

## Temporal and severity correlation of COVID-19 with Dermatovenereological disease at Dr. Soetomo General Hospital, Surabaya, Indonesia



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### ABSTRACT

**Background:** Coronavirus disease-19 (COVID-19) is an infectious disease caused by SARS-CoV-2 with various symptoms, including skin manifestations reported in patients with confirmed cases. There were several studies about the relationship between the onset of dermatovenereological manifestation and the severity of COVID-19 with dermatovenereological manifesting itself. However, there was not much research compared with dermatovenereological disease. This study aims to describe the pattern of dermatovenereological disease related to COVID-19 and find out the temporal correlation and severity of COVID-19.

**Method:** This study is an analytic retrospective study using consecutive sampling. The data was taken from the medical records of COVID-19 patients at the RIK RSUD Dr. Soetomo in 2021. Twenty-five patient medical records have been selected based on the inclusion and exclusion criteria. The collected data were then analyzed using the Chi-Square test in SPSS version 25.0 for Windows.

**Results:** From 2907 patients, dermatovenereological diseases were found in 0.86% of COVID-19 patients. The most common onset of dermatovenereological disease was before the diagnosis of COVID-19 (65.7%); the results of this study showed that there was no relationship between dermatovenereological disease and the onset of skin symptoms ( $p>0.05$ ). There was a relationship between dermatovenereological disease pemphigus foliaceus and varicella and the severity of COVID-19 medium ( $p<0.05$ ).

**Conclusion:** Various dermatovenereological diseases can follow the symptoms of COVID-19 and may precede systemic symptoms. Most studies failed to report any correlation between the onset and severity of COVID-19 and dermatovenereological disease. Understanding and classifying dermatovenereological disease in COVID-19 patients is crucial.

**Keywords:** COVID-19, dermatovenereological disease, severity, symptom onset.

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### INTRODUCTION

A French dermatologist first reported cutaneous manifestations of COVID-19 in early April 2020. Incidents in Italy and France were reported by dermatologists who were aware of these skin lesions when COVID-19 rates were high—followed by reports in European countries and America. In a recent review of clinical characteristics of COVID-19 in China, the rash was observed in 0.2% of cases. However, this percentage may be higher when observed by a trained dermatologist.<sup>1</sup> These skin manifestations have been reported more and more since it was reported by Recalcati, who reported a higher percentage of skin manifestations,

namely in 20.4% of 88 patients positive for COVID-19. Skin involvement was found in eight patients before being diagnosed with COVID-19 and after hospitalization in ten patients.<sup>2</sup> Galvan Casas and colleagues have also reported a large clinical study in 375 cases with various skin manifestations related to COVID-19.<sup>3</sup>

Some dermatological manifestations appear distinct in disease before the more common signs and symptoms associated with COVID-19 and are associated with different duration, severity, and probable prognosis. However, the temporal relationship and severity of COVID-19 with dermatovenereological manifestations is still being debated.<sup>4</sup> Recognizing the pattern of dermatovenereological

manifestations related to COVID-19 can assist doctors in early diagnosis of the right disease and identifying complications that require treatment. These manifestations of dermatovenereological disorders can help identify people without symptoms of COVID-19. Dermatovenereological manifestations that may arise before respiratory symptoms in COVID-19 patients can raise awareness with self-isolation and prompt examination, which will help to slow the transmission rate of this highly infectious virus.<sup>5</sup>

Many studies have been conducted on the temporal relationship and severity of COVID-19 with dermatovenereological manifestations, and the results found several mucocutaneous manifestations

that have a relationship with the onset and the severity of COVID-19.<sup>6-9</sup> However, no studies have analyzed the relationship between dermatovenereological disease and the onset of COVID-19 and its severity. This study aims to describe the pattern of dermatovenereological disease related to COVID-19 and find out the temporal correlation and severity of patients with COVID-19 in isolation room RSUD Dr Soetomo Surabaya in 2021 so that in the future, diagnosis, treatment, and prognosis predictions can be more accurate.

