmed COVID-19 Cases

95.7% (517/540) of the whole study cohort underwent baseline chest radiography. Of the patients who tested positive for SARS-CoV-2, 98.4% (316/321) had a baseline chest radiograph. Just over a third of these were abnormal (34.5%; 109/316). In contrast, nearly two-thirds (62.2%) of patients who tested negative for SARS-CoV-2 had a baseline radiograph that was reported as abnormal.

Among the confirmed COVID-19 cases, the commonest radiographic abnormalities, present in isolation or in combination, were ground-glass opacity (28.5%, 90/316) and consolidation (10.8%, 34/316). These changes were evident bilaterally in 16.1% of cases and predominated in the middle and lower zones (Table I). Other radiographic findings are listed in Supplementary Table S6. COVID-19 patients who presented sporadically were more likely to have abnormal chest radiograph at baseline (57.1% vs. 32.9%, $p<0.05$) with nearly half of the patients (42.9%) presenting with bilateral radiographic changes with more diffuse distribution.

Abnormalities on the baseline radiographs of COVID-19 patients who subsequently required ICU admission were more likely to be distributed diffusely or to show mixed central and peripheral opacities without clear zonal demarcation (68.8% vs 18.7%, $p<0.001$). As a result, total zonal involvement quantified as a median value was higher in the ICU subgroup (4 [IQR 3.2-5.0] vs. 2 [IQR 1.0-2.5], $p<0.001$) (Figure 1 and Table II).

Performance of the WHO Clinical Definition for Suspected COVID-19

Approximately 1 in 5 (104/540; 19.2%) of the entire study cohort met the WHO clinical definition for suspected COVID-19. This definition was met by a significantly higher proportion of cases that had no links to a cluster outbreak (32.1%; 61/190) than those who were identified from clusters (12.3%; 43/350; $p<0.001$). Among the confirmed COVID-19 cases, only 11.8% (38/321) met the WHO case definition for suspected COVID-19.

Overall, the WHO clinical definition correctly classified only 35.4% of COVID-19 patients in our study cohort, with an overall sensitivity of 11.8% and positive predictive value of 36.5%. The addition of an abnormal baseline chest radiograph increased both parameters to 38.3% and 45.8%, respectively but was associated with decreased specificity. This change translated to an overall diagnostic accuracy of 34.6%, which was not different from employing the case definition alone with radiography.

Among cluster-associated cases, the WHO definition correctly identified only 19.4% of patients and misclassified the remaining 80.6%. The misclassification rate was reduced to 60.4% with the addition of a chest radiograph obtained at the presentation. In contrast, 64.7% of the self-presenting (non-cluster associated) cases were correctly classified by the same definition, although the addition of radiographic information reduced this classification accuracy to 24.5% (Figure 2). The details of the overall diagnostic performance with corresponding 95% confidence intervals are shown in Table III.

DISCUSSION

Our study, conducted across four major hospitals, provides an account of the characteristics of first-wave COVID-19 in Malaysia. The majority of individuals who tested positive for SARS-CoV-2 were identified by screening the contacts of index COVID-19 cases within epidemiologic clusters (groups of individuals aggregated by common geographic, temporal and exposure factors).[12] Our cohort therefore differs from reports of predominantly sporadic or isolated case transmission, with its distinctively lower median age, higher proportion of asymptomatic cases, fewer co-morbidities, infrequent radiographic abnormalities and low mortality.

The low COVID-19-associated case fatality rate in the present study is in line with the officially published first-wave death rate of 1.4% in Malaysia and comparable to the mortality rate of COVID-19 in neighbouring countries.[6,23-27] Patients in our study population presented with symptoms similar to those reported in high-incidence regions.[28-30] Descriptions of cluster outbreaks elsewhere have similarly highlighted a high number of mild cases with few deaths.[31] The reasons underpinning the low mortality in cluster transmissions are poorly understood; like patients who present sporadically and have no link to clusters, such cases are managed according to their clinical status and were not pre-emptively given corticosteroids or other treatments. However, younger age, a common characteristic amongst cluster-linked cases, has been associated with a lower likelihood of acquiring SARS-CoV-2 infection and reduced susceptibility to the severe clinical manifestations of COVID-19.[32,33] There is also a broad acknowledgement that children do not develop COVID-19 as readily as adults and those of older age run the highest risk of a fatal outcome.[26,30,32,34]

