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Role of serum soluble interleukin-2 receptor level in the diagnosis of ocular and non-ocular sarcoidosis: a systematic review and meta-analysis

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Abstract. *Background and aim:* Serum Soluble Interleukin-2 receptor (sIL-2R) levels are used clinically as a disease activity marker for systemic sarcoidosis. Studies have investigated the diagnostic role of serum soluble interleukin-2 receptor (sIL-2R) level for sarcoidosis relative to biopsy. We performed a systematic review and meta-analysis of studies evaluating the diagnostic utility of sIL-2R. *Methods:* We carried out an electronic search in Medline, Embase, Google Scholar, and Cochrane databases using keyword and Medical Subject Heading (MeSH) terms: sarcoidosis and sIL-2R. Studies evaluating-the sIL-2R levels as a diagnostic tool in clinically diagnosed or biopsy-proven sarcoidosis patients compared to control groups with non-sarcoidosis patients were included. Forest plots were constructed using a random effect model depicting pooled sensitivity, specificity, positive and negative predictive values, and diagnostic accuracy. *Results:* We selected ten studies comprising 1477 patients, 592 in the sarcoidosis group and 885 in the non-sarcoidosis group. Pooled sensitivity and specificity of sIL-2R levels were 0.88 (95% CI: 0.75-0.95) and 0.87 (95% CI 0.73-0.94), respectively. Pooled negative predictive value and positive predictive value were 0.91 (95% CI 0.77-0.97) and 0.85 (95% CI 0.59-0.96), respectively, with a diagnostic accuracy of 0.86 (95% CI 0.71- 0.93). *Conclusion:* In addition to its utility as a marker of sarcoidosis disease activity, sIL-2R has high diagnostic accuracy. Despite the limitations of the heterogenous sarcoidosis population and different sIL-2R cutoffs, our results suggest that sIL-2R is an important biomarker that can be used to confirm sarcoidosis diagnosis in unconfirmed or unclear cases.

Key words: Sarcoidosis, soluble interleukin-2 receptor, diagnostics

Introduction

Sarcoidosis is a heterogenous multi-systemic immune-mediated disease characterized by non-caseating granulomas often localized in the lung or the mediastinal lymph nodes. It is notoriously difficult to diagnose as it is a diagnosis of exclusion and requires an in-depth patient evaluation. The diagnosis of sarcoidosis is based on three major criteria: a compatible clinical or radiological presentation, the histological evidence of non-necrotizing granulomatous inflammation in one or more tissues, and the exclusion of alternative causes of this granulomatous disease (1). The absence of a specific diagnostic serum biomarker makes it a challenging diagnosis since some patients may hesitate to undergo invasive testing like bronchoscopy or biopsy for histological diagnosis.

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Many biomarkers have been studied for the diagnosis and prognostication in patients with sarcoidosis, most of which are produced by inflammatory cells involved in granuloma formation (2). The most intensely studied and largely used clinically is serum Angiotensin-Converting Enzyme (ACE) levels. ACE is a peptidase secreted by activated macrophages and epithelioid cells within sarcoid granulomas. Even though ACE levels are elevated in up to 80% of patients with sarcoidosis, it lacks sensitivity (22-86%), making it less helpful in a clinical setting (3,4). Other potential biomarkers studied include serum and bronchoalveolar lavage levels of adenosine deaminase (ADA), serum amyloid A (SAA), serum chitotriosidase, and serum neopterin levels. However, none has demonstrated enough sensitivity and specificity to recommend routine real-world clinical use (2).

In sarcoidosis, the Th1 cytokine pattern seems to predominate mainly in the areas of granuloma formation. Upon activation, Th1 cells upregulate the expression of IL-2R on the cell surface and can shed sIL-2R into circulation (5). sIL-2R levels are therefore used clinically as a disease activity marker for systemic sarcoidosis, as they are an indirect measurement of granuloma burden in the patient (4).

Recently there have been studies evaluating the role of sIL-2R in establishing the diagnosis of sarcoidosis in patients with clinically suspected sarcoidosis. In our review, we aimed to perform a systematic review and meta-analysis of prior studies that evaluated the diagnostic utility of sIL-2R in sarcoidosis.

Methods

Literature search

We carried out an extensive electronic search in Medline (PubMed), Embase, Google Scholar, and Cochrane database of systematic reviews, Cochrane central register of controlled trials, Scopus, and Web of science using the keywords/Medical Subject Heading (MeSH) "Sarcoidosis", "Sarcoid", "interleukin2 OR interleukin*2*", "sIL 2r OR sIL-2R", "il 2 OR IL-2" terms. The search was performed from 1947 until April 2021 in Medline and Embase (Search strategy detailed in Supplementary 1 and Supplementary 2). The search also included unpublished articles as well as conference abstracts. The search included articles in all languages.

Selection of studies

The studies found on extensive data research were compiled in Covidence software. Covidence software was used for primary and secondary screening by two reviewers. We applied the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement to the methods of this study. After removing the duplicated studies, two authors (SG and RPP) independently screened the title and abstracts. Studies evaluating the sIL-2R levels as a diagnostic tool in clinically diagnosed or biopsy-proven sarcoidosis patients as subjects and the control group with non-sarcoidosis patients were included. Studies done in pulmonary and extra-pulmonary sarcoidosis patients were included. Studies without a control group or addressing only the prognostic performance of the sIL-2R levels were excluded. Studies with less than five patients, including case reports and case series, were excluded. Secondary screening of the included articles was done by two independent authors reviewing the full text (SG and RPP), and the data were extracted. The consensus of the authors resolved any discrepancies.

Further, the reference lists from the retrieved articles were also checked to avoid missing any important studies. The Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool was used to assess the quality of included studies. Two independent authors did the quality assessment.

Data extraction

The data was extracted to a Microsoft Excel sheet which included the following variables: type of study, number of assessed patients, number of patients included in sarcoidosis group and control group with non-sarcoidosis patients, age, gender, number of patients with pulmonary and extra-pulmonary sarcoidosis, number of patients with a positive sIL-2R in sarcoidosis and non-sarcoidosis group, sensitivity(%), specificity (%), positive and negative predictive value(%).

Statistical analysis

Forest plots were constructed using a random effect model depicting pooled sensitivity, specificity, positive predictive value, negative predictive value,

and diagnostic accuracy. The summary ROC curve was drawn with the calculated area under the curve. Heterogeneity was assessed and reported in I2 and τ2. Data were analyzed using R V.4.0.3.

