Cutaneous manifestations, viral load, and prognosis among hospitalised patients with COVID-19: a cohort study

Christina SM Wong * #, Ivan FN Hung #, Mike YW Kwan, Martin MH Chung, Mandy WM Chan, Adrian KC Cheng, YM Lau, CK Yeung, Henry HL Chan, CS Lau

ABSTRACT

Introduction: Various cutaneous manifestations have been reported as symptoms of coronavirus disease 2019 (COVID-19), which may facilitate early clinical diagnosis and management. This study explored the incidence of cutaneous manifestations among hospitalised patients with COVID-19 and investigated its relationships with viral load, co-morbidities, and outcomes.

Methods: This retrospective study included adult patients admitted to a tertiary hospital for COVID-19 from July to September 2020. Clinical information, co-morbidities, viral load (cycle threshold [Ct] value), and outcomes were analysed.

Results: In total, 219 patients with confirmed COVID-19 were included. Twenty patients presented with new onset of rash. The incidence of new rash was 9.1% (95% confidence interval=6.25%-14.4%). The most common manifestations were maculopapular exanthem (n=6, 42.9%, median Ct value: 24.8), followed by livedo reticularis (n=4, 28.6%, median Ct value: 21.3), varicella-like lesions (n=2, 14.3%, median Ct value: 19.3), urticaria (n=1, 7.1%, median Ct value: 14.4), and acral chilblain and petechiae (n=1, 7.1%, median Ct value: 33.1). The median Ct values for patients with and without rash were 22.9 and 24.1, respectively (P=0.58). There were no significant differences in mortality or hospital stay between patients with and without rash. Patients with rash were more likely to display fever on admission (P<0.01). Regardless of cutaneous manifestations, patients with older age, hypertension, and chronic kidney disease stage ≥3 had significantly higher viral load and mortality (P<0.05).

Conclusion: This study revealed no associations between cutaneous manifestation and viral load or clinical outcomes. Older patients with multiple co-morbidities have risks of high viral load and mortality; they should be closely monitored.

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New knowledge added by this study

- Patients with coronavirus disease 2019 (COVID-19) could display various cutaneous manifestations. The incidence of new rash in our cohort was 13.6%. The most common manifestation attributed to COVID-19 was maculopapular exanthem, followed by livedo reticularis.
- Informal extrapolation of our results to the general population in Hong Kong suggested that 0.91% solely involve rash presentation; these patients would remain undiagnosed without severe acute respiratory syndrome coronavirus 2 testing. This lack of diagnosis is a potential health threat and could facilitate viral spread.

Implications for clinical practice or policy

- Rash is self-limiting in patients with COVID-19, potentially because of a more robust immune response among patients with rash.
- Older patients with multiple co-morbidities should undergo early screening and receive close monitoring if they develop symptoms of COVID-19; early treatment beginning at symptom onset can improve clinical outcomes.

新冠肺炎住院患者的皮膚表徵、病毒載量和預測臨床病程的研究

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簡介：各種皮膚表徵已被報告為新冠肺炎症狀，這可能有助於早期臨床診斷和治療。本研究探討了住院的新冠肺炎患者皮膚表徵的發生率，並調查了其與病毒載量、合併症和結果的關係。

方法：這項回顧性研究納入了2020年7月至9月入住一所三級醫院的新冠肺炎成年患者，分析了他們的臨床資料、合併症、病毒載量（Ct值）和結果。

結果：本研究共納入219名確診新冠肺炎的患者。20名患者出現新的皮疹。新發皮疹的發生率為9.1%（95%置信區間=6.25%-14.4%）。最常見的表徵是斑丘疹（n=6，42.9%，Ct值中位數：24.8），其次是網狀青斑（n=4，28.6%，Ct值中位數：21.3）、水痘樣病變（n=2，14.3%，Ct值中位數：19.3）、蕁麻疹（n=1，7.1%，Ct值中位數：14.4）以及肢端凍瘡和瘀點（n=1，7.1%，Ct值中位數：33.1）。有皮疹和無皮疹患者的Ct值中位數分別為22.9和24.1（P=0.58）。有皮疹和無皮疹患者的死亡率或住院時間沒有顯著差異。出現皮疹的患者入院時更有可能出現發燒症狀（P<0.01）。無論皮膚表徵如何，年齡較大、高血壓和慢性腎臟病第三期或以上患者的病毒載量和死亡率均顯著較高（P<0.05）。

結論：這項研究表明皮膚表徵與病毒載量或臨床結果之間沒有關聯。患有多種合併症的年長患者存在高病毒載量和高死亡率的風險；應對他們進行密切監測。

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first identified in December 2019 in Wuhan, Hubei, China.[1,2] According to World Health Organization Coronavirus (COVID-19) data, as of 7 May 2022, 188 countries and territories had reported more than 510.2 million cumulative confirmed cases and more than 6.23 million deaths[3]; in Hong Kong, there were 330 670 confirmed cases and 9308 (2.81%) deaths.[4] Common symptoms of COVID-19 include fever, sore throat, cough, malaise, dyspnoea, and anosmia or aguesia.[1] Although most people have mild symptoms, some develop acute respiratory distress syndrome, which may lead to cytokine storm, multiorgan failure, septic shock, and even death.[5]

There is evidence that rash is an early symptom or the only symptom in patients who are 'asymptomatic' or paucisymptomatic.[6-9] Early detection of this 'silent' sign and corresponding diagnosis are important for epidemiologic management because asymptomatic or paucisymptomatic cases may function as sources of community spread. Various dermatologic manifestations of COVID-19 have been reported including maculopapular eruption, urticarial eruption, livedo reticularis, pernio/chilblain, vasculitis, vesicular eruption, and papulonecrotic eruption.[10-15] The incidences of cutaneous manifestations in patients with COVID-19 have varied among case series (from 0.2% to 20.4%[10-13]), possibly because of the under-recognition of asymptomatic or paucisymptomatic cases.

