

# Cutaneous manifestations of COVID-19 in a tertiary COVID-19 referral hospital in the Philippines



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**Background:** Reports on COVID-19 skin manifestations and associated clinical outcomes are limited. Like viral diseases, cutaneous findings may be present and can help in confirmation and prognostication among those suspected or diagnosed with COVID-19.

**Objective:** To determine COVID-19 cutaneous manifestations and their association with disease severity and course.

**Methods:** This study was conducted in a designated COVID-19 referral hospital from January 1 to March 31, 2021. Skin manifestations recorded from January 1 to February 17 were retrospectively gathered. Reports from February 18 to March 31 were prospectively collected using a dermatologic checklist which was incorporated into all official medical records.

**Results:** A total of 507 confirmed patients with COVID-19 were included. COVID-19 skin signs were detected in 39 patients (7.7%). Morbilliform lesions were most common. Skin signs were significantly associated with severe or critical cases (odds ratio, 3.4; 95% CI, 1.3-8.7) and mortality (relative risk, 2.9; 95% CI, 2.0-4.2).

**Limitations:** Underestimation of prevalence of COVID-19 skin signs due to exclusion of outpatient and discharged patients and the subjective assessment in the retrospective part.

**Conclusion:** Cutaneous signs were significantly associated with severe/critical COVID-19 as well as death among 507 hospitalized patients in a Philippine COVID-19 referral hospital. (JAAD Int 2022;7:44-51.)

**Key words:** clinical outcome; COVID-19; cutaneous manifestations; disease severity; skin.

## INTRODUCTION

In Wuhan, China, in late 2019, cases of pneumonia with unknown etiology were being reported. By the end of January 2020, cases were already reported outside China.<sup>1-5</sup> In March 2020, COVID-19 was declared a pandemic.

In the Philippines, new cases were noted between January and March 2020. In response, the

Department of Health in the Philippines designated institutions as official COVID-19 referral hospitals. By March 30, 2020, the University of the Philippines – Philippine General Hospital began its COVID-19 operations. Since reverse transcription polymerase chain reaction testing was still limited due to lack of kits and facilities, diagnosis was made through symptomatology,

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probable exposure history, other diagnostics, and imaging.

Although complaints were mainly respiratory and gastrointestinal, there were few reports on COVID-19 dermatologic manifestations. Viral infections, like COVID-19, may present with skin signs that can help confirm diagnosis. Dermatologic signs and symptoms may give an uncommon perspective and correlation to disease course and prognostication.

During protocol development, there was still scarcity of evidence on COVID-19 cutaneous manifestations. A literature search done through the PubMed database using the following search terms generated a collection of anecdotal evidence: “Coronavirus 19”, “COVID-19”, “SARS Cov-2”, “skin”, “cutaneous”, and “dermatologic” (Table I<sup>5-18</sup>).

This study aimed to document cutaneous manifestations among patients with COVID-19 and to determine associations between skin manifestations and disease severity and clinical outcomes.

## METHODS

This study was conducted in the University of the Philippines – Philippine General Hospital, a COVID-19 referral hospital in Metro Manila. There were 2 parts: a preliminary retrospective cross-sectional study of all COVID-19 inpatient records from January 1 to February 17, 2021, and a subsequent prospective cohort study of admitted patients with COVID-19 from February 18 to March 31, 2021. The study protocol was approved by the institution’s research ethics board.

