Dermatology

Dermatology , DOI: 10.1159/000528968
Received: June 30, 2022
Accepted: December 9, 2022
Published online: January 11, 2023

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ISSN: 1018-8665 (Print), eISSN: 1421-9832 (Online)
https://www.karger.com/DRM
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External validation of the IHS4-55 in a European antibiotic-treated HS cohort

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Running title: External validation of the IHS4-55

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Key message:
This study shows the external validity of the novel IHS4-55 by demonstrating a significant association between IHS4-55 achievement and a reduction in inflammatory lesion counts as well as achievement of MCIDs for DLQI, NRS Pain and NRS Pruritus in an antibiotics-treated cohort.

Number of Tables:	3
Number of Figures:	0
Word count:	1523

Key words: IHS4, endpoint, clinical trial, treatment, outcome, validation, hidradenitis suppurativa

ABSTRACT

Background: Previously, a new dichotomous outcome was developed, calculated as 55% reduction in the International Hidradenitis Suppurativa 4 score (IHS4-55). It was validated in datasets of adalimumab and placebo treated HS patients. External validation is an important aspect of clinical outcomes.

Objectives: We aimed to externally validate the novel dichotomous IHS4-55 in a non-biologic treated dataset of HS patients.

Methods: Data from a previously published European-wide prospective clinical study of antibiotic treatment of HS patients was used to assess the association of IHS4-55 achievement with individual reduction in inflammatory nodules, abscesses and draining tunnels. Moreover, the associations between IHS4-55 positivity and achievement of the minimal clinically important differences (MCID) for Dermatology Life Quality Index (DLQI), numerical rating scale (NRS) Pain, and NRS Pruritus were analyzed.

Results: Data was obtained from 283 individual patients, of which 36.4% (103/283) were treated with clindamycin and rifampicin and 63.6% (180/283) with tetracyclines for 12 weeks. Achievers of the IHS4-55 demonstrated a significant reduction the counts of inflammatory nodules, abscesses, and draining tunnels (all $p<0.001$). Additionally, IHS4-55 achievers had an odds ratio (OR) for achieving the minimal clinically important difference (MCID) of DLQI, NRS Pain and NRS Pruritus of 2.16 (95% CI 1.28-3.65, $p<0.01$), 1.79 (95% CI 1.10-2.91, $p<0.05$), and 1.95 (95% CI 1.18-3.22, $p<0.01$), respectively.

Conclusions: This study shows the external validity of the novel IHS4-55 by demonstrating a significant association between IHS4-55 achievement and a reduction in inflammatory lesion counts as well as achievement of MCIDs for DLQI, NRS Pain and NRS Pruritus in an antibiotic-treated cohort. These findings support the use of the IHS4-55 as a novel primary outcome measure in clinical trials.

INTRODUCTION

The International Hidradenitis Suppurativa Severity Score System (IHS4) is calculated by adding the number of nodules (multiplied by 1) plus the number of abscesses (multiplied by 2) and the number of draining tunnels (multiplied by 4) [1]. Recently, a novel dichotomous score was developed from the continuous IHS4, the IHS4-55, which identifies 55% reduction in the IHS4 as clinically meaningful [2]. This IHS4-55 is an effort to improve on the limitations of the Hidradenitis Suppurativa Clinical Response score (HiSCR), which is the current gold standard in clinical trials. HiSCR measures success as a $\geq$ 50% reduction in inflammatory lesion count (sum of abscesses and inflammatory nodules, AN) and no increase in abscesses or draining tunnels compared to baseline [3].

In a cohort of adalimumab and placebo treated HS patients, the IHS4-55 performed similarly to the HiSCR in identifying treated patients and associations with reductions in inflammatory lesion counts [1]. However, the IHS4-55 addresses some major drawback of the HiSCR. HiSCR cannot be calculated in patients with an AN-count <3 but many draining tunnels [2,4]. This limitation of HiSCR has led to the exclusion of a potentially large moderate-severe patient group with few nodules but many tunnels from current clinical trials and fully excludes patients with mild or mild-moderate disease, even though this group forms the majority of HS patients [5]. Moreover, the HiSCR has not been validated for the use in trials with other treatments than adalimumab, hampering the comparability of these studies.

The novel IHS4-55 could fill this gap. Therefore, we aimed to determine the external validity of the IHS4-55 in a previously published, prospective cohort of HS patients treated with different types of antibiotics.

MATERIALS AND METHODS

De-identified, individual, patient data was obtained from a previously established prospective European cohort of HS patients [6]. This study aimed to assess the 12-week efficacy of tetracyclines or a combination of clindamycin and rifampicin in patients with mild-severe HS [6]. Patients were included in a real-life clinical practice setting from 15 European centers. All patients originally included in this cohort study were used in for the external validation of the IHS4-55.

