The Egyptian Journal of Hospital Medicine (July 2022) Vol. 88, Page 3916-3924

Dermatological Manifestations Associated with Covid-19 Patients in Elbagour General Hospital, El-Menoufia Governorate

Azza Gaber Antar Farag[1], Azza Zagloul labeeb[2], Marwa Abo El-Nour Gamal Amin[1], Mustafa Elsayed Elshaib[1], Nada Farag Elnaidany[3]

Dermatology, Andrology and STDs department[1] and Microbiology and Immunology department[2], Faculty of Medicine- Menoufia University, Egypt. Clinical Pharmacy department, Faculty of Pharmacy, MSA University[3], Egypt.

Corresponding author: Azza Gaber Antar Farag, **Mobile:** +201097787204,

Email: azzagaber92@yahoo.com, **ORCID**: 0000-0002-0333-5506

ABSTRACT

Background: Corona virus-19 disease (COVID-19) marked the beginning of a new pandemic COVID-19 after massive numbers of acute pneumonia with unknown origin. Some COVID-19 confirmed patients experienced some skin lesions that might be a clinical sign of COVID-19.

Objective: This study aimed to determine the diversity of skin lesions caused by COVID-19 in Elbagour Hospital admitted COVID-19 positive cases.

Methods: A prospective cohort study included patients from both sex who were COVID-19 confirmed and experienced skin lesions. 1020 patients having COVID-19 were examined. Out of them, 600 cases showed skin lesions. They were evaluated in El-Bagour General Hospital during the isolation period from March 2020 to March 2021. Dermatological examinations were done to assess skin lesions. The ABCD score was used to determine the severity of COVID-19 patients.

Results: We reported eight types of skin lesions in the form of pityriasis rosea like lesions (387; 63%), vesicular like exanthema (320; 53.3%), erythema multiform (298; 49.7%), petechiae (232; 38.7%), urticarial lesions (231; 38.5%), maculo-papules (220; 36.7%), livedo reticularis (84; 14%) and pseudo-chilblain (74; 12.3%). Presence of skin lesions were significantly associated with moderate and severe cases ($p < 0.05$). Livedo reticularis was significantly linked to a high mortality rate ($p < 0.001$).

Conclusion: Presence of skin lesions, as well as their number, onset and type were associated with COVID-19 prognosis. Presence of early (within the first 4 days) and more than 2 skin lesion types denoted disease severity. Moreover, livedo reticularis and maculo-papules warn against more disease severity, while presence of pseudo-chilblain points to moderate disease.

Keywords: COVID-19, SARS-COV-2, Skin lesions.

INTRODUCTION

COVID-19 marked the beginning of a new pandemic coronavirus disease 2019, which has been declared on 11th of March 2019 by World Health Organization (WHO) after massive numbers of acute pneumonia with unknown origin that have been reported [1]. COVID-19 is caused by beta subgroup of SARS family. It is well known for causing severe disease in lower respiratory tract and fecal-oral infectivity**.** COVID-19 virus is RNA virus having many glycoproteins including spike glycoprotein, nucleocapsid phosphoprotein, and small envelope glycoprotein. The spike glycoprotein (S) is critical for the viral entry and as an attractive antiviral target. While nucleocapsid phosphoprotein with vRNA are responsible for viral replication [2]**.**

A protease called transmembrane serine type 2 (TMPRSS2) in the host cell enhances viral uptake by slashing angiotensin converting enzyme-2 (ACE2) and activating the S protein of SARS-CoV-2, which controls coronavirus entry into host cells. ACE2 and TMPRSS2 are affirmed in target cells of the host, specifically epithelial cell type II cells [3]**.**

The main common symptoms that were reported caused by COVID-19 were fever, fatigue, cough, production of sputum, muscle aches, and lastly dyspnea; while other less common symptoms reported were diarrhea, olfactory, and gustatory dysfunction**.** Initially, there were no skin lesions reported among COVID-19 patients, however some patients who have been confirmed as COVID-19 patients experienced some skin lesions that might be a clinical sign of COVID-19. Types of lesions were noted as pityriasis rosea, petechiae, erythema multiform, urticarial lesions, maculo-papular like lesions, livedo reticularis, and pseudo-chilblain[4]**.**

Different viewpoints about the mechanism of COVID-19 inducing skin lesions have been proposed. SARS-CoV-2 strikes cells including nasal and bronchial epithelial cells, as well as pneumocytes (alveolar cells), through the viral structural S glycoprotein that binds to ACE2 receptor that was found on keratinocytes**.** Viral replication in the cells leads to direct cell injury, causing proinflammatory alarmins to be released (direct viral effect). Moreover, viral particles can activate the complement cascade and alveolar macrophages via the lectin pathway, resulting in innate immune responses [5]**.**

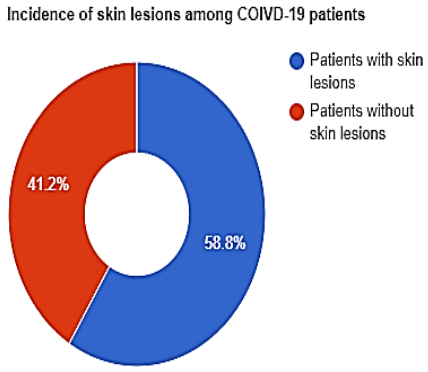
Received: 24/03/2022
Accepted: 23/05/2022

