Associations between onychomycosis and COVID-19 clinical outcomes: a retrospective cohort study from a US metropolitan center

Uros Rakita1 · Trisha Kaundinya2 · Armaan Guraya3 · Kamaria Nelson4 · Brittany Maner5 · Jaya Manjunath4 · Gabrielle Schwartzman4 · Brittany Lane6 · Jonathan I. Silverberg4,7

Received: 29 August 2021 / Revised: 15 October 2021 / Accepted: 26 October 2021 / Published online: 12 November 2021
© The Author(s), under exclusive licence to Springer-Verlag GmbH Germany, part of Springer Nature 2021

Abstract
Little is known about the relationship of COVID-19 outcomes with onychomycosis. We investigated the relationship of onychomycosis with COVID-19 outcomes. A retrospective cohort study was performed on SARS-CoV-2 positive adult outpatients or inpatients who had onychomycosis and other skin diseases. Overall, 430 adults were identified with SARS-CoV-2 and a skin disease, including 98 with diagnosed onychomycosis. In bivariable logistic regression models, onychomycosis was associated with increased hospitalization (odds ratio [OR] [95% confidence interval (CI)]: 3.56 [2.18–5.80]), initial inpatient vs. outpatient visits (OR [95% CI]: 2.24 [1.35–3.74]), use of oxygen therapy (OR [95% CI]: 2.77 [1.60–4.79]), severe-critical vs. asymptomatic-mild severity (OR [95% CI]: 2.28 [1.32–3.94]), and death (OR [95% CI]: 7.48 [1.83–30.47]) from COVID-19, but not prolonged hospitalization (OR [95% CI]: 1.03 [0.47–2.25]). In multivariable models adjusting for socio-demographics, comorbidities, and immunosuppressant medication use, the associations with onychomycosis remained significant for hospitalization, inpatient visits, oxygen therapy, severe-critical COVID-19. Onychomycosis was a significant independent risk factor for COVID-19 severity, hospitalization, and receiving supplemental oxygen therapy.

Keywords Onychomycosis · Fungus · Nail · COVID-19 · SARS-CoV-2 · Epidemiology

Introduction
Identifying predictors of COVID-19 severity and morbidity are critical for risk stratification, effective disease prevention, and management. To date, multiple lifestyle (e.g. smoking) and sociodemographic (e.g. advanced age, male sex) factors, and various comorbidities (e.g. obesity, diabetes mellitus, cardiovascular disease, malignancy, and immunodeficiency) were found to be associated with worse COVID-19 outcomes [1–3].

However, the relationship between different skin diseases and COVID-19 outcomes is incompletely understood [4]. Inflammatory skin diseases may be associated with increased COVID-19 susceptibility [5]; however, study findings have been mixed [6–8]. Onychomycosis is a common and often chronic fungal nail infection caused by dermatophytes, non-dermatophyte molds and yeast [9]. Patients with onychomycosis may have an immune predisposition that increases risk of chronic infection and likewise poor COVID-19 outcomes. Further, onychomycosis occurs more commonly in patients with older age, diabetes, malignancy, immunodeficiency and immunosuppression from medications, all of
which have been linked with worse COVID-19 outcomes. However, no studies examined possible associations between onychomycosis and COVID-19 outcomes. The current study determined whether onychomycosis is related to COVID-19 disease outcomes.

Methods

Data source

A retrospective cohort study was performed on adult patients with onychomycosis or other skin diseases who received SARS-CoV-2 related outpatient or inpatient care at a metropolitan academic medical center in Washington, DC between January, 2020 and February, 2021. SARS-CoV-2 positivity was established using polymerase chain reaction tests, rapid antigen tests and/or antibody tests. Available data included sociodemographic information, medical histories (comorbidities, medication use), dermatologic diagnoses and their treatments, and COVID-19 clinical outcomes. Onychomycosis was diagnosed clinically by a dermatologist and confirmed with culture analysis as needed. The study design was approved by the institutional review board at the George Washington University. This study design complies with all Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations.