Results

After a literature search, there were a total of 796 studies imported from all sources. After removing the duplicate studies, 396 studies were reviewed for abstract screening. Further, 365 studies were excluded on primary screening based on the inclusion and exclusion criteria defined above, and 31 were reviewed for secondary screening (Figure 1). We selected 10 studies that fulfilled the inclusion criteria, 5 of which were done in patients with uveitis (Table 1). The cumulative sample size was 1477, with 592 in the sarcoidosis group and 885 in the non-sarcoidosis group. Pooled sensitivity and specificity of sIL-2 receptor levels were 0.88 (95% CI 0.75-0.95) and 0.87 (95% CI 0.73-0.94), respectively. Pooled negative predictive value (NPV) and positive predictive value (PPV) were 0.91 (95% CI 0.77-0.97) and 0.85 (95% CI 0.59-0.96) respectively, with a diagnostic accuracy of 0.86 (95% CI 0.71-0.93) (Table 2). The area under the receiver operating characteristic summary curve was 0.78.

Additionally, we performed a subgroup analysis of the studies looking at the utility of sIL-2R in patients with uveitis to specifically diagnose ocular

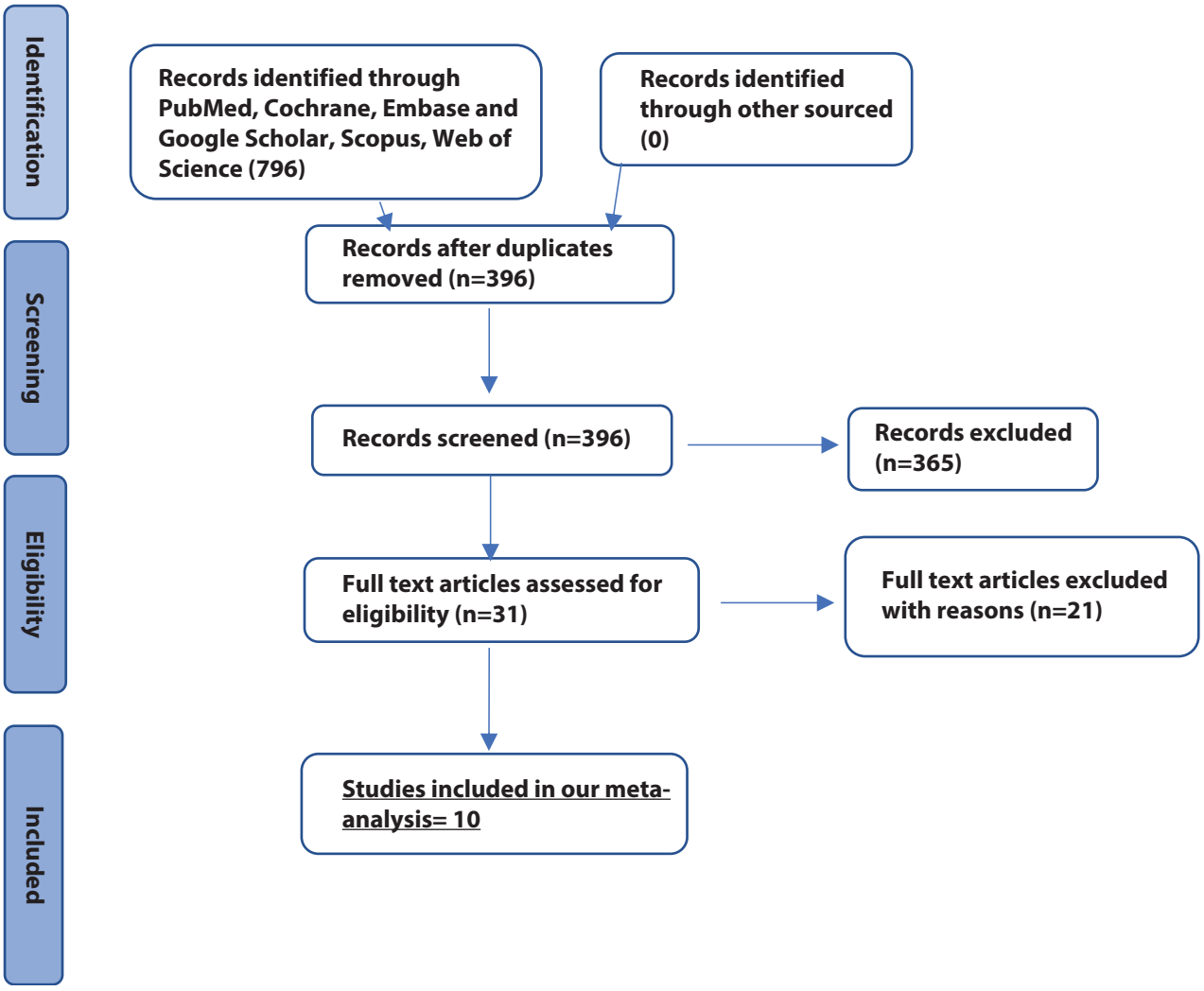

Figure 1. PRISMA flow-chart of inclusion and exclusion of studies in the review.

Table 1. Summary of the included studies.

	Author	Patient Population	Diagnosis of Sarcoidosis	Type of Study	IL-2 level in patients with sarcoidosis (pg/ml)	Optimal cutoff suggested (pg/ml)
1	**Groen-Hakan**(8)	Uveitis (sarcoidosis and non-sarcoidosis)	By IWOS criteria	Retrospective	Mean (SD) 6047 (2533)	4000
2	**Suzuki**(9)	Uveitis (sarcoidosis and non-sarcoidosis)	By IWOS criteria	Retrospective	NA	3487
3	**Schimmelpennink**(10)	Sarcoidosis with and without extra-pulmonary involvement	By ERS/ATS/ WASOG guidelines	Retrospective	5534 (1351 – 55000)	2300
4	**Eurelings**(11)	Immunology clinic: Sarcoidosis and non-sarcoidosis (uveitis of unknown origin, NSIP, SLE, Asthma, RA, ocular vasculitis, COPD	By ERS/ATS/ WASOG guidelines	Prospective	6100 (4500 – 9850)	3550
5	**Fagyas**(12)	Sarcoidosis	By ERS/ATS/ WASOG guidelines	Retrospective	740 (420-1140)	6823
6	**Gundlach**(13)	Uveitis (sarcoidosis and non-sarcoidosis)	By IWOS criteria	Retrospective	11593 (5150 – 102592)	NA
7	**Uysal**(14)	Chronic active(20) and inactive sarcoidosis(39) and healthy subjects	By ERS/ATS/ WASOG guidelines	Retrospective	7000 (5500 – 8500)	5810
8	**Ishihara**(15)	Uveitis (sarcoidosis and non-sarcoidosis)	By IWOS criteria	Retrospective	7385 ± 4310	4805
9	**Unal**(16)	Uveitis (sarcoidosis and non-sarcoidosis)	By IWOS criteria	Retrospective	NA	3154
10	**Bons**(17)	Sarcoidosis	By ERS/ATS/ WASOG guidelines	Retrospective	5592 (3872 – 7606)	4558

Table 2. Summary of the included studies, with first author name, year when article was published (Year), total number of included study subjects (Total), subjects with sarcoidosis (Ns), Subjects without sarcoidosis (Nns), true positives (TP), True negatives (TN), false positives (FP), false negatives (FN), calculated sensitivity and specificity, positive predictive values (PPV), and negative predictive values (PPV).

