Clinical Oral Investigations (2021) 25:3699–3709
https://doi.org/10.1007/s00784-020-03695-6

ORIGINAL ARTICLE

The patient acceptable symptom state in oral lichen planus: identification of cut-off threshold scores in measures of pain and quality of life

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Received: 15 July 2020 / Accepted: 10 November 2020 / Published online: 17 November 2020

Abstract

Objectives To establish thresholds of pain and quality of life scores corresponding to patient acceptable symptom state (PASS) in patients with oral lichen planus (OLP) and to assess demographic and clinical factors associated with achieving the PASS.

Methods Prospective data from baseline and 4-month follow-up including Visual Analogue Scale (VAS), Numerical Rating Scale (NRS), 14-item Oral Health Impact Profile (OHIP-14) and 15-item and 26-item Chronic Oral Mucosal Disease Questionnaire (COMDQ-15; COMDQ-26) were collected from 281 patients with OLP. An anchoring approach based upon the patient's opinion on acceptability of OLP status was applied. Associated factors for achieving the PASS were analysed using multivariate logistic regression.

Results About two-thirds (68.7%) of participants rated their OLP status as acceptable. Cut-off thresholds for PASS were as follows: ≤ 28 mm for VAS, ≤ 3 for NRS, ≤ 18 for total OHIP-14, ≤ 26 for total COMDQ-15 and ≤ 48 for total COMDQ-26. Based upon results of multivariate logistic analysis, factors associated with being in PASS were lower pain intensity, lower depressive symptoms and lower disease activity of OLP.

Conclusion The present study established PASS cut-off thresholds as a tool facilitating interpretation of pain and quality of life outcomes relevant to individuals with OLP.

Clinical relevance Identified PASS estimates could be utilised as clinically important endpoints in clinical practice of OLP as well as eligibility criteria for recruiting participants in clinical trials assessing effectiveness of symptomatic intervention of OLP.

Keywords Quality of life · Oral lichen planus · Patient acceptable symptom state

Introduction

Oral lichen planus (OLP) is a chronic inflammatory immune-mediated condition involving the mucous membranes of the oral cavity [1]. The disease may present with various clinical manifestations, ranging from characteristic white reticular lesions to erythema and ulceration of the oral mucosa [1]. Affected individuals can experience oral discomfort, significant impairment of oral functioning, resulting in poor oral health-related quality of life (OH-QoL) [2]. Like other chronic medical conditions, the primary goal of management of OLP is palliative and is associated with controlling painful oral symptoms and improving OH-QoL of the patients [3].

The interpretation of pain and OH-QoL outcomes is crucial yet challenging for both clinicians and researchers. Pain and OH-QoL outcomes are usually expressed as continuous numerical data, which might not be useful for clinicians,

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researchers, or even patients unless these data have clinically relevant meaning attached to them [4]. In this case, conversion of continuous scores into a dichotomous variable using cut-off scores may be of interest [5]. A recent study defined clinical meanings of pain and OH-QoL change scores using the cut-off scores for meaningful change thresholds in patients with OLP [6]. However, the concept of meaningful change thresholds applies for longitudinal data only and clinically meaningful single scores of pain and OH-QoL have yet to be explored in this population.

The patient acceptable symptom state (PASS) is a clinically relevant threshold and is the highest level of symptoms beyond which patients consider themselves good enough to continue in that state [7]. The concept of PASS has been adopted in a number of medical fields including rheumatology and orthopaedics [8–10]. The PASS can be used as a patient-relevant monitoring tool that reflects patient's satisfactory to their current condition. Achieving PASS can be indicative of therapeutic success at the individual level and may be used as the target for treatment strategies particularly in case of symptomatic treatment in clinical practice as well as a tool for standardised responder criteria for clinical trials [9, 11].

There are currently no studies investigating PASS cut-off thresholds for patients with OLP, limiting clinical meaningfulness of scores of pain and OH-QoL instruments in this patient population. The primary objective of the present study was to determine the cut-off scores of the PASS in measures of pain and OH-QoL for use in patients with OLP. The secondary objective was to assess demographic, clinical and psychological factors associated with achieving the PASS.

Methods

Study design

The present study was cross-sectional secondary analysis of data from the Determination of Minimal Important Difference and Patient Acceptable Symptom State of Patient Reported Outcome Measures in Immunologically mediated Oral Mucosal Diseases (MEAN-IT) study, which was approved by the London – Queen Square Research Ethics Committee (REC reference 12/LO/1825; approval date 3 November 2017).

Participants

Data were drawn from a total of 281 patients with OLP who attended regular review appointments at the oral medicine clinic, UCLH Eastman Dental Hospital, London, UK, from January 2018 to August 2019. The eligibility criteria of study participants are listed in Table 1. The recruitment of the MEAN-IT study was based upon convenience sampling. All potentially eligible participants, in all specialist oral medicine clinics, were invited to participate (conducted by PW). All participants provided verbal and written informed consent to take part in the study. To ensure sufficient numbers of patients with different states of symptom level (acceptable/non-acceptable), the data included in this study consisted of two patient groups at different time points (baseline and 4-month follow-up) of the MEAN-IT study.