## METHODS

This study was a retrospective analytic investigation that employed total sampling. Data were obtained from the medical records of patients diagnosed with COVID-19 with dermatovenereological manifestations treated at the Special Isolation Room (RIK) at RSUD Dr. Soetomo Surabaya in 2021. Inclusion criteria were as follows: (1) all patients with medical records indicating a diagnosis of COVID-19 based on RT-PCR nasopharyngeal swab results at RSUD Dr. Soetomo and presenting with dermatovenereological abnormalities (A term that describes the signs, symptoms, or physiological changes of a dermatological disorder. Manifestations of systemic disease on the skin vary extensively, ranging from specific to nonspecific); (2) COVID-19 patients classified as asymptomatic, mild, moderate, or severe; (3) availability of complete medical records containing the study variables, including data on diagnosis, clinical presentation, comorbidities, and therapy; and (4) no restrictions on age or gender. The study variables included COVID-19 patient status, severity of COVID-19 (asymptomatic, mild, moderate, severe), onset of dermatovenereological symptoms (before or during COVID-19), and dermatovenereological disease related to COVID-19.

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) software version 25.0 for Windows. The data were categorized and arranged in an SPSS sheet for result analysis and tabulation. The test used Chi-Square and Spearman, declared significant if  $<0.05$ . The research was conducted in the

Special Isolation Room (SIR) at RSUD Dr. Soetomo Surabaya in 2021.

## RESULTS

This study revealed that 25 (0.86%) patients diagnosed with COVID-19 and treated at isolation room RSUD Dr Soetomo Surabaya in 2021 presented with dermatovenereological manifestations. The majority of these patients were male (56%), in the late elderly age group (24%), and had comorbid diabetes mellitus (52%). The most common dermatovenereological

disease was candidiasis (26%), with an onset before the diagnosis of COVID-19 in 65.7% of cases. The majority of patients had moderate severity COVID-19 (76%).

The cross table above shows patients with dermatovenereological disease before and after the diagnosis of COVID-19. The chi-square test was done to determine the differences between the onset of the disease, and the result showed a p-value of 0.174 ( $p > 0.05$ ). It can be concluded that there is no difference in dermatovenereological disease with onset before and after COVID-19.

**Table 1. Baseline characteristics of subjects**

Characteristics of subjects	N (%)
Gender	
Man	14 (56.00)
Woman	11 (44.00)
Age (years)	
0-5	1 (4.00)
6-11	1 (4.00)
12 -16	1 (4.00)
17-25	2 (8.00)
26-35	4 (16.00)
36-45	2 (8.00)
46-55	5 (20.00)
56-65	6 (24.00)
> 66	3 (12.00)
Comorbidity	
Heart disease	2 (8.00)
Diabetic mellitus (DM)	13 (52.00)
Hypertension	7 (28.00)
Immunocompromised	4 (16.00)
Autoimmune disease	5 (20.00)
Cerebrovascular disease	1 (4.00)
Disease onset	
Before COVID-19	16 (65.70)
After COVID-19	9 (34.30)
Severity of COVID-19	
Mild	3 (12.00)
Intermediate	19 (76.00)
Severe	3 (12.00)
Diagnosis dermatovenereology disease	
Syphilis	1 (4.00)
Allergic contact dermatitis	3 (12.00)
Atopic dermatitis	5 (20.00)
Candidiasis of the skin and nail	6 (24.00)
Generalized skin eruption due to drugs and medicaments taken internally	3 (12.00)
Pemphigus foliaceus	1 (4.00)
Psoriasis vulgaris	1 (4.00)
Seborrheic dermatitis	1 (4.00)
Urticaria	2 (8.00)
Varicella without complication	1 (4.00)
Viral wart	1 (4.00)

