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Article

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

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Abstract: (1) Background: It is unclear whether the reported presenting clinical features of coronavirus disease 2019 (COVID-19) are useful in identifying high-risk patients for early testing and isolation in the emergency department (ED). We aimed to compare the exposure history, clinical, laboratory, and radiographic features of ED patients who tested positive and negative for COVID-19; (2) Methods: We conducted a case-control study in seven EDs during the first five weeks of the COVID-19 outbreak in Hong Kong. Thirty-seven laboratory-confirmed COVID-19 patients were compared with 111 age- and gender-matched controls; (3) Results: There were no significant differences in patient characteristics and reported symptoms between the groups, except patient-reported fever. A positive travel history or contact history was the most significant predictor for COVID-19 infection. After adjustment for age and presumed location of acquiring the infection in Wuhan/Hubei, patient-reported fever (OR 2.6, 95% CI 1.1 to 6.3), delayed presentation (OR 5.0, 95% CI 2.0 to 12.5), having medical consultation before ED presentation (OR 7.4, 95% 2.9 to19.1), thrombocytopenia (OR 4.0, 95% CI 1.6 to 9.7), raised lactate dehydrogenase (OR 5.9, 95% CI 1.9 to 18.5), haziness, consolidation or ground-glass opacity on chest radiography (OR 5.6, 95% CI 2.0 to 16.0), and bilateral changes on chest radiography (OR 13.2, 95% CI 4.7 to 37.4) were associated with a higher odds of COVID-19 separately while neutrophilia was associated with a lower odds (OR 0.3, 95% CI 0.1-0.8); and (4) Conclusions: This study highlights several features that may be useful in identifying high-risk patients for early testing and isolation while waiting for test result. Further studies are warranted to verify the findings.

Keywords: COVID-19; SARS-CoV-2; emergency department; early diagnosis; case-control studies

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1. Introduction

On 11 March 2020, the World Health Organization (WHO) declared a pandemic for the coronavirus disease 2019 (COVID-19) outbreak [1]. Within 3 months of its first emergence in Wuhan [2, 3], severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly spread all over the world, having infected more than 4.3 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]. Health systems worldwide now need to respond to the rising demand for rapid diagnosis and isolation in patients suspected to have COVID-19.

Emergency departments (ED) are patient's first contact point with the health care system in most countries and they play a critical role in diagnosis and decision-making 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 to include all inpatients with pneumonia and ED patients with fever or respiratory symptoms as the pandemic evolves [7], the turnaround time of RT-PCR is long, frequently up to several hours even in university hospitals [8]. Given the limited number of negative pressure rooms, 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 patients with COVID-19 in the ED setting.

Published studies thus far have mainly focused on clinical features of confirmed COVID-19 cases. Data from Wuhan, other places in China, and many other countries portray a diverse clinical spectrum of the disease, ranging from asymptomatic infection to acute respiratory distress syndrome, rapid progression to multi-organ failure, and death [9-19]. A significant proportion of COVID-19 patients have fever [9, 11-19], cough [9, 11-19], fatigue [9, 12, 16-18], dyspnea [9, 11], leukopenia [13, 16, 18], lymphopenia [9, 11-14, 16-19], elevated levels of C-reactive protein [11, 13, 19], and lactate dehydrogenase [11, 12, 14], patchy shadowing on chest radiography [13, 14], and ground-glass opacities on computed tomography (CT) of the thorax [9, 11-14, 16, 18]. Although these clinical, laboratory, and radiographic features are consistently reported across different case series, it is unclear whether they can help in differentiating patients with COVID-19 from those without. In a study that evaluated patient initial presenting features in the ED, Zhu and colleagues found that fever, lymphopenia, and presence of pneumonia on CT thorax were more common in confirmed cases compared with negative cases [20]. However, a lack of statistical analysis put the significance of their findings into question.

