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Accuracy of the No-Biopsy Approach for the Diagnosis of Celiac Disease in Adults: A Systematic Review and Meta-Analysis

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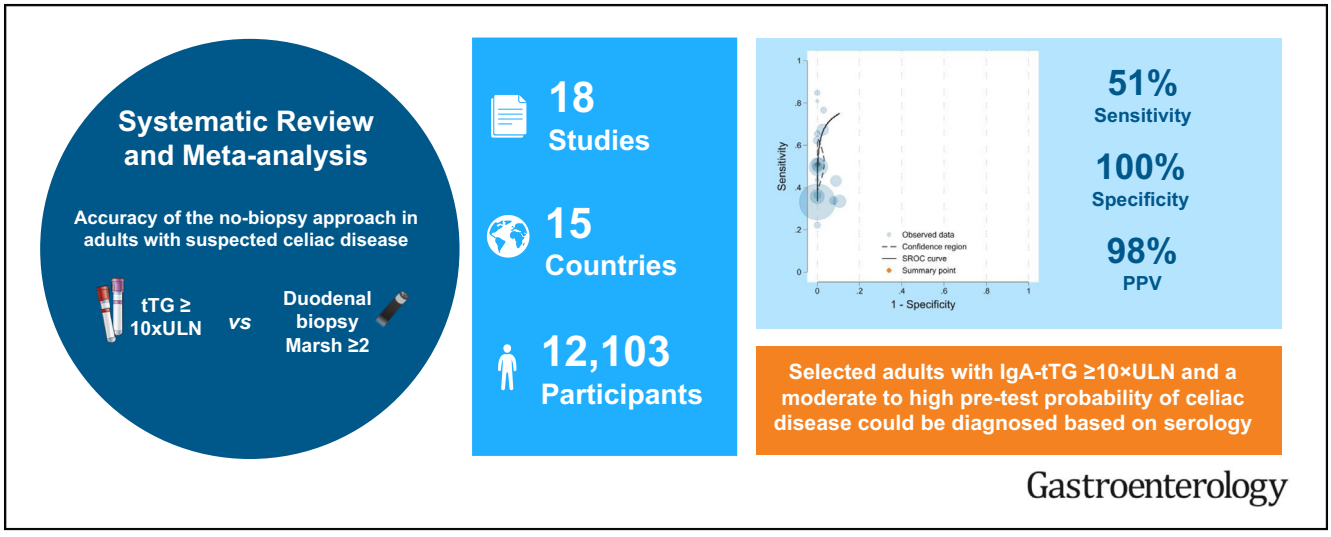
This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e9. Learning Objective: Upon completion of this CME activity, successful learners will be able to apply evidence-based strategies for the diagnosis of celiac disease in adults, including the implementation of the no-biopsy approach in different common clinical scenarios.



See editorial on page 557.

BACKGROUND & AIMS: Current international guidelines recommend duodenal biopsies to confirm the diagnosis of celiac disease in adult patients. However, growing evidence suggests that immunoglobulin A (IgA) anti-tissue transglutaminase (tTg) antibody levels ≥10 times the upper limit of normal (ULN) can accurately predict celiac disease, eliminating the need for biopsy. We performed a systematic review and meta-analysis to evaluate the accuracy of the no-biopsy approach to confirm the diagnosis of celiac disease in adults. **METHODS:** We systematically searched MEDLINE, EMBASE, Cochrane Library, and Web of Science from January 1998 to October 2023 for studies reporting the sensitivity and specificity of IgA-tTG ≥10×ULN against duodenal biopsies (Marsh grade ≥2) in adults with suspected celiac disease. We used a bivariate random effects model to calculate the summary estimates of sensitivity, specificity, and positive and negative likelihood ratios. The positive and negative likelihood ratios were used to calculate the positive predictive value of the no-biopsy approach across different pretest probabilities of celiac disease. The methodological quality of the included studies was evaluated using the QUADAS-2 tool. This study was registered with PROSPERO, number CRD42023398812. **RESULTS:** A total of 18 studies comprising 12,103 participants from 15 countries were included. The pooled prevalence of biopsy-proven celiac disease in the included studies was 62% (95% confidence interval [CI], 40%–83%). The proportion of patients with IgA-tTG ≥10×ULN was 32% (95% CI, 24%–40%). The summary sensitivity of IgA-tTG ≥10×ULN was 51% (95% CI, 42%–60%), and the summary specificity was 100% (95% CI, 98%–100%). The area under the summary receiver operating characteristic curve was 0.83 (95% CI, 0.77 – 0.89). The positive predictive value of the no-biopsy approach to identify patients with celiac disease was 65%, 88%, 95%, and 99% if celiac disease prevalence was 1%, 4%, 10%, and 40%, respectively. Between-study heterogeneity was moderate (I^2 =30.3%), and additional sensitivity

