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

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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

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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 $\leq 93\%$, 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, while the remainder had a single 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 ($P \le 0.03$; Table 1).

Whereas, COVID-19 severity was associated with non-white race, immunosuppressant use, diabetes mellitus, older age, and higher BMI ($P \le 0.0368$; 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		Severe-critical		P value*
	n	%	n	%		n	%	n	%	
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	
	n	Mean (SD)	n	Mean (SD)	P value**	n	Mean (SD)	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 accuminata ($n=8$), hand dermatitis ($n=7$), hemangioma($=2$), 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 ($n=39$), seborrheic keratosis ($n=22$), squamous cell carcinoma ($n=3$), tinea ($n=53$), and urticaria ($n=17$)

Boldface indicates significance, $p \leq 0.05$

++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%), hydroxychloroquine ($n=20$; 4.65%), infliximab ($n=3$;0.7%), ixekizumab ($n=1$; 0.23%), methotrexate ($n=12$;2.79%), methylprednisolone ($n=8$;1.86%), mycophenolate mofetil ($n=8$; 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%)

Table 2 Association of onychomycosis with COVID-19 severity and hospitalization

Outcome	Onychomycosis n (%)		Crude OR (95% CI)	P value	Adjusted OR (95% CI)	P value
	Yes	No				
Hospitalization[a]						
No	49 (52.13)	248 (79.49)	1.00 (ref)	–	1.00 (ref)	–
Yes	45 (47.87)	64 (20.51)	3.56 (2.18–5.80)	**< 0.0001**	2.79 (1.46–5.36)	**0.0020**
Visit type[a]						
Outpatient	24 (24.49)	139 (42.12)	1.00 (ref)	–	1.00 (ref)	–
Inpatient	74 (75.51)	191 (57.88)	2.24 (1.35–3.74)	**0.0019**	1.85 (1.03–3.32)	**0.0410**
Oxygen therapy[a]						
No	70 (71.43)	284 (87.38)	1.00 (ref)	–	1.00 (ref)	–
Yes	28 (28.57)	41 (12.62)	2.77 (1.60–4.79)	**0.0003**	2.85 (1.36–5.98)	**0.0055**
COVID-19 severity[a]						
Asymptomatic-mild	72 (73.47)	284 (86.32)	1.00 (ref)	–	1.00 (ref)	–
Severe–critical	26 (26.53)	45 (13.68)	2.28 (1.32–3.94)	**0.0032**	2.22 (1.09–4.55)	**0.0290**
Hospital duration[b]						
1–6 days	25 (58.14)	37 (58.73)	1.00 (ref)	–	1.00 (ref)	–
≥ 7 days	18 (41.86)	26 (41.27)	1.03 (0.47–2.25)	0.9517	0.75 (0.24–2.32)	0.6163
Course[b]						
Recovered	81 (88.04)	303 (96.5)	1.00 (ref)	–	1.00 (ref)	–
Chronic complications	5 (5.43)	8 (2.55)	2.34 (0.75–7.34)	0.1456	1.40 (0.35–5.69)	0.6343
Death	6 (6.52)	3 (0.96)	7.48 (1.83–30.57)	**0.0051**	6.09 (0.68–54.43)	0.1062

Boldface indicates significance, $p \le 0.05$

[a]Binary logistic regression models were constructed with onychomycosis diagnosis as the independent variable and COVID-19 outcomes as the dependent variables. Dependent variables included hospitalization (yes vs. no), visit type (inpatient vs. outpatient), oxygen therapy (yes vs. no), COVID-19 severity (severe-critical vs. asymptomatic-mild) and hospital duration (1–6 days vs ≥ 7 days)

[b]Multinomial logistic regression models were constructed with onychomycosis diagnosis as the independent variable (yes/no) and COVID course as the dependent outcome variable (chronic complications or death vs. recovered)

Crude odds ratios (OR) and 95% confidence intervals (CI) were generated for unadjusted models. Adjusted OR and 95% CI were generated for age [continuous], sex [male/female], race [white/non-white], immunosuppressant use [yes/no], smoking [current-former/never], BMI [continuous], insurance status [public/private]), diagnosis of cancer [yes/no], AIDS [yes/no]

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.

Declarations

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