COVID-19 cases, of any sex and age group, and disease severity types were included in the retrospective study. All patient records were retrieved using standard data collection forms with strict selection criteria. Records which did not meet at least 30% of the criteria were excluded. Information extracted were demographics; clinical data, that is, disease severity (mild/moderate/severe/critical); comorbidities; clinical outcome (good/improved/discharged or poor/deceased); and all dermatologic signs and symptoms. Case definitions were adapted from the Philippine Society for Microbiology and Infectious Diseases Interim Guidance.<sup>19</sup>

The prospective part of the study included all admitted COVID-19-confirmed patients and excluded probable and suspect cases. A dermatologic checklist was developed based on current literature of the COVID-19 cutaneous presentations (Table I). These presentations were categorized according to morphology: morbilliform rash, pernio

or chilblains, urticarial, vesicular, petechial, and livedo reticularis. Patients with preexisting dermatologic conditions or predisposing comorbidities with cutaneous signs and symptoms were categorized as “others.” The dermatologic checklist was approved by the Hospital Infection Control Unit, Department of Medicine, and COVID-19 Clearing House, and was incorporated into all official

## CAPSULE SUMMARY

- Worldwide, COVID-19 cutaneous signs have been documented, but reports are still limited. Association of skin signs to disease course and severity needs to be further investigated.
- Documentation of COVID-19 skin signs contributes to the growing knowledge base of the various clinical features of this disease.

COVID-19 medical records.

Demographic, clinical, and the dermatologic checklist data were likewise extracted. Documentation of cutaneous manifestations was done by the health care workers attending in the COVID-19 wards. An infographic on the identification of dermatologic findings was provided in the wards for reference.

For patients warranting dermatologic management, the attending physicians sent official tele dermatology referrals to the Department of Dermatology. The investigators secured informed consent from the patient or a legally-authorized representative (for incapacitated patients) either through face-to-face or phone call. Tele dermatology followed a standard format of confidentiality and privacy protocols on photography of skin lesions and patient information. In-person dermatologic assessment and management were executed when deemed necessary and subsequently documented in the electronic medical records.

Data from the 2 study parts underwent independent analyses. Outcomes of interest for both parts were age, COVID-19 disease severity at the time of appearance of skin signs and symptoms, cutaneous manifestations (morphology), and clinical outcome.

Categorical variables (ie, age, disease severity, clinical outcome) were reported as numbers and percentages of patients.

Pearson’s  $\chi^2$  test or Fisher’s exact test were used to determine associations between skin signs and age, disease severity, clinical outcome. The latter was

**Table I.** COVID-19 cutaneous manifestations in literature

Skin sign morphology
Livedoid eruptions, <sup>7</sup> livedo reticularis, <sup>10</sup> livedo or necrosis <sup>14</sup>
Erythematous rash, <sup>8</sup> maculopapular eruptions, <sup>13,14</sup> papulosquamous rash <sup>15</sup>
Urticaria, <sup>8</sup> urticarial eruption/lesions <sup>11,14</sup>
Petechial rash, <sup>6,13</sup> purpuric macules <sup>9</sup>
Vesicles, <sup>8</sup> vesicular eruptions, <sup>14</sup> varicella-like/papulo-vesicular rash <sup>17</sup>
Pruritic papules on bilateral heels <sup>12</sup> ; acral areas of erythema, vesicles, or pustules/pseudo-chilblain <sup>14</sup> ; acral ischemia <sup>16,18</sup>
Unspecified rash <sup>5</sup>

used when more than 20% of the cells had an expected value of less than or equal to 5. Furthermore, each cutaneous morphology was statistically analyzed for association with disease severity and clinical outcome.

A bivariate analysis was done to estimate the odds of severe/critical disease and poor outcome given the presence or absence of a cutaneous sign. The crude odds ratios were presented along with their 95% confidence intervals (CIs) and *P* values. For the prospective cohort, relative risk and 95% CI of skin signs and poor outcome (ie, mortality) were calculated. STATA 16 (StataCorp LLC) and an online evidence-based medicine calculator (<https://ebm-tools.knowledgetranslation.net/calculator/prospective/>) were used for data analyses. Cases which necessitated in-person dermatologic assessment and management were presented as brief descriptive reports.

## RESULTS

A total of 507 patients (252 men and 255 women) were included in this study. The mean age was 53.0 years (SD, 17.6; range, 0-94 years).