In this study in Hong Kong, we compared the clinical characteristics on ED presentation, including exposure history, symptoms and signs, laboratory and radiological findings of ED patients with COVID-19 with those who were not infected but who were tested for suspected infection. We further determined the risk of COVID-19 for each clinical characteristic that was significantly different between the groups.

2. Methods

We conducted a case-control study in the emergency departments of seven public hospitals managed by the Hospital Authority (HA) of Hong Kong. The HA is a statutory body that manages all public hospitals in Hong Kong, which are organized into seven hospital clusters based on geographical locations[21]. At present, all confirmed and suspected cases of COVID-19 in Hong Kong are treated in public hospitals. The seven study sites, one in each of the seven hospital clusters, included two university-affiliated hospitals and five 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,

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KWC-2020-0032, NTWC-2020-0026). Written consent was 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]. Active surveillance, based on a set of clinical and epidemiological criteria that has evolved as the epidemic further spread beyond Wuhan, is performed upon patient presentation to any healthcare facilities in Hong Kong. All ED patients are screened by staff for possible COVID-19 infection with epidemiological and clinical criteria, and all suspected cases are hospitalized and isolated in negative pressure rooms for RT-PCR testing after admission. At this stage of the outbreak in Hong Kong, the local health authority still recommends hospital admission for all suspected cases.

Some patients are hospitalized and isolated directly from sources other than EDs under the direction of the Centre for Health Protection (CHP), part of the DoH. On 14 January 2020, the CHP further expanded laboratory surveillance to cover all inpatient community-acquired pneumonias irrespective of travel history. On 19 February 2020, deep throat saliva testing, a non-invasive method of specimen collection with reasonable sensitivity [22], was introduced in EDs and government outpatient clinics. Low risk patients with mild febrile illnesses are instructed to produce an early morning sample of saliva at home on the following day for RT-PCR testing.

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 epidemic to inform clinical decision making. During that period of time, Hong Kong witnessed the first imported case from Wuhan (22 January 2020), followed by intermittent presentations of local cases. We recruited cases who were admitted to the hospital from the study EDs as inpatients with laboratory confirmation of infection with COVID-19, irrespective of clinical signs and symptoms, as defined in the WHO interim guidance [6].

RT-PCR tests were performed in the respective hospitals and/or the government public health laboratory in accordance with prevailing local practice [8]. Controls were patients admitted through the study EDs during the same period for RT-PCR testing for COVID-19 but who tested negative. Patients of all age groups were included. We excluded patients who were (1) admitted to the study hospitals under CHP isolation orders from sources other than ED, such as fever clinics or quarantine camps because these patients might have different risk profiles and clinical presentations compared with ED patients; (2) patients who were transferred to the study hospitals 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 (CDARS), which is a centralized repository of electronic medical records in the HA that contains data on patient characteristics, dates of various clinical activities, diagnoses, laboratory tests, procedures, and drug prescriptions for audit and research purposes. The system has a high accuracy in coding and has been used in many population-based research studies [23].

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 9,283 negative cases were admitted through the ED (Figure 1). We matched each confirmed case with three negative control cases, who were randomly selected from the same hospital within five days of presentation, and were the same gender and similar age (+/- five 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 [24].

