Received: 5 July 2021 | Revised: 9 November 2021 | Accepted: 16 November 2021

DOI: 10.1111/myc.13399

ORIGINAL ARTICLE

mycoses Diagnosis, Therapy and Prophylaxis of Fungal Diseases WILEY

Prevalence of *Candida species* in Psoriasis

Kevin Elsner[1] | Julia Holstein[1] | Franz Joachim Hilke[2] | Gunnar Blumenstock[3] | Birgit Walker[1] | Sybille Schmidt[1] | Martin Schaller[1] | Kamran Ghoreschi[2] | Katharina Meier[2]

[1]Department of Dermatology, Eberhard Karls Universität Tübingen, Tübingen, Germany

[2]Department of Dermatology, Venereology and Allergology, Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany

[3]Deptartment of Clinical Epidemiology and Biostatistics, Eberhard Karls Universität Tübingen, Tübingen, Germany

Correspondence
Katharina Meier, Department of Dermatology, Venereology and Allergology, Charité - Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany.
Email: katharina.meier@charite.de

Abstract

Background: Psoriasis patients are more frequently colonised with *Candida species*. The correlation between fungal colonisation and clinical severity is unclear, but may exacerbate psoriasis and the impact of antipsoriatic therapies on the prevalence of *Candida* is unknown.

Objectives: To examine the prevalence of *C species* in psoriasis patients compared to an age- and sex-matched control population, we investigated the influence of *Candida* colonisation on disease severity, immune cell activation and the interplay on psoriatic treatments.

Methods: The prevalence of *C species* was examined in 265 psoriasis patients and 200 control subjects by swabs and stool samples for fungal cultures. Peripheral mononuclear blood cells (PBMCs) were collected from 20 fungal colonised and 24 uncolonised patients and stimulated. The expression of interferon (IFN)-γ, IL-17A, IL-22 and tumour necrosis factor (TNF)-α from stimulated PBMCs was measured by quantitative real-time polymerase chain reaction (qPCR).

Results: A significantly higher prevalence for *Candida* was detected in psoriatic patients ($p \leq .001$) compared to the control subjects; most abundant in stool samples, showing *Candida albicans*. Older participants (≥51 years) were more frequent colonised, and no correlation with gender, disease severity or systemic treatments like IL-17 inhibitors was found.

Conclusions: Although *Candida* colonisation is significantly more common in patients with psoriasis, it does not influence the psoriatic disease or cytokine response. Our study showed that Candida colonisation is particularly more frequent in patients with psoriasis ≥51 years of age. Therefore, especially this group should be screened for symptoms of candidiasis during treatment with IL-17 inhibitors.

KEYWORDS
Candida albicans, *Candida species*, candidiasis, interleukin-17, interleukin-17 inhibitors, prevalence, psoriasis

1 | INTRODUCTION

Psoriasis is a chronic inflammatory multisystem disease and known for its characteristic skin lesions that affects 2–4% of the western population.[1] The inflammatory immune reaction in psoriasis shows some cytokine features to the physiological host defence reaction against *Candida*. T helper17 (Th17) cells and the interleukin (IL) 17 family are key components in both the immune defence against *Candida* and the inflammatory cascade in psoriasis.[2-7] Yet, several studies found an increased prevalence of *Candida species* in psoriasis patients and observed an amelioration of psoriatic lesions under antifungal therapy.[8-15] It is hypothesised that *C species* may produce superantigenic factors and, like streptococcal infections, may trigger and exacerbate psoriasis.[16-19] Still, it is unclear whether colonisation with *C species* may influence disease activity or the treatment response.[12,13,20-22] In this regard, the therapeutic options for psoriasis have widened substantially with the introduction of new targeted drugs like IL-23 and IL-17 inhibitors. But the latter are also associated with an increased but acceptable risk of candidiasis.[23] The influence of IL-17 antagonists and other antipsoriatic treatments on the prevalence of *C species* colonisation has been rarely studied in the setting of clinical practice.[15,24]

Therefore, we examined the prevalence of *C species* in a large group of psoriasis patients and investigated whether systemic drugs lead to an increased colonisation of *C species* especially IL-17 inhibitors. Additionally, we investigated a possible correlation between colonisation with *Candida* and disease severity as well as an altered immune response. Here, we compared the ex vivo cytokine expression of interferon (IFN)-γ, IL-17A, IL-22 and tumour necrosis factor (TNF)-α in colonised and uncolonised patients, subsequently to the stimulation with *Candida albicans*.

2 | MATERIALS AND METHODS

2.1 | Patients, sample collection and yeast differentiation

The study was performed in accordance with the Declaration of Helsinki and was approved by the ethic committee of the University of Tübingen (758/2016B02). In total, 265 patients with diagnosed psoriasis were recruited between June 2017 and April 2018 at the Department of Dermatology of the University Hospital Tübingen, Germany. Patients who received inhalable or systemic glucocorticoids, antimycotics or participated in other clinical trials were excluded from the study. As a control group, 200 participants without any history of psoriasis or other inflammatory skin diseases were recruited.