Associations of the IHS4-55 and the reduction in counts of inflammatory nodules, abscesses, and draining tunnels after treatment were assessed using Paired t-tests considering the differences between week 0 (W0) and W12 separately for achievers and non-achievers.

To determine if the dichotomous IHS4 correlated with clinically meaningful patient reported outcomes (PROMs) rather than simply change on a scale, the minimal clinically important difference (MCID) was calculated for the Dermatology Life Quality Index (DLQI), NRS Pain and NRS Pruritus [6]. Briefly, as previously calculated, the MCID for DLQI was considered to be $\geq$ 4 point reduction from baseline (maximum 30 points), and the MCID for Pain was considered to be $\geq$ 30% and $\geq$ 1 point reduction from baseline (maximum 10) [6]. The MCID for Pruritis was also considered to be $\geq$ 30% and $\geq$ 1 point reduction from baseline (maximum 10) [6]. Binary logistic regression analyses were performed to quantify the odds ratios for the associations between IHS4-55 achievement and achievement of the MCIDs for the DLQI, NRS Pain, NRS Pruritus.

All statistical analyses were performed in SPSS (IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY.), two-sided p-values <0.05 were considered significant.

RESULTS

Data was obtained from 283 individual patients, of which 36.4% (103/283) were treated with clindamycin and rifampicin and 63.6% (180/283) with tetracyclines for 12 weeks [6]. Patient characteristics were previously published and showed no significant differences between the groups for sex, age, age at onset, disease duration, BMI, smoking status (Table 1) [6].In this dataset HiSCR could not be calculated for 63 patients (22.3%) as the AN-count was less than three. Therefore we chose not compare HiSCR with the new IHS4-55 in this dataset as we would be comparing two different populations and would dismiss the main strength of the IHS4-55; that it can be calculated in all patients.

Overall, 38.5% (109/283) of patients achieved the IHS4-55. Achievers of IHS4-55 demonstrated a significant reduction in the individual parameters of inflammatory nodules, abscesses, and draining tunnels (all p<0.001, Table 2) regardless of treatment. IHS4-55 non-achievers only showed a significant reduction of inflammatory nodules (p<0.001).

Achievers of the IHS4-55 had 2.16 times the odds of achieving the MCID for the DLQI (OR 2.16, 95% CI 1.28-3.65, p=0.004) compared with non-achievers. IHS4-55 achievers were twice as likely to achieve either the MCID for NRS

Pain or NRS Pruritus than non-achievers (OR 1.79 (95% CI 1.10-2.91), p=0.018 and OR 1.95 (95% CI 1.18-3.22), p=0.009, respectively), Table 3. Furthermore, IHS4-55 achievers had 2.58 times the odds of achieving Hurley stage improvement (OR 2.58, 95% CI 1.33-4.99, p=0.004) compared with non-achievers.

DISCUSSION

This study aimed to externally validate the novel dichotomous IHS4-55 in a non-biologic treated dataset of HS patients [2]. The significant associations of the IHS4-55 with reductions in abscesses, inflammatory nodules, and draining tunnels demonstrate the external validity of this novel score in antibiotic-treated patients.

For all clinician-reported outcomes it is important that they not only capture clinical improvement in physical signs but also reflect change in patient reported outcomes (PROMs). This is of particular importance in a disease such as HS which is characterized by high pain scores and one of the lowest quality of life scores among dermatological disease [7,8]. Change in PROMs is often reported as a significant change in the absolute score, yet this does not indicate whether that difference is clinically meaningful. Therefore, we used MCIDs rather than the continuous scores in our analyses, showing that achievement of the novel IHS4-55 is significantly associated with achievement of the MCIDs for DLQI, NRS Pain, and NRS Pruritus. This demonstrates that the new IHS4-55 not only adequately measures clinical improvement but also reflects changes in important PROMs.

One limitation of this study is the lack of direct comparison between HiSCR and IHS4-55 due to the criteria for the HiSCR. However, in the dataset used for this study, HiSCR analysis would have excluded 22.3% of patients, illustrating a clear limitation of the HiSCR [6]. As different lesion types have been associated with different phenotypes, excluding patients presenting with AN<3 but many tunnels may not just exclude a part of the patient population but also unintentionally introduce a phenotype (and potentially genotype) bias [9]. Moreover, including patients with many draining tunnels but only a few nodules or abscesses is of increasing interest now that several novel therapies have shown efficacy particularly on draining tunnels [10]. The novel IHS4-55 allows for the inclusion of these previously excluded patient groups, aiding the inclusivity of future clinical trials. Another limitation is that, while our study assesses the performance of the IHS4-55 in a dataset of antibiotic treated patients and our previous study identified its validity in a biologics cohort [2], validation of this score in other treatment settings, for example surgery, remains to be tested.