Complement initiation and divergent immune responses promote leukocyte recruitment, lymphocyte proliferation, and the massive production of proinflammatory cytokines such as interleukin [IL] 1B, IL-6, IL-8, interferon-gamma (IFN-gamma), and tumor necrosis factor alpha (TNF-alpha), among others. IFN stimulates macrophage activation and ferritin production, which may be attributed to the presence of acro-ischemic presentations (rather than chilblain-like lesions), necrosis, and also racemosa and livedo reticularis [6]. Furthermore, viral sepsis has been proposed as an explanation for the systemic and cutaneous changes accompanied with COVID-19 [7]. In the present study, we aimed to shed light on the diversity of skin lesions (its onset, types and numbers) associated with COVID-19 patients based on a suggested disease severity, and the case mortality.

PATIENTS AND METHODS

This was a prospective cohort study carried out on 1020 confirmed patients with COVID-19 during the isolation period from March 2020 to March 2021 at Elbagour Hospital. We included COVID-19 positive patients from both sexes and having different age groups. COVID-19 was diagnosed clinically and confirmed by a PCR analysis of nasopharyngeal swab.

The investigated patients were allocated to full history including personal history (age, sex, residence, and socioeconomic level) and present history including questions regarding any skin lesion and its onset [before or after 4 days of COVID-19] as well as its course and any associated symptoms as pruritis, pain, and burning. Past history of pervious systematic disease such as cancer, hypertension or chronic renal failure, chronic heart failure, chronic obstructive pulmonary disease (COPD), or diabetes Mellitus (DM) was noted. Assessment of vital signs and general examinations including heart rate, and respiratory rate were done.



A complete dermatological examination regarding skin, hair, nails and mucous membrane was performed. Skin lesions were evaluated considering their type (macule, papule, nodule, patches, and plague), site, and shape. Presence of scales, and scratch marks was recorded. Scalp examination for detection of hair falling, presence of scales and/ or erythema was done. Nail examination was also performed assessing its luster, and presence of any pigmentations, striations or pitting.

Laboratory investigations as complete blood count (CBC) (Hb, WBCs count, RBCs count, and platelets), C-reactive protein (CRP) and D-dimer were done. Also, chest X-ray and CT scan were undertaken.

For COVID-19 severity assessment, an ABCD was used [8, 9]. This score took into account the patient's age (50 years and older), lab tests (lymphocytopenia, leucopenia, LDH level, CRP level, D-dimer), chest imaging and CT-scan, dyspnea, and comorbidities (0 or 1). The highest score was 14 and the lowest score was 0. The score was divided into three categories: mild (0-4), moderate (4-8) and severe (> 8) **(Table 1).**

Table (1): Suggested COVID-19 severity score
CRP: C-reactive protein, LDH: lactate dehydrogenase, COPD: chronic obstructive lung disease, DM: diabetes mellitus, PR: pulmonary rehabilitation.

Study Variable	**Values**	**Score**	
		0	1
Age (Years)	Young, Elderly	0-50	>50
Blood Test	Leucopenia	No	Yes
	Lymphocytes (<1500 per mm3)	No	Yes
	CRP (>10 mg/L)	No	Yes
	LDH (>250 U/L)	No	Yes
	D Dimer (>0.5 mg/L)	No	Yes
Chest X-ray or CT	Ground glass & Bilateral patchy shadows	No	Yes
Comorbidities	COPD/smoker	No	Yes
	Cancer	No	Yes
	Hypertension & chronic heart failure	No	Yes
	Chronic renal disease	No	Yes
	DM	No	Yes
Dyspnea	PR > 30/minute	No	Yes
	O2 saturation < 90%	No	Yes
Total Score			

Ethical approval:

This work was conducted in accordance with the Code of Good Practice and the guidelines of Declaration of Helsinki, 7th revision, 2013 and being approved by the Medical Ethics Committee of the Faculty of Medicine, Menoufia University. Informed consent was obtained from each patient. In addition,

an official permission letter was obtained and sent to the Ministry of Health's undersecretary in Menoufia as well as the administrators at El-Bagour Hospital.

Statistical analysis

The data was coded, collected on an Excel spreadsheet, and processed on a laptop with SPSS 20. Descriptive statistics were represented by percentages (%) and numbers (n). To describe quantitative data, the terms median, range (minimum and maximum), mean, and standard deviation (SD) were used for qualitative data. Analytical statistics were performed using the Chi-square test to investigate the relationship between two qualitative variables. To compare two groups with quantitative variables that are not normally distributed, Mann Whitney U test was used and the Kruskal-Wallis test was used to compare groups with more than two quantitative variables that are not normally distributed. If $P \leq 0.05$, the difference was considered significant.

RESULTS

Personal and clinical characteristics of COVID-19 patients:

Figure 1: Incidence of COVID-19 patients.

