Clinical, laboratory, and radiological features indicative of novel coronavirus disease (COVID-19) in emergency departments: a multicenter case-control study in Hong Kong

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Abstract

Objectives: Little is known about the value of routine clinical assessment in identifying patients with coronavirus disease 2019 (COVID-19) in the emergency department (ED). We aimed to compare the exposure history, signs and symptoms, laboratory, and radiographic features of ED patients who tested positive and negative for COVID-19.

Methods: This was a case-control study in 7 EDs in Hong Kong from 20 January to 29 February 2020. Thirty-seven patients with laboratory-confirmed COVID-19 were age- and sex-matched to 111 controls. We compared the groups with univariate analysis and calculated the odds ratio (OR) of having COVID-19 for each characteristic that was significantly different between the groups with adjustment for age and presumed location of acquiring the infection.

Results: There were no significant differences in patient characteristics and reported symptoms between the groups. A positive contact history within 14 days (adjusted OR 37.61, 95% CI: 10.86–130.19), bilateral chest radiograph shadow (adjusted OR 13.19,

95% CI: 4.66–37.35), having prior medical consultation (adjusted OR 7.43, 95% 2.89–19.09), a lower white blood cell count (adjusted OR 1.30, 95% CI: 1.11–1.51), and a lower platelet count (adjusted OR 1.07, 95% CI: 1.01–1.12) were associated with a higher odds of COVID-19 separately. A higher neutrophil count was associated with a lower odds of COVID-19 (adjusted OR 0.77, 95% CI: 0.65–0.91).

Conclusion: This study highlights a number of clinical features that may be useful in identifying high-risk patients for early testing and isolation while waiting for the test result. Further studies are warranted to verify the findings.

KEYWORDS
2019 novel coronavirus disease, COVID-19, severe acute respiratory syndrome coronavirus 2, emergency department, early diagnosis, case-control studies

1 | INTRODUCTION

2 | Background

On 11 March 2020, the World Health Organization (WHO) declared the coronavirus disease 2019 (COVID-19) a pandemic.[1] Within 5 months of its first emergence in Wuhan,[2,3] severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly spread globally, having infected 6.4 million people[4] and caused many more deaths than severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) combined.[5] WHO advises to test every suspected case and isolate those who test positive.[1,6] Healthcare systems worldwide now face the overwhelming demand for rapid testing and isolation.

2.1 | Importance

Emergency departments (EDs) are patients' first contact point with the healthcare system in most countries and they play a critical role in diagnosis and decisionmaking on isolation. However, access to real-time reverse transcriptase-polymerase-chain-reaction (RT-PCR) testing is limited, especially in the initial phases of the outbreak and in resource-poor settings. In Hong Kong, even though the laboratory testing capacity has been expanded as the pandemic evolves,[7] the turnaround time of RT-PCR, frequently up to several hours even in university hospitals,[8] is too long to support clinical decision. Given the limited number of airborne infection isolation rooms (AIIRs), emergency physicians still rely on travel or contact history, presenting signs and symptoms, routine laboratory tests, and imaging when deciding where to place the suspected cases while waiting for test results. Despite this, little is known about the value of routine clinical assessment in identifying COVID-19 patients in the ED setting.

Published studies thus far have mainly focused on clinical features of confirmed COVID-19 cases and have portrayed a diverse clinical spectrum of the disease, ranging from asymptomatic infection to acute respiratory distress syndrome, rapid progression to multi-organ failure, and death.[9–20] Fever,[9,11–19] cough,[9,11–19] fatigue,[9,12,16–18] dyspnea,[9,11,19] leukopenia,[13,16,18] lymphopenia,[9,11–14,16–18,20] elevated levels of C-reactive protein[11,13,19] and lactate dehydrogenase,[11,12,14,19] patchy shadowing on chest radiography,[13,14] and ground-glass opacities on computed tomography (CT) of the thorax[9,11–14,16,18] are consistently reported across different case series. However, it is unclear whether they are useful in differentiating patients with COVID-19 from those without in the ED setting.

2.2 | Goals of this investigation

We conducted this study in the first 5 weeks of the pandemic in Hong Kong with an aim to identify clinical characteristics, laboratory and radiological findings on ED presentation that may aid early recognition of COVID-19 infection. We compared laboratory confirmed COVID-19 cases with patients who were tested for suspected infection but tested negative and determined the risk of COVID-19 for each clinical characteristic that was significantly different between the groups.

3 | METHODS

3.1 | Study design and setting

We conducted a case-control study in the ED of 7 public hospitals under the Hospital Authority (HA) of Hong Kong, which manages all public hospitals organized in 7 geographical clusters.[21] The 7 study sites, 1 in each of the 7 hospital clusters, included 2 university-affiliated hospitals and 5 acute regional hospitals. The study was approved by the institutional review boards of all study hospitals (HKU/HKWC IRB UW 20–087, HKECREC-2020-017, NTEC-2020-0092, REC (KC/KE)-20-0049/ER-2, REC (KC/KE)-20-0051/ER-2, KWC-2020-0032, NTWC-2020-0026) with written consent waived in light of the retrospective study design and anonymized use of data.

