

Effectiveness of narrowband UVB phototherapy and psoralen plus UVA photochemotherapy in the treatment of generalized lichen planus: *Results from a large retrospective analysis and an update of the literature*

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Abstract

Background: The aim of this retrospective study was to compare the efficacy and safety of different phototherapeutic modalities in the treatment of cutaneous lichen planus (LP).

Methods: We retrospectively analyzed the chart data of 53 patients with generalized LP who had been subjected to narrowband UVB (NB-UVB) or photochemotherapy (PUVA) between January 1997 and April 2020. Of these, 30 patients had received NB-UVB, 18 patients oral PUVA and 5 patients bath PUVA.

Results: Fifty patients completed a full treatment course. The percentage of patients with a complete (>90% clearing) or good (51%-90% clearing) response was similar for NB-UVB versus PUVA (86.2% vs. 90.5%; $P = 1.00$). The number of exposures required for obtaining a complete or good response was also comparable for both treatment groups (NB-UVB: 28.9 ± 12.3 vs. PUVA: 25.4 ± 10.1 ; $P = .209$). Adverse events, in particular gastrointestinal upsets, were recorded in 26.1% of patients treated with oral PUVA while none were observed with NB-UVB.

Conclusion: The therapeutic outcome and the number of treatments required for achieving a complete or good response were comparable for NB-UVB and PUVA; however, PUVA therapy was associated with a substantially higher rate of moderate adverse events.

KEYWORDS

effectiveness, lichen planus, photochemotherapy, phototherapy, safety

1 | INTRODUCTION

Lichen planus (LP) is a chronic skin disease characterized by pruritic polygonal, purple, planar, and papular skin lesions that on the surface often show white lines known as "Wickham striae".¹ Also, the

scalp, mucous membranes, or nails may be affected rendering LP a skin disorder with a broad spectrum of clinical presentations.²⁻⁴ The exact prevalence of cutaneous LP in the general population is unknown but estimated to be 0.5%-1%.³ While middle-aged men and women are equally affected by LP, incidence rates in children

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are low. Genetic predisposition has a role in the development of LP with high incidence rates being found in India, Mexico, and the Middle East.⁵⁻⁷ The pathogenesis of LP remains to be unraveled but has been linked to the action of different immune cells such as NK cells, T cells, and dendritic cells altering keratinocytes.⁸⁻¹⁰ The clinical course of LP is characterized by chronicity with spontaneous remissions and occasional relapses which impairs the patients' quality of life and may pose a therapeutic challenge.^{11,12} Treatment options with different levels of evidence for cutaneous LP include topical treatments such as corticosteroids and systemic treatments such as acitretin, methotrexate, cyclosporine, or TNF α inhibitors.^{8,13,14} In addition, different phototherapeutic modalities such as narrowband ultraviolet B (NB-UVB), psoralen and UVA (PUVA), and UVA-1¹³ have been successfully used for treating LP.¹³ While the clinical efficacy of phototherapies for LP has been proven in multiple studies,^{8,13,15,16} its precise mode of action still needs to be elucidated. NB-UVB phototherapy provides high response rates and has an excellent safety profile.^{16,17} PUVA appears to provide for an even higher initial response rate.¹¹ Concomitantly, various topical agents such as corticosteroids or vitamin D analogues can be used as an adjunctive treatment to further enhance the therapeutic response. Mild-to-moderate short-term side effects like phototoxic erythema or dryness of the skin are generally well tolerated and easily manageable. However, most of the aforementioned studies have been carried out on small numbers of patients and a systematic comparison of different phototherapeutic modalities based on a large series of patients is lacking so far. In the present study, we therefore retrospectively analyzed the treatment outcome of all patients with cutaneous lichen planus who received phototherapy at our Phototherapy Unit between January 1997 and April 2020.

