Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(2), 477-485 | ISSN:2251-6727

The Study of Cutaneous Manifestations in Covid-19 Patients in a Tertiary Care Hospital

1Dr Priyadharshini B V, 2Dr Bijaylaxmi Sahoo, 3Dr Gajanand Antakanavar, 4Dr. S. Anuradha, 5Dr Vineet Relhan, 6Dr Aneet Kaur,

1MBBS, MD, Senior Resident, Dept of Dermatology, Maulana Azad Medical College, New Delhi

2MBBS, MD, Director and Professor, Dept of Dermatology, Maulana Azad Medical College, New Delhi

3MBBS, MD , Senior Resident Dept of Dermatology, Maulana Azad Medical College, New Delhi

4MBBS MD, Infectious Diseases Specialist, Director-Professor of Medicine, Maulana Azad Medical College, New Delhi-110002 India

5MBBS, MD, Professor, Dept of Dermatology, Maulana Azad Medical College, New

6Senior Resident, MBBS, MD, Dept of Dermatology, Maulana Azad Medical College, New Delhi

Corresponding author: Dr Gajanand Antakanavar, MBBS, MD , Senior Resident Dept of Dermatology, Maulana Azad Medical College, New Delhi

(Received: 16 January 2025 Revised: 20 February 2025 Accepted: 20 March 2025)

KEYWORDS

Cutaneous Manifestations, Covid-19

ABSTRACT:

Background: The clinical spectrum of SARS-CoV-2 infection appears to be wide. Cutaneous manifestations can acts as a windows for the diagnosis, severity assessment and risk stratification of COVID-19 patients.

Aims and objectives: To study cutaneous manifestations in patients with COVID-19 infection at a tertiary care hospital and to study the association of cutaneous manifestations of COVID-19 with the disease severity.

Materials and methods: This was a 1 year, observational study involving 34 cases (>12 years) of RT-PCR or Rapid antigen test confirmed COVID-19 patients with cutaneous manifestations.

Results: Mean age of 43.41±17.43 years and male group was predominantly observed. Most common presentation was maculopapular rash (35.3%), followed by vesicular rash (29.4%), urticarial lesions (17.6 %), psuedochilblain (8.8%), livedoid lesion (5.9 %), and telogen effluvium (2.9 %). Vesicular lesions were divided into diffuse monomorphic (n=4, 40%) and herpes zoster (n=6, 60%). Livedoid lesion and maculopapular lesion noticed in severe category of the COVID-19 illness in terms of derangement of blood parameters, high flow oxygen, ICU admission and mortality. Urticarial group (100%) were having mild, vesicular and psuedochilblain were in all severity of the disease.

Conclusion: The severity of the associated disease followed a gradient, from less severe disease in urticaria, and pseudo-chilblain to most severe in patients with livedoid, maculopapular lesions, and vesicular lesions and heralding a bad prognosis with high mortality.

Introduction

The World Health Organization (WHO) proclaimed the novel coronavirus illness (COVID19) to be a pandemic in March 2020 after it first appeared in China in late 2019 and spread throughout the world killing millions of infected patients.[1] The virus is mainly spread by droplets. The primary target of SARS-CoV-2 is the upper respiratory mucosa, with angiotensin-converting enzyme 2 (ACE2) serving as a functional receptor for viral spikes and facilitating the spread of infection.[2] Confirmed by detection of viral RNA by reverse transcriptase

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JCHR (2025) 15(2), 477-485 | ISSN:2251-6727

polymerase chain reaction (RT-PCR) from nasopharyngeal or pharyngeal swabs and/or bronchoalveolar fluid. The clinical spectrum of SARS-CoV-2 infection appears to be broad, ranging from asymptomatic infection to severe viral pneumonia with respiratory failure and even death. In addition to systemic manifestations skin involvement is also a part of the disease.[3] These cutaneous manifestations can appear during the prodromal phase, during the disease, or have a delayed onset. Various skin lesions can also acts as a window for the disease severity.[3] Therefore, understanding these cutaneous manifestations may aid in the early diagnosis, triage, and risk stratification of patients with COVID-19.[2]

Methods

Study design and setting

This observational study was conducted at the Department of Dermatology, in a tertiary centre, University of Delhi, India for a period from March 2021 to April 2022.

A total 34 of RT-PCR or Rapid antigen test confirmed admitted COVID-19 patients above 12 years of age with cutaneous manifestations were included in the study. Patients with active lesions of known major dermatoses (psoriasis, pemphigus, urticarial (cause other than covid-19 infection), cutaneous tuberculosis, atopic dermatitis, etc.) were excluded from the study.