### Part 1: Retrospective chart review

Of the 152 records reviewed, 96.30% were adults and there was an almost equal proportion of mild/moderate cases and severe/critical cases. Only 27 patients (17.8%) presented with skin lesions, of which 13 (8.6%) showed the reported COVID-19 skin signs. The morbilliform rash was the most common sign (Table II).

### Part 2: Prospective cohort

There were 355 patients included in this cohort, and the majority (97.46%) was adults. Mean age was 52.9 years old (SD, 17.6). Forty-three patients (12.1%) presented with skin lesions, and only 26 patients (7.3%) presented with the reported COVID-19 skin signs. Majority were severe/critical (59.3%). The morbilliform morphology was still most common, followed by livedo reticularis. Urticarial,

petechial, vesicular, and pernio lesions were also documented (Table II).

### Association of COVID-19 cutaneous signs to disease severity and clinical outcomes

Separate analyses for the retrospective and prospectively collected data were done. In both parts, there was no association between cutaneous manifestations and age.

Skin signs were significantly associated with more severe COVID-19. In the review of records, the odds of having a severe/critical disease among patients with COVID-19 with any cutaneous sign was almost 6 times the odds of those who did not have cutaneous signs (odds ratio, 5.9; 95% CI, 1.3-27.6). This estimate, however, was not precise (ie, wide CI). Furthermore, skin signs were not associated with poor clinical outcomes (ie, death) in this part of the study (odds ratio, 3.5; 95% CI, 1.0-11.8) (Table III).

However, in the prospective cohort, the odds of having a severe/critical disease among those with any cutaneous sign disease was 3.4 times the odds of those who did not have cutaneous signs (odds ratio, 3.4; 95% CI, 1.3-8.7). Moreover, the risk of death was significantly higher among those with COVID-19 skin signs (relative risk, 2.9; 95% CI, 2.0-4.2) (Table IV).

Due to the relatively low number of cases with COVID-19 skin signs, an association between each cutaneous lesion morphology and disease severity or outcomes was not detected.

### Histopathologic examination of inpatient referrals

There were 6 inpatient referrals for in-person dermatologic assessment and management for COVID-related skin signs. Of these, 5 patients had morbilliform lesions and 1 patient had discrete dusky nodules on the abdomen and a perianal plaque (Table V).

Five of the 6 patients presented with multiple erythematous macules and papules on different areas of the body (Fig 1, A-E). On histopathology,

**Table II.** Frequency distribution of skin signs by morphology

Skin sign morphology*	Part 1: Retrospective		Part 2: Prospective		Total (n = 70, N = 507)	
	COVID-19 cases (n = 27, N = 152)		COVID-19 cases (n = 43, N = 355)			
	No.	%	No.	%	No.	%
Morbilliform rash	7	4.6	10	2.8	17	3.4
Livedo reticularis	1	0.7	6	1.7	7	1.4
Petechial rash	3	2.0	3	0.9	6	1.2
Vesicular rash	1	0.7	3	0.9	4	0.8
Urticaria	0	0.0	3	0.9	3	0.6
Pernio or chilblains	1	0.7	1	0.3	2	0.4
Others	14	9.2	17	4.8	31	6.1

\*A patient may have more than 1 skin sign reported.

**Table III.** COVID-19 skin signs versus case severity and clinical outcomes (retrospective)

COVID-19 skin sign	Severity			Clinical outcome		
	Severe/critical	Mild/moderate	Odds ratio (95% CI)	Poor	Good	Odds ratio (95% CI)
Present	11	2	5.9 (1.3-27.6)	5	8	3.5 (1.0-11.8)
Absent	67	72		21	118	
Total	78	74		26	126	

**Table IV.** COVID-19 skin signs versus case severity and clinical outcomes (prospective cohort)

COVID-19 skin sign	Severity			Clinical outcome		
	Severe/critical	Mild/moderate	Odds ratio (95% CI)	Poor	Good	Relative risk (95% CI)
Present	20	6	3.4 (1.3-8.7)	16	10	2.9 (2.0-4.2)
Absent	163	166		69	260	
Total	183	172		85	270	

4 cases showed superficial and superficial to deep perivascular dermatitis. Three of 4 cases had early or beginning leukocytoclastic vasculitis and focal areas of vessels in the papillary dermis with sparse perivascular infiltrates of neutrophils and neutrophilic nuclear dust (Fig 2, A and B). One case showed thrombotic vasculopathy. The last case showed interface dermatitis.