After written informed consent had been obtained by the participants, swabs (eSwab™) were sampled from psoriatic lesions, the oral cavity and the armpit of 265 psoriasis patients and 200 healthy controls. Further, one stool sample was collected from each of 179 psoriasis patients and 113 healthy controls. All swabs and stool samples were analysed by the laboratory for molecular mycology. The samples were cultivated up to five days aerobically at 28°C on Sabouraud-Agar (Lab M, Heywood, UK). *C species* were identified by colour, texture and microscopical morphology. For further differentiation, yeasts were grown on chromID™ CAN2 agar (bioMérieux SA, Marcy-l'Étoile, France), Kimmig-Agar (Mast Diagnostica GmbH, Reinfeld, Germany) and Rice agar (Oxoid, Wesel, Germany) and precisely identified by the assimilation test api® 20°C AUX (bioMérieux SA, Marcy-l'Étoile, France) and the latex agglutination tests (Bichro-Dubli FUMOUZE®, Bichro-Latex Albicans FUMOUZE®, Glabrata RTT FUMOUZE® and Krusei Color FUMOUZE® (Biosynex SA, Illkirch-Graffenstaden, France).

2.2 | Cell stimulation, ribonucleic acid (RNA) isolation and quantitative real-time polymerase chain reaction (qPCR)

Blood samples were collected in lithium-heparin tubes (SARSTEDT, Nümbrecht, Germany) from 44 psoriasis patients, 20 with *C species* colonisation and 24 without. The peripheral mononuclear blood cells (PBMCs) were separated by density-gradient centrifugation,[25] washed in phosphate-buffered saline (PBS) (Sigma-Aldrich®, Steinheim, Germany) and adjusted to a concentration of 2×10^6 cells/ml in X-VIVO 15 medium (Lonza, Verviers, Belgium). Subsequently, 1 ml of this solution was transferred into wells of a 24-well cell culture plate and stimulated with the highly virulent *C albicans* strain SC5314.[26] Prior to the stimulation, the fungi were synchronised in a modified manner to the semi-synchronisation of yeast cells that was first described by Schaller et al.[27] The cells were first cultivated at 29°C on Sabouraud-Agar (Günter Keul GmbH, Steinfurt, Germany). After 48 hours, 25×10^6 yeast cells were transferred to 10 ml Yeast Extract-Peptone-Dextrose Medium (BD™, Le-Pont-de-Claix, France) and cultivated for 24 hours at 37°C and 150 rpm in a shaking incubator. After synchronisation, yeast cells were centrifuged, washed three times in PBS and adjusted to a concentration of 4×10^5 yeast cells/ml PBS. Subsequently, the previously isolated PBMCs were either stimulated with 25 µl of this yeast suspension (containing 10^4 fungi) or with 25 µl lipopolysaccharides (LPS) (InvivoGen, Toulouse, France) suspension (containing 1 ng LPS) and incubated for four hours at 37°C and 5% CO_2. Controls were incubated with 25 µl PBS. Following the incubation, PBMCs were lysed by adding 400 µl RNA Lysis Buffer T (VWR International, Leuven, Belgium) and stored at −80°C.

The isolation of RNA from the previously lysed PBMCs was performed using the peqGold Total RNA Kit (VWR International, Leuven, Belgium) according to the manufacturer's protocol. Complementary deoxyribonucleic acid (cDNA) was transcribed using the Maxima First Strand cDNA Synthesis Kit for RT-qPCR (Thermo Scientific, Vilnius, Lithuania) according to the manufacturer's protocol. The relative expression of IFN-γ, IL-17A, IL-22 and TNF-α was measured by qPCR using the Roche LightCycler® 480 system (Roche, Mannheim, Germany) and TaqMan probes (TIB MolBiol, Berlin, Germany). B-actin was used as a house-keeping gene. The following primers and probes were used: AGCCTCGCCTTTGCCGA (forward), CTGGTGCCTGGGGCG

(reverse) and 6FAM-CCGCCGCCCGTCCACACCCCC-BBQ (probe) for β-actin. GCATCCAAAAGAGTGTGGAG (forward), GGACATTCAAGTCAGTTACCGA (reverse) and 6FAM-ATCAAGGAAGACATGAATGTCAAGTTTTTCAA -BBQ (probe) for IFN-γ. AACCTGAACATCCATAACCGGAA (forward), GTCCTCATTGCGGTGGAGA (reverse) and 6FAM-CCAATACCAATCCCAAAAGGTCCTCAGA-BBQ (probe) for IL-17A. TGATGACCTGCATATCCAGAGGAAT (forward), ATCCAGTTCTCCAATTGCTTTGATC (reverse) and 6FAM-TGCAAAAGCTGAAGGACACAGTGAAAAA-BBQ (probe) for IL-22. CTTCTCCTTCCTGATCGTGGC (forward), GGGT TTGCTACAACATGGGC (reverse) and 6FAM-CGCCACCACG CTCTTCTGCCT-BBQ (probe) for TNF-α.

2.3 | Statistical analysis

The statistical analysis was performed using SPSS Statistics, Version 24.0 (IBM, Armonk, USA). The data were analysed using the chi-squared test (χ^2), Fisher's exact test (FET) and Mann-Whitney *U* test (U). Significance level was set at <.05. The strength of an association was quantified using the odds ratio (OR) with 95% confidence interval (95%-CI). Graphs were created using GraphPad Prism 8.4.3 (GraphPad Software, San Diego, USA).

3 | RESULTS

3.1 | Prevalence of *Candida* colonisation in patients with psoriasis

In the study, 465 individuals, 265 psoriasis patients and 200 subjects were screened for *C species* colonisation. The median age of both groups was 51 years, with a mean age of 50.21 years (±13.54) for the psoriasis patients and 50.76 years (±16.01) in the control group. There was a slight preponderance of male individuals in both groups, with 138 (52.1%) males and 127 (47.9%) females in the psoriasis and 102 (51%) men and 98 (49%) women in the control group.