The examined 1020 COVID-19 patients were 508 males and 512 females. Out of them, 600 (58.8%) patients reported skin lesions (Figure 1). The baseline characteristics and laboratory investigations were summarized in table (2)**.**

Table 2: Descriptive data of COVID-19 patients with skin lesions

Clinical characteristics	Total (n=1020)	patients with skin lesions (n=600)	Patients without skin lesions (n=420)	p-value
Age (years) Mean ± SD median range	 57.95 ± 16.23 59 2 months – 89 years	 57.96 ± 16.3 61 2 months - 89 years	 57.94 ± 16.18 60 6 years– 76 years	 0.986
Gender, n (%) Males Females	 508 (49.8%) 512 (50.1%)	 294 (49%) 306 (51%)	 215 (51.2%) 205 (48.8%)	 0.491
Comorbidities (at admission), n (%) HTN DM CKD Cancer COPD	 423 (41.4%) 217 21.2%) 225 (22%) 125 (12.2%) 165 (16.2%)	 262 (43.6%) 129 (21.5%) 123 (20.5%) 95 (15.8%) 105 (17.5%)	 161 (38.3%) 88 (20.9%) 102 (24.2%) 30 (0.7%) 60 (14.2%)	 **0.04*** 0.4 0.07 **<0.001*** 0.08
ABCD scoring, n (%) Mild Moderate Severe	 522 (51.1%) 304 (29.9%) 194 (19%)	 253 (42.2%) 203 (33.8%) 144 (24%)	 269 (64%) 101 (24%) 50 (12%)	 **<0.001*** **<0.001*** **<0.001***
Hb (gm/dl) mean ± SD median	 --	 10.81 ± 1.56 11	 10.65 ± 1.44 10.59-14	 0.098
WBCs (per mL) mean ± SD median	 --	 3.45 ± 0.44 3.60	 3.57 ± 0.34 3.6	 **<0.001***
Platelets (per mL) mean ± SD median	 --	 144.33 ± 8.76 149	 146.73 ± 6.58 149	 **<0.001***
TSB (mg/dL) mean ± SD median	 --	 1.34 ± 0.36 1.2	 1.2 ± 0.24 1.2	 **0.001***
D-Dimer (ng/mL) mean ± SD median range	 --	 0.87 ± 0.28 0.80.6-1.6	 0.8 ± 0.23 0.7	 **<0.001***
CRP (mg/L) mean ± SD median	 --	 46.56 ± 5.28 24	 34.46 ± 3.79 24	 **0.008***

SD: standard deviation, HTN: hypertension, DM: diabetes mellitus, CKD: chronic kidney disease, COPD: chronic obstructive pulmonary disease. Hb: hemoglobin, WBCs: white blood cells count, TSB: total serum bilirubin, CRP: C-reactive protein.
*Significant.

COVID-19 associated skin lesions:

In this study, we reported eight skin lesion types **(Figures 2-5)** associated with COVID-19 as follows: pityriasis rosea like lesions in 378 (63%) patients, vesicular like exanthema rash in 320 (53.3%) patients, erythema multiform in 298 (49.7%) patients, petechiae in 232 (38.7%) patients, urticarial lesions in 231 (38.5%) patients, maculo-papules in 220 (36.7%) patients, livedo reticularis in 84 (14%) patients, and pseudo-chilblain in 74 (12.3%) patients.

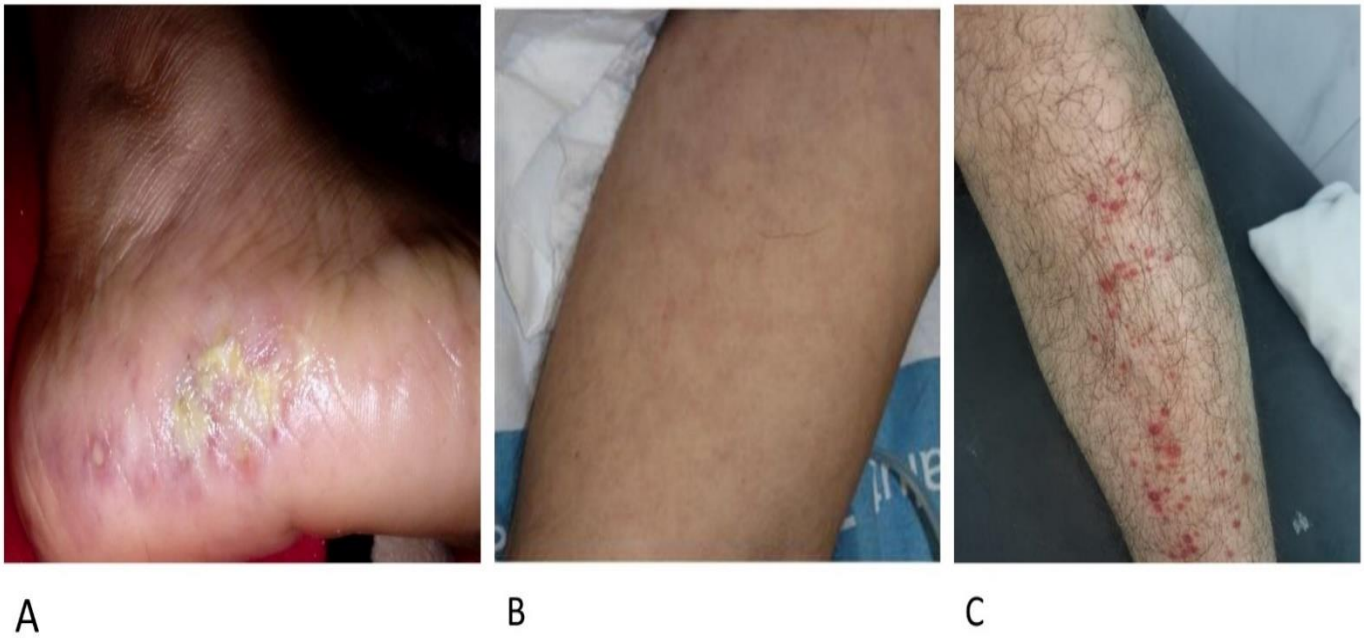


Figure 2: (A) pseudo-chilblain, (B) livedo reticularis and (C) petechiae.

