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[CURRENT](#) [ARCHIVES](#) [AUTHOR GUIDELINES](#)

[Home](#) > [Archives](#) > **Vol 7, No 2 (2021)**

Vol 7, No 2 (2021)

March-April 2021

Table of Contents

Original Research Articles

[The effects of topical steroid fears and concerns on patients with eczema: first TOPICOP© scale-based study in Saudi Arabia](#)

Abdulmajeed A. Alharbi, Ghadah I. Alhetheli, Reema Alqahtani, Mujahid Alshehri

DOI: [10.18203/issn.2455-4529.IntJResDermatol20210472](#)

PDF
155-162

[Prevalence and associated risk factors of superficial and cutaneous mycoses among children attending Halibet referral hospital in Asmara, Eritrea](#)

John J. Prabakaran, Yordanos Kesete, Eyob Yohannes, Eyorusalem Tsehaye, Natsnet Teklezghi, Eyorusalem Araya, Winta Arefaine

DOI: [10.18203/issn.2455-4529.IntJResDermatol20210564](#)

PDF
163-170

[Application of smartphones in dermatology practice: a cross-sectional survey](#)

Priya Prabhakaran Nair, Leela Manju

DOI: [10.18203/issn.2455-4529.IntJResDermatol20210464](#)

PDF
171-176

[A study on the clinical profile of dermatoses induced by topical corticosteroids](#)

Vontela Rohit, S. Rajesh Reddy, Narendar Gajula, Karing Deepthi

DOI: [10.18203/issn.2455-4529.IntJResDermatol20210041](#)

PDF
177-183

[A descriptive study of clinico-epidemiological profile of chronic urticaria from a tertiary care center](#)

Olasseri Kalathingal Reena Mariyath, Sreekanth Sukumarakurup, Sanjayan Rosamma Roopasree Pinky, Mohandas Ajina, Kollarukandy Vijayan Anagha

DOI: [10.18203/issn.2455-4529.IntJResDermatol20210075](#)

PDF
184-187

[Comparison of seminar and lecture as teaching method and](#)

PDF

User

Username

Password

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Journal Content

Search

Search Scope

All

Browse

[By Issue](#)

[By Author](#)

[By Title](#)

Font Size

Information

[For Readers](#)

[For Authors](#)

[For Librarians](#)

Notifications

[View](#)

[Subscribe](#)

Current Issue

- student perception on the seminar and lecture in medical education 188-191
Chidambaram Dharmambal, Somasundaram Anavarathan
DOI: [10.18203/issn.2455-4529.IntJResDermatol20210565](https://doi.org/10.18203/issn.2455-4529.IntJResDermatol20210565)
- A clinical and mycological study of superficial mycosis PDF
Suma Patil, Dayanand Raikar 192-194
DOI: [10.18203/issn.2455-4529.IntJResDermatol20210566](https://doi.org/10.18203/issn.2455-4529.IntJResDermatol20210566)
- A study to compare clinico-histopathological and dermoscopic findings in patients of vitiligo PDF
Krishnendra Varma, Ujjwal Kumar, Siddharth Sethi 195-200
DOI: [10.18203/issn.2455-4529.IntJResDermatol20210567](https://doi.org/10.18203/issn.2455-4529.IntJResDermatol20210567)
- A clinical study on linear dermatoses at a tertiary care teaching hospital in Davangere PDF
Sowmya Manangi, Marri Anirudh Reddy, Aishwarya Sivuni, Hosalli Amrutha, Suga Reddy 201-206
DOI: [10.18203/issn.2455-4529.IntJResDermatol20210568](https://doi.org/10.18203/issn.2455-4529.IntJResDermatol20210568)
- Study of clinico-epidemiological profile of leprosy patients at tertiary care center PDF
Ujjwal Kumar, Krishnendra Varma, Kamalapat Baraithiya 207-212
DOI: [10.18203/issn.2455-4529.IntJResDermatol20210569](https://doi.org/10.18203/issn.2455-4529.IntJResDermatol20210569)
- Recurrent and chronic dermatophytosis: culprit- not just antifungal resistance PDF
Shruti Appannavar, Kiran ., Gajanan Pise, Rohith ., Ashwini P., Vinitha Sanagoudar, Shradha Gurudev 213-217
DOI: [10.18203/issn.2455-4529.IntJResDermatol20210570](https://doi.org/10.18203/issn.2455-4529.IntJResDermatol20210570)
- Study of quality of life in patients with premature graying of hair in Western Indian population PDF
Dipti Mathias, Milind A. Patvekar, Mahendra S. Deora, Kalyan T. Dalave, Aishwarya Raheja 218-222
DOI: [10.18203/issn.2455-4529.IntJResDermatol20210571](https://doi.org/10.18203/issn.2455-4529.IntJResDermatol20210571)
- Fractional erbium-YAG laser vs platelet rich plasma in acne scar: a comparative study PDF
Neeti Kumari, Arun Kumar, Jitendra S. Bist, Anil K. Mehta 223-228
DOI: [10.18203/issn.2455-4529.IntJResDermatol20210572](https://doi.org/10.18203/issn.2455-4529.IntJResDermatol20210572)
- Pregnancy outcomes in sexually transmitted infections or human immunodeficiency viruses infected women at a tertiary care center: a retrospective study PDF
Saradha K. P., Anitha Christy Stephen, Vikram V. Huddar 229-231
DOI: [10.18203/issn.2455-4529.IntJResDermatol20210573](https://doi.org/10.18203/issn.2455-4529.IntJResDermatol20210573)
- A clinico-epidemiological study of mask induced facial dermatoses due to increased mask usage in general public during COVID-19 pandemic PDF
Ramesh A., Thamizhinian K. 232-238
DOI: [10.18203/issn.2455-4529.IntJResDermatol20210574](https://doi.org/10.18203/issn.2455-4529.IntJResDermatol20210574)
- A study of dermatoses in antenatal patients attending tertiary care centre PDF
Valay Desai, Avani C. Patel, Anjum M. Momin, Jignesh B. Vaishnani 239-244
DOI: [10.18203/issn.2455-4529.IntJResDermatol20210575](https://doi.org/10.18203/issn.2455-4529.IntJResDermatol20210575)