The spread of SARS-CoV-2 mainly involves droplets; it can also occur via direct contact and is speculated to occur through faecal excretion.[2] The primary target of SARS-CoV-2 is the upper respiratory mucosa, where angiotensin-converting enzyme 2 (ACE2) serves as a functional receptor for viral spikes and eventual viral entry into host cells. Gene expression of the SARS-CoV-2 cellular receptor ACE2 has been demonstrated in multiple human tissues, including skin and adipose tissue.[16-18] Therefore, the proposed mechanisms by which SARS-CoV-2 affect cutaneous tissues include direct attacks on epidermal basal cells and vascular endothelial cells (possibly targeting ACE2 expressed on skin keratinocytes) and indirect impacts through the antiviral inflammatory response.[16-18]

There is speculation that patients with rash occurrence may have a better prognosis because they display better antiviral immunity.[19] Early in the COVID-19 pandemic, little was known about relationships among cutaneous manifestations, viral load, co-morbidities, and clinical outcomes. A recent systematic review showed inconclusive results about the relationship between COVID-19 severity and viral load; however, it suggested that older age and higher SARS-CoV-2 viral load were directly related.[20] Likewise, some rashes such as maculopapular rash and chilblain-like lesions were found to be strongly associated with paucisymptomatic disease course and lower severity of COVID-19 while skin changes such as acro-ischaemia, livedo reticularis and purpura may be useful indicators of higher severity of COVID-19.[21,22] In 2020, according to the Public Health Ordinance of Hong Kong, all patients with SARS-CoV-2–positive test results were hospitalised for quarantine, regardless of symptoms.[4] Here, we explored the incidences and patterns of clinical and cutaneous manifestations among hospitalised patients with confirmed COVID-19, then investigated associations with viral load, co-morbidities, and prognosis.

Methods

This retrospective cohort study was conducted from 1 July to 30 September 2020 in an acute tertiary hospital, Queen Mary Hospital (ie, a major public hospital within one of seven hospital clusters) serving one-fifth of the population of 7.5 million in Hong Kong. Electronic hospital records were used to identify adult patients aged ≥18 years who were admitted during the study period for suspected COVID-19.

The flow of patient recruitment is illustrated in Figure 1. Patients included in this study were adults with laboratory confirmation of COVID-19 by real-time reverse transcription polymerase chain reaction (rRT-PCR) assay from a nasopharyngeal swab. Clinical information was collected from electronic clinical photographs of patients who had provided informed consent to receive treatment. A physical examination was performed by a dermatologist within 48 hours of rash onset to confirm clinical signs; follow-up was conducted monthly until 3 months after discharge. Rashes were considered COVID-19–related if they were new, could not be explained by the patient's previous or pre-existing skin conditions or an alternative diagnosis (eg, drug eruption or other viral exanthem of varicella, parvovirus, enterovirus, influenza, parainfluenza, adenovirus, or respiratory syncytial virus detected in nasopharyngeal swab [performed as clinically indicated and excluded]), occurred along with the SARS-CoV-2–positive rRT-PCR test results, and resolved when other symptoms improved.

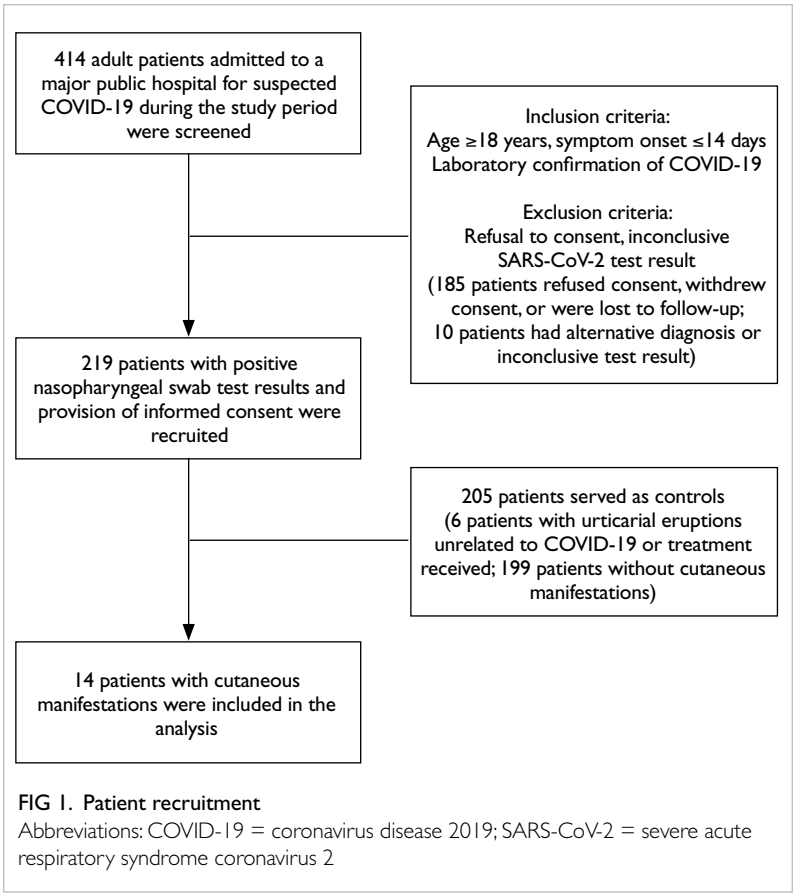

FIG 1. Patient recruitment
Abbreviations: COVID-19 = coronavirus disease 2019; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