S.No	Author	Year	Total	Ns	Nns	TP	TN	FP	FN	Sensitivity	Specificity	PPV	NPV
1	**Groen-Hakan**	2017	249	37	212	37	212	119	9	0.81	0.64	0.24	0.96
2	**Suzuki**	2020	170	79	91	79	91	15	15	0.84	0.86	0.84	0.86
3	**Schimmelpennink**	2020	174	104	70	104	70	0	5	0.95	1	1	0.93
4	**Eurelings**	2019	189	101	88	101	88	16	14	0.88	0.85	0.86	0.86
5	**Fagyas**	2019	104	69	35	69	35	13	64	0.52	0.73	0.84	0.35
6	**Gundlach**	2016	247	42	205	42	205	13	1	0.98	0.94	0.76	1
7	**Uysal**	2018	84	59	25	59	25	0	0	1	1	1	1
8	**Ishihara**	2020	126	52	74	52	74	6	23	0.69	0.93	0.9	0.76
9	**Unal (Letter to the editor)**	2018	64	14	50	14	50	33	1	0.92	0.6	0.3	0.98
10	**Bons**	2007	70	35	35	35	35	26	21	0.62	0.57	0.57	0.63

sarcoidosis. In our analysis of the five studies (n=856), our pooled sensitivity was 0.86 (95% CI 0.73-0.93) and specificity 0.83 (95% CI 0.68-0.92). PPV was 0.64 (95% CI 0.35-0.86), and NPV was 0.95 (95% CI 0.84-0.99). On subgroup analysis of only the studies with non-ocular sarcoidosis (n=592), our pooled sensitivity was 0.89 (95% CI 0.61-0.98), and specificity was 0.94 (95% CI 0.57-0.99). Further, the PPV of sIL-2R was 0.96 (95% CI 0.63-1.00), and NPV was 0.84 (95% CI 0.53-0.96).

Discussion

Our systematic review and meta-analysis aimed to assess whether the serum levels of sIL-2R molecules could be used as a potential biomarker for diagnosing sarcoidosis in patients with suspected ocular and non-ocular sarcoidosis. The diagnostic performance of sIL-2R was also compared by pooling the sensitivity, specificity, positive predictive value, and negative predictive values.

A positive correlation between sIL-2R levels with disease activity in sarcoidosis was demonstrated by Oswald-Richter et al. in 2013 (6). On similar grounds, Gungor et al. observed that elevated sIL-2R levels were associated with extra-pulmonary involvement (7). Since then, multiple small-scale studies have looked to demonstrate the diagnostic performance of this biomarker. However, these studies primarily suffered from small sample sizes. sIL-2R levels showed potential as a biomarker with good diagnostic performance in these studies. Our cumulative review included ten studies and 1477 patients. The diagnosis of sarcoidosis in five of these included studies was based on the ERS/ATS/WASOG guidelines (8), and the other five studies diagnosed intraocular sarcoidosis based on IWOS guidelines (9). (Table 1)

Our analysis indicates that sIL-2R levels have a pooled sensitivity of 88% and a specificity of 87%. The previously proposed biomarkers, such as ACE levels, have demonstrated sensitivity and specificity of 62% and 76%, respectively, in a cohort study (10). The area under the ROC curve is 0.78, acceptable for its use as a diagnostic test in the clinical setting. Serum chitotriosidase is another promising marker in diagnosing sarcoidosis, with a sensitivity of 82.5% and specificity of 70% (11). Enyedi et al. showed the combined application of ACE and chitotriosidase analysis improved the diagnosis of sarcoidosis with a sensitivity of 90.5% and specificity of 79.3% (12). The potential of sIL-2R combined with other biomarkers for diagnostic potential has not been extensively studied. In patients with clinically suspicious sarcoidosis, an elevated sIL-2R level has a high positive predictive value of up to 91%. The cost of testing serum sIL-2R level (~500$) is higher than serum ACE level (~50$). However, given the increased sensitivity of sIL-2R, it may allow clinicians to avoid additional costs of radiological and invasive testing (10). Serum sIL-2R testing is performed with the sandwich ELISA method, which requires standard laboratory equipment, which may make it more readily available in the future with increasing demand. Based on these findings, we believe that sIL-2R can be a useful serum biomarker for suspected cases of sarcoidosis. It may be of value in patients who are hesitant to undergo invasive testing.

The primary limitation of our study is the heterogeneity in the patient population and control groups included in the analyses. The sample sizes of the included studies varied from 64-249, and the study population ranged from patients with ocular sarcoidosis to patients with chronic inactive sarcoidosis. This heterogeneity was also demonstrated in the cutoff of sIL-2R levels used in the studies, which varied from 2300-5800 pg/ml. Since there is no diagnostic gold standard for sarcoidosis, what was considered positive cases in these studies also varied greatly, with not all patients having biopsy-proven sarcoidosis. Hence, even though our observations show great promise for using sIL-2R in a clinical setting, the diagnostic performance of this marker will need to be reassessed in a large-scale study. Levels of sIL-2R can also be affected by factors such as renal function; hence, diagnostic interpretation of these results in a clinical setting should also be cautiously approached (13). Additional factors that would have affected the levels include the variations in the laboratory methods used to assess the sIL-2R levels.

Conclusion

Our meta-analysis showed that in addition to its utility as a marker of sarcoidosis disease activity, sIL2R has high diagnostic accuracy. Despite the limitations of the heterogenous sarcoidosis population and different sIL-2R cutoffs, our results suggest that sIL-2R can potentially be a clinically relevant biomarker in patients with a high suspicion of sarcoidosis to aid in diagnosis.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangement, etc.) that might pose a conflict of interest in connection with the submitted article

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Supplementary files

Figure S1. Forest plots for analysis of all included studies.