Data on demography (age and sex), presenting complaints (cough, fever, etc), and duration of disease, cutaneous history (Onset, duration, site, number, and morphology). After general, systemic, and mucocutaneous examination, the morphology of skin lesions was documented and photographed. Relevant investigations including inflammatory markers (LDH, CRP, IL-6, Ferritin), thrombotic markers (D-Dimer, PT-INR) were noted.

The Severity of COVID-19 was assessed as per National Early Warning Score ($NEWS_2$) - in which 0-4 was mild, 5-6 was considered moderate and >7 was considered severe.

All participants provided written informed consent and the study protocol was approved by the Institutional ethical committee (ethics approval number F.1/IEC/MAMC/ (82/10/2020/No.44).

Statistical analysis

The data was first coded and entered in Microsoft excel and analyzed using SPSS version 27. The collected information was presented using descriptive statistics in the form of frequency, mean, and percentage. Chi-square with yate's correction/ Fisher exact test were used for analysis. A p-value of <0.05 was considered statistically significant.

Results

The age of the patients ranged from 13 to 80 years and the mean age was 43.41±17.43 years. The majority of the patients i.e. 29.4% (n=10) were in the 21-30 years age group, and 20.6% (n=7) were in the age group of 51-60 years and > 60 years each. There were 20 (58.8%) male patients and 14 (41.17%) female patients. Most of the patients (76.5 %, n=26) presented with flu-like symptoms, whereas 20.58% (n=7) presented with cutaneous lesions with itching or pain as their first presenting complaint. A single patient (2.94%) presented with both symptoms. Majority of the patients i.e. 35.3% (n=12) had maculopapular rash while 29.4% (n=10) had vesicular rash, 17.6 % (n=6) patients had urticarial lesions, 8.8% (n=3) had pseudochilblain, 5.9 % (n=2) had livedoid lesion and 2.9 % (n=1) had telogen effluvium. The most common cutaneous lesion in males was urticarial plaques (n=6) followed by vesicular (n=6). (Table 1) Urticarial plaques (p-value 0.03) and telogen effluvium were exclusively seen in male subjects. Among females the most common clinical presentation was maculopapular rash (n=7, 58.3%) followed by vesicular lesions (n=4, 40.0%). In terms of onset livedoid (n=2, 100%), maculopapular lesions (n=12, 100%), 2 patients (66.7%) pseudochilblain, 83.3% (n=5) of the urticarial lesions, and 90.0% (n=9) of vesicular lesions appeared during covid illness, whereas telogen effluvium was observed only in the post-covid phase. One patient (33.3%) of pseudochilblain, and 16.7% (n=1) of urticarial presented before the covid illness. In maculopapular lesions, the majority (i.e. 66.7%; n=8) involved the extremities, while in 16.7% of patients each (n=2), lesions involved the trunk and whole body respectively. In the urticarial group, lesions were distributed in a generalized manner in 66.7% (n=4)

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JCHR (2025) 15(2), 477-485 | ISSN:2251-6727

(Figure 3). In the vesicular group, most of the lesions were observed on the trunk (90%, and n=9). Maculopapular lesions were further subdivided into macular n=4 (33.3%), purpuric (Figure 1) (n=4, 33.3%), and papular (n=4, 33.3%). Macular and purpuric lesions (Figure 2) occurred in the patients who were in ICU (75%, 100% respectively) with haematological derangement (75% each). (Table 2) Both macular and purpuric group patients were on higher antibiotics (Meropenam, Tazobactum), dexamethasone, and remdesivr while papular group patients were managed symptomatically. The average duration of drug therapy was for 7.5 and 13 days in macular and purpuric groups respectively. Whereas the average duration of onset of these lesions from prodrome were 8, 4, and 7 days for macular, purpuric, and papular lesions respectively. The papular rash was observed in the mild COVID-19 variety. Vesicular lesions were further subcategorized into diffuse monomorphic varicella-like vesicles (n=4, 40%) and grouped vesicles along the dermatomes diagnosed as herpes zoster (n=6, 60%). (Table 3) (Figure 6)

Two patients each were in the mild, moderate, and severe categories. The average duration of onset was 11.8 days from prodrome (ranging from 6-20 days). No comorbidities were noted except HIV and diabetes mellitus in two patients. All patients were on dexamethasone, one was on dexamethasone with remdesvir. The duration of drug therapy ranged from 2-15 days.

Livedoid lesion and maculopapular lesion groups showed the highest derangement of parameters in patients. Among livedoid lesions, all of them showed increased serum IL-6, serum ferritin, and serum D-Dimer. Among maculopapular lesions, 4 of the patients (33.3%) showed increased TLC, serum IL-6, serum ferritin, and serum D-Dimer. In the vesicular group, 5 (50%) patients and among pseudochilblain group, a single patient showed deranged haematological parameters.