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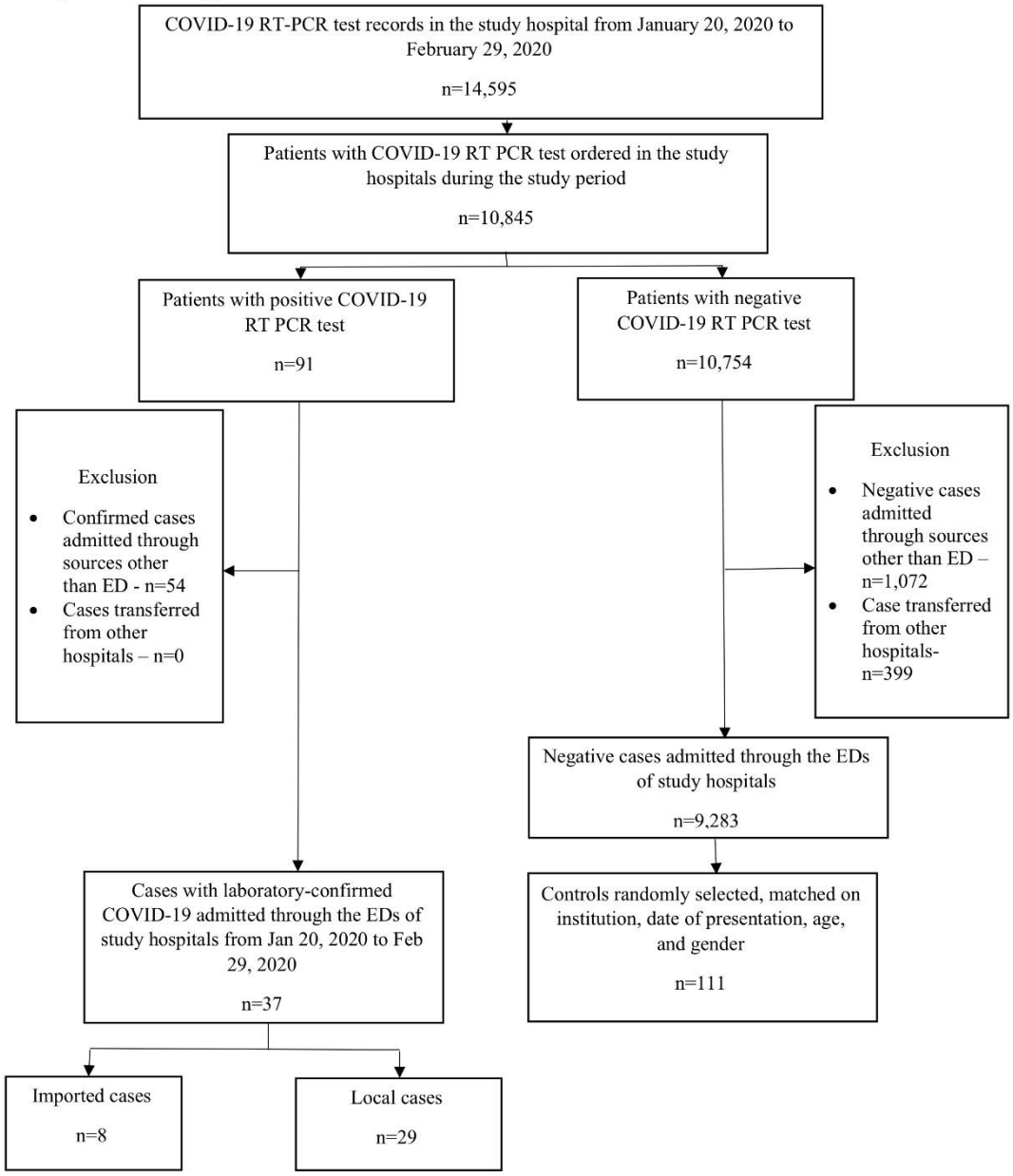
Figure 1. Flow diagram of cases and controls selection.



We reviewed electronic medical records and extracted demographic, epidemiological, clinical, laboratory, radiological, treatment and outcome data using a standardized data collection form. Each patient record was reviewed by the study lead investigator and a local co-investigator independently to ensure accuracy of data entry. Both of them were aware of the COVID-19 test results. Any disagreement was resolved by discussion between the case reviewers. We defined the date of symptom onset as the date when the first symptom was reported. Since the exposure history might

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not be available or reliable at ED presentation, we cross-checked the exposure history of each confirmed case with the official account released by the CHP. For travel history outside Wuhan/Hubei, we defined a place with active community transmission of COVID-19 based on the prevailing CHP's criteria for disease notification, which is determined according to the situation of local outbreak in different countries by public health officials.