No significant correlation was observed within the sexes, neither in psoriasis patients nor in control subjects (Table 1). Importantly, in both the patients and the control group, a significantly higher prevalence of colonisation with *C species* was found when the age was equal or above the median of 51 years. (Table 1).

The analysis of the swaps and stool samples revealed an overall colonisation with *C species* in 161 (60.8%) patients with psoriasis and 77 (38.5%) of the control subjects respectively. Thus, patients with psoriasis have a significantly higher prevalence of *Candida* colonisation compared to control individuals (OR: 2.47; 95%-CI: 1.68–3.6; χ^2; p = <.001) (Figure 1). The most common species in both groups was *C albicans*, detected in 110 (41.51%) patients and 58 (29%) control subjects (Table 2). In addition, the number of different *C species* was assessed, resulting in the detection of just one *C species* in the majority (50.57%) of psoriasis patients and 34% of the control subjects. At least two different *C species* were detected in 9.4% of patients with psoriasis and 4.5% of controls. Two patients (0.75%) were colonised with three species. A full list of the isolated *C species* is shown in Table 2. Additionally, ten (3.77%) of the 265 psoriasis patients and six (3%) of the 200 control subjects were colonised with yeast other than *Candida*. The yeast like fungus *Geotrichum candidum* was found in 24 (9.06%) psoriasis patients and 28 (14%) of the control subjects. Moulds were found in four (1.51%) stool samples of the patients with psoriasis. *Trichophyton mentagrophytes* was detected in the armpit of a single (0.38%) patient.

The analysis of the different body sites revealed the highest prevalence of *C species* in stool samples and oral swabs. A colonisation with *C species* was detected in 56.98% (102 of the 179)

TABLE 1 Prevalence of *Candida species* in relation to age and gender

Psoriasis patients (*n* = 265)				
Age	<51 years	≥51 years	*p*	Odds ratio
	68 colonized (51.5%)	93 colonized (69.9%)	.002	2.19 (95%-CI: 1.32–3.62)
Gender	Female	Male	*p*	Odds ratio
	81 colonized (63.8%)	80 colonized (58%)	.333	0.78 (95%-CI: 0.48–1.29)
Control subjects (*n* = 200)				
Age	<51 years	≥51 years	*p*	Odds ratio
	28 colonized (28.3%)	49 colonized (48.5%)	.003	2,39 (95%-CI: 1.33–4.29)
Gender	Female	Male	*p*	Odds ratio
	37 colonized (37.8%)	40 colonized (39.2%)	.832	1.06 (95%-CI: 0.6–1.88)

Notes: Data were analysed using chi-squared test. Significance level was set at <.05. The strength of association was quantified by using the odds ratio with 95% confidence interval (95%-CI). A significantly higher prevalence of *Candida species* was found in psoriasis patients and in control subjects older or equal to the median age of 51 years. There was no significant difference between the sexes.

