

## ORIGINAL ARTICLE

# Prevalence of cutaneous manifestations in COVID-19: A meta-analysis

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**Abstract**

The global epidemic of coronavirus disease 2019 (COVID-19) endangers more and more people. Many studies on cutaneous manifestations related to COVID-19 have emerged, but their prevalence has varied widely. The objective of this study was to conduct a meta-analysis estimating the prevalence of skin manifestations in COVID-19. Four databases PubMed, Web of Science, CBM, and CNKI were searched, and the results were screened by two reviewers. A random-effects model was used to evaluate the overall prevalence. Heterogeneity was assessed by  $I^2$ . Further subgroup analyses were conducted by region, sample size, sex, age, and severity of COVID-19. A funnel plot and Egger's test were performed to assess publication bias. The pooled prevalence of cutaneous manifestation of 61089 patients in 33 studies was 5.6% (95% confidence intervals [CI] = 0.040–0.076,  $I^2 = 98.3%$ ). Severity of COVID-19 was probably the source of heterogeneity. Studies with sample size <200 report higher prevalence estimates (10.2%). The prevalence of detailed types was as follows: maculopapular rash 2%, livedoid lesions 1.4%, petechial lesions 1.1%, urticaria 0.8%, pernio-like lesions 0.5%, vesicular lesions 0.3%. Petechial lesions and livedoid lesions contain a higher proportion of severe patients than other skin manifestations. The prevalence rates of pernio-like lesions, urticaria and petechial lesions vary greatly in different regions.

**KEYWORDS**

COVID-19, cutaneous manifestations, meta-analysis, prevalence, systematic review

## 1 | INTRODUCTION

In December 2019, a new type of virus named severe acute respiratory syndrome, coronavirus type 2, emerged and has spread to nearly every corner of the globe causing societal instability, and it has generated unprecedented global concern and responses. Globally, as of 3 June 2022, there have been 528816317 confirmed cases of COVID-19, reported to the World Health Organization (WHO).<sup>1</sup>

The most effective way to address the pandemic is the prevention of further infection. Thus, early diagnosis and subsequent quarantine is an effective strategy. The symptoms of COVID-19 infection are various, it can be asymptomatic,<sup>2</sup> and it can span from a mild influenza-like illness to life-threatening complications.<sup>3</sup> While

the lung is the primary viral target, a significant proportion of patients presented initially with atypical symptoms, such as diarrhea and nausea. In some severe cases, it may be associated with cellular immune deficiency, coagulation activation, myocardia injury, hepatic injury, and kidney injury.<sup>4</sup> More and more studies have reported that COVID-19 is associated with dermatological manifestations. The skin, including mucous membranes, is an organ that frequently presents lesions caused by viral infections.<sup>5</sup> In a viral infection, exanthems usually occur as an immune hypersensitivity response to viral DNA or RNA.<sup>6</sup> Jamiolkowski et al.<sup>7</sup> and Guarneri C et al.<sup>8</sup> showed the significance of paying attention to skin manifestations in the diagnosis of COVID-19. However, the prevalence of skin manifestations in COVID-19 patients varies widely, from 0.2% to 20.4%.<sup>9,10</sup> Evidence is accumulating that cutaneous manifestations associated

with COVID-19 are extremely polymorphic.<sup>11</sup> A study in Spain has identified five common skin symptoms in 375 patients, containing pseudo-chilblain, vesicular eruptions, urticarial lesions, maculopapular eruptions, and livedo or necrosis.<sup>12</sup> With increasing research, the main types of reported skin manifestations connected with COVID-19 are also distinct.<sup>13-15</sup>

Although there are two meta-analyses<sup>16,17</sup> focusing on the prevalence of skin lesions in COVID-19 patients, their prevalence rates are different, with 5.69% in Rajan et al.<sup>16</sup> study and 1.0% in Sameni et al.<sup>17</sup> study. Moreover, many of the included studies were case reports. Therefore, with the increasing number of studies, the data needs to be updated in time. In this study, we performed a meta-analysis to estimate the prevalence of cutaneous manifestations and their main types related to COVID-19.

## 2 | MATERIALS AND METHODS

### 2.1 | Search strategy

The literature search was performed using four databases (PubMed, Web of Science, CBM, and CNKI) from 1 December 2019 to 25 April 2022. The following keywords were used: 'SARS-CoV-2', 'Coronavirus Disease 2019 Virus', '2019 Novel Coronavirus', '2019 Novel Coronaviruses', 'Coronavirus, 2019 Novel', 'Novel Coronavirus, 2019', 'Wuhan Seafood Market Pneumonia Virus', 'SARS-CoV-2 Virus', 'SARS CoV 2 Virus', 'SARS-CoV-2 Viruses', 'Virus, SARS-CoV-2', '2019-nCoV', 'COVID-19 Virus', 'COVID 19 Virus', 'COVID-19 Viruses', 'Virus, COVID-19', 'Wuhan Coronavirus', 'Coronavirus, Wuhan', 'SARS Coronavirus 2', 'Coronavirus 2, SARS' or 'Severe Acute Respiratory Syndrome Coronavirus 2' and 'exanthema', 'skin manifestation', 'skin disease', 'exanthema', 'cutaneous', 'rash', 'chilblain-like', 'vesicular', 'maculopapular', 'pernio', 'urticarial', 'livedo', 'vesicular', or 'petechial'.

### 2.2 | Study setting and design

Our study is a systematic literature review conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.<sup>18</sup>

### 2.3 | Selection criteria

The inclusion criteria were as follows: (1) Study population: patients diagnosed with COVID-19 irrespective of age and sex; (2) Study design: cross-sectional studies, case-control studies, and retrospective/prospective cohort studies; (3) Outcome: prevalence rate of cutaneous manifestations related to COVID-19 was the outcome measure, and (4) no language limit.

Studies with any of the following exclusion criteria were excluded from our study: (1) Studies exclusively reporting drug-related

skin manifestations or skin adverse events related to personal protective equipment related to COVID-19; (2) Case reports.

### 2.4 | Quality assessment

Quality assessment was performed by two researchers using Agency for Health Research and Quality (AHRQ) for the cross-sectional study and the Newcastle-Ottawa scale for the cohort study.

### 2.5 | Data extraction

Two independent researchers pulled out the data from the articles included. All disagreements were resolved by consensus with a third researcher. Information about the enrolled studies is listed in [Table 1](#), including: (1) the first author's name, (2) publication time, (3) country, (4) number of total patients diagnosed with COVID-19, (5) number of patients with cutaneous manifestations, and (6) type of cutaneous manifestations and their respective numbers.

### 2.6 | Statistical analyses

The pooled prevalence of cutaneous manifestations related to COVID-19 was calculated using a random-effects model. Statistical heterogeneity was assessed by  $I^2$  and  $p$ -value.  $I^2$ : 0%–25% indicates no heterogeneity; 25%–50%, modest heterogeneity; 50%, high heterogeneity. When the heterogeneity is higher than 50%, random-effects models are used to obtain estimates, while the heterogeneity is lower than 50%, we use fixed-effects models. We conducted a sensitivity analysis to evaluate the stability of the results and investigate each study's influence by excluding a single study sequentially. A funnel plot and Egger's test were performed to assess publication bias. All statistical analyses were carried out by STATA 14.0. A  $p$ -value <0.05 was considered as a statistical difference.