## DISCUSSION

This study conducted a chart review and prospectively collected data over 3 months from 507 COVID-19 admitted patients in a tertiary medical facility. Significant associations with the presence of skin signs and severe/critical cases and those with poor clinical outcomes (ie, death) among patients with COVID-19 were noted.

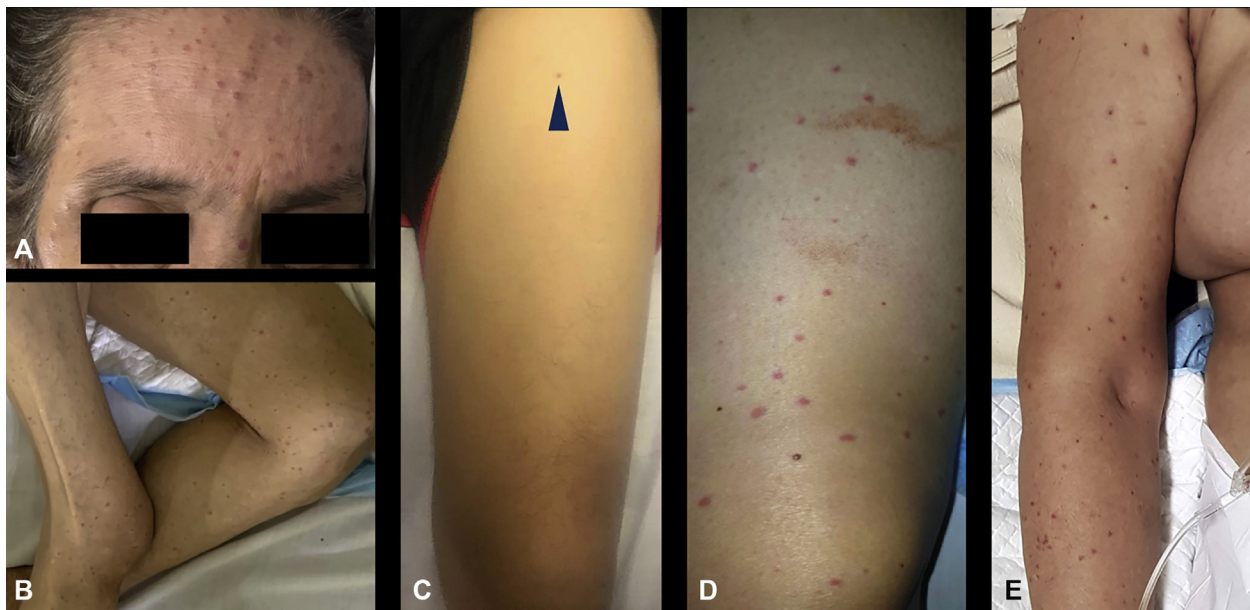
Joob et al<sup>6</sup> reported on how proper assessment of skin manifestations was useful in the diagnosis of COVID-19. They noted a case in Thailand who was initially diagnosed as dengue fever due to a petechial

rash. Only with the presentation of respiratory symptoms was a reverse transcription polymerase chain reaction test done, which was positive for COVID-19.<sup>6</sup> Henry et al<sup>11</sup> reported a case of urticarial eruption prior to the onset of other classic respiratory features of COVID-19. The initial assessment by a dermatologist was urticaria, which was managed with antihistamines. However, 2 days later, the patient noted fever, chills, and chest pain and subsequently tested positive for COVID-19.<sup>11</sup>