In conclusion, this study demonstrates the external validity of the novel IHS4-55 by demonstrating an association between IHS4-55 achievement and a reduction in inflammatory lesion counts as well as achievement of MCIDs for the DLQI, NRS Pain and NRS Pruritus in an antibiotic-treated cohort of HS patients. These findings support the use of the IHS4-55 as a novel primary outcome measure in clinical trials and demonstrate how the use of this score could increase the inclusivity and comparability of these studies.

STATEMENTS

Acknowledgements

The Department of Dermatology, Erasme Hospital, Brussels, Belgium; the Department of Dermatology, Zeeland University Hospital, Roskilde, Denmark; the Department of Dermatology, Erasmus University Medical Center, Rotterdam, The Netherlands; and the Departments of Dermatology, Venereology, Allergology and Immunology, Dessau Medical Center, Dessau, Germany are health care providers of the European Reference Network for Rare and Complex Skin Diseases (ERN Skin-ALLOCATE Skin group).

Statement of Ethics

For this post-hoc study, no ethics approval was required. The initial study was performed within daily practice and in accordance with current guidelines; therefore, it was deemed exempt from IRB review [6].

Conflict of interest Statement

K.R. van Straalen, T. Tzellos, A. Alavi, F. Benhadou, C. Cuenca-Barrales, M. Daxhelet, M. Daoud, O. Efthymiou, P. Guillem, W. Gulliver, G.B.E Jemec, A.C. Katoulis, A. Koenig, E. Lazaridou, M.A. Lowes, A.V. Marzano, A. Molina-Leyva, C. Moltrasio, A. Pinter, C. Potenza, E.P. Prens, J. Romaní, D.M. Saunte, N. Skroza, D. Stergianou, J. Szepietowski, A. Trigoni, E. Vilarrasa, A. Kyrgidis, C.C. Zouboulis, H.H. van der Zee report not conlict of interest regarding this manuscript. E.J. Giamarellos-Bourboulis reports honoraria from Abbott CH, bioMérieux France, Sobi AB, Menarini, Brahms GmbH; and grants from Abbott CH, bioMérieux France, UCB, Sobi AB, Horizon 2020

Grant ImmunoSep, Horizon Health Grands RISKinCOVID and EPIC-CROWN-2. Ł. Matusiak reports honoraria from Leo pharma, Pierre Fabre, Novartis, Abbvie, Valeant; and grants from Leo pharma, Pierre Fabre, Novartis, Abbvie, UCB, Regeneron, Kiniksa, Teva pharmaceuticals, InflaRx, AnaptysBio, Pfizer, Incyte, Celltrion, Boehringer Ingelheim, Galderma, Medimmune, Argenix, Janssen. C.J. Sayed reports honoraria from AbbVie, Novartis, UCB, and grants from AbbVie, InflaRx, Novartis, Incyte, Chemocentryx.

Funding Sources
This work was not funded.

Author contributions
Conceptualization: T. Tzellos, A. Kyrgidis, C.C. Zouboulis. *Methodology:* K.R. van Straalen, T. Tzellos, A. Kyrgidis, C.C. Zouboulis. *Formal analysis:* K.R. van Straalen, T. Tzellos, A. Kyrgidis. *Investigation:* K.R. van Straalen, T. Tzellos, A. Alavi, F. Benhadou, C. Cuenca-Barrales, M. Daxhelet, M. Daoud, O. Efthymiou, E.J. Giamarellos-Bourboulis, P. Guillem, W. Gulliver, G.B.E Jemec, A.C. Katoulis, A. Koenig, E. Lazaridou, M.A. Lowes, A.V. Marzano, Ł. Matusiak, A. Molina-Leyva, C. Moltrasio, A. Pinter, C. Potenza, E.P. Prens, J. Romaní, D.M. Saunte, C.J. Sayed, N. Skroza, D. Stergianou, J. Szepietowski, A. Trigoni, E. Vilarrasa, A. Kyrgidis, C.C. Zouboulis, H.H. van der Zee. *Writing - Original Draft:* K.R. van Straalen. *Writing - Review & Editing:* K.R. van Straalen, T. Tzellos, A. Alavi, F. Benhadou, C. Cuenca-Barrales, M. Daxhelet, M. Daoud, O. Efthymiou, E.J. Giamarellos-Bourboulis, P. Guillem, W. Gulliver, G.B.E Jemec, A.C. Katoulis, A. Koenig, E. Lazaridou, M.A. Lowes, A.V. Marzano, Ł. Matusiak, A. Molina-Leyva, C. Moltrasio, A. Pinter, C. Potenza, E.P. Prens, J. Romaní, D.M. Saunte, C.J. Sayed, N. Skroza, D. Stergianou, J. Szepietowski, A. Trigoni, E. Vilarrasa, A. Kyrgidis, C.C. Zouboulis, H.H. van der Zee. *Visualization*: K.R. van Straalen, T. Tzellos, A. Kyrgidis.