Procedures

A comprehensive oral examination was performed on all study participants (conducted by PW) to assess disease activity using the Oral Disease Severity Score [13]. Participants were categorised into three groups on the basis of the clinical variant of OLP: (i) keratotic (presence of white reticular, papular, or plaque-like lesions without apparent erythema/ulceration), (ii) erythematous (presence of atrophic/erythematous lesions with/without reticular/papular/plaque-like features and no evidence of erosion/ulceration) and (iii) erosive/ulcerative (presence of erosive or ulcerative lesions with/without the presence of keratotic and/or erythematous changes of OLP).

Participants were then asked to complete a set of questionnaires including a demographic form; a set of patient-reported questionnaires associated with oral symptoms, psychological status (level of anxiety, depression, distress and perceived stress) and OH-QoL; and an additional question to determine the PASS. Information regarding medical history, social history and past OLP-related history including disease duration, extraoral involvement of lichen planus (either patient-reported or confirmed by a dermatologist) and current management was obtained from review of electronic patient records.

Outcomes and outcome measures

The primary outcome of the present study was the cut-off scores for the PASS in measures of pain and OH-QoL for use in patients with OLP. To examine associated determinants of achieving PASS in patients with OLP, selected demographic characteristics, psychological and OLP-related factors were assessed. Demographic variables included age (continuous variable) (female/male), ethnicity (White/Mixed/Asian/Black), smoking status (non-smoker/ex-smoker/current smoker), alcohol use based upon the UK alcohol unit guidelines [14] (no/up to 14 units/more than 14 units per week) and systemic comorbidities (no/one/at least two disease comorbidities) were recorded.

Regarding psychological factors, the Hospital Anxiety and Depression Scale (HADS) was used to measure level of anxiety, depression and distress, while level of perceived stress was evaluated by the 10-item Perceived Stress Scale (PSS-10). OLP-related factors included disease duration (time since symptom onset of OLP (years)), clinical types (keratotic/

Table 1 Study eligibility criteria

Inclusion criteria	Exclusion criteria
- Aged 18 years or older	- Evidence of oral epithelial dysplasia in biopsy specimen
- Clinically and histopathologically proven OLP based upon modified WHO diagnostic criteria (van der Meij & van der Waal, 2003)	- Evidence of proven hypersensitivity to dental materials
- Able to understand and complete questionnaires	- Evidence of oral lichenoid lesions associated with graft-versus-host disease and systemic lupus erythematosus
- Agree to participate and provide written informed consent	- Having coexisting chronic neuropathic orofacial pain, such as post-traumatic trigeminal neuropathic pain, persistent idiopathic facial pain or burning mouth syndrome
	- Severe systemic disease (ASA 3 or more) and/or some psychiatric conditions which might affect the participation of the study such as schizophrenia

erythematous/erosive-ulcerative), level of disease activity using the validated Oral Disease Severity Score (ODSS; site score/activity score/total score), presence of self-reported extraoral lichen planus (LP) (no/yes-genital area/ skin) and treatment types (no treatment or topical anaesthetic agents only/topical corticosteroids only/topical corticosteroids and other topical treatment/topical and systemic treatment).

Clinical disease activity scoring

The *Oral Disease Severity Score (ODSS)* is a validated clinical scoring for the measurement of the severity of oral mucosal conditions with special reference to OLP [13]. The ODSS assesses the presence, extent and severity of mucosal lesions in 17 oral subsites. A total ODSS score is the addition of clinician-assessed site and activity scores with a score of 0–10 verbal rating scale for average oral pain over the last 2 weeks, with theoretical combined scores ranging from 0 to 106.

Patient-reported outcome measures

The *Visual Analogue Scale (VAS)* for pain is a measure of pain intensity comprising a 100-mm horizontal line, labelled with 'no pain' at one end and 'worst pain imaginable' on the other end. Participants were asked to place a vertical mark on the point of the VAS line that best reflected the degree of pain they were currently experiencing from OLP.

The *Numerical Rating Scale (NRS)* for pain estimated severity of oral pain currently experienced by a patient on a whole number scale of 0–10 (11-point scale). Both the VAS and NRS were validated for use in the OLP population with psychometric evidence supporting their validity and reliability [15].

The *14-item Oral Health Impact Profile (OHIP-14)* is a 14-item, 5-point (0–4) Likert-type questionnaire measuring general OH-QoL on seven domains (each with 2 items) including functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability and handicap. The maximum possible subscale and total score of this scale are 8 and 56, respectively. The greater the OHIP-14 score, the poorer level of OHRQoL patient perceives [16].

The *26-item Chronic Oral Mucosal Disease Questionnaire (COMDQ-26)* is an instrument measuring the impact of chronic oral mucosal condition and related treatment on patient's OH-QoL in four different aspects including pain and functional limitation (PF, 9 items), medication and treatment (MT, 6 items), social and emotional (SE, 7 items) and patient support (PS, 4 items) [17].