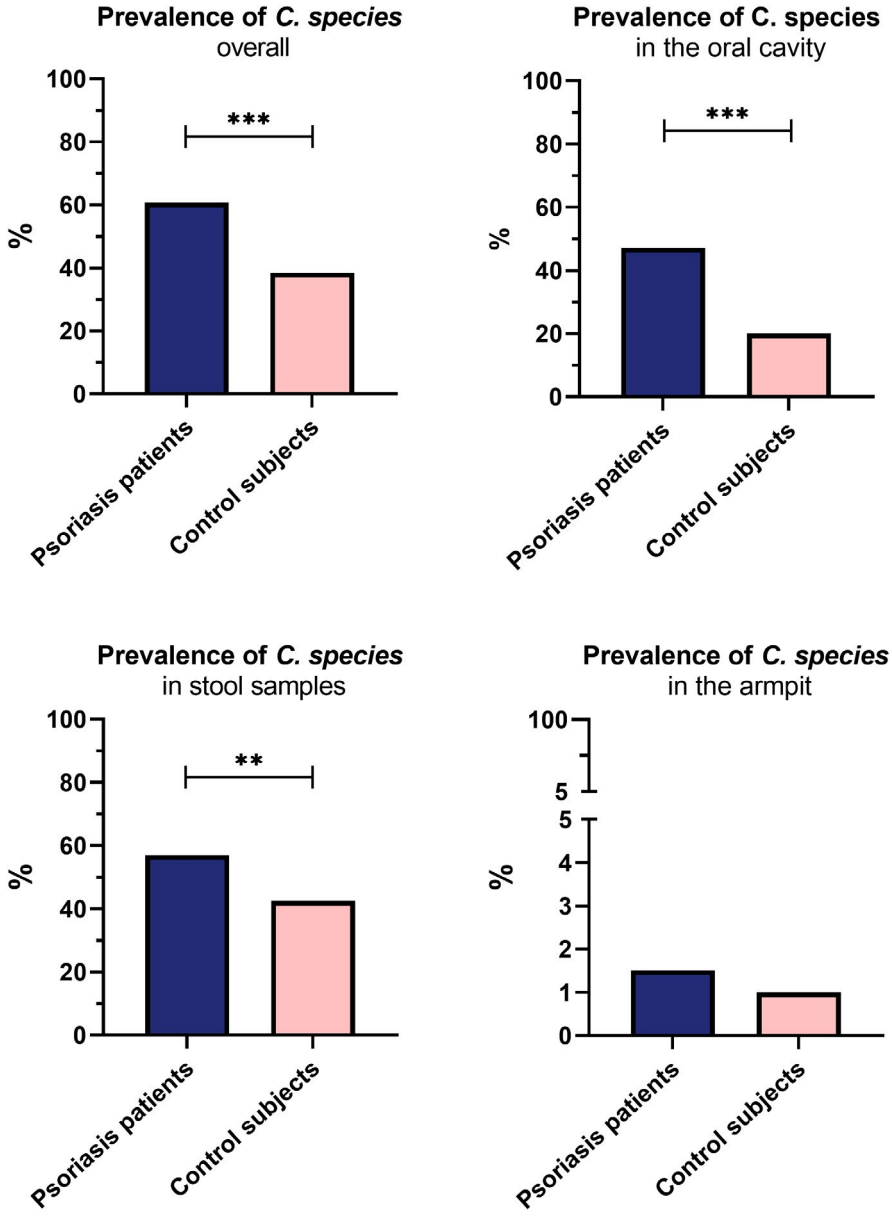

FIGURE 1 Relative prevalence of *Candida* (*C.*) *species* in psoriasis patients and control subjects. Data were analysed using chi-squared test. Significance level was set at <.05. When all collected samples were considered (skin, mucosa, stool), 60.8% of the psoriasis patients (n = 265) (blue) and 38.5% of the control subjects (n = 200) (pink) were colonized. The prevalence of *C. species* was significantly higher in psoriasis patients ($\chi 2$; p =< .001). Likewise, a significantly higher prevalence of *C. species* was found in oral swabs ($\chi 2$; p =< .001) and stool samples ($\chi 2$; p = .016) from psoriasis patients. *C. species* were isolated in 47.17% of the oral swabs (n = 265) and 56.98% of the stool samples (n = 179) from psoriasis patients. In the control group C. species were found in 20% of the oral swabs (n = 200) and 42.48% of the stool samples (n = 113). No significant difference (FET; p = .656) was found in the armpit. 1.51% of the psoriasis patients (n = 265) and 1% of the control subjects (n = 200) were colonized with *C. species* in their armpit

of the patients and 42.48% (48 of the 113) of control subjects. Statistically, the psoriasis group had a significantly higher prevalence of *C species* in stool samples (OR: 1.79; 95%-CI: 1.11–2.89; χ^2; p = .016) (Figure 1), where *C albicans* was the most widespread yeast. Samples from the oral cavity also showed a significantly higher prevalence of *C species* in patients with psoriasis (OR: 3.57; 95%-CI: 2.34–5.45; χ^2; p =< .001). A positive result was detected in 47.17% of the oral swabs from patients with psoriasis and in 20% from control subjects (Figure 1). *C albicans* was again the most common fungus.

Only a few yeast cells were found in the armpit and on psoriatic lesions. A positive axillary swap was found in four (1.51%) patients and two (1%) controls. A significant difference in prevalence of *C species* was not detectable (OR: 0.66; 95%-CI: 0.12–3.64; FET; p = .704) (Figure 1). Additionally, only four of the 248 lesional swaps were positive for *C species* (1.6%).

3.2 | Correlation between medication and the prevalence of *Candida species* and effects of *Candida* colonisation on the disease severity and immune response

In the group of the psoriasis patients, a total of 226 (85.3%) received systemic treatment at the time of study recruitment. Unexpectedly, no significant difference in the prevalence of *C species* was observed between patients with systemic treatment (apremilast, fumaric acids, ixekizumab, methotrexate (MTX), retinoids, secukinumab, TNF-antagonists and ustekinumab) when compared to patients who did not receive systemical drugs (OR: 0.85; 95%-CI: 0.42–1.72; χ^2; p = .643). Also, the cohort of patients receiving IL-17A antagonists did not show higher colonisation frequencies compared to patients who did not receive systemic drugs (OR: 0.77; 95%-CI: 0.25–2.36; χ^2; p = .647) (Table 3).

TABLE 2 Isolated *Candida species*

Candida species	Psoriasis patients (n = 265)	Members of the control group (n = 200)
Candida albicans[a]	110	58
Candida dubliniensis[a]	22	7
Candida famata	1	0
Candida glabrata[a]	19	6
Candida guilliermondii	1	0
Candida intermedia	1	0
Candida krusei[a]	3	1
Candida lambica	1	0
Candida lipolytica[a]	1	0
Candida parapsilosis[a]	3	2
Candida sphaerica	1	0
Not further differentiated *Candida species*[a]	24	11
Candida tropicalis[a]	2	0
Candida zeylanoides	1	0

[a]Ten psoriasis patients were simultaneously colonised with *Candida (C.) albicans* and *C glabrata*. Five were colonised with *C albicans* and not further differentiated *C species (spp.)*. Three were colonised with *C albicans* and *C dubliniensis*. *C albicans* and *C krusei*, *C albicans* and *C parapsilosis*, *C dubliniensis* and *C glabrata*, *C dubliniensis* and *C lipolytica*, *C glabrata* and not further differentiated *C spp*., *C krusei* and not further differentiated *C spp*., *C parapsilosis* and not further differentiated *C spp*. were each found in one patient. Another was colonised simultaneously with *C albicans*, *C dubliniensis* and *C glabrata*. Likewise, *C dubliniensis*, *C glabrata* and *C tropicalis* were isolated simultaneously in one psoriasis patient. [b]Three control subjects were simultaneously colonised with *C albicans* and *C glabrata*. Three more were colonised with *C albicans* and not further differentiated *C spp*. *C albicans* and *C dubliniensis* were isolated simultaneously in one control subject. Another was colonised with *C albicans* and *C parapsilosis*.

