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Cutaneous Manifestations of Covid-19 Infection in Patients at AlKufra Hospital

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Abstract:

Introduction: The outbreak of severe acute respiratory syndrome caused by coronavirus 2 turned into a huge pandemic and resulted in a worldwide panic with global economic and political impacts. The disease affects lungs as well as other organs including skin and mucous membranes.

Aim of the study: To study the pattern of Cutaneous disorders among Libyan patients with active COVID 19 infection.

Patients and methods: We included eighty-nine patients with COVID-19 infection in Al-Kufra hospital. Laboratory investigations done.

Result: The mucocutaneous manifestations detected in the present study in 28.1% of cases, 10.1% had maculopapular rash, 6.7%had urticarial like lesion, 3.4%had puerperal rash, 3.4% chilblains, 2.2%had vesicular lesion, 1.1% had erythema multiforme and 1.1% had livedo. Regarding the outcome of the disease in 89 patients with total hospital admission range from 2-14 day, 6.7% died, 10.1% need dialysis, 11.1% need ventilation, 10.1% had acute kidney injury, 4.5% transferred to ICU. None of the analyzed associations showed a statistically significant result.

Conclusion: Maculopapular rash and urticarial like lesions are most frequent skin manifestations among COVID 19 patients in Al-Kufra hospital. Skin lesions should be considered as indicators for serious viral infections in dermatology practice.

Keywords: AlKufra Hospital; Covid-19; Patients

1.1. INTRODUCTION

The outbreak of severe acute respiratory syndrome caused by coronavirus 2 (SARS-CoV-2) turned into a huge pandemic emerged from Wuhan, China in late December 2019 and resulted in a worldwide panic with global economic and political impacts. [1]

World Health Organization (WHO) given the disease the name of coronavirus disease 2019 (COVID-19) and declared the outbreak as a pandemic on 11 March 2020.[2]

Coronaviruses is a member of the order Nidovirales in the family coronaviridae. Coronavirinae and Torovirinae are subfamilies of this order. Coronavirinae can be further divided into four genera: Alpha, Beta, Gamma and Delta coronavirus. [3]

Coronaviruses are enveloped, 80–220 nm in size, pleomorphic but mostly spherical, and carry characteristic and large (20 nm long) club-shaped spikes (trimers spike protein). The combination of nucleocapsid (N) protein with the genomic RNA forms the helical nucleocapsid that is surrounded by a viral membrane (M) protein which are composed of icosahedral structures. Some coronaviruses often have a second peripheral short (5 nm long) spikes (hemagglutinin-esterase (HE) protein), which is a peculiar feature of certain betacoronaviruses. Coronaviruses genome is linear positive- sense, infectious, single-stranded RNA 5′ capped and 3′ polyadenylated, the biggest known non-segmented RNA viral genomes (27.6–31 kb). However, the overall organization of the genomes is similar. [4]

Maintaining such a large CoV genome may be linked to the unique features of the CoV replication transcription complex (RTC), which contains many RNA processing enzymes such as the non-structural protein 14's (nsp14's) 3′–5′ exoribonuclease. The 3′–5′ exoribonuclease is unique to CoVs in all RNA viruses and is likely to provide an RTC proofreading function. [5 – 7]

The major virion proteins include a nucleocapsid protein (N, 50–60 kDa) and several envelope proteins; the spike glycoprotein trimer (S, 180–220 kDa per monomer), a triple-spanning transmembrane protein (M, 23–35 kDa) and a minor transmembrane protein (E, 9–12 kDa), which together with the M protein is essential for coronavirus virion assembly and budding. Cellular immune responses are generated primarily against the S and N proteins. The 5′-terminal two thirds of the genome include two open reading frames (ORFs), 1a and 1b, that together encode all non-structural proteins for the formation of the RTC, whereas the 3′- proximal third encodes the structural and accessory proteins. [8]

The transmission of SARS-CoV-2 is mainly through virus-containing respiratory droplets or by contaminated objects and has an incubation period varies between 2 and 14 days, with an average of 5 days. [9, 10]

The mechanism of SARS-CoV-2 infection depends on the binding of the S protein of the virus to a receptor that is a metallopeptidase called Angiotensin- converting enzyme 2 (ACE2). Researchers had identified this receptor as the functional receptor for SARS-CoV-2 and had localized it in almost all human organs such as oral and nasal mucosa, nasopharynx, lung, stomach, small intestine, colon, skin, lymph nodes, thymus, bone marrow, spleen, liver, kidney, and brain. [11, 12]

The full spectrum of COVID-19 presentations and its association with disease severity is still unclear. The symptoms of fever, cough, chills, dyspnea, myalgia, and sore throat are the most common clinical presentations of COVID-19 and as time goes on, there are a wealth of different other manifestations have been reported. [13]

As skin is not an exception from the target organs in COVID-19, the cutaneous involvement as patterns and lesions have been described as potential manifestations of COVID-19. [14 – 16]

The main cutaneous changes reported to date include viral exanthems and maculopapular rash, vesicular lesions, urticaria-like lesions, as well as vasculopathy or vasculitis-associated–like skin. [14 – 18]

Vasculitis-associated–like skin lesions typically appear weeks after systemic symptom onset and include livedo, acral cyanosis, chilblains, purpura. [19 – 27]

Some of these skin manifestations arise before the signs and symptoms more commonly associated with COVID-19, suggesting that they could be presenting signs of COVID-19. [28]

Moreover, COVID-19 vaccine can provoke a spectrum of immune reactions that may manifest in skin lesions. They vary from de novo to flare of pre-existing dermatosis. These reactions may be divided according to their cytokine profiles, based on the preponderance of specific T-cell subsets. Reactions may mimic those caused by the natural infection or can involve other immune mediated and inflammatory conditions like erythema multiform or psoriatic like lesions, especially in vulnerable individuals. [29]

However, the link between skin manifestations and the severity of the disease remains debatable. Due to the great variety of reported dermatologic presentations as well as the inconsistency of data. In addition, very few studies have investigated the cutaneous manifestations of COVID 19 infection and none published from Libyan data up to the time of submitting this proposal.

1.2. AIM OF THE STUDY

1. To study the pattern of mucocutaneous manifestations of active COVID 19 infection among Libyan patients at AlKufra hospital during the period from 1st February 2021 to 31 August 2021.
2. To compare our results with previous studies

REVIEW OF LITERATURE

2.1. Coronavirus

Classification and structure:

The outbreak of severe acute respiratory syndrome caused by coronavirus 2 (SARS-CoV-2) turned into a huge pandemic emerged from Wuhan, China in late December 2019 and resulted in a worldwide panic with global economic and political impacts.[1]

The novel coronavirus disease-2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is an animal and a human pathogen. The disease originated in Wuhan City, China, and then spread to the rest of the world. [30]

COVID- 19 is member of sarbecovirus sub- genus, beta- coronavirus, belongs to Coronaviridae family. Coronaviridae family is a large group of viruses affecting animal and human their structure is based on a single- stranded RNA. COVID- 19 closely related (88%) with two bats- derived SARS- like coronaviruses from Zhoushan, China in 2018. Anyhow; a bit less concordant with SARS- CoV (79%) and MERS- CoV (50%). [31]

Similar to other coronaviruses, COVID- 19 has four structural proteins spike(S); membrane (M); envelope (E) and nucleocapsid (N). S protein has close resemblance with angiotensin- converting enzyme 2 (ACE- 2) receptor on human cells and was confirmed as a receptor for SARS- CoV- 2, that is, COVID-19. [32]