- [Cutaneous manifestations in patients with chronic kidney disease on hemodialysis](#) PDF
245-249
Saijal Gupta, Hemant V. Talanikar, Mahendra S. Deora, Ankita Agrawal, Yugal K. Sharma
DOI: [10.18203/issn.2455-4529.IntJResDermatol20210576](https://doi.org/10.18203/issn.2455-4529.IntJResDermatol20210576)
- [Study of the various cutaneous adverse reactions to radiotherapy](#) PDF
250-254
Priyatharshini Venkatakrisnan, Govardhan Jagadeesh Kumar, Bhavana Sampadarao
DOI: [10.18203/issn.2455-4529.IntJResDermatol20210577](https://doi.org/10.18203/issn.2455-4529.IntJResDermatol20210577)
- [Clinico-etiological study of genital lesions at a tertiary care center in Pune, India](#) PDF
255-261
Prachiti S. Tekam, Vasudha A. Belgaumkar, Ravindranath B. Chavan, Nitika S. Deshmukh, Neelam Bhatt
DOI: [10.18203/issn.2455-4529.IntJResDermatol20210578](https://doi.org/10.18203/issn.2455-4529.IntJResDermatol20210578)
- [Melasma and sun exposure: a clinicoepidemiological study](#) PDF
262-266
Suman B. Parsam, Swetha Tallam
DOI: [10.18203/issn.2455-4529.IntJResDermatol20210579](https://doi.org/10.18203/issn.2455-4529.IntJResDermatol20210579)
- [Study on prevalence of Frank's sign in cardiac patients in a tertiary care centre, Kanyakumari district](#) PDF
267-270
Nivin Simon, Mulamoottil George Varghese, A. J. S. Pravin, M. K. Padmaprasad, S. Rajagopal, M. Vijaya Bharathi, Sushma I.
DOI: [10.18203/issn.2455-4529.IntJResDermatol20210580](https://doi.org/10.18203/issn.2455-4529.IntJResDermatol20210580)
- [Clinical correlation of foot eczema and patch test: a cross sectional study from South India](#) PDF
271-278
Sharim Fathima, Kunnummal Muhammed, Gopalapillai Nandakumar
DOI: [10.18203/issn.2455-4529.IntJResDermatol20210581](https://doi.org/10.18203/issn.2455-4529.IntJResDermatol20210581)
- [Comparative study of efficacy of minoxidil versus minoxidil with platelet rich plasma versus minoxidil with dermaroller in androgenetic alopecia](#) PDF
279-284
Adarsh Gowda, Sana Mariam Sankey, Sharath Kumar B. C.
DOI: [10.18203/issn.2455-4529.IntJResDermatol20210582](https://doi.org/10.18203/issn.2455-4529.IntJResDermatol20210582)
-

Case Series

- [Hailey Hailey-a blooming disease](#) PDF
285-288
Ilakkia P. Sadasivam, Govardhan Jagadeeshkumar, Oudeacoumar Paquirissamy, Jude E. Dileep, Rajkiran Takharya, Lisa J. D'souza
DOI: [10.18203/issn.2455-4529.IntJResDermatol20210068](https://doi.org/10.18203/issn.2455-4529.IntJResDermatol20210068)
-

Case Reports

- [Merkel cell carcinoma associated with chronic treatment with hydroxyurea: a case report](#) PDF
289-292
Saulo Esteves Saraiva, Virginia Mareco, André Florindo, Diogo Delgado, Maria Filomena de Pina
DOI: [10.18203/issn.2455-4529.IntJResDermatol20210538](https://doi.org/10.18203/issn.2455-4529.IntJResDermatol20210538)