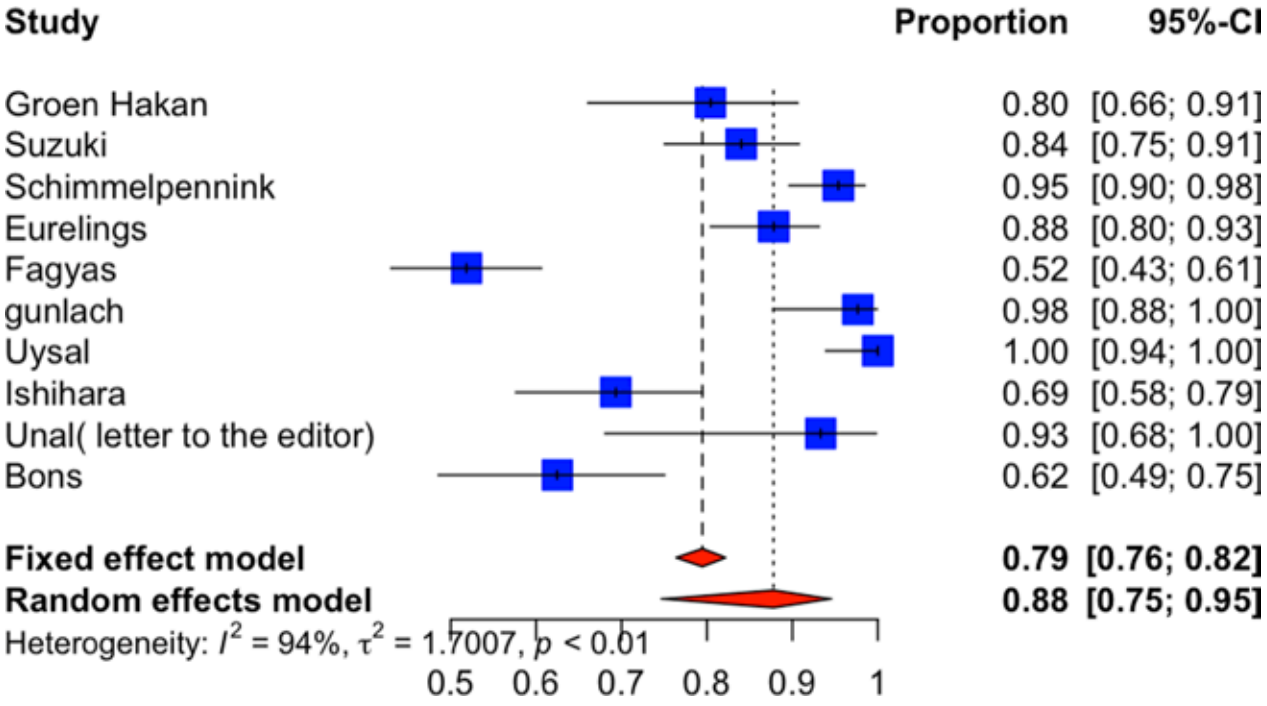

Figure S1a. Sensitivity

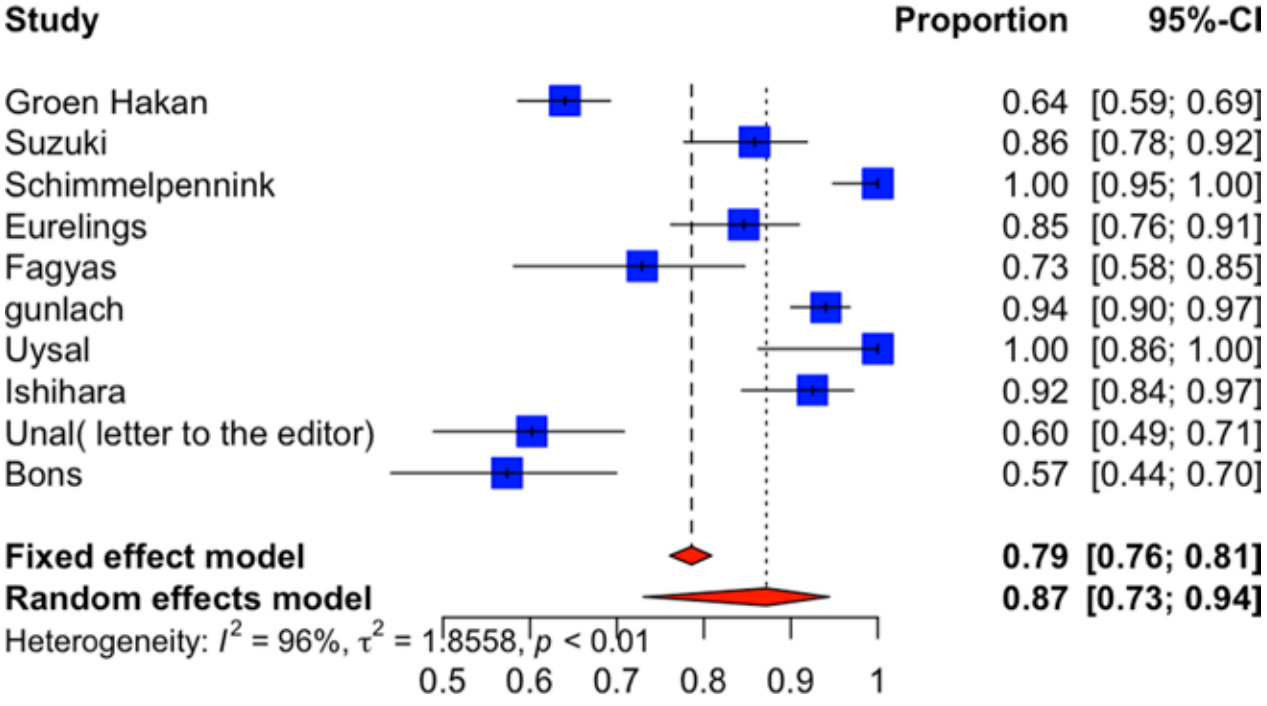

Figure S1b. Specificity

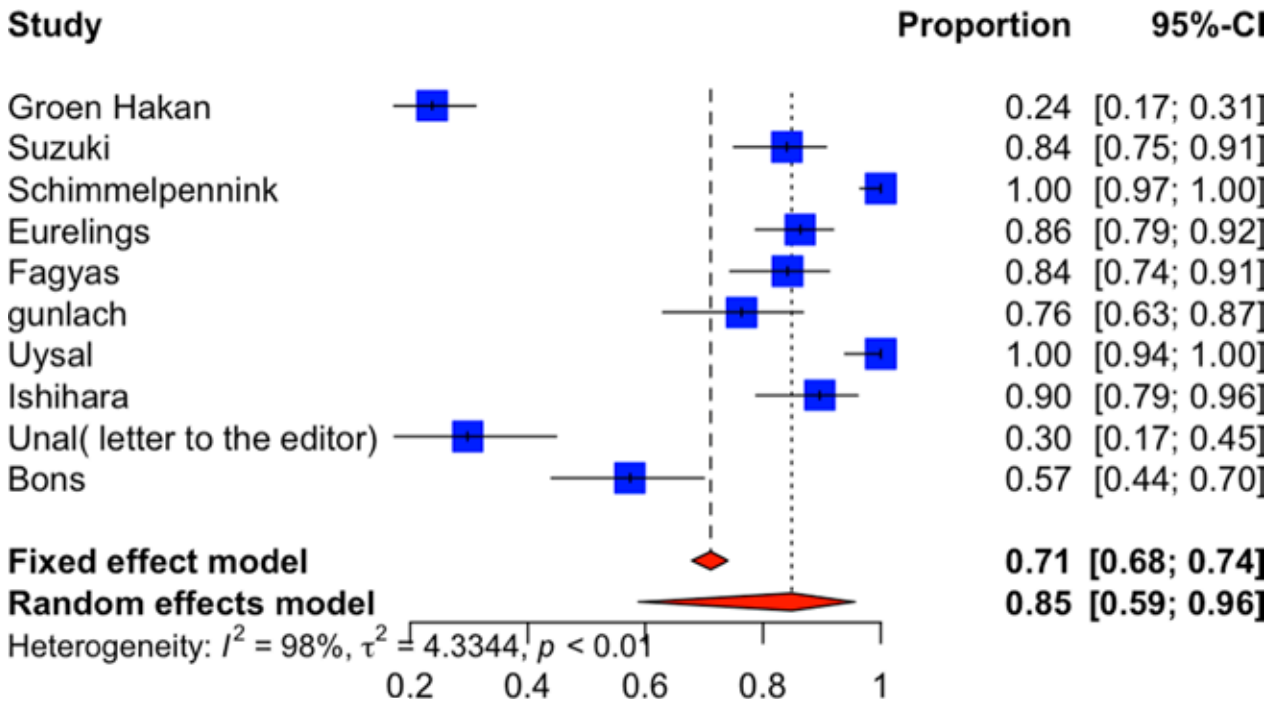

Figure S1c. Positive Predictive Value

