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Eruptions and related clinical course among 296 hospitalized adults with confirmed COVID-19



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Background: Limited information exists on mucocutaneous disease and its relation to course of COVID-19.

Objective: To estimate prevalence of mucocutaneous findings, characterize morphologic patterns, and describe relationship to course in hospitalized adults with COVID-19.

Methods: Prospective cohort study at 2 tertiary hospitals (Northwell Health) between May 11, 2020 and June 15, 2020.

Results: Among 296 hospitalized adults with COVID-19, 35 (11.8%) had at least 1 disease-related eruption. Patterns included ulcer (13/35, 37.1%), purpura (9/35, 25.7%), necrosis (5/35, 14.3%), nonspecific erythema (4/35, 11.4%), morbilliform eruption (4/35, 11.4%), pernio-like lesions (4/35, 11.4%), and vesicles (1/35, 2.9%). Patterns also showed anatomic site specificity. A greater proportion of patients with mucocutaneous findings used mechanical ventilation (61% vs 30%), used vasopressors (77% vs 33%), initiated dialysis (31% vs 9%), had thrombosis (17% vs 11%), and had in-hospital mortality (34% vs 12%) compared with those without mucocutaneous findings. Patients with mucocutaneous disease were more likely to use mechanical ventilation (adjusted prevalence ratio, 1.98; 95% confidence interval, 1.37-2.86); $P < .001$. Differences for other outcomes were attenuated after covariate adjustment and did not reach statistical significance.

Limitations: Skin biopsies were not performed.

Conclusions: Distinct mucocutaneous patterns were identified in hospitalized adults with COVID-19. Mucocutaneous disease may be linked to more severe clinical course. (J Am Acad Dermatol 2021;84:946-52.)

Key words: adults; COVID-19; eruption; hospitalized; morbilliform; mucocutaneous; necrosis; Northwell; purpura; rash; SarsCoV-2; ulcer.

INTRODUCTION

Little is understood about the morphologic spectrum of eruptions and their relation to clinical course among acutely ill adults infected with SARS-CoV-2, the pathogen in COVID-19. Several knowledge gaps,

including estimating prevalence of mucocutaneous disease, its detailed description, and its related outcomes were discussed in a call to action to develop high-quality prospective studies on mucocutaneous disease in COVID-19.¹ In spring of 2020, the New

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York metropolitan area was an epicenter for the COVID-19 pandemic in the United States,² and this provided an opportunity to characterize disease-related integumentary findings. The purpose of this study was to estimate prevalence of mucocutaneous findings in hospitalized adults with COVID-19, to characterize morphologic patterns, and to evaluate whether eruptions were related to more severe clinical course.

METHODS

This study was performed at Long Island Jewish Medical Center and North Shore University Hospital, both of which are tertiary hospitals at Northwell Health located in Queens and Manhasset, New York, respectively. The study sample consisted of patients hospitalized between May 11, 2020 and June 15, 2020 who were 18 years of age and older and suspected of having COVID-19. Clinical characteristics for the cohort were monitored until August 11, 2020. The analysis sample was further limited to patients who had confirmed SARS-CoV-2 infection via positive polymerase chain reaction test or IgM/IgG antibody test.

Consecutive prospective integumentary examinations were performed once by study personnel, which included trained medical students, for hospitalized patients suspected of having COVID-19 during the study period. Photographs of abnormal findings for each patient were captured as part of their care. These photographs were independently evaluated by 2 dermatologist raters (SR and AG) who classified morphologic patterns and locations of SARS-CoV-2–related findings. These raters also assessed whether each cutaneous observation was pre-existing or likely to be unrelated to SARS-CoV-2 infection. Examples of unrelated observations included xerosis cutis, nummular eczema, furunculosis, and prurigo nodularis. All patients who had eruptions without an otherwise known etiology were considered to have a COVID-19–related rash in the context of their acute clinical presentation. Clinical variables were selected a priori and included demographics, comorbidities, laboratory observations, imaging results, treatments, and other interventions. Clinical data were extracted from the enterprise electronic health record (Sunrise Clinical Manger; Allscripts). Clinical data were validated

by the Northwell Health COVID-19 Research Consortium, and separately a sample of the dataset was verified against electronic medical records for accuracy. This study was approved by the Institutional Review Board at the Feinstein Institutes for Medical Research at Northwell Health.