## 3 | RESULTS

### 3.1 | Description of eligible studies

The initial search yielded 6237 articles. We removed 1868 duplicates and assessed 4369 articles for title/abstract screening, among them 101 articles were selected for full-text reading, and seven articles were added by manual searching. After screening the literature based on the inclusion criteria, 33 articles were identified for analysis ([Figure 1](#)). Among them, 24 articles described specific rash types. Ten studies focused on adults and five were related to children. The countries of origin were Spain, Turkey, India, China, Italy, America, Thailand, Oman, Philippines, Austria, Japan, and France. Most of the research was in Asia containing the largest patient population

**TABLE 1** Characteristics of all studies describing cutaneous manifestations related to COVID-19 in the meta-analysis

Author	Published time	Country	Total patients	Patients with cutaneous manifestations	Types of cutaneous manifestations	Quality evaluation score
Mendez <sup>57</sup>	September 2020	Spain	75	14	Pernio-like lesions (6), maculopapular rash (4), urticaria (2), livedo reticularis-like lesions (1), vesicular eruption (1)	9
Askin <sup>58</sup>	July 2020	Turkey	210	34 (17 cases of erythema caused by hand washing and 1 case of itching related to vancomycin were excluded)	Maculopapular rash (12), urticaria (7), purpuric rash (4), necrosis (4), enanthema and aphthous stomatitis (3), vesicular eruption (3), pernio (1)	6
Fernandez <sup>59</sup>	December 2020	Spain	144	5	Livedo reticularis-like lesions (4), maculopapular rash (1)	7
Dalal <sup>60</sup>	June 2020	India	102	13	Pruritus (8), maculopapular rash (3), urticaria (2)	6
De Giorgi <sup>11</sup>	May 2020	Italy and China	678	53	Erythematous rash (37), urticaria (14), vesiculation (2)	7
Jimenez <sup>61</sup>	July 2020	America	21	6	Erythema multiforme-like (3), purpuric (2), papulovesicular (1)	7
Rerknimitr <sup>20</sup>	September 2020	Thailand	153	12 (5 cases were not sure whether related to COVID-19, and 6 cases caused by complications or treatment or equipment were excluded)	Urticaria (5), maculopapular rash (4), vesicular (2), necrosis (1)	7
Recalcati <sup>9</sup>	March 2020	Italy	88	18	Erythematous rash (14), urticaria (3), chickenpox-like vesicles (1)	6
Guan <sup>10</sup>	April 2020	China	1099	2	-	9
Andina <sup>62</sup>	April 2021	Spain	50	18	Erythematous macules and papules (17), acral ischemic lesion (1)	8
Pangti <sup>63</sup>	August 2021	India	138	10	Weals (3), purpura and petechiae (3), Chilblain-like (1), macular erythematous rash (1), desquamation (1), aphthous ulcers (1)	6
Thuangtong <sup>15</sup>	June 2021	Thailand	93	7 (1 case of psoriasis was excluded as the basic disease)	Maculopapular rash (3), urticaria (2), petechiae (1), eczema (1)	8
Rekhtman <sup>24</sup>	April 2021	America	296	35	Ulcer (13), purpura (9), necrosis (5), nonspecific erythema (4), morbilliform eruption (4), pernio-like lesions (4), vesicles (1)	8
Yildiray <sup>64</sup>	June 2021	Turkey	266	5	Urticaria (3), vesicular (2)	7
Al Ali <sup>13</sup>	July 2021	Oman	374	5 (6 cases related to drugs and 1 case of acute attack of atopic dermatitis were excluded)	Maculopapular rash (2), transient pruritic erythema (1), palmoplantar erythema (1), urticaria (1)	10
G Brancacci <sup>65</sup>	March 2021	Italy	417	7	Chilblain-like (4), purpuric (2), papular and pustular rash (1)	6
Unterluggauer <sup>14</sup>	July 2021	Austria	102	16 (1 case caused by drugs was excluded)	Livedo reticularis (6), splinter hemorrhage-like lesions (4), subcutaneous nodules (2), others (4)	7
Parcha <sup>25</sup>	May 2021	America	1230	887	-	8

(Continues)

TABLE 1 (Continued)

Author	Published time	Country	Total patients	Patients with cutaneous manifestations	Types of cutaneous manifestations	Quality evaluation score
Sun <sup>66</sup>	August 2020	China	3128	52	Urticaria (27), erythema and papules (15), scratch (5), rhagades (3), chilblains (2)	7
Gaspari <sup>27</sup>	April 2021	Italy	1409	21	-	6
Jakhar <sup>67</sup>	December 2021	India	71	13	Urticarial lesions (4), macular erythema (2), morbilliform rash (2), mucosal manifestations (5)	6
Bryan <sup>68</sup>	2022	America	1086	10	Erythematous papules (4), blisters (3), pruritic rash (1), urticarial rash (1), diffuse vitiligo-like rash (1)	6
Tan <sup>23</sup>	June 2022	Philippines	507	39	Morbilliform rash (17), livedo reticularis (7), petechial rash (6), vesicular rash (4), pernio or chilblains (2), urticaria (3)	6
Zengarini <sup>69</sup>	January 2022	Italy	1053	0	-	9
Vera <sup>22</sup>	March 2022	Spain	2929	96	-	8
Murugan <sup>26</sup>	March 2022	India	988	23	-	8
Sugai <sup>70</sup>	March 2022	Japan	1245	7	-	6
Rekhtman <sup>71</sup>	February 2021	America	12	4	Nonspecific erythema (3), morbilliform (1)	7
Hedou <sup>72</sup>	April 2020	France	103	5	Erythematous rash (2), urticaria (2), other (1)	6
Mascitti <sup>73</sup>	October 2021	Thailand	28 957	2756	-	7
Giavedoni <sup>74</sup>	October 2020	Spain	2761	58	Maculopapular rash (12), urticaria (4), chilblain-like lesions (17), papulo-vesicular eruptions (8), livedo reticularis (4), other (13)	6
Jobb <sup>75</sup>	May 2020	Thailand	48	1	Maculopapular rash (1)	5
Garg <sup>76</sup>	April 2020	America	180	2	-	8

( $n = 37\,379$ ). In addition, 33 participants with skin manifestations were excluded due to excessive hand washing, drug allergy, and recurrence of original skin disease in five articles.<sup>13-15,19,20</sup> In total, 33 studies including 61 089 patients met the inclusion criteria and were selected for meta-analysis. The characteristics of the selected studies were summarized in Table 1.

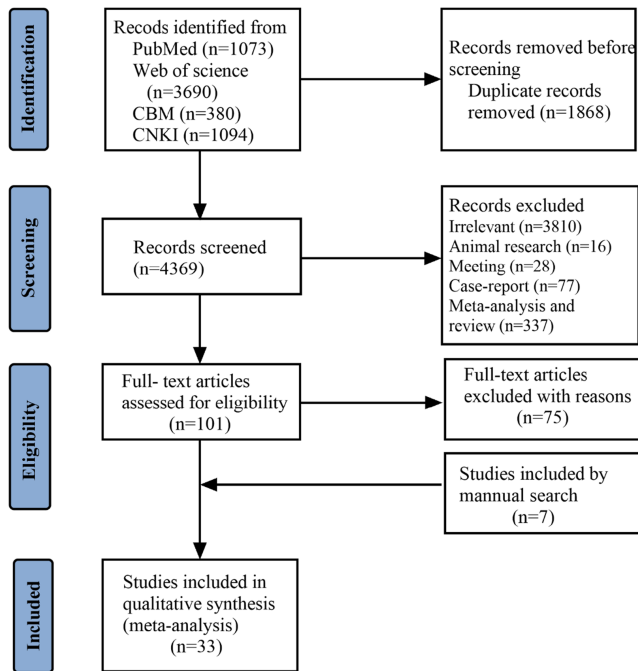
### 3.2 | Results of the meta-analysis

The severity and impacts of COVID-19 around the world have not been uniformly distributed across populations.<sup>21</sup> A total of 16 among 33 studies describe the detailed number of severe and critical COVID-19 patients, with the pooled prevalence of 15.7% (1597/24 951). There were 10 studies in Asia, occupying the highest prevalence of 21.5% (1306/5006). The lowest prevalence estimates of 1.0% (118/12 306) was conducted by America, which was contained in one study. The pooled prevalence of Europe in five studies lies between Asia and America, accounting for 11.9% (173/7639).