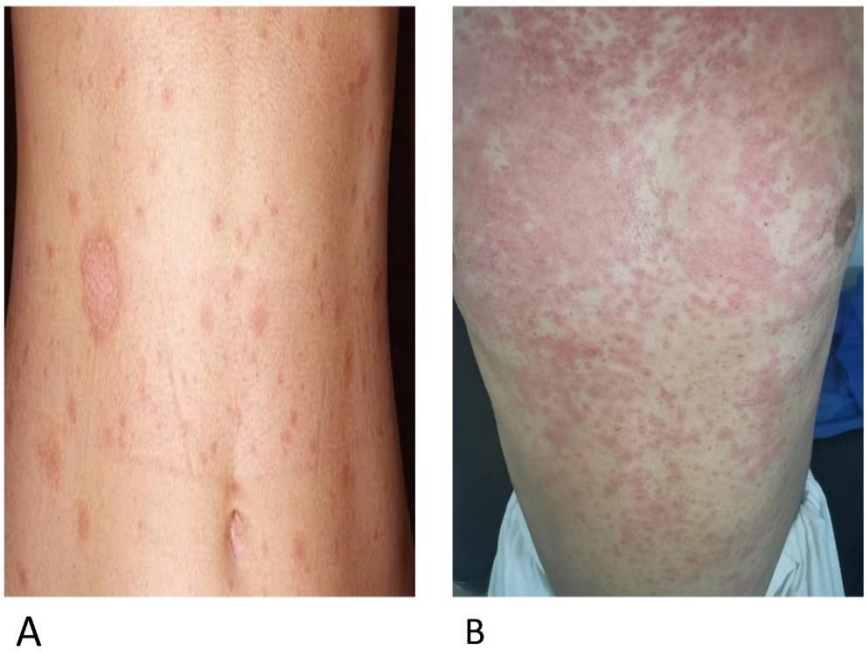


Figure 3: (A) Erythema multiform and (B) urticarial lesions.

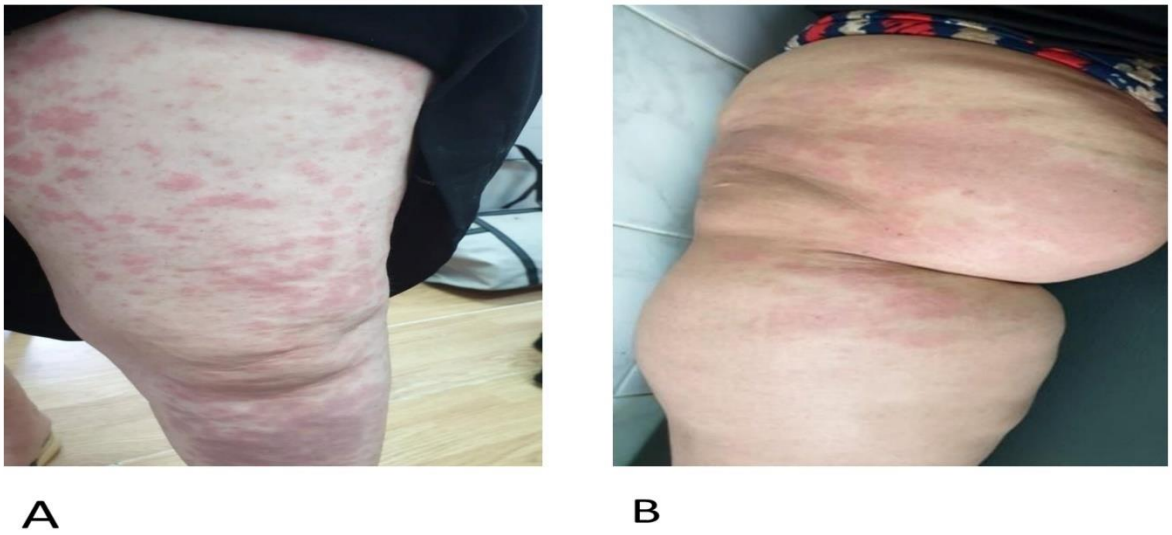


Figure 4: (A) pityriasis rosea and (B) maculopapular rash.