**Table 2. Cross-tabulation and analysis of differences between diagnoses and onset of skin symptoms in COVID patients**

Diagnosis ICD-10	Onset of dermatoveneorology disease		p
	Before COVID-19 n (%)	After COVID-19 n (%)	
Syphilis	0 (0.00)	1 (100.00)	0.174
Allergic contact dermatitis	1 (33.33)	2 (66.67)	0.238
Atopic dermatitis	5 (100.00)	0 (0.00)	0.061
Candidiasis of the skin and nail	3 (50.00)	3 (50.00)	0.412
Generalized skin eruption due to drugs and medicaments taken internally	3 (100.00)	0 (0.00)	0.166
Pemphigus foliaceus	1 (100.00)	0 (0.00)	0.444
Psoriasis vulgaris	1 (100.00)	0 (0.00)	0.444
Seborrheic dermatitis	0 (0.00)	1 (100.00)	0.174
Urticaria	1 (100.00)	1 (100.00)	0.667
Varicella without complication	1 (100.00)	0 (0.00)	0.444
Viral wart	0 (0.00)	1 (100.00)	0.174

Chi-Square test; \*Significant p-value <0.05

**Table 3. Cross-tabulation and analysis of the relationship between diagnosis and Severity of COVID-19**

Diagnosis ICD-10	Severity COVID-19			p
	Mild n (%)	Intermediate n (%)	Severe n (%)	
Syphilis	0 (0.00)	1 (100.00)	0 (0.00)	0.848
Allergic contact dermatitis	0 (0.00)	2 (66.67)	1 (33.33)	0.419
Atopic dermatitis	0 (0.00)	5 (100.00)	0 (0.00)	0.373
Candidiasis of the skin and nail	1 (16.67)	3 (50.00)	2 (33.33)	0.147
Generalized skin eruption due to drugs and medicaments taken internally	0 (0.00)	3 (100.00)	0 (0.00)	0.584
Pemphigus foliaceus	1 (100.00)	0 (0.00)	0 (0.00)	0.022*
Psoriasis vulgaris	0 (0.00)	1 (100.00)	0 (0.00)	0.848
Seborrheic dermatitis	0 (0.00)	1 (100.00)	0 (0.00)	0.848
Urticaria	0 (0.00)	2 (100.00)	0 (0.00)	0.709
Varicella without complication	1 (100.00)	0 (0.00)	0 (0.00)	0.022*
Viral wart	0 (0.00)	1 (100.00)	0 (0.00)	0.848

Chi-Square test; \*Significant p-value <0.05

An analysis regarding the difference in the incidence of dermatovenerological manifestations and the severity of COVID-19 was carried out using the chi-square test. The results showed that there was a significant difference in the incidence of foliaceus pemphigus and uncomplicated varicella with a p-value of 0.022 each ( $p \leq 0.05$ ), so it can be concluded that there was a difference in the presence of foliaceus pemphigus and uncomplicated varicella at the severity level of mild COVID-19 compared to moderate and heavy. Meanwhile, other dermatovenerological diagnoses have insignificant differences compared to mild, moderate, and severe COVID-19 severity.

## DISCUSSION

The subjects of this study were patients with male sex (56%) greater than women (44%). The same study reported that more COVID-19 infections were found in men (54.6%) than women (45.4%). Male patients had a cure rate of 31.62% and a death rate of 6.84%, relatively higher than women.<sup>10</sup> Several research reports also observed that more cases of COVID-19 in Indonesia occurred in men than women, with the death rate for men being slightly higher than for women.<sup>11</sup> Women are known to be more resilient when it comes to viral infections; this is related to protecting the X chromosome and the hormone estrogen, which are essential in the adaptive immunity mechanism. The X chromosome involves several genes related to immunological processes, such

as several cytokine receptors, T-cell and B-cell activity genes, and transcription and translation regulatory factors. In addition, women have more estrogen receptors that protect the body and help the immune system, including T cells, B cells, macrophages, neutrophils, dendritic cells, and natural killer cells.<sup>12</sup>