The *15-item Chronic Oral Mucosal Disease Questionnaire (COMDQ-15)* is a recently developed short version of the original COMDQ-26 [12]. Similar to its parent version, the COMDQ-15 assesses four OHRQoL domains including physical discomfort (PD, 5 items), medication and treatment (MT, 3 items), social and emotional (SE, 5 items) and patient support (PS, 2 items). The items of both COMDQ-26 and COMDQ-15 were answered on a 5-point Likert-type scale (0–4), ranging from 'not at all' to 'extremely'. Total COMDQ-26 and COMDQ-15 score are calculated by summation of the responses of all items, giving the possible maximum score of 104 and 60, respectively. Both the original and short version of the COMDQ have good evidence supporting validity and reliability for use in patients with OLP [12, 18].

The *Hospital Anxiety and Depression Scale (HADS)* is a brief 14-item, 0–3 Likert-type scale with seven questions (HADS-A) assessing anxiety symptoms, and the other seven (HADS-D) assessing depressive symptoms over 1 week recall period. Subscale HADS scores of 8 or over indicate the presence of anxiety or depressive symptoms [19], and the total score (HADS-T) from the sum scores of HADS-A and HADS-D of 15 or over indicates the presence of psychological distress [20].

The *10-item Perceived Stress Scale (PSS-10)* is a 10-item, 5-point Likert-type scale examining participant's level of

perceived stress over the last month. Four items of the PSS-10 (items 4, 5, 7, 8) are positively stated items and require reverse coding. PSS-10 scores of 14 or above are indicative of moderate-to-high level of perceived stress [21]. Both the HADS and PSS-10 have been validated for use in patients with OLP [22].

Anchor question

To determine the PASS, additional question is required as gold standard to determine acceptability of current state of OLP from the patient's perspective. In this study, the following *PASS question* was used as external anchor: 'Thinking about all the ways your symptoms related to your oral mucosal conditions are affecting you, do you consider that your current state is acceptable?'. The response options (yes/no) dichotomised participants into the PASS+ group (achieving acceptable symptom state; 'yes' to the PASS question) and the PASS− group (not achieving acceptable symptom state; 'no' to the PASS question).

Statistical analyses

Statistical analyses were performed using STATA version 15.1 (StataCorp, College Station, TX, USA). Data distribution of all continuous outcomes was first checked by the Kolmogorov-Smirnov test. As all the data was skewed, descriptive cross-sectional analyses were summarised using median and interquartile range (IQR) for continuous variable Descriptive analyses of demographics and OLP-related characteristics were summarised using frequencies and accompanying percentages for categorical variables, while median and interquartile range (IQR) were used as summary statistics for continuous variables.

Patient acceptable symptom state

Before establishing PASS cut-points, Spearman correlation coefficients between scores of studied measures and PASS anchor question were calculated to ensure validity of anchor question. The values of coefficient of at least 0.30 were considered acceptable. PASS threshold scores were identified using the receiver-operator characteristic (ROC) curves to calculate sensitivity and specificity of each of the potential cut-points on each of the measures of pain and OH-QoL. The ROC curve plotted sensitivity (true-positive (TP) rate; y-axis) against one minus specificity (false-positive rate; x-axis) at various cut-off scores of each studied instrument. Using ROC approach, the optimal cut-points corresponded to PASS thresholds were scores on studied measures that best distinguish participants answering 'yes' to the PASS anchor question (PASS+) from participants answering 'no' (PASS−) and were the points nearest to the uppermost left-hand corner of the ROC curve, where both sensitivity and specificity are maximised. The area under the curve (AUC) indicated the probability of the cut-off points in correctly discriminating between participants who achieved PASS and those who did not, and an AUC value of > 0.7 is considered satisfactory [23].

Impact of associated factors on achieving the PASS

To identify associated factors of achieving the PASS in patients with OLP, bivariate analysis between subgroups based on demographics, psychological and OLP-related factors were performed using the chi-square or Fisher's exact tests for categorical variables as appropriate, while Mann-Whitney *U* test or independent sample *t* tests were performed for comparisons of medians and means of continuous variables between subgroups, respectively. All tests were two-tailed, and a *p* value of less than 0.05 was considered statistically significant. Independent variables with statistical significance from bivariate analysis were entered into univariate logistic regression, and the crude odds ratio (OR), 95% confidence interval (CI) and *p* value were calculated. Each of the demographic, clinical and psychological variables with a *p* value of less than 0.1 on univariate analyses were all entered into multivariate logistic regression model. Quality of life outcomes were excluded from the multivariate analysis due to high collinearity with other variables. Adjusted odds ratios (Adj-ORs) with 95% CI for each independent variable were calculated.