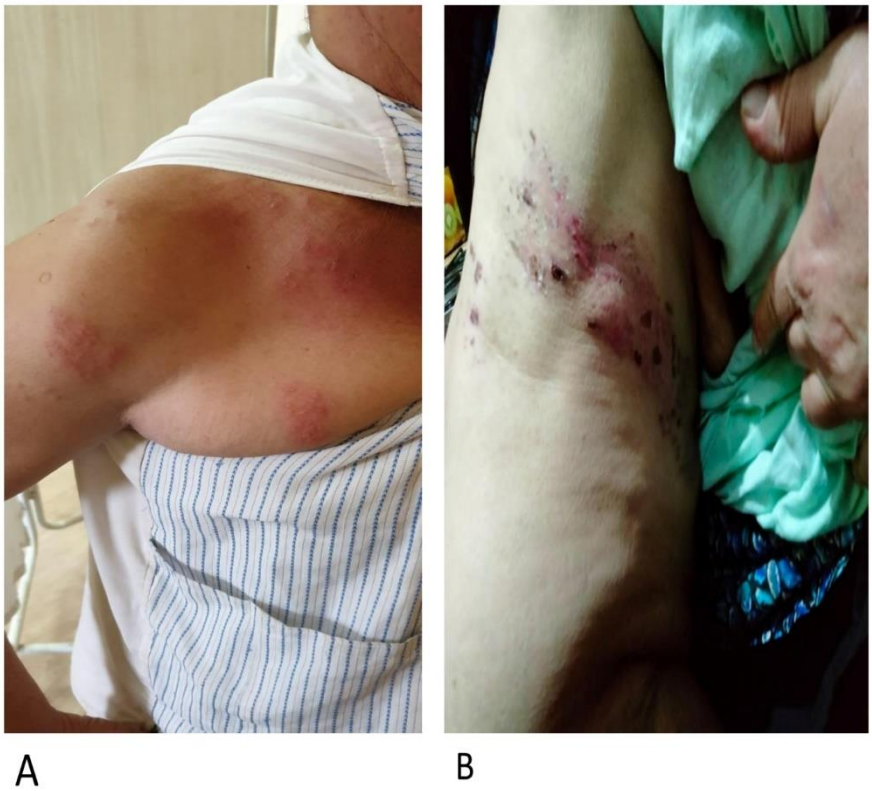


Figure 5: (A) male patient with herpes zoster and (B) female patient with herpes zoster

Table (3) showed that the common cutaneous symptoms associated with skin lesions in COVID-19 patients were pain, burning and pruritis showing variable percentages among skin lesions**.** The frequency of skin lesions associated with COVID-19 were mainly four types (222, 37%), followed by three (191, 31.8%), then five (92, 15.3%), two (50, 8.3%), six (33, 5.5%), seven (7, 1.2%), one (4, 0.7%), and eight (1, 0.2%) types. Concerning the association between types of skin lesions and their onset, livedo reticularis (84.5%) and pseudo-chilblain (67.6%) were significantly developed early (within 4 days) ($p < 0.001$). While pityriasis rosea like lesion was significantly developed after 4 days. However, varicella-like exanthema (52.2%), erythema multiform (50.7%), petechiae (51.3%) and urticarial lesions (53.2%) were insignificantly developed after 4 days

COVID-19 associated skin lesions in relation to patients' and COVID-19 criteria:

Livedo reticularis was significantly associated with older ages (p = 0.024) and male patients (p=0.005), while urticarial lesions were significantly found in female patients (p =0.017) (Table 3). Regarding distribution of skin lesions according to ABCD scoring, livedo reticularis and maculo-papules were significantly more associated with severe COVID-19 cases (54.8% and 44.4% respectively) than mild and moderate, while pseudo-chilblain was significantly more associated with moderate COVID- 19 cases (17.2%) (Table 3).

Table 3: Associated cutaneous symptoms with skin lesions in the studied COVID-19 patients

Variables	Livedo reticularis (n=84)	Pseudo-chilblain (n=74)	Vesicular like lesions (n=137)	Maculo-papular (n=220)	Petichea (n=232)	Urticarial lesions (n=231)	Erythema (n=244)	Pityriasis rosea like lesion (n=378)
Associated cutaneous symptoms	51 (84%)	48 (64%)	103 (75%)	163 (74%)	165 (71%)	185 (80%)	244 (82%)	333 (88%)
Pain Burning Pruritis	22 (42%) 17 (34%) 15 (29%)	32 (66%) 28 (58%) 21 (41%)	14 (13.5%) 22 (21.3%) 87 (84%)	50 (31%) 20 (12%) 124 (76%)	76 (46%) 59 (36%) 68 (41%)	13 (6%) 23 (11%) 56 (30%)	146 (60%) 141 (58%) 98 (40%)	163 (49%) 133 (40%) 87 (26%)
ABCD score Mild Moderate Severe	0 (0) 6 (3.0) 78 (54.8)	0 (0) 35 (17.2) 39 (7.1)	142 (56.1) 102 (50.2) 76 (52.8)	96 (37.9) 60 (29.6) 64 (44.4)	97 (38.3) 81 (39.9) 54 (37.5)	98 (38.7) 72 (35.5) 61 (42.4)	125 (49.4) 102 (50.2) 71 (49.3)	167 (66) 120 (59.1) 91 (63.2)
Lesion onset 1-4 days >4 days p-value	71 (84.5) 13 (15.5) **<0.001***	50 (67.6) 24 (32.4) **<0.001***	153 (47.8) 167 (52.2) 0.11	110 (50.0) 110 (50.0) 1	113 (48.7) 119 (51.3) 0.43	108 (46.8) 123 (53.2) 0.051	147 (49.3) 151 (50.7) 0.63	177 (46.8) 201 (53.2) **0.01***
Age mean± SD t-test p-value	61.68±14.15 2.26 0.024	60.14±14.74 1.23 0.22	58.34±16.90 0.61 0.54	58.39±15.28 0.49 0.624	57.25±16.50 0.84 0.4	58.58±16.81 0.74 0.642	58.68±16.42 1.08 0.282	57.80±16.32 0.31 0.757
Gender, n (%) Male Female χ^2 p-value	53 (18.0) 31 (10.1) 0.77 **0.005***	36 (12.2) 38 (12.4) 0.01 0.949	156 (53.1) 164 (53.6) 0.02 0.896	101 (43.4) 119 (38.9) 1.33 0.249	115 (39.1) 117 (38.2) 0.05 0.825	99 (33.7) 132 (43.1) 5.67 **0.017***	151 (51.4) 147 (48.0) 0.66 0.416	189 (64.3) 189 (61.8) 0.41 0.523
Outcome, n (%) Discharged Dead χ^2 p-value	34 (40.5) 50 (59.5) 57.05 **<0.001***	42 (56.8) 32 (43.2) 13.05 **<0.001***	98 (71.5) 39 (28.5) 0.56 0.454	15 (69.1) 68 (30.9) 4.35 **0.037***	174 (75.0) 58 (25.0) 0.2 0.567	167 (7.3) 64 (27.7) 0.57 0.451	225 (75.5) 73 (24.5) 0.7 0.404	278 (73.5) 100 (26.5) 0.11 0.74