Immediately following the official announcement of a cluster of patients with pneumonia of unknown etiology in Wuhan by the National Health Commission of the People's Republic of China, the Hong Kong Department of Health (DoH), through the HA, implemented a bundle of measures to facilitate early recognition, isolation, notification, and molecular testing for all suspected cases.[8] All ED patients are screened by staff for possible COVID-19 infection at the entrance based on the DoH's epidemiological and clinical criteria that have evolved as the pandemic unfolded (Supplementary Table 1).

> **The Bottom Line**
>
> This is a study of consecutive COVID-19 patients presenting to 7 EDs in Hong Kong during the early pandemic. During this time period, every patient with suspected COVID-19 was admitted to the hospital, so this study provides valuable insight into the clinical features of this early group of infected patients.

3.2 | Selection of participants

We set our study period from 20 January 2020 to 29 February 2020, with the intention to gather information from the initial phase of the pandemic to inform clinical decisionmaking. During that period of time, Hong Kong witnessed the first imported case from Wuhan (22 January 2020), followed by intermittent presentations of local cases. All suspected cases in ED were admitted to the hospital as inpatients, isolated preferably in AIIRs, and tested for SARS-CoV-2 after admission to minimize community spread of the infection. We recruited cases who were admitted to the hospital from the study EDs as inpatients with laboratory confirmation of COVID-19 infection. Controls were patients admitted through the study EDs during the same period for COVID-19 RT-PCR testing but who tested negative. Patients of all age groups were included. We excluded patients who were (1) admitted to the study hospitals under DoH isolation orders from sources other than ED, such as quarantine camps, because they might have different risk profiles and clinical presentations compared with ED patients; (2) patients transferred from another hospitals because interventions received before transfer may have altered the clinical characteristics.

Eligible patients were identified by searching the Hospital Authority Clinical Data Analysis and Reporting System, which is a centralized repository of electronic medical records in the HA. We used laboratory test orders for COVID-19 RT-PCR as the search criterion. During the study period, 14,595 RT-PCR tests were ordered for 10,845 patients in the study hospitals, of whom 37 confirmed cases and 9283 negative cases were admitted through the ED (Figure 1). We matched each confirmed case with 3 negative control cases, who were randomly selected from the same hospital within 5 days of presentation, and were the same sex and similar age (±5 years). The controls were selected by a biostatistician using the statistics software R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria) with no knowledge of their clinical presentations. They represented the population at risk of COVID-19 infection.[22]

3.3 | Exposures

During the study period, there was no standard data collection in the study sites. We reviewed electronic medical records and used a standardized data collection to extract demographic, epidemiological, clinical, laboratory, radiological, treatment and outcome data. Each patient record was reviewed independently by the study lead investigator and a local co-investigator, with any disagreement resolved by discussion. All data abstractors were emergency medicine specialists with >8 years of clinical experience. We cross-checked the exposure history of each confirmed case with the official account released by the DoH. Starting from 6 February 2020, ED staff had access to all patient cross-border travel records to mainland China or other countries within 30 days of ED registration. This information, provided by the Immigration Department, further improved the accuracy of travel history. For travel history outside Wuhan/Hubei, we defined a place with active community transmission of COVID-19 based on the prevailing DoH's criteria for disease notification (Supplementary Table 1).

3.4 | Measurements

We extracted symptoms as reported in the medical record. For patient-reported fever, we did not specify the temperature threshold because most clinicians did not record the temperature reported by the patients and how it was measured. We reviewed the consultation history of each patients and considered any visit to any health care provider for the same physical complaints within 1 month before their index ED presentation as "prior medical consultation." For patients with multiple ED attendances within the study period, only the visit that led to hospital admission and COVID-19 testing were selected.

