Non-invasive Instrument-based Tests for Quantifying Anterior Chamber Flare in Uveitis: A Systematic Review

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Abstract

Purpose: Anterior chamber (AC) flare is a key sign for anterior uveitis. New instrument-based techniques for measuring AC flare can offer automation and objectivity. This review aims to identify objective instrument-based measures of AC flare.

Methods: In this systematic review, we identified studies reporting correlation between instrument-based tests versus clinician AC flare grading, and/or aqueous protein concentration, as well as test reliability.

Results: Four index tests were identified in 11 studies: laser-flare photometry (LFP), optical coherence tomography, ocular flare analysis meter (OFAM) and the double-pass technique. The correlation between LFP and clinician grading and protein concentration was 0.40-0.93 and 0.87-0.94, respectively. The double-pass technique showed no correlation with clinician grading and insufficient information was available for OFAM.

Conclusion: LFP shows moderate to strong correlation with clinician grading and aqueous protein concentration. LFP could be a superior reference test compared to clinician AC flare grading for validating new index tests.

Keywords

Systematic review, uveitis, anterior chamber flare, aqueous humor, aqueous humour, Tyndall effect, diagnostic test, aqueous protein concentration, optical coherence tomography, laser flare photometry.

Introduction

Anterior uveitis describes inflammatory mediated breakdown of the blood-aqueous barrier with resultant leakage of blood constituents into the aqueous humour. Clinically this is predominantly characterised by anterior chamber (AC) cells and flare. AC flare is an important clinical marker of inflammation, and has been shown to be the predominant sign in syndromes such as childhood chronic anterior uveitis.[1,2] To measure the true extent of blood-aqueous barrier breakdown requires sampling of the aqueous humour through paracentesis using a needle inserted into the AC, and measurement of the protein concentration in that sample. Whilst this invasive test provides the most accurate quantification of aqueous constituents, it is not feasible for repeated measurement in the context of disease monitoring. The more common approach is to observe this change using slit lamp biomicroscopy, as 'flare', an appearance of haziness of the aqueous humour. Flare can be graded using semi-quantitative scales, of which the Standardization of Uveitis Nomenclature (SUN) grading system is most commonly used.[3] The SUN system measures flare according to the observer's ability to visualise details of the iris and lens behind the aqueous. Grades range from 0, which corresponds to no visible flare, to +4, which corresponds to intense flare **(Table 1)**. Although this clinician-based method is subjective,[4] quantifying aqueous inflammation this way is widely accepted as a clinical standard and is used to inform treatment decisions.[5] It is recognised that non-invasive and objective methods for measuring aqueous inflammatory change would significantly improve clinical assessment of anterior uveitis.

Instrument-based techniques such as laser flare photometry (LFP) have been available for the last 20 years but have not been widely adopted. This is despite the evidence supporting the validity and clinical utility of LFP.[6–9] More recently, newer imaging techniques such as anterior segment optical coherence tomography (AS-OCT) have also demonstrated the potential to quantify AC flare.[10] Given the need for an objective non-invasive method for assessing aqueous inflammation, a systematic examination of the evidence of such technologies is timely.[11] This review aims to identify all instrument-based tools for measuring aqueous humour inflammation in uveitis and evaluate their

correlation with laboratory measurements of aqueous protein concentration and/or slit-lamp based clinician grading systems.

Table 1: The Standardisation of Uveitis Nomenclature (SUN) working group grading scheme for anterior chamber flare.[3]

Grade	Flare	Description
0	None	No alteration to iris and lens visualization
1+	Faint	Barely detectable
2+	Moderate	Iris and lens details clear despite discernible haze
3+	Marked	Iris and lens details hazy
4+	Intense	Fixed coagulated aqueous with considerable fibrin

Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Jabs DA, Nussenblatt RB, Rosenbaum JT. 2005.

Methods

This review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[12] The methodology was specified in advance and the protocol registered with PROSPERO (CRD42017084167).[13] The primary aim of this review was to evaluate all non-invasive, instrument-based methods for measuring aqueous humour inflammation and their level of correlation with, 1) the gold standard reference test: analysis of protein concentration in aqueous samples, and/or 2) the clinical reference test: slit-lamp based AC flare grading performed by a clinician. We accepted both as reference tests in recognition that aqueous paracentesis is rarely performed, and clinician grading is widely used as the basis for final clinical

decision-making in practice. A secondary aim was to identify studies which also reported the reliability of index tests and compare the reliability between different tests.