There were six countries in seven studies describing the mortality of COVID-19 patients, with the total mortality rate of 1.96% (442/22 535). The lowest mortality rate 0.02% (1/5933) was reported by Spain.<sup>22</sup> The mortality rate of 21.89% (111/507) reported by Philippines ranked first.<sup>23</sup> Furthermore, the mortality rates in the other five studies from low to high were as follows: less than 0.43% (54/12 599) in America,<sup>24,25</sup> 1.01% (1/988) in India,<sup>26</sup> 1.36% (15/1099) in China,<sup>10</sup> 17.81% (251/1409) in Italy,<sup>27</sup> respectively.

### 3.3 | Meta-analysis of the prevalence of cutaneous manifestations in COVID-19 patients

The overall pooled prevalence of cutaneous manifestations in COVID-19 patients was 5.6%, which was shown in the forest plot in Figure 2, with significant heterogeneity stated among studies (95% confidence interval [CI] = 0.040–0.076,  $n = 61\,089$ ,  $I^2 = 98.3\%$ ). Sensitivity analysis excluding one study, did not significantly affect the overall prevalence of COVID-19 patients with skin lesions, which



**FIGURE 1** Flow diagram of the study selection process

indicated that our analysis was stable (Figure 3). There were signs of publication bias when the funnel plot of overall skin manifestations was examined visually (Figure 4), however, Egger's test did not show publication bias ( $p = 0.274$ ).

### 3.4 | Subgroup analysis

To explore the potential factors of heterogeneity, we carried out subgroup analyses according to region, sample size, sex, age and severity of COVID-19. The results are summarized in Table 2.

#### 3.4.1 | Stratification by region

We found 15 studies conducted in Asia, with a pooled prevalence estimate of 5.7% (95% CI 0.032–0.081),  $I^2 = 99.4\%$ . In Europe, there were 10 studies, the pooled prevalence was 4.3% (95% CI 0.028–0.058),  $I^2 = 89.8\%$ . The pooled prevalence estimates of six studies conducted in America was 7.2% (95% CI 0.025–0.119),  $I^2 = 98.8\%$ . The results of the subgroup analysis related to region demonstrated that the heterogeneity also remained high. We found no study conducted in Africa reporting the prevalence of skin manifestations in COVID-19.

#### 3.4.2 | Stratification by sample size

A pooled prevalence of 10.2% (95% CI 0.070–0.134),  $I^2 = 86.0\%$  was estimated from 16 studies with a sample size <200. There were 17 studies presenting prevalence estimates with a sample size

>200, and the pooled prevalence was 4.3% (95% CI 0.024–0.062),  $I^2 = 99.4\%$ . The results grouped by sample size still showed high heterogeneity.

#### 3.4.3 | Stratification by sex

There were nine studies conducting prevalence estimates stratified by sex. The pooled prevalence was 4.6% in men (95% CI 0.026–0.067),  $I^2 = 89.2\%$  and 2.7% in women (95% CI 0.011–0.042),  $I^2 = 81.2\%$ , respectively. Which also displayed high heterogeneity.

#### 3.4.4 | Stratification by age

There were 10 studies involving adults, with pooled prevalence of 6.9% (95% CI 0.039–0.099),  $I^2 = 96.2\%$ . Children were included in five studies, the pooled prevalence was 7.2% (95% CI 0.034–0.110),  $I^2 = 98.2\%$ . The high heterogeneity noticed remained in both subgroups.

#### 3.4.5 | Stratification by severity of COVID-19

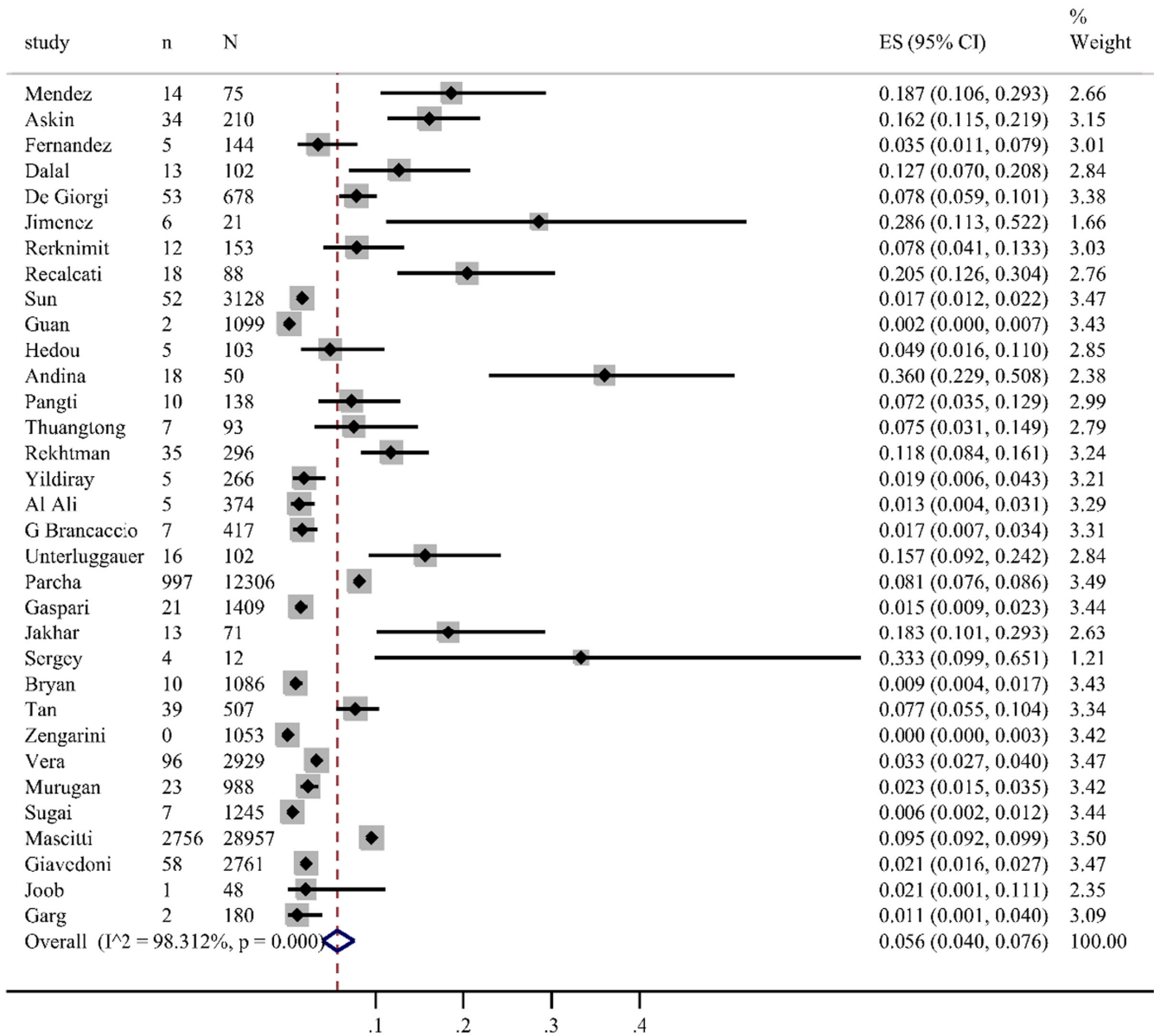
We found six studies involving non-severe (asymptomatic, mild to moderate symptoms) COVID-19 patients, the pooled prevalence was 8.1% (95% CI 0.040–0.122),  $I^2 = 86.0\%$ . Severe COVID-19 patients were included in three studies, with the pooled prevalence of 12.1% (95% CI 0.083–0.159),  $I^2 = 0.0\%$ , which indicated the severity of COVID-19 was probably the source of high heterogeneity.

