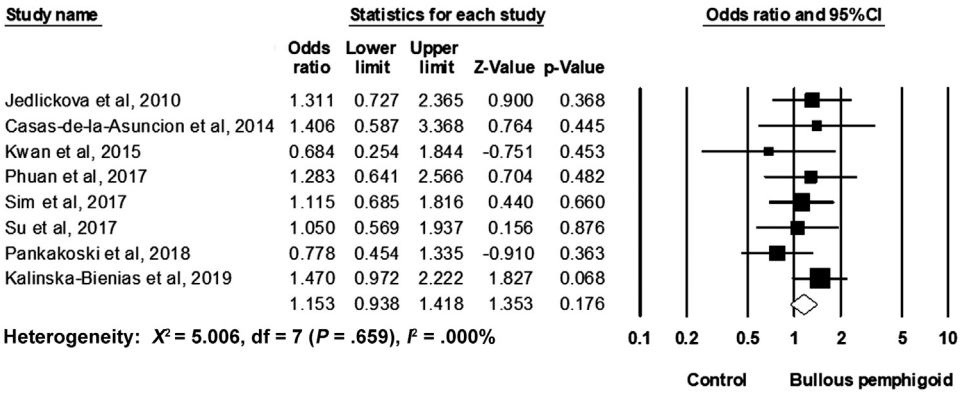

Fig 1. Meta-analysis of association of bullous pemphigoid with ischemic heart diseases. The size of the square corresponds to the relative weight assigned in the pooled analysis. The diamond denotes the pooled odds ratio, and the lateral tips of the diamond indicate the associated confidence interval (*CI*).

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Supplemental material for this study is available at https://data.mendeley.com/datasets/xmrb5bp34f/1.

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Green nail syndrome: Analysis of the association with onychomycosis

To the Editor: Green nail syndrome (GNS) is an infectious disorder caused by *Pseudomonas aeruginosa* that presents as greenish pigmented nails. Although an anecdotal association between GNS and onychomycosis has been reported,[1-4] data in the literature are limited. Therefore, we conducted this study to investigate the association of fungal coinfection with GNS.

We retrospectively evaluated patients with GNS from 2 hospitals from 2015 to 2018. Patients with clinical findings of greenish nails with bacterial culture results positive for *P aeruginosa* were included. During the study period, we cut or clipped the involved nail plate in all cases to detect fungal organisms. The samples were histopathologically stained with Grocott methenamine silver (GMS) and periodic acid—Schiff, which is the most sensitive method for diagnosing onychomycosis.[1] Detection of fungal hyphae or pseudohyphae and spores in the nail plates with clinical features of onychomycosis was regarded as a positive finding. This study was approved by the institutional review boards (Seoul National University Hospital 1809-106-974 and Seoul Metropolitan Government Seoul National University Boramae Medical Center 20181204/30-2018-97/123).

Twenty-three patients (6 men and 17 women) with a mean age of 53.8 years (standard deviation, 12.2; range, 32-81 years) were included, most of whom were referred by health care providers. The mean disease duration was 11.9 months (standard deviation, 13.5; range, 1-48 months). Five patients (21.7%) had immunosuppressive conditions such as internal malignancy, autoimmune disorders, or diabetes mellitus. A previous history of nail diseases was reported in 13 cases (56.5%), including 12

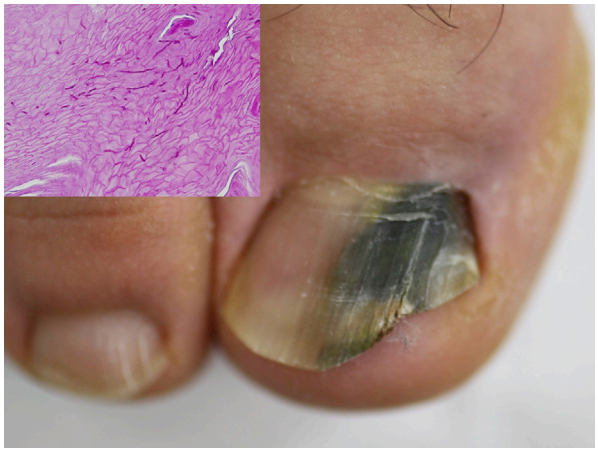

Fig 1. Clinical photograph of green nail syndrome. Greenish coloration was observed in the right great toenail. Fungal hyphae were detected in the nail plate. Inset: periodic acid–Schiff staining. (Original magnification: ×400.)

patients with a history of onychomycosis and 1 patient with nail psoriasis. Eighteen affected nails (78.3%) were toenails, and 5 (21.7%) were fingernails. Involvement of the great toenail or thumbnail was found in 22 patients (95.7%). Fungal coinfection was found in 15 patients (65.2%) (Figs 1 and 2).