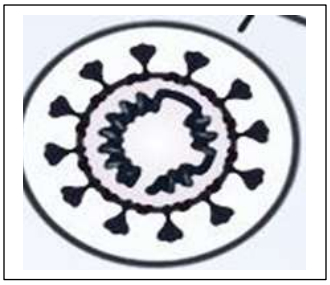

Figure 1: The morphology and structure of SRAS –CoV-2. [33]

2.2.Coronavirus disease-2019 (COVID-19):

The chief features of the disease are as follows: (1) a high viral-multiplying capacity, (2) an extensive spread leading to a high prevalence, (3) being a newly discovered novel disease, there are no standardized treatment regimens until recently, and (4) a high mortality rate in some communities. The disease may present as mild, moderate, or severe in terms of the severity of presentation. The mild disease may be characterized by symptoms such as body aches, coughs, or mild fever, while in its moderate form the disease may present with mild pneumonia along with other symptoms. [34]

Clinical manifestations of COVID -19 infection:

Pulmonary manifestations are most well-known because these cases are critical, difficult to manage, and have poor outcomes. The severe form of the disease presence may be characterized by severe pneumonia and hypoxia. Critical cases with significant hypoxia and organ failure may need admission to the intensive care unit (ICU) and mechanical ventilation support. Besides the symptomatic cases, asymptomatic cases have also been reported. [2, 35 – 38]

Pulmonary manifestations in COVID-19 may be mild, moderate, and severe. Mild cases such as upper respiratory tract infection (URTI), cough, or sore throat can progress to moderate and severe degrees. The moderate type of pulmonary presentation of COVID-19 could be pneumonia and fever. The COVID-19 pneumonia type has been reported in some cases as silent pneumonia with fever or silent pneumonia in a sick patient. [39 - 42]

Due to the rapid spread of the disease worldwide, many countries were forced to close their borders and impose internal lockdowns to curb the spread. With an incubation period of 14 days, the symptoms can be detected ~4–5 days after exposure. [34, 36]

Currently, the mortality rate due to the disease is ~2–5% according to the community, but it may reach as high as 7% as observed in Italy. [43 – 45]

Severe and critical forms can be easily identified based on the presence of SARS symptoms and confirmed with chest radiography. [34, 37]

Extrapulmonary manifestations of COVID-19 are common in moderate and mild cases and may also occur together with pulmonary manifestations or in severe infection cases, with multiple complications. The mild and moderate forms may have non-specific symptoms such as fever, gastroenteritis, vomiting, dysgeusia (loss of taste), and headache with no or mild respiratory symptoms. Knowledge of these extrapulmonary manifestations can help in detecting the mild and moderate forms, which can aid in early diagnosis, and rapid quarantining can prevent community spread. [46]

The extrapulmonary features may include any organ with ACE 2 receptors and include; gastroenteritis (small intestine); insomnia, dysgeusia, and headache (brainstem, cerebral cortex, and hypothalamus, respectively), high blood pressure, and tachycardia (heart and blood vessels, respectively), and some skin infections (basal epidermis). ACE2 receptors may be present in the retina and other eye tissues, leading to conjunctivitis when infected. [47, 48]

Transmission and spread:

Coronavirus disease-2019 spreads through physical contact and inhalation of infected droplets or air. It then invades the airway epithelium, where the viral load is increased by replication. Pyroptosis occurs by the leaking of the virus from the upper respiratory tract vasculature into the bloodstream, which then travels to other target organs that have ACE2 receptors. This process induces a T-cell-mediated inflammatory response, which releases interleukins and cytokines. This cytokine storm may lead to the development of ARDS. [49, 50]

Determinants of disease severity:

Many factors can determine the severity of COVID-19, including viral load, genetic factors, presence of comorbidities, age, sex, use of immune-suppressive agents, and immunity. Some authors believe that genetic factors also play a role in the severity of COVID-19 because the ACE2 receptor gene has multiple polymorphisms, which means that there are multiple variations in the relationship between SARS-CoV-

2 and ACE2 receptor according to ethnicity and gene form. This difference in a relationship can explain the severity of the disease in a specific race than others. [51, 52]

People with comorbidities such as diabetes mellitus, hypertension, chronic obstructive pulmonary disease (COPD), chronic lung disease, chronic kidney disease, cancer, and low immunity may have a greater affinity for severe infections and serious complications of COVID-19. [39]

Role of the cytokine storm:

The cytokine storm is a physiological immunological reaction by the innate immune system can cause an excessive release of proinflammatory cytokines such as interleukins and cytokines. It occursin COVID -19 and may contribute to acute respiratory distress and multiple organ failure by immune-mediated reactions against the body tissue and organs. Acute kidney injury (AKI), ARDS, myocarditis, skin manifestations, ocular manifestations, and neurological manifestations of COVID-19 may occur due to the cytokine storm. [53, 54]

Cardiovascular Manifestations of COVID-19:

Many cardiac manifestations have been reported in COVID-19 cases such as arrhythmias, hypertension, palpitations, myocarditis, myocardial injuries, cardiomyopathies, sudden cardiac death and heart failure. [55]

Gastro-enteric Manifestations:

The COVID-19 patient may present with loose motion, anorexia, nausea, vomiting, abdominal pain, epigastric pain, liver injury, and pancreatic injury. Elevated levels of liver enzymes including ALT, AST, and alkaline phosphatase have been reported. In addition, high levels of lipase and amylase were reported in some patients with COVID-19. [56, 57]

Renal Manifestations:

The most important renal manifestation of COVID-19 is acute kidney injury (AKI). Some studies have shown an increased risk of mortality in COVID-19 patients who have AKI to a greater extent than the other patients who have normal kidney function. Haematuria and proteinuria were reported as renal complications of COVID-19. [58 - 60]

The Neurological Manifestations:

The neurological manifestations of COVID-19 may be central or peripheral symptoms. The central nervous symptom manifestations may be headaches, dizziness, ischaemic stroke, intracranial hemorrhage, encephalitis, seizures, loss of smell (dysgeusia), or insomnia. Peripheral nervous manifestations may include neuropraxia, ophthalmoplegia, ataxia, loss of tendon reflex, Miller Fisher syndrome, and Guillain– Barre syndrome. Acute transverse myelitis with hypotonia has been reported in some patients with COVID-19. [61 – 64]

Psychiatric Manifestations:

Coronavirus disease-2019 has two categories of psychological manifestations. The first is psychiatric symptoms because of isolation and quarantine, and this type is frequent and showed depression, anxiety, sleeping disorders, eating disorders, somatizations, and phobias. The second category is the psychiatric disorder because of the effect of COVID-19 itself (SARS-CoV-2 in the brain tissue). This type may be rare but was documented in a case series study for some patients with COVID-19 who developed psychosis in Spain. [65, 66]

Mucocutaneous manifestations of COVID-19:

Some authors mention the basal layer of the skin as the location of ACE2 receptors in the human body. [67]

The cutaneous manifestations of COVID-19 may appear as erythema maculopapular redness, skin rash, and erythema. Some of the quarantine patients experienced skin erythema after a few days of quarantine. One study showed that COVID-19 patients presented with skin rash and erythema. Skin manifestations of COVID-19 may present before respiratory symptoms. [68 – 73]

Skin manifestations of COVID-19 are reported as primary manifestations of COVID-19, also reported as late manifestations in patients in isolation and quarantine. The pathophysiological process may be the

primary effect of SARS-CoV-2 on ACE2 in the basal layer of the skin, or secondary to the cytokine storm effect, or drug reaction used in COVID-19 management. Genetic factors may have a role in the appearance of the dermatological feature of COVID-19. The dermatological manifestations of COVID-19 are reported in mild, moderate and severe cases of COVID-19. [72, 73]