- [Adult-onset eccrineangiomatous hamartoma treated with excision and skin grafting: a case report](#) PDF
293-296
Yogesh Devaraj, Ranga Swaroop Mukunda, Priyanka Yogananda Yadav, Shaila Shree Devendra, Premika Meenakshi Sundaram
DOI: [10.18203/issn.2455-4529.IntJResDermatol20210583](https://doi.org/10.18203/issn.2455-4529.IntJResDermatol20210583)
- [Young lady with acral pustulosis and psoriatic arthritis](#) PDF
297-299
Mary Nnenda Amaewhule, Chidinma Wekhe
DOI: [10.18203/issn.2455-4529.IntJResDermatol20210584](https://doi.org/10.18203/issn.2455-4529.IntJResDermatol20210584)
- [Familial leiomyoma: a case report](#) PDF
300-302
Swetha Gutha, Shalini Sampath
DOI: [10.18203/issn.2455-4529.IntJResDermatol20210585](https://doi.org/10.18203/issn.2455-4529.IntJResDermatol20210585)
- [Familial median canaliform dystrophy of heller affecting multiple nails: a rare clinical entity](#) PDF
303-305
Chandni Jain, Harris Ishtiyahq Shaafie, Mustaqueem Farooque, Zarin Wahab
DOI: [10.18203/issn.2455-4529.IntJResDermatol20210586](https://doi.org/10.18203/issn.2455-4529.IntJResDermatol20210586)
- [Trachyonychia in a child with concomitant alopecia areata and lichen planus](#) PDF
306-309
Abhinav David, Inderpreet Kaur
DOI: [10.18203/issn.2455-4529.IntJResDermatol20210587](https://doi.org/10.18203/issn.2455-4529.IntJResDermatol20210587)
- [Purpura fulminans secondary to indian tick typhus: a case report](#) PDF
310-313
Yogesh Devaraj, M. Ranga Swaroop, Rashmi R. Mallya, Aneesa Sajeed, K. Yashwanth Reddy
DOI: [10.18203/issn.2455-4529.IntJResDermatol20210588](https://doi.org/10.18203/issn.2455-4529.IntJResDermatol20210588)
-

Review Articles

- [Cutaneous manifestations of COVID-19 in pediatric patients: literature review](#) PDF
314-320
Ghadah Alhetheli
DOI: [10.18203/issn.2455-4529.IntJResDermatol20210537](https://doi.org/10.18203/issn.2455-4529.IntJResDermatol20210537)
- [Management of androgenetic alopecia: a review](#) PDF
321-326
Deepa Dev Chhetri, Xin Huang
DOI: [10.18203/issn.2455-4529.IntJResDermatol20210013](https://doi.org/10.18203/issn.2455-4529.IntJResDermatol20210013)
- [Literature review: manifestation of skin lesion on COVID-19](#) PDF
327-335
Yohanes Firmansyah, Sukmawati Tansil Tan, Jessica Elizabeth, Christopher Lauren
DOI: [10.18203/issn.2455-4529.IntJResDermatol20210589](https://doi.org/10.18203/issn.2455-4529.IntJResDermatol20210589)
- [Consensus on management of acne-induced post-inflammatory hyperpigmentation: an Indian perspective](#) PDF
336-345
Jayakar Thomas, Krupa Shankar, Sudhir Pujara, Rajeev Sharma, David Pudukadan, Maleeka Sachdev, Satish Udhare, Vikrant Saoji, D. M. Mahajan, Anchala Parthasaradhi
DOI: [10.18203/issn.2455-4529.IntJResDermatol20205923](https://doi.org/10.18203/issn.2455-4529.IntJResDermatol20205923)
- [Dermatological manifestations of COVID-19 and its therapies: a review](#) PDF
346-353

Heena Singdia, Rachita Mathur, Shivi Nijhawan, Neha Rani,
Deepika Kothari, Rohit Garg, Puneet Bhargava, Deepak K.
Mathur

DOI: [10.18203/issn.2455-4529.IntJResDermatol20210590](https://doi.org/10.18203/issn.2455-4529.IntJResDermatol20210590)

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Review Article

Literature review: manifestation of skin lesion on COVID-19

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ABSTRACT

New cases of pneumonia, which spread rapidly and are deadly, have spread throughout the world. This disease is known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or corona virus disease 2019 (COVID-19) with a viral etiology in the form of novel coronavirus 2019 (2019-nCoV). This disease has extensive clinical manifestations starting from the lungs, hematology system, heart, nerves, reproduction, and the skin. The thing to be aware of is that the skin manifestations in the form of atypical lesions are often found in COVID-19. Common skin manifestations on COVID-19 are erythema-edema with vesicles or pustules (pseudo-chilblain), vesicular eruption, maculopapular rash, urticaria, and livedo lesion. This literature review discusses comprehensively what kind of skin lesions can be suspected of being part of a COVID-19 infection. This literature review is useful for increasing the awareness of doctors about COVID-19 infection and may help in early diagnose of COVID-19 infection and prevent further transmission.