Clinical and laboratory data

Clinical and laboratory data, including patient demographics, initial COVID-19 viral load according to cycle threshold (Ct) value, treatment received, co-morbidities (diabetes mellitus, hypertension, and chronic kidney disease [CKD]), and pre-existing skin diseases, were retrieved from electronic medical records for analysis. For the detection of viral nucleic acids, rRT-PCR is considered a gold standard diagnostic assay. The Ct value refers to the number of rRT-PCR cycles needed to amplify viral RNA to a detectable level; it is inversely related to viral load.[23] Thus, the Ct value can indicate the relative quantity of viral RNA in a specimen (lower Ct values reflect greater quantities of viral RNA). In this study, Ct values of <26, 26-30, and ≥31 were regarded as high, intermediate, and low viral load, respectively.[24,25]

Statistical analysis

Continuous variables were expressed as medians (interquartile ranges) or means (± standard deviations), as appropriate. The Mann-Whitney *U* test and Kruskal-Wallis test were used to compare median values between two groups and among ≥3 groups, respectively. Categorical variables, expressed as proportions, were compared using the Chi squared test or Fisher's exact test, as appropriate.

To identify factors independently associated with outcomes, variables with P values <0.1 in univariate analyses were subsequently entered into binary logistic regression multivariate analyses; odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. All statistical analyses were performed using SPSS (Windows version 26.0; IBM Corp, Armonk [NY], United States). Two-tailed P values <0.05 were considered statistically significant.

Results

From 1 July to 30 September 2020, 414 patients with suspected COVID-19 were admitted to our hospital. This study included 219 patients who had SARS-CoV-2–positive rRT-PCR results in analyses of nasopharyngeal swab samples (from 213 recovered patients and six patients who had died). One hundred and ninety-five patients were excluded because of non–COVID-19 diagnosis, unconfirmed status, non-Asian ethnicity, or refusal to consent (Fig 1).

The mean patient age was 54.7 ± 17.5 years (range, 18-99), the male-to-female ratio was approximately 1:1, and 90.4% of the patients were Chinese (Table 1). The mean duration of hospitalisation was 9.87 ± 6.99 days and the overall mortality rate was 2.7%. The mean SARS-CoV-2 rRT-PCR Ct values for nasopharyngeal swab on admission was 24.2 ± 7.1. The median time to the first post-discharge visit was 38 days (range, 28-42) and the median duration of follow-up was 14 weeks (range, 13.1-15.5).

TABLE 1. Characteristics of patients with nasopharyngeal swab–confirmed coronavirus disease 2019 (n=219)*

	No. (%)
Age, y	54.7 ± 17.5 (18-99)
Male sex	110 (50.2%)
Chinese ethnicity†	198 (90.4%)
Habitual smoking	31 (14.2%)
Habitual alcohol consumption	28 (12.8%)
Co-morbidities	
Hypertension	31 (14.2%)
Diabetes mellitus	52 (23.7%)
CKD (stage ≥3)	20 (9.1%)
Hospitalisation	
Duration of admission, d	9.87 ± 6.99 (2-52)
Mortality	6 (2.7%)
Vital signs on admission	
Oxygen saturation (pulse oximetry on room air), %	97.4 ± 2.6 (70-100)
Desaturation during admission	15 (6.8%)
Respiratory rate, breaths/min	17.0 ± 2.4 (12-26)
Tachypnoea (respiratory rate >21 breaths/min)	18 (8.2%)
Blood pressure, mm Hg	
Systolic	139 ± 22 (74-243)
Diastolic	83 ± 14 (40-150)
Pulse, beats/min	89 ± 17 (44-193)
Tachycardia (heart rate >100 beats/min)	48 (21.9%)
Temperature, °C	37.5 ± 0.7 (36.0-39.9)
Fever	93 (42.5%)
Pulmonary infiltrates on CXR	19 (8.7%)
Laboratory results	
Haemoglobin, g/dL	13.3 ± 1.8 (5.8-16.9)
Leucocyte count, ×10⁹/L	5.4 ± 2.1 (2.06-17.60)
Neutrophils	3.5 ± 2.03 (0.57-16.51)
Lymphocytes	1.3 ± 0.58 (0.2-3.42)
Platelet count, ×10⁹/L	227.7 ± 67.7 (97-464)
Creatinine, μmol/L	77.0 ± 34.5 (33-196)
eGFR, mL/min‡	81.48 ± 14.64 (12-90)
Alanine transaminase, U/L	32.3 ± 32.5 (6-335)
Aspartate aminotransferase, U/L	33.0 ± 25.4 (8-224)
TnT, ng/L	13.4 ± 30.7 (5-327)
TnT level in patients with CKD stage ≥3, ng/L	42.1 ± 70.8 (5.6-93)
HbA1c, %	5.82 ± 0.9 (3.7-11.2)
SARS-CoV-2 rRT-PCR Ct value on admission§	
Nasopharyngeal swab	24.2 ± 7.1 (11.9-42.2)
Ct value <26	130 (59.4%)
Age ≥70 years (n=39)	21.96 ± 7.4 (12.9-35.3)
Ct value <26	29 (74.4%)

Abbreviations: CKD = chronic kidney disease; Ct = cycle threshold; CXR = chest X-ray; eGFR = estimated glomerular filtration rate; HbA1c = glycated haemoglobin; rRT-PCR = real-time reverse transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TnT = troponin T

* Data are shown as No. (%) or mean ± standard deviation (range)

† Non-Chinese Asian ethnicity (n=21, 9.6%): domestic workers/visitors from Indonesia (8), the Philippines (8), India (3), and Thailand (2)

‡ Stage 1: ≥90 mL/min, normal kidney function; stage 2: 60-89 mL/min, mildly reduced kidney function; stage 3: 30-59 mL/min, moderately reduced kidney function; stage 4: 15-29 mL/min, severely reduced kidney function; stage 5: <15 mL/min or on dialysis, very severely reduced kidney function or end-stage kidney failure

§ Initial Ct values of <26, 26-30, and ≥31 were considered high, intermediate, and low viral load, respectively

Clinical presentation of coronavirus disease 2019

The three most frequent symptoms were upper respiratory symptoms: cough (51.5%), fever (42.5%), and sputum production (27.8%). Among the 219 patients with positive SARS-CoV-2 test results, 58 (26.5%) were asymptomatic and had undergone compulsory SARS-CoV-2 testing in accordance with the Public Health Ordinance. Of the 58 patients, 75.9% reported contact with identifiable index cases, such as household members, domestic helpers, or work colleagues.