Endocrinology Manifestations of COVID-19:

Some observational studies have shown abnormalities in thyroid function in COVID-19 patients. COVID-19 is a cause of ketosis in non-diabetes patients and may also create a high risk for diabetic keto acidosis (DKA) in diabetes patients. In addition, the pancreatic injury was reported in 19 cases, and amylase and lipase levels were elevated. Adrenal insufficiency may occur as secondary adrenal insufficiency in COVID-19 patients because of pituitary hypofunction. Primary adrenal insufficiency is reported because of a thrombotic cause and it is a sign of worsening in ARDS. The unexplained body aches in COVID-19 patients may result from a defect in the hypothalamus–pituitary–adrenal axis, which leads to defective production of ACTH, causing secondary adrenal insufficiency. [74, 75]

Some studies have reported that testosterone levels decreased in COVID-19 patients, while the luteinizing hormone (LH) levels increased. Therefore, the T: LH ratio may decrease in COVID-19 patients. [76]

Coagulopathy Manifestations:

Angiotensin-converting enzyme-2 has receptors on endothelial cells, indicating that SARS-CoV-2 has a direct effect on endothelial integrity that can induce VTE disease, which can cause deep vein thrombosis (DVT) and pulmonary embolism (PE). [77]

Laboratory Manifestations of COVID-19:

Many studies showed some changes in blood test results as abnormal values in COVID-19 patients. The studies recorded decreased lymphocyte and platelet counts and increased lactate dehydrogenase (LDH), D-dimer, prothrombin time PT, C-reactive protein (CRP), G6PD, and ferritin. [78]

Musculoskeletal Manifestations:

Generalized bone ache and muscle pain were reported in COVID-19 patients. Rhabdomyolysis was reported in a COVID-19 patient with high CK and AKI. [79, 80]

COVID-19 Manifestations and Diagnosis:

Coronavirus disease investigations may involve laboratory or radiological investigations. Laboratory investigations include diagnostic studies such as the detection of SARS-CoV-2 RNA, antigen, or antibodies. Other laboratory tests may include leukopenia, leucocytosis, lymphopenia, increased LDH levels, high ferritin levels, unexplained ketosis, and high D-dimer levels. [81]

The CT scan is a diagnostic tool for COVID-19, which reveals a bilateral ground-glass appearance that discovers silent pneumonia or the cause of silent hypoxia in many patients with COVID-19. The common feature of COVID-19 on a CT scan is the bilateral ground appearance; however, COVID-19 features may appear on CT as follows: bilateral peripheral patches, bilateral reticular opacity, bilateral congestion or vascular thickness, unfrequented pleural effusion (reported), and lymphadenopathy. However, the American College of Radiology recommends avoiding the use of CT as a screening tool to diagnose COVID 19, which should be used only for hospitalized patients. Other studies have reported the effectiveness of CT scans in diagnosing asymptomatic COVID-19 patients. [82, 83]

An X-ray can be used to diagnose COVID-19 patients, as the X-ray findings in COVID-19 pneumonia are bilateral infiltration, patches, or glass-ground appearance.

2.3.Relevant research:

In a systematic review by Jamshidi P et al (2021); out of 381 articles, 47 met the inclusion criteria and a total of 1,847 patients with confirmed COVID-19 were examined. The overall frequency of cutaneous manifestations in COVID-19 patients was 5.95%. The maculopapular rash was the main reported skin involvement (37.3%) commonly occurred in middle-aged females with intermediate severity of the disease. Forty-eight percentage of the patients had a mild, 32% a moderate, and 20% a severe COVID-19 disease. The mild disease was mainly correlated with chilblain-like and urticaria-like lesions and

patients with vascular lesions experienced a more severe disease. Seventy-two percentage of patients with chilblain-like lesions improved without any medication. The overall mortality rate was 4.5%. Patients with vascular lesions had the highest mortality rate (18.2%) and patients with urticaria-like lesions had the lowest mortality rate (2.2%). [85]

According to Gallman AE et al (2021); many skin manifestations of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection reflect activation of cutaneous and systemic immune responses involving effector pathways of both the innate and adaptive arms of the immune system. This article reviews evidence from the recent clinical and scientific literature that informs the current understanding of the consequences of coronavirus disease 2019 (COVID-19)–induced immune cell activation, as relevant to dermatology. Topics include the clinical consequences of autoantibody production in patients with COVID-19, immunologic evidence for chilblains as a manifestation of SARS-CoV-2 infection, and the relationship between type I interferons and COVID-19 disease severity .[86]

Zhang Q.et al (2020) and Bastard Pet al (2020) described chilblains as one of the few clinically apparent signs of a robust type I IFN response which is associated with SARS-CoV-2 infection. The patients with severe COVID-19 infection are more likely to have disruptions in their type I IFN pathway, this suggests that this axis is one of the major determinants of how an individual's immune system interacts with SARS-CoV-2. [87, 88]

Elrobaa IH and New KJ. (2021) found that a patient with COVID-19 may be either asymptomatic or symptomatic. Symptomatic cases may have either pulmonary or extrapulmonary manifestations. Pulmonary manifestations occur as mild, moderate, or severe cases. In mild and moderate cases, extrapulmonary manifestations such as gastroenteritis, fever, or vomiting may present alone. Some of these cases may be missed for diagnosis, and the patient may receive symptomatic treatment without a COVID-19 diagnosis, leading to increased spread of the infection. Extrapulmonary manifestations may occur in severe and critical cases as complications of severe infections (high viral overload) or the cytokine storm, such as in acute kidney injury (AKI), heart failure (HF), and venous thromboembolic (VTE) manifestation. [89]

Skin manifestations of COVID-19 Macular popular rash, skin rash and Erythema are reported as primary manifestations of COVID-19, also reported as late manifestations in patients in isolation and quarantine. The pathophysiological process may be the primary effect of SARS-CoV-2 on ACE2 in the basal layer of the skin, or secondary to the cytokine storm effect, or drug reaction used in COVID-19 management. Genetic factors may have a role in the appearance of the dermatological feature of COVID-19. The dermatological manifestations of COVID-19 are reported in mild and moderate cases of COVID-19.[89]

According to Recalcati S. (2020); the incidence of cutaneous manifestations exceeded the rate of 20%. [90]

Skin rashes and purpuric plaques are an interesting clinical presentation of classical coronavirus infections. The first report of the cutaneous manifestations was reported from Italy, where 20.4% (18/88) hospitalized COVID-19 patients developed an erythematous rash (14), widespread urticaria (3), and chickenpox-like vesicles (1) distributed in the trunk area. [89]

Guan W.et al (2020) found in severe cases that erythematous rash, and localized or widespread urticarial rashes seem to be the most common cutaneous manifestation whereas in China only 0.2% (2/1099) confirmed COVID-19 cases had skin rashes [91]

Fernandez-Nieto D et al (2020) had reported a skin biopsy of a 32-year-old woman from France with COVID-19 having urticariform rash with perivascular infiltration of lymphocytes, eosinophils, and upper dermal edema on histopathology. Urticaria (1.4%) is also reported as cutaneous symptoms.[92]

According to Marzano AV et al (2020); a rare COVID-19 associated varicella- like papulovesicular exanthem was first observed in Italian patients by Marzano et al. Lesions were varied from scattered to diffuse with vesicular predominance in 12 (54.5%) patients with trunk and limbs involvement generally appearing 3 days after systemic symptoms. Fever, cough, headache, weakness, coryza, dyspnea, hyposmia, and hypogeusia were common systemic symptoms reported. However, SARS-CoV-2

detection in skin lesional was not performed but still represents a useful clue to suspect COVID-19 in asymptomatic patients. [93]