Search strategy

We combined free text terms and index terms reflecting the pathological finding of interest, ‘flare’ or ‘proteins’ and ‘anterior chamber’ or ‘aqueous humor’, and the disease context ‘uveitis’ or ‘inflammation’ (search strategy available in **Supplementary Materials**). Database searches were carried out in MEDLINE, Embase, Cochrane Controlled Register of Trials (CENTRAL), Centre for Reviews and Dissemination Database (Health Technology Assessments and the Database of Abstracts and Reviews of Effects), Clinicaltrials.gov, WHO International Clinical Trials Registry Platform (ICTRP portal), British Library’s ZETOC, Conference Proceedings Citation Index (Web of Science), British Library Ethos, ProQuest and OpenGrey. We searched all databases from inception to 07 August 2019, with no date or language restrictions. We manually searched citations of review articles and included studies to identify additional relevant articles.

Study selection

Two reviewers independently assessed study eligibility, and disagreements were resolved through consensus, or referral to a third reviewer if needed. Studies were eligible if they described one or more instrument-based methods for measuring aqueous humour protein levels (index test) and compared its measurements to actual aqueous protein concentration and/or clinician grading (reference tests). We also included studies reporting test reliability. The primary outcome of interest was the level of correlation between index tests and either of the two reference tests. The secondary outcome was intra/inter-observer reliability of the index test. We did not exclude studies based on subject age, gender, ethnicity, underlying aetiology or disease activity status. Animal studies and studies involving only healthy participants, single case reports, commentaries and opinion articles were excluded.

Data extraction

Two reviewers independently extracted data using a pre-specified data extraction sheet. Two texts were translated from Chinese into English. We contacted two authors for further information and both responded.[14,15] If only individual patient data were reported, we used this information to calculate the correlation coefficient.

Risk of Bias assessment

Two reviewers independently assessed the risk of bias, in studies comparing correlation between two tests, using a modified version of the Quality Assessment of Diagnostic Accuracy Studies tool (QUADAS-2).[16] We pre-specified adaptations to the original QUADAS-2 signalling questions to address the review question. For example, one signalling question was added in the index test section on whether index test protocols were determined *a priori* and standardised for all participants.

Data analysis

For each outcome, studies were grouped by the reference test against which comparisons were made: aqueous protein concentration or clinician grading. For each index test, we tabulated the extracted information and provided a narrative synthesis of methodological characteristics and index tests evaluated. Where confidence intervals for correlation coefficients were not reported, we estimated them using sample size and correlation coefficient and presented this on a forest plot. All statistical analyses were performed using Stata Statistical Software (Release 15. College Station, TX: StataCorp LP.)

Results

Results of the Search

The study selection process is summarised in the PRISMA flow diagram **(Figure 1)**. The search yielded 3741 unique bibliographic records after removal of duplicates. Of these, 3629 were excluded based on screening of titles and abstracts. The large number of excluded articles is owing to the unrestrictive nature of our search strategy, which was deliberately designed to not include any index test terms, to ensure full

capture of all relevant studies. The remaining 110 articles were obtained in full text for further scrutiny and a further 99 articles were excluded. The reasons for exclusion were due to not matching the criteria for outcome (n=52), population (n=24), study design (n=19) and for the lack of an appropriate reference test (n=4). Eleven unique studies met the eligibility criteria and were included **(Table 2)**.

Participants' Characteristics and Study Design Features

The 11 studies included a total of 876 participants (at least 1016 eyes; one study did not report the number of eyes[17]), and dated from 1989 to 2017.[10,17–26] Study characteristics are summarised in **Table 2.** One study used retrospectively collected routine clinical care data[19], whilst all other studies collected data prospectively. Gender was reported in 8 of the 11 studies, 44% of participants (n = 360) were male. Age was reported in 8 of the 11 studies[10,17,19–21,24–26], ranging from 12 to 86 years. Three studies included mixed etiologies, including sarcoidosis, Behcet's disease, Vogt-Koyanagi Harada disease, acute retinal necrosis, lyme disease, progressive outer retinal necrosis, retinal vasculitis, herpes zoster ophthalmicus and FHC.[17,18,23] Five studies did not report specific uveitis entities and instead reported anatomical classification or disease activity (active, inactive and healthy controls).[10,22,24–26] Two studies did not report any aetiological classifications.[20,21] One study included only eyes with Fuch's Heterochromic Cyclitis (FHC).[19]

Methodological Quality of the Included Studies

A summary of the risk of bias assessment for the included studies is presented in **Supplementary Figure 1.** Eight out of eleven studies did not report how subjects were recruited into the study[18–21,23–26] and had an unclear risk of bias regarding participant selection. Given the known limitations of the clinician grading system, all studies which utilised clinician grading as the reference test (n=8) were marked as unclear due to concerns around disease misclassification. It was unclear in 5 studies[18–21,24] whether the index test was interpreted without knowledge of the reference tests and vice versa. One study was identified as having a high risk of bias for patient flow as readings were unsuccessful in 31 of the 121 included subjects.[21] Another study had high applicability concerns as the entire patient cohort was eyes with FHC.[19]