Results

Descriptive statistics

Data of 281 MEAN-IT participants including 144 from the baseline dataset and 137 from the 4-month follow-up dataset were included in the present analysis. Descriptive statistics of baseline demographics, psychological and OLP-related factors of all study participants including PASS+ and PASS− group are presented in Table 2. The characteristics of sample between baseline and 4-month follow-up group of the MEAN-IT study were generally similar except for disease comorbidities, disease activity and types of treatment. The average age of all participants was 63.3 ± 11.3 years (range: 27–88 years), and the majority were female (76.9%). Approximately two-thirds (66.9%) of participants had erythematous OLP.

Patient acceptable symptom state

Of the 281 participants with OLP, 193 participants (68.7%) rated their current OLP state as acceptable (PASS+ group). The proportion of patients with PASS+ and PASS− were similar between baseline (68%/32%) and 4-month follow-up

Table 2 Descriptive characteristics of 281 study participants according to patient acceptable symptom state (PASS) status

Patient characteristics	Sample 1 (baseline group; $N = 144$)	Sample 2 (4-month F/U group; $N = 137$)	p value	Total sample (sample 1 + 2; $N = 281$)			
				Characteristics	PASS negative ($N = 88$; 31.3%)	PASS positive ($N = 193$; 68.7%)	p value
Demographic variables							
Age (y; median, IQR)	66.1 (55.7, 70.9)	65.0 (55.4, 71.3)	0.75	65.5 (55.6, 71.0)	65.5 (55.6, 70.7)	65.5 (55.4, 71.3)	0.87
Female (n, %)	111 (77.1)	105 (76.6)	0.93	216 (76.9)	69 (78.4)	147 (76.2)	0.68
Ethnicity (n, %)			0.75				0.003
White	98 (68.1)	90 (65.7)		188 (66.9)	47 (25.0)	141 (75.0)	
Mixed	3 (2.1)	3 (2.2)		6 (2.1)	1 (16.7)	5 (83.3)	
Asian	36 (25.0)	40 (29.2)		76 (27.1)	36 (47.4)	40 (52.6)	
Black	7 (4.9)	4 (2.9)		11 (3.9)	4 (36.4)	7 (63.6)	
Smoking (n, %)			0.25				0.15
Non-smoker	109 (75.7)	102 (74.5)		211 (75.1)	61 (28.9)	150 (71.1)	
Ex-smoker	27 (18.8)	32 (23.4)		59 (21.0)	21 (35.6)	38 (64.4)	
Current smoker	8 (5.6)	3 (2.2)		11 (3.9)	6 (54.6)	5 (45.5)	
Alcohol consumption (n, %)			0.15				0.17
No	49 (34.0)	47 (34.3)		96 (34.2)	34 (35.4)	62 (64.6)	
≤ 14 units/week	80 (55.6)	84 (61.3)		164 (58.4)	51 (31.1)	113 (68.9)	
> 14 units/week	15 (10.4)	6 (4.4)		21 (7.5)	3 (14.3)	18 (85.7)	
Comorbidity (n, %)			0.01				0.51
No	15 (10.42)	33 (24.1)		48 (17.1)	15 (31.3)	33 (68.8)	
1 comorbidity	35 (24.3)	31 (22.6)		66 (23.5)	17 (25.8)	49 (74.2)	
≥ 2 comorbidities	94 (65.3)	73 (55.3)		167 (59.4)	56 (33.5)	111 (66.5)	
OLP-related characteristics							
OLP duration (y; median, IQR)	5.8 (2.8, 10.8)	6.7 (3.4, 10.8)	0.5	6.4 (3.0, 10.8)	5.8 (3.1, 10.0)	6.6 (2.8, 10.8)	0.89
Clinical types			0.21				< 0.001
Keratotic	21 (14.6)	31 (22.6)		52 (18.5)	7 (13.5)	45 (86.5)	
Erythematous	100 (69.4)	88 (64.2)		188 (66.9)	59 (31.4)	129 (68.6)	
Ulcerative	23 (16.0)	18 (13.1)		41 (14.6)	22 (53.7)	19 (46.3)	
ODSS score (median, IQR)	13 (9, 21)	11 (6, 19)	0.02	12.5 (7, 20)	19.5 (13, 26)	10 (6, 17)	< 0.001
ODSS-site	5.5 (4, 7)	4 (3, 7)	0.07	5 (3, 7)	6 (4, 9)	4 (2, 6)	< 0.001
ODSS-activity	5 (2, 10)	4 (1, 8)	0.01	5 (2, 9)	8 (5, 13)	4 (1, 7)	< 0.001
VAS-pain (median, IQR)	25 (7, 50)	20 (2, 50)	0.16	22 (7, 50)	50 (36, 68)	12 (2, 27)	< 0.001
NRS-pain (median, IQR)	3 (1, 5)	3 (0, 4)	0.12	3 (1, 5)	5 (3.5, 7)	2 (0, 4)	< 0.001
0: no pain (n, %)	21 (14.6)	37 (27.0)	0.05	58 (20.6)	2 (3.5)	56 (96.6)	< 0.001

Table 2 (continued)