Joob Wiwanitkit V (2020) described a dengue-like petechial rash with thrombocytopenia in a COVID-19 patient from Thailand.[94] Estébanez A et al (2020) published a report describing an unusual skin manifestations like confluent erythematous-yellowish papules on both heels of a 28- year-old COVID-19 infected woman with symptoms of diarrhea, ageusia, and anosmia has been reported. [95]

According to Joob B and Wiwanitkit Vet al (2020), in a few COVID-19 patients, atopic dermatitis, and psoriasis has been aggravated as pre-existing skin disease. They presented an 84-year-old woman with arterial hypertension history having COVID-19 related bilateral pneumonia, later developed mild pruriginous rashes in the peri-axillary area and coalescing macules in flexural regions. Thus, various studies have reflected the possibilities of potential skin lesions of COVID-19. [96]

Regarding associations, Patrick MT et al (2021) stated that; skin conditions, including psoriasis and atopic dermatitis, increase the risk of COVID-19 (odds ratio, 1.55; P <0.001) but decrease the risk of mechanical ventilation (odds ratio, 0.22; P <0.001). They observed significant overlap in gene expression between the infected normal bronchial epithelial cells and inflammatory skin diseases, such as psoriasis and atopic dermatitis. For genes that are commonly induced in both the severe acute respiratory syndrome coronavirus 2 infection and skin diseases, there are 4 S100 family members located in the epidermal differentiation complex, and we also identified the "IL-17 signaling pathway" (P <0.001) as one of the most significantly enriched pathways. Furthermore, a shared genome-wide significant locus in the epidermal differentiation complex was identified between psoriasis and severe acute respiratory syndrome coronavirus 2 infection, with the lead marker being a significant expression quantitative trait locus for S100A12 (P <0.001). [97]

González F.G et al (2021) proposed a pathophysiological hypothesis based on the interpretation of various clinical manifestations related to COVID-19, dividing these expressions into two categories: (i) Those manifestations that are mainly based on the direct viral cytopathic effect on cells of the organism such as keratinocytes, including in this group maculopapular, urticaria and chickenpox-like eruptions; (ii) those manifestations due to changes in specific white blood cells, T lymphocytes, and macrophages, such as secondary infection with uncontrolled overexpression of cytokines (stage of cytokine storm). In turn, the latter group will be subdivided into: (a) Dermatological manifestations with features such as macrophage activation syndrome including acral ischemia, gangrene, petechiae/purpura; (b) liveoid lesions, which are associated with high patient morbidity and mortality; and (c) cutaneous manifestations due to activation of an early response to type I interferon (IFN-1), including chilblain- like lesions. [98]

Fernandez-Nieto D et al (2020), found that vesicular lesions are mostly located on the trunk and to a lesser extent on the extremities: diffuse pattern eruptions tend to affect more than one body area, palms of the hands, and soles of the feet; localized pattern lesions tend to affect the central area of the body. Also, 58.3% presented mild symptoms of the disease without requiring hospitalization and 41.7% developed pneumonia. Among them, only 4.2% required admission to the intensive care unit (ICU) and all patients survived.[99]

Jindal R and Chauhan P (2020) and Conforti C et al (2020) found that maculopapular-erythematous eruptions have the highest prevalence (40–70%) of the cutaneous manifestations associated with SARS-CoV-2, including (a) erythematous eruptions 38.5%, (b) maculopapular eruptions 18.3%, (c) macular erythema 6.8%, and (d) papulo-squamous eruption (2%). [100, 101]

According to Rekhtman S et al (2021); the prevalence of petechiae/purpura rashes is 4% in COVID-19 patients who did not require hospitalization [46] while in hospitalized patients the prevalence of purpura was 25.7% [47] These eruptions are frequent in middle-aged and elderly adults and without significant differences between sexes [102]

Rekhtman S et al (2021) found that 66.7% of patients with purpura were mechanically ventilated. [102]

Galván Casas C et al (2020) reported prevalence of acral ischemia is 6%. [103] These lesions are frequent

in elderly patients and in those with severe SARS- CoV-2 disease and up to 80% may require mechanical ventilation [103]

Jimenez-Cebrian A et al (2021) defined liveoid lesions as "lesions with a reticulated pattern of slow blood flow, with consequent blood desaturation and bluish skin discoloration". An incidence of 6% is reported during the first peak of the epidemic in Spain in April 2020. [103]

Liveoid lesions are common in older or elderly adults with more severe SARS- CoV-2 infections and with no significant differences between sexes. [104] Fernández-Lázaro D et al (2021) described the prevalence of urticaria with respect to all dermatological manifestations associated with COVID-19 is variable, ranging between 7% and 40%, depending on the general condition of the patient. [105]

Regarding the prevalence by sex and age; according to Algaadi S.A. (2020) Abuelgasim E et al (2021) found overall rate of 64% in women and 36% in men, urticarial rash is more frequent in middle-aged people between 45 and 65 years. Those differences were not significant. [106, 107]

PATIENTS AND METHODS

Subjects

This is a case series design study. Eighty-nine (89) adult patients (older than 18 years) of either sex, with confirmed COVID 19 infection (by Polymerase chain reaction; PCR) attending to Al Kufra hospital, from 1st February 2021 to 31 August 2021, were included in the present study.

Exclusion criteria

1. The critically ill patients who are unconscious or unable to communicate.
2. Patients younger than 18 years.
3. Patients who were not willing to participate in the study.

Methods

Verbal informed consent was obtained from all participants after simplified explanation of the nature of the study. Detailed case history of each patient with special attention to cutaneous lesions was taken. Detailed dermatological examination was performed.

Statistical analysis

Data were analyzed using statistical package for social science (SPSS) version 23. Regarding numerical variables, the appropriate test was used to check homogeneity of the distribution with normal distribution. Descriptive statistics as mean, standard deviation and median were estimated. Inferential statistics: were applied as needed. Student t test (or Mann-Whitney U test) was used to find the difference between the means of the groups, and Chi-square (X^2) to find the difference in the distribution of the categorical variables between the groups. *P*-value was considered significant when ≤ 0.05. Data were presented in form of tables and figures. The figures were generated using Microsoft Excel 2010

4. RESULTS

4.1. Demographic characteristics:

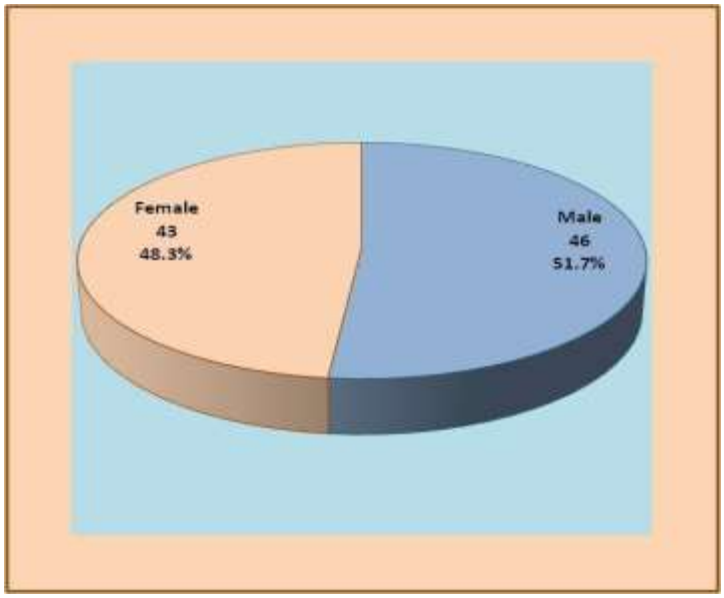

Figure 2: Distribution of the study population according to gender.