Variables

The following COVID-19 related clinical outcomes were assessed: hospitalization (yes vs. no), hospitalization duration (days), acuity level at first point of medical contact (inpatient [emergency department, hospital admission, urgent care] vs. outpatient [primary care, specialty clinic]), COVID-19 severity (asymptomatic to mild/moderate vs. severe to critical), supplemental oxygen therapy (yes vs. no), mechanical ventilation (yes vs. no), extracorporeal membrane oxygenation (ECMO; yes vs. no), coagulopathy secondary to COVID-19 (yes vs. no) and COVID-19 course (death or chronic COVID-19 disease vs. recovered). COVID-19 severity was defined as: mild to moderate (symptomatic disease with or without radiographic evidence of COVID-19 pneumonia that did not qualify as either severe or critical), severe (respiratory frequency ≥ 30/minute, blood oxygen saturation ≤ 93%, PaO2/FiO2 ratio < 300, and/or lung infiltrates > 50% of the lung field), critical (respiratory failure, septic shock, and/or multiple organ dysfunction/failure).

Socio-demographic characteristics analyzed included age, body mass index (BMI), sex (male/female), self-reported race (white/non-white), insurance status (public/private), and smoking (yes [current or former]/never). Other variables included history of diabetes mellitus, acquired immunodeficiency syndrome (AIDS), malignancy, and immunosuppressant use (all yes/no).

Statistical analyses

Statistical analyses were conducted using SAS version 9.4.3 (SAS Institute, Cary, NC). Summary statistics were generated for sociodemographic factors in those with vs. without onychomycosis and asymptomatic to mild-moderate vs. severe-critical COVID-19. Chi-squared tests were used to evaluate categorical sociodemographic factors. Student’s t tests were used to evaluate BMI and other continuous variables.

Binary logistic regression models were used to examine the impact of onychomycosis (independent variable) on various COVID-19 outcomes (dependent variables), including hospitalization (yes vs. no), COVID-19 severity (mild-moderate vs. severe-critical), oxygen therapy (yes vs. no), initial visit type (inpatient vs. outpatient), and prolong hospital duration (≥ 7 vs. < 7 days). Multinomial logistic regression was conducted to evaluate the impact of onychomycosis (independent variable) on COVID-19 course (dependent variable; death or chronic COVID-19 vs. recovered). Crude odds ratio (OR) and 95% confidence intervals (CI) were estimated. Multivariable models were constructed that controlled for age (continuous), sex (male vs. female), race (non-white vs. white), immunosuppressant use (yes vs. no), smoking history (yes vs. no), BMI (continuous), insurance status (private vs. public), diagnosis of malignancy, AIDS, and diabetes (each yes vs. no). Adjusted odds ratios (aOR) and 95% CI were reported.

Results

Population characteristics

Overall, 98 and 332 adults were identified who had a positive test for SARS-CoV-2 and were diagnosed with and without onychomycosis, respectively. Twenty-three (28.75%) patients were treated with oral terbinafine; whereas 7 (8.75%) and 50 (62.50%) patients received no treatment or were treated with only topical modalities, respectively. Fifty-eight (76.32%) patients had multiple (2–10) digit involvement. The median (interquartile range) duration of onychomycosis was 730 (792) days. Other than onychomycosis, the most common diagnoses were tinea, alopecia, and atopic dermatitis.

Onychomycosis was associated with male sex, non-white race, current or former smoking, public insurance,
diabetes mellitus, older age, but less immunosuppressant use ($P \leq 0.03$; Table 1).

Whereas, COVID-19 severity was associated with non-white race, immunosuppressant use, diabetes mellitus, older age, and higher BMI ($P \leq 0.0368$; Table 2).