Cutaneous manifestations of coronavirus disease 2019

Twenty patients presented with new rash. The incidence of new rash was 9.1% in this 3-month study period (95% CI=6.25%-14.4%). At the time of this study, there were no biomarkers or diagnostic tests for COVID-19–related cutaneous manifestations. Any new cutaneous manifestation not attributable to a previous/pre-existing skin disease or alternative diagnosis was considered COVID-19–related. Upon review by a dermatologist, six patients were diagnosed with localised urticarial eruptions after interferon injection treatment; 6.4% of patients (14/219) displayed various forms of COVID-19–related rash (Fig 2 and Table 2).

The most common manifestations were maculopapular exanthem (n=6, 42.9%, median Ct value: 24.8), followed by livedo reticularis (n=4, 28.6%, median Ct value: 21.3), varicella-like lesions (n=2, 14.3%, median Ct value: 19.3), urticaria (n=1, 7.1%, median Ct value: 14.4), and acral chilblain and petechiae (n=1, 7.1%, median Ct value: 33.1) [Fig 2].

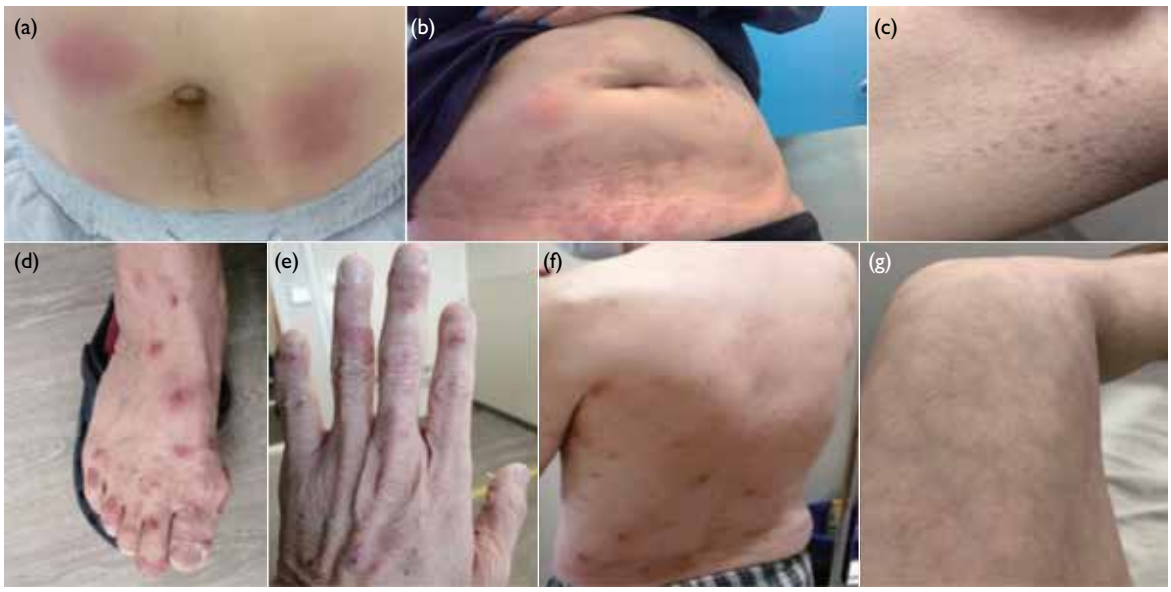

FIG 2. Cutaneous manifestations in patients with coronavirus disease 2019. (a) Urticarial eruptions. A 60-year-old man had tender urticarial plaques on the abdomen after interferon injection. (b) Maculopapular exanthem. A 40-year-old woman presented with maculopapular eruptions on the trunk as well as urticarial plaques on the right abdomen secondary to interferon injection. (c) Petechiae. A 37-year-old woman presented with petechial rash on the thighs. (d-f) A 59-year-old man presented with symmetrical erythematous vesicular papules on his extremities and back. (g) A 59-year-old woman presented with reticular erythema on the bilateral lower legs

The median Ct values for patients with and without rash were 22.9 and 24.1, respectively (P=0.58). The timing of symptom onset ranged from day 1 to day 9 (median, 4; mean, 4.28 ± 2.26). Skin symptoms were the sole symptoms in two patients with COVID-19 (0.91%), highlighting the importance of carefully evaluating patients who only display initial cutaneous symptoms or signs.

Outcomes and prognostic factors

Characteristics of patients with confirmed coronavirus disease 2019: rash vs no rash

Compared with patients without rash, patients with rash were more likely to exhibit fever (OR=5.73; P=0.008) and display pulmonary infiltrates on chest X-ray (OR=5.06; P=0.013). Among patients with pulmonary infiltrates (n=19), four of them had rash. The episodes of desaturation requiring supplemental oxygen were less common in patients with rash (25%, 1/4) than in those without (93.3%, 14/15; OR=0.02, 95% CI=0.001-0.49; P=0.02). Furthermore, among these 19 patients with pulmonary infiltrates, systemic corticosteroids were less frequently required by patients with rash (25%, 1/4) than by those without (73.3%, 11/15; OR=0.12, 95% CI=0.01-1.53; P=0.10), but it was not statistically significant. There were no significant differences in age, sex, co-morbidities or Ct values between patients with and without rash. The estimated glomerular filtration rate (eGFR) was slightly lower in older patients without rash (P=0.024); 10.2% of these patients had CKD stage ≥3. In terms of outcomes, patients with and without rash had mortalities of 0.0% and 2.9%, respectively (P=0.97). The length of hospitalisation was similar in both groups (Table 3).

