Introduction

The World Health Organization on March 13, 2020 declared coronavirus disease 2019 (COVID-19) to be the cause of a pandemic. Although it predominantly affects the respiratory system, there are increasing reports of new manifestations, including diarrhea, anosmia, and dysgeusia. The recent literature shows a surge in reports of the cutaneous manifestations seen in COVID-19. These range from varicella-like eruptions, acute urticaria, chilblain-like lesions, and maculopapular exanthem to livedo reticularis. The incidence of cutaneous manifestations in COVID-19 has varied widely in the limited studies reported to date, ranging from as low as 0.2% to as high as 20.4%. In sick patients, cutaneous manifestations probably remain undocumented or overlooked due to other demanding issues. This review aims to discuss the reported manifestations of COVID-19. These might attain diagnostic or prognostic significance with the passage of time as we get better documentation and insight into their incidence as well as pathogenesis.

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Methods
A literature search was conducted using “PubMed” for original articles, case series, and case reports using the search terms “cutaneous manifestations” and “skin manifestations” in combination with “COVID-19” published up to 31 May. The inclusion criteria were studies reporting cutaneous manifestations in confirmed cases published in the English language. Exclusion criteria were studies reporting suspected cases, review articles, and cutaneous manifestations attributed to drug hypersensitivity or use of personal protective equipment and hand hygiene practices. Two reviewers independently reviewed the abstracts and full text. A manual search of the reference lists of relevant papers and reports was performed to identify additional studies. Data regarding authors, region, number of participants, cutaneous manifestations, and time of onset with respect to systemic features were extracted.

Results
Nine original research papers [Table 1] and 35 case series/case reports that met the inclusion criteria were analyzed for this review [Table 2]. All studies were published between February 2020 and May 2020. The highest number of publications were from Spain (13), Italy (11), and France (5). The rest were from China, Kuwait, Russia, Indonesia, Belgium, Mexico, Poland, and the United States of America.

There were 458 patients with confirmed COVID-19 with cutaneous manifestations. For studies reporting both confirmed and suspected cases, only confirmed cases were included in the analysis. The age of patients ranged from 2 months to 84 years. Because of the heterogeneity among studies, the mean age could not be calculated as some studies reported mean age while others reported median age. However, the maximum number of patients was in the 50–70 years age group. Data regarding sex were available for 412 patients. Of these, 200 (48.6%) were male and 212 (51.4%) were female. Information about the onset of cutaneous signs and symptoms with respect to systemic manifestations, including fever, cough, malaise, and respiratory distress, was available for 433 patients. Cutaneous lesions developed after, simultaneously with, or before the onset of systemic features in 212 (48.9%), 200 (48.6%), and 42 (9.7%) patients, respectively. Seven patients (1.6%) had only cutaneous manifestations and were otherwise asymptomatic.

The most common cutaneous manifestation observed was macular/maculo-papular exanthem in 195 (42.5%) patients. In most cases, it was generalized. Acute urticaria was reported in 82 (17.9%), vesicular/varicella-like rash in 70 (15.3%), chilblain/pernio-like lesions in 69 (15.1%), and livedo reticularis in 20 (4.4%) patients. Vesicular lesions were localized in a few patients and generalized in others. Livedo reticularis was transient and was present for less than a day in some patients, while in others it persisted for weeks. Less commonly reported manifestations include erythema multiforme (6), panniculitis (3), cutaneous hyperesthesia (2), small vessel vasculitis (1), and purpuric lesions (2). Reactivation of herpes simplex virus was reported in four patients and herpes zoster in two patients.

Analysis of the available data revealed that the age of patients with pseudo-chilblain lesions ranged from 16 years to 74 years, with most patients in their 5th to 6th decade. No sex-related predilection was noted. However, Casas et al. reported that young patients presented more commonly with such lesions. Similarly, for vesicular lesions, there appeared to be no sex-related predilection and a substantial proportion of patients were in their 5th or 6th decade. Casas et al. and Giorgi et al. reported an association between cutaneous manifestations and the severity of COVID-19 infection. Both reported that diffuse petechiae, dependent purpura, and acral ischemia/necrosis are associated with severe disease with coagulation defects. Casas et al. reported livedo reticularis in older patients and vesicular rash in middle-aged patients.