Keywords: Skin manifestation, COVID-19, SARS-CoV-2

INTRODUCTION

A new and unexplained pneumonia case started in Wuhan city, China in December 2019. Experts and the government are taking immediate steps to determine the etiology to prevent the epidemic. The world health organization (WHO) gave the new virus terminology as novel coronavirus 2019 (2019-nCoV) on January 12, 2020 and gave the disease caused by 2019-nCoV as corona virus disease 2019 (COVID-19) and coronavirus study group (CSG) from the international committee on virus taxonomy called 2019-nCoV a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and became a global epidemic as a marker of a very serious problem on January 20, 2020.¹⁻³ The confirmed case of infection from SARS-COV2 on August 20, 2020 has infected 22,213,869 cases worldwide with a total death of 781,677 people. The country with the highest SARS-CoV infection is the United States with 11,887,224 cases,

Europe 3,841,452 cases, Southeast Asia 3,308,987 cases, Eastern Mediterranean with 1,776,889 cases, and Africa with 966,352 cases.⁴ Indonesia as part of a Southeast Asian country reported 147,211 confirmed cases, 40,119 in treatment, 100,674 recovered and 6,418 deaths (case fatality rate: 4.4%) on 20 August 2020.^{5,6}

The clinical manifestations of COVID-19 infection are very unclear and resemble many other diseases. Reports from around the world have revealed that the spectrum of this disease is not only centered on the lungs but can extend to various organs to multiple organs with clinical symptoms from mild to severe and lead to death. Reports from various studies state that Covid-19 can attack the nervous system, gastrointestinal-hepatobiliary system, urological system, cardiovascular and metabolic systems, hematology system, reproductive system especially in pregnancy, integumentary or mucocutaneous system with

a form of efflorescence that is actually typical for other diseases, such as varicella.⁷⁻²⁸

The most common symptoms form COVID-19 are fever, myalgia, cough, fatigue, pneumonia, and respiratory problems. Rare disorders include headache, hemoptysis, diarrhea and coughing up blood.²⁹⁻³¹

EPIDEMIOLOGY AND ONSET

In mid-August 2020 cases of COVID-19 were found that hit all countries, even though several countries had started declaring countries free of new COVID-19 cases but in fact, COVID-19 infection had to be watched out for because the transmission method was easy and had very clinical symptoms. diverse. One of the clinical symptoms that appear is skin manifestation. Symptoms or skin lesions do not always appear in all patients with confirmed COVID-19. Recalcati described that only 20.45% of COVID-19 patients treated at the Lecco hospital (Lombardy region, Italy) manifested in the form of an erythematous rash (n=14), extensive urticaria (n=3) or varicella-like vesicles (n=1).³² Firmansyah, Elizabeth and colleagues' study that reviewed clinical manifestations in key populations found that only 42.86% of patients presented with skin lesions.³⁰

Regarding the onset of skin manifestations presented in the literature in a very varied range. Research by Zhao et al reviewed skin lesions appearing 9.92 (1-30) days after the appearance of systemic symptoms such as fever, cough, diarrhea, weakness, fatigue, lethargy, and difficulty breathing.²⁹ Research by Firmansyah, Elizabeth, and colleagues revealed that maculopapular skin manifestations appeared 10.7 (7-13) days after the appearance of clinical symptoms of COVID-19.³⁰ Other studies have also revealed that skin manifestations can appear more than 30 days after the first onset of symptoms of COVID-19.³⁵

PATHOGENESIS

The new study concluded ACE-2 as a functional host receptor for infection from SARS-CoV-2. The expression of the ACE-2 receptor with its binding affinity for the SARS-Cov 2 virus was 10 to 20 times higher. It is on the basis of this receptor expression that clinical manifestations, replication, severity, and transmission of the SARS-Cov 2 virus are explained at the level of molecular biology. Research using animal or mouse studies found that the expression of ACE-2 plays an important role in the incidence of vascular disorders, lung pathology, severity of infection, and the occurrence of respiratory acidosis mechanisms that trigger respiratory failure.³⁶ Physiologically, the ACE-2 receptor is spread in various body tissues, one of which is excreted in keratinocyte tissue and epidermal basal cells.^{37,38} Recent research has shown that the expression of ACE-2 extends to the basal cell layer of hair follicles, sebaceous gland cells and smooth muscle cells surrounding the sebaceous

glands, and eccrine cells.³⁹ These results were further confirmed by IHC, which showed ACE2 positive keratinocytes in the basal stratum, spinosum stratum, and epidermal granulosum stratum.⁴⁰ In addition, Li et al. found that CD8 and T cells had a significant positive correlation with ACE2 expression in the skin.⁴¹ On the basis of the pathophysiology and pathogenesis of SARS-Cov 2 virus infection and its relationship with the ACE-2 receptor which is not only spread in the lungs but throughout the skin layer, it is not surprising if the manifestation of skin lesions also appears as a result of the similarity of the ACE-2 receptor on both types of organs