STATISTICAL ANALYSIS

Prevalence of mucocutaneous manifestations was estimated by the percentage of eligible patients with at least one COVID-19–related rash. Medians (interquartile range [IQR]) were reported for continuous variables, and frequencies (percentages) were reported for categorical variables. Summary statistics for laboratory values were calculated based on the maximum value during hospitalization.

Hypothesis tests were 2 sided, and statistical significance was assessed at the .05 α level. Analysis was performed using R version 3.6.3.

Acute kidney injury (AKI) was defined according to the KDIGO Clinical Practice Guideline for AKI (increase in serum creatinine by >0.3 mg/dL within 48 hours or increase in serum creatinine to >1.5 times baseline), or based on initiation of dialysis during hospitalization.³ Baseline serum creatinine was estimated using the most recent value in the year before the current admission, if available, otherwise, the median value during hospitalization. Patients with a history of chronic kidney disease were not included in calculations of AKI incidence.

Prespecified primary outcomes for comparison between patients with rash and without rash included (1) requirement for invasive mechanical ventilation, (2) requirement for vasopressors, (3) initiation of dialysis during hospitalization, (4) thrombosis or venous thromboembolism diagnosed by duplex or computed tomography angiography, and (5) in-hospital mortality. Prevalence of each outcome during hospitalization was compared between groups using Poisson regression with robust variance estimates,⁴ adjusting for age, sex, race, body mass index (BMI), Charlson Comorbidity Index, and use of invasive mechanical ventilation (except when ventilation was itself the outcome). Multiple imputation was used to account for missing race and BMI data in the analysis of primary outcomes, with $m = 10$ imputations.

CAPSULE SUMMARY

- Little is understood about the morphologic spectrum of mucocutaneous disease and its relation to clinical course in hospitalized adults with COVID-19.
- Eruptions are common among adults with COVID-19, and their presence may be linked to a more severe course of illness.

Abbreviations used:

AKI: acute kidney injury
 BMI: body mass index
 CI: confidence interval
 IQR: interquartile range

Prespecified secondary outcomes of interest for comparison between those with and without rash included age, BMI, maximum neutrophil-to-lymphocyte ratio, and maximum D-dimer during hospitalization. Mann-Whitney U tests were used to compare variable distributions between groups, stratified by use of mechanical ventilation during hospitalization.

In exploratory analyses, we also compared length of stay and presence of AKI in patients with and without rash, stratified by ventilation status. Hypothesis tests were not performed for exploratory analyses.

RESULTS

Among 338 hospitalized patients identified as possibly having COVID-19 during the study period, 10 did not have laboratory confirmation of SARS-CoV-2 infection, and 32 others were not available for examination or declined examination. Demographic characteristics and comorbidities of patients with and without rash are summarized in [Table I](#). Laboratory values representing markers of infection and inflammation for COVID-19 patients stratified by presence of rash and use of mechanical ventilation are described in the supplement (Supplementary Table I; available at: <https://data.mendeley.com/datasets/hx5xfv9tpc/1>).

Among the 296 included patients, 35 (11.8%) had at least 1 related eruption during the course of hospitalization. Type, locations, and frequencies of morphologic patterns observed in patients with COVID-19 are described in [Table II](#). Morphologic patterns were varied and included ulcer (13/35, 37.1%) ([Fig 1](#)), purpura (9/35, 25.7%), necrosis (5/35, 14.3%) ([Fig 2](#)), red erythema (4/35, 11.4%), morbilliform pattern (4/35, 11.4%), pernio-like lesions (4/35, 11.4%), and vesicles (1/35, 2.9%). All 13 (100%) of the ulcers involved the face, lips, or tongue. All 9 (100%) of the purpuric lesions involved the extremities. All 5 (100%) of the necrotic lesions involved the toes. Red erythema most frequently involved the face, neck, and chest. The morbilliform pattern was most frequently observed on the trunk. All 4 (100%) of the pernio-like lesions involved the hands or feet. The vesicular eruption, noted in 1 patient, involved the abdomen.