### 3.5 | Meta-regression

Results from the meta-regression of prevalence on sample size indicate that studies with sample size <200 report higher prevalence estimates ( $p' = 0.023$ ). The results of meta-regression are summarized in Table 2.

### 3.6 | Specific dermatological manifestations

According to the results of these studies, 12 countries reported 20 types of skin manifestations among patients with COVID-19. Among them, maculopapular rash/morbilliform exanthem was the most common, with a pooled prevalence of 2.0% (95% CI = 0.014–0.026,  $n = 10069$ ,  $I^2 = 85.4\%$ ) in 19 studies, with a forest plot in supplementary. The prevalence of maculopapular rash/ morbilliform exanthem ranged from 0.4% to 34%. Livedoid lesions were displayed in five studies, with pooled prevalence 1.4% (95% CI = 0.001–0.027,  $n = 3589$ ,  $I^2 = 74.9\%$ ), the range was 0.1%–5.9%. Eight studies covered petechial lesions. The prevalence ranged from 0.5% to 10.8%, and the pooled prevalence was 1.1%



**FIGURE 2** Forest plot showing the prevalence rate of overall cutaneous manifestations in COVID-19 patients, with 95% CI

(95% CI = 0.006–0.015,  $n = 1784$ ,  $I^2 = 44.1\%$ ). Sixteen studies displayed urticaria. The prevalence ranged from 0.1% to 5.6%, and the pooled prevalence of it was 0.8% (95% CI = 0.005–0.012,  $n = 9833$ ,  $I^2 = 74.4\%$ ). Pernio-like lesions were shown in eight studies, the prevalence varied from 0.1% to 8%, and the pooled prevalence was 0.5% (95% CI = 0.001–0.009,  $n = 7532$ ,  $I^2 = 74.6\%$ ). There were 12 studies describing vesicular lesions, the prevalence ranged from 0.3% to 4.8%, the pooled prevalence was 0.3% (95% CI = 0.002–0.005,  $n = 6558$ ,  $I^2 = 0.0\%$ ). The forest plots are displayed in [Figures 5–10](#). The estimates of the six types of skin manifestations are shown in [Table 3](#).

We also estimated the proportion of severe/critical patients in each skin type. Among these six skin types, the largest proportion of severe/critical patients was petechial lesions, with a percentage of 59.5% (10/17). The second was livedoid lesions, the proportion was 35.4% (2/5). Then followed by vesicular lesions and urticaria, the

percentages of them were 18.2% (3/11) and 17.8% (4/15), respectively. Pernio-like lesions contained the least severe/critical patients, there was only one in 32. The prevalence of severe/critical patients in each skin type are summarized in [Table 4](#).

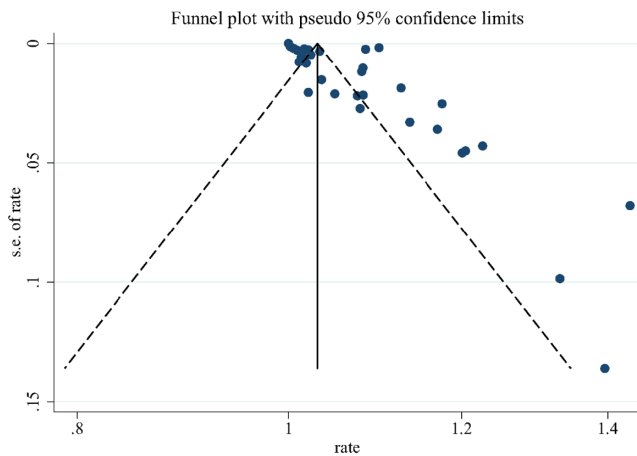
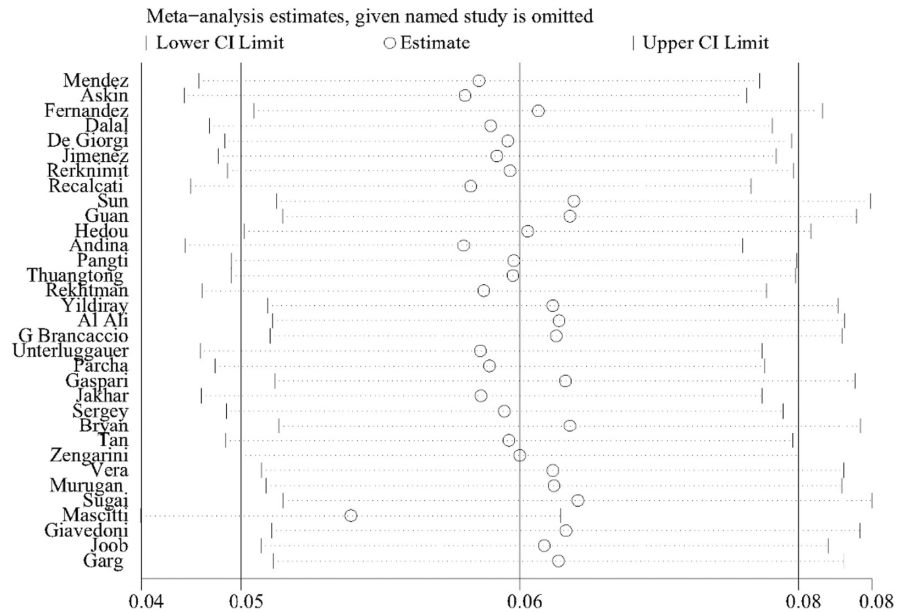
### 3.7 | Subgroup analysis of each skin type according to region

#### 3.7.1 | Maculopapular rash/morbilliform exanthem

We found nine studies in Asia, with a pooled prevalence of 2.2% (95% CI = 0.011–0.032,  $n = 4776$ ). Six studies were conducted in Europe, their pooled prevalence was 4.1% (95% CI = 0.014–0.069,  $n = 3221$ ). There were three studies in America, occupying the lowest pooled prevalence of 1.8% (95% CI = 0.001–0.049,  $n = 1394$ ).



**FIGURE 3** Sensitivity analysis of overall cutaneous manifestations in COVID-19 patients



**FIGURE 4** Funnel plot of overall cutaneous manifestations in COVID-19 patients

### 3.7.2 | Livedoid lesions

There was one study in Asia, the prevalence of livedoid lesions was 1.4% ( $n = 507$ ). Europe had 4 studies, with a pooled prevalence of 1.8% (95% CI =  $-0.003-0.039$ ,  $n = 3082$ ). There was no report about livedoid lesions in America.

