Diagnostic value of skin manifestation of SARS-CoV-2 infection

Bataille V.[1,2,*], Visconti A.[1,*], Rossi N.[1], Murray B.[3], Bournot A.[4], Wolf J.[4], Ourselin S.[3], Steves C.[1], Spector T.D.[1,†], Falchi M.[1,†]

[1]Department of Twin Research and Genetic Epidemiology, King's College London, London, UK

[2]Dermatology Department, West Herts NHS Trust, Herts, UK.

[3]School of Biomedical Engineering & Imaging Sciences, King's College London, London, UK

[4]Zoe Global Ltd

*These authors contributed equally

[†]These authors jointly supervised this work

Abstract

SARS-CoV-2 causes multiple immune-related reactions at various stages of the disease. The wide variety of skin presentations has delayed linking these to the virus. Previous studies had attempted to look at the prevalence and timing of SARS-COV-2 rashes but were based on mostly hospitalized severe cases and had little follow up. Using data collected on a subset of 336,847 eligible UK users of the COVID Symptom Study app, we observed that 8.8% of the swab positive cases (total: 2,021 subjects) reported either a body rash or an acral rash, compared to 5.4% of those with a negative swab test (total: 25,136). Together, these two skin presentations showed an odds ratio (OR) of 1.67 (95% confidence interval [CI]: 1.41-1.96) for being swab positive. Skin rashes were also predictive in the larger untested group of symptomatic app users (N=54,652), as 8.2% of those who had reported at least one classical COVID-19 symptom, *i.e.*, fever, persistent cough, and/or anosmia, also reported a rash. Data from an independent online survey of 11,546 respondents with a rash showed that in 17% of swab positive cases, the rash was the initial presentation. Furthermore, in 21%, the rash was the only clinical sign. Skin rashes cluster with other COVID-19 symptoms, are predictive of a positive swab test and occur in a significant number of cases, either alone or before other classical symptoms. Recognising rashes is important in identifying new and earlier COVID-19 cases.

Introduction

During the COVID-19 pandemic, it became clear that the SARS-CoV-2 virus, whilst mainly targeting the lungs, also affected multiple other organs, including the heart, kidneys, and brain[1]. Skin manifestations were slower to be reported, possibly because in patients in critical conditions the need for documenting skin changes was less pressing, and because the virus causes a wide variety of skin symptoms that delayed recognising their link with COVID-19[2]. The first cases of COVID-19 affecting the skin were documented in China, but the prevalence was very low at 0.2% in 1,099 hospital cases[3]. Italy then reported that 20% of the patients on a COVID-19 ward (N=88) had skin signs[4]. A large series of 375 patients from Spain as well as from other groups[2,5,6] have described urticarial, dengue fever-like, chickenpox-like rashes as well as less frequent cases of chilblains affecting fingers or toes (acral rash), thought to be due to minor thrombotic events or damage to the endothelial walls of small distal vessels of the digits.

Here, using a population approach, we investigated the diagnostic value of body and acral rashes for SARS-CoV-2 infections using data from 336,847 users of the COVID Symptom Study app[7], and from an independent survey on COVID-19 related skin symptoms in 11,546 subjects, 2,328 of whom also shared photos of their skin complaints.

Results

Among 336,847 UK users of the COVID Symptom Study app who registered between May 7th and June 22nd 2020, 6,403 reported the presence of skin signs and symptoms (**Table 1**). Most of the users included in this study were white European (94.0%), and ethnicity, smoking status, chronic diseases, and medications are summarised in **Supplementary Table 1**. Results for SARS-CoV-2 swab tests were provided by 27,157 users (8.1%), 2,021 of whom (7.4%) were positive. Among users who were not tested for SARS-CoV-2, 54,652 were symptomatic (*i.e.*, reported at least one of the 16 collected symptoms), including 17,371 individuals presenting with at least one of the three main symptoms of COVID-19 (*i.e.*, fever, persistent cough, and/or anosmia) whose presence, as suggested by the NHS guidelines, would require isolation and testing for SARS-CoV-2 infection.