Clinical reference test: slit-lamp based clinician grading

Nine out of 11 studies[10,17,19–22,24–26] compared an index test with AC flare grading based upon clinician slit-lamp examination. Six studies[10,19–22,24] used the SUN grading system and 3 studies[17,25] did not specify a standardised grading system. Six studies reported the number of eyes at each AC flare grade.[10,20,21,24–26] Three of these studies included patients in all 4 grades of severity, 2 studies had eyes with each grade except grade 4, and 1 study included eyes with grades 0.5 and grade 1 of AC flare only. Three studies did not report the number of patients in each grade of AC flare.[17,21]

Laboratory reference test: aqueous protein concentration

Three out of 11 studies compared an index test with aqueous protein concentration.[18,23,24] Two studies[23,24] used paracentesis samples taken from individuals with uveitis prior to routine cataract surgery, one study[18] used diagnostic paracentesis samples for eyes with endogenous uveitis. Two studies[18,23] included IgG and albumin concentrations, one of which also measured total protein, and the other study[24] did not specify which proteins were measured.

Instruments for measuring AC cells

Four different classes of index tests that fit the description of non-invasive imaging techniques were identified. The majority of studies evaluated the use of LFP (9 studies). LFP devices included various models produced by KOWA, including the FC-1000, FC-2000, FC-500 and the only two models which are currently commercially available, the FM-600 and FM-700. Most studies reported taking between 3-7 repeated measurements at each observation and taking the averaged value, as is the usual procedure according to LFP instructions. The sampling volume was reported as 0.075mm^3 for the FC-1000 (mean anterior chamber volume being approximately 145mm^3)[27] and sampling area was reported to be 0.3mm by 0.5mm for the FC-2000, FC-600 and FC-700. All measurements were derived using the built-in software of the LFP. One study evaluated a swept-source OCT device (Casia SS-1000, Tomey Corporation, Japan), taking two 6mm cross-sectional scans in the anterior chamber. The AS-OCT images were then used to derive an image brightness ratio between the aqueous and

air anterior to the cornea, using custom software, producing an ‘aqueous-to-air’ relative intensity (ARI).[10] One study used a custom-built ocular flare analysis meter (OFAM)[21] and one study used an optical quality analysis system (OQAS II, Visionmetrics, Terrassa, Spain) based on the double-pass technique, a technique measuring the amount of ocular scatter caused by the presence of flare.[22]

Index test reliability

Only two studies reported index test reliability. Invernizzi *et al.* reported an intraclass correlation of 0.78 for the OCT-derived ARI index measurement, and Shah *et al.* reported a coefficient of variation of 7.3% for the Kowa FC-1000 LFP. Nanavaty *et al.* performed a reproducibility study, however these were on healthy pseudophakic eyes, rather than uveitis eyes.

Correlation between index tests and the clinical reference test: slit-lamp based clinician grading

Six studies reported correlation between an index test and clinician grading of AC flare (five studies using the LFP and one study using the optical quality analysis system).[17,19,22,24–26] The total number of eyes included in these six studies was 478. Various statistical methods including Kendall’s, Spearman’s and Pearson’s correlation coefficients were used. The level of correlation between the LFP and clinician grading ranged from 0.40 - 0.93. The one study using the optical quality analysis system reported a Pearson’s r^2 of 0.0048.[22] Although the OFAM and OCT devices were compared against SUN grading, no correlation coefficient was reported.

Correlation between index tests versus the laboratory reference test: aqueous protein concentration

Three studies reported correlation between an index test and aqueous protein concentration, all of which used LFP as the index test.[18,23,24] Shah *et al* and Shoughy *et al* included non-uveitic eyes in the correlation analysis, whereas Chiou *et al* included eyes with endogenous uveitis only. The total number of eyes included across all three studies was 59. One study[23] calculated a Pearson’s *r* and another study[18] did not report which statistical test was used. In the last study, individual patient data was reported so we

derived the correlation between the two tests for uveitic eyes using Pearson's *r* .[24] The level of correlation between index test measurements and protein concentrations ranged from 0.87 - 0.99. From the limited data, there were no apparent associations between type of protein and level of correlation.

The forest plot showing correlation between LFP and the two reference tests: clinician grading and aqueous protein concentration is shown in **Figure 2**. None of the included studies reported confidence intervals to correlation coefficients and those shown in the forest plot were estimated using sample size and correlation coefficient.

Study Heterogeneity

There was considerable heterogeneity between the methodology and populations across the included studies. These characteristics were wide ranging particularly in regard to the various device models used, the distribution of disease subtype and severity, and the statistical tests used to calculate correlation. Given this level of heterogeneity, any meta-analysis of correlation coefficients for would be inappropriate.