TABLE 3 Medication and prevalence of *Candida species*

Therapy	Colonized with *Candida species* (%)
No treatment, *n* = 12	5 (41.7)
Only topical tretatment,[a] *n* = 27	20 (74.1)
Retinoids, *n* = 6	2 (33.3)
Apremilast,[b] *n* = 12	7 (58.3)
Fumaric acids, *n* = 43	24 (55.8)
Methotrexate (MTX), *n* = 69	44 (63.8)
TNF inhibitors, *n* = 32	19 (59.4)
MTX + TNF inhibitors, *n* = 19	14 (73.7)
IL-17A antagonists,[c] *n* = 19	11 (57.9)
Ustekinumab,[d] *n* = 26	15 (57.7)

[a]Corticosteroids, vitamin D_3 analogues and/or calcineurin inhibitors.
[b]One Patient combined apremilast and MTX.
[c]One Patient combined secukinumab and MTX.
[d]One Patient combined ustekinumab and MTX.

TABLE 4 Psoriasis area and severity index (PASI) and prevalence of *Candida species*

PASI	Colonized with *Candida species* (%)
0, *n* = 15	9 (60)
>0 ≤ 10, *n* = 160	93 (58.1)
>10, *n* = 8	5 (62.5)

Note: The prevalence of *Candida species is* shown in relation to the Psoriasis area and severity index (PASI).

The psoriasis area and severity index (PASI), assessed for 183 patients, revealed a median PASI of 2 (0.5–4; 0–14.8). While the vast majority of patients suffered from mild psoriasis (160 patients PASI of >0 and ≤10), 15 patients were in remission (PASI of 0) and eight others suffered from a moderate-to-severe form of psoriasis with a PASI >10. Within this group of mild psoriasis, more than half of the patients showed a *Candida* colonisation. A PASI ≥10 did not lead to a higher prevalence of *C species* (OR: 1.19; 95%-CI: 0.28–5.15; FET; p = 1). There was also no significant difference between patients with a PASI of 0 and those with a PASI of >0 (OR: 1.07; 95%-CI: 0.37–3.15; χ^2; p = .9) (Table 4).

A similar observation could be made in the comparison of psoriasis patients with and without *C species* colonisation in terms of immune response. The ex vivo stimulation of PBMCs with *C albicans* from colonised versus uncolonised patients did not lead to an altered immune response. There was no significant difference in IFN-γ (U; p = .141), IL-17A (U; p = .58), IL-22 (U; p = .387) or TNF-α (U; p = .823) production. Similarly, no significant differences were found in their IFN-γ (U; p = .113), IL-17A (U; p = .104), IL-22 (U; p = .473) and TNF-α (U; p = .661) response to LPS stimulation (Figure 2).

4 | DISCUSSION

Th17 cells and IL-17 are crucial for both the physiological immune defence response against *Candida* and the dysregulated inflammatory response in psoriasis. Therefore, this study aimed to comprehensively investigate the colonisation with *C species* in psoriasis patients compared to a healthy control group without any history of inflammatory skin diseases. To understand whether there is a correlation between the prevalence of *Candida*, the severity and the treatment of psoriasis, swabs of the typical colonisation areas of the skin, mucosa and stool samples were collected from both groups.

First, the study showed that psoriasis patients have a significantly higher prevalence of *Candida* colonisation, more precisely, they have a 2.5-fold increased risk of colonisation compared to healthy subjects. Our results are consistent to previous studies with a smaller number of participants, which showed a significantly higher prevalence of *C species* in stool samples and in the oral cavity of patients with psoriasis.[12-15,20] Although Candidiasis often affects the intertriginous areas, we did not observe any significant difference