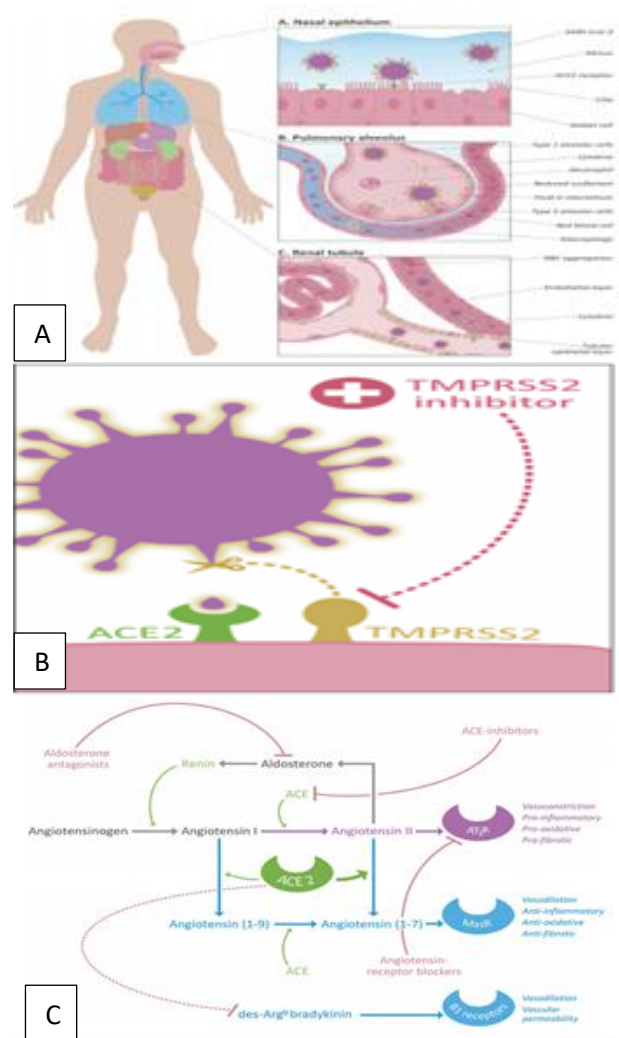


Figure 1 (A-C): Distribution and pathogenesis of ACE-2.³⁰

CLASSIFICATION

The various efflorescence of the skin manifestations caused by COVID-19 make it difficult to classify COVID-19 because of its manifestations that resemble other diseases. Joob et al reported a petechial rash in a COVID-19 patient from Thailand.⁴² The Italian study reported on varicella-like lesions, Fernandez (Spain)

reported the appearance of urticaria rash (urticaria from rash) after 6 days of symptom onset.³⁷ Zhang (China) reported urticaria lesions.³⁸ Estebanez (Spain) reported a pruritic lesion of the heel, Henry (France) reported urticarial lesions and disseminated erythematous plaques eruption.³⁹⁻⁴³ Sachdeva (Italy) reported maculo-papular

lesions, morbilliform spots and hemorrhagic macular patches.²⁰ Mazzota (Italy) reported round red-purple lesions measuring 5-15 mm with indistinct margins on the soles of the feet.⁴⁰ Alramthan (Qatar) reported bilateral ischemic lesions on the acral with purplish red color on the dorsal part of the fingers.⁴¹

Table 1: Comparison of skin lesions from different case reports.

Author	Country	Efflorescence	Author's Comments Regarding Clinical Associations
Alramthan 2020⁴¹	Qatar	Reported 2 cases of 2 ischemic lesions and papules on the acral area with red-purplish color.	Ischemic lesions have the most common distribution appearing in the distal limbs, especially the lower limbs.
Firmansyah, et al³⁰	Indonesia	Reported 3 cases with the maculopapular lesions with and without the itching which generally focused on lower limb area.	It is a key population group, namely health workers with an age range of 22-25 years.
Estébanez 2020³⁹	Spain	Reported 1 case of urticaria with itching (Confluent-erythematous-yellowish papules).	The patient is 28 years old (Female). The skin lesions appeared on the thirteenth day with persistent lesions and continued to evolve into thickened erythematous plaques and severe itching.
Fernandez 2020³⁷	Madrid, Spain	Reported 1 case of urticaria.	The patient was 32 years old (female) who appeared on the sixth day of symptoms. Treatment therapy using hydroxychloroquine and azithromycin.
Gianotti, 2020⁴²	Milan, Italy	5 cases with varying efflorescence in the form of exanthema on the trunk and legs, papular erythematous exanthema on the trunk, and undefined maculopapular eruption in 3 cases on the trunk, and maculo-papular purpura.	Male sex with papular erythematous exanthema.
Henry 2020⁴³	Orléans, France	Reported 1 case with disseminated erythematous plaques eruption and urticaria lesions on face, hands and feet.	Generally, these lesions focus on the limb area, with pruritic lesions (similar to neurodermatitis).
Hunt 2020⁴⁴	New York, USA	Reported 1 case with varying efflorescence starting from indefinitely demarcated, morbilliform, maculopapular lesions, and patches without itching spread over the trunk and extremities and even the face area.	Variety of efflorescence over large areas may be due to prolonged fever.
Jimenez 2020⁴⁵	Madrid, Spain	Reported a case of purpura-erythematous measuring millimeters in the peri-axillary flexural region.	The possibility of these lesions arising from old age (84 years) with treatment therapy in the form of hydroxychloroquine and lopinavir/ritonavir.
Joob 2020³⁶	Thailand	Reported skin patches with petechia.	No further data regarding follow-up symptoms.
Kolivras 2020⁵⁷	Brussels, Belgium	Reported 1 case with plaque lesion with infiltration and redness on the dorsal and lateral part of the foot.	Symptoms appear after 3 days of respiratory manifestations. This lesion is the only lesion with subjective pain.
Mahé 2020⁴⁷	Colmar, France	Reported 1 case of erythematous spots in the antecubital fossa area that spread to the trunk and armpit folds	The patient was 64 years old (female) who appeared 4 days after fever and disappeared on the ninth day.
Manalo 2020⁴⁸	Atlanta, Georgia	Reported 2 cases of unilateral livedoid patch resembling livedo reticularis without itching in the anterior thigh area and 1 case of asymptomatic patches such as livedo reticularis.	There was no association between age and gender because the respondents aged 67 (male) and 47 (female) generally appeared 7-10 days after the onset of symptoms.