We reviewed the results of complete blood count, coagulation profile, erythrocyte sedimentation rate (ESR), liver and renal function, lactate dehydrogenase, C-reactive protein, procalcitonin, creatine kinase, d-dimer, lactate, bacterial cultures, and RT-PCR for other viruses, wherever available, collected on presentation or hospital admission. For laboratory tests ordered later in the clinical course, we obtained the first test results available up to 48 hours of ED presentation in order to reduce missing values. Beyond that, the laboratory results are likely to have been affected by medical interventions after admission and possible nosocomial infection. As for radiographic findings, we recorded the interpretation of the reporting radiologist or treating clinicians, wherever available. We followed up the clinical outcome of all patients up to 16 March 2020. To avoid misclassifying false negative cases as controls, we reviewed their clinical notes after hospital discharge and did not identify any COVID-19-related reattendance.
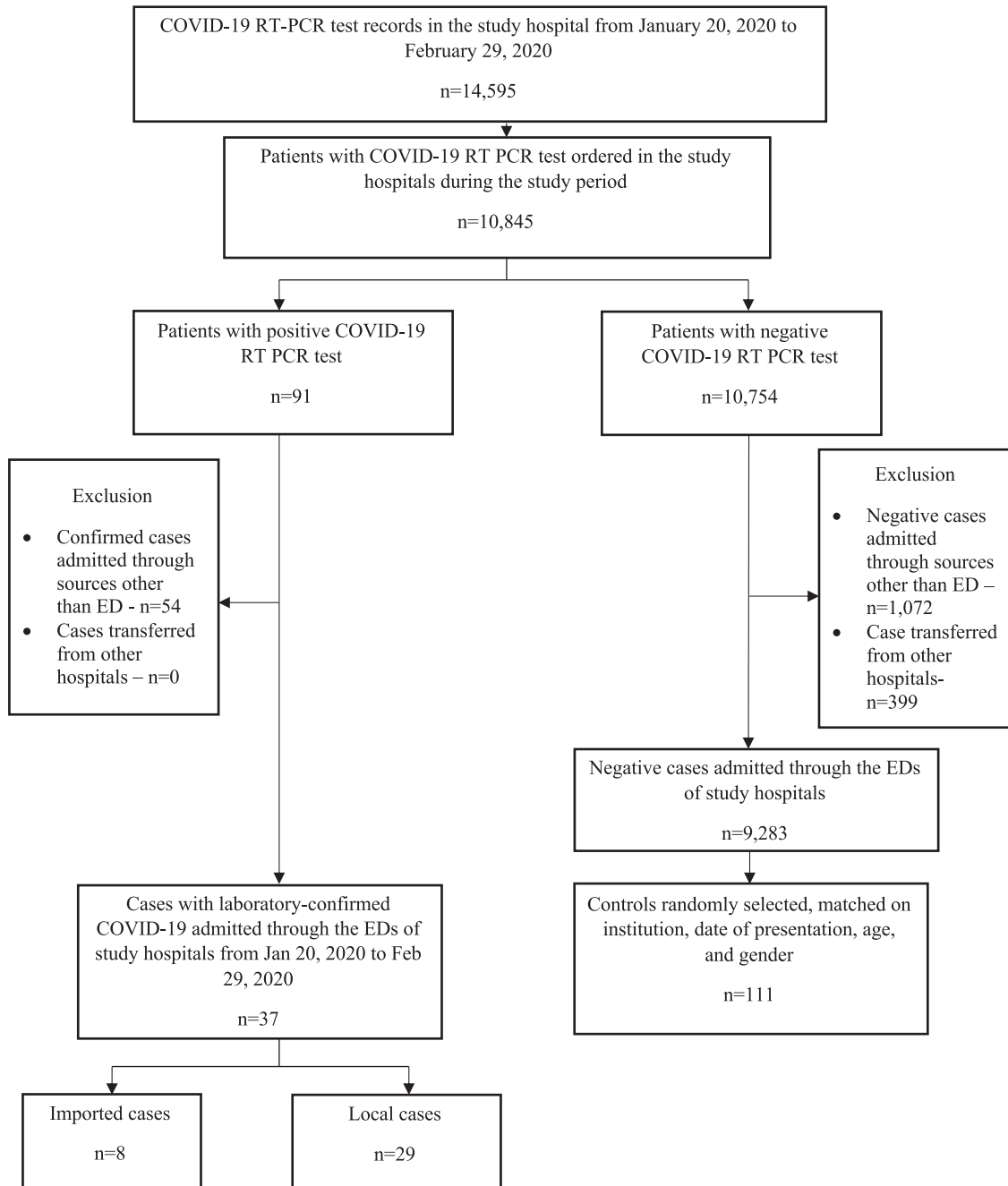
FIGURE 1 Flow diagram of cases and controls selection.

3.5 | Primary outcome

The primary outcome was laboratory-confirmed COVID-19 infection, defined as a positive result on RT PCR test for SARS-CoV-2 in any biological specimen collected from the patient irrespective of clinical signs and symptoms, as defined in the WHO interim guidance.[6] RT-PCR tests were ordered at the discretion of the attending clinicians based on the HA's three-tier extended laboratory surveillance criteria (Supplementary Table 2). In-house RT-PCR tests were developed and performed in parallel in the respective hospitals and the government public health laboratory in accordance with prevailing local practice.[8]

3.6 | Analysis

A priori sample size calculation was not feasible because we could not predict the number of cases at the outset of the pandemic. It was our intention to include and analyze all cases who were eligible for inclusion during the study period. Missing values were not imputed and they were labeled with a designated code for exclusion in analysis when individual variables were compared.