### 3.7.3 | Petechial lesions

Four studies were conducted by Asia, and the pooled prevalence was 1.4% (95% CI =  $0.006-0.021$ ,  $n = 948$ ). There were two studies in Europe, with the pooled prevalence of 0.6% (95% CI =  $-0.001-0.012$ ,  $n = 519$ ). America had two studies either, with a higher prevalence of 3.2% (95% CI =  $0.013-0.051$ ,  $n = 317$ ).

### 3.7.4 | Urticaria

We found 10 studies in Asia, with a pooled prevalence of 1.0% (95% CI =  $0.005-0.015$ ,  $n = 5042$ ). Four studies were conducted by Europe, their pooled prevalence was 1.4% (95% CI =  $-0.003-0.031$ ,  $n = 3027$ ). One study was reported in America, with the smallest prevalence rate of 0.1% ( $-0.001-0.003$ ,  $n = 1086$ ).

### 3.7.5 | Pernio-like lesions

There were four studies in Asia, their pooled prevalence was 0.1% (95% CI =  $0.000-0.002$ ,  $n = 3983$ ). Three studies were contained in Europe, with a pooled prevalence of 1.0% (95% CI =  $-0.001-0.020$ ,  $n = 3253$ ). America had one study, the prevalence was 1.4% (95% CI =  $0.000-0.027$ ,  $n = 296$ ), which was the highest.

### 3.7.6 | Vesicular lesions

Four studies were contained in Asia, with a pooled prevalence of 0.9% (95% CI =  $0.004-0.015$ ,  $n = 1136$ ). The pooled prevalence rate of four studies (95% CI =  $0.001-0.005$ ,  $n = 3341$ ) in Europe was the same as that of three studies (95% CI =  $0.000-0.006$ ,  $n = 1403$ ) in America, both of them were 0.3%.

The data of subgroup analysis of each skin type according to region was summarized in [Table 5](#).

## 3.8 | Sensitivity analysis and publication bias

Sensitivity analysis excluding one study did not significantly affect the prevalence of these cutaneous manifestations. The funnel plots

**TABLE 2** Subgroup analyses and meta-regression of studies based on region, sample size, sex, age, and severity of COVID-19

Groups	Included studies	Sample size	Prevalence (95% CI)	<i>p</i>	<i>ph</i>	<i>I</i> <sup>2</sup> (%)	Meta-regression	
							(95% CI)	<i>p</i> '
Total			0.056 (0.040–0.076)	0.000	0.000	98.3%		
Region								
Asian	15 studies	37 379	0.057 (0.032–0.081)	0.000	0.000	99.4%	0.975–1.053	0.479
Europe	10 studies	8078	0.043 (0.028–0.058)	0.000	0.000	89.8%		
America	6 studies	13 901	0.072 (0.025–0.119)	0.003	0.000	98.8%		
Sample size								
>200	17 studies	58 656	0.043 (0.024–0.062)	0.000	0.000	99.4%	0.900–0.991	0.023
<200	16 studies	1524	0.102 (0.070–0.134)	0.000	0.000	86.0%		
Sex								
Male	9 studies	2308	0.046 (0.026–0.067)	0.000	0.000	89.2%	0.924–1.053	0.671
Female	9 studies	1865	0.027 (0.011–0.042)	0.001	0.000	81.2%		
Age								
Adults	10 studies	31 172	0.069 (0.039–0.099)	0.000	0.000	96.2%	0.932–1.132	0.563
Children	5 studies	16 285	0.072 (0.034–0.110)	0.000	0.000	98.2%		
Severity								
Non-severe	6 studies	982	0.081 (0.040–0.122)	0.000	0.000	86.0%	0.911–1.200	0.466
Severe	3 studies	283	0.121 (0.083–0.159)	0.000	0.441	0.0%		

Abbreviations: CI, confidence interval; *I*<sup>2</sup>, 0–25, no heterogeneity; 25–50, modest heterogeneity; 50, high heterogeneity; *ph*, *p*-value of heterogeneity, *p*-value of *Q*-test for the heterogeneity test.

and Egger's tests of maculopapular rash/morbilliform exanthem, urticaria, vesicular lesions, pernio-like lesions, and petechial lesions indicated publication bias ( $p < 0.05$ ).

## 4 | DISCUSSION

To our knowledge, two meta-analyses have reported the prevalence of skin manifestations in COVID-19.<sup>16,17</sup> Most of the included articles in the previous meta-analysis<sup>17</sup> are case reports, and the involved countries and sample size are few. Furthermore, all articles are reported in 2020, which do not cover the newly published research in the last 2 years. Meta-analyses and reviews in the study of Lee DS et al.<sup>28</sup> and Zhao et al.<sup>29</sup> only emphasized the proportion of each skin manifestation type other than the prevalence of skin manifestations in COVID-19 patients. The chief strength of our study is that we evaluate newer and more large-scale studies and present a more accurate meta-analysis.

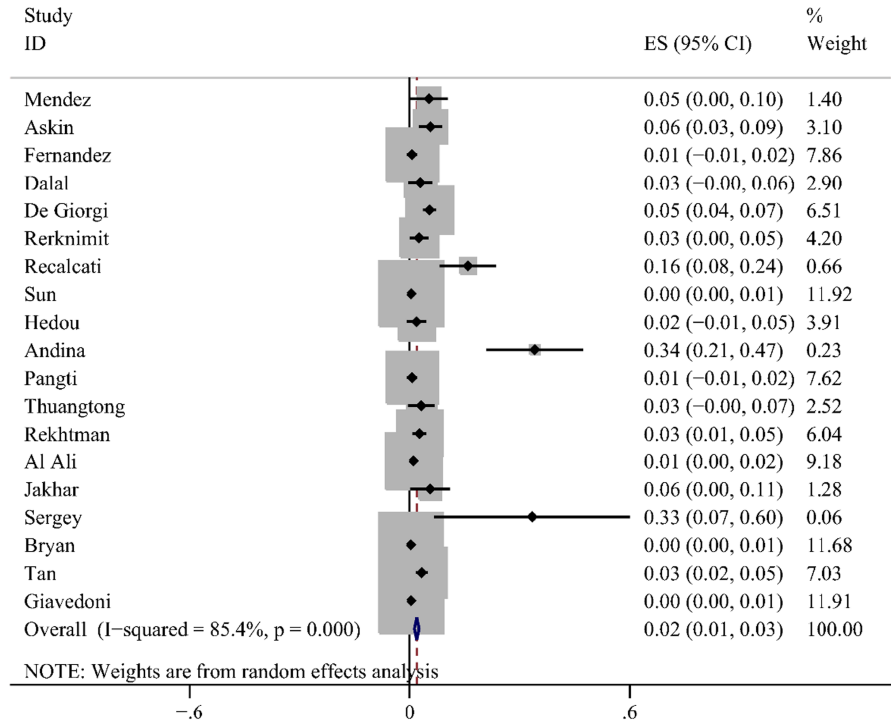
In our meta-analysis, we evaluated the data from 33 studies covering 61 089 patients. The pooled prevalence of severe and critical COVID-19 patients in 16 studies is 15.7% (1597/24951), and the total mortality rate of six countries in seven studies is 2.0% (442/22 535), which are higher than 0.3% (38 640/14 149 190) and 1.0% (6 565 854/628 404 291) respectively reported by the WHO.<sup>30</sup> This is largely due to the fact that most of our data come from inpatients, and the proportion of outpatients is very small. Besides, one study has shown that among hospitalized COVID-19 patients, the risk of mortality is substantially higher, ranging from 1.4% to 28%.<sup>31</sup>