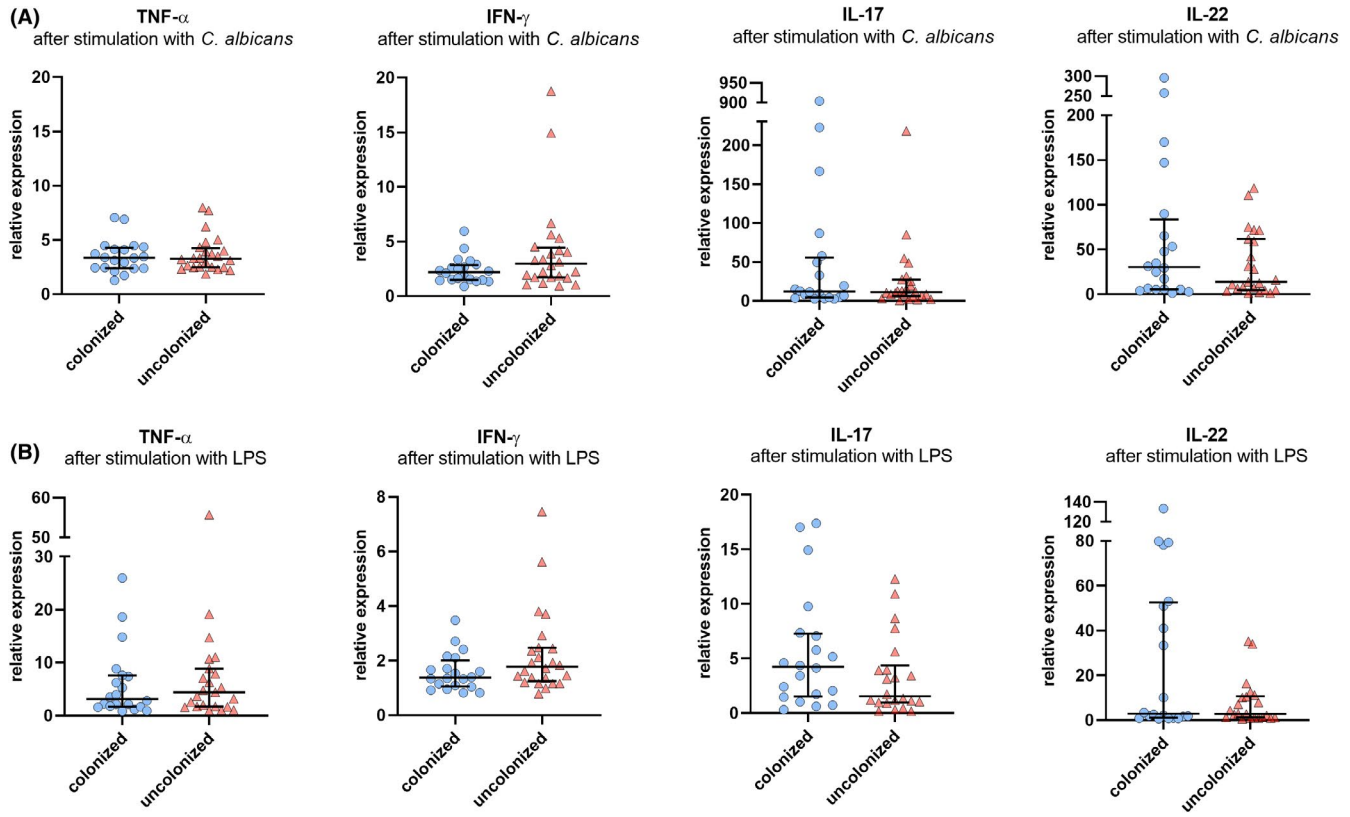

FIGURE 2 Relative expression of IFN-γ, interleukin IL-17A, IL-22 and TNF-α in psoriasis patients after stimulation with *Candida albicans* (A) and LPS (B). Data were analysed using Mann-Whitney U test (U). Significance level was set at <.05. Psoriasis patients colonized with *Candida species* (n = 20) (blue) and uncolonized patients (n = 24) (pink) did not significantly differ in their expression of interferon (IFN)-γ (U; p = .141), interleukin (IL)-17A (U; p = .58), IL-22 (U; p = .387) and tumor necrosis factor (TNF)-α (U; p = .823) after stimulation with *Candida albicans* (strain SC53143). Likewise, there were no significant differences in the expression of IFN-γ (U; p = .113), IL-17A (U; p = .104), IL-22 (U; p = .473) and TNF-α (U; p = .661) after stimulation with lipopolysaccharides (LPS)

in axillary swabs and found only a few fungi in both groups. As expected, we found only few psoriatic lesions with *Candida* colonisation. Previous studies found a low prevalence of *C species* on healthy skin.[14,21] Nevertheless, in a previous examination, Taheri Sarvtin et al were able to detect a significantly higher prevalence of *C species* on the trunks of patients with psoriasis, but were unable to isolate *C species* from swabs of the extremities, flexures, and scalp.[14]

Of special interest was the identification of factors that could promote an increased prevalence of *C species*. Therefore, the group of psoriasis patients was examined for a correlation between the prevalence of *Candida* and patients' characteristics like age, gender, therapy and disease severity. Unlike previous studies, who did not observe a correlation between age and fungal colonisation, we found a substantially higher prevalence of *C species* in psoriasis patients and control subjects older than a median age of 51 years.[13,20,21] Consistent to previous examinations, we did not find any significant difference between the sexes.[13,20,21]

Whether systemic drugs have an impact on the prevalence of *C species* is controversial. Studying a small cohort, Chularojanamontri et al showed a correlation between systemic drugs and the presence of *Candida*,[15] whereas Picciani et al found no correlation between the type of medication and oral candidiasis.[24] To better understand the potential correlation, this study investigated the influence of systemically active drugs on the colonisation with *Candida* in psoriasis patients. In particular, we were interested to examine, whether IL-17–based therapies lead to an increased *Candida* colonisation. Of note, IL-17A is a key element in the host defence against candidiasis and congenital deficiencies in the Th17/IL-17 pathway are associated with an increased risk of mucocutaneous and invasive candidiasis.[2,4,28-34] Moreover, candidiasis is a rare but typical finding in patients with psoriasis treated with IL-17–neutralising antibodies. However, our study did not reveal any significant association between systemic antipsoriatic drugs and an increase in the prevalence of *C species*. Even when focusing on patients receiving IL-17–neutralising antibodies, we did not find any signal for *Candida* colonisation. Although a colonisation with *C species* does not necessarily lead to an infection, colonised patients may have a higher risk of candidiasis.[35] Our findings reflect the analysis by Saunte et al This systemic review of clinical trials found an overall incidence of candidiasis of 3.3% during treatment with ixekizumab, and 1.7% during treatment with secukinumab was observed. While the overall incidence of candidiasis was slightly lower at 2.3% after treatment with ustekinumab, 0.8% after treatment with the TNF-blocker etanercept and 0.3% in the placebo groups.[35]