Regarding the relationship between skin lesion onset and COVID-19 severity, there was a significant relationship between disease severity and the onset of skin lesions in COVID-19 cases, where the more COVID-19 severity the earlier the skin lesion. Most lesions in severe (120; 83.3%) and moderate cases (129; 63.5%) developed within 1- 4 days in COVID-19 course, while most lesions in mild cases (214; 84.6%) developed after 4 days ($p < 0.001$).

There was a significant higher mortality rate in patients with livedo reticularis ($p < 0.001$). On the other hand, there were significant lower mortality rates in patients having pseudo-chilblain and maculo-papules ($p < 0.001$ and 0.037 respectively) (Table 4).

Table 4: The onset and number of skin lesions in relation to severity of the disease in the studied COVID-19 patients.

Onset of skin lesions	ABCD scoring groups			χ^2	P- value
	Mild (n=253) No (%)	Moderate (n=203) No (%)	Severe (n=144) No (%)		
Lesion onset (days):					
1-4	39 (15.4)	129 (63.5)	120 (83.3)	199.31	**<0.001**
> 4	214 (84.6)	74(36.5)	24 (17.7)		
Number of lesions					
≤ 2	22 (8.7)	28 (13.8)	4 (2.8)	12.53	**0.002**
> 2	219 (86.5)	185 (91.1)	140 (97.2)		

DISCUSSION

Out of 1020 patients admitted to Elbagour general hospital, 600 patients (58.8%) had skin lesions, and 420 hadn't any skin lesions. However, **Tan *et al.*** [10] reported that the prevalence of skin lesions was 0.2% in China, 7.25% in India, and 20.4% in Italy. The difference among these studies and ours (58.87%) can be attributed to our study design as we followed up our patients up to 21 days. During this relatively long period, multiple skin lesions were reported. Livedo reticularis were reported around day 2, urticarial lesions, pseudo-chilblain and varicella like lesions were observed around day 5, and pityriasis rosea like lesions developed around day 7.

COVID-19 associated skin lesions can be allocated into two categories, either inflammatory exanthemas or vascular lesions [11]**. Freeman *et al.*** [12] reported multiple skin lesions accompanied with COVID-19 disease. The authors observed that the most commonly reported lesion were maculopapular eruptions (44%), followed by pernio-like acral lesions (18%), urticarial lesions (16%), macular erythema (13%), vesicular eruption (11%), vasculitic pattern (7.1%), livedo reticularis (6.4%), and retiform purpura (6.4%). Recently, **Genovese *et al.*** [13] reported main six clinical patterns of skin lesions including the confluent erythematous/ maculopapular/morbilliform rash (45.5%), chilblain-like acral pattern (28.9%), urticarial rash (16.7%), and purpuric "vasculitic" pattern (15.4%). varicella like exanthema (9%), and livedo reticularis/racemosa-like pattern (3.5%)**.**

In present study, we reported eight skin lesion types accompanied with COVID-19 as pityriasis rosea like lesions which was the most common (63%), followed by vesicular like exanthema (53.3%), erythema multiform (49.7%), petechiae (38.7%), urticarial lesions (38.5%), maculo-papules (36.7%), livedo reticularis (14%) and pseudo-chilblain (12.3%). The differences in skin lesions percentage between the current study and others might be attributed to socio-economic factors and environmental factors. As high spread of COVID-19 pandemic was proven to be in much cold areas. Additionally, racial or genetic factors could have a role in ACE2 change expression. Many factors, including age, gender, ethnicity, taking medication, and several co-morbidities, such as metabolic syndrome and cardiovascular disease, have been linked to both altered ACE2 expression and severity of COVID-19 and progression [13]**.**

As previously reported [14]**,** we recognized cutaneous symptoms associated with skin lesions as pain, burning and pruritis. The highest prevalence associated symptoms were reported in 88% of patients with pityriasis rosea like lesions, in 84% of patients with livedo reticularis and in 82% in patients with erythema multiform

In the present study, livedo was more commonly seen in older patients (median age was 57 years). In accordance with this result, **Galvan *et al.*** [15] noticed that livedoid lesions are seen in elderly patients as these lesions were complications resulted from vascular occlusion, as COVID-19 has been linked to coagulation changes and vascular damage in the elderly.