Characteristics of patients with coronavirus disease 2019: co-morbidities and viral load

Patients aged ≥70 years had a significantly higher viral load (as reflected by a lower Ct value), compared with those aged <70 years (mean Ct value: 21.97 vs 24.65, P=0.03). Regardless of age, patients with hypertension and CKD stage ≥3 had a significantly higher viral load and lower initial Ct value on admission (OR=2.65, 95% CI=1.08-6.45 and OR=3.65, 95% CI=1.18-11.3, respectively; both P<0.05).

All six patients who died were men; their mean age was 87.0 ± 7.3 years. The rates of hypertension, diabetes mellitus, a glycated haemoglobin level of ≥6.5%, CKD stage ≥3, and higher viral load (ie, lower Ct value on admission) were significantly greater among patients who died than among those who survived (Table 4). Older age, hypertension, and low eGFR were associated with a higher risk of mortality (all P<0.05) [Table 5].

Treatment received

Treatment varied in this cohort because there was no standard of care in the early days of the COVID-19 pandemic. Symptomatic treatment was administered

TABLE 2. Characteristics of patients with confirmed coronavirus disease 2019 and cutaneous manifestations (n=14)

Sex/age, y	Day of symptom onset	Temperature, °C	Symptoms	Rash	Ct value	CXR	Hospital stay, d	Treatment regimen	SARS-CoV-2–IgG, d
Female/40	3	37.7	F, C, R, myalgia, hypogeusia, hyposmia	MPE over trunk	22.7	Clear	11	5D R & I	11
Male/47	4	37.9	F, C, SP	MPE over limbs	32.1	Clear	6	5D R & I	6
Female/58	9	37.6	F, C, ST, hyposmia, hypogeusia, diarrhoea	MPE over limbs	31.7	Clear	6	5D R & I	6
Female/59	2	37.8	F, C, R	MPE over limbs	14.1	Clear	9	5D R & I	5
Male/68	4	37.7	C, SOB, O2 requirement	MPE over limbs	21.6	Peripheral infiltrates with AT	13	5D R & I Dexamethasone	7
Female/73	7	37.3	Nil	MPE over limbs	27.1	Clear	7	5D R & I	4
Female/37	3	38.0	F, C, diarrhoea	Livedo reticularis over thighs, petechiae	15.4	RLZ infiltrates	6	5D R & I	13
Female/50	2	38.3	F, C, R, headache, myalgia	Livedo reticularis over limbs	17.9	Clear	12	5D R &I	12
Female/51	4	37.6	F, headache, myalgia	Livedo reticularis over limbs	29.3	Clear	10	5D R & I	6
Female/59	7	38.1	F, C, SP, chills, myalgia, malaise, hypogeusia, mild SOB	Livedo reticularis over limbs	22.5	Bilateral peripheral infiltrates	12	5D R & I	5
Male/58	6	37.1	F, C, R, ST, SP, hyposmia, hypogeusia, diarrhoea	Acral chilblain-like tender lesions over fingers	33.1	Clear	4	Symptomatic treatment	6
Male/22	3	37.9	F, C, R, SP	Varicella-like lesions over extremities, palms, and soles	23.3	Clear	8	5D R & I	12
Male/59	5	38.3	F, ST, hyposmia, hypogeusia	Varicella-like lesions over the trunk and limbs	15.4	RLZ infiltrates	9	5D R & I	9
Female/60	1	36.7	Nil	Urticaria over trunk and limbs	14.4	Clear	14	5D R & I	6

Abbreviations: 5D R & I = ribavirin and interferon beta-1b for 5 days; AT = atelectasis; C = cough; CXR = chest X-ray; F = fever; MPE = maculopapular exanthem; R = rhinorrhoea; RLZ = right lower zone; SARS-CoV-2–IgG = duration from day of symptom onset to severe acute respiratory syndrome coronavirus 2 immunoglobulin detection; SOB = shortness of breath; SP = sputum; ST = sore throat

to 53 patients (24.2%); 166 patients (75.8%) received early treatment within the first week of symptom onset, including interferon beta-1b and ribavirin, which were administered based on the results of a triple therapy clinical study.[21] Emollients and topical corticosteroids of mild to moderate potency (1% hydrocortisone cream and 0.1% mometasone furoate cream) were prescribed for symptomatic relief.

Follow-up and dermatological outcome

During follow-up, we observed that urticarial eruption after interferon injection resolved within 10 to 14 days upon completion of treatment. With respect to COVID-19–related skin eruptions, most lesions (maculopapular exanthem, livedo reticularis, and urticaria) were self-limiting and spontaneously resolved without specific treatment; there were no severe sequelae. Two patients with varicella-like lesions had mild post-inflammatory hyperpigmentation without scarring.