Discussion
The true incidence of cutaneous manifestations is difficult to ascertain due to the lack of large-scale prospective studies. The current literature reveals a wide disparity in the incidence of cutaneous manifestations, ranging from 0.6% to 20.4%. Whether this reflects geographical variation or erroneous documentation remains to be seen. The likelihood of identifying skin changes are high if the primary care team involves a dermatologist. The analysis of 458 reported cases found an almost equal number of male and female patients (male: female = 0.94), ruling out sex as a risk factor. Cutaneous lesions appeared after systemic features in close to half of the cases. However, in 11.3% of patients, cutaneous lesions were the presenting manifestation, with 1.6% of patients being otherwise asymptomatic. Thus, a high index of suspicion can help in the diagnosis of this subset, which, if missed, could increase the spread of COVID-19.

The literature on cutaneous manifestations in COVID-19 is growing, and a few recent large case series have tried to classify them systematically. Casas et al. in a multi-center study from Spain, including 375 patients, categorized cutaneous findings into five sub-groups: pseudo-chilblain-like lesions, other vesicular eruptions, urticarial lesions, other maculo-papular exanthems, and livedo reticularis/necrosis. The limitation of their study was the inclusion of suspected as well as confirmed cases.

Pseudo-chilblain-like eruptions are described as erythema and edema with few vesicles or pustules with or without purpura over the hands and feet. Casas et al. reported this in 19% of their patients. These were reported to occur in younger patients with less severe disease and manifested late during the course of the disease. On average, these lasted for 12.7 days. Alramthan et al. and Recalcati et al. reported similar findings in two and
Table 1: Original articles reporting cutaneous manifestations of COVID-19

| Study          | Country      | Number of cases with cutaneous manifestations | Gender | Age (years) | Onset of symptoms No. of patients (time) | Pseudo-chilblain/pernio like/acral necrosis | Vesicular/varicella like exanthem | Maculo-papular exanthem | Urticarial reticularis (no. of patients) | Others |
|----------------|--------------|---------------------------------------------|--------|-------------|----------------------------------------|---------------------------------------------|--------------------------------------|--------------------------|--------------------------------------|---------|
| Casas et al[9] | Spain        | 234                                         | 113 (M) 121 (F) | 56.38 (mean) | 9 (before) 147 (simultaneously) 77 (after) | 29                                           | 17                                    | 122                 | 49                        | 17      |
| De Giorgi et al[3] | China, Italy | (n=678)                                      | 53     | 32 (M) 21 (F) | 55.9 (mean) 23 (before) 30 (after) | -                                           | 2                                    | 37                   | 14                      | -       |
| Nieto et al[9]  | Spain        | 24                                          | 6 (M) 18 (F) | 40.5 (mean) | 2 (before) 3 (simultaneously) 19 (after) | -                                           | 24                                    | -                    | -                      | -       |
| Freeman et al[7] | Multinational (8 countries) | 23                                          | 12 (M) 11 (F) | 41 (median) | 4 (before) 3 (simultaneously) 11 (after) | 23                                          | -                                    | -                    | -                      | -       |
| Marzano et al[9] | Italy        | 22                                          | 16 (M) 6 (F) | 60 (median) | After 3 day median latency | -                                           | 22                                    | -                    | -                      | -       |
| Recalcati et al[3] | Italy        | (n=88)                                      | 18     | NA          | 8 (simultaneously) 10 (after) | -                                           | 1                                    | 14                   | 3                      | -       |
| Guarneri et al[9] | Italy        | (n=125)                                     | 13     | NA          | NA | 3 | - | 2 | 2 | - | Parainfluenza (3) |
| Zhang et al[9]  | China        | (n=140)                                     | 2      | NA          | NA | NA | - | - | - | 2 | - |
| Moyano et al[11] | Spain        | (n=1177)                                    | 8      | 4 (M) 4 (F) | 72.2 (mean) After 27.6 days mean latency | -                                           | -                                    | 8                    | -                      | -       |

\*n = the number of COVID-19 confirmed cases reported in the study

one patient, respectively.[1,17] They described them as red-purple papules over the dorsal aspect of the fingers. Estebanez et al. reported a similar presentation in Spain, where a patient with COVID-19 developed erythematous, yellow papules and plaques over the heels during the convalescent period (12 days after testing positive) that resolved without treatment.[26] Small vessel occlusion similar to that seen in the autopsies of lung specimens could be the underlying pathology behind this cutaneous presentation. This is potentiated by visualizing hyaline thrombi in microvessels of the skin in the histopathology of such lesions.[17]