We used descriptive statistics to analyze the data, with categorical variables reported as proportions and continuous variables as mean +/- standard deviation or median with interquartile range (IQR), as

appropriate. We used Chi-square test or Fisher's exact test for comparison of categorical variables between groups, and the Student's t-test or Mann-Whitney U test for continuous variables, as appropriate. We determined the odds ratio (OR) and the corresponding 95% confidence interval (CI) for variables with a significant association in univariate analysis. Since age has been associated with a poor outcome [14-16,23] and infection outside Wuhan appeared to be milder in previous studies,[16,17] we used multivariable logistic regression to adjust the ORs for the patient's age (<65 or $>/ = 65$ years) and presumed location of acquiring the infection in Wuhan/Hubei (we used travel history to Wuhan/Hubei as a surrogate since patients with such a travel history were regarded as having contracted COVID-19 infection there).[24] The Statistical Package for the Social Sciences for Windows version 23.0 (IBM Corp., Armonk, NY, USA) was used for data analysis. To account for multiple comparison, we conducted Bonferroni correction of the P value by dividing $\alpha = 0.05$ by 65 (the number of comparisons). A P value <0.0008 (shown as $P < 0.001$ in the tables) was considered to be statistically significant.

4 | RESULTS

4.1 | Characteristics of study subjects

During the study period, there were 37 confirmed cases, including 8 imported cases and 29 local cases, who were matched to 111 controls admitted through the EDs of the study hospitals as inpatients. The median age of the confirmed cases was 63.0 years (IQR 55.5–71.0) and there was no sex preponderance.

4.2 | Main results

There were no significant differences between the cases and controls regarding age, sex, smoking history, and co-morbidities (Table 1). A significantly higher proportion of cases had a travel history to Wuhan/Hubei (21.6% vs 0.9%, $P < 0.001$) and a contact history with a person with confirmed COVID-19 infection (48.6% vs 2.7%, $P < 0.001$). Compared with the controls, a higher proportion of them had had prior medical consultation before their ED presentation (62.2% vs 29.7%, $P < 0.001$).

The clinical features of cases and controls are summarized in Table 2. Overall, the symptoms and triage vital signs did not differ significantly between the groups. Of note, only 86.5% of the confirmed cases were directly admitted to an isolation or surveillance ward from the ED. Five confirmed cases were admitted to general wards, all were local cases and 1 had close contact with another confirmed case that was only discovered after admission. During the course of hospitalization, 7 (18.9%) confirmed cases, 2 of whom had a travel history to Wuhan/Hubei, and 7 control patients required admission to intensive care. Two confirmed COVID-19 cases and 5 controls died.

Table 3 shows the laboratory and radiographic characteristics of the confirmed cases and controls. Compared with controls, COVID-19-confirmed cases had a lower total white blood cell count (median 4.9 $\times 10^9$/L vs 8.6 $\times 10^9$/L, $P < 0.001$), neutrophil count (3.4 $\times 10^9$/L vs 6.9 $\times 10^9$/L, $P < 0.001$), and platelet count (median 171.0 $\times 10^9$/L vs 232.5 $\times 10^9$/L, $P < 0.001$). Confirmed cases had higher serum lactate dehydrogenase levels than controls but the difference did not reach statistical significance (median 280.0 U/L vs 194.0 U/L, $P = 0.001$). Other laboratory parameters, such as prothrombin time, activated partial thromboplastin time, albumin, alanine aminotransferase, creatinine, creatine kinase, and C-reactive protein did not differ significantly between the groups. The number of cases and controls with procalcitonin, d-dimer, ESR, and lactate were 28, 5, 18, and 17, respectively, which were too small to allow a meaningful comparison between the groups.

SARS-CoV-2 was detected in upper respiratory specimens (including nasopharyngeal aspirate, nasopharyngeal swab, and throat swab or their combination), lower respiratory specimens (sputum, tracheal aspirate, bronchoalveolar lavage), and stool in 33, 19, and 7 confirmed cases, respectively. In 3 confirmed cases, other human coronaviruses, including human coronavirus OC43 in 2 cases and human coronavirus 229E in 1 case, were also detected with RT-PCR in nasopharyngeal swab specimens. As for the controls, 6 had influenza A virus H1, 4 had adenovirus, 1 had parainfluenza virus 3, 1 had enterovirus/rhinovirus, 1 had human metapneumovirus, and 1 had cytomegalovirus detected by RT-PCR in their nasopharyngeal specimens, and 25 had a positive bacterial culture.

The crude and adjusted ORs of having COVID-19 for variables found to have a significant association in univariate analysis are shown in Table 4. After adjustment for age and presumed location of acquiring the infection in Wuhan/Hubei, a positive contact history with a person with confirmed COVID-19 infection within 14 days (adjusted OR 37.61, 95% CI: 10.86–130.19), bilateral distribution of chest radiograph shadow (adjusted OR 13.19, 95% CI: 4.66–37.35), having prior medical consultation before ED presentation (adjusted OR 7.43, 95% CI: 2.89–19.09), a low white blood cell count (per 10^9/L decrease; adjusted OR 1.30, 95% CI: 1.11–1.51), a low platelet count (per 10 $\times 10^9$/L decrease; adjusted OR 1.07, 95% CI: 1.01–1.12) were associated with a higher odds of COVID-19 separately. A higher neutrophil count was associated with a lower odds of COVID-19 after adjustment (per 10^9/L increase; adjusted OR 0.77, 95% CI: 0.65–0.91).

