

Paucity of cutaneous manifestations of COVID-19 among inpatients at a referral hospital in India



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Background: Varied cutaneous manifestations of COVID-19 have been described, but most studies are based on photographic or application-based observations, without a direct observed-based evaluation by dermatologists.

Objective: To study the types of cutaneous manifestations of COVID-19 among confirmed inpatients admitted to COVID-19 wards and intensive care units (ICUs).

Methods: This cross-sectional analysis was conducted at a referral hospital in Delhi, India. Four hundred forty consecutive reverse transcription-polymerase chain reaction (RT-PCR)—confirmed cases diagnosed with moderate or severe COVID-19 and admitted to COVID-19 wards or ICUs, respectively, were included. A cutaneous finding was considered to be associated with COVID-19 if it had been described earlier as a consequence of COVID-19 and was observed at the time of or within the first 48 hours of admission (after excluding drugs and comorbidities as causes).

Results: Two hundred seventy patients with moderate COVID-19 were admitted to COVID-19 wards, whereas 170 with severe disease were admitted to ICUs. Only 7 of the 270 ward patients (2.59%) and 3 of the 170 ICU patients (1.76%) had cutaneous findings associated with COVID-19.

Conclusion: Cutaneous findings attributable to COVID-19 are infrequent, and we believe that these might have been overestimated or overemphasized in earlier studies. Although coagulopathic findings may be associated with severe COVID-19, causation cannot be established in this cross-sectional study. (JAAD Int 2022;8:10-5.)

Key words: coagulopathy; COVID-19; COVID toes; digital ischemia; DVT; morbilliform rash; mottling; peer review; prognosis; RT-PCR; skin; systemic; urticaria.

INTRODUCTION

India has recorded over 35 million cases of COVID-19 and is the new epicenter of the pandemic, second only to the United States. Although various authors have reported heterogeneous cutaneous manifestations purportedly due to SARS-CoV-2,¹⁻⁴ these skin lesions have not been conclusively linked to COVID-19. Our referral hospital has been a designated COVID-19 center since the beginning of the pandemic in India. Hence, we were privy to the experience of multidisciplinary specialists and residents involved in the care of COVID-19 patients across the spectrum of COVID-19 severity. We sought to study whether cutaneous findings reported in patients with COVID-19 in the literature were seen among inpatients at our referral hospital.

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MATERIALS AND METHODS

This cross-sectional observational analysis involved a direct examination of all reverse transcription-polymerase chain reaction (RT-PCR)-confirmed COVID-19 cases admitted to COVID-19 wards and intensive care units (ICUs) at our hospital over a 20-week period. A dermatologic examination was performed by dermatology residents who were posted in the wards and ICUs, and all skin lesions were cross verified by board-certified specialists both at the time of admission and in case of appearance of any new lesions within 48 hours of hospital stay. Comorbidities, drugs administered, and eventual outcomes in the patients were noted.

Cutaneous findings that had been described earlier as a consequence of COVID-19 (including morbilliform rash, pseudochilblains, urticaria, vesicles, and livedo or retiform purpura) and appeared at the time of or within 48 hours of the diagnosis of COVID-19, after excluding other causes, were noted.¹⁻⁵ Incidental cutaneous findings that could be explained by other causes, such as sepsis, drugs, and comorbidities, were also noted. A comparison of severe and moderate cases was performed with respect to fatality rate, comorbidities, and specific and incidental manifestations. Cross tabulations were made, and the results were recorded as crude or unadjusted odds ratio (OR) (severe-to-moderate cases) along with 95% CI. The Mann-Whitney's U test, Fisher's exact test, and χ^2 test were used to obtain *P* values, and a *P* value of <.05 was considered significant.

RESULTS

A total of 440 RT-PCR-confirmed cases of COVID-19 were recruited in a 20-week study period, with 270 (moderate) cases in the wards and 170 (severe) in the ICUs (Table 1). The patients were stratified into moderate and severe cases as per the Clinical Guidance for Management guideline issued by the AIIMS/ICMR-COVID-19 National Task Force/Joint Monitoring Group (Dte. GHS), Ministry of Health and Family Welfare, Government of India.⁶ The patients were on multiple drugs, with or without oxygen and supportive treatment.