Table I. Demographic and clinical characteristics of COVID-19 patients

Characteristic	Rash (n = 35)	No rash (n = 261)
Age, median (IQR), y	64 (57-77)	65 (55-74)
Male sex, n (%) [*]	25 (71)	159 (61)
Race, n (%)		
White	13 (37)	98 (38)
Black	4 (11)	53 (21)
Asian	8 (23)	38 (15)
Native American/Alaskan	0 (0)	1 (0.4)
Other/Multiracial	10 (29)	65 (25)
Missing	0	6 (2)
Hispanic or Latino ethnicity, n (%)	5 (14)	37 (14)
Missing ethnicity	1 (3)	25 (10)
BMI, median (IQR), kg/m ²	27.3 (23.7-31.0)	26.1 (22.7-31.1)
Missing, n (%)	4 (11)	60 (23)
Comorbidities, n (%)		
Coronary artery disease	8 (23)	48 (18)
Congestive heart failure	5 (14)	44 (17)
Asthma	3 (9)	24 (9)
Chronic obstructive pulmonary disorder	5 (14)	28 (11)
Diabetes mellitus	12 (34)	97 (37)
Hypertension	25 (71)	183 (70)
Chronic kidney disease	6 (17)	45 (17)
Charlson comorbidity index, median (IQR)	4 (3-7.5)	6 (3-8)

^{*}For categorical variables, percentages are for those with nonmissing data.

All 13 (100%), 6 of 9 (66.7%), and 4 of 5 (80%) patients with ulcer, purpura, and necrosis, respectively, were mechanically ventilated. Clinical course for adult COVID-19 patients with and without mucocutaneous disease is described in [Table III](#). A greater proportion of patients with rash required invasive mechanical ventilation compared with those without rash (61% vs 30%; adjusted PR, 1.98 [95% confidence interval (CI), 1.37-2.86]; $P < .001$). A greater proportion of patients with rash also had use of vasopressors (77% vs 33%; adjusted PR, 1.03 [95% CI, 0.94-1.13]; $P = .52$), initiation of dialysis during hospitalization (31% vs 9%; adjusted PR, 1.62 [95% CI, 0.91-2.90]; $P = .10$), and thrombosis or venous thromboembolism (17% vs 11%; adjusted PR, 0.84 [95% CI, 0.40-1.77]; $P = .65$), although these differences were attenuated after adjustment for covariates and did not reach statistical significance in adjusted analyses. In-hospital mortality was higher for patients with rash compared with those without rash, but this difference was not statistically significant in adjusted analysis (34% vs 12%; adjusted PR, 1.29 [95% CI, 0.78-2.13]; $P = .32$).

Table II. Frequencies and morphologic types of rash among 296 COVID-19 patients[‡]

Location* [‡]	Any rash, n = 35, n (%)	Ulcer, n = 13	Purpura, n = 9	Necrosis, n = 5	Red erythema, n = 4	Morbilloform, n = 4	Pernio-like, n = 4	Vesicles, n = 1
Face	2 (5.7)	—	—	—	2	—	—	—
Cheeks	9 (25.7)	9	—	—	—	—	—	—
Chin	6 (17.1)	6	—	—	—	—	—	—
Ear	1 (2.9)	1	—	—	—	—	—	—
Nose	3 (8.6)	3	—	—	—	—	—	—
Lips	2 (5.7)	2	—	—	—	—	—	—
Tongue	1 (2.9)	1	—	—	—	—	—	—
Neck	2 (5.7)	—	—	—	2	—	—	—
Chest	5 (14.3)	—	—	—	2	2	—	—
Abdomen	5 (14.3)	—	—	—	1	2	—	1
Back	4 (11.4)	—	—	—	1	2	—	—
Axilla	2 (5.7)	—	—	—	2	0	—	—
Arms	5 (14.3)	—	2	—	—	3	—	—
Hands	5 (14.3)	—	2	—	1	1	1	—
Fingers	3 (8.6)	—	—	—	—	—	3	—
Legs	5 (14.3)	—	2	—	—	2	—	—
Groin	1 (2.9)	—	—	—	1	—	—	—
Feet	3 (8.6)	—	1	—	1	—	1	—
Toes	8 (22.9)	—	4	5	—	—	2	—

*Location counts within each rash may sum to more than the overall frequency of the rash because of patients having the same rash in multiple locations. Sum of patients with individual rashes exceeds the number with any rash because of patients who had multiple types of rash.

[‡]Percentages for morphology locations are not presented for each rash individually due to small numbers.

[‡]In addition to the rashes presented in the table above, 1 patient had conjunctivitis, and 1 patient had desquamation, with both rashes considered COVID-19-related.



Fig 1. Necrotic ulcer on the face at the placement of a medical device.