4.3 | Limitations

Our study has several limitations. First, multiple comparisons were performed in a small sample. This was limited by a lack of similar comparative study to guide variable selection and the small case number in the early phase of the pandemic in Hong Kong. The small sample size limits the statistical power and the number of confounding variables we can use to adjust the ORs. Bonferroni correction of the P value makes it more difficult to reach statistical significance. Despite this, we could still identify a number of variables worth for further study. Second, the selection of controls based on RT-PCR results irrespective of symptoms and signs, though performed with a random process,

TABLE 1 Demographic and exposure history of cases with laboratory-confirmed COVID-19 infection and controls

Variable	COVID-19 confirmed case (n = 37)	Control (n = 111)	P value[a]
Age—median (IQR), year	63.0 (55.5–71.0)	64.0 (57.0–72.0)	0.68
Sex—no. (%)			
Female	17/37 (45.9)	51/111 (45.9)	1.0
Male	20/37 (54.1)	60/111 (54.1)	
Smoking history—no./total no. (%)			
Never smoked	27/34 (79.4)	64/99 (64.6)	0.16
Former smoker	5/34 (14.7)	16/99 (16.2)	
Current smoker	2/34 (5.9)	19/99 (19.2)	
Healthcare worker—no./total no. (%)	0/37 (0)	2/111 (1.8)	1.0
Comorbidity—no./total no. (%)			
Hypertension	12/37 (32.4)	46/110 (41.8)	0.31
Diabetes	11/37 (29.7)	35/110 (31.8)	0.81
Coronary heart disease	4/37 (10.8)	13/110 (11.8)	1.0
Chronic obstructive pulmonary disease	1/37 (2.7)	6/110 (5.5)	0.68
Malignancy	1/37 (2.7)	18/110 (16.4)	0.04
Chronic liver disease	0/37 (0)	5/111 (4.5)	0.33
Chronic renal disease	1/37 (2.7)	14/111 (12.6)	0.12
Exposure history—no./total no. (%)			
Travel history to Wuhan/Hubei within 14 days	8/37 (21.6)	1/111 (0.9)	<0.001
Travel history to a place with active community transmission of COVID-19 within 14 days	8/37 (21.6)	3/111 (2.7)	0.001
Visit to a health care facility in mainland China within 14 days	2/37 (5.4)	4/111 (3.6)	0.64
Contact history with a person with confirmed COVID-19 infection within 14 days	18/37 (48.6)	4/111 (2.7)	<0.001
Contact history of a person from Wuhan/Hubei within 14 days	3/37 (8.1)	1/111 (0.9)	0.05
Time from symptom onset to ED presentation			
Median (IQR), day	7.0 (2.0–9.8)	2.0 (1.0–6.0)	0.001
Distribution			
> 7 days—no./total no. (%)	13/36 (36.1)	16/110 (14.5)	0.005
Any prior medical consultation—no./total no. (%)	23/37 (62.2)	33/111 (29.7)	<0.001

CI, confidence interval; IQR, interquartile range; OR, odds ratio.

[a]Chi-Square/Fisher Exact test for categorical variables, Mann-Whitney U test for continuous variable

might introduce selection bias. The liberal ordering of testing by clinicians might include some controls who did not have infection and that might inflate the ORs of some variables in comparison. Yet, this reflects the current context better because a well-defined set of clinical criteria for a "COVID-19-like illness" simply does not exist. This discounting of symptoms and signs in the selection of cases and controls is consistent with the current WHO definition of the disease. Third, different in-house RT-PCR tests were used in the study hospitals and government laboratory during this period of time. The sensitivity and specificity of these tests were not available at the time of the study. We minimized the risk of misclassification by reviewing the clinical progress after hospital discharge uniformly of all cases and controls.

Forth, several inadequacies were noted in the chart review procedure compared with the best practice: a lack of blinding of the chart reviewers to the study purpose and patient outcome; a lack of training of the chart reviewers; use of data collection form without pretest; data abstraction without an explicit protocol; a lack of inter-rater reliability assessment in data extraction.[25] However, we believe the risk of introducing bias was low because all chart reviewers were experienced clinicians and most clinical parameters, such as triage vital signs and laboratory results, were objective data with little room for subjective interpretation. Travel and contact history were based on official source of information, although inevitably the controls received less attention from DoH in contact history tracing once they tested

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TABLE 2 Clinical characteristics of cases with laboratory-confirmed COVID-19 infection and controls