Skin-related symptoms were reported by 1,534 users who had a swab test, and by 3,672 untested symptomatic users. Among the 2,021 users who tested positive on swab test, 178 users (8.8%) reported skin related changes. Of those, 138 (6.8%) reported body rashes and 62 (3.1%) acral rashes (**Table 1).** Only 22 (1.1%) of them reported both body and acral skin-related symptoms. Infected individuals reporting acral rashes were slightly older (mean age = 50.2) than those who did not report this skin symptom (mean age = 43.7; Wilcoxon's test $P = 6.27 \times 10^{-3}$). In addition, body rashes prevalence was

slightly higher among females (odds ratio [OR] = 1.60, 95% Confidence Interval [CI] = 1.08-2.44, P = 0.02). We did not observe any age differences for body rashes or sex differences for acral rash prevalence (P > 0.05).

Similar skin symptoms were also seen in symptomatic untested users: 1,429 (8.2%) of users who did not have a swab test but reported any of the three classical COVID-19 symptoms also reported a rash, compared to 6.0% for those whom were not tested and did not report any of the three classical COVID-19 symptoms (OR = 1.40, 95% CI = 1.31-1.50, $P < 2.2x10^{-16}$). We could not assess whether ethnicity affected the prevalence of skin symptoms as the number of non-European users with skin symptoms was too low (**Supplementary Table 1**).

Association analysis highlighted higher prevalence of either body or acral rashes among individuals who tested positive for SARS-CoV-2 compared to those who tested negative (OR=1.67, 95% CI=1.41-1.96, $P=1.45x10^{-9}$). The subtypes were similar. Body rashes were associated with SARS-CoV-2 positive swab with an OR of 1.65 (95% CI =1.37-1.99, $P=1.30x10^{-7}$), whereas the OR for acral rashes was 1.73 (95% CI=1.32-2.27, $P=7.25x10^{-5}$; see **Methods)**. Sensitivity analyses are reported in **Supplementary Table 2.** The comparison between 17,371 symptomatic untested users who reported at least one of the classical COVID-19 symptoms and those who did not report any of the three yielded an OR of 1.46 (95% CI=1.35-1.58, $P=2.92x10^{-20}$) for body rash, while the association with the rarer acral rash was not significant (P = 0.22). In comparison, the odd ratio for fever was 1.47 (95% CI= 1.31-1.65, $p=5.77x10^{-7}$).

To better investigate the duration of these skin rashes and their timing in relation to other COVID-19 symptoms, we collected data from 11,546 individuals who responded to an independent on-line survey on possible COVID-19 related skin rashes. Median age [1^{st}-3^{rd} quartile] was 53 years old [41-63], 77% of whom were female. Among them, 694 surveyees reported a positive SARS-CoV-2 swab or antibody test, and 3,109 were not tested but reported to have had one of the three classical COVID-19 symptoms. Photos of rashes were shared by 2,328 surveyees, and 365 photos were randomly selected across sexes and age ranges. These were assessed by an experienced dermatologist and divided in three categories (see **Methods**). Of these, 56 photos were removed because of bad quality and 42 were judged not attributable to SARS-CoV-2 infection (13.6%). The three most common presentations were papular rashes (including erythemato-papular and erythemato-vesicular types, 41%), urticaria (28%), and acral lesions (23%). The average duration of symptoms was 24 days for acral lesions, 18 days for papular, and 10 days for urticaria (significantly shorter duration; Wilcoxon's $P < 1.3x10^{-3}$; **Figure 1**). We did not observe significant differences in either age or sex distribution between the three types of rashes.

The 694 surveyees that declared to have been tested positive to SARS-CoV-2 *via* a swab or antibody test, with skin signs, also reported other classical COVID-19 related symptoms: fatigue (11%), headaches

(9%), loss of smell (9%), fever (7%), muscle pain (6%), shortness of breath (6%) and persistent cough (6%) being the most common. Interestingly, while most surveyees declared skin changes to appear at the same time as other COVID-19 symptoms (47%) or afterwards (35%), in 17% of the cases skin symptoms appeared before any other symptoms, and in 21% of the cases they were the only symptom. Similar estimates were obtained when focusing on the 3,109 untested subjects presenting with at least one of the classic COVID-19 symptoms, where 47%, 39%, and 15% surveyees declared to have had skin symptoms during, after, and before any other symptoms, respectively.