Ethnicity has emerged as an important risk factor for COVID-19 globally. The reasons why Malay ethnicity was associated with a higher proportion of COVID-19 cases from the cluster-screened group in our analysis are unclear; however, the prevalence of Malay ethnicity in the current study closely reflected the background ethnic distribution in Malaysia.[35] A higher frequency of Malay ethnicity has also been reported in patients with severe COVID-19 in Malaysia, including those who were admitted to the ICU.[27] A higher risk of acquiring the infection amongst the Malay population may potentially be linked to a greater proportion of multigenerational families, more frequent social congregation within common domiciliary areas and the smaller size of dwellings in Malay-populated semi-urban locations. A higher diagnostic rate of COVID-19 may also have resulted from a number of well-publicised large outbreaks of COVID-19 linked to mass religious gatherings during the first wave of COVID-19 pandemic in Malaysia.[5]

Descriptions of the plain radiographic presentation of COVID-19 in South-East Asia are few. A recent study reported that COVID-19 patients with bilateral and predominantly upper and middle zone abnormalities were more likely to require supplementary oxygen.[36] In the present study, only a third of the baseline chest radiographs were abnormal, lower than the 50–69% frequency of radiographic abnormalities reported by others.[37-40] This disparity likely reflects differences in cohort constitution such as the higher rate of acute symptomatic COVID-19 cases in studies that did not involve active contact tracing. Two of our main observations were consistent with the experience of others, namely that COVID-19 pneumonia has a predilection for the peripheral lower zones and that patients who require ICU admission have more diffuse radiographic changes on admission.[36-40] Crucially, there was also considerable overlap in the radiographic findings between COVID-19 patients and individuals with alternative diagnoses in the population that we studied.

Application of the WHO case definition of suspected COVID-19 to our overall population resulted in the misclassification of 64.6% of cases, a rate that was not diminished by the addition of chest radiographic information. This phenomenon was likely related to the high prevalence of asymptomatic cases in this population as the WHO clinical case definition released during the early part of the SARS-CoV-2 outbreak emphasised 'alert' symptoms namely fever, cough or dyspnoea.[10] Amongst the non-cluster identified cases in our study, the WHO clinical criteria correctly identified 64.7% with COVID-19. However, its accuracy was paradoxically reduced by the addition of radiographic information due to the misdiagnosis of alternative conditions that presented with similar clinical and radiographic features. In effect, our observations reveal the limitations of the WHO case definition when applied to populations with sparse or non-specific symptomatology and who may not

reveal themselves to have been potentially exposed to SARS-CoV-2 within a case cluster at the time of presentation. They also show that plain chest radiography has low diagnostic sensitivity for COVID-19 when the rate of community transmission of SARS-CoV-2 is not high.

The following limitations are notable. The high proportion of cluster-screened cases may have biased our study towards a higher COVID-19 identification rate. However, our observations reflected the prevailing disease transmission situation in Malaysia at the time of the study. The cases presenting to HSB were enriched for SARS-CoV-2 positivity, given its role as the national infectious disease referral centre. Inclusion of two hospitals on the island of Borneo allowed us to include cross-sectional cohorts of suspected COVID-19 from two centres distant from the capital city. The lack of detailed epidemiologic information on the clusters from which some of our patients came precluded an in-depth analysis of the transmission chain. Similarly, we did not have information on viral clearance or clinical sequelae beyond the period of hospitalisation as the study was not designed to collect follow-up data. However, we note that the case fatality rate of COVID-19 in Malaysia has remained static since the completion of the study. The absence of a detailed acute blood work-up including D-dimer was due to the inconsistent availability of these assays across the study sites. Nonetheless, the clinico-radiographic features of COVID-19 patients in this study are similar to those reported from other countries. Finally, the true performance of the WHO suspected case definition may have been underestimated as the diagnosis of probable COVID-19 was based on a single rather than serial negative swab results. Repeat testing would have been ideal but it was not possible within the limitations of this study. Admittedly, the group of patients in question constituted a minority (3.5%) of the overall cohort.

CONCLUSION

In Malaysia, one consequence of the common occurrence of cluster outbreaks is the higher frequency of asymptomatic cases present within small geographic areas. Whether this observation helps explain the low case fatality rate in this country is unclear. Our findings show that the WHO case definition for identifying suspected COVID-19 performed poorly in this setting and support the view that large-scale viral testing, rigorous contact screening and strict containment measures, including movement control policies, remain key to efforts to control SARS-CoV-2 transmission.

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