Continued.

Author	Country	Efflorescence	Author's Comments Regarding Clinical Associations
Marzano 2020²³	Italy	Reported 22 cases with Varicella-like papulovesicular exanthem skin lesions on the limbs and trunk.	The age distribution is quite wide with a mean age of 60 years with 73% of respondents being male. Symptoms appear on days 2-12 and disappear after 4-15 days of treatment.
Mazzotta 2020⁴⁰	Italy	Reported 1 case of red-purplish patches with a circular shape measuring 9-15 mm and indistinct borders, focusing on the extremities.	This case occurs in children. Such lesions are generally in the lower leg area with additional manifestations of irritating itching
Najarian 2020⁴⁹	New Jersey, USA	Reported 1 case of morbilliform skin lesions in all four extremities and the entire trunk.	These numerous and extensive lesions appeared 1 day after the onset of respiratory symptoms. Case treated with azithromycin and benzonatate.
Recalcati, 2020²⁷	Recalcati	Reported 18 cases with 14 cases of erythematous patches, 3 cases of urticaria that spread over the trunk, and 1 case of chickenpox-like vesicles.	There was no association between the type of skin lesion and the severity of the disease, generally symptoms appeared on days 8-10 of illness or after hospital admission.
Sachdeva et al 2020²⁰	Milan, Italy	Reported 3 cases with maculopapular skin lesions with 1 case of Maculopapular itchy rash resembling Grover disease, 1 case of Diffuse maculopapular exanthem (morbilliform), macular hemorrhagic rash, and 1 case of Papular-vesicular, pruritic eruption.	Generally, patients are elderly group > 70 years.
Zhang 2020⁵⁰	Wuhan, China	Reported 7 cases that were quite unique in the form of ischemia in the acral area with accompanying symptoms such as cyanosis of the toes, bullae, and dry gangrene.	All of these cases focused on the leg area with symptom onset on day 19 (11-23) day. The possibility of such efflorescence arises due to COVID-19 therapy using low molecular weight heparin Treatment

There is a study that categorizes these skin manifestations very well, namely the study of Casas and colleagues who classified these skin manifestations into 5 main classifications based on three hundred seventy-five cases of patients infected with COVID-19 in Spain. The classification includes:⁵²

Erythema-edema with vesicles or pustules (pseudo-chilblain) in the leg area is found in 19% of cases in Spain. Some additional manifestations of this classification are the possible presence of cold acral, and there is purpura which focuses on the area of the extremities (hands and feet) which are generally asymmetric.

Vesicular eruptions that generally appear in the trunk area are monomorphic to poliform and contain hemorrhagic content in these vesicles which, if not managed properly, will become larger and spread rapidly to other areas of the body.



Figure 2: Efflorescence erythema-edema with vesicles and pustules (pseudo-chilblain) in the acral area.⁵²



Figure 3: Distribution of monomorphic vesicles in the trunk area of a person with COVID-19 is confirmed.⁵²

Urticaria lesions mostly spread over trunk to extremities. It was found in 19% of cases of skin manifestations.



Figure 4: Urticaria lesions in lower extremity of COVID-19 confirmed.⁵²

Maculopapular rash of various sizes and numbers (Figure 5 A). Several case reports reveal a similar distribution picture of pityriasis rosea. A review of other cases also revealed infiltrated papules in the extremities (dorsum of the hands), pseudo vesicles (Figure 5 B) and erythema multiforme is (Figure 5 C).

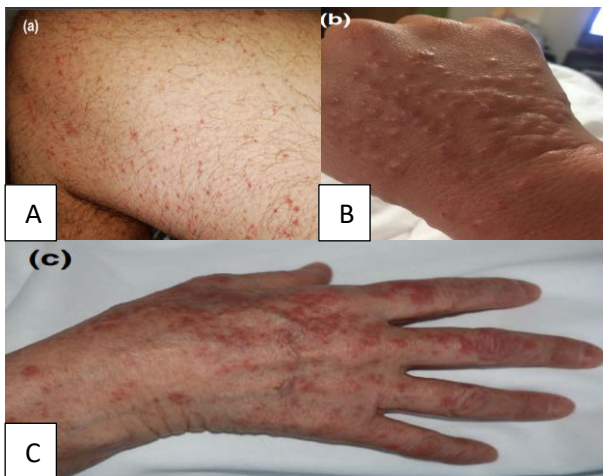


Figure 5: Erythema multiforme in the acral area of a confirmed COVID-19 patient.⁵²



Figure 6: Livedo or necrosis arising as a manifestation of occlusive vascular.⁵²

Livedo or necrosis that arises as a manifestation of vascular occlusive and is spread over the trunk and acral areas. This type of lesion was reported to occur in 6% of

cases of patients with confirmed COVID-19 manifestations (Figure 6).