Varicella-like vesicular eruptions were one of the first manifestations reported in COVID-19 patients. Recalcati et al. reported chickenpox-like vesicles in one of their 18 patients and Tammaro et al. in two patients.[3,19] Marzano et al. reported a large series of 22 patients with varicella-like exanthem from Italy.[10] These developed after a median latency period of three days after the onset of systemic features. These lesions were scattered in 72.7% of patients and diffuse in 27.3% of patients. The trunk was almost always involved, and the face and mucosae were spared. In seven patients in whom a biopsy was performed, it was reported to be consistent with viral infection. Casas et al. described such lesions in 9% of their patients. The important differentiating point is that these vesicles are monomorphic, unlike varicella, where polymorphic vesicles are seen. These lesions were seen more commonly in middle-aged patients with intermediate disease severity, and developed even before the onset of fever and cough and lasted for an average of 10.4 days.[4] Similar eruptions were reported in an 8-year-old girl who had a history of varicella infection. Five days later, she and her family members tested positive for COVID-19.[34] The varicella-like eruptions could be coincidental as they resemble lesions produced by other paroviruses.

Acute urticaria as a manifestation of COVID-19 has been reported quite widely. Recalcati et al. first described cutaneous findings in three of their patients.[9] Casas et al. reported acute urticaria in 19% of patients.[8] It is widespread and involves the palms. Urticaria develops simultaneously with systemic features, such as fever and cough, and resolves after an average of 6.8 days.
Table 2: Case reports and case series reporting cutaneous manifestations of COVID-19

| Study                        | Country    | No. of cases | Gender | Age (years) | Onset of lesions (days) | Pseudo-chilblain/pernio like/acral necrosis | Vesicular/varicella like | Maculopapular exanthem | Urticarial reticularis | Livedo | Others (no. of patients) |
|------------------------------|------------|--------------|--------|-------------|-------------------------|---------------------------------------------|--------------------------|-------------------------|-----------------------|--------|--------------------------|
| Zhang et al.[27]             | China      | 7            | 4 (M)  | 59 (median) Median 19 days (after) | 7                                      | -                                           | -                        | -                      | -                     | -      |                          |
| Gianotti et al.[13]          | Italy      | 5            | NA     | NA          | NA                      | -                                           | -                        | 4                      | -                     | -      | -                        |
| Hedou et al.[24]             | France     | 5            | NA     | 1 patient (before) | -                      | 2                                          | 2                        | -                      | HSV-1 reactivation (1) | -      |                          |
| (n=103)                      | Spain      | 4            | 4 (F)  | 66.75 (mean) Mean 19.5 days after | -                      | -                                           | -                        | -                      | Erythema multiforme like (4) | -      |                          |
| Sachdeva et al.[25]          | Italy      | 3            | 3 (F)  | 71          | NA, 4 days after 2 days before | -                                           | -                        | 1                      | 2                    | -      |                          |
| Atramtham et al.[27]         | Kuwait     | 2            | 2 (F)  | 27          | Asymptomatic            | 2                                          | -                        | -                      | -                    | -      |                          |
| Tammaro et al.[30]           | Italy      | 2            | NA     | NA          | NA                      | -                                           | 2                        | -                      | -                    | -      | -                        |
| Van Damme et al.[28]         | Belgium    | 2            | 1 (M)  | 71          | Same day                | -                                           | -                        | 2                      | -                    | -      | -                        |
| Manalo et al.[29]            | Atlanta    | 2            | 1 (M)  | 67          | 7 days (after)          | -                                           | -                        | -                      | -                    | 2      | -                        |
| Janah et al.[21]             | Morocco    | 2            | 2 (M)  | 17          | 15 days (after)         | -                                           | -                        | -                      | -                    | -      | Erythema multiforme (2)   |
| Morey-Olive et al.[25]       | Spain      | 2            | 1 (M)  | 6           | 16 days after, same day | -                                           | -                        | 1                      | 1                    | -      | -                        |
| Elsaie et al.[25]            | Egypt      | 2            | 1 (M)  | 68          | 2 days before, same day | -                                           | -                        | -                      | -                    | -      | Herpes zoster (2)         |
| Cepeda-Valdes et al.[26]     | Mexico     | 2            | 2 (F)  | 50          | Same day                | -                                           | -                        | -                      | -                    | 2      | -                        |
| Krajewski et al.[27]         | Poland     | 2            | 1 (M)  | 40          | Same day                | -                                           | -                        | -                      | -                    | -      | Cutaneous hyperesthesia (2) |
| Estebanez et al.[28]         | Spain      | 2            | 1 (F)  | 28          | 13 days after           | -                                           | -                        | -                      | -                    | -      | Erythematous papuloplaques over heels (1) |
| Nieto et al.[27]             | Spain      | 1            | 1 (F)  | 32          | 6 days after            | -                                           | -                        | -                      | -                    | 1      | -                        |
| Moreno et al.[29]            | Spain      | 1            | 1 (F)  | 32          | 6 days after            | -                                           | -                        | 1                      | -                    | -      | -                        |
| Amatore et al.[25]           | France     | 1            | 1 (M)  | 39          | Same day                | -                                           | -                        | 1                      | -                    | -      | -                        |
| Joob et al.[29]              | Thailand   | 1            | NA     | NA          | NA                      | -                                           | -                        | -                      | -                    | -      | Patchel rash (1)          |
| Ehsani et al.[31]            | France     | 1            | 1 (M)  | 27          | 3 days after            | -                                           | -                        | -                      | -                    | 1      | -                        |
| Paolino et al.[29]           | Italy      | 1            | 1 (F)  | 37          | 3 days after            | -                                           | -                        | 1                      | -                    | -      | -                        |
| Olisova et al.[31]           | Russia     | 1            | 1 (F)  | 12          | 3 days after            | -                                           | -                        | -                      | -                    | -      | Purpuric rash over face (1) |
| Genovese et al.[29]          | Italy      | 1            | 1 (F)  | 8           | 5 days before           | -                                           | 1                        | -                      | -                    | -      | -                        |
| Henry et al.[29]             | France     | 1            | 1 (F)  | 27          | 2 days before           | -                                           | -                        | -                      | 1                    | -      | -                        |
| Dominguez-Santos[30]         | Spain      | 1            | 1 (F)  | 71          | 7 days after            | -                                           | -                        | -                      | -                    | -      | Small vessel vasculitis (1) |
| Gracia-Gil et al.[27]        | Spain      | 1            | 1 (M)  | 51          | 3 days after            | 1                                           | -                        | -                      | -                    | -      | -                        |
| Gunawan et al.[29]           | Indonesia  | 1            | 1 (M)  | 51          | 5 days after            | -                                           | -                        | -                      | 1                    | -      | -                        |
| Mahe et al.[29]              | France     | 1            | 1 (F)  | 64          | 4 days after            | -                                           | -                        | 1                      | -                    | -      | -                        |
| Hunt et al.[31]              | USA        | 1            | 1 (M)  | Same day    | 1                        | -                                           | -                        | -                      | -                    | -      | -                        |