Patient characteristics	Sample 1 (baseline group; $N = 144$)	Sample 2 (4-month F/U group; $N = 137$)	p value	Total sample (sample 1 + 2; $N = 281$)			
				Characteristics	PASS negative ($N = 88$; 31.3%)	PASS positive ($N = 193$; 68.7%)	p value
1–3: low pain	61 (42.4)	47 (34.3)		108 (38.4)	20 (18.5)	88 (81.5)	
4–6: moderate pain	41 (28.5)	40 (29.2)		81 (28.8)	39 (48.2)	42 (51.9)	
7–10: severe pain	21 (14.6)	13 (9.5)		34 (12.1)	27 (79.4)	7 (20.6)	
Presence of extraoral LP (n, %)	37 (25.7)	32 (23.4)	0.65	69 (24.6)	21 (23.9)	48 (24.9)	0.86
Treatment (n, %)			< 0.001				< 0.001
Tanes	12 (8.3)	34 (24.8)		46 (16.4)	4 (4.6)	42 (21.8)	
TCS	90 (62.5)	76 (55.5)		166 (59.1)	52 (59.1)	114 (59.1)	
Tanes + TCS	34 (23.6)	26 (19.0)		60 (21.4)	31 (35.2)	29 (15.0)	
Systemic treatment	8 (5.6)	1 (0.7)		9 (3.2)	1 (1.1)	8 (4.2)	
Psychological outcomes							
HADS-A (median, IQR)	6 (3, 9)	7 (3, 9)	0.62	6 (3, 9)	8 (5, 12)	5 (3, 8)	< 0.001
< 8: no anxiety symptoms	97 (67.4)	80 (58.4)	0.12	177 (63)	40 (22.6)	137 (77.4)	< 0.001
≥ 8: with anxiety symptoms	47 (32.6)	57 (41.6)		104 (37)	48 (46.2)	56 (53.9)	
HADS-D (median, IQR)	4 (1, 6)	3 (1, 6)	0.2	3 (1, 6)	6 (4, 9)	2 (1, 5)	< 0.001
< 8: no depressive symptoms	116 (80.6)	112 (81.8)	0.8	228 (81.1)	57 (25.0)	171 (75.0)	< 0.001
≥ 8: with depressive symptoms	28 (19.4)	25 (18.3)		53 (18.9)	31 (58.5)	22 (41.5)	
HADS-T (median, IQR)	9.5 (5.5, 15)	9 (4, 15)	0.4	9 (5, 15)	15 (8.5, 20)	7 (4, 12)	< 0.001
< 15: no psychological distress	105 (72.9)	100 (73.0)	0.99	205 (73.0)	43 (21.0)	162 (79.0)	< 0.001
≥ 15: with psychological distress	39 (27.1)	37 (27.0)		76 (27.1)	45 (59.2)	31 (40.8)	
PSS-10 (median, IQR)	16 (10, 21)	15 (10, 20)	0.8	16 (10, 21)	20 (13, 25)	14 (8, 19)	< 0.001
0–13: mild perceived stress	56 (38.9)	61 (44.5)	0.63	117 (41.6)	23 (19.7)	94 (80.3)	< 0.001
14–26: moderate perceived stress	77 (53.5)	66 (48.2)		143 (50.9)	51 (35.7)	92 (64.3)	
27–40: severe perceived stress	11 (7.6)	10 (7.3)		21 (7.5)	14 (66.7)	7 (33.3)	
Quality of life outcomes							
OHIP-14 (median, IQR)	15 (6, 26)	13 (5, 22)	0.22	14 (6, 25)	26 (15.5, 34)	10 (5, 18)	< 0.001
Functional limitation	2 (0, 3)	1 (0, 2)	0.05	1 (0, 3)	2.5 (1, 4)	1 (0, 2)	< 0.001
Physical pain	4 (3, 6)	4 (3, 6)	0.46	4 (3, 6)	6 (5, 7)	4 (2, 4)	< 0.001
Psychological discomfort	2 (0, 4)	2 (0, 4)	0.8	2 (0, 4)	4 (3, 6)	1 (0, 3)	< 0.001
Physical disability	3 (0, 4)	2 (0, 4)	0.1	2 (0, 4)	4 (2.5, 6)	1 (0, 3)	< 0.001
Psychological disability	2 (0, 4)	1 (0, 3)	0.31	2 (0, 3)	3.5 (2, 5)	1 (0, 2)	< 0.001
Social disability	1 (0, 3)	1 (0, 2)	0.19	1 (0, 3)	3 (1, 4)	0 (0, 2)	< 0.001
Handicap	1 (0, 3)	1 (0, 2)	0.36	1 (0, 2)	2 (1, 3.5)	1 (0, 2)	< 0.001

Table 2 (continued)