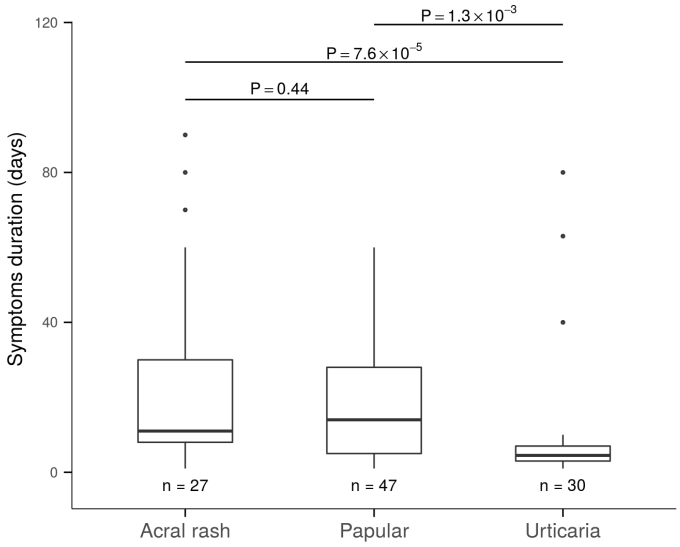

Figure 1. Distribution of duration of symptoms for the three most common skin symptoms diagnosed from the photos of 267 users of our survey.

Table 1. Sample characteristics. Categorical values are reported as number and percentage, and compared using Pearson's χ^2 test. Continuous values are reported as mean ± standard deviation and compared using Wilcoxon's test. Associations P values with body and acral rash are from logistic regression, and with BMI from linear regression, adjusted for the relevant covariates (see **Methods**). "Users tested" refers to individuals self-reporting a positive or negative swab test result. "Symptomatic untested users" refers to individuals who reported at least one of the 16 collected symptoms, did not believe that they had already had COVID-19 when first registering with the app, had not yet been tested for SARS-CoV-2. "Classic symptoms" refers to those included in the NHS guidelines (*i.e.*, fever, persistent cough, and/or anosmia).

	All users	**Users tested for SARS-CoV-2**				**Symptomatic untested users**			
		All	**Positive**	**Negative**	**P value**	**All**	**With classic symptoms**	**Without classic symptoms**	**P value**
N	336,847	27,157	2,021	25,136	-	54,652	17,371	37,281	-
Females (%)	188,118 (55.8%)	16,474 (60.7%)	1,376 (68.1%)	15,098 (60.1%)	1.47×10^{-12}	34,789 (63.7%)	10,684 (61.5%)	24,105 (64.7%)	1.03×10^{-12}
Age	43.9±19.7	43.9±17.5	43.9±15.6	43.9±17.7	0.09	41.4±18.5	38.2±19.4	42.9±17.8	1.51×10^{-145}
BMI	26.2±6.4	27.0±6.5	28.2±6.8	26.9±6.5	$<2.20 \times 10^{-16}$	26.6±6.7	26.7±7.2	26.5±6.4	$<2.20 \times 10^{-16}$
Healthcare workers (%)	31,915 (9.5%)	7,494 (27.6%)	1190 (58.9%)	6,304 (25.1%)	2.94×10^{-234}	5,344 (9.8%)	1,541 (8.9%)	3,803 (10.2%)	1.18×10^{-6}
Body rash (%)	4,812 (1.4%)	1,177 (4.3%)	138 (6.8%)	1,039 (4.1%)	1.30×10^{-7}	2,729 (5.0%)	1,128 (6.5%)	1,601 (4.3%)	2.92×10^{-20}
Acral rash (%)	2,188 (0.6%)	520 (1.9%)	62 (3.1%)	458 (1.8%)	7.25×10^{-5}	1,210 (2.2%)	419 (2.4%)	791 (2.1%)	0.22

Discussion

COVID-19 is now known to have varied clinical manifestations and to target multiple organs, including the skin[1,3]. COVID-19 rashes may present in many forms and at different stages of the disease. The heterogeneous presentations, the time delay, as well as the focus on severely ill patients during the early phases of the pandemic, led to the skin being overlooked as an important target organ for COVID-19.