GNS risk factors include trauma, frequent wet conditions, immunosuppressive conditions, and underlying nail diseases such as onycholysis and onychomycosis. Distal onycholysis, which is a separation of the nail plate from the underlying nail bed, is a common finding of GNS, because it acts as an entry for consequent bacterial proliferation. The most common presentations of onychomycosis are yellowing, subungual hyperkeratosis, and onycholysis.[1] Currently, no detailed investigation exists regarding the presence of fungi in GNS. Our data show several interesting findings. First, GNS commonly affected the great toenail (69.6%), which is a common location of onychomycosis.[2] Second, the disease duration shows that GNS is a chronic condition. Third, the GNS-affected nails presented a high prevalence of fungi. Possible hypotheses include fungi potentiating *P aeruginosa* growth in the nail[5] and creating tunnel-like structures in the nail plate through which *P. aeruginosa* proliferates.[4]

This study has some limitations. First, selection bias may exist, considering that the data were collected from 2 referral hospitals. Second, although periodic acid–Schiff/GMS staining of nail clippings is regarded as the most sensitive diagnostic method for onychomycosis, it does not provide information on taxonomizing species and fungal viability.

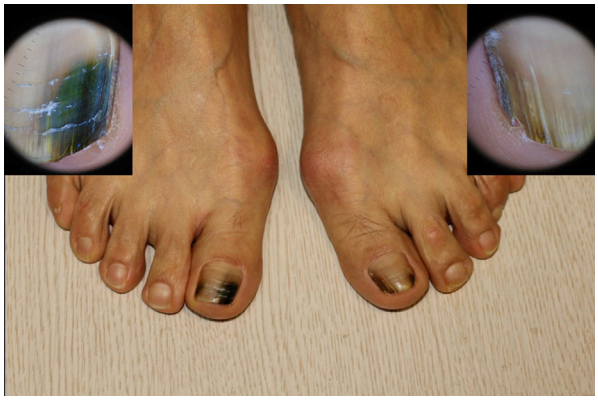

Fig 2. Clinical photograph of green nail syndrome. Green nail syndrome on the right first toenail and onychomycosis on the left first toenail. Inset: dermoscopic images. Histopathologic analysis of the right first toenail plate showed fungal hyphae.

In conclusion, this study shows that onychomycosis was frequently associated with GNS and might be a predisposing factor of GNS. Therefore, we recommend that physicians carefully examine the nails of patients with GNS to detect possible fungal infections.

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Variability in skin microbiota between smokers, former smokers, and nonsmokers

To the Editor: Smoking may induce significant changes in the skin milieu that may affect microbial communities harbored by the skin, potentially disrupting the normal functions of the skin microbiome.[1,2]

We performed a case-control study of the skin microbiota of current (n = 11), former (n = 5), and never smokers (n = 7). Current smokers included 6 heavy smokers (≥5 pack-years) and 5 light smokers (<5 pack-years). The study was approved by the Johns Hopkins School of Medicine institutional review board, and participants provided written informed consent. The bilateral cheeks and dorsal aspect of the forearms were separately swabbed with sterile foam-tipped swabs moistened with Amies medium. After DNA extraction, the V4 region of the bacterial 16S ribosomal RNA gene was amplified with polymerase chain reaction and sequenced using Illumina (San Diego, CA) MiSeq. Comparison of alpha diversity with the Shannon metric was performed by using *t* tests with Monte Carlo permutations on QIIME1 open-source software. Beta diversity, computed with UniFrac metric, was compared by using analysis of similarity. Metagenomic profiles were created with MetaStats 2.0 software.

At the phylum level, smokers were overall enriched in *Actinobacteria* species and depleted in *Fusobacteria* species compared with never smokers (Fig 1). We also detected numerous genera that were significantly enriched/depleted in smokers (Table I).

We found no significant difference in mean alpha diversity (± standard deviation) between heavy smokers (cheeks: 4.909 ± 0.654; arms: 5.563 ± 0.706), light smokers (cheeks: 5.639 ± 0.633; arms: 5.562 ± 0.514), former smokers (cheeks: 4.993 ± 0.946; arms: 5.186 ± 0.702), or never smokers (cheeks: 5.348 ± 1.243; arms: 5.793 ± 0.627). However, significant differences were observed in beta diversity between participant groups (cheeks: $R = 0.171$, $P = .001$; arms: $R = 0.182$, $P = .002$).

Although the diversity within each sample (alpha diversity) was not significantly different among participant groups, we observed significant differences among participant groups at each sampling site when examining diversity among samples (beta diversity). Therefore, although sample-to-sample differences in diversity were insignificant, significant differences existed between the overall diversity of the microbial communities.

Interestingly, our findings correlate fairly well with studies investigating the oral microbiota in smokers, suggesting that smoking has similar effects on the microbiota of the mouth and skin.[3,4] Many of the genera that were enriched/depleted in the skin microbiota of smokers have been shown to be enriched/depleted in oral microbiota as well.[4] The effect of smoking on the oral microbiome has been attributed to the direct effect of toxicants, impaired host immunity, and the depletion of oxygen, mechanisms that may also be at play in the skin.[4] Furthermore, we found that fewer bacterial taxa were significantly enriched/depleted in former smokers than in current smokers, which may suggest that some of the skin microbiota perturbations associated with smoking may be reversible.

Our study was limited by a relatively low sample size in each group. Secondhand smoke exposure was not evaluated. Additionally, participants were not directly matched by demographics to control individuals. V4 sequencing may also underestimate the relative abundance of some skin commensals.[5]

In this study, we found that smoking is associated with significant changes in microbial beta diversity and the relative abundance of many bacterial taxa on the skin. Future studies will be useful to understand the significance of these microbial disturbances and their role in the physiology of the skin.

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