Moreover, we have found that the highest proportion of severe and critical patients is in Asia, followed by Europe, and the lowest is in America. Many factors could influence the severity of the disease such as country average age and weather temperatures, and administration of vaccine.<sup>32</sup> The lowest mortality rate is reported by Spain, and the report of Philippines ranks first. Up to now, the risk factors related to the mortality of COVID-19 patients in low and middle-income countries have not been well studied.<sup>33</sup>

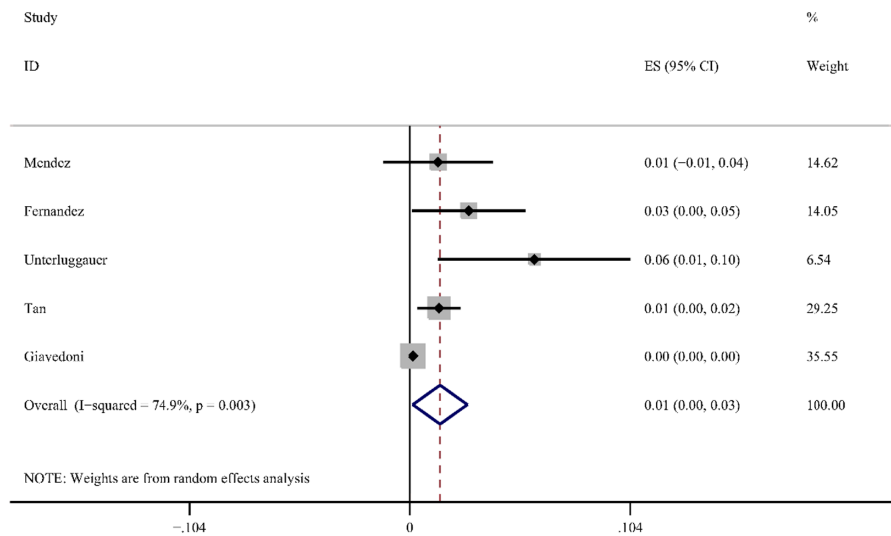
The pooled prevalence of overall cutaneous manifestations associated with COVID-19 in our study is 5.6% (95% CI = 0.040–0.076, *I*<sup>2</sup> = 98.3%). We conducted subgroup analysis due to the high level of heterogeneity in the present study. Our subgroup analysis revealed that *I*<sup>2</sup> value of studies including severe COVID-19 patients was 0.0%, indicating that the severity of COVID-19 was probably the source of heterogeneity in our study. Some skin manifestations are more common in severe patients, urticarial eruptions are usually an indicator of severe disease.<sup>34</sup> A study in Spain indicates that 19% of COVID-19 patients had urticarial lesions, which is a bad prognosis, as the mortality rate is 2%.<sup>12</sup> COVID-19 adults with livedoid lesions tend to need intensive care support.<sup>35</sup> Mohammed et al. study<sup>36</sup> showed that vascular rashes in the spectrum of livedo/purpura/necrosis were significantly related to severe forms of COVID-19. The skin manifestations related to COVID-19 deserve physicians' continuous attention, especially in patients with severe COVID-19 infection. Results from the meta-regression of prevalence on sample size indicate that studies with sample size <200 report higher prevalence estimates. Subgroup analysis by age shows that the prevalence of children (7.2%, 95% CI 0.034–0.110) is comparable to that



**FIGURE 5** Forest plot showing prevalence rate of maculopapular rash in COVID-19 patients, with 95% CI



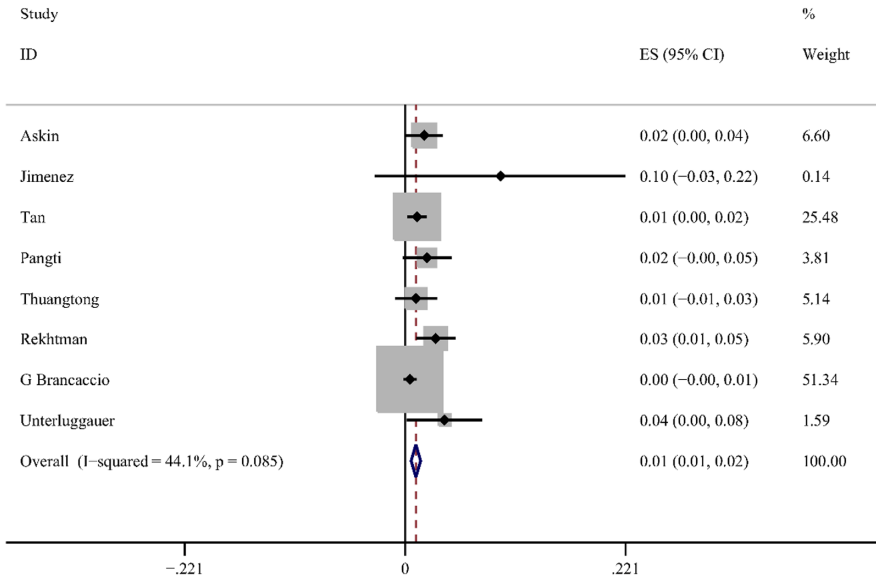
**FIGURE 6** Forest plot showing prevalence rate of livedoid lesions in COVID-19 patients, with 95% CI



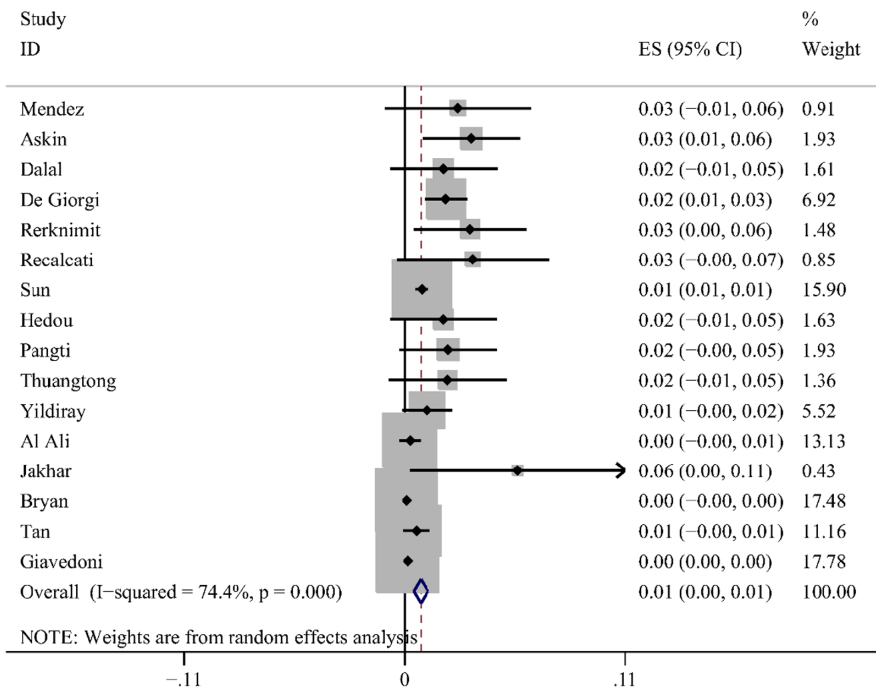
in adults (6.9%, 95% CI 0.039–0.099). In children, cutaneous signs of COVID-19 may be the predominant or only clue of infection.<sup>37</sup> Multisystem inflammatory syndrome in children (MIS-C) is considered a rare but serious complication of SARS-CoV-2 infection. The clinical symptoms usually include continuous fever, gastrointestinal symptoms (abdominal pain, vomiting, diarrhea), skin rashes, and conjunctivitis,<sup>38</sup> and this syndrome is currently being seen worldwide, especially among children 0–5 years of age, the prevalence of dermatologic symptoms was highest.<sup>39</sup> We found no study conducted in Africa reporting the prevalence of skin manifestations in COVID-19; subgroup analyses on Asia, Europe, and America shows that there is no significant difference of pooled prevalence among them. Sex was not a factor affecting the prevalence of skin manifestations in COVID-19 either.