Discussion

Cutaneous manifestations of the COVID-19 pandemic have been gaining increasing attention because they may be useful in the early diagnosis of COVID-19, triage of patients with SARS-CoV-2–positive test results, and risk stratification. There is speculation that the mechanism involves the direct action of SARS-CoV-2 on tissues, the complement/interferon-driven immune response, and the coagulation system; alternatively, it involves nonspecific skin symptoms of systemic viral

TABLE 3. Characteristics of patients with confirmed coronavirus disease 2019: rash vs no rash*

	Rash (n=14)	No rash (n=205)	OR (95% CI)	P value
Male sex	5 (35.7%)	105 (51.2%)	0.53 (0.17-1.63)	0.27
Age, y	52.9 ± 13.2	54.9 ± 17.3	-	0.85
Hypertension	1 (7.1%)	30 (14.6%)	0.44 (0.05-3.56)	0.44
Diabetes mellitus	4 (28.6%)	48 (23.4%)	1.31 (0.39-4.36)	0.66
CKD (stage ≥3)	0	20 (9.8%)	0.31 (0.02-5.42)	0.42
Creatinine, μmol/L	66.9 ± 11.5	77.7 ± 35.4	-	0.26
eGFR, mL/min	88.9 ± 2.56	80.9 ± 14.9	-	0.024
TnT, ng/mL	6.67 ± 2.56	13.8 ± 31.5		0.39
Ct value of NPA	22.9 ± 6.78	24.1 ± 7.12	-	0.58
Rash and Ct value				
MPE (n=6)	24.8 ± 6.86	-		
Urticaria (n=1)	14.4	-		
Varicella-like (n=2)	19.3 ± 5.35	-		
Livedo reticularis (n=4)	21.3 ± 6.13	-		
Chilblain (n=1)	33.1	-		
Fever†	11 (78.6%)	80 (39.0%)	5.73 (1.55-21.2)	0.008
Pulmonary infiltrates on CXR‡	4 (28.6%)	15 (7.3%)	5.06 (1.42-18.0)	0.013
Episodes of desaturation§	1 (7.1%)	14 (6.8%)	1.05 (0.12-8.68)	0.96
Tachypnoea (respiratory rate ≥21 breaths/min)	2 (14.3%)	15 (7.3%)	1.80 (0.37-8.57)	0.40
Systemic corticosteroids‖	1 (7.1%)	11 (5.4%)	1.36 (0.16-11.3)	0.78
Mortality	0	6 (2.9%)	1.06 (0.06-19.7)	0.97
Hospital stay, d	8.16 ± 4.18	9.76 ± 6.94	-	0.29

Abbreviations: CI = confidence interval; CKD = chronic kidney disease; Ct = cycle threshold; CXR = chest X-ray; eGFR = estimated glomerular filtration rate; MPE = maculopapular exanthem; NPA = nasopharyngeal aspirate; OR = odds ratio; TnT = troponin T

* Data are shown as No. (%) or mean ± standard deviation, unless otherwise specified

† Fever on admission or within 7 days of symptom onset

‡ Excluding changes secondary to nosocomial/secondary bacterial pneumonia, pulmonary oedema, heart failure or pre-existing disease

§ Definition of pulse oximetry on room air: normal = ≥96%; mild desaturation = 90%-95%; moderate desaturation = 80%-89%; severe desaturation = <80% on room air

‖ Dexamethasone in a dosage of 6-8 mg daily (median, 8 d; range, 5-14)

infection.[16,17,22,26-28] Although more investigations are needed, it is possible that some symptoms are clinical signs of milder COVID-19, whereas others are indicators of more severe clinical illness.

Maculopapular exanthem: the most common cutaneous manifestation

Our study showed that patients with confirmed COVID-19 could display various cutaneous manifestations. The most common manifestation attributed to COVID-19 was maculopapular exanthem, followed by livedo reticularis. Because most skin lesions were transient and self-limiting, skin biopsy was only performed in one patient. In that 40-year-old female patient, skin biopsy of the left trunk revealed low to moderate numbers of perivascular lymphocytes and histiocytes, as well as sparse eosinophils, in the superficial dermis; focal parakeratosis was present in the epidermis. There was no evidence of vasculitis or interfacial changes. These findings were compatible with maculopapular exanthem.

In previous reports, erythema multiforme–like lesions, chilblain-like acral eruptions, and livedo erythema were identified in children and young adult patients with asymptomatic or mild disease.[26,28,29] In contrast, maculopapular rash and acro-ischaemic lesions were often observed among adult patients with more severe disease. Among our patients who presented with rash, there were no instances of mortality; the duration of hospitalisation was similar regardless of rash status. The results of a previous study has suggested that the cutaneous manifestation is the only manifestation of COVID-19 in some patients[30]; thus, careful documentation of any cutaneous symptoms during the COVID-19

TABLE 4. Comparison of characteristics between patients with coronavirus disease 2019 who died (mortality group) and those who recovered (recovered group)*

	Mortality (n=6)	Recovered (n=213)	OR (95% CI)	P value
Male sex	6 (100%)	104 (48.8%)	13.76 (0.76-247.1)	0.07
Age, y	87.0 ± 7.3	53.7 ± 16.4	-	<0.01
Nursing home residents	3 (50.0%)	10 (4.7%)	20.4 (3.65-114.1)	<0.01
Hypertension	4 (66.7%)	27 (12.7%)	13.85 (2.42-79.3)	<0.01
Diabetes mellitus	4 (66.7%)	48 (22.5%)	6.92 (1.23-38.9)	0.03
HbA1c level ≥6.5%	4 (66.7%)	41 (19.2%)	8.44 (1.49-47.6)	0.02
Creatinine, μmol/L	111.2 ± 28.7	75.9 ± 34.1	-	0.01
eGFR, mL/min	54.0 ± 16.5	82.3 ± 13.1	-	<0.01
CKD (stage ≥3)	4 (66.7%)	16 (7.5%)	23.18 (3.95-135.8)	<0.01
Ct value of NPA	18.54 ± 6.07	24.41 ± 7.07	-	0.04
Hospital stay, d	16.33 ± 5.85	7.58 ± 4.85	-	<0.01
Pulmonary infiltrates on CXR†	5 (83.3%)	14 (6.6%)	71.1 (7.76-650.7)	<0.01
Episodes of desaturation‡	6 (100%)	9 (4.2%)	279.8 (14.4-5432.1)	<0.01
Tachypnoea (respiratory rate ≥21 breaths/min)	5 (83.3%)	13 (6.1%)	76.9 (8.36-707.6)	<0.01
Systemic corticosteroids§	5 (83.3%)	7 (3.3%)	147.1 (15.1-1431.9)	<0.01