Figure 2. Level of correlation between LFP and clinician grading and aqueous protein concentration

Discussion

This is the first systematic review evaluating all non-invasive instrument-based tests for quantifying aqueous humour inflammation. We found four non-invasive index tests: OCT, LFP, OFAM and the Double Pass technique (using the OQAS). Of all the index tests, we found LFP to have the strongest evidence base, with good correlation with clinician grading and very good correlation with aqueous sample protein concentration. However, only a small number of studies provided sufficient information to support this finding and incomplete reporting and inconsistent methodology of included studies meant we were unable to pool estimates of correlation between index and reference tests.

Our review found a strong correlation between the LFP and clinician grading of AC flare, as well as aqueous protein concentration, in most studies. There was no apparent relationship between the device model and level of correlation, and the current available model (FM-600) validated in one study, was reported to have good correlation (r = 0.86 - 0.87) with clinician grading. An interesting finding was that LFP measurements showed a stronger correlation with protein concentration (r = 0.87 - 0.99) than with clinician grading (r = 0.40 - 0.93). If aqueous paracentesis was assumed to be the true gold standard, then this finding would suggest LFP is a more accurate marker of aqueous protein levels than clinician grading. Shoughy et al. was the only study which reported all three methods at the individual eye level, allowing us to calculate correlation between all three methods. Their measurements showed a higher correlation between aqueous protein concentration and LFP (r = 0.99) than aqueous protein concentration and clinician grading (r = 0.93), however this is based on only ten eyes (five of which were grade 0 by SUN grading).

The OFAM is a new device utilising the Rayleigh scattering effect with a theoretically higher sensitivity to smaller molecules than the Tyndall effect used by LFP. Although the authors report significant differences in OFAM measurement in eyes with grade 1 and 2, when compared with grade 0, the device could not differentiate between grades 1 and 2. The double pass technique using the OQAS showed poor correlation with AC flare grading, but the authors reported a significant correlation with AC cells (r = 0.87) and significantly more ocular scatter in eyes with anterior uveitis than intermediate and posterior subtypes.

Invernizzi *et al* reported the only evaluation of OCT for quantifying AC flare. Although they did not report a correlation coefficient between OCT or LFP compared against clinician grading, they showed that OCT derived ARI index significantly increased with each grade of AC flare. Similarly, LFP readings in their study significantly increased with each grade of AC flare, with the exception of grade 0 to grade 1. When comparing the two index tests, LFP and ARI index, they found a moderate correlation (r = 0.61). OCT has the added advantage of sampling a larger theoretical volume of AC compared to LFP and is fast and convenient to acquire. Additionally, the counting of AC cells using anterior segment OCT has been described by Invernizzi *et al* and others and has been

shown to be an automatable process. Therefore, OCT has the added advantage of offering a comprehensive all-in-one multi-faceted assessment of AC inflammation.[28]

Strengths and limitations of the review

This review represents the first systematic evaluation of technologies for measuring AC flare or aqueous inflammation. Previous reviews have summarised the level of validation for LFP, however this is the first review to consider all technologies, including newer imaging modalities such as OCT. Our search strategy was designed to be highly sensitive and included a broad range of databases, including conference proceedings, dissertation databases and the grey literature. However, our review also has a number of limitations. We only included studies reporting correlation between tests or reliability of tests, therefore any other methods of test comparison (such as those demonstrating significant difference in index test measurements across SUN grades) were not included. This is because our original intention was to choose a commonly reported metric which would enable comparison between index tests. Whilst correlation is useful, it is limited to demonstrating agreement and non-inferiority to the comparator. From correlation, it is not possible to determine if the index test is more accurate than the reference test. This is an important consideration when the clinician grading system is the reference test, where the index test may in fact provide a more accurate measurement.

Limitations of the evidence

First, due to the small number of included studies and heterogeneity in study design, it was not possible to provide pooled estimates of correlation or reliability. Second, authors sometimes reported correlation coefficients estimated from a mixed cohort of uveitic and healthy eyes. Where the two groups could be separated, or where individual patient data was available, we extracted and calculated correlation coefficients from uveitic eyes only. However, this was not possible in all studies and non-uveitic eyes were included in the original analysis as grade 0. Third, in two studies correlation was derived from eyes with two clinical grades of AC flare only (i.e. SUN grade 1 and grade 2 only). In these cases, there is an applicability concern around whether the study

population adequately represents the target population and the correlation coefficient is also less meaningful.