Data availability statement
All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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Table 1. Characteristics of included patients

	Tetracyclines n=180		Clindamycin and Rifampicin n=103		p-value
Patient characteristics					
Gender					
Females, *n (%)*	106	(58.9)	56	(54.4)	0.533
Age, *median [IQR]*	37	[26-46]	36	[27-45]	0.917
Missing, *n*	0		1		
Age of onset, *median [IQR]*	21	[15-30]	21	[16-28]	0.854
Missing, *n*	3		0		
Disease duration, *median [IQR]*	10	[6-19]	10	[5-17]	0.415
Missing, *n*	3		1		
BMI, *mean (SD)*	29.81	(6.1)	29.21	(6.2)	0.428
Missing, *n*	6		0		
Current smoker, *n (%)*	110	(61.8)	56	(56.6)	0.443
Missing, *n*	2		4		
Family history of HS, *n (%)*	58	(34.3)	34	(35.1)	1.000
Missing, *n*	11		6		
Patient reported outcomes					
DLQI, *mean (SD)*	13.3	(7.5)	15.1	(7.9)	0.071
Missing, *n*	8		7		
NRS Pain, *median [IQR]*	6	[4-8]	7	[5-8]	**0.005**
Missing, *n*	7		3		
NRS Pruritus, *median [IQR]*	3	[0-6]	4	[0-7]	0.204
Missing, *n*	13		8		
Physician scores					
Inflammatory nodules, *median [IQR]*	3.5	[1.0-6.0]	4	[2-9]	**0.029**
Abscesses, *median [IQR]*	0.0	[0.0-2.0]	0	[0-2]	0.975
Draining sinus tracts, *median [IQR]*	1.0	[0.0-2.0]	1	[0-4]	**0.003**
Hurley stage					
Stage I, *n (%)*	54	(30.2)	14	(13.6)	**0.004**
Stage II, *n (%)*	90	(50.3)	58	(56.3)	
Stage III, *n (%)*	35	(19.5)	31	(30.1)	
Missing, *n*	1		0		
IHS4, *median [IQR]*	9.0	[5.0-18.5]	13.0	[6.0-27.0]	**0.019**
Mild, *n (%)*	29	(16.1)	8	(7.8)	**0.032**
Moderate, *n (%)*	77	(42.8)	38	(36.9)	
Severe, *n (%)*	74	(41.1)	57	(55.3)	

BMI; Body mass index, *DLQI;* Dermatology Quality of Life Index, *HS;* hidradenitis suppurativa, *IHS4;* International Hidradenitis Suppurativa Severity Score System, *IQR;* interquartile range, *NRS;* Numerical Rating Scale, *SD;* standard deviation.

Table 2. Association of IHS4-55 with reduction in inflammatory lesion counts in HS patients treated with antibiotics

	IHS4-55 Achiever (n=109)			**IHS4-55 Non-achiever (n=174)**		
	mean	*±SD*	*p-value*	*mean*	*±SD*	*p-value*
Δ Inflammatory nodules	4.06	±3.98	<0.001	1.50	±3.65	<0.001
Δ Abscesses	1.01	±1.87	<0.001	0.21	±1.69	0.098
Δ Draining tunnels	1.10	±2.02	<0.001	0.12	±1.16	0.194

Δ; Difference in counts between baseline and week 12, SD; standard deviation.

Table 3. Association of IHS4-55 with achievement of MCID in PROMs

	IHS4-55 Achiever (n=109)		
	OR	*(95% CI)*	*p-value*
MCID DLQI	2.16	(1.28-3.65)	0.004
MCID NRS Pain	1.79	(1.10-2.91)	0.018
MCID NRS Pruritus	1.95	(1.18-3.22)	0.009

IHS4; International Hidradenitis Suppurativa Severity Score System, *OR*; odds ratio, 95% CI; 95% confidence interval, *MCID;* minimal clinically important difference, *DLQI*; Dermatologic Quality of Life Index, *NRS*; numerical rating scale.