For controls, such an official account was not available because no epidemiological investigation is normally conducted by the CHP if a patient is tested negative for COVID-19. Starting from 6 February 2020, ED staff had access to patient cross-border travel records to mainland China or other countries within 30 days of ED registration; these data were provided by the Immigration Department. We believe the travel history recorded in the clinical notes should be accurate for control cases after that date. Since the RT-PCR tests were new tests in the study hospitals, the sensitivity and specificity had not been reported. To avoid misclassifying false negative cases as controls, we reviewed all re-attendance records of the controls after hospital discharge up to 16 March 2020 and did not find any reattendance due to COVID-19.

We extracted symptoms as reported in the medical record. We defined fever as a patient-reported symptom in the clinical notes without specifying 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 as prior medical consultation before their ED presentation. For patients with multiple ED attendances within the study period, only clinical characteristics recorded on the episode that led to hospital admission and COVID-19 testing were extracted. As for laboratory tests, 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, collected within 48 hours of ED presentation. Beyond that, the laboratory results are likely to have been affected by medical interventions after admission and possible nosocomial infection.

Since CT thorax was seldom ordered for ED patients who tested negative for COVID-19 in public hospitals, we only compared the chest x-ray findings. As for radiographic findings, we adopted the interpretation of the reporting radiologist or treating clinicians, wherever available. All laboratory tests and radiological studies were ordered by the attending clinicians based on clinical need and local hospital practice. We followed up the clinical outcome of all patients up to 16 March 2020.

Statistical analysis

Missing values were not imputed. 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 conducted a univariate analysis to study the association of individual variables with laboratory-confirmed COVID-19 infection. We then determined the odds ratio (OR) with 95% confidence interval (CI) of COVID-19 infection for variables with a significant association in univariate analysis.

Because of the association of age with a poor outcome [14-16, 25] and apparently milder infections outside Wuhan as shown in previous studies [16, 17], we used multivariable logistic regression to adjust the odds ratios 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) [26]. The Statistical Package for the Social Sciences for Windows version 23.0 (IBM Corp., Armonk, NY, USA) was used for data analysis with a two-sided p-value of <0.05 considered to be statistically significant.

3. Results

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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. The median age of the confirmed cases was 63.0 years (IQR 55.5-71.0) and there was no gender preponderance. There were no significant differences between the cases and controls regarding age, gender, smoking history, and co-morbidities, except that a history of cancer was more common in the control group (Table 1). A significantly higher proportion of cases had a travel history to Wuhan/Hubei (21.6% vs 0.9%, p<0.001) or a place with active community transmission of COVID-19 according to the prevailing local health authority advice (21.6% vs 2.7%, p=0.001), and a contact history with a person with confirmed COVID-19 infection (48.6% vs 2.7%, p<0.001).

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**
Age – median (IQR), year	63.0 (55.5-71.0)	64.0 (57.0-72.0)	0.64***
Gender – 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)	46/111 (41.8)	0.31*
Diabetes	11/37 (29.7)	35/111 (31.8)	0.81*
Coronary heart disease	4/37 (10.8)	13/111 (11.8)	1.00**
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 according to the prevailing local health authority advice	8/37 (21.6)	3/111 (2.7)	0.001**

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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	2/37 (5.4)	1/111 (0.9)	0.15**
Time from symptom onset to ED presentation			
Median (IQR), day	7.0 (2.0-9.8)	2.0 (1.0-6.0)	0.013***
Distribution			
</= 7 days	23/36 (63.9)	94/111 (84.7)	0.007*
Any prior medical consultation – no./total no. (%)	23/37 (62.2)	33/111 (29.7)	<0.001*