Patient characteristics	Sample 1 (baseline group; $N = 144$)	Sample 2 (4-month F/U group; $N = 137$)	p value	Total sample (sample 1 + 2; $N = 281$)			
				Characteristics	PASS negative ($N = 88$; 31.3%)	PASS positive ($N = 193$; 68.7%)	p value
COMDQ-15 (median, IQR)	21.5 (14, 32)	19 (12, 28)	0.03	20 (13, 30)	32 (27, 40)	16 (10, 22)	< 0.001
Physical discomfort	9 (6, 14)	8 (4, 12)	0.02	9 (5, 12)	14 (11, 16)	7 (4, 10)	< 0.001
Medication and treatment	4 (2, 6.5)	3 (1, 5)	0.005	3 (1, 6)	5 (3.5, 8)	2 (1, 5)	< 0.001
Social and emotional	5 (3, 10)	5 (2, 9)	0.41	5 (3, 9)	10 (7, 15)	4 (2, 6)	< 0.001
Patient support	2 (1, 4)	2 (0, 4)	0.13	2 (1, 4)	3 (1, 5)	2 (0, 4)	< 0.001
COMDQ-26 (median, IQR)	38 (25, 53)	32 (21, 48)	0.05	34 (22, 51)	54.5 (45, 66.5)	29 (18, 38)	< 0.001
Pain and functional limitation	15 (9, 22)	13 (7, 20)	0.08	14 (8, 20)	21.5 (16, 25)	10 (6, 15)	< 0.001
Medication and treatment	9 (6, 13)	8 (4, 11)	0.001	9 (5, 13)	13 (10, 16)	7 (4, 10)	< 0.001
Social and emotional	9 (4, 15)	8 (4, 14)	0.43	8 (4, 14)	15 (10.5, 21)	6 (4, 10)	< 0.001
Patient support	4 (2, 7)	3 (1, 6)	0.08	4 (2, 7)	6 (4, 8)	3 (1, 6)	< 0.001

TCS topical corticosteroids, *Tanes* topical anaesthetic agents

group (69%/31%). The vast majority of patients with keratotic OLP (86.5%) achieved PASS, while less than half of those with ulcerative OLP (46.3%) reported an acceptable symptom state. Over 95% of OLP patients who reported no painful symptoms achieved PASS, while only about 20% of those with severe oral pain (NRS: 7–10) were in PASS+ group. When stratifying patients' responses to PASS according to presence of psychological comorbidities, only 53.9%, 41.5%, 40.8% and 33.3% of OLP patients with comorbid symptoms of anxiety, depression, distress and severe perceived stress achieved PASS when compared to the percentages of 75–80% of achieving PASS in those without these psychological comorbidities. In addition, it was observed that patients in PASS+ group reported significantly lower level of OLP disease activity (ODSS) and better oral health-related quality of life (OHIP-14, COMDQ-15, COMDQ-26) than patients in PASS− group.

Independent determinants of achieving the PASS in patients with OLP

Univariate and multivariate analysis with crude and adjusted OR of significant demographic, clinical and psychological variables are shown in Table 3. After potential confounders were controlled, achieving PASS was independently associated with lower level of oral pain (NRS; AOR = 0.65 (95% CI: 0.55–0.78); $p < 0.001$), lower level of depressive symptoms (HADS-D; AOR = 0.86 (95% CI: 0.75–1.00); $p = 0.044$) and lower disease activity scores (ODSS-activity; AOR = 0.93 (95% CI: 0.86–1.00); $p = 0.047$).

Thresholds for PASS in common measures of pain and OHRQoL for use in patients with OLP

The absolute magnitudes of Spearman correlation coefficients between scores of the studied instrument and PASS anchor question were over 0.30 in all measures, supporting validity of the anchor question (data not shown). According to the ROC curve analysis, PASS threshold for the NRS and VAS for pain in patients with OLP was 3 and 28 mm, respectively. Regarding PASS cut-points for scores of OHRQoL instruments, values of 18, 26 and 45 corresponded to PASS level of total scores of OHIP-14, COMDQ-15 and COMDQ-26, respectively. Detailed characteristics of PASS cut-points including area under the curve (AUC), sensitivity and specificity in common measures of pain and OHRQoL for use in patients with OLP are provided in Table 4.

Discussion

The patient acceptable symptom state (PASS) reflects acceptance of self-perceived overall health state of an individual

Table 3 Results of univariate and multivariate logistic regression of factors associated with achieving PASS status in patients with OLP ($N = 281$)