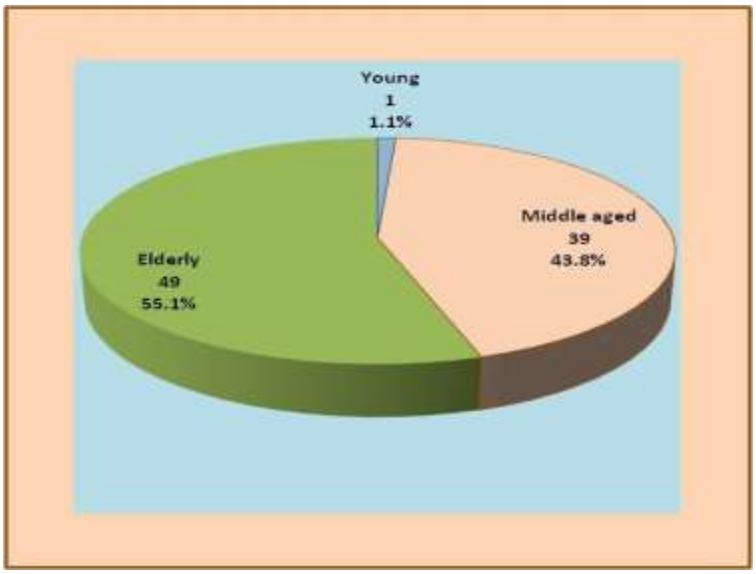

Figure 3: Distribution of the study population according to age category
Age: Range: 42 – 82, Mean ±SD: 63.62 ±10.444, Median: 66.00.

4.2. Co-morbid conditions and health background:

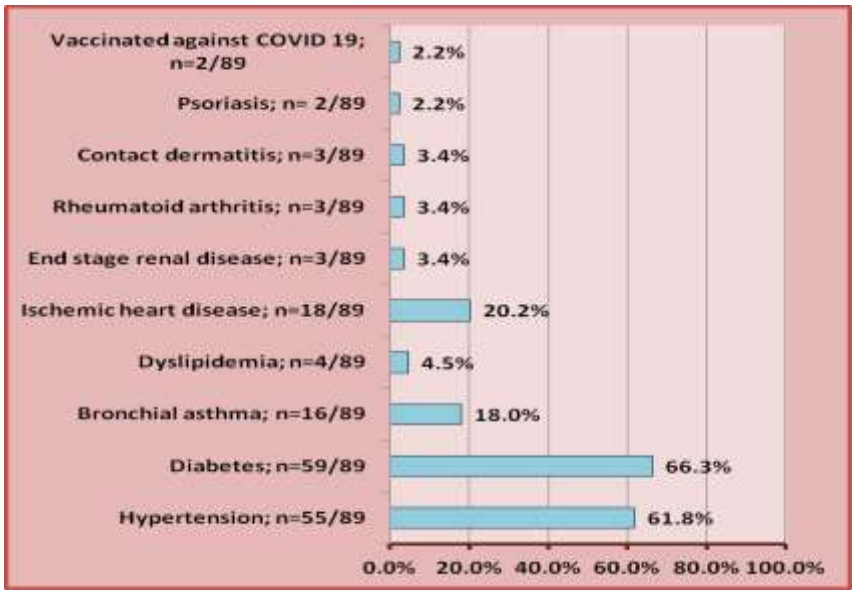

Figure 4: Rates of health conditions across the study population

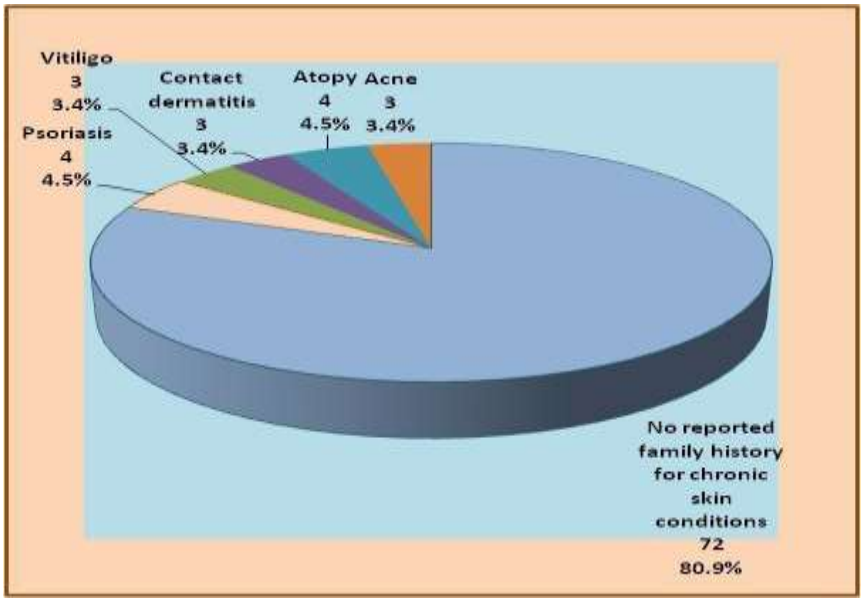

Figure 5: Distribution of the study population according to reported family history for skin disorders

4.3.Clinical and laboratory characteristics of the study population:

Table 1: Parameters of selected clinical and laboratory measurements during admission

Characteristic	Range	Mean ±SD	Median
Days from symptoms to admission	2 - 9	5.28 ±1.617	5.00
Lowest reported O2 saturation	55.0% - 92.0%	85.9% ±7.66%	8.8%
Highest reported temperature	38.0 - 40.0	39.017 ±0.365	39.0
Lowest Platelet count	120 - 470	261.06 ±79.458	260.00
Highest D dimer level	700 - 10000	3028.76 ±2210.201	2500.00
Highest S. Ferritin level	170 - 740	364.84 ±133.983	350.00

4.4.Cutaneous manifestations detected:

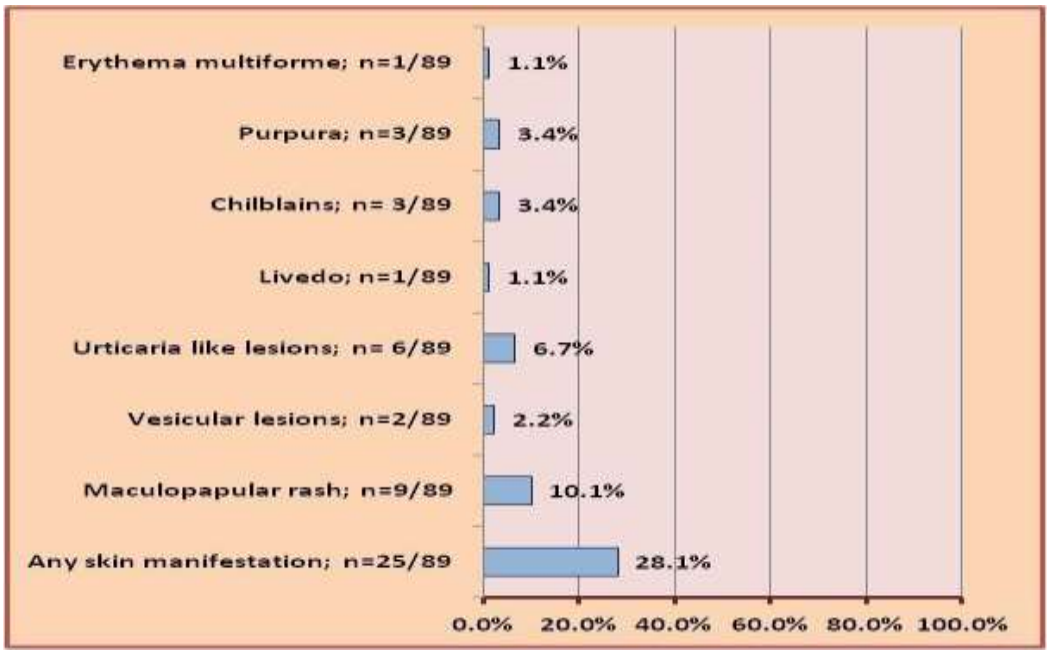

Figure 6: Rates of skin manifestations among the study population.