The distribution of age groups in this study shows that all age groups can potentially be infected with COVID-19 accompanied by dermatovenerological manifestations. However, the highest distribution is found in the late elderly age group, namely 56-65 years (24%), and the early elderly age group, namely 46-55 years (20%). The UK study of over 10,000 COVID-19 patients was <0.01% in 18 to 39 years of age and 0.67% and 0.44%, respectively, in men and women

aged 80 and over.<sup>2</sup> Similar research by Karyono DR et al. found that most cases of COVID-19 occurred in the late adult age group (31-45 years), followed by the early elderly age group (46-59 years). Patients of reproductive age (18-59 years) dominate the incidence of COVID-19 in Indonesia.<sup>10</sup> The percentage of elderly patients with COVID-19 is 15%. However, the mortality rate for elderly Indonesians with COVID-19 is the highest compared to other age groups. COVID-19 mainly infects older people because of their low immune systems due to aging. In addition, most of the elderly have multimorbidity, which makes them more susceptible to COVID-19 infection. The elderly have been identified as a high-risk group for COVID-19 infection.<sup>11</sup> These results are consistent with the overall demographic characteristics of reported COVID-19 infections; lower infection rates have been noted in children, and higher infection rates and disease severity have been reported in males.<sup>13</sup> Thus, elderly patients with COVID-19 should receive priority medical care because of their vulnerability. This study also found many active adult age groups (17-45 years). The adult age group is actively working and involved in many daily activities, so they are easily infected if they do not strictly adhere to the COVID-19 control protocol.

The comorbid factors of COVID-19 patients with the most dermatovenereological manifestations were chronic diseases, including diabetes mellitus (DM) in 13 (52%) patients and hypertension in 7 (28) patients, other comorbid factors including autoimmune diseases (20%), and immunocompromised states (16%). Research Roncon L et al. reported the same results, namely, COVID-19 patients with comorbid DM were found to be the most and had a risk almost three times higher for ICU admission (OR 2.79; 95% CI: 1.85-4.22) and death (OR 3, 21; 95% CI: 1.82-5.64).<sup>14</sup> Other studies reported that the top three comorbid diseases in COVID-19 patients were hypertension (52.1%), DM (33.6%), and other cardiovascular diseases (20.9%).<sup>10</sup> DM patients are a high-risk group for COVID-19 infection. Researchers have identified that poor glycemic control is associated with

poor outcomes in patients with severe COVID-19 severity.<sup>14</sup> Hypertension was identified as the dominant factor for COVID-19 infection. Many assumptions exist that patients with unstable blood pressure have more renin-angiotensin-aldosterone system (RAAS) inhibitors, such as ACE-2, associated with increased susceptibility to COVID-19. In addition, COVID-19 patients with hypertension have twice the risk of death. Among other comorbidities, hypertension is recognized as the leading cause of death among patients with COVID-19.<sup>15,16</sup> These findings highlight that DM and hypertension are high-risk factors for severe COVID-19 infection, requiring more medical attention and care.

In this study, it was found that 0.86% of COVID-19 patients had dermatovenereological disease. These results are less than those of Giavedoni's study in Spain in 2020; data showed that skin lesions affect around 2% of patients with COVID-19.<sup>17</sup> Dermatovenereological diagnosis was reported in 65.7% before the diagnosis of COVID-19, and 34.3% developed dermatovenereological manifestations at the diagnosis of COVID-19. Another study reported from the collected data (88 patients with COVID-19) that 18 patients (20.4%) experienced skin manifestations, eight developed skin involvement before hospitalization, and ten patients after hospitalization.<sup>18</sup> Differences in the pattern of timing of the appearance of dermatovenereological manifestations may be related to patients' subjective reports of remembering the exact presentation time, few reported cases, and a lack of photography or inadequate understanding of the term dermatovenereological manifestations. Regardless of the dermatovenereological diagnosis type, this study found that 76% of COVID-19 patients with dermatovenereological manifestations had moderate COVID-19 symptoms, and 12% had mild and severe COVID-19 symptoms. These results are similar to the research reported by Jamshidi P et al., who found that as many as 80% of COVID-19 patients with skin manifestations experienced mild and moderate disease, and 20% experienced severe COVID-19 disease. A previous

study from the Chinese Center for Disease Control and Prevention reported that 81% of COVID-19 patients experienced mild illness, 14% severe, and 5% critical. No specific data exists on patients without skin manifestations, but comparing the severity of COVID-19 in patients with skin manifestations and COVID-19 patients, regardless of symptoms, shows no apparent difference.<sup>4</sup>