2 | MATERIALS AND METHODS

2.1 | Patient recruitment and data analysis

The study was approved by the institutional ethics committee from the Medical University of Vienna, Austria (EK-Nr: 1297/2020). We extracted data of LP patients who were treated with phototherapy (NB-UVB, oral or bath PUVA) between January 1997 and April 2020 at the Department of Dermatology, Medical University of Vienna, using the internal hospital data management tool. The primary objective was to analyze and compare the effectiveness and safety of phototherapeutic modalities for LP. The inclusion criteria of the study were as follows: patients diagnosed with generalized lichen planus with insufficient treatment response to topical therapy and one or more completed phototherapy courses (NB-UVB or PUVA) received between January 1997 and April 2020. In patients with several treatment courses, only the data of the first treatment course were entered into the analysis. Patients with an insufficient documentation of their treatment response were excluded from evaluation. Overall, the following parameters were recorded and evaluated: sex, age, disease duration, skin phototype, phototherapeutic modality,

treatment duration, number of total treatments, and adjuvant therapy. Concomitant topical treatments (glucocorticosteroids, calcineurin inhibitors) for severely affected predilection sites, for example, the wrist or ankles, were usually continued. The clinical response (percentage of reduction of affected body surface area as compared to baseline) was defined as follows: no response (0% reduction of BSA), partial response (1%-50% reduction of BSA), good response (51%-90% reduction of BSA), and complete response (>90% reduction of BSA).

2.2 | Phototherapy treatment modalities

NB-UVB was administered using a Waldmann UV 7002 cabinet (Herbert Waldmann GmbH & Co. KG, Villingen-Schwenningen, Germany) 2-3 times per week (mean 2.3 ± 0.8). The irradiance was measured with an integrated radiometer and was on average 10.5 mW/cm^2 . The initial NB-UVB dose was chosen according to skin phototype and ranged between 0.3 and 0.6 J/cm^2 . Dose increments of 10-20% were performed at each visit in the absence of treatment-induced erythema up to a maximum exposure dose of 3.0 J/cm^2 .

For patients receiving oral or bath PUVA therapy, a Waldmann PUVA 4000 lie-down unit (Herbert Waldmann GmbH & Co. KG) with 40 Sylvania FR 90 T 12/PUVA fluorescent tubes was used. The determination of the minimal phototoxic dose (MPD) was performed prior to treatment using a Waldmann PUVA 800 irradiation unit (Herbert Waldmann GmbH & Co. KG) with a 10 Philips TLK 40 W/09 N UVA lamp. 8-methoxypsoralen (8-MOP; Oxsoralen[®]; Gerot) at a dose of 0.6 mg kg^{-1} was administered one hour prior to treatment. Two patients did not tolerate 8-MOP and were switched to 5-methoxypsoralen (5-MOP, Geralen[®]; Gerot) 1.2 mg kg^{-1} 2 hours before irradiation. UVA irradiance was on average 9.5 mW cm^{-2} as measured by an integrated radiometer. The starting dose was set at 70% of the MPD, and treatment was administered 2 or 3 times per week (mean 2.4 ± 0.6). For skin phototypes I or II, the UVA dose was increased by 15% in the absence of treatment-induced erythema or by 5% when slight erythema was present but never earlier than 96 hours after the last dose increment. The respective dose increments for darker skin phototypes (III, IV) were 20% and 10%, respectively. Bath PUVA was done with 8-methoxypsoralen at a concentration of 5 mg/l (0.0005%) for which purpose 100 ml of a 0.5% 8-MOP stock solution was diluted in 100 liters of tap water (37°C). The patient's body was immersed in the bathtub for 15 minutes and subsequently irradiated with UVA. As with oral PUVA, treatment was administered 2-3 times weekly (mean 2.3 ± 0.2).

2.3 | Statistical analysis

SPSS software (SPSS-24; SPSS Inc.) and Excel-2016 macOS-software (Microsoft Corp.,) were used to analyze the results. Imputation of missing values was performed if required prior to the statistical

analysis. For comparison of the treatment characteristics (total numbers of exposures, number of exposures until reaching the final response) between NB-UVB and PUVA treatment, a Mann-Whitney U test was used. For analyzing differences in the clinical outcome (complete clearance vs. no response) and the rate of adverse effects a Fisher's exact test was performed. For the main study outcome, that is, the difference between NB-UVB and PUVA in percentage of patients achieving a complete or good response, an adequate post hoc statistical power of 0.9906548 was calculated. In all tests, a P -value $\leq .05$ was considered statistically significant.