The patients' ages ranged from 3 to 92 years (the mean age of the patients in the wards [moderate cases] was 46.1 years, whereas that of the patients in the ICUs [severe cases] was 53.9 years, [difference in means, 7.8 {4.27-11.32}, *P* < .001]); furthermore, males predominated both in the wards and ICUs (64.1% in each group). The average incidence of

comorbidities (OR, 6.29 [3.81-10.38]; *P* < .001) and fatality rate (OR, 4.58 [3.04-6.91]; *P* < .001) were significantly higher in the ICUs (Table 1). Diabetes mellitus was the most common comorbidity in both the groups, followed by hypertension.

Dermatologic findings were divided into those that have been described earlier in published literature on COVID-19 and those that were pre-existing or incidental. Morbilliform rash

and urticaria were seen in 7 of the 270 ward patients (2.59%) (Fig 1), but no vesicles or pityriasis rosea-like or chilblain-like lesions were observed. Three out of 170 ICU patients (1.76%), coagulopathic skin lesions (retiform purpura or skin mottling [n = 2] and acral ischemia [n = 1]) were observed (Figs 2-4). All of these patients had abnormal D-dimer (>1000 ng/mL) and PT-INR (prothrombin time - international normalized ratio) levels (>3). Drugs and comorbidities accounted for most incidental skin findings. No significant difference was observed in cutaneous findings associated with COVID-19 between the severe (ICU) and moderate (ward) cases, although, as expected, higher odds were observed for incidental manifestations (OR, 2.64 [1.41-4.97]; *P* = .002) among the ICU patients.

DISCUSSION

The redeployment of most specialties to COVID-19 areas of care has enabled dermatologists to have first-hand experience with COVID-19, and cutaneous findings in such patients were first reported in Lombardy, Italy, by Recalcati¹ in March 2020. The major skin lesions described in the literature are morbilliform rashes, pseudochilblains, urticaria, vesicular eruptions, and livedo or retiform purpura.^{1,2} A review of noncase report studies estimated that skin manifestations were present in 0.19% to 20.45% of cases, although most studies included both confirmed and unconfirmed cases.⁶ Fernandez-Nieto et al⁷ reported skin lesions in 132 of 346

CAPSULE SUMMARY

- Cutaneous lesions attributed to COVID-19 in the literature are morbilliform rash, pseudochilblains, urticaria, vesicular eruptions, and retiform purpura.
- Cutaneous findings attributable to COVID-19 are infrequent in our setting. We emphasized the need for a more cautious interpretation and large-scale analysis before ascertaining the association of skin lesions with COVID-19.

Abbreviations used:

ICU:	intensive care unit
RT-PCR:	reverse transcription-polymerase chain reaction

patients (38.2%), but none of the patients had pneumonia, more so only 2 cases were confirmed as having COVID-19 using RT-PCR testing. Recalcati¹ reported skin manifestations in 20.5% (18 of 88) of patients; however, the author had selected a smaller sample out of 148 cases based on the patients' history of drug intake. There is a rising speculation that such high figures¹ might have been overestimated because they have not been replicated in other studies.⁸ In our study, only 2.6% of the ward patients and 1.7% of the ICU patients demonstrated skin

manifestations that were associated with COVID-19 and those that did not have any other discernible cause.