Abbreviations: CI = confidence interval; CKD = chronic kidney disease; Ct = cycle threshold; CXR = chest X-ray; eGFR = estimated glomerular filtration rate; HbA1c = glycated haemoglobin; NPA = nasopharyngeal aspirate; OR = odds ratio

* Data are shown as No. (%) or mean ± standard deviation, unless otherwise specified

† Excluding changes secondary to nosocomial/secondary bacterial pneumonia, pulmonary oedema, heart failure or pre-existing disease

‡ Definition of pulse oximetry on room air: normal = ≥96%; mild desaturation = 90-95%; moderate desaturation = 80-89%; severe desaturation = <80% on room air

§ Dexamethasone in a dosage of 6-8 mg daily (median, 8 d; range, 5-14)

pandemic may be necessary for early recognition and diagnosis.[30] Additionally, urticaria with fever has diagnostic implications because this combination may be an early symptom of subsequently confirmed SARS-CoV-2 infection.[19] In our cohort, patients with cutaneous manifestations were more likely to present with fever. Although most of our patients had symptoms other than rash alone, two patients (0.9%) presented with rash only (one with urticaria and one with maculopapular exanthem); the clinical significance of these symptoms should not be ignored. Informal extrapolation of these results to the general population in Hong Kong suggested that 2477 cases (2/219; ie, 0.91% × 272 235 confirmed cases)[4] solely involve rash presentation; these patients would remain undiagnosed if they did not undergo SARS-CoV-2 testing. This lack of diagnosis is a potential health threat and could facilitate viral spread.

Incidence of cutaneous manifestations

In our cohort, the incidence of new rash was 13.6%. In the study by Guan et al[31] in China, the prevalence of rash was much lower in patients with COVID-19 (0.2%; 2/1099). In that study, patients with rash may have been underdiagnosed because patients with suspected COVID-19 were managed by general practitioners or hospitalists who had less familiarity with cutaneous manifestations.[31] In contrast, our patients underwent prompt assessment by in-hospital dermatologists to detect cutaneous manifestations. In an Italian study, the prevalence of rash presentation was much higher (20.4%),[13] presumably because asymptomatic patients were excluded through a lack of testing. However, if we exclude the 58 asymptomatic patients in our cohort (all of whom underwent compulsory testing in accordance with the Public Health Ordinance), the incidence of new rash in our study was 16.7% (95% CI=14.5-18.8), which remains lower than the incidence in the Italian study. We speculate that this difference is related to the early initiation of combined treatment (ribavirin and interferon beta-1b) in our cohort, which may modify or halt the SARS-CoV-2–induced inflammatory process.[21] Importantly, the genomic characteristics of SARS-CoV-2 spread are under investigation worldwide; this approach helps identify transmission routes in various regions. In a case series in the United States, SARS-CoV-2 genomes in one region were predominantly associated with isolates that originated in Europe (>80%), similar to the distributions of viral strains in other regions in the United States[32]; a smaller

TABLE 5. Multiple Cox regression of all-cause mortality in patients with coronavirus disease 2019 (n=219)

	Crude model		Adjusted model	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Age	1.17 (1.08-1.26)	<0.01	1.27 (1.04-1.53)	<0.01
Female sex	0.02 (0.00-10.7)	0.21	0.00 (0.00-4.38)	0.93
Habitual smoking	2.38 (0.31-19.5)	0.16	2.25 (0.36-15.6)	0.36
Hypertension	7.18 (1.15-45.1)	0.04	2.39 (1.30-17.2)	0.04
Diabetes mellitus	1.61 (0.22-11.7)	0.63	3.18 (0.19-52.2)	0.41
CKD (stage ≥3)	10.6 (2.61-52.0)	<0.01	5.97 (0.93-43.1)	0.07
Fever	1.43 (0.26-7.83)	0.67	1.44 (0.26-7.89)	0.66
Rash	0.51 (0.06-4.39)	0.54	0.06 (0.01-1.22)	0.07
Hospital stay	1.07 (1.01-1.14)	0.03	0.99 (0.91-1.07)	0.72
Ct value of NPA	0.91 (0.79-1.05)	0.18	0.92 (0.76-1.11)	0.40
Pulmonary infiltrates on CXR	6.63 (0.72-61.0)	0.08	4.50 (0.82-24.6)	0.09
SpO2 desaturation	2.19 (0.80-6.0)	0.53	1.18 (0.70-1.99)	0.13
Tachypnoea	1.28 (1.01-1.62)	0.03	0.79 (0.27-2.27)	0.66
HbA1c	2.70 (1.03-7.08)	0.04	2.67 (0.97-7.60)	0.05
Creatinine	1.01 (1.00-1.02)	0.03	1.04 (1.01-1.15)	0.48
eGFR	0.94 (0.91-0.97)	0.02	0.88 (0.82-0.96)	0.01
TnT	1.00 (0.99-1.02)	0.74	1.00 (0.99-1.99)	0.64
AST	1.01 (0.99-1.02)	0.07	1.03 (1.00-1.07)	0.05
Interferon beta-1b and ribavirin	0.16 (0.03-0.88)	0.04	0.27 (0.03-2.79)	0.28

Abbreviations: AST = aspartate transferase; CI = confidence interval; CKD = chronic kidney disease; Ct value of NPA = cycle threshold value of nasopharyngeal aspirate on admission; CXR = chest X-ray; eGFR = estimated glomerular filtration rate; HbA1c = glycated haemoglobin; SpO2 = pulse oximetry on room air; TnT = troponin T

subgroup of SARS-CoV-2 genomes displayed similarity to strains that originated in Asia (15%), indicating multiple sources of viral spread within the community.[32] Differences in the prevalences of cutaneous manifestations may represent variations in SARS-CoV-2 genomic characteristics among regions; in Hong Kong, a cosmopolitan city with many travellers from mainland China and other countries, the prevalences of cutaneous manifestations may be the result of viral strains from all provinces of China as well as Europe and other regions. Further studies are needed concerning genomic variations and clinical manifestations.