As for telogen effluvium, patient showed no hematological abnormatility. Eight patients who had macular lesions (66.7%), 6 patients (60%) from the vesicular group, both patients who had livedoid lesions needed high flow oxygen. It was statistically significant (p-value 0.025) across the lesions group compared to who were not on oxygen (50%). None of the patients in the urticarial group or telogen effluvium were on any kind of 0_2 support. Livedoid lesions were noticed exclusively in ICU admitted patients (100%). Five patients with maculopapular lesions (41.7%) were admitted to ICU. Four patients (40%) among the vesicular group were in ICU. In the pseudochilblain group, a single patient (33.3%) was in ICU though it was not statistically significant across the group. (P-value 0.142) (Figure 4). In the maculopapular group, 5 (41.7%) were in the mild category, 6 (50%) were in the moderate group, and one patient (8.3%) was in severe category. In vesicular 4 (40%) were having mild severity, 4 (40%) belonged to moderate severity, and 2 (20%) belonged to severe category of the disease. Among pseudochilblain 2 (66.7%) were having mild disease and one (33.3%) had moderate severity. All patients in the urticarial group (n=6, 100%) were having mild disease severity of COVID disease whereas all patients (n=2, 100%) in the livedoid group were in the severe disease category. (P-value 0.056). Mortality was observed in 3 patients (8.8%). These 3 patients had livedoid (n=1) and maculopapular (n=2) lesion.

Discussion

The World Health Organization (WHO) proclaimed the novel coronavirus illness (COVID19) to be a pandemic in March 2020. [1] Apart from systemic involvement the skin manifestation also acts as a window for the severity of the disease which helps in prognosticating the disease. The prevalence of cutaneous manifestation in COVID-19 is variable from 1 to 24%.[1,62] We attempted to study the cutaneous manifestation and its association with the severity of the disease in 34 COVID-19 RT-PCR confirmed hospitalized patients.

Current study pool had patients ranging from 13 to 80 years of age. The mean age of the patients in this study was 43.41±17.43 years. The male to female ratio was 1.4:1. As described in the existing literature, elderly men suffering from COVID-19 are more frequently hospitalized as they have high proportion (20-40%) of underlying medical comorbidities.[35, 66, 59]

The majority (67.6%) of the patients presented with typical flu-like (fever, cough/sore throat myalgia, vomiting, and diarrhoea) symptoms whereas 20.5% presented directly with urticaria and pseudochilblain before developing flu-like symptoms. This has also been reported earlier in a few case reports.[68, 69] The reason was

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explained by Daneshjhou et al, where antibody titers levels in mild or asymptomatic disease do not meet the titer cut-off for positivity with robust immune response.[70]

We observed maculopapular rash as the most common manifestation i.e 35.3% (n=12), followed by vesicular rash (29.4%; n=10), urticarial lesions (17.6 %; n=6), pseudochilblain (8.8%; n=3), livedoid lesion (5.9 %; n=2) and telogen effluvium (2.9 %; n=1). The findings are inconcordance with various other Indian and western studies.[3, 14, 67, 64, 71, 72, 73]

In the Indian scenario, there is a limited studies on cutaneous manifestations in COVID patients. A study conducted by Dalal et al in north India observed dermatological manifestations of COVID in 12.7% of their 102 patients in which only maculopapular and urticarial rash were discussed and there was no comment on the association with disease severity.[63] Similarly, a cross-sectional analysis conducted at a referral hospital in Delhi showed a paucity of cutaneous manifestation in admitted RT-PCR confirmed COVID cases.[59]

In the maculopapular group majority of the lesions (75%) were noticed in the extremities (arms and forearms), while the rest (n=25%) were noted over the trunk and was associated with itching (58.3%). These lesions usually appeared within a week of the onset of flu-like symptoms. Patients with maculopapular rash suffered from moderate (50.0%) and severe (8.3%) systemic COVID illness; 41.7% were in ICU care, and 66.7% required oxygen support. Fifty percent showed a rise in inflammatory markers and a mortality rate of 16.7%.These results are in concordance with other western and Indian studies in which the majority of them suffered from severe COVID illness in 30-50% of the patients. [1, 3, 14, 63, 64, 67,72]