3 | RESULTS

3.1 | Patients' characteristics and treatment allocation

In total, 53 patients with generalized LP were treated with phototherapy. Thirty patients (56.6%) received NB-UVB and 23 (43.4%) PUVA. The PUVA cohort consisted of 18 patients (78.3%) receiving oral PUVA and 5 patients (21.7%) receiving bath PUVA. One NB-UVB patient discontinued treatment prematurely, and one patient each on oral and bath PUVA required transition to NB-UVB due to PUVA-related side effects (nausea and painful phototoxic reaction, respectively). Thus, 29 patients on NB-UVB and 21 patients on PUVA (oral PUVA 17, bath PUVA 4) completed a full treatment course. No significant difference with respect to pretreatments (topical or systemic glucocorticosteroids, topical calcineurin inhibitors, methotrexate) or disease duration was found between both treatment modalities ($P = .086$). However, 7 patients on PUVA had received adjunctive retinoid treatment as opposed to only one NB-UVB patient. Patients on combination treatment had a significantly longer disease duration than those without concomitant retinoid administration (61 ± 48 months vs. 22 ± 38 months; $P = .006$) indicating a more severe disease. The demographic data and treatment allocation of the patients are summarized in Table 1.

3.2 | Treatment outcome and adverse effects

Of 50 treatment courses, 72.0% ($n = 36$) resulted in a complete response (NB-UVB: 72.4%; PUVA: 71.4%), 16.0% ($n = 8$) in a good response (NB-UVB: 13.8%; PUVA: 19.0%), 4.0% ($n = 2$) in a partial response (NB-UVB: 3.4%; PUVA: 4.8%) and 8.0% ($n = 4$) in non-response (NB-UVB: 10.3%; PUVA: 4.8%). Representative photographs of a complete clinical response are shown in Figure 1. The rate of patients achieving a complete or good response at the end of treatment was almost identical for NB-UVB (25/29; 86.2%) and PUVA (19/21; 90.5%) ($P = 1.00$). Likewise, the rate of non-responders was comparable in both groups (NB-UVB: 3/29 (10.3%); PUVA 1/21 (4.8%); ($P = .63$). The mean number of treatments per week was similar for NB-UVB and PUVA (2.3 ± 0.8 vs. 2.3 ± 0.5 ; $P = .636$). The

TABLE 1 Demographic data and treatment allocation of the patients

Patients (n = 50)	NB-UVB (n = 29)	PUVA (n = 21)
Male	8	9
Female	21	12
Mean (\pm SD) age, (y)	50 (\pm 16)	42 (\pm 12)
Age range (y)	16-76	25-66
Skin phototype		
I	1	-
II	6	5
III	16	12
IV	4	4
V	2	-
Concomitant retinoid therapy	1	7
Mean (\pm SD) disease duration (mo)		
all patients: n = 50	20 (\pm 34)	40 (\pm 51)
patients on NB-UVB or PUVA monotherapy: n = 42	21 (\pm 32)	25 (\pm 49)
patients with adjunctive retinoid treatment: n = 8	7 (\pm 0)	68 (\pm 46)

mean number of exposures to achieve a complete or good response was insignificantly higher for NB-UVB (28.9 ± 12.3) as compared to PUVA (25.4 ± 10.1) ($P = .209$). A subanalysis of the PUVA cohort revealed no significant difference in treatment outcome between oral and bath PUVA (data not shown). Figure 2 summarizes the entire spectrum of treatment responses.

To exclude a bias in the therapeutic outcome due to the additional retinoid administration, we performed a subanalysis of the 42 patients with PUVA or NB-UVB monotherapy. No significant difference regarding disease duration (25 ± 49 vs. 21 ± 32 months; $P = .917$) number of treatments required to achieve a complete or good response (24.6 ± 10.5 vs. 28.9 ± 12.3 ; $P = .227$) or treatment outcome ($P = 1.000$) was found in these patients.