From the results of this study, 11 types of dermatovenereological diagnoses were found in COVID-19 patients treated in the isolation room of Dr. Soetomo Hospital Surabaya, namely syphilis, allergic contact dermatitis, atopic dermatitis, candidiasis, drug reactions, pemphigus foliaceus, psoriasis vulgaris, seborrheic dermatitis, urticaria, varicella and viral warts. Most dermatovenereological diagnoses in COVID-19 patients were candidiasis (24%), atopic dermatitis (20%), allergic contact dermatitis, and the same drug reactions (12%). A similar study was conducted by Kutlu and Metin in 2020, which found that the most common dermatologic diseases were superficial fungal infections (11; 21.2%), seborrheic dermatitis (7; 13.5%), actinic keratosis (6; 11.5%), psoriasis (5, 9.6%), herpes simplex (3; 5.8%), and eczema (3; 5.8%), respectively.<sup>19</sup> Recent publications have proposed a framework for classifying the skin manifestations of COVID-19. One approach is to classify based on pathophysiology, as some skin manifestations of COVID-19 appear to be directly virally mediated. In contrast, others appear to be secondary to a robust host response to infection.<sup>20</sup> The dermatovenereological manifestations of viral infection may lead to several distinct clinical patterns, especially since the different patterns do not coexist in the same patient. This hypothetical polymorphism may be due to several alternative causes or differences in the virus or host. Some lesions, even in patients with confirmed COVID-19, are similar to those of other viral infections. So far, no data in the literature on skin manifestations in COVID-19. Information regarding the classification of dermatovenereological manifestations in COVID-19 is essential for clinicians, identifying important patterns or information that can predict



cases reported so far.<sup>21</sup>

The similarity between cutaneous and mucosal immunity suggests that decreased cutaneous immunity may indicate decreased mucosal immunity.<sup>19,22</sup> SARS-CoV-2 makes infection pass through nasal mucosa by using the angiotensin-converting enzyme two receptors, which is found in the basal layer of the nonkeratinizing squamous epithelium.<sup>23</sup> The previous studies revealed that the power of the mucosal innate and adaptive immune systems, which contain CD4+ T-helper cells, Th17, high-avidity CD8+ CTL, and secretory IgA and IgG1 neutralizing antibodies, may prevent viral spreading into the nasal mucosa. These suggestions allow us to know the importance of mucosal immunity on the SARS-CoV-2.<sup>20,24</sup> Of note, the previous animal study reported that Th1 and Th17 immune responses (including IL-17A and IFN- $\gamma$ ), which are also essential factors in preventing viral damage in the nasal mucosa, are individually unnecessary but together contribute to the optimal healing of superficial fungal infections.<sup>25</sup> Therefore, it can be concluded that patients with a superficial fungal infection may have decreased cutaneous and mucosal immunity; this may explain why a patient with superficial fungal infections may be more prone to COVID-19 infections. Determining the relationship between cutaneous and mucosal immunity may lead to the development of a preventive treatment approach strategy in patients with immune-related skin diseases in COVID-19 and possibly other viral pandemics.<sup>26</sup> Drug-induced eruptions may occur during COVID-19. COVID-19 patients usually use a set of medications that can potentially cause cutaneous rashes. The current study found that paracetamol, azithromycin, hydroxychloroquine, lopinavir/ritonavir, and remdesivir were the most common medications used for COVID-19 patients. Paracetamol has been reported to cause asymmetrical drug-related intertriginous and flexural exanthema (STRIFE). However, in the Mahé A et al. study, despite keeping the drug, skin lesions disappeared, which is very uncommon in drug reactions.<sup>4,27</sup> Najarian DJ mentioned that maculopapular lesions of their patient

could be due to azithromycin use or hypersensitivity reaction to azithromycin due to concurrent viral infection.<sup>28</sup>