4.5.Outcomes of the disease:

Total days in hospital Range: 2 – 14 Mean ±SD: 10.04 ±2.412 and a Median of 10 days.

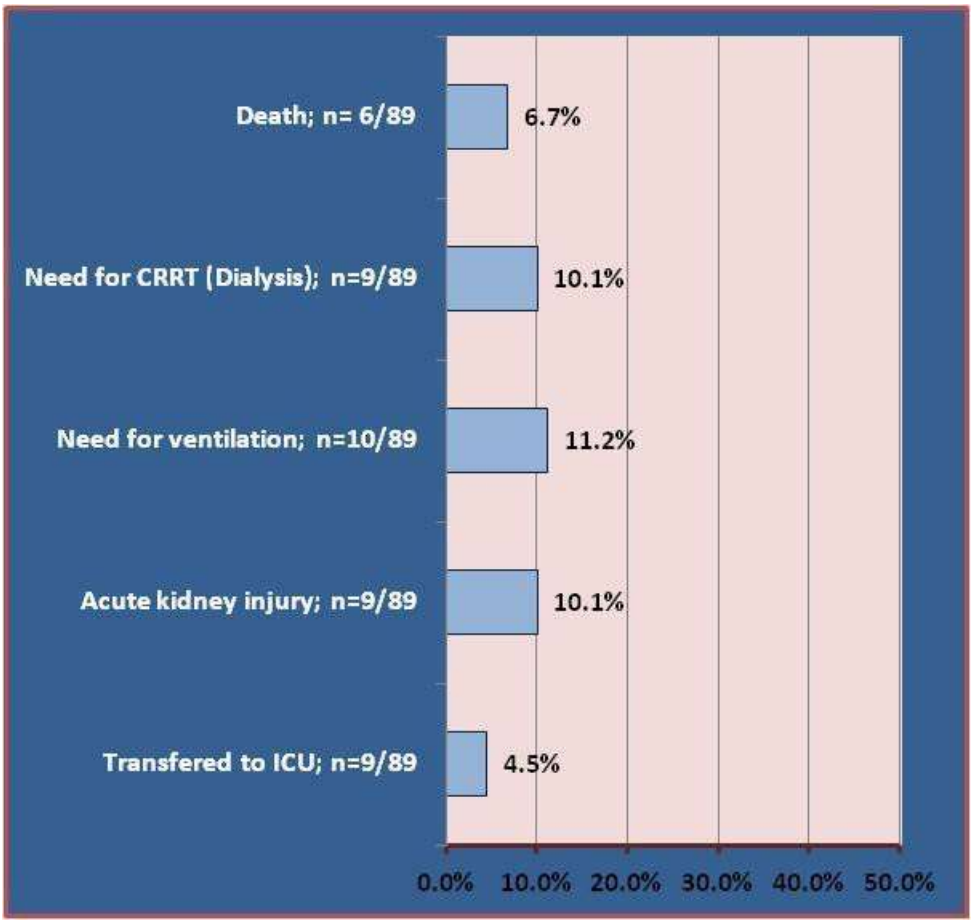

Figure 7: Rates of different outcomes across the study population

4.6.Analysis of associations of skin manifestations:

Background and demographic factors and observing any skin condition. Table 2 shows the analysis of the association between demographic and co morbid conditions of the patients in the study population with presence of any skin manifestations.

Tables 3 – 8 show the analysis of the association between demographic and co morbid conditions of the patients in the study population with specific skin manifestations.

None of the analyzed associations showed a statistically significant result.

Table 2: Factors and co-morbidities associated with presence of any skin lesion among COVID 19 patients

Factor		Any skin manifestation detected		*X*2	*P*
		N	%		
Gender	Male	12	26.1%	0.189	0.664
	Female	13	30.2%		
Age group	Elderly	16	32.7%	1.124	0.289
	Young and middle aged	9	22.5%		
Vaccine against COVID 19	Vaccinated	0	0.0%	-*	1.000
	Not	25	28.7%		
Psoriasis	Yes	0	0.0%	-*	1.000
	No	25	28.7%		
Contact dermatitis	Yes	2	66.7%	-*	0.189
	No	23	26.7%		
Rheumatoid arthritis	Yes	0	0.0%	-*	0.556
	No	25	29.1%		
ESRD	Yes	1	33.3%	-*	1.000
	No	24	27.9%		
IHD	Yes	5	27.8%	0.001	0.974
	No	20	28.2%		
Hypertension	Yes	14	25.5%	0.495	0.482
	No	11	32.4%		
DM	Yes	13	22.0%	3.178	0.075
	No	12	40.0%		
Bronchial asthma	Yes	5	31.3%	-*	0.765
	No	20	27.4%		
Dyslipidemia	Yes	0	0.0%	-*	0.573
	No	25	29.4%		
Family history of skin disease	Yes	5	29.4%	-*	1.000
	No	20	27.8%		

Fisher exact test applied. N = number of cases. COVID 19 = coronavirus disease 2019. ESRD = end stage renal disease. IHD = ischemic heart disease. DM = diabetes mellitus.

Table 3: Factors and co morbidities associated with presence of maculopapular rash among COVID 19 patients

Factor		Maculopapular rash		*X*2	*P*
		N	%		
Gender	Male	5	10.2%	-*	1.000
	Female	4	10.0%		
Age group	Elderly	6	13.0%	-*	.487
	Young and middle aged	3	7.0%		
Vaccine against COVID 19	Vaccinated	0	0.0%	-*	1.000
	Not	9	10.3%		
Psoriasis	Yes	0	0.0%	-*	1.000
	No	9	10.3%		
Contact dermatitis	Yes	1	33.3%	-*	.277
	No	8	9.3%		
Rheumatoid arthritis	Yes	0	0.0%	-*	1.000
	No	9	10.3%		
ESRD	Yes	1	33.3%	-*	.277
	No	8	9.3%		
IHD	Yes	2	11.1%	-*	1.000
	No	7	9.9%		
Hypertension	Yes	4	7.3%	-*	.294
	No	5	14.7%		
DM	Yes	4	6.8%	-*	.158
	No	5	16.7%		
Bronchial asthma	Yes	2	12.5%	-*	.662
	No	7	9.6%		
Dyslipidemia	Yes	0	0.0%	-*	1.000
	No	9	10.6%		
Family history of skin disease	Yes	2	11.8%	-*	0.680
	No	7	9.7%		

Fisher exact test applied. N = number of cases. COVID 19 = coronavirus disease 2019. ESRD = end stage renal disease. IHD = ischemic heart disease. DM = diabetes mellitus.