Finally, the impact of a colonisation with *Candida* on the immune response and the disease severity in patients with psoriasis was examined. If a colonisation with *C species* affects the disease activity, it should lead to an altered immune reaction. However, colonised and uncolonised patients did not differ in their expression of IFN-γ, IL-17A, IL-22 and TNF-α neither after stimulation with *C albicans* nor after stimulation with an immune activator like LPS. These findings argue that *Candida* colonisation does not affect the activation of psoriasis promoting cytokines and also the Th17 response towards *Candida* is not influenced by colonization. Thus, it is not surprising that our study did not observe any correlation between the PASI and the prevalence of *C species*. However, it must be mentioned that the group of patients with moderate-to-severe disease (PASI ≥10) were underrepresented in our monocentre examination. Our results are consistent to three previous studies, who did not find a correlation between disease activity and *Candida* colonisation.[12,13,21] This is in conflict to some other reports, where such a correlation was described[20,22] However, Ovčina-Kurtović et al could only prove this connection in skin swabs of highly affected patients (PASI >50) and not in stool samples from the same participants.[22]

Taken together, our results indicate that the impact of *Candida* colonisation on the disease activity and type 1/17 cytokine response to *C species* is rather negligible. Interestingly, patients with psoriasis are significantly more likely to be colonised by *C species* compared to an age-matched control group. Especially, the group of patients above the age of 51 years was affected. A colonised patient has at least theoretically an increased risk of candidiasis. Therefore, especially elderly patients should be monitored for symptoms of candidiasis during anti IL-17A treatment. In the future, further studies should be aimed at investigating the relationship between colonisation with *Candida* and resulting candidiasis in psoriasis patients, also with regard to the severity of the disease and the therapy used.

AUTHOR CONTRIBUTION

Kevin Elsner: Conceptualization (equal); Data curation (lead); Formal analysis (lead); Funding acquisition (equal); Investigation (lead); Methodology (equal); Project administration (equal); Visualization (lead); Writing – original draft (lead); Writing – review & editing (equal). **Julia Holstein:** Data curation (supporting); Formal analysis (supporting); Methodology (supporting); Validation (supporting). **Franz Joachim Hilke:** Formal analysis (supporting); Supervision (supporting); Validation (equal); Visualization (equal); Writing – original draft (equal); Writing – review & editing (equal). **Gunnar Blumenstock:** Formal analysis (supporting); Validation (supporting); Visualization (supporting); Writing – review & editing (supporting). **Birgit Walker:** Data curation (supporting); Methodology (supporting). **Sybille Schmidt:** Data curation (supporting); Methodology (supporting). **Martin Schaller:** Conceptualization (supporting); Methodology (supporting); Project administration (supporting); Resources (supporting); Supervision (supporting); Validation (supporting); Writing – review & editing (supporting). **Kamran Ghoreschi:** Conceptualization (lead); Data curation (equal); Formal analysis (equal); Funding acquisition (equal); Investigation (equal); Methodology (equal); Project administration (equal); Resources (lead); Software (equal); Supervision (lead); Validation (equal); Visualization (equal); Writing – original draft (equal); Writing – review & editing (equal). **Katharina Meier:** Conceptualization (equal); Data curation (equal); Formal analysis (equal); Funding acquisition (equal); Investigation (equal); Methodology (equal); Project administration (equal); Resources (equal); Software (equal); Supervision (equal); Validation (equal); Visualization (equal); Writing – original draft (equal); Writing – review & editing (lead).

ORCID

Katharina Meier https://orcid.org/0000-0002-4687-3195

REFERENCES

1. Parisi R, Symmons DP, Griffiths CE, et al. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. *J Invest Dermatol*. 2013;133(2):377-385.
2. Huang W, Na L, Fidel PL, Schwarzenberger P. Requirement of interleukin-17A for systemic anti-Candida albicans host defense in mice. *J Infect Dis*. 2004;190(3):624-631.
3. Acosta-Rodriguez EV, Rivino L, Geginat J, et al. Surface phenotype and antigenic specificity of human interleukin 17-producing T helper memory cells. *Nat Immunol*. 2007;8(6):639-646.
4. Conti HR, Shen F, Nayyar N, et al. Th17 cells and IL-17 receptor signaling are essential for mucosal host defense against oral candidiasis. *J Exp Med*. 2009;206(2):299-311.
5. Wilson NJ, Boniface K, Chan JR, et al. Development, cytokine profile and function of human interleukin 17-producing helper T cells. *Nat Immunol*. 2007;8(9):950-957.
6. Nograles KE, Zaba LC, Guttman-Yassky E, et al. Th17 cytokines interleukin (IL)-17 and IL-22 modulate distinct inflammatory and keratinocyte-response pathways. *Br J Dermatol*. 2008;159(5):1092-1102.
7. van der Fits L, Mourits S, Voerman JS, et al. Imiquimod-induced psoriasis-like skin inflammation in mice is mediated via the IL-23/IL-17 axis. *J Immunol*. 2009;182(9):5836-5845.
8. Rosenberg EW, Belew PW. Improvement of psoriasis of the scalp with ketoconazole. *Arch Dermatol*. 1982;118(6):370-371.
9. Farr PM, Krause LB, Marks JM, Shuster S. Response of scalp psoriasis to oral ketoconazole. *Lancet*. 1985;2(8461):921-922.
10. Buslau M, Hanel H, Holzmann H. The significance of yeasts in seborrheic eczema. *Hautarzt*. 1989;40(10):611-613.
11. Kumar B, Kaur I, Talwar P, Kaur S. Nystatin in Psoriasis. *Indian J Dermatol Venereol Leprol*. 1989;55(3):170-172.
12. Waldman A, Gilhar A, Duek L, Berdicevsky I. Incidence of Candida in psoriasis–a study on the fungal flora of psoriatic patients. *Mycoses*. 2001;44(3–4):77-81.
13. Bedair AA, Darwazeh AM, Al-Aboosi MM. Oral Candida colonization and candidiasis in patients with psoriasis. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2012;114(5):610-615.
14. Taheri Sarvtin M, Shokohi T, Hajheydari Z, Yazdani J, Hedayati MT. Evaluation of candidal colonization and specific humoral responses against Candida albicans in patients with psoriasis. *Int J Dermatol*. 2014;53(12):e555-e560.
15. Chularojanamontri L, Wongpraparut C, Tuchinda P, et al. Oral candida colonization in thai patients with psoriasis. *J Med Assoc Thai*. 2016;99(1):84-87.
16. Leung DY, Walsh P, Giorno R, Norris DA. A potential role for superantigens in the pathogenesis of psoriasis. *J Invest Dermatol*. 1993;100(3):225-228.
17. Norrlind R. The significance of infections in the origination of psoriasis. *Acta Rheumatol Scand*. 1955;1(2):135-144.