**Onychomycosis and COVID-19 outcomes**

In bivariable models, onychomycosis was associated with increased hospitalization (crude OR [95% CI]: 3.56 [2.18–5.80]), inpatient vs. outpatient visits (OR [95% CI]: 2.24 [1.35–3.74]), use of oxygen therapy (OR [95% CI]: 2.77 [1.60–4.79]), severe-critical vs. asymptomatic-mild severity (OR [95% CI]: 2.28 [1.32–3.94]), and death (OR [95% CI]: 7.48 [1.83–30.57]) from COVID-19, but not prolonged hospitalization (OR [95% CI]: 1.03 [0.47–2.25]).

In multivariable models adjusting for socio-demographics, comorbidities, and immunosuppressant medication use, the associations with onychomycosis remained significant for hospitalization, inpatient visits, oxygen therapy, severe-critical COVID-19 (Table 2).

When diabetes mellitus was as a covariable in adjusted regression models, onychomycosis remained a significant predictor of hospitalization (aOR [95% CI]: 2.38 [1.21–4.67], $P = 0.0118$) and supplemental oxygen therapy requirement (aOR [95% CI]: 2.39 [1.12–5.14], $P = 0.0264$), but not inpatient visits (aOR [95% CI]: 1.75 [0.96–3.19], $P = 0.0682$), severe-critical COVID-19 severity (aOR [95% CI]: 1.98 [0.95–4.14], $P = 0.0706$) or death (aOR [95% CI]: 3.80 [0.39–36.64], $P = 0.2488$).

Intubation with mechanical ventilation ($n = 12$, 2.8%), use of extracorporeal membrane oxygenation (ECMO; $n = 3$, 0.7%) and diagnosis of coagulopathy secondary to COVID-19 ($n = 5$, 1.2%) were rare and occurred with insufficient frequency for regression modeling. Though, 5 of 12 (41.7%) patients who were intubated, 1 of 3 who received ECMO (33.3%) and 3 of 5 (60.0%) with coagulopathy had onychomycosis.

**Discussion**

This study identified onychomycosis as a significant independent risk factor for multiple poor COVID-19 related clinical outcomes, including being hospitalized, higher acuity level of initial care, requiring supplemental oxygen therapy, and experiencing severe disease. These outcomes remained significant even after controlling for socio-demographics and multiple medical comorbidities known to be predictors of greater COVID-19 severity. A large subset of patients who were intubated, received ECMO or had coagulopathy for COVID-19 also had onychomycosis. In addition, onychomycosis was associated with increased death from COVID-19 in bivariable models, but these associations did not remain significant in multivariable models. This may be due to confounding effects of other medical disorders and insufficient powering of the model given the low frequency of COVID-19 deaths observed. In contrast, onychomycosis was not a significant predictor of prolonged hospitalization duration or chronic COVID-19 symptoms.

Some prior studies suggested that patients with inflammatory skin diseases, such as psoriasis and atopic dermatitis, have increased susceptibility to SARS-CoV-2 infection [5]. However, current evidence suggests these patients do not have increased risk of mechanical ventilation [5], hospital stay, ICU admission or death [6]. To our knowledge, no studies examined the relationship between onychomycosis and COVID-19 outcomes. Our findings suggest that patients with onychomycosis have poor COVID-19 outcomes. It is possible that the association of onychomycosis with COVID-19 is due to confounding factors. However, we controlled for age, diabetes mellitus, immunosuppression, obesity and other documented risk factors for both disorders [1–3, 9, 10].

The mechanism behind the association of onychomycosis and COVID-19 severity is unknown. It is unlikely that the dermatophytes or yeasts causal to onychomycosis play any direct role in COVID-19 outcomes. However, the two infections may have common immunologic predispositions. Despite being a superficial infection, onychomycosis clearance relies on a robust systemic cellular immune response [11–13]. Blunted T cell mediated inflammatory responses [11, 14] and T-helper 2 skewing of immune responses [15] may contribute to onychomycosis. Similarly, T-helper 2 driven immune responses may contribute to worse COVID-19 outcomes [16, 17]. Moreover, risk of onychomycosis and COVID-19 are both elevated in those with genetic polymorphisms at the HLA-DR locus, specifically at the HLA-DR*08 allele [18–21]. These hypotheses are speculative and further studies are needed to determine the mechanisms of association between onychomycosis and COVID-19.