Table 4: Factors and co morbidities associated with presence of vesicular rash among COVID 19 patients

Factor		Vesicular rash		*X*2	*P*
		N	%		
Gender	Male	0	0.0%	-*	0.231
	Female	2	4.7%		
Age group	Elderly	2	4.7%	-*	0.499
	Young and middle aged	0	0.0%		
Vaccine against COVID 19	Vaccinated	0	0.0%	-*	1.000
	Not	2	2.3%		
Psoriasis	Yes	0	0.0%	-*	1.000
	No	2	2.3%		
Contact dermatitis	Yes	0	0.0%	-*	1.000
	No	2	2.3%		
Rheumatoid arthritis	Yes	0	0.0%	-*	1.000
	No	2	2.3%		
ESRD	Yes	0	0.0%	-*	1.000
	No	2	2.3%		
IHD	Yes	0	0.0%	-*	1.000
	No	2	2.8%		
Hypertension	Yes	2	3.6%	-*	0.522
	No	0	0.0%		
DM	Yes	1	1.7%	-*	1.000
	No	1	3.3%		
Bronchial asthma	Yes	0	0.0%	-*	1.000
	No	2	2.7%		
Dyslipidemia	Yes	0	0.0%	-*	1.000
	No	2	2.4%		
Family history of skin disease	Yes	0	0.0%	-*	1.000
	No	2	2.8%		

Fisher exact test applied. N = number of cases. COVID 19 = coronavirus disease 2019. ESRD = end stage renal disease. IHD = ischemic heart disease. DM = diabetes mellitus.

Table 5: Factors and co morbidities associated with presence of Urticaria like lesion among COVID 19 patients

Factor		Urticaria like lesions		X2	P
		N	%		
Gender	Male	3	6.5%	-*	1.000
	Female	3	7.0%		
Age group	Elderly	3	6.1%	-*	1.000
	Young and middle aged	3	7.5%		
Vaccine against COVID 19	Vaccinated	0	0.0%	-*	1.000
	Not	6	6.9%		
Psoriasis	Yes	0	0.0%	-*	1.000
	No	6	6.9%		
Contact dermatitis	Yes	1	33.3%	-*	0.191
	No	5	5.8%		
Rheumatoid arthritis	Yes	0	0.0%	-*	1.000
	No	6	7.0%		
ESRD	Yes	0	0.0%	-*	1.000
	No	6	7.0%		
IHD	Yes	0	0.0%	-*	0.341
	No	6	8.5%		
Hypertension	Yes	3	5.5%	-*	0.671
	No	3	8.8		
DM	Yes	3	5.1%	-*	0.401
	No	3	10.0%		
Bronchial asthma	Yes	1	6.3%	-*	1.000
	No	5	6.8%		
Dyslipidemia	Yes	0	0.0%	-*	1.000
	No	6	7.1%		
Family history of skin disease	Yes	3	17.6%	-*	0.081
	No	3	4.2%		

Fisher exact test applied. N = number of cases. COVID 19 = coronavirus disease 2019. ESRD = end stage renal disease. IHD = ischemic heart disease. DM = diabetes mellitus.

Table 6: Factors and co morbidities associated with presence of livedo among COVID 19 patients.

Factor		Livedo		X2	P
		N	%		
Gender	Male	1	2.0%	-*	1.000
	Female	0	0.0%		
Age group	Elderly	1	2.2%	-*	1.000
	Young and middle aged	0	0.0%		
Vaccine against COVID 19	Vaccinated	0	0	-*	1.000
	Not	1	1.1%		
Psoriasis	Yes	0	0	-*	1.000
	No	1	1.1%		
Contact dermatitis	Yes	0	0	-*	1.000
	No	1	1.2%		
Rheumatoid arthritis	Yes	0	0	-*	1.000
	No	1	1.2%		
ESRD	Yes	0	0	-*	1.000
	No	1	1.2%		
IHD	Yes	1	5.6%	-*	0.202
	No	0	0.0%		
Hypertension	Yes	1	1.8%	-*	1.000
	No	0	0.0%		
DM	Yes	1	1.7%	-*	1.000
	No	0	0.0%		
Bronchial asthma	Yes	0	0.0%	-*	1.000
	No	1	1.4%		
Dyslipidemia	Yes	0	0.0%	-*	1.000
	No	1	1.2%		
Family history of skin disease	Yes	0	0.0%	-*	1.000
	No	1	1.4%		

Fisher exact test applied. N = number of cases. COVID 19 = coronavirus disease 2019. ESRD = end stage renal disease. IHD = ischemic heart disease. DM = diabetes mellitus.

Table 7: Factors and co morbidities associated with presence of chilblains among COVID 19 patients

Factor		Chilblains		*X*2	*P*
		N	%		
Gender	Male	1	2.2%	-*	0.608
	Female	2	4.7%		
Age group	Elderly	2	4.1%	-*	1.000
	Young and middle aged	1	2.5%		
Vaccine against COVID 19	Vaccinated	0	0.0%	-*	1.000
	Not	3	3.4%		
Psoriasis	Yes	0	0.0%	-*	1.000
	No	3	3.4%		
Contact dermatitis	Yes	0	0.0%	-*	1.000
	No	3	3.5%		
Rheumatoid arthritis	Yes	0	0.0%	-*	1.000
	No	3	3.5%		
ESRD	Yes	0	0.0%	-*	1.000
	No	3	3.5%		
IHD	Yes	1	5.6%	-*	0.497
	No	2	2.8%		
Hypertension	Yes	1	1.8%	-*	0.555
	No	2	5.9%		
DM	Yes	1	1.7%	-*	0.262
	No	2	6.7%		
Bronchial asthma	Yes	1	6.3%	-*	0.452
	No	2	2.7%		
Dyslipidemia	Yes	0	0.0%	-*	1.000
	No	3	3.5%		
Family history of skin disease	Yes	0	0.0%	-*	1.000
	No	3	4.2%		

Fisher exact test applied. N = number of cases. COVID 19 = coronavirus disease 2019. ESRD = end stage renal disease. IHD = ischemic heart disease. DM = diabetes mellitus.

Table 8: Factors and co morbidities associated with presence of purpuric rash among COVID 19 patients

Factor		Purpura		*X*2	*P*
		N	%		
Gender	Male	1	2.2%	-*	0.508
	Female	2	4.7%		
Age group	Elderly	2	4.1%	-*	1.000
	Young and middle aged	1	2.5%		
Vaccine against COVID 19	Vaccinated	0	0.0%	-*	1.000
	Not	3	3.4%		
Psoriasis	Yes	0	0.0%	-*	1.000
	No	3	3.4%		
Contact dermatitis	Yes	0	0.0%	-*	1.000
	No	3	3.5%		
Rheumatoid arthritis	Yes	0	0.0%	-*	1.000
	No	3	3.5%		
ESRD	Yes	0	0.0%	-*	1.000
	No	3	3.5%		
IHD	Yes	1	5.6%	-*	1.000
	No	2	2.8%		
Hypertension	Yes	3	5.5%	-*	0.284
	No	0	0.0%		
DM	Yes	2	3.4%	-*	1.000
	No	1	3.3%		
Bronchial asthma	Yes	1	6.3%	-*	0.452
	No	2	2.7%		
Dyslipidemia	Yes	0	0.0%	-*	1.000
	No	3	3.5%		
Family history of skin disease	Yes	0	0.0%	-*	1.000
	No	3	4.2%		

Fisher exact test applied. N = number of cases. COVID 19 = coronavirus disease 2019. ESRD = end stage renal disease. IHD = ischemic heart disease. DM = diabetes mellitus.