18. Whyte HJ, Baughman RD. Acute guttate psoriasis and streptococcal infection. *Arch Dermatol*. 1964;89:350-356.
19. Telfer NR, Chalmers RJ, Whale K, Colman G. The role of streptococcal infection in the initiation of guttate psoriasis. *Arch Dermatol*. 1992;128(1):39-42.
20. Lesan S, Toosi R, Aliakbarzadeh R, et al. Oral Candida colonization and plaque type psoriasis: Is there any relationship? *J Investig Clin Dent*. 2018;9(3):e12335.
21. Leibovici V, Alkalay R, Hershko K, et al. Prevalence of Candida on the tongue and intertriginous areas of psoriatic and atopic dermatitis patients. *Mycoses*. 2008;51(1):63-66.
22. Ovcina-Kurtovic N, Kasumagic-Halilovic E, Helppikangans H, Begic J. Prevalence of candida species in patients with psoriasis. *Acta Dermatovenerol Croat*. 2016;24(3):209-213.
23. Armstrong AW, Bukhalo M, Blauvelt A. A clinician's guide to the diagnosis and treatment of candidiasis in patients with psoriasis. *Am J Clin Dermatol*. 2016;17(4):329-336.
24. Picciani BL, Michalski-Santos B, Carneiro S, et al. Oral candidiasis in patients with psoriasis: correlation of oral examination and cytopathological evaluation with psoriasis disease severity and treatment. *J Am Acad Dermatol*. 2013;68(6):986-991.
25. Boyum A. Separation of leukocytes from blood and bone marrow. Introduction. *Scand J Clin Lab Invest Suppl*. 1968;97:7.
26. Odds FC, Van Nuffel L, Gow NA. Survival in experimental Candida albicans infections depends on inoculum growth conditions as well as animal host. *Microbiology*. 2000;146(Pt 8):1881-1889.
27. Schaller M, Zakikhany K, Naglik JR, Weindl G, Hube B. Models of oral and vaginal candidiasis based on in vitro reconstituted human epithelia. *Nat Protoc*. 2006;1(6):2767-2773.
28. Kisand K, Boe Wolff AS, Podkrajsek KT, et al. Chronic mucocutaneous candidiasis in APECED or thymoma patients correlates with autoimmunity to Th17-associated cytokines. *J Exp Med*. 2010;207(2):299-308.
29. Puel A, Doffinger R, Natividad A, et al. Autoantibodies against IL-17A, IL-17F, and IL-22 in patients with chronic mucocutaneous candidiasis and autoimmune polyendocrine syndrome type I. *J Exp Med*. 2010;207(2):291-297.
30. Puel A, Cypowyj S, Bustamante J, et al. Chronic mucocutaneous candidiasis in humans with inborn errors of interleukin-17 immunity. *Science*. 2011;332(6025):65-68.
31. van de Veerdonk FL, Plantinga TS, Hoischen A, et al. STAT1 mutations in autosomal dominant chronic mucocutaneous candidiasis. *N Engl J Med*. 2011;365(1):54-61.
32. Chandesris MO, Melki I, Natividad A, et al. Autosomal dominant STAT3 deficiency and hyper-IgE syndrome: molecular, cellular, and clinical features from a French national survey. *Medicine (Baltimore)*. 2012;91(4):e1-19.
33. Boisson B, Wang C, Pedergnana V, et al. An ACT1 mutation selectively abolishes interleukin-17 responses in humans with chronic mucocutaneous candidiasis. *Immunity*. 2013;39(4):676-686.
34. Drewniak A, Gazendam RP, Tool AT, et al. Invasive fungal infection and impaired neutrophil killing in human CARD9 deficiency. *Blood*. 2013;121(13):2385-2392.
35. Saunte DM, Mrowietz U, Puig L, Zachariae C. Candida infections in patients with psoriasis and psoriatic arthritis treated with interleukin-17 inhibitors and their practical management. *Br J Dermatol*. 2017;177(1):47-62.

How to cite this article: Elsner K, Holstein J, Hilke FJ, et al. Prevalence of *Candida species* in Psoriasis. *Mycoses*. 2022;65:247–254. doi:10.1111/myc.13399