In Lombardy, Italy, a study by Recalcati<sup>8</sup> assessed the presence of cutaneous involvement in 88 patients with COVID-19 and showed that approximately 20% developed different types of skin manifestations, some presenting at disease onset while others after hospitalization. Kaya et al<sup>19</sup> reviewed 57 articles and reported that cutaneous involvement in COVID-19 varies between 1.8% and 20.4%. In this present study, a total of 39 out of 507 cases (7.7%) showed cutaneous manifestations among admitted patients with COVID-19, a

**Table V.** Summary of inpatient referrals

Patient	Demographic profile	Case severity	Cutaneous manifestation	Histologic findings	Outcome
1	63-year-old woman	COVID-19 (+), severe	Morbilloform rash	Superficial and deep perivascular dermatitis, with focal area of vasculitic leukocytoclasia	Discharged
2	58-year-old man	COVID-19 (+), severe	Morbilloform rash	Superficial perivascular dermatitis, with focal area of vessels in the papillary dermis with sparse perivascular infiltrates of neutrophils and neutrophilic nuclear dust	Discharged
3	64-year-old woman	COVID-19 (+), severe	Morbilloform rash	Superficial perivascular dermatitis with focal leukocytoclastic vasculitis	Discharged
4	35-year-old woman	COVID-19 (+), severe	Morbilloform rash	Interface dermatitis	Mortality
5	8-year-old boy	COVID-19 (+), severe	(A) Discrete, deep red nodules on the abdomen (B) Well-demarcated perianal plaque	(A) and (B) Thrombotic vasculopathy	Mortality
6	1-year-old boy	COVID-19 (+), severe	Morbilloform rash	Superficial perivascular dermatitis, with no evidence of vasculitis	Mortality