Strengths of this study include inclusion of outpatients and inpatients, testing of multiple COVID-19 outcomes, and controlling for multiple confounding variables in multivariate models. However, potential limitations exist. Our sample was predominantly non-white from a US metropolitan area receiving care at a specific medical center and may not be generalizable to the entire US population. Several serious COVID-19 outcomes (intubation, ECMO, clotting) had inadequate sample size for modeling. Since our entire cohort was comprised of SARS-CoV-2 positive patients, we were unable to evaluate overall SARS-CoV-2 infection susceptibility. Data were collected prior to widespread availability of COVID-19 vaccination, precluding assessment of vaccination status on COVID-19 outcomes. Lastly, we cannot exclude the possibility that unmeasured confounders such as...
Table 1 Socio-demographic and other health-related associations related to diagnosis of onychomycosis

| Variable                  | Onychomycosis | COVID-19 severity |
|---------------------------|---------------|-------------------|
|                           | Yes           | No               | P value* | Asymptomatic-mild | No | P value* |
|                           | n  | %  | n  | %  | P value* | n  | %  | n  | %  | P value* |
| Sex                       | 0.0335 |       | 0.1972 |       |       |       |       |       |       |       |
| Male                      | 43  | 43.88 | 106  | 32.22 | 128  | 36.16 | 20  | 28.17 |       |       |
| Female                    | 55  | 56.12 | 223  | 67.78 | 226  | 63.84 | 51  | 71.83 |       |       |
| Race                      | 0.0093 |       | 0.0175 |       |       |       |       |       |       |       |
| White                     | 8  | 8.16  | 64  | 19.34 | 66  | 18.54 | 5  | 7.04  |       |       |
| Non-white                 | 90  | 91.84 | 267  | 80.66 | 290  | 81.46 | 66  | 92.96 |       |       |
| Smoking                   | 0.012 |       | 0.1907 |       |       |       |       |       |       |       |
| Current/former            | 36  | 38.71 | 79  | 25.32 | 91  | 26.92 | 23  | 34.85 |       |       |
| Never                     | 57  | 61.29 | 233  | 74.68 | 247  | 73.08 | 43  | 65.15 |       |       |
| Insurance status          | <0.0001 |       | 0.1322 |       |       |       |       |       |       |       |
| Private                   | 22  | 22.45 | 169  | 51.06 | 165  | 46.35 | 26  | 36.62 |       |       |
| Public                    | 76  | 77.55 | 162  | 48.94 | 191  | 53.65 | 45  | 63.38 |       |       |
| Cancer#                   | 0.7413 |       | 0.6446 |       |       |       |       |       |       |       |
| Yes                       | 9  | 9.18  | 27  | 8.13  | 31  | 8.71  | 5  | 7.04  |       |       |
| No                        | 89  | 90.82 | 305  | 91.87 | 325  | 91.29 | 66  | 92.96 |       |       |
| Immunosuppressant use##   | <0.0001 |       | 0.0275 |       |       |       |       |       |       |       |
| Yes                       | 6  | 6.12  | 95  | 28.61 | 77  | 21.63 | 24  | 33.80 |       |       |
| No                        | 92  | 93.88 | 237  | 71.39 | 279  | 78.37 | 47  | 66.20 |       |       |
| AIDS                      | 0.0528** |       | 0.9999** |       |       |       |       |       |       |       |
| Yes                       | 5  | 5.10  | 5  | 1.51  | 9  | 2.53  | 1  | 1.41  |       |       |
| No                        | 93  | 94.90 | 327  | 98.49 | 347  | 97.47 | 70  | 98.59 |       |       |
| Diabetes mellitus         | <0.0001 |       | <0.0001 |       |       |       |       |       |       |       |
| Yes                       | 50  | 51.02 | 54  | 16.27 | 71  | 19.94 | 32  | 45.07 |       |       |
| No                        | 48  | 48.98 | 278  | 83.73 | 285  | 80.06 | 39  | 54.93 |       |       |