There are six types of skin manifestations which are the most common among all skin manifestations. The prevalence of skin manifestation in COVID-19 patients is as follows: maculopapular rash/morbiliform exanthem 2%, livedoid lesions 1.4%, petechial lesions 1.1%, urticaria 0.8%, pernio-like lesions 0.5%, and vesicular lesions 0.3%. Which is different from some studies showing that pernio-like lesions may represent the most common and characteristic skin manifestations of COVID-19.<sup>40,41</sup> One possible reason is that most of the patients screened in our study are inpatients, and the moderate severity was correlated with maculopapular rash,<sup>42</sup> and many of the pernio-like lesions appeared either in asymptomatic individuals or in patients who endorsed mild symptoms.<sup>43,44</sup>

Maculopapular rash/ morbilliform exanthem occupies the highest prevalence (2.0%) among all cutaneous manifestations, and



**FIGURE 7** Forest plot showing prevalence rate of petechial lesions in COVID-19 patients, with 95% CI



**FIGURE 8** Forest plot showing prevalence rate of urticaria in COVID-19 patients, with 95% CI

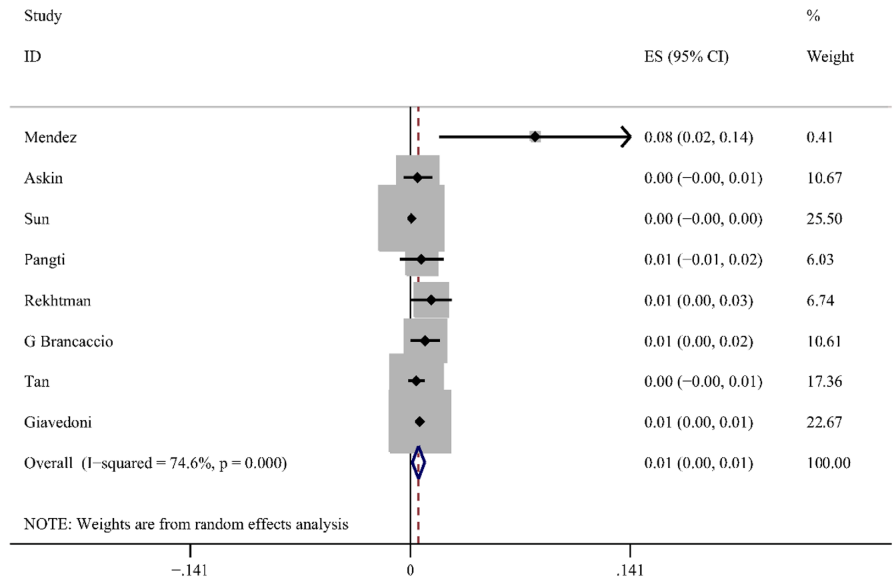
accounts for 41% (166/405) in COVID-19 patients with skin manifestations, which is consistent with the study of Matteo Bassetti et al.<sup>45</sup> These lesions mainly occur either because of viral infections or as side effects of the administered drugs,<sup>46</sup> and the side effects of drugs are also an influence factor that is difficult to eliminate completely. These may be the possible reasons for the highest prevalence of maculopapular rash in our study. Moreover, we estimated the proportion of severe and critical patients with maculopapular rash, and found it was relatively low with a rate of 8.9%. There is no distinct difference in the prevalence of maculopapular rash among three regions.

The pooled prevalence of livedoid lesions is the second among these skin rashes, and they account for the second highest

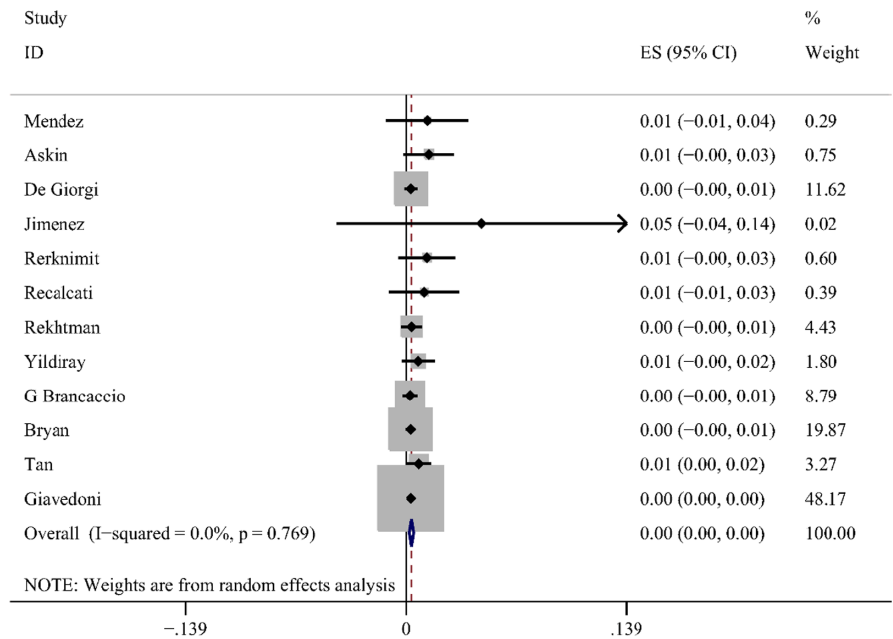
proportion of severe and critical patients (35.4%). The major reason is that livedoid lesions mainly appeared in severe patients. Harjas et al.<sup>47</sup> study also indicates that livedoid lesions primarily appeared in elderly patients with more severe infections. In addition, livedoid lesions are considered as the pattern most associated with mortality.<sup>48</sup> The prevalence rates of livedoid lesions have no significant difference among these three regions.

Petechial lesions have the highest proportion of severe and critical patients, with a rate of 59.5%. That's mainly because petechial lesions usually appear in the most severe cases of SARS-CoV-2 infection,<sup>49</sup> which is further confirmed by Rabia Ghafoor et al.<sup>42</sup> study. Genovese et al.<sup>50</sup> study indicated that purpuric lesions have the highest rate of COVID-19 related mortality. The

**FIGURE 9** Forest plot showing prevalence rate of pernio-like lesions in COVID-19 patients, with 95% CI



**FIGURE 10** Forest plot showing prevalence rate of vesicular lesions in COVID-19 patients, with 95% CI



**TABLE 3** Prevalence of six types of skin manifestations

Type	Included studies	Sample size	Prevalence (95% CI)	p	ph	I <sup>2</sup> (%)
Maculopapular rash/morbilloform exanthem	19 studies	10069	2% (0.014-0.026)	0.000	0.000	85.4%
Livedoid lesions	5 studies	3589	1.4% (0.001-0.027)	0.031	0.003	74.9%
Urticaria	16 studies	9833	0.8% (0.005-0.012)	0.000	0.000	74.4%
Petechial lesions	8 studies	1784	1.1% (0.006-0.015)	0.000	0.085	44.1%
Pernio-like lesions	8 studies	7532	0.5% (0.001-0.009)	0.007	0.000	74.6%
Vesicular lesions	12 studies	6558	0.3% (0.002-0.005)	0.000	0.769	0.0%

Abbreviations: CI, confidence interval; I<sup>2</sup>, 0-25, no heterogeneity; ph, p-value of heterogeneity, p-value of Q-test for the heterogeneity test.

prevalence of petechial lesions in America occupies the highest position, Europe has the lowest rate, and the possible reason is not yet quite clear.