Figure 8: Cutaneous Manifestations of Covid-19 Infection. Palpable purpura vasculitis

Figure 9: Cutaneous Manifestations of Covid-19 Infection. Maculopapular lesion

Figure 10: Cutaneous Manifestations of Covid-19 Infection. Maculopapular lesion

Figure 11: Cutaneous Manifestations of Covid-19 Infection. Urticaria like lesions

Figure 12: Manifestations of Covid-19 Infection. Urticaria like lesions

Figure 13: Cutaneous Manifestations of Covid-19 Infection. Urticaria like lesion

5. DISCUSSION

A total number of study population were 89 pateint, distribution of these population according to gender was 46 male (51.7%) and 43 female (48.3%). Regarding the age of patient which ranging from 42 to 82-year, distribution of patients according to this category was elderly 49 patients (55.1%), middle age 39 patients (43.8%), young one patient (1.1%).

According to the rates of health conditions in these study, 59 (66.3%) were diabetic, 55(61.8%)were hypertensive, 18 (20.2%) had ischemic heart disease, 16 (18%) had bronchial asthma, 4 (4.5%) had dyslipidemia, 3 (3.4%) had rheumatoid arthritis, 3 (3.4%)had contact dermatitis , 3 (3.4%) had end stage renal disease, 2 (2.2%) had psoriasis, and 2 (2.2%) were vaccinated against covid 19.

Regarding the distribution of study population according to family history of skin disorder there are 72 patient (80.9%) did not have family history of skin disease ,4 (4.5%) had psoriasis ,3 (3.4%) had vitiligo ,3 (3.4%) had contact dermatitis ,3 (3.4%) had acne, and 4 (4.5%) had atopy.

According to cutaneous manifestation detected in these study population one case (1.1%) had erythema multiform, one case (1.1%) had livedo, 2 cases (2.2%) had vesicular lesion,3 cases (3.4%) had purpura, 3cases (3.4%) chilblains ,6cases (6.7%) had urticarial like lesion ,9 cases (10.1%) had maculopapular rash, and 25 (28.1%) had any skin manifestation.

Regarding the outcome of the disease in 89 patients with total hospital admission range from 2-14 day, 6 cases (6.7%) was died, 9 cases (10.1%) need dialysis, 10cases (11.1%) need ventilation, 9 cases (10.1%) had acute kidney injury ,4 cases (4.5%) transferred to ICU.

The analysis of the association between demographic and co morbid conditions of the patients in the study population with presence of any skin manifestations or with specific skin manifestations showed no statistically significant result. This is in concordance to Algaadi S.A. (2020) Abuelgasim E et al (2021) found overall rate of 64% in women and 36% in men, urticarial rash is more frequent in middle-aged people between 45 and 65 years. Those differences were not significant. 106, 107

Nevertheless, the current study was conflicting with Patrick MT et al (2021) stated that; skin conditions, including psoriasis and atopic dermatitis, increase the risk of COVID-19. 97

Jamshidi P et al (2021); the overall frequency of cutaneous manifestations in COVID-19 patients was 5.95%. The maculopapular rash was the main reported skin involvement (37.3%) commonly occurred in middle-aged females with intermediate severity of the disease. Forty-eight percentage of the patients had a mild, 32% a moderate, and 20% a severe COVID-19 disease. The overall mortality rate was 4.5%. Patients with vascular lesions had the highest mortality rate (18.2%) and patients with urticaria-like lesions had the lowest mortality rate (2.2%). 85

According to Recalcati S. (2020); the incidence of cutaneous manifestations exceeded the rate of 20%. 90

Skin rashes and purpuric plaques are an interesting clinical presentation of classical coronavirus infections. The first report of the cutaneous manifestations was reported from Italy, where 20.4% (18/88) hospitalized COVID-19 patients developed an erythematous rash (14), widespread urticaria (3), and chickenpox-like vesicles (1) distributed in the trunk area. 89

González F.G et al (2021) proposed a pathophysiological hypothesis based on the interpretation of various clinical manifestations related to COVID-19, dividing these expressions into two categories: (i) Those manifestations that are mainly based on the direct viral cytopathic effect on cells of the organism such as keratinocytes, including in this group maculopapular, urticaria and chickenpox-like eruptions; (ii) those manifestations due to changes in specific white blood cells, T lymphocytes, and macrophages, such as secondary infection with uncontrolled overexpression of cytokines (stage of cytokine storm). In turn, the latter group will be subdivided into: (a) Dermatological manifestations with features such as macrophage activation syndrome including acral ischemia, gangrene, petechiae/purpura; (b) liveoid lesions, which are associated with high patient morbidity and mortality; and (c) cutaneous manifestations due to activation of an early response to type I interferon (IFN-1), including chilblain- like lesions. 98

Fernandez-Nieto D et al (2020), found that vesicular lesions are mostly located on the trunk and to a lesser extent on the extremities: diffuse pattern eruptions tend to affect more than one body area, palms of the hands, and soles of the feet; localized pattern lesions tend to affect the central area of the body. Also, 58.3% presented mild symptoms of the disease without requiring hospitalization and 41.7% developed pneumonia. Among them, only 4.2% required admission to the intensive care unit (ICU) and all patients survived.99

Jindal R and Chauhan P (2020) and Conforti C et al (2020) found that maculopapular-erythematous eruptions have the highest prevalence (40–70%) of the cutaneous manifestations associated with SARS-CoV-2, including (a) erythematous eruptions 38.5%, (b) maculopapular eruptions 18.3%, (c) macular erythema 6.8%, and (d) papulo-squamous eruption (2%). 100, 101

According to Rekhtman S et al (2021); the prevalence of petechiae/purpura rashes is 4% in COVID-19 patients who did not require hospitalization 101 while in hospitalized patients the prevalence of purpura was 25.7% 102 These eruptions are frequent in middle-aged and elderly adults and without significant differences between sexes 102

Rekhtman S et al (2021) found that 66.7% of patients with purpura were mechanically ventilated. 102 Galván Casas C et al (2020) reported prevalence of acral ischemia is 6%. 103

These lesions are frequent in elderly patients and in those with severe SARS- CoV-2 disease and up to 80% may require mechanical ventilation 103 Jimenez-Cebrian A et al (2021) found the incidence of livedoid lesions of 6% is reported during the first peak of the epidemic in Spain in April 2020. 104

According to Fernández-Lázaro D et al (2021) the prevalence of urticaria was ranging between 7% and 40%, depending on the general condition of the patient. 105

The present study shows some limitations regarding laboratory and histology facilities as well poor reporting of clinical manifestations. Anyhow, this study presents a piece of knowledge about the cutaneous behavior of COVID 19 infection among Libyan patients.

6.1. CONCLUSION

The mucocutaneous manifestations detected in the present study in 28.1% of cases, the most frequent was maculopapular rash (10.1%) and urticarial like lesion (6.7%). Another 3.4%had puerperal rash, 3.4% chilblains, 2.2% had vesicular lesion, 1.1% had erythema multiforme and 1.1% had livedo. Regarding the outcome of the disease in 89 patients with total hospital admission range from 2-14 day, 6.7% died, 10.1% need dialysis, 11.1% need ventilation, 10.1% had acute kidney injury, 4.5% transferred to ICU. No significant association was proved with any of the skin manifestations

6.2. RECOMMENDATION

- The cutaneous lesions should be considered as a part of clinical manifestations of serious viral infections and should be of importance in dermatology practice especially in times of pandemics, especially skin lesion poorly recognized because of the lack of routine dermatological consultations during the pandemic.
- Topic needs to be explored with further studies.
- Retrospective analysis of cases with skin rash during the time of pandemic may be considered.
- However, there are still many unanswered questions, further research will be needed in the future to better understand the relationship between the COVID-19 and skin manifestions.
- More research, including a greater number of patients are required**.**

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