In an international registry of 716 COVID-19 patients with skin lesions, the most common morphologies were morbilliform rash, pernio-like lesions, urticaria, macular erythema, vesicles, papulosquamous rash, and retiform purpura.³ However, rash and urticaria are the common signs of various viral exanthems and cannot be considered specific to COVID-19. Moreover, authors have shown that other viruses, particularly those belonging to the Herpesviridae family, can be linked to vesicular eruptions, erythema multiforme lesions, and pityriasis rosea-like eruptions.⁹⁻¹¹ A recent article re-emphasized that an increased frequency of pityriasis rosea may be consequent to Human Herpesvirus 6 reactivation.¹²

Table I. Demographic data and cutaneous findings observed in 440 COVID-19 inpatients

Clinical characteristic	Moderate COVID-19* (n = 270)	Severe COVID-19† (n = 170)	Total n = 440 (%)	Mean difference/OR (severe-to-moderate cases)	P value
Males (%)	173 (64.1)	109 (64.1)	282 (64.1)	-	-
Females (%)	97 (35.9)	61 (35.9)	158 (35.9)	-	-
Mean age, y	46.1 (SD, 23.6)	53.9 (SD, 14.03)	-	Mean difference (95% CI) = 7.8 (4.27-11.32)	< .001 [¶]
Cutaneous findings associated with COVID-19‡	Morbilliform rash (n = 3) Urticaria (n = 4)	Skin mottling or retiform purpura (n = 2) Acral ischemia (n = 1)	Moderate—7/270 (2.59) Severe—3/170 (1.76)	OR = 0.675 (0.172-2.65)	.831 [#]
Pre-existing or incidental cutaneous findings§	Pruritus (n = 4) Urticaria (n = 1) Tinea cruris or corporis (n = 5) Prurigo nodularis (n = 5) Scabies (n = 3)	FDE (n = 2) Oral candidiasis (n = 5) Candidal balanoposthitis (n = 6) Ecchymoses (n = 10) Friction blisters (n = 4)	Moderate—18/270 (6.67) Severe—27/170 (15.9)	OR = 2.64 (1.41-4.97)	.002**
Comorbidities (%)	136 (50.3)	147 (86.5)	-	OR = 6.29 (3.81-10.38)	< .001**
Fatality rate (%)	83 (30.74)	114 (67.05)	-	OR = 4.58 (3.04-6.91)	< .001**

FDE, Fixed drug eruption; OR, odds ratio.

*Moderate pneumonia—Child or adult with dyspnea and/or hypoxia, fever, cough, SpO₂ of 90% to 94% on room air, respiratory rate of ≥24 breaths/min admitted to COVID-19 wards.

†Severe pneumonia—Child or adult with pneumonia plus one of the following: respiratory rate > 30 breaths/min; severe respiratory distress; SpO₂ of <90% on room air, acute respiratory distress syndrome, sepsis, or septic shock—admitted to COVID-19 intensive care unit.

‡Cutaneous findings reported in the literature in COVID-19 patients.

§Incidental or nonspecific cutaneous findings.

||Diabetes mellitus, hypertension, coronary artery disease, pre-existing respiratory disease or tuberculosis, chronic kidney disease, and malignancy.

¶Mann-Whitney U test.

#Fisher's exact test.

**χ² test.



Fig 1. Morbilliform rash: Erythematous blanchable eruptions on the leg of a patient.



Fig 2. Acrocyanosis of the finger tips in a COVID-19 patient in the intensive care unit.

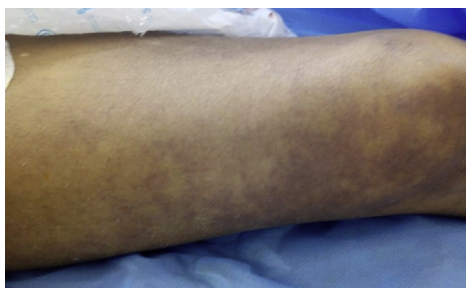


Fig 3. Mottling of the skin seen on the thighs of a COVID-19 patient admitted to the intensive care unit.



Fig 4. Extensive retiform purpura in a patient with severe COVID-19 admitted to the intensive care unit.