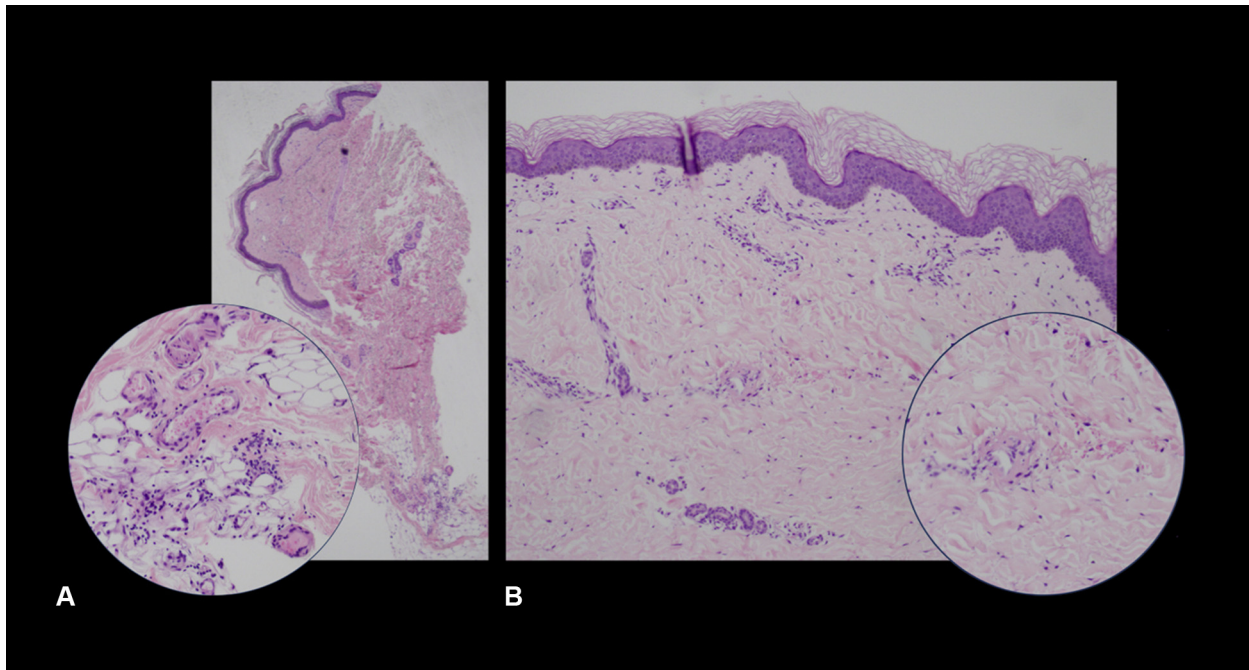


**Fig 1.** Clinical cutaneous findings in patients with COVID-19. Multiple erythematous macules and papules spread over the face (A), thighs (B-D), and the upper portion of the arm (E).

percentage that falls within the above-mentioned international range.

COVID-19 has been shown to affect any age, with adult predominance, as seen in this study with

more than 95% of cases older than 18 years, and a mean age of around 50 years. Currently, there are scarce data on the association of skin manifestations of COVID-19 with age. This study showed no



**Fig 2.** Histopathologic review of 4-mm punch biopsies taken from morbilliform skin eruptions in patients with COVID-19. **A**, Section showed superficial to deep sparse perivascular and perieccrine lymphocytic infiltrates with rare eosinophils, with inset showing a focal area of mild perivascular infiltrate of neutrophils, neutrophilic dust, and extravasated erythrocytes in the reticular dermis, with fibrin deposition involving a vessel. **B**, Section showed mild perivascular infiltrates of lymphocytes and occasional neutrophils in the papillary to mid dermis, with inset showing a focal area of extravasated erythrocytes surrounding a vessel with endothelial swelling and fibrin deposition.

association of cutaneous signs and symptoms with age.

According to Recalcati,<sup>8</sup> lesions varied in presentation such as erythematous rash, urticaria, and vesicles. Marzano et al<sup>17</sup> stated that skin manifestations were similar to common viral exanthems, close to varicella-like exanthems. Suchonwanit et al<sup>20</sup> attempted to classify the cutaneous manifestations into 2 categories, viral exanthems or systemic consequences; the former was related to an immune response to viral nucleotides while the latter was attributed to vasculopathy. There have been anecdotal reports of patients with COVID-19 presenting with transient livedoid eruptions. Manalo et al<sup>10</sup> hypothesized that the most plausible etiology could be microthromboses, such as in 2 cases reported of transient unilateral livedo reticularis on the lower extremities with spontaneous resolution within 24 hours. Jimenez-Cauhe et al<sup>9</sup> reported a case presenting with multiple erythematopurpuric macules in the peri-axillary areas on the third day of hospitalization, and Estébanez et al<sup>12</sup> presented a case of pruritic erythematous-yellowish papules on bilateral heels after approximately 2 weeks of

symptoms. Other dermatologists have suggested that COVID-19 may also present with signs of acral ischemic lesions.<sup>16,18</sup> A nationwide case collection survey through a standardized questionnaire and collection of images by Galván Casas et al<sup>14</sup> described 5 major cutaneous clinical patterns: pseudo-chilblain, vesicular eruptions, urticarial lesions, macules and papules, and livedo or necrosis. These were noted to present at different times in the disease course and with varied duration and severity.<sup>14</sup>

To date, several reviews have been done on COVID-19 cutaneous manifestations. However, reports on association of skin manifestations with disease severity and clinical outcome are still scarce. Aside from documentation of COVID-19 skin signs, this study attempted to determine, retrospectively and prospectively, any associations with the cutaneous manifestations. There was a significant association between the presence of COVID-19 skin signs, severe/critical disease, and death. This association may be very helpful to attending physicians, not only in the diagnosis of COVID-19 itself but also in the management and prognostication of the disease.