Abbreviations: IQR, interquartile range

*Chi-squared test

**Fisher's exact test

***Mann-Whitney U test

The proportion of patients with a history of visiting healthcare facilities in mainland China and contact with a person from Wuhan/Hubei with no known COVID-19 infection did not differ significantly between the groups, but the number was too small for a meaningful comparison. Compared with the controls, COVID-19-confirmed cases presented to the ED later after symptom onset (median 7.0 days vs 2.0 days, p=0.007) and 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, except there was a higher proportion of COVID-19 cases reporting fever (73.0% vs 48.6%, p=0.01) and these patients had a higher temperature at ED triage than controls (37.4°C vs 36.9°C, p=0.004), though the difference is not clinically significant. 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 one had close contact with another confirmed case that was only discovered after admission. During the course of hospitalization, seven (18.9%) confirmed cases, two of whom had a travel history to Wuhan/Hubei, and seven control patients required admission to intensive care. Two confirmed COVID-19 cases and five controls died.

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**
Symptoms – no./total no. (%)			
Fever	27/37 (73.0)	53/109 (48.6)	0.01*

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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)	0.45***
Diastolic blood pressure - median (IQR), mm Hg	81.0 (72.5-86.5)	81.0 (71.0-93.0)	0.64***
Pulse rate - median (IQR), beat per minute	95.0 (85.0-107.5)	94.0 (81.0-109.0)	0.85***
Respiratory rate – median (IQR), breath per minute	16.0 (16.0-20.0)	16.0 (16.0-20.0)	0.98***
SpO_2 – median (IQR), %	97.0 (94.0-98.0)	97.0 (95.8-99.0)	0.37***
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)	0.004***
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)	0.003*
Clinical outcome – no./total no. (%)			
Hospitalized	37/37 (100.0)	111/111 (100)	N/A
ICU admission	7/37 (18.9)	7/111 (6.3)	0.045**
Death	2/37 (5.4)	5/111 (4.5)	1.0**

Abbreviation: ICU, intensive care unit; IQR, interquartile range; N/A, not applicable.

*Chi-squared test

**Fisher's exact test

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***Mann-Whitney U test

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 x 10^9/L vs 8.6 x 10^9/L, p<0.001), and lower neutrophil (median 3.4 x 10^9/L vs 6.9 x 10^9/L, p=0.001), and platelet counts (median 171.0 x 10^9/L vs 232.5 x 10^9/L, p<0.001). A significantly higher proportion of cases had a lymphocyte count <1.0 x 10^9/L (62.2% vs 40.4%, p=0.025). Conversely, neutrophilia (defined as a neutrophil count >8.0 x 10^9/L) was more common in the control group (10.8% vs 37.2%, p=0.003). Confirmed cases had significantly higher serum lactate dehydrogenase levels than controls (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. Only a few patients had procalcitonin tested and the proportion of patients with a level ≥0.5 ng/mL were significantly higher in the control group (17.4% vs 80.0%, p=0.015). The number of cases and controls with d-dimer, ESR, and lactate were 5, 18, and 17, respectively, which were too small to allow a meaningful comparison between the groups.

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
Laboratory findings			
White blood cell count			
Median (IQR), x 10^9/L	4.9 (4.2-6.9)	8.6 (6.3-12.2)	<0.001***
Distribution – no./total no. (%)			
<4 x 10^9/L	7/37 (18.9)	4/108 (3.7)	0.001*
4-10 x 10^9/L	27/37 (73.0)	66/108 (61.1)	
>10 x 10^9/L	3/37 (8.1)	38/108 (35.2)	
Neutrophil count			
Median (IQR), x 10^9/L	3.4 (2.6-5.2)	6.9 (4.7-9.7)	0.001***
Distribution – no./total no. (%) >8 x10^9/l	4/37 (10.8)	35/94 (37.2)	0.003*
Lymphocyte count			
Median (IQR), x 10^9/L	0.9 (0.6-1.4)	1.1 (0.7-1.8)	0.059***
Distribution – no./total no. (%)			
<1 x 10^9/L	23/37 (62.2)	38/94 (40.4)	0.025*
Hemoglobin – median (IQR), g/L	13.1 (11.9-14.3)	12.8 (11.1-14.0)	0.67***
Platelet count			
Median (IQR), x 10^9/L	171.0 (135.5-197.0)	232.5 (178.3-286.3)	<0.001***
Distribution – no./total no. (%)			
<150 x 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)	0.842***
Activated partial thromboplastin time – median (IQR), s	32.1 (30.1-34.0)	31.2 (28.2-34.9)	0.408***