Notably, we did not see any case of pernio-like lesions, unlike Galván Casas et al,² who reported them as the most common skin lesions in their crowd-sourced, questionnaire-based study, with patients who were suspected as having COVID-19 but were unverified using RT-PCR (as high as 41%). Despite the widespread use of the moniker “COVID toes,” a growing body of recent research has suggested that these lesions are unrelated to COVID-19 infection.¹³⁻¹⁶ The unusual manifestations reported that like exfoliative shock syndrome, COVID-19–Induced Rash and Mucositis, and calciphylaxis with thrombotic vasculopathy might have been consequent to dysregulation of the immune and coagulation pathways rather than to direct viral skin toxicity because SARS-CoV-2 messenger RNA was not detected in skin lesions.¹⁷

A recent article concurred that although millions of cases of COVID-19 have been seen, the skin findings have neither been consistent nor diagnostic or predictive.¹⁸ Thus, at present, it is safe to conclude that it is unlikely that a direct causal association exists unless a large-scale case-control study is able to predict rashes that precede COVID-19 or those that herald a more severe course.

Coagulopathic lesions, on the other hand, are most likely related to profound systemic inflammation in patients with COVID-19, leading to activation of the coagulation cascade and subsequent venous thromboembolism. Our patients with coagulopathic skin findings (acral ischemic lesions and skin mottling) had very high D-dimer levels and abnormal prothrombin times. This has also been noted by other authors, and thus, these lesions probably indicate a poorer prognosis.¹⁹⁻²¹

Drugs and comorbidities accounted for most unrelated skin findings in the ICUs in our study: fixed drug eruptions (n = 2), venipuncture site ecchymoses (n = 10), frictional blisters (n = 4), oral candidiasis (n = 5), and candidal balanoposthitis (n = 6). The plethora of drugs administered to the patients might account for the varied rashes reported, and this possibility has probably been ignored in various application-based studies.

Our experience concurs with a recent observational study conducted in India that reported a very low incidence of skin findings in asymptomatic and mildly symptomatic COVID-19 patients.²² Our work takes this observation 1 step ahead by showing that skin findings attributable to COVID-19 are, in fact, infrequent even in patients with moderate-to-severe COVID-19 at least in India, and it would be prudent to re-examine the relevance of these skin findings in other settings as well. One reason for the misleading published data was alluded to by Kittler et al,²³ who observed that expedited peer reviews early on during the pandemic could have led to unfiltered reporting of cutaneous manifestations, whereas Vesely and Perkins²⁴ pertinently advised caution in the interpretation of skin findings and linked these to COVID-19. Along similar lines, Barrera-Godínez et al²⁵ emphasized the need for histopathologic confirmation before attributing a skin finding to COVID-19.

Although observational in nature, the advantages of our study are the large sample size, recruitment of only RT-PCR-confirmed inpatients, and direct examination of all skin lesions by dermatologists, keeping in mind the drawbacks of earlier published studies in which telephonic or questionnaire-based assessments were performed and RT-PCR was not uniformly performed. In fact, in an international registry of patients from 31 countries, only a quarter of the cases were laboratory-confirmed.³

However, the fact that we included only hospitalized patients might have impacted the nature of our findings. In addition, ours was a cross-sectional study that aimed at estimating the prevalence of cutaneous manifestations among hospitalized COVID-19 patients. The comparison of the moderate and severe cases was performed subsequently as a subanalysis, and the results thus obtained may be considered as a hypothesis-generating study for further comparative studies between moderate and severely ill COVID-19 patients.

We would like to reiterate that our study, in conjunction with another large study conducted in India, largely delinks the specificity of skin lesions to COVID-19.²² The lacunae in the studies currently available in literature include lack of directly observed patient data, lack of recruitment of consistently positive patients, inconsistent data on examination 2 days before to 2 days after diagnosis, detractors such as drug exposure and other viral etiologies, and lack of case-control data. Moreover, without a well-defined diagnostic or prognostic value, the focus on cutaneous findings is probably misplaced. This explains why no guideline places credence to any form of cutaneous rash as a

prerequisite for performing RT-PCR because this would probably lead to unnecessary overtesting.

Conflicts of interest

None disclosed.

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