Clinical relevance and impact

Anterior chamber flare is an important measure in the assessment of uveitic inflammation. This review finds that instrument-based tools such as the LFP can achieve good agreement with widely accepted clinical and laboratory reference tests and may be a more accurate marker of true aqueous protein concentration than clinical grading. Despite being available for some time, the LFP has not been widely adopted in clinical care. This may be due to practical reasons, as using the LFP involves taking up to seven readings with a degree of manual input, including discarding spurious readings and computing an average value. Additionally, the LFP is sensitive to ambient lighting and therefore requires a completely dark room, and acquisition can be more difficult for eyes with posterior synechiae and a shallow AC. Such practical considerations may outweigh the added clinical value of such a device. However, we would argue that in a clinical trial context, accuracy and reliability should take precedence and the LFP could be adopted in place of AC flare grading.

We would also suggest that for the validation of newer imaging methods, the LFP may be a more appropriate reference test in comparison to clinician grading, when aqueous protein concentration is not available. However, this is based on findings from a small number of eyes in a single study. We would suggest that a well-conducted study on a larger cohort of eyes, comparing AC flare grading using the slit-lamp, aqueous paracentesis and LFP, would be helpful for confirming whether LFP can replace clinician grading as the clinical reference test.

Conclusion

Instrument-based tests have the potential to offer more objectivity to measurements of AC inflammation compared to the widely used clinician grading using slit-lamp. The validation of LFP is the most mature for this purpose and has shown strong correlation with clinician grading of AC flare and more importantly with aqueous protein concentrations. Although LFP may not be widely adopted in clinical practice, it may

have value as a non-invasive reference test with which to validate emerging technologies for measuring AC flare.

Disclosure of interest

AKD and PAK receive a proportion of their funding from the Department of Health's NIHR Biomedical Research Centre for Ophthalmology at Moorfields Eye Hospital and UCL Institute of Ophthalmology. XL and AKD receive a proportion of their funding from the Wellcome Trust, through a Health Improvement Challenge grant (200141/Z/15/Z). ALS is supported by an NIHR Clinician Scientist award (CS-2018-18-ST2-005). LED has no disclosures relating directly to this work. She has received research funding from Allergan Pty Ltd, Alcon Pty Ltd and Azura Ophthalmics, and consulting income from Seqirus and Medmont International, outside of this work.

Author Contributions

XL: lead reviewer, manuscript drafting, manuscript reviewing. TWM: second reviewer, data extraction manuscript drafting, manuscript reviewing. SB: data extraction, manuscript drafting, manuscript reviewing. LF, LD, ALS, SH: manuscript drafting, manuscript reviewing. PAK, DJM, AKD project conception, supervision, manuscript reviewing.

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Figure 1. PRISMA flow diagram