The results of this study found that most dermatovenereological manifestations appeared before the diagnosis of COVID-19 (65.7%) and at the time of diagnosis of COVID-19 (34.3%). The association of symptom onset with each dermatovenereological diagnosis was analyzed using the Chi-square test. This analysis found no statistically significant association between the onset of skin symptoms and each dermatovenereological disease ( $p > 0.05$ ). The results of this study are different from the study conducted by Galván Casas and colleagues, who reported that the most dermatovenereological manifestations in COVID-19 patients (56.8%) were found when the patient was hospitalized or when diagnosed with COVID-19 after the patient was treated. In hospitals (37.3%) and only a few (5.9%), dermatovenereological manifestations in COVID-19 patients were reported before the patient was diagnosed with COVID-19.<sup>3</sup> Several studies have analyzed the temporal relationship between the onset of mucocutaneous manifestations and COVID-19. The results show that the temporal relationship between the onset of symptoms and dermatovenereological manifestations in COVID-19 patients is still being debated. However, no studies have analyzed differences in the incidence of dermatovenereological diseases. The large variety of dermatological presentations reported in COVID-19 patients and the inconsistency of data regarding the relationship between skin presentations of COVID-19 and temporal onset.<sup>4</sup> There is no more complete data regarding the exact relationship between the onset of symptoms and dermatovenereological disease in COVID-19 patients due to the lack of complete information data from COVID-19 patients during anamnesis. The risk of transmission is too high, so there are restrictions on communication and taking pictures of patients, and a lack of understanding regarding the classification of dermatovenereological manifestations by doctors or other medical personnel. Recognizing COVID-19-related cutaneous manifestations may assist clinicians in the early diagnosis

of disease before the development of respiratory symptoms and may also be used to identify complications requiring treatment. The current study found that 10.5% of COVID-19 patients reported skin lesions before initiating other symptoms or as their chief complaint. On the other hand, considering cutaneous manifestations is essential to make the proper diagnosis; as Joob B et al. reported, a COVID-19 patient with petechiae was misdiagnosed with dengue fever.<sup>29</sup> This study also demonstrated that 34.5% of cutaneous manifestations occurred simultaneously with other symptoms, particularly urticaria-like lesions (47%). It may suggest that urticaria-like lesions may be a diagnostic sign of COVID-19.<sup>4</sup> However, in our study, there were 8% of COVID-19 patients who experienced urticaria, and the analysis showed no difference between urticaria that appeared before and after the diagnosis of COVID-19.

Until now, several reports have been on cutaneous manifestations in COVID-19 patients. However, the link between skin manifestations and the severity of the disease remains debatable. The dermatovenereological diagnosis in this study was primarily found in patients with moderate symptoms of COVID-19 (76%). The analysis showed a significant difference between the incidence of pemphigus foliaceus disease and uncomplicated varicella at mild COVID-19 severity levels compared to moderate and severe. Meanwhile, other dermatovenereological diagnoses have insignificant differences compared to mild, moderate, and severe COVID-19 severity. This result differed from the study's systematic review of case reports/series of AIBD patients in association with the COVID-19 outbreak performed in the initial phase of the pandemic. Out of a total of 732 AIBD cases (211 pemphigus, 112 pemphigoids, 409 not specified), COVID-19 symptoms were reported in 70 (9.5%) patients, and in 16 (2.1%) patients, the diagnosis was confirmed. Six (0.8%) patients had severe symptoms requiring hospitalization, and 3 (0.4%) died of COVID-19; all older people had comorbidities. Compared with the general population, this systematic review concluded that patients with