As we observed, **Jamshidi *et al.*** [14] reported that urticaria-like lesions were more commonly seen among females and vascular lesions were more commonly seen in males. This finding could be attributed to a gender difference in immune response to infections, which has been proposed as a possible factor, as well as other contributing factors such as severity of underlying comorbidities and smoking history, which cannot be ruled out [15]**.**

Based on ABCD scoring system, 253 (42.2%), 203 (33.8%) and 144 (24%) of the current studied patients (n=600) were classified as mild, moderate and severe cases respectively. It was found that livedo reticularis and maculo-papules were significantly associated with severe than mild and moderate COVID-19 cases. The molecular mechanisms of livedoid are thought to be affected by COVID-19 severity. Livedoid eruptions could be attributed to disseminated intravascular coagulopathy (DIC) and macrothromboses in more severe infections [16]**.** Hyperactive immune responses (particularly IL6) can attribute to the

induction of a "cytokine storm" in severe COVID-19 cases. These cytokines can enter the skin and activate dermal dendritic cells, macrophages, lymphocytes, mast cells, and neutrophils, assisting in the development of lesions like maculopapular rash [17, 18].

In the current study, pseudo-chilblain was significantly more associated with moderate COVID- 19 cases. However, **Askin *et al.*** [19] concluded that pseudo-chilblain lesions have been accompanied with a greater severity of COVID-19 infection. Development of COVID-19 associated pseudo-chilblain was attributed to increased interferon (IFN) concentrations that was released early in the course of COVID-19, inducing antiviral effect and suppressing the uncontrolled release of diverse pro-inflammatory cytokines (less severe disease) [20]. On the other hand, endothelial damage caused by the virus, as well as an obliterative microangiopathy and coagulation abnormalities in the severe form of COVID-19, were also proposed as mechanisms involved in the development of pseudo-chilblain [21].

Regarding rash onset, it varies between studies. The majority are seen after the onset of systemic symptoms, with only a few cases indicating onset prior to systemic symptoms [22]. In this study, skin lesions that significantly developed within 1- 4 days of the disease were livedo reticularis and pseudo-chilblain. On the other hand, pityriasis rosea like lesions significantly developed later (> 4 days) in the disease courses. In line with this result, **Askin *et al.*** [19] concluded that pseudo-chilblain lesions onset is typically after the onset of COVID-19 systemic symptoms. However, **Tan *et al.*** [10] conducted that pseudo-chilblain appeared in the later stage of the disease as it was very subtle and asymptomatic, so it was unnoticed by patients and reported later (more than 4 days). Additionally, COVID-19 associated pseudo-chilblain is mediated through IFN release that's generated as early [19] or as delayed [21] responses.

Maculopapular rash, pityriasis rosea and urticarial rash developed late (> 4 days) during course of COVID-19 infection [22]. These lesions could be the result of an allergic response to pharmacological COVID-19 drugs or an overproduction of cytokines caused by hyperinflammation [23], and all need time to induce these lesions.

The current study reported a wide range frequency of skin lesions among COVID-19 cases where four skin lesions were reported in 222 (37%) patients followed by three lesions (191; 31.8%) and then five lesions (92; 15.3%). To our knowledge, no other studies had mentioned the frequency of multiple skin lesions in COVID-19 patients. Therefore, further studies to investigate frequency of skin lesions among COVID-19 patients are recommended.

In the present study, it was observed that development of skin lesions early (within the first 4 days) in the course of COVID-19 as well as presence of more than 2 types of skin lesions denoted severe form of the disease. The presence of viral particles in the cutaneous vascular system causes lymphocytic vasculitis and induces release of cytokine, leading to the development of cutaneous lesions in COVID-19 cases. Viral particles can form immune complexes with cutaneous lymphocytes and Langerhans cells, resulting in the release of IL-1, INF-, and TNF-, as well as the recruitment of eosinophils, CD8+ cytotoxic T cells, B cells, and natural killer (NK) cells, all of which can lead to lymphocytic thrombophilic arteritis [24]. Therefore, we suggested that presence of multiple skin lesions early in COVID-19 may be an indicator of major vascular and immunological disorders that may notify and warn against development of severe form of COVID-19.

In this study, the mortality rate was reported in 156 (26%) COVID-19 patients with skin lesions. A higher mortality rate was significantly linked to presence of livedo reticularis lesion, which was accompanied with severe form of COVID-19 disease as well as old age. While, there were lower mortality rates in those having pseudo-chilblain and maculo-papules, as both lesions were accompanied with less severe form of COVID-19.

In line with these findings, **Jamshidi *et al.*** [14] reported that the patients with vascular skin lesions had the highest mortality rate (18.2%). However, the authors found that the overall mortality rate among COVID-19 patients with skin lesions was 4.5%. We reported a higher mortality rate compared to others, as most of our patients were admitted and mainly having moderate and severe form of COVID-19.

CONCLUSIONS

COVID-19 confirmed patients develop high percentage of cutaneous manifestations that are of variable types. The most common skin lesions among COVID-19 positive patients were pityriasis rosea like lesions, followed by vesicular like exanthema and erythema multiform. The common cutaneous symptoms associated with skin lesions in COVID-19 patients were pain, burning and pruritis. Presence of skin lesions, as well as their number, onset and type were associated with COVID-19 prognosis. As presence of more than 2 types and early (within the first 4 days) denoted disease severity. Moreover, livedo reticularis and maculo-papules warned against more disease severity, while presence of pseudo-chilblain pointed to moderate disease.

