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SARS-CoV, Mers-CoV and COVID-19: what differences from a dermatological viewpoint?

Editor,

Over the past two decades, 3 zoonotic global coronavirus outbreaks have occurred: 1. SARS starting in 2002 in China due to SARS-CoV; 2. MERS starting in 2012 in Saudi Arabia due to MERS-CoV; 3. COVID-19 due to SARS-CoV-2 starting in 2019 in Wuhan, China.¹ Both beta-coronaviruses, SARS-CoV and MERS-CoV, caused a severe disease in most infected people. In fact, as many as 8700 cases were confirmed from 37 countries with 775 deaths for SARS, while 2494 MERS cases and 858 deaths have been reported worldwide in 27 countries. SARS-CoV-2 caused a pandemic that spread across 203 countries in all 5 major continents involving many more cases than its predecessors.² Phylogenetic analysis of SARS-CoV-2 indicated that it is related to SARS-CoV (~79%) and MERS-CoV (~50%).³ Pathological manifestations of COVID-19 greatly resemble what has been seen in SARS and MERS infection and the pathologic findings indicate that a similar cytokine cascade storm plays a critical role in patient rapid death.⁴

However, it is clear now that the epidemic of COVID-19 is different from SARS and MERS. Although presenting symptoms are similar – fever and cough, progressing to pneumonia in severe cases, with poorer outcomes associated with men gender, older age and comorbidities – SARS and MERS were/are much less transmissible but more likely to be severe or fatal than COVID-19. In fact, COVID-19 has a general fatality rate of 3.4% lower than that of SARS (9.6%) and much lower than that of MERS (34.4%)⁵ but SARS-CoV-2 caused many more deaths.

As for dermatology, the most relevant difference between COVID-19 and SARS/MERS is the absolute lack of reports of skin manifestations in the latter. Actually, many cutaneous manifestations have been described in association with SARS-CoV-2 infection, although their prevalence is controversial ranging from 0.2% in a cohort of 1099 Chinese patients to 20.4% in an Italian study of 88 patients.^{8,9}

They include the following: pseudo-chilblain lesions, livedoid or necrotic lesions and vesicular eruptions which appear as the

most characteristic ones and urticarial, purpuric and maculopapular eruptions which are the most frequent rashes, albeit less specific.^{6,7}

The reasons why there is a robust evidence in the literature of cutaneous manifestations in COVID-19 due to SARS-CoV-2 and not even one report of skin rashes both in SARS-CoV and MERS-CoV infections is unclear. One possible explanation is that the international response to COVID-19 has been more transparent and efficient when compared to the SARS/MERS outbreaks. The rapidly progressing of COVID-19 pandemic has become a global concern stimulating a lot of dermatological researches with many more cases than its predecessors. Another explanation is that a part of these skin manifestations of COVID-19 is not directly related to the virus but to the multodrugs which have been used in a relatively large amount in COVID-19 compared to the therapies used for the previous epidemic of SARS and MERS.¹⁰ In this setting, we cannot rule out that, in view of the greater severity of lung and multiorgan involvement in SARS and MERS, the skin has received less attention or that SARS-CoV and MERS-CoV may have less tropism for the skin than SARS-CoV-2.

There is still much more to know about skin manifestations associated with COVID-19 but unfortunately, we cannot learn from the experience of previous coronavirus epidemics. It is only with this new pandemic that dermatologists are exploring a new chapter whose aim is not only to identify patients or asymptomatic carriers in the risk population throughout skin signs but also to understand whether skin rashes could be a part of a potential transmission route for SARS-CoV-2.

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Conflicts of interest

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LETTERS TO THE EDITOR

Sensitivity and specificity of SkinVision are likely to have been overestimated

Editor

Udrea *et al.*¹ reported 95.1% sensitivity and 78.3% specificity using the SkinVision app for risk assessment of skin lesions. These are likely to be overestimated due to the nature of the study design and flaws in sampling.

The study design, where inclusion of those with and without disease is undertaken separately, is known as a diagnostic case-control study or a two-gate design.² These studies have been shown to overestimate both sensitivity and specificity across many clinical applications compared to the ideal design, where all using the test as intended are recruited to a study prior to ascertaining disease status.³

The risk of bias in this study is further increased by the method of lesion selection. The app is intended for use by laypersons to self-assess skin lesions; thus, its accuracy should be assessed in this context. Three previous studies of SkinVision have been entirely based on clinically selected cohorts.^{4–6} Udrea *et al.* did use some app users' data for evaluation; however, these data are mixed with clinical cohorts, and the app users have been selected in a way that is almost certain to have introduced bias.

The sensitivity of the app was evaluated in two cohorts of clinically investigated patients combined with a cohort of app users. The clinical cohorts are from previous studies^{5,6} including 48

malignant melanomas (40 from Munich,⁵ 8 from Eindhoven⁶) with 147 other malignant and premalignant lesions (all from Eindhoven: 107 basal and 8 squamous cell carcinomas; 18 actinic keratosis; 14 Bowen's Disease). Although inclusion of secondary care cohorts ensures histological verification, these patients have gone through several selection steps (choosing to present to primary care, referral from primary care, excision decision in secondary care) and are thus unlikely to be representative of typical app users, and possibly reflect more clearly defined cases than the early skin cancer that the app aims to detect.

However, it is the selection of data collected from app users which is the more serious flaw. All app users had used a previous SkinVision app, with the image checked by a dermatologist – a senior dermatologist for high-risk images and a junior dermatologist for low-risk images. Users with high-risk results were invited to provide follow-up data, resulting in the inclusion of 90 high-risk-rated melanomas. Malignant lesions previously missed by the app (estimated as 20% in the Eindhoven cohort⁶) and the check by junior dermatologists could not have been included and are likely to be the more difficult to diagnose cases. The proportion of those invited to follow-up who provided histology results (338 of 48 547 – 0.7%) is very small, with substantial further potential for selection bias. Verification of the 6000 benign lesions was based on the junior dermatologist's assessment of a single image taken by the app with no histology or follow-up data, which is suboptimal. Recruitment of benign lesions seems to have been restricted to those judged as low or medium risk by the previous SkinVision app and clinical assessment, and the false-positive cases from that app (22% of benign lesions in the Eindhoven data⁶) will have been automatically excluded, and are likely to have been more difficult to diagnose. These flaws make overestimation of both sensitivity and specificity highly likely.

Whilst skin cancer diagnosis apps might make valuable contributions, screening applications for public use can easily do harm through missing skin cancer cases and from over-investigation of false positives. It is essential that appropriate studies are done before recommendations are made to widely disseminate technologies, as is happening with SkinVision.⁷ We have recently reviewed all evidence of the accuracy of skin diagnosis apps which use inbuilt algorithms and failed to find any examples of well-done studies.⁸ Our review contains constructive guidance for investigators to minimize bias and increase external validity to app users – we hope that future studies can meet these criteria.

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Conflict of Interest

All authors indicate that they have no conflicts of interest to declare.