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Albumin - median (IQR), g/L	37.0 (32.5-38.0)	37.0 (33.0 – 41.0)	0.255***
ALT – median (IQR), U/L	26.0 (19.0-41.5)	22.0 (16.0-37.0)	0.232***
Creatinine – median (IQR), μmol/L	71.0 (59.0-87.0)	80.0 (66.0-104.0)	0.057***
Lactate dehydrogenase			
Median (IQR), U/L	280.0 (240.0-349.0)	194.0 (170.0-270.0)	0.001***
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)	0.083***
C-reactive protein – median (IQR), mg/L	47.5 (17.9-136.0)	32.4 (2.9-119.1)	0.946***
Procalcitonin ≥0.5 ng/mL – no./total no. (%)	4/23 (17.4)	4/5 (80.0)	0.015**
SARS-CoV-2 detected in any upper respiratory tract specimen – no./total no. (%)	33/35 (94.3)	0/104 (0)	<0.001*
SARS-Cov-2 detected in any lower respiratory tract specimen† – no./total no. (%)	19/19 (100.0)	0/29 (0)	<0.001*
SARS-CoV-2 detected in stool specimen‡ – no./total no. (%)	7/11 (63.6)	N/A	N/A
Influenza virus detected in any respiratory specimen – no./total no. (%)	0/36 (0)	6/104 (5.8)	0.34**
Other respiratory viruses detected in any respiratory specimen# – no./total no. (%)	3/36 (8.3)	8/104 (7.7)	1.0 **
Positive bacterial culture in any specimen collected within 48 h of admission – no./total no. (%)	0/27 (0)	25/77 (32.5)	0.001*
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)	0.131*
Bilateral distribution	20/37 (54.1)	10/110 (9.1)	<0.001*

Abbreviations: ALT, alanine aminotransferase; IQR, interquartile range; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Footnote:

† upper respiratory specimens included nasopharyngeal aspiration, nasopharyngeal swab and throat swab and their combination

‡ lower respiratory specimens included sputum, tracheal aspirate, and bronchoalveolar lavage.

Other respiratory viruses included adenovirus, parainfluenza virus 1-4, respiratory syncytial virus, human metapneumovirus, enterovirus or rhinovirus.

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*Chi-squared test

**Fisher's exact test

***Mann-Whitney U test

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 three confirmed cases, other human coronaviruses, including human coronavirus OC43 in two cases and human coronavirus 229E in one case, were also detected with RT-PCR in nasopharyngeal swab specimens. As for the controls, six had influenza A virus H1, four had adenovirus, one had parainfluenza virus 3, one had enterovirus/rhinovirus, one had human metapneumovirus, and one had cytomegalovirus detected by RT-PCR in their nasopharyngeal specimens, and 25 had a positive bacterial culture.

The odds ratios of having COVID-19 infection in patients with a positive travel or contact history, fever, delayed presentation, prior consultation, leukopenia, lymphopenia, neutrophilia, thrombocytopenia, raised lactate dehydrogenase, and abnormalities on chest radiographs are shown in Table 4. After adjusting for age, the odds ratios were almost unchanged, indicating that age may not be an important factor in confounding clinical presentations. However, when the presumed location of acquiring the infection in Wuhan/Hubei was adjusted for, the association between COVID-19 and leukopenia, and with lymphopenia, was not statistically significant.