Contd...
Patients developing urticaria were found to have severe disease with higher mortality. However, it appears unclear if these urticarial lesions represent a manifestation of COVID-19 itself or are drug-induced as sick patients are on multiple drugs. Viral infections are a known trigger for urticaria, especially in children, and thus is likely to be seen in COVID-19.

Maculo-papular exanthems have been described variably by researchers as erythematous, morbilliform, and purpuric rash. However, all fit the description of maculo-papular rash similar to that seen in other viral exanthems. Casas et al. reported different morphologies of maculo-papular rash in 47% of patients. These include pityriasis rosea-like, purpuric, perifollicular rash with scaling, erythema multiforme-like, and erythema elevatum diutinum-like. Some patients develop erythematous infiltrated papules over the extremities resembling pseudo-vesicles. Like urticarial lesions, maculo-papular rash is also associated with severe disease and high mortality. These last for a mean of 8.6 days and subside without any post-inflammatory pigmentation. Underlying lymphocytic vasculitis with red blood cell extravasation and papillary dermal edema exacerbated by complement deposition, as seen in histopathology. Occlusive vascular disease can also explain the development of livedo reticularis. Casas et al. reported livedo reticularis in older patients with severe disease. However, age is a poor prognostic factor itself and may be responsible for the higher mortality. Livedo reticularis has been reported as a transient finding in some patients who do not require specific treatment. A few patients also developed cutaneous necrosis secondary to small vessel thrombosis. Other manifestations include exanthems, purpuric flexural lesions, and reactivation of herpes simplex and varicella zoster virus.

It is difficult to specifically attribute the cutaneous manifestations to COVID-19 to the virus itself because of a lack of histopathological and virological confirmation in most studies. It is even difficult to obtain photographs because of the risk of disease transmission. The findings reported to date may be incomplete, and new manifestations will be added with time. There is a need to develop countrywide registries to maintain records of cutaneous manifestations. With a better understanding of the pathogenesis of the disease, as well as its cutaneous manifestations, their significance will be clear.

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Conflicts of interest
There are no conflicts of interest.

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