The vesicular rash was the second most common in this study (29.4%). Majority of them i.e 90.0% presented during covid illness. These monomorphic varicella-like lesions were observed in 4 patients and had a median latency period of 11.5 days from the onset of prodrome (Figure 5). The majority (80.0%) of the lesions appeared over the trunk. The same pattern was noted in various studies including Galvano et al with 9% (33/375) vesicular lesion patients and a case series of 22 patients by Marzano et al with diffuse monomorphic vesicular lesions. [2, 3, 21, 76] Even though the analogous outcome was noted in different other reports in terms of site and latency period, they failed to bring up the clear relationship with severity.[3, 22]

Vesicular lesions were observed in mild (n=2) to moderate (n=2) COVID illness and only one was (25%) in ICU care. All mild cases were treated symptomatically and all had negative drug history prior to the onset. Contrary to this Spanish studies reported severe COVID illness where 70%-80% needed hospital admission with 30-90% of their cases needing ICU and mortality rate of 8.8%.[3, 14, 67, 20, 64, 76, 1, 3, 20]

Criado et al have hypothesized that the vesicular eruptions arise from cytokine storms, resulting in cutaneous endothelial damage. These lesions are specific to COVID-19, and their identification could be a useful tool in aiding the diagnosis in a resource-poor setting.[70, 77]

Herpes zoster was on a rising trend following COVID infection, especially in the elderly.[54] In this study we observed 6 patients had herpes zoster. It was observed almost equally in all categories of disease severity i.e 33% mild, 33% moderate, and 33% severe, and five out of 6 patients (83.3%) needed O2 support and were on immunosuppressants (systemic steroids). Three patients (50%) ICU support. Inflammatory markers were raised in four patients. Zheng et al proposed that SARS-CoV-2 induced functional exhaustion of cytotoxic lymphocytes leading to reactivation of VZV, responsible for herpes zoster secondary to COVID-19 infection. Even though various studies considered and excluded herpes zoster as a nonspecific finding following COVID, a Brazillian study with a total of 394,677 control-matched subjects of ≥50 years old had a 15% higher risk of herpes zoster risk than those without COVID. The risk was more pronounced (21%) following hospitalization.[54] Absence of significant predisposing comorbidities, a short duration of immunosuppressant drugs before the onset, and a close temporal relationship strengthens the likelihood of COVID in this study.

Six patients presented with urticarial lesions, out of which five patients (83.3%) presented during covid illness and 16.7% presented during the prodrome. These lesions persisted for a period of 1 week (mean 2-8 days) which was in concordance with the study by Galvan[12]et al showed that in10-55% of cases, urticarial lesions occurred before or at the same time as pseudo-flu symptoms of COVID-19 and disappeared in less than a week. [9, 14, 49] Direct mast cell degranulation and direct

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cytopathic effect of SARS-CoV-2 was thought to be implicated in the pathogenesis of these urticarial rashes.[80]

Lesions were exclusively noted in males, which may be an incidental finding in our study. The lesion first appeared over the trunk in the majority (83.3%) of cases and later affected the whole body (66.7%). This is in concordance with other studies where 50-80% of the urticaria was noticed over the trunk.[1, 3, 71, 73] In current study, none of the patients in the urticarial group were on any kind of 0_2 support or needed ICU care. Contrary to other studies, Galvan et al and Mohta et al, showed urticarial lesions were associated with more severe COVID-19 disease.[3, 14]

As per literature, pseudochilblain was observed exclusively in younger patients and which appeared during COVID illness.[3, 14, 33, 76] In contrary to this in our study we noticed two younger and one elderly patient and one presented during the prodrome. Similar to Mohta et al study, despite the Indian summer with the negative personal history of perniosis in patients and positive history of COVID-19 strongly favoured the viral origin.[14] Even though 2 patients showed mild flu-like symptoms, a single patient had moderate severity of COVID and required ICU care with high flow oxygen. The same patient showed increased D-dimer, IL-6, and PT-INR. A large case series of 318 subjects reported that chilblain-like acral phenotype was significantly associated with less severe COVID-19 and similar findings were observed in other observational studies. [3, 14, 33, 35, 67]

Livedoid lesions were the least frequent manifestation in the study groups (n=2), and were noticed exclusively on feet as dry, violaceous to erythematous, nonblanchable necrotic painful lesions (Figure 7). These lesions exclusively noted in ICU patients, 100% needed high flow oxygen, they were on multiple medications (dexamethasone, higher antibiotics, remdesvir, and plasma therapy), and all were present in severe category of the COVID illness with 50% mortality. The same findings were noted in the case series of acral ischemia patients in China (with leucopenia, leucocytosis, raised LDH, PT-INR, and D-dimer). [8] However, no patients were in shock or vasoactive at the time of development of lesions similar to current study.