Prognostic factors

In terms of viral load and prognosis, higher viral load on admission was significantly associated with greater mortality in patients with older age, history of hypertension, and CKD stage ≥3. Univariate analysis showed that the risk of mortality was the greatest among patients with older age, hypertension, higher glycated haemoglobin level, and renal impairment. Multivariate Cox regression analysis confirmed that older age, hypertension, and low eGFR were significantly associated with greater mortality risk.

Conversely, patients with renal impairment were less likely to present with rash, suggesting that the immune response is weaker in patients with renal impairment. However, the length of hospitalisation was similar regardless of cutaneous manifestations; the presence of cutaneous manifestations was not associated with other co-morbidities. There was no clear association between Ct values and rash occurrence. Additional studies with larger sample sizes may be necessary to explore the relationship between rash subtype and viral load.

Rash as immunological response

The results of a previous study suggested that cutaneous manifestations of COVID-19 were related to immunological responses rather than the direct results of viral invasion[17]; cutaneous manifestations may be an early sign of immunological responses elsewhere in the body, similar to pulmonary infiltrates secondary to cytokine storm. The present study showed that the incidence of pulmonary infiltrates was considerably higher among patients with rash (28.6%) than among those without (7.3%) [Table 3]; conversely, patients with rash were less likely to display further deterioration, such as oxygen desaturation and a requirement for oxygen supplementation (P=0.016). Only one patient

with rash (25%) received dexamethasone, whereas multiple patients without rash required such treatment (73.3%) [P=0.11]. Another explanation is that, overall, patients with rash tended to seek medical attention earlier than those without, which would increase the likelihood of prompt treatment. A previous study has indicated that patients with cutaneous manifestations may have a better prognosis because those patients develop a more robust immune response.[17]

In patients with new pulmonary infiltrates as well as evidence of respiratory decompensation/failure (eg, desaturation and/or tachypnoea), systemic corticosteroids have been used to prevent tissue destruction from cytokine storm after other causes had been ruled out. In this context, patients receiving systemic corticosteroids had more severe disease that involved evidence or features of respiratory decompensation and carried a greater risk of mortality.

In the present study, after the exclusion of patients with nosocomial/secondary bacterial pneumonia, heart failure, or pulmonary changes related to prior disease, 19 patients (8.7%) had new pulmonary infiltrates on admission. All 19 patients received interferon beta-1b and ribavirin treatment; 12 patients received dexamethasone (daily dosage range, 6-8 mg; mean duration, 8.63 ± 2.53 days) [Table 4]. Among the 12 patients receiving dexamethasone, five patients (41.7%) died despite the use of systemic corticosteroids, together with empirical antibiotics, interferon beta-1b, and ribavirin; in contrast, only one death (14.3%) occurred among seven patients receiving interferon beta-1b and ribavirin without corticosteroids (OR=4.28, 95% CI=0.38-47.6; P=0.23). The mean interval from symptom onset to systemic corticosteroid initiation was shorter among patients who recovered than among those who died (5.14 ± 2.14 days vs 8.61 ± 2.30 days; P=0.0026). These results suggest that the early use of systemic corticosteroids may lead to a better survival outcome.

Mortality

Although no deaths occurred among patients with cutaneous manifestations, the mortality rate did not significantly differ from the rate of 2.9% among patients without rash. Most patients received treatment within the first week after diagnosis of COVID-19 (according to detection of SARS-CoV-2–specific immunoglobulin G within 14 days after symptom onset; mean, 7.71 ± 3.05 days; range, 4-13), which may have improved disease outcomes and shortened hospitalisation. These findings highlighted the importance of early treatment beginning at symptom onset (ie, in the first week) and supported the use of interferon therapy described in a previous report.[21]

Limitations

First, this study had a small number of patients. Second, there was potential selection bias because only hospitalised patients with SARS-CoV-2–positive test results were included in the analysis; patients with COVID-19 who did not undergo screening or seek medical consultation were not diagnosed, and thus they were excluded from the study. Third, Ct value analysis was not conducted according to rash subtype and severity because of the limited number of patients. Fourth, some viral laboratory tests (eg, test for human herpesvirus 6) were not routinely available in our hospital, which may have hindered the interpretation of possible causes of rash or the identification of coexisting infections. Nevertheless, most other possible viral infections were excluded from this study. Additional studies with larger sample sizes and comparisons with treatment outcomes are needed.

Conclusion

This study did not demonstrate direct relationships among rash, viral load, and mortality. Furthermore, cutaneous manifestations may be early signs of immunological responses (similar to pulmonary infiltrates). Patients with older age, hypertension, and renal impairment have greater mortality risk and higher viral load. These high-risk groups should be prioritised in early screening and vaccination efforts to avoid poor clinical outcomes.

Author contributions

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All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors declare no conflicts of interest.

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Ethics approval

This research was approved by the Institutional Review Board of The University of Hong Kong/Hospital Authority

Hong Kong West Cluster (Ref No.: UW20-725) and was conducted in full compliance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki. Appropriate patient consent was obtained for clinical information and images to be publicly reported. All participants' clinical data and reports were deidentified to maintain anonymity.

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