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

Variables	Crude OR of COVID-19 (95% confidence interval)	OR adjusted for age (95% confidence interval)	OR adjusted for age and travel history to Wuhan/Hubei (95% confidence interval)
Travel history to Wuhan/Hubei within 14 days	30.3 (3.6-252.5)	30.1 (3.6-253.2)	
Contact history with a person with confirmed COVID-19 infection within 14 days	25.3 (7.7-83.2)	26.4 (7.9-87.8)	37.6 (10.9-130.2)
Bilateral distribution of chest radiograph shadow	11.8 (4.7-29.4)	15.3 (5.6-42.2)	13.2 (4.7-37.4)
Travel history to a place with active community transmission of COVID-19 within 14 days according to the prevailing local health authority advice	9.9 (2.5-39.8)	9.8 (2.4-39.2)	N/A

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White blood cell count <4 x 10^9/L	6.2 (1.7-22.8)	6.1 (1.7-22.4)	3.5 (0.8-16.0)
Lactate dehydrogenase ≥250 U/L	4.7 (1.7-13.0)	5.5 (1.9-15.9)	5.9 (1.9-18.5)
Any haziness/consolidation/ground-grass opacity on chest radiograph	4.3 (1.7-10.6)	4.9 (1.9-12.4)	5.6 (2.0-16.0)
Any prior medical consultation	3.9 (1.8-8.5)	4.0 (1.8-8.8)	7.4 (2.9-19.1)
Platelet count <150 x 10^9/L	3.8 (1.6-8.7)	3.8 (1.7-8.8)	4.0 (1.6-9.7)
Presenting after 7 days of symptom onset	3.3 (1.4-7.9)	3.3 (1.4-7.9)	5.0 (2.0-12.5)
Fever	2.9 (1.3-6.5)	2.8 (1.2-6.4)	2.6 (1.1-6.3)
Lymphocyte <1 x 10^9/L	2.4 (1.1-5.3)	2.5 (1.1-5.4)	2.3 (1.0-5.2)
Neutrophil >8 x 10^9/L	0.2 (0.1-0.6)	0.2 (0.1-0.6)	0.3 (0.1-0.8)

Abbreviations: N/A, not applicable; OR, odds ratio

4. Discussion

Differentiating COVID-19 from influenza and other respiratory illnesses in the ED during flu season in the Northern Hemisphere is challenging. While RT-PCR test remains the most important diagnostic tool, 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 travel history to the epicentre of COVID-19, Wuhan/Hubei in the initial phase of the epidemic and other countries with active local transmission later in the course of its global spread, and a contact history with a person with confirmed COVID-19 infection, have a much higher odds of having COVID-19 infection. This finding highlights the time-honoured value of a proper travel and contact history assessment at the point of patient entry to hospital. Patients who are screened positive should be directed to a separate area, an isolation room if available, and separated from other suspected cases by at least 1 meter [6]. It is noteworthy that as local outbreaks expand in other countries, travel history may become less important, and 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 epidemic, 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 significantly 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 [27]. Symptoms, predominantly fever and lower respiratory symptoms such as cough and dyspnoea, were similar to those reported elsewhere, except a higher proportion of patients had sputum production in our study [9, 12, 13, 14, 16, 20]. Contrary

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to the observation that cases outside Wuhan/Hubei might be relatively milder [17-19], 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 only two cases admitted to the ICU had a travel history to Wuhan/Hubei [3]. 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, except patient-reported fever, were not useful in identifying patients with COVID-19 in the ED. However, given the retrospective study design, we could not define the temperature range and method of measurement for patient-reported fever. Also, a 0.5°C difference in triage temperature, though statistically significant, might not be clinically useful as an indicator.

In general, we found that patients with COVID-19 presented to ED later than controls. It is also more likely that they had consulted other doctors before ED presentation. Delayed ED presentation could be explained by the non-specific initial symptoms of COVID-19. Multiple consultations 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. Delayed presentation with 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, 19]. 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 till 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 neither lymphopenia or leukopenia, which is less commonly reported [9, 13, 18], was useful in identifying 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.