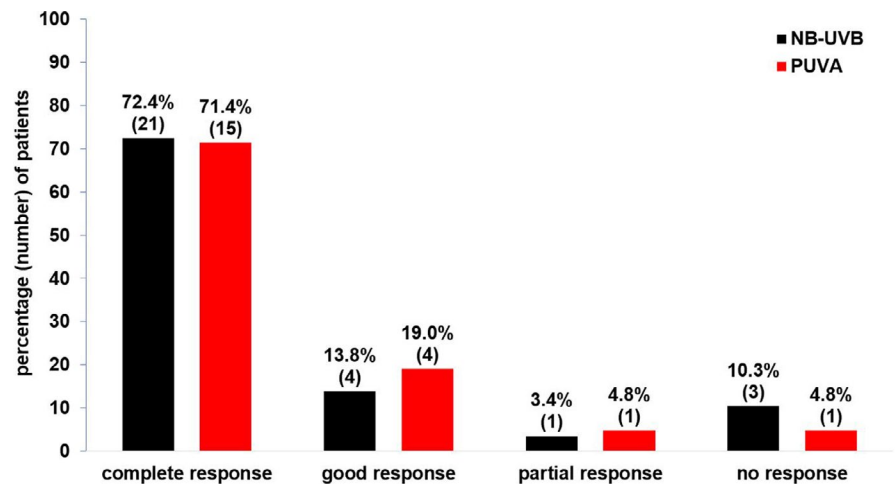
Two patients not responding to NB-UVB were switched to bath PUVA and achieved a complete and good response, respectively. One patient who did not respond to oral PUVA subsequently showed a good response to NB-UVB. From the other 3 patients with partial or no response, one was successfully treated with methotrexate and two were lost to follow-up.

Moderate adverse effects were exclusively observed with PUVA therapy. Six patients had 8-MOP-induced nausea which in all, but one case was manageable with antiemetics and one patient experienced a painful phototoxic erythema. Both patients in whom the side effects necessitated discontinuation of PUVA completely cleared later on with NB-UVB. No side effects were documented for NB-UVB.

FIGURE 1 Representative photographs of a patient (tattoos covered by black squares) at baseline (left side) and after complete response to PUVA treatment (right side)



FIGURE 2 Therapeutic outcome with NB-UVB and PUVA (no response: 0% reduction of BSA, partial response: 1%-50% reduction of BSA, good response: 51%-90% reduction of BSA, complete response: >90% reduction of BSA)



4 | DISCUSSION

A wealth of studies have shown that phototherapies are highly effective, well tolerated, safe, and cost-effective in treating a broad range of inflammatory skin disorders.¹⁸ Both UVB (mostly NB-UVB) phototherapy and psoralen-UVA (PUVA) photochemotherapy have successfully been employed in lichen planus patients.^{11,19-35} Studies on oral PUVA are scarce and mostly included a small number of patients. Ortonne et al¹⁹ observed remission in 6 of 7 patients with disseminated LP after 30 exposures to oral 8-MOP PUVA. Gonzalez et al²⁰ reported on a complete clinical response in 5 and a partial response in 3 of 10 patients after 28 treatments with oral 8-MOP PUVA. By far, the most extensive investigation on PUVA for generalized lichen planus was performed by a German group of authors.²¹ They included 70 patients who were either subjected to conventional long-term PUVA or biphasic cyclic PUVA and found complete response rates of 71% and 92%, respectively. By histological assessment, however, complete response rates were lower and only amounted to 59% and 83%, respectively.

A number of studies with bath PUVA using trioxsalen or 8-MOP as a photosensitizer provided complete response rates ranging from 65%-100%.²³⁻²⁶ In a non-randomized prospective study on 43 patients, Helander et al compared oral PUVA (n = 10), bath PUVA (n = 13) and no PUVA (n = 20). At the end of treatment, the number of patients with a > 75% clearance was higher for bath PUVA (10/13) than for oral PUVA (5/10). Interestingly however, patients continued to improve and all but one bath PUVA patient exhibited >75% clearance at a follow-up 1-2 months after cessation of PUVA.²²

More recent phototherapeutic studies in LP were almost exclusively done with NB-UVB and provided comparably good results.²⁷⁻³⁴ The number of included patients varied between 5 and 50 and the complete response in all but one study ranged between 50% and 100% (Table 2). In one further study on 35 patients treated twice weekly over 3 months, a significant reduction in the body surface affection and serum neopterin levels was reported, also suggesting neopterin as a useful biomarker for assessing severity and treatment efficacy in LP patients.³⁵ Additionally, Iraj et al in a prospective randomized 6 weeks trial on 46 patients compared NB-UVB thrice weekly with daily prednisolone 0.3 mg/kg. At the end of

TABLE 2 Synopsis of the published literature on photo(chemo)therapy for lichen planus