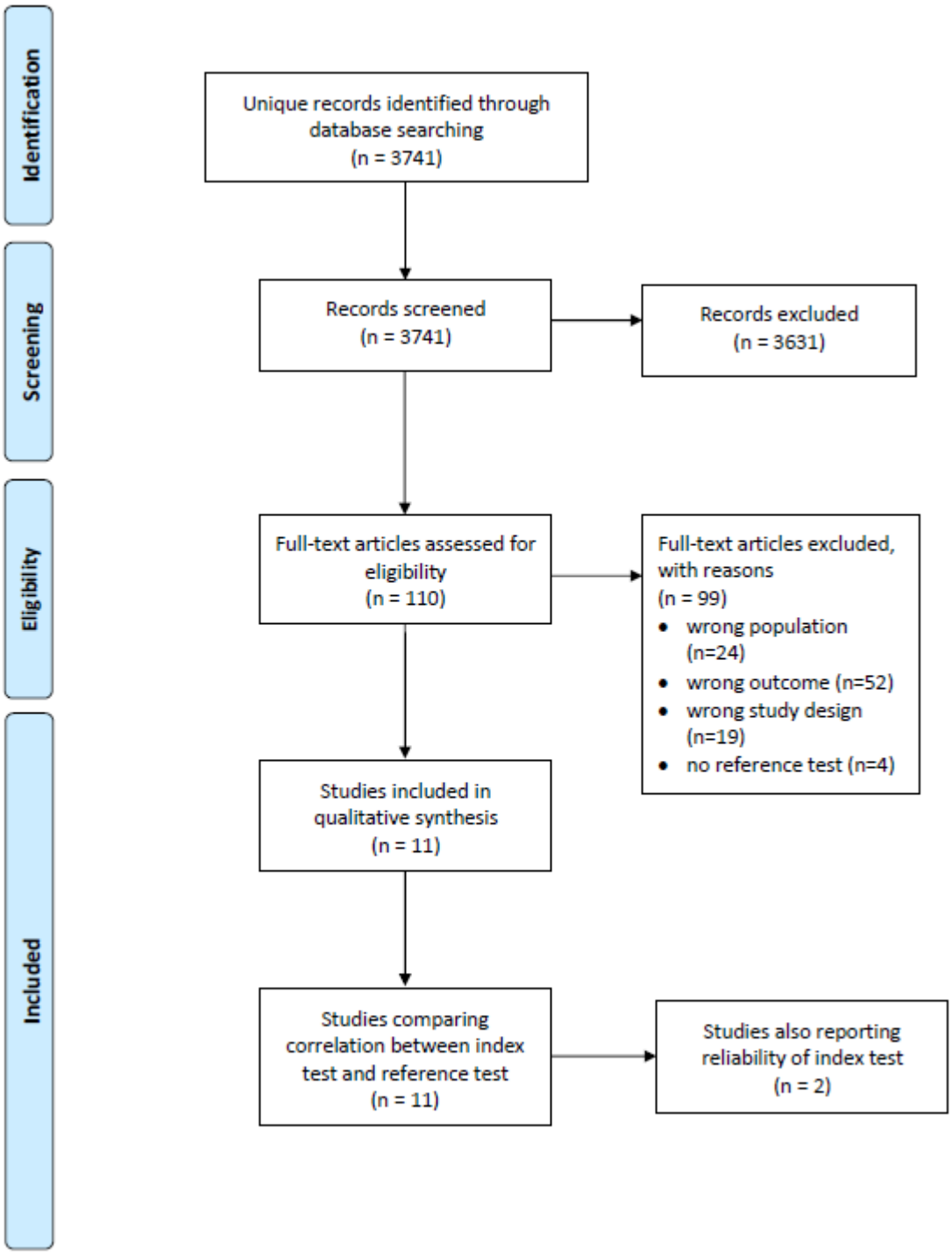

Figure 2. Level of correlation between LFP and clinician grading and aqueous protein concentration