In this community-based study, 8.8% of positive COVID-19 cases *via* swab tests and 8.2% of users who were not tested but reported at least one of the classic COVID-19 symptoms, based on NHS guidelines, also reported skin rashes. Our data suggest that skin rashes are valuable predictors for COVID-19 positivity, with an odds ratio of 1.67 for any type of rashes in users tested for SARS-CoV-2. When looking at types of rashes, body rashes were more frequent than acral lesions (6.8% *vs* 3.1%) although their predictive value was equivalent (OR=1.65 *vs* 1.73, respectively). The odd ratio for both types of rash was greater than for fever (1.47) and fever has been used widely to screen for COVID. Reports of cases with both body rashes and acral lesions were rare, and this suggests different pathogenesis with the former caused by immunological reactions to the virus whilst acral rashes are more likely to be explained by delayed small thrombotic occlusions or damage to vessel walls[2].

The use of the COVID Symptom Study app by UK citizens has been valuable to document the presence of many different types of COVID-19 symptoms in the community [8]. However, data on skin symptoms were only recently collected, and this hindered our ability to identify at which stage of the disease they appear and how long they last. An independent survey was therefore carried out to capture more details on the types of rashes, their duration, timing, results from SARS-CoV-2 swab/antibody test, and co-occurring symptoms. The prevalence of the three types of rashes was assessed with photos by a dermatologist. This showed that papular rashes were the most frequent, acral lesions the longest lasting, while urticaria was short lived. The survey also showed that 17% of the SARS-CoV-2 positive users and 15% of the untested users with at least one of the classical COVID-19 symptoms may not have any other concomitant symptoms when they first become unwell, and, as a result, might miss out on early diagnosis. When additional symptoms co-occurred in infected individuals, the most frequent were the most classical COVID-19 symptoms such as fever, persistent cough, and anosmia. Furthermore, 21% of the SARS-CoV-2 positive surveyees presented with skin symptoms alone, and would have been missed if using the NHS classic symptoms alone. The Spanish study[5] had attempted to investigate the timing and duration of rashes but the cases, as well as those from previous studies, were mostly more severe hospitalized patients and there was little follow up for late skin manifestations.

A major limitation of the current study is the self-reported nature of the data. However, we believe that the presence of a rash, especially if symptomatic, is less subjective and more specific than symptoms such as fatigue, headaches, or chronic cough. About 13.6% of the photos uploaded by the surveyees which were assessed represented likely non-CoVID-19 related dermatological conditions, thus suggesting that the overall number of self-reported rashes may have been overestimated. However, the large number of users of both our COVID Symptom Study app and the survey in this study makes it unlikely that such reporting errors may have significantly affected our estimates. On the other hand, many of the COVID Symptom Study app users may have failed to realise the relevance of skin symptoms and not have reported them if not accompanied by other more known COVID-19 symptoms. Second, our study sample is not fully representative of the general population, as it represents a self-selected group of individuals, and also because of the uneven access to SARS-CoV-2 testing in the early stages of the pandemic, with tested subjects encompassing a mixture of healthcare workers, at-risk subjects with chronic diseases, elderly people, etc. Third, although COVID-19 rashes can be divided into three main types, *i.e.*, urticarial on the face or body, erythemato-papular/vesicular usually present on central body, and chilblains/perniosis on acral sites, the app only classified them into two categories, with the urticarial rash and erythemato-papular/vesicular rashes together, as both tend to be itchy and the users may not be able to differentiate between them.

The NHS in UK lists three main classical symptoms suspicious of COVID-19 (www.nhs.uk/conditions/coronavirus-covid-19/symptoms), whilst the CDC in the USA lists five (https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html). However, these do not currently include skin-related symptoms, although they can be easily spotted by patients.

This study strongly supports the inclusion of skin rashes in the list of suspicious COVID-19 symptoms. Although, it is less prevalent than fever, it is more specific of COVID-19 and last longer. An increased awareness from the public and healthcare professionals regarding COVID-19 skin changes will allow more efficient identification of new and earlier clusters of the disease.