There were no clinically meaningful differences in age, BMI, neutrophil-to-lymphocyte ratio and D-dimer between COVID-19 patients with and without rash stratified by ventilation status (Supplementary Table II; available at: <https://data.mendeley.com/datasets/hx5xfv9tpc/1>). In exploratory analysis, AKI was present in nearly all ventilated patients with and without rash (95.7% vs 92.8%; adjusted PR, 1.02 [95% CI, 0.87-1.21]). In addition, among patients not requiring ventilation, those with rash were more likely to have AKI than those without rash (66.7% vs 25.5%; adjusted PR, 2.43 [95% CI, 1.37-4.31]) (Supplementary



Fig 2. Purpura and necrosis involving the foot and toes.

Table III; available at: <https://data.mendeley.com/datasets/hx5xfv9tpc/1>). Median time to discharge was 91 days for those with rash, compared with 73 days for those without rash, among patients requiring ventilation. Among patients not requiring

Table III. Clinical outcomes in COVID-19 patients with and without cutaneous manifestations

Outcome	No. cases/Total no. (%)		Unadjusted PR (95% CI)	Adjusted PR* (95% CI)	P value (Adjusted PR)
	Rash	No Rash			
Invasive mechanical ventilation [†]	14/23 (60.9)	79/261 (30.3)	2.01 (1.38-2.93)	1.98 (1.37-2.86)	<.001
Use of vasopressors	27/35 (77.1)	86/261 (33.0)	2.34 (1.82-3.01)	1.03 (0.94-1.13)	.52
Dialysis	11/35 (31.4)	24/261 (9.2)	3.42 (1.84-6.36)	1.62 (0.91-2.90)	.10
Thrombosis or VTE	6/35 (17.1)	29/261 (11.1)	1.54 (0.69-3.45)	0.84 (0.40-1.77)	.65
In-hospital mortality [‡]	12/35 (34.3)	32/258 (12.4)	2.76 (1.58-4.85)	1.29 (0.78-2.13)	.32

VTE, Venous thromboembolism.

*Based on multivariable Poisson regression models with robust (sandwich) standard errors. Covariates included age, sex, race, BMI, Charlson Comorbidity Index, and use of invasive mechanical ventilation (for the 4 other outcomes).

[†]Twelve patients who had ulcers of the cheek or chin were excluded from the analysis of the ventilation outcome, as it was difficult to discern whether these cutaneous manifestations were directly related to COVID-19 infection, patients being ventilated for a prolonged period, or a combination of both.

[‡]Three patients who were not discharged as of the date of data extraction were excluded from the analysis of in-hospital mortality.

ventilation, median time to discharge was 8 days in those with rash, compared with 9 days in those without rash (Supplementary Table III). A greater proportion of patients with COVID-19 and mucocutaneous eruptions received anti-inflammatory, anticoagulation, and vasopressor treatments (Supplementary Table IV; available at: <https://data.mendeley.com/datasets/hx5xfv9tpc/1>).

DISCUSSION

In this study of consecutively examined patients with confirmed COVID-19, we estimate the prevalence of related mucocutaneous eruptions among a racially diversified cohort of hospitalized adults to be 11.8%. No distinct morphologic pattern emerged among hospitalized patients, rendering the appearance of mucocutaneous disease less pertinent to diagnosing COVID-19 among suspected cases. It is noteworthy that morphologic patterns demonstrated site specificity. For example, all ulcers appeared on the face, lips, and tongue. All patients who had these ulcers were also mechanically ventilated. Ulcer locations corresponded to areas of increased pressure from endotracheal tubes or medical devices used to hold tubes in place. This occurrence has also been described in case series of COVID-19 patients with ulcerated and/or necrotic lesions at sites in direct contact with medical devices.^{5,6} Whether this is simply a pressure phenomenon related to devices used to secure endotracheal tubes with or without prolonged intubation⁷ or whether microvascular injury with COVID-19 predisposed patients to ulceration warrants further investigation. Most patients in our study with purpura or necrosis were also mechanically ventilated, which raises the question of whether this presentation is the result of microvascular injury in critically ill patients or whether they are the result of iatrogenic (ie, vasopressor, anticoagulation) exposures or other unknown factors.

An iatrogenic basis for pernio-like lesions and morbilliform eruptions also cannot be excluded.