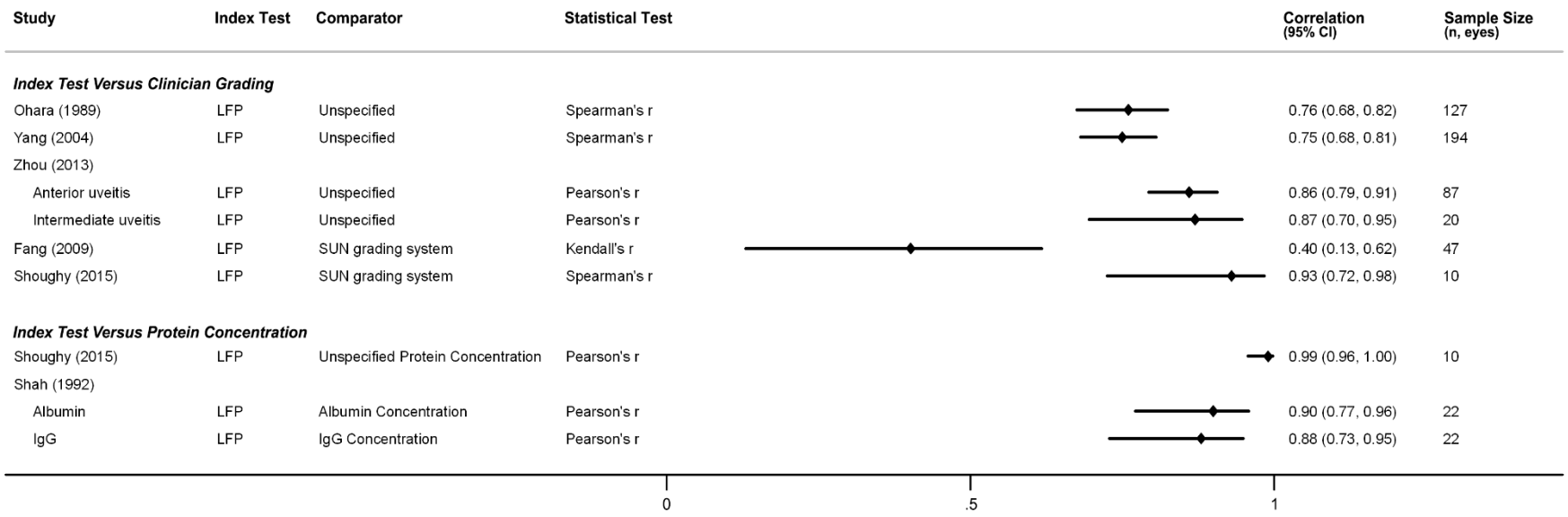

Table 1. Study Characteristics

Author	Index test	Data Collection	No. of subjects	No. of eyes	Gender (%)	Age, years	Aetiological classification, no. of eyes (%)
Ohara (1989)	LFP	Prospective	124	NR	44 (35%) male 80 (65%) female	NR (range 12-76)	Sarcoidosis 53 (43%), Behcet's disease 14 (11%), VKH 6 (5%), ARN 3 (2%), Other 14 (11%), Unknown 34 (27%)
Chiou (1998)	LFP	Prospective	17	17	NR	NR	ARN 5 (29%), Lyme disease 4 (23%), Progressive outer retinal necrosis 2 (12%), Anterior uveitis 1 (6%), Panuveitis 1 (6%), Retinal vasculitis 1 (6%), HZO 1 (6%), FHC 1 (6%), Behcet's disease 1 (6%)
Shah (1992)	LFP	Prospective	22	22	NR	Mean age: Normal 71 (SD 10) FHC 53 (SD 7) Uveitis 68 (SD 6)	FHC 5 (22.5%), Non-uveitic eyes undergoing routine cataract surgery 12 (55%), Chronic uveitis undergoing cataract/glaucoma surgery 5 (22.5%)
Yang (2004)	LFP	Prospective	162	Uveitis (194) Healthy eyes (52)	57 (52%) male 53 (48%) female	Mean 35 (range 3-66)	Anterior uveal inflammation 110 (68%), healthy controls 52 (32%)
Fang (2009)	LFP	Retrospective	40	47	15 (38%) male 25 (62%) female	Mean 34 (SD 10.1)	FHC 47 (100%)
Zhou (2013)	LFP	Prospective	129	171	68 (53%) male 61 (47%) female	Mean 42 (range 14-66)	Anterior uveitis 87 (51%), Intermediate uveitis 20 (12%), Posterior uveitis 64 (37%)
Konstantopolou (2015)	LFP	Prospective	75	110	23 (31%) male 52 (69%) female	Median 42 (IQR 31-54)	NR
Shoughy (2015)	LFP	Prospective	20	20	13 (65%) male 7 (35%) female	Mean 52 (range 17-86)	Anterior non-granulomatous uveitis 5 (25%), VKH 4 (20%), FHC 1 (5%), Non-uveitis 10 (50%)
Invernizzi (2017)	LFP OCT	Prospective	122	237	102 (43%) male 135 (57%) female	Mean age: Control 42 (SD 14) Inactive uveitis 43 (SD 19) Active uveitis 45 (SD 22)	Healthy control 70 (30%), inactive uveitis 97 (40%), active uveitis 70 (30%)
Lam (2015)	OFAM	Prospective	121	90	38 (42%) male 52 (58%) female	Mean age: Active uveitis 44 No uveitis 46	NR
Nanavaty (2011)	Double-pass technique	Prospective	44	56	NR	NR	Anterior uveitis 24 (43%) Intermediate uveitis 9 (16%) Posterior uveitis 10 (18%) Panuveitis 13 (23%)

NR: not reported, OFAM: ocular flare analysis meter, OCT: optical coherence tomography, LFP: laser flare photometry, FHC: Fuch's heterochromic cyclitis. ARN: acute retinal necrosis, VKH: Vogt Koyanagi Harada disease, JIA: juvenile idiopathic arthritis, CMV: cytomegalovirus, HZO: herpes zoster ophthalmicus, *includes repeat visits of same eye.

Table 1 continued. Index test characteristics

Author	Index test	Manufacturer and model	Image acquisition settings	Area/volume	Image analysis software
Ohara (1989)	LFP	Kowa FC-1000	An average of 5 readings taken through dilated pupil	Per 0.075mm^3	Built in software only
Chiou (1998)	LFP	Kowa FC-1000	NR	Per 0.075mm^3	Built in software only
Shah (1992)	LFP	Kowa FC-1000	5 averaged measurements Measurements where BG reading >15% was discarded,	0.3 x 0.5 mm	Built in software only
Yang (2004)	LFP	Kowa FC-2000	5 averaged measurements taken per eye	0.3 x 0.5 mm	Built in software only
Fang (2009)	LFP	Kowa FC-2000	An average of 3 measurements. Measurements with artefacts are discarded.	0.3 x 0.5 mm	Built in software only
Zhou (2013)	LFP	Kowa FM-600	7 consecutive measurements taken, highest and lowest values discarded, and remaining measurements averaged.	0.3 x 0.5 mm	Built in software only
Konstantopolou (2015)	LFP	Kowa FC-500	7 measurements are acquired. The highest and lowest values are discarded, and remaining measurements averaged.	NR	Built in software only
Shoughy (2015)	LFP	Laser flare photometry (model NR)	NR	NR	NR
Invernizzi (2017)	LFP	Kowa FM-700	7 averaged consecutive measurements	0.3 x 0.5 mm	Built in software only
	OCT	Casia SS-1000 OCT device (Tomey Corporation, Nagoya, Japan)	Two 6mm line scans, each consisting of 2048 A scans.	200 x 200 pixel area	Custom software. A ratio of brightness value between aqueous and air anterior to the cornea is derived to produce an aqueous-to-air relative intensity.
Lam (2015)	OFAM	Custom OFAM device	Single measurement on an undilated eye	NR	Custom software
Nanavaty (2011)	Double -pass techniq ue	The Optical Quality Analysis System (OQAS II; Visionmetrics, Terrassa, Spain)	3 averaged measurements taken from dilated pupils.	NR	Built in software only