Financial support and sponsorship: Nil.
Conflict of Interest: Nil.

All authors have read and approved the manuscript.

REFERENCES

1. **World Health Organization (2020):** Coronavirus disease 2019 (COVID-19) Situation Report 51 [Internet]. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200311-sitrep-51-covid-19.pdf?sfvrsn=1ba62e57_10
2. **Zhao X, Li J, Niu P *et al.* (2020):** Genomic characterization and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancelot, 395 (10224): 565-574.
3. **Zhangfu F, Fang Y, Kang W *et al.* (2020):** Clinical characteristics of coronavirus pneumonia 2019 (COVID-19): an updated systematic review. https://doi.org/10.1101/2020.03.07.20032573.
4. **Lam T, Jia N, Zhang Y *et al.* (2020):** Identifying SARS-CoV-2-related coronaviruses in Malayan pangolins. https://doi.org/10.1038/s41586-020-2169-0
5. **Xue X, Mi Z, Wang Z *et al.* (2021):** High Expression of ACE2 on Keratinocytes Reveals Skin as a Potential Target for SARS-CoV-2.doi:10.1016/j.jid. 2020.05.087
6. **Mancia G, Rea F, Ludergnani M *et al.* (2020):** Renin-Angiotensin-Aldosterone System Blockers and the Risk of Covid-19. https://doi.org/10.1056/NEJMoa2006923
7. **Tang N, Li D, Wang X *et al.* (2020):** Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. https://doi.org/10.1111/jth.14768
8. **Salunke A, Warikoo V, Kumar S *et al.* (2020).** A proposed ABCD scoring system for better triage of patients with COVID-19: Use of clinical features and radiopathological findings. https://doi.org/10.1016/j.dsx.2020.08.019.
9. **Nandy K, Salunke A, Pathak K *et al.* (2020):** Coronavirus disease (COVID-19): a systematic review and meta-analysis to evaluate the impact of various comorbidities on serious events. Diabet Metab Syndr., 14 (5):1017–1025.
10. **Tan W, Tam C, Oh C (2021):** Skin manifestations of COVID-19: A worldwide review. https://doi.org/10.1016/j.jdin.2020.12.003.
11. **Rongioletti F (2020):** SARS-CoV, Mers-CoV and COVID-19: what differences from a dermatological viewpoint? https://doi.org/10.1111 /jdv.16738
12. **Freeman E, McMahon E, Lipoff B *et al.* (2020):** The spectrum of COVID-19-associated dermatologic manifestations: An international registry of 716 patients from 31 countries. https://doi.org/10.1016/j.jaad.2020.06.1016
13. **Genovese G, Moltrasio C, Berti E *et al.* (2021):** Skin Manifestations Associated with COVID-19: Current Knowledge and Future Perspectives. doi: 10.1159/000512932
14. **Jamshidi P, Hajikhani B, Mirsaeidi M *et al.* (2021):** Skin Manifestations in COVID-19 Patients: Are They Indicators for Disease Severity? A Systematic Review. Front in Med., 8: 15.
15. **Galván C, Català A, Carretero G *et al.* (2020):** Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. Br J Dermatol., 183: 71–77.
16. **Castelnovo L, Capelli F, Tamburello A *et al.* (2020):** Symmetric cutaneous vasculitis in COVID-19 pneumonia. https://doi.org/10. 1111/jdv.16589
17. **Shams S, Rathore S, Anvekar P *et al.* (2021):** Maculopapular skin eruptions associated with Covid-19: A systematic review. https://doi.org/10.1111/dth.14788
18. **Kolivras A, Dehavay F, Delplace D *et al.* (2020):** Coronavirus (COVID-19) infection-induced chilblains: A case report with histopathologic findings. https://doi. org/10. 1016/j.jdcr.2020.04.011
19. **Askin O, Altunkalem N, Altinisik D *et al.* (2020):** Cutaneous manifestations in hospitalized patients diagnosed as COVID-19. DOI: 10.1111/dth.13896.
20. **Cappel A, Cappel A, Wetter A (2021):** Pernio (Chilblains), SARS-CoV-2, and COVID Toes Unified Through Cutaneous and Systemic Mechanisms. doi: 10.1016/j. mayocp. 2021.01.009.
21. **Recalcati S, Barbagallo T, Frasin A *et al.* (2020):** Acral Cutaneous Lesions in the Time of COVID-19. J Eur Acad Dermatol Venereol., 34 (8): 346-7
22. **Singh H, Kaur H, Singh K *et al.* (2021):** Cutaneous Manifestations of COVID-19: A Systematic Review. https://doi.org/10.1089/wound.2020.1309
23. **Türsen Ü, Türsen B, Lotti T (2020):** Cutaneous sıde-effects of the potential COVID-19 drugs. https://doi.org/10.1111/dth.13476
24. **Gianotti R, Zerbi P, Dodiuk-Gad P (2020):** Clinical and histopathological study of skin dermatoses in patients affected by COVID-19 infection in the Northern part of Italy.https://doi.org/10.1016/j.jdermsci.2020.04.007.