Inasmuch as the medical field is rapidly gaining knowledge on COVID-19, histopathologic studies of cutaneous manifestations may give a better insight of disease pathophysiology. Alramthan et al<sup>16</sup> showed that the presence of parenchymal cell necrosis and hyaline thrombus formation in small vessels of organs could be an underlying pathology for the cutaneous lesions. Diaz-Guimaraens et al<sup>13</sup> reported a case with a sudden appearance of erythematous macules, papules, and petechiae in the lower portion of the abdomen and bilateral peri-flexural areas which resolved after 5 days. Superficial perivascular lymphocytic infiltrate with erythrocyte extravasation, focal papillary edema, focal parakeratosis, and isolated dyskeratotic cells with no note of thrombotic vasculopathy was noted on biopsy.<sup>13</sup> Sanchez et al<sup>15</sup> reported a case of rapidly progressing digitate papulosquamous plaques on the trunk and thighs in an elderly patient with COVID-19, with histology revealing a foci of spongiosis with focal parakeratosis, few spongiotic vesicles with aggregates of lymphocytes and Langerhans cells, and moderate lymphohistiocytic infiltrates and papillary dermal edema. The skin sample was negative for SARS-CoV-2, and the authors noted that the cutaneous manifestations may be secondary to the immune response against the infection.<sup>15</sup>

A review of clinical and histopathologic features of COVID-19 skin lesions noted that macular and papular eruptions revealed superficial and deep perivascular dermatitis and a vasculitic pattern of lymphocytes cuffing adjacent blood vessels.<sup>21</sup> Furthermore, thrombotic vasculopathy of small- and medium-sized vessels was seen in ischemic, livedoid, or necrotic lesions, clinically presenting as painful acral lesions, most commonly as bullae, with development into dry gangrene. Epidermal necrosis was also seen in those lesions.<sup>22</sup>

In this study, 4 skin biopsies similarly showed superficial and deep perivascular dermatitis with focal areas of vasculitic leukocytoclasia (Fig 2, A) or solely superficial perivascular dermatitis with focal leukocytoclastic vasculitis (Fig 2, B). One biopsy showed thrombotic vasculopathy. These histopathologic findings consisting of lymphocytic invasion, vasculopathy, or endothelial damage leading to the various skin signs may strengthen the possible pathophysiologic mechanisms reported and strongly hypothesized in literature. However, as Genovese et al. noted, none of these hypotheses have been substantiated by strong evidence, and they still need to be largely elucidated.<sup>23</sup>

Data in this study only involved admitted patients with COVID-19 from January 1 to March 31, 2021. One limitation is the exclusion of outpatient,

discharged, or post-COVID-19 patients who may have presented with cutaneous manifestations. This exclusion may lead to underestimation of the prevalence of skin signs and association with the outcomes. Another limitation would be the subjective assessment of health care workers prior to the incorporation of the dermatologic checklist during the retrospective part, which may have led to underreporting of cutaneous involvement of COVID-19.

## CONCLUSION AND RECOMMENDATIONS

Cutaneous signs were significantly associated with severe/critical COVID-19 as well as poor clinical outcomes among 507 hospitalized patients of the University of the Philippines – Philippine General Hospital. Skin manifestations may not be as frequent in COVID-19, but particular cutaneous signs have been strongly associated with the disease.<sup>19,20</sup> Proper routine documentation and epidemiologic cohort studies should be done to further strengthen dermatologic association with COVID-19 among admitted or outpatient cases in the future. A significant association of the cutaneous manifestations with disease severity and clinical outcome in this study may help in diagnosis, management, and prognostication of the disease. The authors recommend that clinicians and the public gain an increased awareness and recognition of cutaneous manifestations. These signs may appear even before confirmation of COVID-19 and may lead to early avoidance of unnecessary exposure and transmission of the infection.

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## Conflicts of interest

None disclosed.

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