AIBDs are not at increased risk of severe or fatal COVID-19.<sup>30</sup> Joly P reported that out of 5180 patients with AIBDs, 59 (1.1%) were diagnosed with possible (suggestive clinical symptoms and contact with COVID-19), probable (suggestive computed tomography scan), or confirmed COVID-19 (positive reverse transcriptase polymerase chain reaction). Within this cohort, 30 (0.6%) were hospitalized, 7 (0.1%) were admitted to an intensive care unit, and 15 (0.3%) died. The age and region-standardized incidence ratio of hospitalized confirmed COVID-19 infection was 0.42 for bullous pemphigoid, 1.02 for confirmed COVID-19, was 1.63-fold higher in hospitalized patients with AIBD than in the general population of the same age (23%). Patients with AIBD and COVID-19 had a 5.9-fold higher 3-month death risk than patients with AIBD without COVID-19. Patients with AIBD who were hospitalized due to COVID-19 or had a lethal form of COVID-19 were older than those with a benign form.<sup>31</sup> Kridin K et al. found that out of 1845 patients with bullous pemphigoid and 1236 patients with pemphigus, 24 (1.3%) and 12 (1.0%) were diagnosed with COVID-19, 12 (0.7%) and 5 (0.4%) were hospitalized (without being mechanically ventilated), and 6 (0.3%) and 1 (0.1%) died, respectively. The risk of COVID-19 and COVID-19-associated hospitalization was comparable between patients with bullous pemphigoid and controls. The risk of COVID-19-associated mortality was higher among patients with bullous pemphigoid. The risk of COVID-19, COVID-19-associated hospitalization, and COVID-19-associated mortality were similar in patients with pemphigus and their controls.<sup>32</sup>

Coinfection with other viruses is another potential possibility for COVID-19-related cutaneous manifestations. Some skin lesions in COVID-19 patients are very similar to rashes induced by other viruses like parvovirus18, herpes simplex virus type 1 and 2 (HSV-1, HSV-2), varicella-zoster virus (VZV), and poxviruses, both clinically and histologically. It is probable that because of the attenuation of the immune system, COVID-19 patients are susceptible to coinfection with or relapse of the other viral exanthems. This hypothesis

is strongly suggested for vesicular and some miscellaneous lesions (e.g., erythema multiforme) due to their unique histologic findings compared to other skin lesions of COVID-19.<sup>3,21,33</sup> A study reported four COVID-19 patients presenting diffuse vesicular lesions, and microbiological and serological investigations demonstrated varicella infection.<sup>3</sup> Thus, in COVID-19 patients with vesicular lesions, physicians must investigate other etiological factors besides SARS-CoV-2.

This study has limitations because it was conducted in a tertiary care hospital, so that the manifestation may differ from patients in primary and secondary hospitals. Planning and carrying out research using larger sample sizes in different areas is important, which will help better interpret the population. Limited articles mentioned complete data about all the items, including the onset, severity, and outcome of COVID-19 patients with dermatovenerology disease. Future cohort studies must compare the disease's onset, severity, and prognosis in patients with and without dermatovenerological disease, considering other related characteristics. Such studies help better understand the prognostic value of the dermatovenerological disease in COVID-19 patients.

## CONCLUSION

This study concluded that dermatovenerological disease occurs most often before diagnosis of COVID-19, although there was no significant difference between the onset of dermatovenerological disease and COVID-19 infection. The dermatological disease was found more frequently in patients with severe degrees of COVID-19. However, a significant difference between the incidence of dermatovenerological disease and the severity was found in pemphigus foliaceus and varicella with mild degrees of COVID-19. The occurrence of skin manifestations in COVID-19 patients is not an indicator of the severity of the disease, and it highly depends on the type of skin lesions. However, we highly suggest that emergency and general practitioners evaluate the suspected COVID-19 patients for any cutaneous manifestations.

## ETHICAL CONSIDERATION

The present research was approved and reviewed by the Ethical Committee (Reference no. 0032/LOE/301.4.2/VI/202) of Dr. Soetomo General Teaching Hospital situated in Surabaya, Indonesia.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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## AUTHOR CONTRIBUTIONS

Conceptualization, E.R.Y., A.N.H.; data curation, E.R.Y., A.N.H., C.R.S.P., D.M., M.D.A., B.U.; writing—original draft preparation, E.R.Y., A.N.H.; writing—review and editing, E.R.Y., A.N.H., C.R.S.P., D.M., M.D.A., B.U. All authors contributed significantly to this work, and all agree with the contents of this article.

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