NR: not reported, OFAM: ocular flare analysis meter, OCT: optical coherence tomography, LFP: laser flare photometry

Table 1 continued. Index test versus reference tests

Author	Index test	Clinical Grading System	Manufacturer and model	Observers	No. eyes in each clinical grade	No. eyes included in correlation analysis	Statistical Test	Correlation Coefficient (95% CI)
Ohara (1989)	LFP	NR	Kowa FC-1000	One observer for all clinical assessments	NR	127	Spearman r	0.76
Yang (2004)	LFP	NR	Kowa FC-2000	NR	Grade 0, 74; Grade 1, 98; Grade 2 18; Grade 3, 2; Grade 4, 2	194	Spearman r	0.75
Fang (2009)	LFP	SUN	Kowa FC-2000	One observer for all clinical assessments	Only grade 0.5 and grade 1 eyes were included	47	Kendall r	0.40
Zhou (2013)	LFP	NR	Kowa FM-600	NR	**Anterior uveitis** Grade 1, 48; Grade 2, 35; Grade 3, 2; Grade 4, 2 **Intermediate uveitis** Grade 1, 10; Grade 2, 10	87 (anterior uveitis) 20 (intermediate uveitis)	Pearson r	0.86 (anterior) 0.87 (intermediate group)
Konstantopolou (2015)	LFP	SUN	Kowa FC-500	Two observers independently performed clinical grading	Grade 0, 5; Grade 1, 74; Grade 2, 29; Grade 3, 2; Grade 4, 0	110	NR	NR
Shoughy (2015)	LFP	SUN	Laser flare photometry (model NR)	Two observers independently performed clinical grading	Grade 0, 5; Grade 1, 3; Grade 2, 1; Grade 3, 1; Grade 4, 0	10	Spearman r	0.93
Invernizzi (2017)	OCT	SUN	Casia SS-1000 OCT device	NR	Grade 0, 32; Grade 1, 21; Grade 2, 15; Grade 3, 2	70	NR	NR
	LFP	SUN	Kowa FM700	NR	Grade 0, 32; Grade 1, 21; Grade 2, 15; Grade 3, 2	70	NR	nr
Lam (2015)	OFAM	SUN	Custom OFAM device	One observer for all clinical assessments	NR	NR	NR	NR
Nanavaty (2011)	Double-pass technique	SUN	The Optical Quality Analysis System	Two independent observers for clinical assessment Double-pass technique by a technician who was blinded to clinical assessment	NR	56	Pearson r^2	0.0048

NR: not reported, OFAM: ocular flare analysis meter, OCT: optical coherence tomography, LFP: laser flare photometry, ARI: aqueous-to-air relative intensity [ARI] index, CC: correlation coefficient, *(including repeat visits of same eye)

Table 1 continued. Index test versus aqueous protein concentration

Author	Index test	Protein concentration test	Proteins measured	Protein concentration range	No. eyes included in correlation analysis	Statistical Test	Correlation Coefficient (95% CI)
Chiou	Kowa FC-1000 LFCP	Diagnostic paracentesis	IgG Albumin	NR	17 (IgG) 10 (albumin)	NR	0.87 (IgG) 0.94 (albumin)
Shah	Kowa FC-1000 LFCP	Paracentesis before routine cataract surgery	Total protein Albumin IgG	Normal IgG 0.3 - 4 mg/dl Normal Alb 3.1-14 mg/dl Normal Total protein 14 - 45 mg/dl FHC IgG <2 - 8 mg/dl FHC Alb 6-36 mg/dl FHCs Total protein 14-51 mg/dl Uveitis IgG 6-50mg/dl Uveitis Alb 48-290 mg/dl Uveitis Total protein 62 - 388 mg/dl	22	Pearson r	0.90 (albumin) 0.88 (IgG)
Shoughy	LFP (Model NR)	Paracentesis before routine cataract surgery	NR	Normal 10-35.48 mg/dl Anterior non-granulomatous uveitis, 10 - 1490 mg/dl FHC, 23.95 mg/dl* VKH, 30 - 600 mg/dl	10	Pearson r	0.99

NR: not reported, LFP: laser flare photometry, CC: correlation coefficient, FHC: Fuch's heterochromic cyclitis, VKH: Vogt Koyanagi Harada syndrome *one subject only