Variables[1]	Achieving PASS			
	Crude OR [95% CI]	*p* value	Adj-OR [95% CI]	*p* value
Demographic variable				
Ethnicity (white = ref.)				
Mixed	1.67 [0.19–14.63]	0.645	1.90 [0.11–32.11]	0.656
Asian	0.37 [0.21–0.65]	< 0.001	0.69 [0.33–1.47]	0.34
Black	0.58 [0.16–2.08]	0.406	2.28 [0.34–15.46]	0.397
Clinical variables				
Clinical types (reticular = ref.)				
Erythematous	0.34 [0.14–0.80]	0.013	0.54 [0.18–1.60]	0.265
Ulcerative	0.13 [0.05–0.37]	< 0.001	0.38 [0.10–1.50]	0.167
Pain (NRS)	0.56 [0.48–0.64]	< 0.001	**0.65 [0.55–0.78]**	**< 0.001**
Disease activity score (ODSS-activity)	0.90 [0.87–0.93]	< 0.001	**0.93 [0.86–1.00]**	**0.047**
Treatment (no treatment/Tanes = ref.)				
TCS	0.21 [0.07–0.61]	0.004	0.49 [0.13–1.85]	0.294
Tanes + TCS	0.09 [0.03–0.28]	< 0.001	0.26 [0.06–1.09]	0.065
Systemic treatment	0.76 [0.08–7.74]	0.818	5.20 [0.29–91.70]	0.26
Psychological variables				
Anxiety symptoms (HADS-A)	0.85 [0.80–0.91]	< 0.001	0.98 [0.86–1.10]	0.701
Depressive symptoms (HADS-D)	0.78 [0.72–0.84]	< 0.001	**0.86 [0.75–1.00]**	**0.044**
Perceived stress (PSS-10)	0.91 [0.87–0.94]	< 0.001	0.99 [0.93–1.06]	0.813

[1] Due to collinearity with other variables, VAS, ODSS-site score, ODSS-total score and HADS-total score (distress) were excluded from multivariate analysis

Bold values: $p < 0.05$ in multivariate analysis

TCS topical corticosteroids, *Tanes* topical anaesthetic agents

patient. For the analysis of the PASS threshold in patients with OLP, the data of participants from two different time points of the MEAN-IT study (baseline, 4-month follow-up) were used to ensure sufficient number of patients who considered their OLP status acceptable (PASS+) and those who did not (PASS −) were achieved. Based upon the present analysis, about two-thirds of patients with OLP in the present cohort were being in PASS, and this figure was comparable between baseline group and 4-month follow-up group. Perhaps this could be due to the fact that the majority of OLP patients in both subgroups were able to adapt their lives to the extent of OLP-related symptoms and accept living with a certain degree of symptoms over time, as median values of time since diagnosis of OLP were over 5 years in both subgroups. However, the figures could be different between groups of new patients with a recent diagnosis of OLP and those with longer disease duration, and future studies investigating on this matter are required.

Descriptive bivariate analysis showed that a number of factors were significantly associated with the attainment of PASS in patients with OLP. Understanding determinants of achieving PASS could help clinicians understand how patients manage the impact of symptomatic OLP on a daily basis and develop the most appropriate management strategies, particularly in cases when there is a discordance in the perceptions of the disease between patients and clinicians. For instance, those who consider themselves in the PASS, despite active ulcerative disease, may require careful explanations to ensure adherence to the treatment if deemed necessary.

Among studied factors, lower intensity of oral pain was found to be the strongest independent determinant of achieving PASS in patients with OLP, and this is in line with previous research in different medical conditions. This again highlights the importance of pain control as an important key to OLP management. As for psychological factors, lower levels of depressive symptoms as reflected by the HADS-D were also an important predictor of being in PASS in the present study, and this finding is supported by the analysis of predictors of PASS in rheumatoid arthritis, which also found depression as an independent factor influencing PASS status. On the other hand, levels of anxiety symptoms (HADS-A) and perceived stress (PSS-10) were not found to be significantly associated with achieving PASS after adjustment of potential confounders. The present multivariate analysis also identified low level of clinical activity of OLP (extent and severity of clinical signs based on ODSS-activity score) to be marginally associated with being in acceptable symptoms state in OLP patients.

Table 4 PASS cut-off scores for self-reported measures of pain and OH-QoL in patients with OLP

Instruments	PASS	AUC	Sensitivity	Specificity
VAS (0–100 mm)	≤ 28	0.78	76	77
NRS (0–10)	≤ 3	0.75	75	75
OHIP-14				
Total	≤ 18	0.74	69	78
Functional limitation	≤ 1	0.64	68	60
Physical pain	≤ 4	0.76	77	76
Psychological discomfort	≤ 2	0.73	76	69
Physical disability	≤ 3	0.72	64	80
Psychological disability	≤ 1	0.72	81	63
Social disability	≤ 1	0.68	64	72
Handicap	≤ 1	0.72	73	71
COMDQ-15				
Total	≤ 26	0.8	76	84
Physical discomfort	≤ 10	0.79	80	80
Medication and treatment	≤ 3	0.69	75	63
Social and emotional	≤ 6	0.77	78	75
Patient support	≤ 2	0.58	55	61
COMDQ-26				
Total	≤ 45	0.81	74	87
Pain and functional limitation	≤ 15	0.79	81	77
Medication and treatment	≤ 9	0.76	80	30
Social and emotional	≤ 9	0.76	82	71
Patient support	≤ 3	0.65	77	52

All three identified independent predictors of PASS in OLP accentuate the importance of holistic patient care of patients with OLP. In other words, to aid affected individuals in entering acceptable OLP symptom state, clinicians should not only focus on treating physical symptoms and signs of OLP, but identification and management of related psychological symptoms could improve patient's perception of acceptability on their OLP status. Therefore, to ensure that all factors related to PASS have been evaluated in patients with OLP, incorporation of instruments assessing psychological impacts of OLP in conjunction with the use of pain and disease activity measures of OLP is crucial. This could be done by applying OLP-validated general psychological measures such as the HADS or the use of specific OH-QoL measures including the COMDQ, which provide assessment of both physical and psychological impacts of OLP, in clinical practice and research of OLP.