PREDISPOSITION FACTORS WITH SKIN MANIFESTATIONS ON COVID-19 INFECTION

There are still few studies that describe predisposing factors for the appearance of skin manifestations in COVID-19. Several studies have attempted to reveal the factors predisposing to the appearance of skin lesions in COVID-19, although they have not yet reached an advanced stage of research but can be considered as a factor predicting the appearance of skin lesions in COVID-19.

Age and gender

The distribution of data on age and sex in people with COVID-19 with skin manifestations is very broad. The distribution of age data in Zhao and colleagues' study revealed a very large age range starting from 5 years old to 91 years old with a mean age of 49.03 years. Research in China is also in line with Zhao's research, with the average age of people with COVID -19 and skin manifestations of 45.55 years. The distribution of sex also cannot be used as a benchmark for the appearance of skin manifestations, but from some epidemiological data it is found that men are more likely to develop skin manifestations when compared to women (53 to 65%).³⁴

An interesting thing about the relationship between age and skin manifestations was shown by the research of Nieto and colleagues which revealed a tendency for younger ages (children) with a mean age of 12 years (1-29 years) to have a tendency for skin lesions in the form of erythema multiforme while at age the older adults with a mean age of 23.4 (2-56) years were dominated by erythema-edema efflorescence with vesicles and pustules (pseudo-chilblain). The age difference between these two groups was statistically significant ($p < 0.05$).⁵²

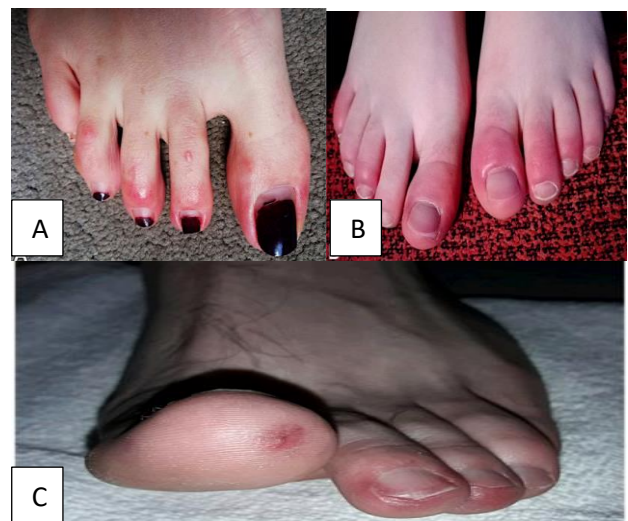


Figure 7: Efflorescence erythema-edema with vesicles and pustules in the acral region.⁵³

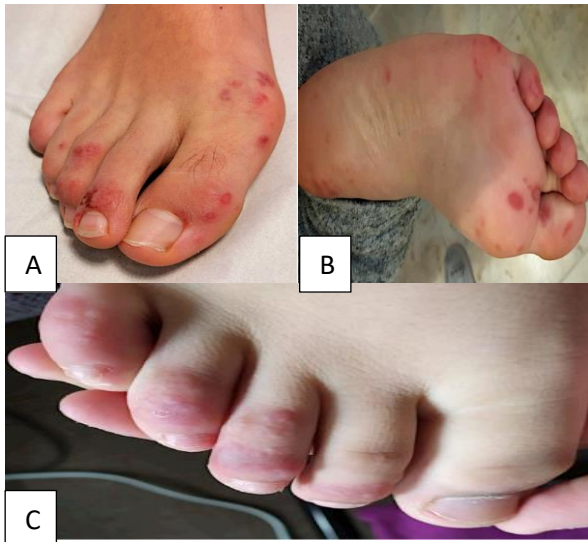


Figure 8: Efflorescence of erythema multiforme in the acral area.⁵³

Comorbidity and history of previous disease

A literature that discusses the relationship between comorbidity and previous disease history is presented by Galvan and colleagues who in their paper found no difference between smoking, hypertension and diabetes on the appearance of skin manifestations in COVID-19 sufferers. The search from various sources revealed 44 of the 375 patients smoked. 10 out of 18 patients had hypertension, and 6 of 18 patients had a history of diabetes mellitus.⁵³ This variable was chosen because the hypothesis in the form of skin manifestations emerged as a result of low body immunity.