Conclusion

SARS-CO-Virus-2 affects various organs including the skin, which serves as a window into the severity of COVID illness. Pseudochilblain and urticaria can occur in the prodromal period without any flu-like symptoms. It was observed that patients admitted in ICU have a high risk of livedoid lesions, macular, and purpuric lesions, and have a poor prognosis with high mortality. Herpes zoster can be triggered by COVID-19 infection or by its management even without underlying comorbidities up to 3 weeks post-COVID illness.

Limitation

Sample size was less.

Data on the duration and severity of the disease and the outcome were limited to the time when the patient was observed.

We were not able to do RT-PCR of the vesicular fluid for COVID-19 or herpes simplex or varicella to rule out the possible other causes.

The lack of biopsy to confirm the findings was also another limitation of our study.

Conflict of interest: None.

Funding source: None.

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Table: 1 Descriptive characteristics of the study population

Sl No.	Characteristics of lesion (Total cases =34)	Percentage N (%)	Onset			Predominant site of involvement
			Before illness	During	After Recovery	
1	Maculopapular	35.3 %	0	100%	0	Extremities
2	Vesicular-Monomorphic, Herpes zoster	29.4%	0	90%	10% (HZ)	Trunk
3	Urticarial	17.6%	16.7%	83.3%	0	Trunk
4	Psuedochilblain	8.8%	33.3%	66.7%	0	Extremities
5	Livedoid	5.9%	0	100%	0	Extremities
6	Telogen effluvium	2.9%	100%			

Abbreviations: N, Number; HZ: Herpes zoster

Table: 2 Characteristics of disease severity of the study population

	Need for O2 support	**ICU admission**	**COVID severity on basis of NEWS score**			**Deranged hematological parameters (IL -6, D-dimer, Ferritin, LDH, TLC)**	**Mortality**
			Mild 0-4	Mod. 5-6	Severe >7		
Livedoid	100%	100%	-	-	100%	100%	50%

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JCHR (2025) 15(2), 477-485 | ISSN:2251-6727

(n=2)							
Maculopapular (n=12)	66.7%	41.7%	41.7%	50%	8.3%	50%	16.7%
Vesicular (n=10)	60%	50%	40%	30%	30%	50%	-
Pseudochillblain (n=3)	33%	33.3%	66.7%	33.3%	-	33.3%	-
Urticarial (n=6)	-	-	100%	-	-	16.67% (TLC)	-
Telogen Effluvium (n=1)	-	-	100%	-	-	-	-

Abbreviation: n= Number, 02 = Oxygen, ICU= Intense care unit, NEWS= National early warning score, LDH= Lactate dehydrogenase, TLC= Total leucocyte count.

Table 3: Characteristics of Herpes Zoster of the study population

Characteristics of herpes zoster				
Dermatome	Severity	Duration of onset from flu symptom	Comorbidities	Immuno Suppressants
T5 Back (right)	Severe/ICU	20 days	Nil	Dexamethasone (15 days)
T1 shoulder (left)	Mild	14 days	PLHIV	Nil
T10-T11 flank (left)	Severe/ICU	14 days	Nil	Dexamethasone (15 days)
T6-T7 back (left)	Moderate/ICU	14 days	Nil	Dexamethasone (16 days)
C5, T1-T2 (right)	Mild	6 days	DM	Nil
T8-T9 flank (left)	Moderate	7 days	Nil	Nil

Abbreviation: ICU= Intense care unit, PLHIV= patient living with HIV, DM= Diabetes Mellitus

Figure legends

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JCHR (2025) 15(2), 477-485 | ISSN:2251-6727

Figure 1: Purpuric type of macular rash over the extremities

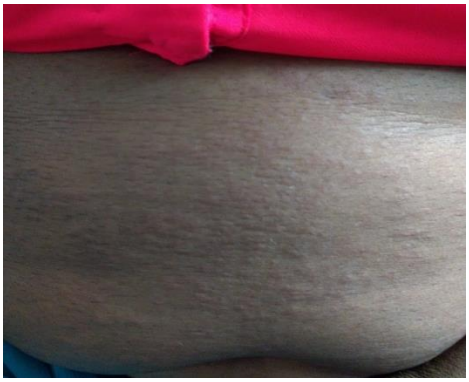

Figure 2: maculo-papular rash over the abdomen and trunk

Figure 3: Urticarial rash over the neck, trunk.

Figure 4: Psuedochilblain lesions over tip of the fingers.

Figure 5: Monomorphic varicella-like vesicular rash over the extremities

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Figure 6: Herpes zoster over left C5 dermatome.

Figure 7: Livedoid lesion over foot.