The present study also identified estimates of PASS thresholds among common measures of pain for use in a cohort of patients with OLP in one referral oral medicine clinic in the UK. According to results of the correlation studies, all included measures of pain and OH-QoL were predictive of acceptable OLP status based upon patient's perception. The results of ROC curve analyses showed the PASS thresholds for patients with OLP to be 28 mm for the pain-VAS, 3 for the pain-NRS, 18 for the total OHIP-14 score, 26 for the COMDQ-15 and 45 for the COMDQ-26. These PASS estimates could be adopted as target for clinically relevant treatment success, which could bring a patient's perspective to the fore of shared decision-making and make it easier for both patient and clinician to understand clinically relevant meanings of pain and OH-QoL scores [11]. Reporting the proportion of treatment responders could facilitate meaningful interpretation and communication of study results in addition to statistically significant mean effects [24]. In addition, PASS threshold can be applied as entry criteria for clinical trials assessing the effectiveness of symptomatic treatment [9]. In other words, only patients who do not achieve PASS are eligible for inclusion in the study.

Importantly, PASS should be used with caution when incorporating this concept in the management of potentially malignant condition including OLP. A recent meta-analysis estimated malignant transformation rate of OLP of approximately 1.1% [25], and the reported figure may be an underestimation due to inconsistent diagnostic criteria used as well as methodological quality of published studies. Therefore, even though some patients reach the stage of PASS, appropriate management and regular review appointment are necessary particularly when oral lesions suspected of malignancy and/or other risk factors of malignant transformation including tobacco, alcohol, HCV infection and atrophic-erosive OLP lesions are present. Thus, the application of PASS in clinical settings may only influence clinical judgement on the provision of symptomatic treatment in OLP cases without clinical signs and symptoms of oral epithelial dysplasia or cancer.

The results of the present study should be cautiously interpreted in light of the study's limitations. There is presently no international consensus on the gold standard of PASS anchor question, which is reflected by the variation in the use of PASS questions in the literature. The cross-sectional design limits the assessment of PASS performance and its associated factors in long-term follow-up, and thus further prospective studies with longer follow-up are required to validate longitudinal stability of the established PASS cut-offs. As the majority of patients in this OLP cohort had erythematous OLP due to the data from a tertiary oral medicine referral centre in the UK, the estimation of PASS in the present study may not be generalisable to real-world patients including asymptomatic cases who did not seek for professional treatment. Again, additionally, some factors including socioeconomic status, educational level, acceptance to live with chronic diseases and initial disease activity, which may be related to PASS, were not investigated in the present study.

Conclusion

The present study established PASS cut-off thresholds as a tool facilitating clinically meaningful interpretation of pain

and OH-QoL outcomes relevant to individuals with OLP. Identified PASS estimates could be utilised as endpoints in clinical practice of OLP as well as eligibility criteria for recruiting participants in clinical trials assessing effectiveness of symptomatic intervention of OLP. Factors including pain intensity, disease activity and depressive symptoms may have a negative impact on patient's acceptability of OLP status.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00784-020-03695-6.

Acknowledgements Paswach Wiriyakijja would like to thank Dr Emma Hayes, Dr Priya Thakrar, Dr Krupali Patel, Dr Barbara Carey, Dr Carolina Venda Nova, Dr Craig Whitelaw, Dr Sanjeet Singhota, Dr Thomas Saunsbury and Dr Valeria Mercadante for their substantial help and supports towards the recruitment process of the study.

Authors' contributions Paswach Wiriyakijja contributed to conceptualisation, methodology, data acquisition, formal analysis and investigation and drafted the original manuscript. Stephen Porter and Stefano Fedele provided supervision and resource and drafted the original manuscript. Tim Hodgson and Roddy McMillan provided resource and drafted the original manuscript. Martina Shephard provided resource. Richeal Ni Riordain contributed to conceptualisation and methodology, provided supervision and drafted the original manuscript.

Funding Paswach Wiriyakijja received a PhD Scholarship from the Faculty of Dentistry, Chulalongkorn University, Bangkok, Thailand. Stefano Fedele received funding from the National Institute for Health Research University College London Hospitals Biomedical Research Centre. The MEAN-IT study received service support funding from the National Institute for Health Research University College London Hospitals Biomedical Research Centre and the NIHR Clinical Research Network Portfolio.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards (REC reference number: 17/LO/1825).

Informed consent Informed consent was obtained from all individual participants included in the study.

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