Methods

The COVID Symptom Study app

The COVID Symptom Study app was developed by Zoe Global Limited, supported by physicians and scientists at King's College London and Massachusetts General Hospital, Boston. The COVID Symptom Study app has been described in detail previously[7]. The app collects, on sign up, data on sex, age, ethnicity, and core health risk factors, including height, weight, and common disease (*e.g.*, cancer,

diabetes, heart, kidney, and lung disease) status, the use of a set of medications (*e.g.*, corticosteroids, immunosuppressants, and blood pressure medications), and whether the individual is a healthcare worker. Since May 7th, 2020, the app also prompts users to self-report detailed information, also retrospectively, regarding whether they have ever had a SARS-CoV-2 test, and, for each test, how this was performed (*e.g.*, nose/throat swab, antibody testing), and the test result. By using the app, users can provide updates on their daily health status by answering the question "How do you feel right now?". If they feel unwell, the app further collected self-reported presence of 14 COVID-19-related symptoms, namely: abdominal pain, chest pain, delirium, diarrhoea, fatigue, fever, headache, hoarse voice, loss of smell, persistent cough, shortness of breath, skipped meals, sore throat, and unusual muscle pains. From April 29th, 2020, skin manifestations of the disease were added: raised, red, itchy wheals on the face or body or sudden swelling of the face or lips (body rash), and red/purple sores or blisters on the feet or toes (acral rash). Asking the participants to differentiate between a transient urticarial rash and a fixed erythemato-papular/vesicular rash was problematic, so the body rashes were collected together, and the second skin question only covered the more specific acral rash. Marzano *et al* also divided the many different types of rashes in two broad categories: inflammatory/exanthematous rashes for the various body rashes, and vasculopathic rashes for the fingers or toes[2].

Study population

This study included residents in the UK from 1 to 90 years who downloaded the app and entered regular data between May 7th and June 22nd, 2020, either themselves or *via* proxy. In this study, we excluded individuals with body mass index (BMI) outside the range of 15 to 55 kg/m^2 (for individuals 16 years old or older), or outside two standard deviation from the sample's mean for each age (for individuals younger than 16 years old), pregnant women, and individuals who did not report their sex. When users failed to report other pieces of information (*e.g.*, the presence of a symptom or disease) we considered them as absent. We removed inconsistent daily assessments, such as those with a logged body temperature outside the range of 35 to 43° C, or where individuals reported feeling unwell but had no symptoms. This resulted in 336,847 individuals, 17,407 of whom also provided valid (*i.e.*, positive or negative) results for SARS-CoV-2 swab tests. We further selected 54,652 symptomatic users (*i.e.*, users reporting at least one of the 16 collected symptoms during their daily log history) who did not believe of having already been infected when first registering with the app and had not yet been tested for SARS-CoV-2 *via* nose/throat swab. These users were divided in two groups: those reporting at least one of the of the three main symptoms of COVID-19 (*i.e.*, fever, persistent cough, and/or anosmia) either at the time or logging or retrospectively, and who, according to the NHS guidelines, would require isolation and testing for SARS-CoV-2 infection, and those that did not. Sample characteristics are summarised in **Table 1 and Supplementary Table 1**.

The study has been approved by the King's College London Research Ethics Committee REMAS ID 18210, review reference LRS-19/20-18210 and all subscribers provided informed consent.

The skin rash survey

To further collect more detailed information on body and acral rush duration and timing with respect to other COVID-19 symptoms, and to create a repository of photos for COVID-19 related skin symptoms, Zoe Global Limited delivered an on-line questionnaire *via* Survey Monkey asking whether the rash was the only symptom, how many days it lasted, and, if other COVID-19 related symptoms were present, whether the rash started before, during or after the other symptoms. The questionnaire was open from 12th to 17th June, 2020. We removed 895 surveyees reporting more than six weeks duration of their skin symptoms, as well as those not reporting age, or reporting a number outside the 1-90 years old range. We selected 365 photos from individuals having a positive SARS-CoV-2 test, or reporting at least one of the three classic COVID-19 symptoms used in the UK, from both sexes to be assessed and categorised independently by an experienced dermatologist. The categories were papular, urticarial, vasculitic body and acral lesions.