Author	Study design	No. of patients	Treatment modality	Therapeutic outcome
Ortonne ¹⁹ 1978	Prospective, non-randomized	7	Oral PUVA	6/7 (86%) complete response
Gonzalez ²⁰ 1984	Prospective, non-randomized	10	Oral PUVA	5/10 (50%) complete response 3/10 (30%) >50% improvement
Narwutsch ²¹ 1986	Prospective, non-randomized	70	Monophasic oral PUVA ³⁵ Monophasic local PUVA ⁶ Biphasic short-term oral PUVA ²⁵ Biphasic short-term local PUVA ⁴	25/35 (71%) complete response 4/6 (67%) complete response 23/25 (92%) complete response 3/4 (75%) complete response
Helander ²² 1987	Prospective, non-randomized	43	oral PUVA ¹⁰ 8-MOP bath PUVA ¹³ no PUVA ²⁰	5/10 (50%) >75% clearing 10/13 (77%) >75% clearing no comparative data
Wackernagel ¹¹ 2007	Retrospective	28	oral PUVA ¹⁵ NB-UVB ¹³	10/15 (67%) complete response (>90% clearing) 5/15 (33%) partial response (>50% clearing) 4/13 (31%) complete response (>90% clearing) 6/13 (46%) partial response (>50% clearing)
Väättäin ²³ 1981	Prospective, non-randomized	19	trioxsalen bath PUVA	18/19 (95%) complete response 1/19 (5%) good response (60%-90% cured)
Karvonen ²⁴ 1985	Prospective, non-randomized	75	trioxsalen bath or cream PUVA	49/75 (65%) complete response 11/75 (15%) good response (most lesions disappeared)
Kersch ²⁵ 1995	Prospective, non-randomized	4	8-MOP bath PUVA	4/4 (100%) complete response
von Kobyletzki ²⁶ 1997	Prospective, non-randomized	12	8-MOP bath PUVA	9/12 (75%) complete response 2/12 (17%) marked improvement
Taneja ²⁷ 2002	Prospective, non-randomized	5	NB-UVB	5/5 (100%) complete remission
Habib ²⁸ 2005	Retrospective	20	NB-UVB	11/20 (55%) complete response (>90% clearing) 4/20 (20%) partial response (>50% clearing)
Gamil ²⁹ 2009	Prospective, non-randomized	16	NB-UVB	11/16 (69%) complete response (≥ 90% clearing) 2/16 (13%) partial response (51%-89% clearing)
Saricaoglu ³⁰ 2003	Prospective, non-randomized	10	NB-UVB	8/10 (80%) complete response (>90% clearing) 1/10 (10%) partial response (51%-89% clearing)
Pavlotsky ³¹ 2008	Retrospective	50	NB-UVB ³⁴ BB-UVB ⁷ UVB plus topical steroids ⁹	25/34 (74%) complete response 4/7 (57%) complete response 5/9 (56%) complete response

(Continues)

TABLE 2 (Continued)

Author	Study design	No. of patients	Treatment modality	Therapeutic outcome
Iraji ³² 2011	Prospective, randomized	46	NB-UVB ²³ systemic corticosteroids ²³	12/23 (52%) complete response (>90% clearing) 11/23 (48%) partial or weak response (20%-90% clearing) 3/23 (13%) complete response (>90% clearing) 17/23 (74%) partial or weak response (20%-90% clearing)
Solak ³³ 2016	Retrospective	24	NB-UVB	11/24 (46%) complete response (≥90% clearing) 5/24 (21%) partial response (51%-89% clearing)
Fernández-Guarino ³⁴ 2019	Prospective, non-randomized	10	NB-UVB	8/10 (80%) complete response (>90% clearing) 2/10 (20%) partial response (70%-90% clearing)
Khattab ³⁵ 2020	Prospective, non-randomized	35	NB-UVB	significant reduction of mean body surface affection

the study, a significantly better response was found for NB-UVB as opposed to treatment with the systemic steroid.³²

So far there is only one single study that aimed at assessing the relative therapeutic efficacy of PUVA versus NB-UVB. In a retrospective analysis of 28 LP patients, Wackernagel et al found a better initial clinical response to oral PUVA than to NB-UVB; however, in the long-term (mean follow-up in months: PUVA: 20.5; NB-UVB: 35.7), no significant difference in the sustained overall response rate was found between the two treatment groups.¹¹ Table 2 gives a summary of all studies using phototherapeutic modalities for lichen planus including patients' number, study design and study outcome.