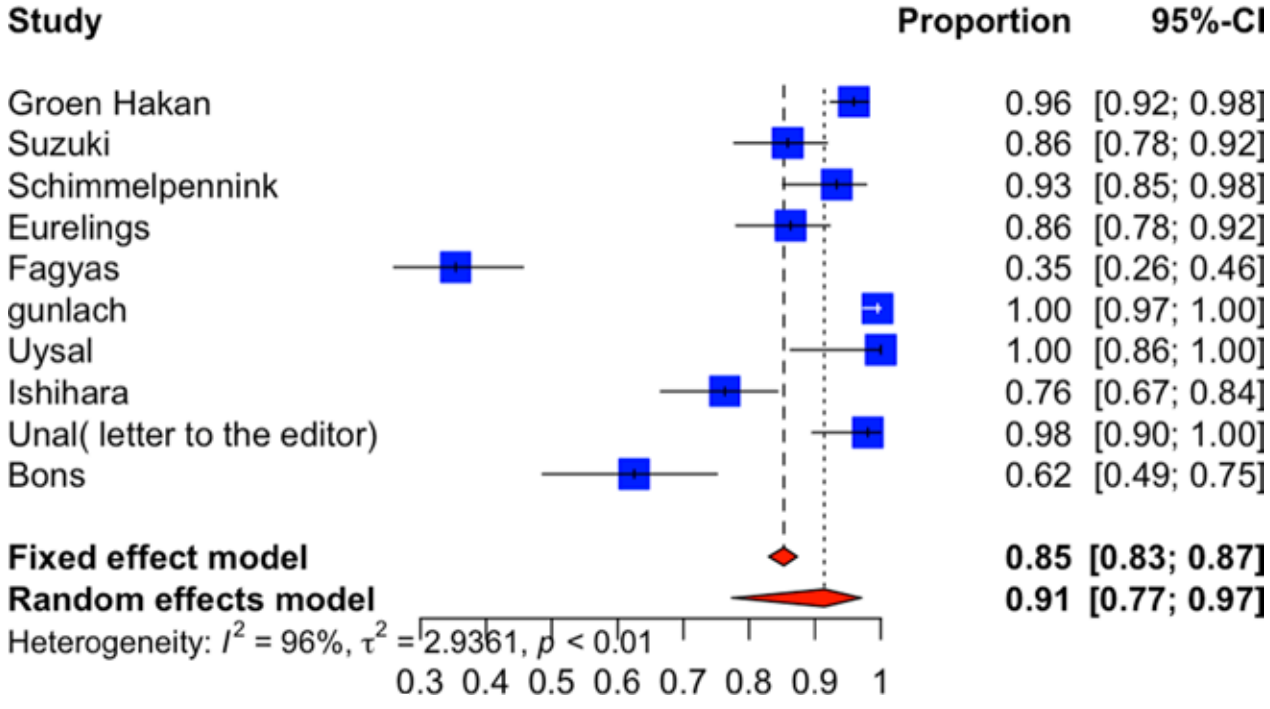

Figure S1d. Negative Predictive Value

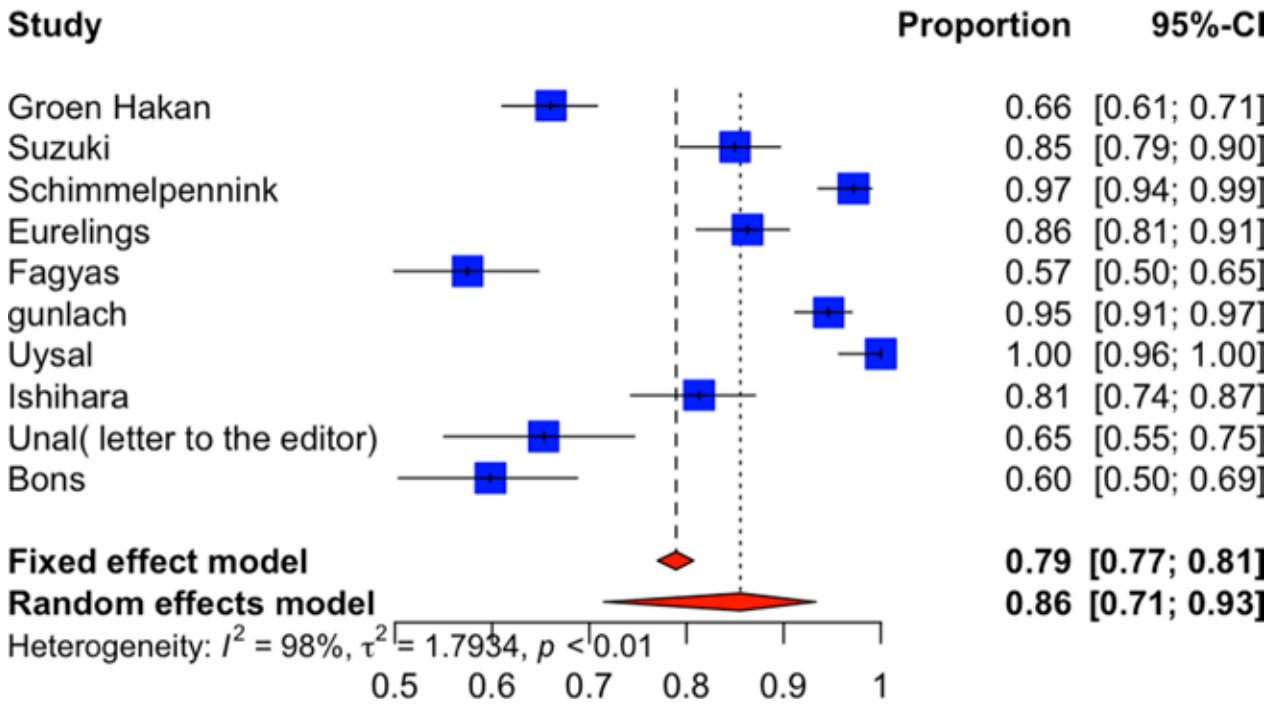

Figure S1e. Diagnostic Accuracy

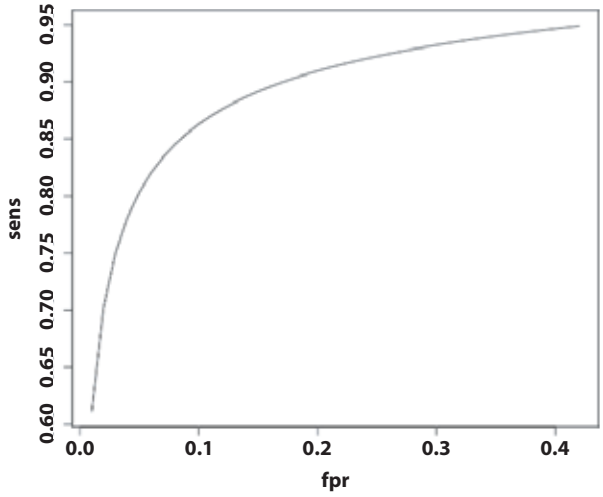

Figure S1f. Moses-Shapiro-Littenberg SROC curve (Intercept 3.10, Slope 0.57)

Figure S2. Forest plots for analysis of all studies with ocular sarcoidosis per IWOS guidelines.