Statistical analyses

Statistical analyses were carried out using R (v. 3.6.1). Comparisons between categorical and continuous values were carried out using logistic regression and Wilcoxon's test, respectively. Associations between the presence/absence of self-reported skin-related symptoms and, in tested individuals, SARS-CoV-2 test results, and, in symptomatic untested individuals, the presence/absence of the three classic COVID-19 symptoms, were carried out through multivariate logistic regression, and the following variables were included as covariates: sex, age, BMI, ethnicity (namely: Asian, Black, Chinese, Middle Eastern, White, or mixed), smoking status (namely: never, ex, current), common disease status (namely: cancer, diabetes, lung, heart, or kidney disease) and whether corticosteroids, immunosuppressants, or blood pressure medications were administered.

Contributors

VB, AV, TDS, and MF conceived the study. JW, CS, and TDS conceived COVID Symptom Study app. VB, AB, TDS conceived the survey. AV, NR, BM, and SO curated the COVID Symptom Study app data. AV, NR, and MF curated the survey data. VB assessed and categorised the photos. VB, AV, and MF drafted the manuscript. All authors read and approved the final version of the manuscript.

Declaration of interests

AB and JW are employees of Zoe Global Limited. TDS is a consultant to Zoe Global Ltd. The other authors have no conflict of interest to declare.

Data availability

Data collected in the app are being shared with other health researchers through the NHS-funded Health Data Research UK (HDRUK)/SAIL consortium, housed in the UK Secure e-Research Platform (UKSeRP) in Swansea. Anonymized data collected by the symptom tracker app can be shared with *bonafide* researchers *via* HDRUK, provided the request is made according to their protocols and is in the public interest (see https://healthdatagateway.org/detail/9b604483-9cdc-41b2-b82c-14ee3dd705f6). Data updates can be found at https://covid.joinzoe.com. The app code is publicly available from https://github.com/zoe/covid-tracker-react-native. The main data cleaning script is publicly available from https://github.com/KCL-BMEIS/zoe-data-prep.

Acknowledgements

Zoe Global Limited provided in kind support for all aspects of building, running, and supporting the app and service to all users worldwide. Investigators received support from the Wellcome Trust, the MRC/BHF, Alzheimer's Society, EU, NIHR, CDRF, and the NIHR-funded BioResource, Clinical Research Facility and BRC based at GSTT NHS Foundation Trust in partnership with King's College London.

TwinsUK is funded by the Wellcome Trust, Medical Research Council, European Union, Chronic Disease Research Foundation (CDRF), and the National Institute for Health Research (NIHR)-funded BioResource, Clinical Research Facility and Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust in partnership with King's College London.

This work was also supported by the UK Research and Innovation London Medical Imaging & Artificial Intelligence Centre for Value Based Healthcare

References

1 Phelan AL, Katz R, Gostin LO. The Novel Coronavirus Originating in Wuhan, China: Challenges for Global Health Governance. *JAMA* 2020; published online Jan 30. DOI:10.1001/jama.2020.1097.

2 Marzano AV, Cassano N, Genovese G, Moltrasio C, Vena GA. Cutaneous manifestations in patients with COVID-19: A preliminary review of an emerging issue. *Br J Dermatol* 2020; published online June 1. DOI:10.1111/bjd.19264.

3 Guan W-J, Ni Z-Y, Hu Y, *et al.* Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020; **382**: 1708–20.

4 Recalcati S. Cutaneous manifestations in COVID-19: a first perspective. *J Eur Acad Dermatol Venereol* 2020; **34**: e212–3.

5 Casas CG, Galván Casas C, Català A, *et al.* Classification of the cutaneous manifestations of COVID -19: a rapid prospective nationwide consensus study in Spain with 375 cases. British Journal of Dermatology. 2020. DOI:10.1111/bjd.19163.

6 Henry D, Ackerman M, Sancelme E, Finon A, Esteve E. Urticarial eruption in COVID-19 infection. *J Eur Acad Dermatol Venereol* 2020; **34**: e244–5.

7 Drew DA, Nguyen LH, Steves CJ, *et al.* Rapid implementation of mobile technology for real-time epidemiology of COVID-19. *Science* 2020; **368**: 1362–7.

8 Menni C, Valdes AM, Fredin MB et al. Real-time tracking of self-reported symptoms to predict potential COVID-19. Nat Nat Med. 2020 May 11. doi: 10.1038/s41591-020-0916-2. Online ahead of print.PMID: 32393804