Variable	COVID-19 confirmed case (n = 37)	Control (n = 111)	P value[a]
Symptoms—no./total no. (%)			
Fever	27/37 (73.0)	53/109 (48.6)	0.01
Cough	26/37 (70.3)	68/103 (66.0)	0.64
Sputum production	16/29 (55.2)	49/90 (54.4)	0.95
Nasal congestion	8/24 (33.3)	27/68 (39.7)	0.58
Sore throat	8/21 (38.1)	21/60 (35.0)	0.80
Headache	0/5 (0)	7/22 (31.8)	0.28
Fatigue	16/19 (84.2)	18/28 (64.3)	0.13
Myalgia or arthralgia	8/13 (61.5)	5/14 (35.7)	0.18
Shortness of breath	12/29 (41.4)	36/90 (40.0)	0.90
Chest pain	2/37 (5.4)	14/111 (12.6)	0.36
Hemoptysis	0/7 (0)	5/27 (18.5)	0.56
Nausea or vomiting	4/28 (14.3)	15/73 (20.5)	0.47
Abdominal pain	3/16 (18.8)	7/55 (12.7)	0.68
Diarrhea	6/28 (21.4)	13/69 (18.8)	0.77
Anorexia	5/37 (13.5)	5/111 (4.5)	0.12
Triage vital signs			
Systolic blood pressure – median (IQR), mm Hg	143.0 (119.0–163.0)	152.0 (129.0–168.0)	0.21
Diastolic blood pressure – median (IQR), mm Hg	81.0 (72.5–86.5)	81.0 (71.0–93.0)	0.44
Pulse rate—median (IQR), beat per minute	95.0 (85.0–107.5)	94.0 (81.0–109.0)	0.84
Respiratory rate—median (IQR), breath per minute	16.0 (16.0–20.0)	16.0 (16.0–20.0)	0.53
SpO_2—median (IQR), %	97.0 (94.0–98.0)	97.0 (95.8–99.0)	0.04
Supplemental oxygen required at triage—no./total no. (%)	3/37 (8.1)	15/111 (13.5)	0.56
Alert in AVPU scale—no. (%)	37/37 (100.0)	107/111 (96.4)	0.57
Temperature—median (IQR), °C	37.4 (37.0–38.1)	36.9 (36.5–37.8)	0.005
Triage category—no./total no. (%)			
Category 1—Critical	1/37 (2.7)	9/111 (8.1)	0.52
Category 2—Emergent	2/37 (5.4)	7/111 (6.3)	
Category 3—Urgent	14/37 (37.8)	48/111 (43.2)	
Category 4—Semi-urgent	20/37 (54.1)	45/111 (40.5)	
Category 5—Non-urgent	0/37 (0)	2/111 (1.8)	
Direct admission to isolation/surveillance ward—no. (%)	32/37 (86.5)	66/110 (60.0)	
Clinical outcome—no./total no. (%)			
Hospitalized	37/37 (100.0)	111/111 (100)	
ICU admission	7/37 (18.9)	7/111 (6.3)	
Death	2/37 (5.4)	5/111 (4.5)	

CI, confidence interval; OR, odds ratio; ICU, intensive care unit; IQR, interquartile range; N/A, not applicable.

[a]Chi-Square/Fisher Exact test for categorical variables, Mann-Whitney U test for continuous variable.

negative for COVID-19. The lead investigator and site investigators verified all data fields and only 21 discrepancies in data entry were found, all being resolved by consensus. Fifth, clinical practice and the quality of documentation naturally varied considerably across the study hospitals, over which we had no control.

Finally, this study is an account of the early outbreak of COVID-19 in Hong Kong. The observed strength and magnitude of associa-

tions may change as the pandemic further evolves in Hong Kong and elsewhere. The sample is also not representative of patients admitted to hospital from sources other than ED in Hong Kong and patients in other countries. Given the small sample size, the observed difference between cases and controls in our study may not be generalizable to other ED patients. Our findings should be interpreted with caution as they are exploratory. Further studies, preferably

TABLE 3 Laboratory and radiological characteristics of cases with laboratory-confirmed COVID-19 infection and controls

Variables	COVID-19 confirmed case (n = 37)	Control (n = 111)	P value[a]
Laboratory findings			
White blood cell count			
Median (IQR), $\times 10^9$/L	4.9 (4.2–6.9)	8.6 (6.3–12.2)	<0.001
Distribution—no./total no. (%)			
<4 $\times 10^9$/L	7/37 (18.9)	4/108 (3.7)	0.006
Neutrophil count			
Median (IQR), $\times 10^9$/L	3.4 (2.6–5.2)	6.9 (4.7–9.7)	<0.001
Distribution—no./total no. (%) >8$\times 10^9$/l	4/37 (10.8)	35/94 (37.2)	0.003
Lymphocyte count			
Median (IQR), $\times 10^9$/L	0.9 (0.6–1.4)	1.1 (0.7–1.8)	0.04
Distribution—no./total no. (%)			
<1 $\times 10^9$/L	23/37 (62.2)	38/94 (40.4)	0.03
Hemoglobin—median (IQR), g/L	13.1 (11.9–14.3)	12.8 (11.1–14.0)	0.31
Platelet count			
Median (IQR), $\times 10^9$/L	171.0 (135.5–197.0)	232.5 (178.3–286.3)	<0.001
Distribution—no./total no. (%)			
<150 $\times 10^9$/L	15/37 (40.5)	17/111 (15.3)	0.001
Prothrombin time—median (IQR), s	12.6 (11.9-13.2)	12.6 (11.5-14.1)	0.57
Activated partial thromboplastin time—median (IQR), s	32.1 (30.1–34.0)	31.2 (28.2–34.9)	0.51
Albumin—median (IQR), g/L	37.0 (32.5–38.0)	37.0 (33.0–41.0)	0.21
ALT—median (IQR), U/L	26.0 (19.0–41.5)	22.0 (16.0–37.0)	0.16
Creatinine—median (IQR), μmol/L	71.0 (59.0–87.0)	80.0 (66.0–104.0)	0.04
Lactate dehydrogenase			
Median (IQR), U/L	280.0 (240.0–349.0)	194.0 (170.0–270.0)	0.002
Distribution			
≥250 U/L	21/31 (67.7)	12/39 (30.8)	0.002
Creatine kinase—median (IQR), U/L	89.5 (52.8–145.8)	129.0 (69.0–228.0)	0.05
C-reactive protein—median (IQR), mg/L	47.5 (17.9–136.0)	32.4 (2.9–119.1)	0.09
Procalcitonin ≥0.5 ng/mL—no./total no. (%)	4/23 (17.4)	4/5 (80.0)	0.02
Chest radiograph features—no./total no. (%)			
Any haziness/consolidation/ground-grass opacity	30/37 (81.1)	55/110 (50.0)	0.001
Unilateral distribution	10/37 (27.0)	45/110 (40.9)	0.13
Bilateral distribution	20/37 (54.1)	10/110 (9.1)	<0.001