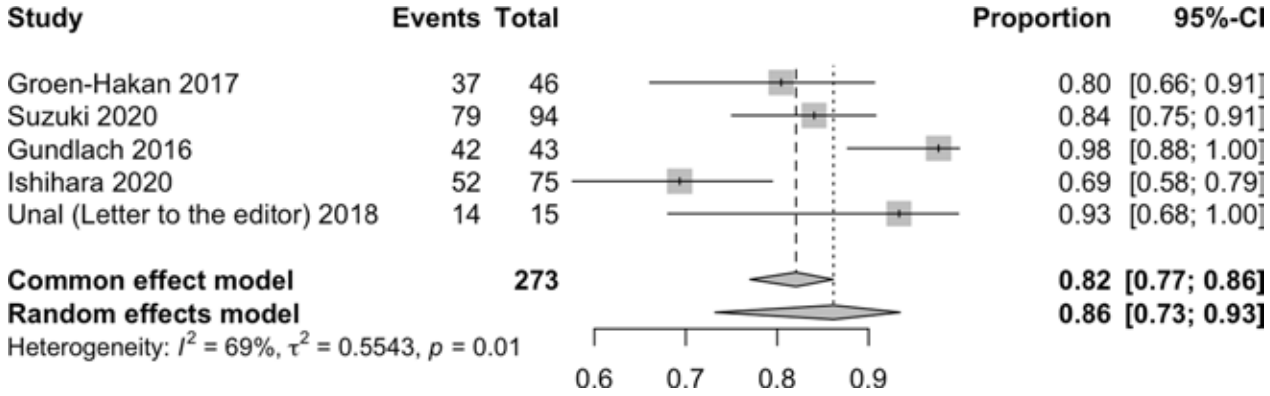

Figure S2a. Sensitivity

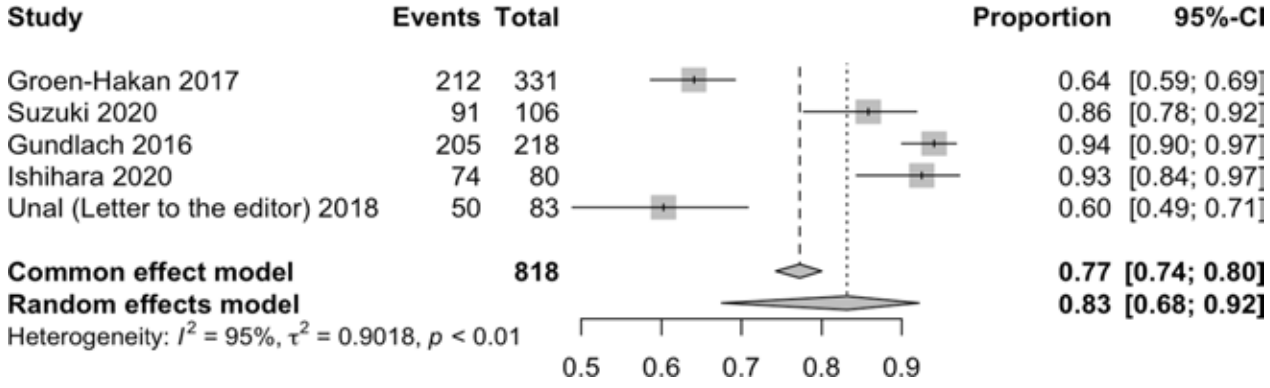

Figure S2b. Specificity

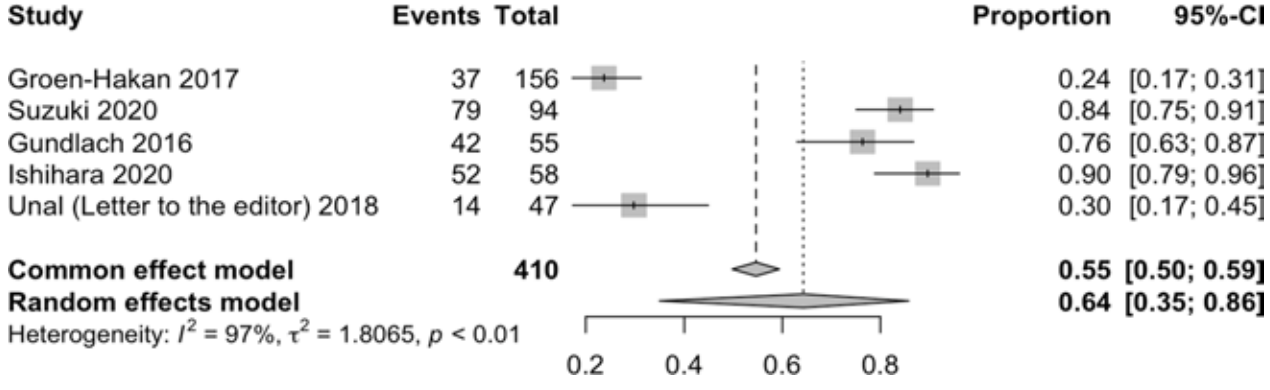

Figure S2c. PPV

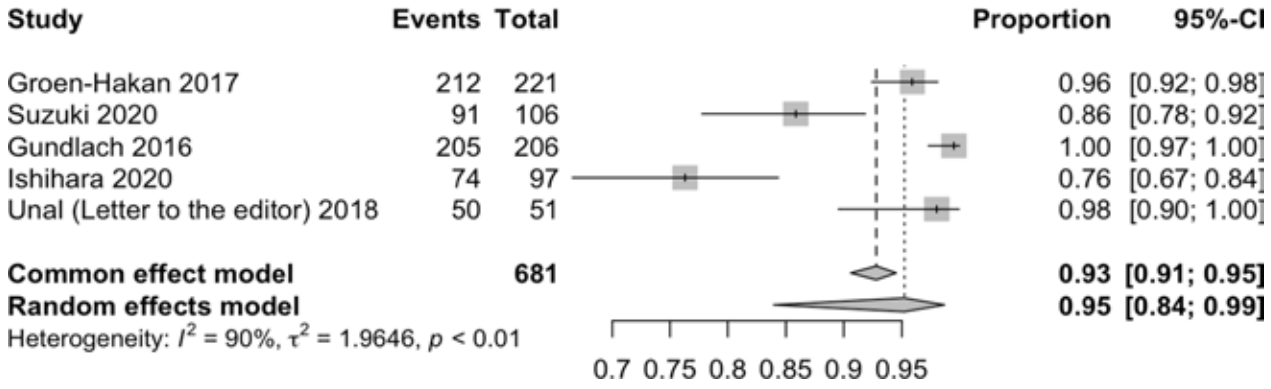

Figure S2d. NPV

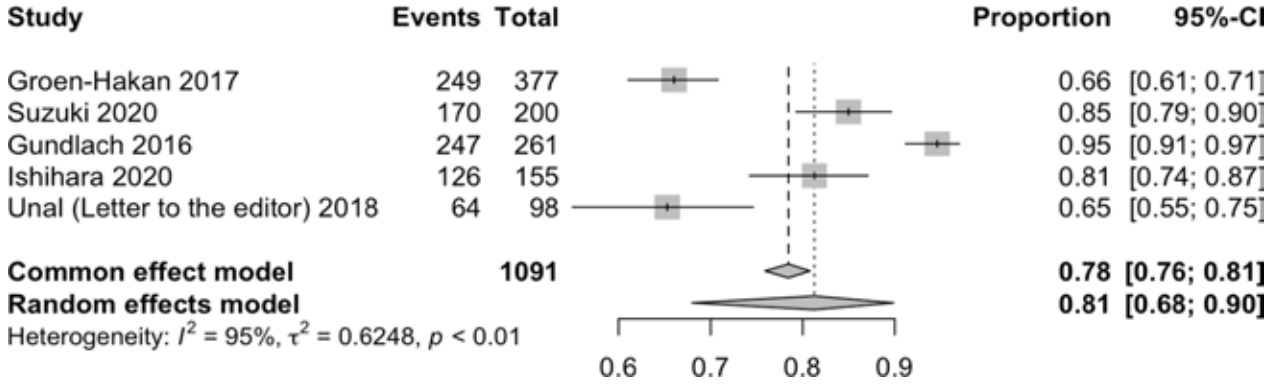

Figure S2e. Diagnostic accuracy

Figure S3. Forest plots for analysis of all studies with sarcoidosis per WASOG guidelines.