Although presence of mucocutaneous eruptions in patients with COVID-19 has been reported previously, prevalence estimates of mucocutaneous eruptions and morphologic characterization in a large cohort of hospitalized adults with COVID-19 is, to our knowledge, absent to date. Several reports, case series, and 1 cross-sectional study of patients from the international medical community have described chilblain-like lesions involving the fingers and toes, maculopapular eruptions, livedo, petechiae, purpura, necrosis, wheals, and vesicles.^{5,8-16} The series of 171 confirmed, predominantly ambulatory COVID-19 cases from the American Academy of Dermatology's registry is an important resource for description of the breadth of mucocutaneous findings.⁸ This registry also has limitations that impact the interpretation of observations. Prevalence of mucocutaneous disease could not be established in this case series. Patients in this series were predominantly white, whereas nonwhite adults have been disproportionately infected with COVID-19.¹⁷ Approximately 50% of cases were submitted by nondermatology physicians, midlevel practitioners, nurses, and other medical professionals, and it is possible that use of morphologic nomenclature was inconsistent among contributors, or that some eruptions may have been misclassified altogether. A series of 15 hospitalized adults with COVID-19 reported observations of acral ischemia, livedo racemosa, purpura, petechiae, and erythema multiforme-like lesions. However, these were selected cases for which a dermatology consult was requested.⁹

Here we also describe clinical course among hospitalized adults with COVID-19 and mucocutaneous disease. Patients with eruptions had nearly twice the prevalence of mechanical ventilation,

suggesting that presence of rash in adults may be related to more severe course. Although values for laboratory markers of inflammation and severity of illness were increased among mechanically ventilated patients, we did not observe a pattern of differences between patients with and without mucocutaneous disease, after stratifying by ventilation status. Other clinical outcomes that may be associated with rash, including AKI, coagulopathy, length of stay, and mortality, may warrant further study. Impressions of disease course among adults hospitalized with COVID-19 appear to contrast with our observations in hospitalized children and adolescents with COVID-19 or multisystem inflammatory syndrome in children and rash, in whom presence of mucocutaneous disease may suggest a less severe clinical course.¹⁸

Prior studies reporting on clinical outcomes in relation to mucocutaneous manifestations in COVID-19 are limited to case series^{8,10,11} and one cross-sectional study¹² including 53 hospitalized patients with rash from China and Italy. Study methods and clinical outcomes were not described in detail in the cross-sectional study; however, a link between mucocutaneous disease and COVID-19 severity was not established.¹² The American Academy of Dermatology's series described worse prognosis among 11 patients with retiform purpura.⁸ In a Spanish series of 375 patients with cutaneous manifestations, those having livedo, necrosis, and maculopapular eruptions experienced pneumonia, hospital admission, intensive care unit admission, and mortality more frequently than with other patterns.¹⁰ However, maculopapular eruptions comprised approximately half of the cases, for which drug-induced eruptions could not be ruled out. More than one-third of cases in the series did not have confirmation of COVID-19, and there was limited follow-up time for data on disease course.

There are limitations that warrant consideration when interpreting observations in this study. Our cohort may not be representative of those with milder disease or those who do not require hospitalization. We could not ascertain exact onset of rash from acutely ill patients and, as such, cannot describe the temporal relationship between rash and clinical course. Duration of illness before admission was not established for patients, and the variability between time from admission to mucocutaneous examination was also not captured. Accordingly, we could not describe the temporal relationship between rash onset and clinical course. It is also possible that some patients had integumentary findings after their examination. Oral mucosal examination was not possible for all patients, as a significant proportion

were intubated, and some could not adequately cooperate in the context of their acute illness. The extent to which these limitations influence the prevalence estimate or spectrum of disease is unclear. We did not perform skin biopsy of the patterns observed; therefore, we cannot provide histopathologic correlations for the eruptions observed. It was not clear that biopsy, beyond clinical impression, would result in changes to management. Safety of study personnel was also an important consideration in deciding not to systematically pursue skin biopsies.

Adults with COVID-19, unlike those with other acute viral infections, commonly have mucocutaneous eruptions, the presence of which may indicate a more severe course of illness. Although confirmatory studies may be required to assess the generalizability of these observations, this study provides insight into prevalence, morphologic characterization, distribution, and clinical course associated with eruptions in hospitalized adults with COVID-19.

Conflicts of Interest

Dr Garg has received honoraria from AbbVie, Amgen, Boehringer Ingelheim, Incyte, Janssen, Novartis, Pfizer, UCB, and Viela Bio. The rest of the authors have no conflicts to disclose.

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