| Variable |  | Mean (SD) | n  |  | Mean (SD) | P value* | n  |  | Mean (SD) | P value* |
|----------|-----------------|----------|-----------------|-----------------|----------|-----------------|----------|-----------------|----------|
| Age      | 98  | 61.08 (16.47) | 331 | 49.04 (15.88) | <0.001 | 356 | 50.18 (16.26) | 71 | 60.38 (16.83) | <0.0001 |
| BMI      | 95  | 32.13 (8.27) | 320 | 31.10 (8.03) | 0.2769 | 344 | 30.97 (7.95) | 69 | 33.20 (8.58) | 0.0368 |

Missing values were encountered in 3 (0.7%) for sex, 1 race (0.2%), 25 (5.8%) smoking, 1 (0.2%) insurance status. There were no missing values for immunosuppressant use, cancer diagnosis, AIDS diagnosis, or diabetes mellitus diagnosis.

The other skin diseases included acne (n = 47), actinic keratosis (n = 16), allergic contact dermatitis (n = 18), alopecia unspecified (n = 52), atopic dermatitis (n = 48), basal cell carcinoma (n = 5), cutaneous lupus (n = 2), unspecified dermatitis (n = 25), dermatomyositis (n = 1), condyloma acuminate (n = 8), hand dermatitis (n = 7), hemangiomata (n = 2), herpes simplex infection (n = 32), herpes zoster infection (n = 8), hidradenitis suppurativa (n = 15), hirsutism (n = 8), hyperhidrosis (n = 10), impetigo (n = 2), irritant contact dermatitis (n = 8), melanoma (n = 1), paronychia (n = 1), pityriasis rosea (n = 1), plantar wart (n = 11), psoriasis (n = 11), prurigo nodularis (n = 1), rosacea (n = 9), scabies (n = 1), seborrheic dermatitis (n = 39), seborrhoeic keratosis (n = 22), squamous cell carcinoma (n = 3), tinea (n = 53), and urticaria (n = 17).

Boldface indicates significance, p ≤ 0.05

* Fisher Exact test
* Chi-squared test
** T test
# Cancer diagnosis includes solid tumor, leukemia, and lymphoma. Specific diagnosis and cancer treatment status not available
## Immunosuppressant drugs (n; % of total dataset) included adalimumab (n = 4; 0.93%), azathioprine (n = 2; 0.47%), cyclosporine (n = 1; 0.23%), dupilumab (n = 1; 0.23%), etanercept (n = 1; 0.23%), hydroxycloroquine (n = 20; 4.65%), infliximab (n = 3; 0.7%), ixekizumab (n = 1; 0.23%), methotrexate (n = 12; 2.79%), methylprednisolone (n = 8; 1.86%), mycophenolate moftel (n = 8; 1.86%), prednisone (n = 49; 11.4%), rituximab (n = 1; 0.23%), sirolimus (n = 1; 0.23%), tacrolimus (n = 8; 1.86%), tofacitinib (n = 1; 0.23%), other (n = 7; 1.63%)
particular COVID-19 variants or other comorbidities may be important drivers of the observed associations.

In conclusion, the present study suggests that onychomycosis is an indicator of more severe COVID-19 and poor outcomes. Future studies are required to confirm the findings and better elucidate the mechanism of association between onychomycosis and COVID-19 outcomes.

Funding None.

Declarations

Conflict of interest None.