ALT, alanine aminotransferase; IQR, interquartile range; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
[a]Chi-Square/Fisher Exact test for categorical variables, Mann-Whitney *U* test for continuous variable.

prospective studies with a larger sample size, are warranted to verify our findings.

5 | DISCUSSION

Differentiating COVID-19 from influenza and other respiratory illnesses in the ED during flu season in the Northern Hemisphere is challenging. In Hong Kong, the policy of admitting all patients suspected to have COVID-19 to hospital for clinical workup early in the pandemic provided us with a unique opportunity of comparing those who tested positive and negative in a comprehensive manner. This study shows that a number of features in exposure history, clinical presentation, laboratory and radiological findings may be useful for clinicians in identifying patients with COVID-19 for early testing and isolation while waiting for test results.

Patients with a positive travel history, Wuhan/Hubei in the initial phase of the pandemic, and a contact history with a person with

TABLE 4 Crude and adjusted odds ratios for COVID-19 of different variables

Variables	Crude OR of COVID-19 (95% CI)	OR adjusted for age and travel history to Wuhan/Hubei (95% CI)
Travel history to Wuhan/Hubei within 14 days	30.35 (3.65–252.49)	N/A
Contact history with a person with confirmed COVID-19 infection within 14 days	25.34 (7.72–83.15)	37.61 (10.86–130.19)
Bilateral distribution of chest radiograph shadow	11.77 (4.70–29.43)	13.19 (4.66–37.35)
Any prior medical consultation	3.88 (1.78–8.46)	7.43 (2.89–19.09)
White blood cell count (per 1×10^9/L decrease)	1.37 (1.18–1.59)	1.30 (1.11–1.51)
Neutrophil count (per 1×10^9/L increase)	0.72 (0.61–0.85)	0.77 (0.65–0.91)
Platelet count (per 10×10^9/L decrease)	1.08 (1.03–1.13)	1.07 (1.01–1.12)

CI, confidence interval; N/A, not applicable; OR, odds ratio.

†Not applicable because travel history to Wuhan/Hubei was used to adjust the odds ratio.

confirmed COVID-19 infection, have a much higher odds of having the infection. This finding highlights the time-honored value of a proper travel and contact history assessment at the point of patient entry to hospital. It is noteworthy that a contact history may not be apparent at presentation, but only after contact tracing is completed by the local public health authority. Our study shows that despite heightened awareness among healthcare staff from the outset of the pandemic, as local transmission progressed a small proportion of local cases were still admitted to general wards initially, highlighting the importance of infection control measures even in the general ward setting. Compared with the cases, a lower proportion of the controls were admitted to an isolation or surveillance ward directly from the ED, though they were offered COVID-19 testing. This discrepancy may reflect the limited capacity of isolation facilities in the study hospitals or liberal use of testing even for those who were perceived to be less likely to have the infection.

Compared with those reported in the published case series, the confirmed cases in our study were older patients with more comorbid conditions.[26] Symptoms, predominantly fever and lower respiratory symptoms such as cough and dyspnea, were similar to those reported elsewhere, except a higher proportion of patients had sputum production in our study.[9,12,13,14,16] Contrary to the observation that cases outside Wuhan/Hubei might be relatively milder,[17-18] we did not observe such a pattern here in Hong Kong. The intensive care unit (ICU) admission rate (18.9%) was higher in our cohort compared with mainland China (5%)[13] and in the States (14.2%).[20] This can be explained by the older age of our patients, which has been associated with a poorer outcome,[14,15] differences in ICU admission policy, better accessibility to ICU beds in the initial phase of the outbreak when the number of confirmed cases was still small, and our sampling strategy of recruiting ED patients only.