Neutrophilia, on the other hand, has been reported in one-third of cases with COVID-19 [11] and non-survivors appeared to have a higher neutrophil count than survivors [12]. Interestingly, we found that those with neutrophilia had a lower odds of COVID-19 even after adjustment, indicating that a high neutrophil count at ED presentation 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 [32, 33], 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. In our study, less than half of the confirmed cases had a platelet count lower than 150 x 10^9/L. Using that threshold would have missed more than half of the cases.

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 SARS from other causes of community-acquired pneumonia [34]. In our study, 21 out of 31 cases who were offered testing had an elevated lactate dehydrogenase level in serum, but its role in diagnosis requires further evaluation. It only has a value if its turnaround time is shorter than that of RT-PCR testing. 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]. Despite our small numbers, our findings support that an elevated procalcitonin level might indicate infection by pathogens other than SARS-CoV-2. As for other sepsis biomarkers, such as lactate, d-dimer, and ESR,

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the number of patients tested was too small in our cohort to allow a meaningful comparison between groups.

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, 35, 36], with their appearance correlating with the stage of disease [16] and the number of lung segments involved increasing with time [37]. Tao and colleagues demonstrated the high sensitivity of CT thorax in diagnosing COVID-19 and its good correlation with disease progression [38]. 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, 36].

Limitations

Our study has several limitations. First, we could only compare a small number of confirmed cases with selected controls. The sample size was small but is necessarily limited by the time frame of the early phase of the outbreak in Hong Kong. On one hand, we do not have enough statistical power to detect the differences in certain variables between the groups, neither could we adjust the odds ratios for more confounding variables. Lymphopenia, in particular, almost reaches statistical significance and we cannot totally exclude its role in early case identification. On the other hand, a significant p value seen in comparison only indicates statistical significance between the cases and the selected controls and it does not imply clinical significance. For instance, we believe that the significant difference in triage temperature between the groups is not clinically useful. Second, the selection of controls based on RT-PCR results irrespective of symptoms and signs might introduce selection bias since a number of controls might not have infection at all. That might inflate the odds ratios of some variables in comparison. Yet, we think the liberal strategy of control selection 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, information bias still existed. Compared with the cases, controls might have less detailed travel or contact history. Access to the Immigration Department cross-border travel record by medical staff has already reduced the chance of omitting important travel information. However, controls received less attention from the health authority in contact tracing once they tested negative. Extracting data without blinding to the test result might also introduce information bias. However, many clinical parameters, such as triage temperature, laboratory and reported radiological findings were objective data and we believe the risk of introducing such a bias is low. Fourth, clinical practice and the quality of documentation naturally varied considerably across the study hospitals, over which we had no control. A notable example is that not all controls had two negative RT-PCR tests that were spaced 24 hours apart before hospital discharge. We reviewed the re-attendance records of all controls and found that none were re-admitted subsequently for COVID-19 infection up to 16 March 2020.

Finally, this study is an account of the early outbreak of COVID-19 in Hong Kong. The current findings were based on ED patients who presented within the first five weeks of the epidemic in Hong Kong. The observed strength and magnitude of associations 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. Our findings should be interpreted with caution as they are exploratory. Further studies, preferably prospective studies in other affected areas, are warranted to verify our findings. We are also aware that the insights found in this study will likely be superceded by findings from emerging larger series elsewhere.

Taken together, a positive travel or contact history still remains the most significant predictor for COVID-19 infection among ED patients with undifferentiated presentations in the early phase of the outbreak. As the outbreak progresses with more local transmissions, delayed ED presentation and prior consultation before ED presentation should alert clinicians of a possible novel infection. Radiological abnormalities, including haziness, consolidation and ground-glass opacity on chest radiography, especially if bilateral, may indicate a higher risk of COVID-19 infection. Patient-reported fever appears to more likely in COVID-19 patients. Neutrophilia may suggest infection by pathogens other than SARS-CoV-2. The discriminatory value of lymphopenia and thrombocytopenia appear to be modest. Elevated lactate dehydrogenase may be useful only when its turnaround time is shorter than that of the RT-PCR test.

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