The present study on 50 patients is the largest comparative trial so far and corroborates the role of phototherapy in the management of patients with generalized LP. Slightly differing from the report by Wackernagel et al¹¹ the rate of patients achieving a complete or good response was comparable for NB-UVB and PUVA (86.2% vs. 90.5%; $P = 1.00$) in our analysis. Likewise, the number of treatments required for attaining a complete or good response was similar in the two patient groups indicating high and equivalent effectiveness of both phototherapeutic modalities in the treatment of generalized lichen planus. Of note, switch within phototherapies due to non-response or adverse reactions resulted in complete or good response. This concurs with the previous observation of complete response to oral PUVA in two patients who had failed treatment with NB-UVB.¹¹ Our study does not provide data on the length of remission since in daily routine patients are not called in for regular follow-up visits after completion of treatment.

Due to its retrospective nature, our study has several limitations such as the lack of a standardized assessment of disease severity at baseline or the lack of a randomized treatment allocation and predefined treatment outcomes. It is also noteworthy to point out

that our treatment protocol employed fixed (skin phototype-based) NB-UVB versus individualized (MPD-based) PUVA starting doses. Finally, more PUVA than NB-UVB patients had received adjunctive retinoid treatment. However, this was taken into account by a sub-analysis of the patients with NB-UVB or PUVA monotherapy which confirmed the comparable effectiveness of both phototherapeutic modalities.

Besides establishing the efficacy and safety of phototherapy for LP, some additional findings can be obtained from the numerous studies performed so far. First, clinical and histopathological response do not always concur. Patients who clinically are cleared might still show histopathological alterations indicative of lichen planus.^{19,21} Second, although residual histological disease activity in apparently cleared patients might in theory herald early relapse this does not necessarily happen in clinical practice. In fact, it has been reported that patients with an incomplete response at termination of phototherapy present with complete clearing a few weeks later suggesting a protracted effect of phototherapy.^{22,34} Third, relapse rates after completion of phototherapy are in general low ranging between 0%-25% over a follow-up period of up to five years.^{19,20,23,24,26-28,30,31,34} Only one study reported recurrence in 37.5% (6/16) patients within 3 to 12 months after the end of treatment.³³ Thus, maintenance treatment is not recommended.

Efficacy and safety, but also availability, are important factors for choosing a particular phototherapeutic modality. As redundantly shown in the literature,³⁶⁻³⁹ our study found a significantly higher rate of side effects in the PUVA cohort as compared to NB-UVB which was mainly due to the frequent occurrence of oral 8-MOP-induced nausea. In contrast, none of our patients on bath PUVA experienced GI upsets which is due to the much lower systemic psoralen levels that are associated with the topical delivery of 8-MOP.

According to current guidelines,⁴⁰ topical and systemic use of corticosteroids, acitretin, and cyclosporine are the first-line treatments for generalized LP. Phototherapy is considered as a second-line treatment in the management of LP; however, the number of studies with larger number of patients and thus a higher statistical power has so far been limited. Our retrospective analysis of the treatment outcome in 50 patients shows that NB-UVB and PUVA are both very effective and adds further weight to their beneficial use in patients with generalized cutaneous LP. Based on the lower rate of side effects and its greater ease of use, NB-UVB should be considered as the first-line phototherapeutic modality for this indication. Our findings concur with a recent review from Thandar et al,⁴¹ which documented that NB-UVB is a suitable treatment option for cutaneous lichen planus and should be considered prior to systemic treatments. In non-responding patients or in case of unavailability of NB-UVB, oral or bath PUVA may serve as a valid alternative therapeutic measure.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

AUTHOR'S CONTRIBUTIONS

Benedikt Weber and Elias Marquart contributed to data collection. Benedikt Weber and Adrian Tanew contributed to study design. Benedikt Weber, Elias Marquart, and Adrian Tanew contributed to data analysis. All authors contributed to data interpretation/revision/final approval.

ETHICAL APPROVAL

The study was approved by the institutional ethics committee from the Medical University of Vienna, Austria (EK-Nr: 1297/2020).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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