References

1. Li X, Zhong X, Wang Y, Zeng X, Luo T, Liu Q (2021) Clinical determinants of the severity of COVID-19: a systematic review and meta-analysis. PLoS ONE 16(5):e250602
2. Gao Y-D, Ding M, Dong X et al (2021) Risk factors for severe and critically ill COVID-19 patients: a review. Allergy 76(2):428–455
3. Tian W, Jiang W, Yao J et al (2020) Predictors of mortality in hospitalized COVID-19 patients: A systematic review and meta-analysis. J Med Virol 92(10):1875–1883
4. Shinkai K, Bruckner AL (2020) Dermatology and COVID-19. JAMA 324(12):1133–1134
5. Patrick MT, Zhan H, Wasiukowski R et al (2021) Associations between COVID-19 and skin conditions identified through epidemiology and genomic studies. J Allergy Clin Immunol 147(3):e857–e859.e857
6. Yang JM, Koh HY, Moon SY et al (2020) Allergic disorders and susceptibility to and severity of COVID-19: A nationwide cohort study. J Allergy Clin Immunol 146(4):790–798
7. Cho SI, Kim YE, Jo SJ (2021) Association of COVID-19 with skin diseases and relevant biologics: a cross-sectional study using nationwide claim data in South Korea. Br J Dermatol 184(2):296–303
8. Rakita U, Kaundinya T, Guraya A, Nelson K, Maner B, Manjunath J, Schwartzman G, Lane B, Silverberg JI (2021) Atopic dermatitis is not associated with SARS-CoV-2 outcomes. Arch Dermatol Res pp. 1–4. https://doi.org/10.1007/s00403-021-02276-1

9. Lipner SR, Scher RK (2019) Onychomycosis: Clinical overview and diagnosis. J Am Acad Dermatol 80(4):835–851

10. Grover C, Khurana A (2012) Onychomycosis: newer insights in pathogenesis and diagnosis. Indian J Dermatol Venereol Leprol 78(3):263–270

11. Gupta C, Das S, Ramachandran VG et al (2016) Possible role of trichophytin antigen in inducing impaired immunological clearance of fungus in onychomycosis. Mycopathologia 181(3–4):247–251

12. Mayer EF, Ita F, Gonzalez E et al (2013) Association between onychodystrophy and human T-lymphotropic virus type 1 infection. Int J Infect Dis 17(5):e312-e316

13. Maleszka R, Adamski Z, Dworacki G (2001) Evaluation of lymphocytes subpopulations and natural killer cells in peripheral blood of patients treated for dermatophyte onychomycosis. Mycoses 44(11–12):487–492

14. Kaya TI, Eskandari G, Guvenc U et al (2009) CD4+CD25+ Treg cells in patients with toenail onychomycosis. Arch Dermatol Res 301(10):725–729

15. Woodfolk JA (2005) Allergy and dermatophytes. Clin Microbiol Rev 18(1):30–43

16. Donlan AN, Sutherland TE, Marie C et al (2021) IL-13 is a driver of COVID-19 severity. JCI Insight. 6(15):2020–06

17. Gil-Etayo FJ, Suárez-Fernández P, Cabrera-Marante O et al (2021) T-Helper Cell Subset Response Is a Determining Factor in COVID-19 Progression. Front Cell Infect Microbiol 11:624483

18. Carrillo-Meléndrez H, Ortega-Hernández E, Granados J, Arroyo S, Barquera R, Arenas R (2016) Role of HLA-DR alleles to increase genetic susceptibility to onychomycosis in nail psoriasis. Skin Appendage Disord 2(1–2):22–25

19. García-Romero MT, Granados J, Vega-Memije ME, Arenas R (2012) Analysis of genetic polymorphism of the HLA-B and HLA-DR loci in patients with dermatophytic onychomycosis and in their first-degree relatives. Actas Dermosifiliogr 103(1):59–62

20. Littera R, Campagna M, Deidda S et al (2020) Human Leukocyte Antigen Complex and Other Immunogenetic and Clinical Factors Influence Susceptibility or Protection to SARS-CoV-2 Infection and Severity of the Disease Course. The Sardinian Experience. Front Immunol 11:605688

21. Amoroso A, Magistroni P, Vespasiano F et al (2021) HLA and AB0 Polymorphisms May Influence SARS-CoV-2 Infection and COVID-19 Severity. Transplantation 105(1):193–200

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.