Overall, we found that symptoms were not useful in identifying patients with COVID-19 in the ED. Symptoms that are subsequently reported in the literature, such as anosmia and ageusia,[27] were not assessed or documented by the attending clinicians early in the pandemic. Therefore, we are not able to comment on their value based on our data. Patients with a prior medical consultation for the same physical complaints had higher odds of COVID-19 infection. This might reflect failure to respond to treatment offered by other clinicians, which often targeted other pathogens, or disease deterioration along its clinical course. Huang and colleagues showed that the median time from symptom onset to first hospital admission was 7 days,[9] a time interval that was also observed in our confirmed cases. Prior medical consultation before ED presentation should be a red flag of a possible novel infection that is not responding to usual treatment.

In the absence of tell-tale clinical features, similarities in certain abnormalities in laboratory tests between betacoronaviruses, COVID-19, SARS, and MERS, may offer some clues for diagnosis. Lymphopenia is the most widely reported characteristic of COVID-19.[9,11,12-15,18] In a group of critically ill COVID-19 patients, the lymphocyte count fell to the lowest point 7 days after symptom onset in survivors and remained low until death in non-survivors.[14] Likewise, lymphopenia is also observed in other betacoronavirus infections, with evidence of lymphocyte infection in SARS[28] and virus-induced T lymphocyte apoptosis in MERS.[29] Chen and colleagues suggested using lymphopenia as a reference index for diagnosis of COVID-19 in clinics.[11] However, we found that lymphopenia was not associated with a high odds of COVID-19 after adjusting for age and location of acquiring the infection. Other viral infections, such as influenza,[30,31] can also cause lymphopenia, making it less discriminatory during the flu season.

In our study, a lower white cell count was associated with a higher odds of COVID-19 infection. This is consistent with previous studies that report leukopenia in COVID-19 patients.[9,13,18] Mao and colleagues showed that leukopenia $<4 \times 10^9$/L was an independent risk factor for COVID-19[32] but leukopenia defined with such a cut-off point

did not reach statistical significance in our analysis. Neutrophilia, on the other hand, has been reported in one-third of COVID-19 patients[11] and non-survivors appeared to have a higher neutrophil count than survivors.[12] Interestingly, we found that those with a higher neutrophil count had a lower adjusted odds of COVID-19, indicating that a high neutrophil count may suggest infection by pathogens other than SARS-CoV-2. Further studies are required to investigate the diagnostic role of neutrophilia at different stages of the disease in light of these contradictory findings. Thrombocytopenia, a feature also reported in SARS and MERS,[33,34] remained significant after adjustment in our study. It occurred in up to one-third of cases in a large case series in China,[11] but it is not consistently reported across different studies. Likewise, the usual cut-off point of 150×10^9/L was not useful in differentiation in our cohort. It remains unclear which thresholds of white cell count, neutrophil, and platelet counts are the most discriminatory in diagnosis.

As for biochemical tests, elevated lactate dehydrogenase is frequently reported in COVID-19[9,11-14] and its discriminatory value has been demonstrated in differentiating COVID-19 from other causes of fever.[32] However, a lactate dehydrogenase level > 250 IU/L did not reach statistical significance in our study. C-reactive protein has been shown to be elevated in COVID-19 cases,[11,13,16] but we found it unhelpful in differentiating COVID-19 from other infections. Previous studies showed that most COVID-19 patients had normal serum procalcitonin level on admission.[9,11,13,14,18] However, the number of patients tested was too small in our cohort to allow a meaningful comparison between groups. The same occurred in other sepsis biomarkers, such as lactate, d-dimer, ESR. A raised ferritin level has been reported to be useful in screening for COVID-19;[35] however, it was not routinely checked in our setting during the study period.

Early reports suggest patchy shadows, ground-glass opacities, subsegmental areas of consolidation, especially bilateral distributions involving the peripheral lung, are typical radiological abnormalities of COVID-19 found on CT thorax,[9,11,12,18,36,37] with their appearance correlating with the stage of disease[16] and the number of lung segments involved increasing with time.[38] Tao and colleagues demonstrated the high sensitivity of CT thorax in diagnosing COVID-19 and its good correlation with disease progression.[39] However, CT thorax is not readily available in most EDs in Hong Kong except for major trauma or life-threatening chest emergencies, such as acute aortic dissection. Despite the frequent ordering of chest x-rays in the ED, their value in diagnosing COVID-19 has not been fully explored in the literature. Our study shows that patients with any haziness, ground-glass opacity or consolidation on the presenting chest radiograph, though non-specific, are at a higher risk of having COVID-19, especially when both lungs are involved. However, it is noteworthy that even with CT thorax, a significant proportion of cases had no radiographic or CT abnormality, especially among those with mild infection.[13,37]

Taken together, a positive travel or contact history, having prior medical consultation for the same physical complaints or chest radiograph showing haziness, ground-glass opacity or consolidation in both lungs on presentation should flag the possibility of COVID-19 infection during the pandemic. A complete blood count may be useful if the turnaround time is shorter than RT PCR but the best diagnostic thresholds of the white blood cell, neutrophil and platelet counts for diagnosis of COVID-19 are yet to be established.

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