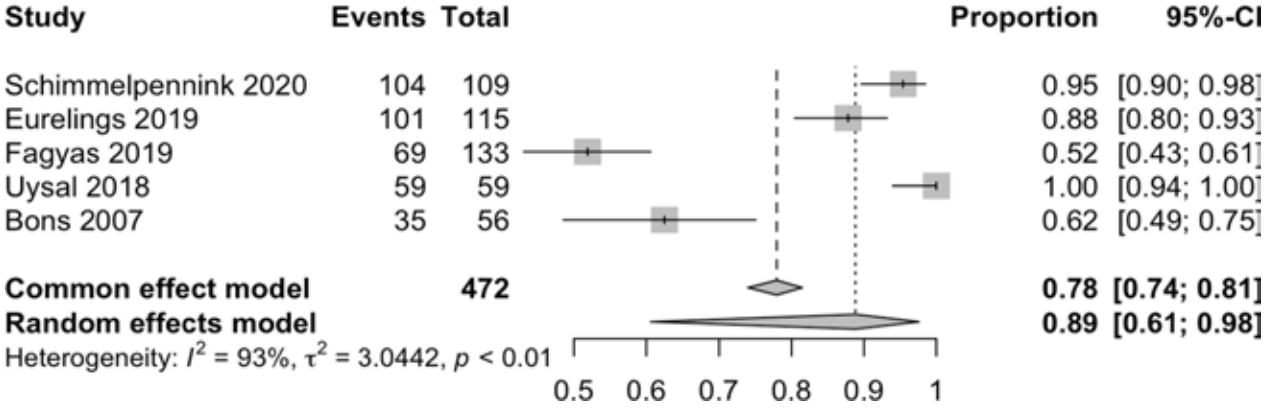

Figure S3a. Sensitivity

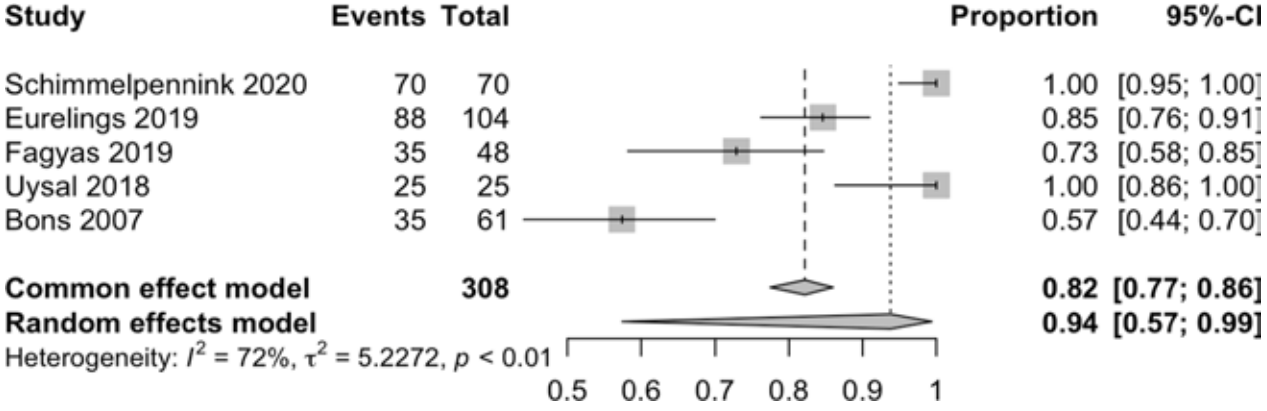

Figure S3b: Specificity

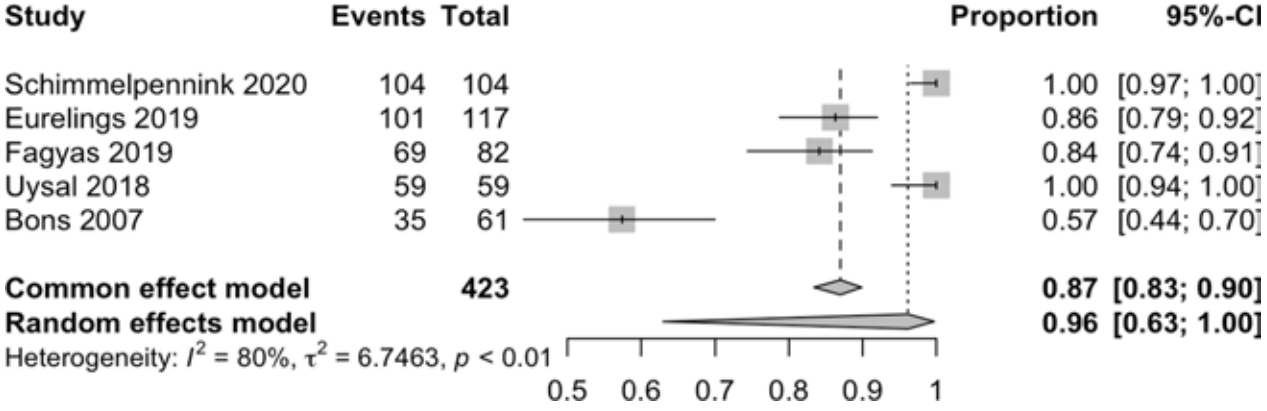

Figure S3c. PPV

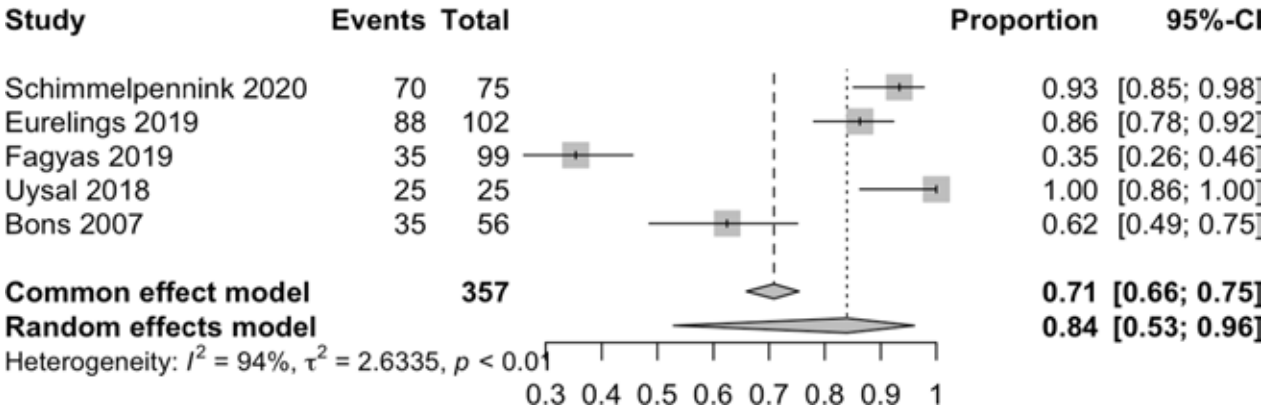

Figure S3d. NPV

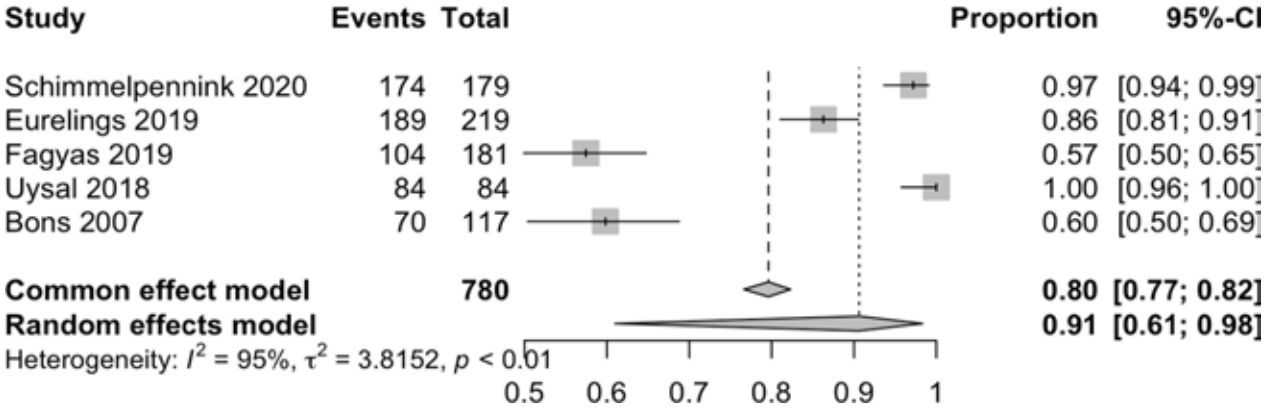

Figure S3e. Diagnostic accuracy