Immunity reaction and laboratory parameters

Deductively, lower immunity will cause more severe clinical manifestations than population groups with a better immune system. Research from Zhao and colleagues revealed that the group with skin manifestations of COVID-19 infection found lymphocytopenia in 76.92% of cases, an increase in CRP in 33.33% of cases, an increase in LDH in 46.17% of cases.³⁴ On the other hand, Zhang et al also revealed thrombocytopenia as an important factor in the occurrence of petechias in confirmed cases of COVID-19 infection.⁵⁰⁻⁵¹

Research from Firmansyah and colleagues also revealed a possible correlation between laboratory profiles and the incidence of COVID-19 skin manifestations in key population groups, namely health workers of the same age, found the fact that levels of hemoglobin, hematocrit, platelets, erythrocytes, leukocytes, and neutrophils-lymphocyte Ratio (NLR) was lower in COVID-19 cases with skin manifestations.³⁰

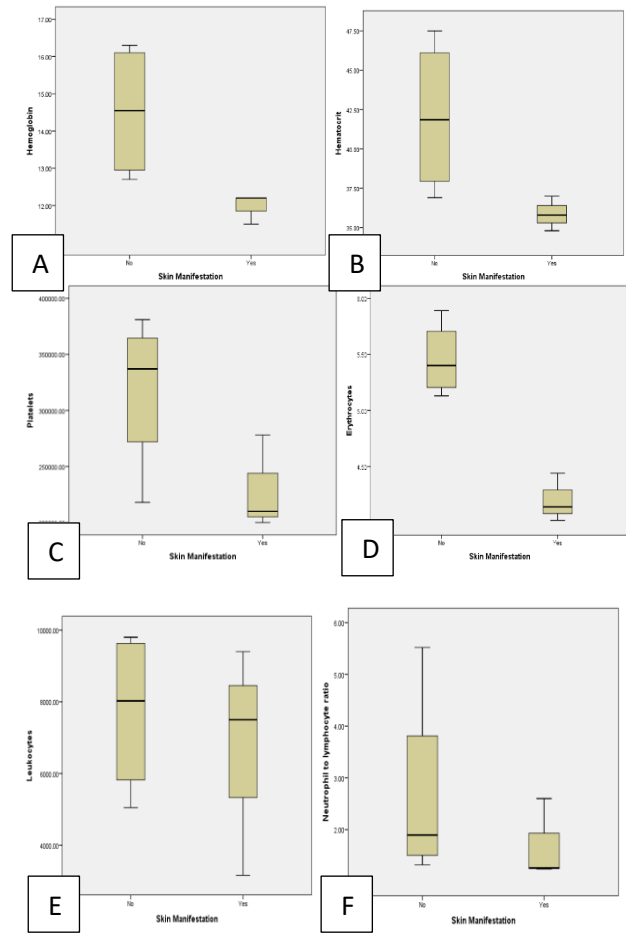


Figure 9: Parameter comparison of laboratory profiles in respondents with confirmed COVID-19 with or without skin manifestations.

Infection severity

The severity of infection as a predictor of the incidence of skin manifestations of COVID-19 was described by Zhang et al who reported 7 cases of COVID-19 infection with critical clinical symptoms and physical parameters that found limb ischemia with various symptoms followed by other manifestations of cyanosis, purpura, and dry gangrene. This may be caused by multiple organ damage due to immune system reactions and vascular disorders.³⁴

Research from Recalcti et al explained that skin manifestations due to COVID-19 are a common manifestation like other viral infections and there is no related relationship between pneumonia due to COVID-19.³² Contradictory to the literacy of Galvan et al revealed that the increasing severity of pneumonia will increase the likelihood of skin manifestations ranging from vascular lesions, urticaria lesions, maculopapular lesions, pseudo-chilblain lesions, to necrotic lesions.⁵³

PROGNOSIS AND MANAGEMENT

Until mid-August 2020 (August 16th 2020), confirmed cases had reached 21,462,593 incidents with a cure rate

of 13,448,779 events and a case fatality rate of 3.59%.⁴ Indonesia has recorded a number of confirmed cases of 137,468 cases with a case fatality rate of 4.4%.^{5,6} The overall prognosis of the incidence of COVID-19 is dubious and bonam. Some cases of death occur because of comorbid factors, with causes of death in the form of respiratory failure, hypoxemia, and respiratory acidosis. Management of the manifestations of skin lesions in COVID-19 is still supportive, such as treatment with antihistamine drugs, topical steroids and other symptomatic drugs. Special management of COVID-19 infection includes administration of hydroxychloroquine, vitamin C, azithromycin, levofloxacin, and others.⁵³

CONCLUSION

COVID-19 infection has various target organs, one of which is the skin. The skin manifestations of COVID-19 infection can resemble other diseases, are not specific and do not necessarily appear in all patients, but can help make the diagnosis. Some of the clinical features that have been reported are erythema-edema with vesicles or pustules (pseudo-chilblain), vesicular eruption, maculopapular rash, urticaria, and livedo lesion. Cutaneous manifestations usually appear at the end of the acute phase, following the respiratory symptoms. Age, sex, and lower immunity are thought to be predisposing factors for skin manifestations. Management of skin manifestations to date has been in the form of conservative medical therapy.

Recommendations

Clinicians should consider cutaneous manifestations as a characteristic feature of COVID-19 infection so that the diagnosis can be made earlier and exclude the differential diagnosis. The most important thing to do in clinical practice is to always keep the hygiene and protect yourself with personal protective equipment. A decrease in awareness of various diseases is a very fatal thing.

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