For urticaria, the proportion of severe/critical patients in urticaria is at a relatively low level among the six skin manifestations. Allegra demonstrates that it may present with a severe clinical course

**TABLE 4** The prevalence of severe/critical patients in each skin type

Type	Included studies	Severe or critical patients/ patients of this type	Percentage (95% CI)	<i>p</i>	<i>ph</i>	<i>I</i> <sup>2</sup> (%)
Pernio-like lesions	5	1/32	0.000 (0.000–0.085)	1.000	0.989	0.000%
Maculopapular rash/ morbilliform exanthem	7	6/36	0.089 (0.000–0.264)	0.049	0.374	7.089%
Urticaria	5	4/15	0.178 (0.000–0.538)	0.084	0.204	32.605%
Vesicular lesions	4	3/11	0.182 (0.000–0.599)	0.123	0.820	0.000%
Petechial lesions	5	10/17	0.595 (0.288–0.875)	0.000	0.791	0.000%
Livedoid lesions	2	2/5	0.354 (0.000–0.908)	0.084	–	–

Abbreviations: CI, confidence interval; *I*<sup>2</sup>, 0–25, no heterogeneity; *ph*, *p*-value of heterogeneity, *p*-value of Q-test for the heterogeneity test.

**TABLE 5** Subgroup analysis of each skin type according to region

Type	Region	Included studies	Sample size	Prevalence (95% CI)	<i>p</i>	<i>ph</i>	<i>I</i> <sup>2</sup> (%)
Pernio-like lesions	Asian	4 studies	3983	0.001 (0.000–0.002)	0.077	0.408	0.0%
	Europe	3 studies	3253	0.010 (–0.001–0.020)	0.073	0.051	66.5%
	America	1 study	296	0.014 (0.000–0.027)	0.044	–	–
Maculopapular rash/ morbilliform exanthem	Asian	9 studies	4776	0.022 (0.011–0.032)	0.000	0.000	76.1%
	Europe	6 studies	3221	0.041 (0.014–0.069)	0.003	0.000	89.0%
	America	3 studies	1394	0.018 (–0.012–0.049)	0.236	0.003	83.0%
Urticaria	Asian	10 studies	5042	0.010 (0.005–0.015)	0.000	0.038	49.3%
	Europe	4 studies	3027	0.014 (–0.003–0.031)	0.110	0.094	53.1%
	America	1 study	1086	0.001 (–0.001–0.003)	0.317	–	–
Vesicular lesions	Asian	4 studies	1136	0.009 (0.004–0.015)	0.001	0.856	0.0%
	Europe	4 studies	3341	0.003 (0.001–0.005)	0.002	0.747	0.0%
	America	3 studies	1403	0.003 (0.000–0.006)	0.043	0.621	0.0%
Petechial lesions	Asian	4 studies	948	0.014 (0.006–0.021)	0.000	0.809	0.0%
	Europe	2 studies	519	0.006 (–0.001–0.012)	0.080	0.078	67.9%
	America	2 studies	317	0.032 (0.013–0.051)	0.001	0.317	0.0%
Livedoid lesions	Asian	1 study	507	0.014 (0.004–0.024)	0.008	–	–
	Europe	4 studies	3082	0.018 (–0.003–0.039)	0.085	0.015	71.5%
	America	–	–	–	–	–	–

Abbreviations: CI, confidence interval; *I*<sup>2</sup>, 0–25, no heterogeneity; *ph*, *p*-value of heterogeneity, *p*-value of Q-test for the heterogeneity test.

of COVID-19.<sup>51</sup> Thus, Seque suggests that it is associated with mild systemic conditions with low mortality.<sup>52</sup> Moreover, Pathania has reported that emotional stress related to COVID-19, rather than the infection itself, may trigger the urticaria.<sup>53</sup> The subgroup analysis of urticaria displayed that the prevalence of urticaria in America was obviously lower than in Asia and Europe, and the possible reason deserves further discussion.

The prevalence of pernio-like lesions is low. However, pernio-like lesions and vesicular lesions may represent the most common and characteristic skin manifestations of COVID-19, and the pernio-like lesions are very useful as epidemiological markers.<sup>40</sup> In addition, the proportion of severe and critical patients with pernio-like lesions is the lowest (0.00%) among the six types of skin manifestations, which is further explained that pernio-like lesions are more common in asymptomatic or mild patients. In the subgroup analysis of pernio-like lesions according

to region, the prevalence of them in Asia is significantly lower than in Europe and America, which is consistent with Tan et al.<sup>54</sup> study. One explanation of this phenomenon is that compared with Chinese and African populations, the frequency of minor allele that is related to antiviral cascade reaction is more common in white populations.<sup>55</sup>

In our study, the prevalence of vesicular lesions is the lowest among the six skin manifestations. Vesicular lesions are considered a specific pattern of skin lesion related to COVID-19, as they are not commonly seen in drug reactions.<sup>52</sup> Mohammed et al.<sup>36</sup> study indicates that vesicular lesions are associated with moderate COVID-19, which may be due to a direct cytopathic effect. Similarly, we did not observe the obvious distinction of prevalence among three regions. The skin manifestations in COVID-19 patients differ by race and country remains controversial, one most likely reason is racial differences or other geopolitical factors,<sup>56</sup> and the possible reasons deserve further discussion.

## 5 | IMPLICATIONS

Our study provides a more comprehensive, up-to-date assessment of currently available evidence. Specifically, this is an attempt to report distinct estimates of the prevalence of various skin manifestations in COVID-19 patients by meta-analysis.

## 6 | LIMITATIONS

Some limitations should be taken into consideration in our meta-analysis. First, most of the studies are aimed at hospitalized patients, excluding isolated outpatients, which may affect the evaluated prevalence of cutaneous manifestations. Second, some factors are as follows: cutaneous adverse drug reaction, other cutaneous diseases, and chance occurrence, which may have an impact on the evaluated prevalence and cannot be eliminated from our analysis. Besides, large heterogeneity was observed among studies as indicated by high  $I^2$  values. Finally, the funnel plots for each type of skin manifestation meta-analysis indicate publication bias, backed up by significant results on Egger's test, suggesting that there are small studies with negative results that have not been published.

## 7 | CONCLUSION

In conclusion, this meta-analysis provides pooled estimates of the prevalence in COVID-19 patients with skin manifestations. We conducted subgroup analysis due to the high level of heterogeneity, and found the severity of COVID-19 was probably the source of heterogeneity in our study. Meta-regression indicates that studies with a sample size <200 report higher prevalence estimates. There are six types of skin manifestations which are the most common among all skin manifestations. Prevalence of these skin manifestations from high to low is: maculopapular rash/morbilloform exanthem, livedoid lesions, petechial lesions, urticaria, pernio-like lesions, vesicular lesions. Different skin manifestations are related to the severity of the patient's condition. Among the six skin manifestations, petechial lesions and livedoid lesions are the most frequent in severe and critical COVID-19 patients. Furthermore, the prevalence rates of pernio-like lesions, urticaria and petechial lesions vary greatly in different regions. The highest prevalence of pernio-like lesions is in America, the lowest in Asia; Europe reported the highest prevalence of urticaria, America showed the smallest; petechial lesions' prevalence locates the first in America, Europe has the least of them. And the possible reasons need to be further explored.

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## CONFLICT OF INTEREST

None declared.

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