analyses did not significantly alter our findings. Only 1 study had a low risk of bias across all domains. **CONCLUSION:** The results of this meta-analysis suggest that selected adult patients with IgA-tTG ≥10×ULN and a moderate to high pretest probability of celiac disease could be diagnosed without undergoing invasive endoscopy and duodenal biopsy.

Keywords: Adult; Biopsy; Celiac Disease; Humans; Immunoglobulin A; Transglutaminases.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

The diagnosis of celiac disease in adults currently involves a 2-step process, starting with the detection of tissue transglutaminase antibodies and/or serum endomysial antibodies, followed by a confirmatory endoscopy and duodenal biopsy. Because of the increased accuracy of serological tests, pediatric guidelines adopted a no-biopsy approach, whereby children with immunoglobulin A–tissue transglutaminase levels ≥10 times the upper limit of normal and positive endomysial antibodies can be diagnosed with celiac disease without biopsy. However, applying this no-biopsy approach to diagnose adult patients with celiac disease is highly controversial.

NEW FINDINGS

In a meta-analysis of 18 studies with >12,000 adult participants, we found that immunoglobulin A–tissue transglutaminase levels ≥10 times the upper limit of normal are highly indicative of celiac disease in adult patients referred to secondary care with a 100% specificity and a positive predictive value of 98%. The predictive value of the no-biopsy approach varies according to the prevalence of celiac disease in the studied population.

LIMITATIONS

All studies were conducted in secondary and tertiary care settings, and results may not be generalizable to primary care.

CLINICAL RESEARCH RELEVANCE

The no-biopsy approach could lead to a shorter time to diagnosis, increased patient satisfaction, and reduced health care costs.

BASIC RESEARCH RELEVANCE

Future studies could focus on evaluating the diagnostic accuracy of the no-biopsy approach in patients with a low-pretest probability of celiac disease in primary care settings and should adhere to standardized reporting guidelines to minimize the risk of bias.

Celiac disease is a common autoimmune disorder characterized by an immunological response to dietary gluten in genetically susceptible individuals.[1] Although it is estimated that celiac disease affects nearly 60 million people worldwide, most patients remain undiagnosed, misdiagnosed, or experience significant diagnostic delays.[2] Undiagnosed celiac disease is associated with significant morbidity, reduced quality of life, and serious long-term complications such as increased risks of osteoporosis, cardiovascular diseases, and cancers.[1,3] Currently, the diagnosis of celiac disease in adults is based on a combination of serological testing followed by endoscopy and duodenal biopsy to confirm the diagnosis.[4] However, this approach is invasive, expensive, and often associated with long waiting times, which can delay diagnosis and treatment.

In recent years, there have been significant advancements in the diagnostic accuracy of serological tests for celiac disease. These have led to a step change in the pediatric guidelines, whereby children with immunoglobulin A (IgA) anti-tissue transglutaminase (tTG) antibody levels ≥10 times the upper limit of normal (ULN) along with positive endomysium antibodies (EMA) can be diagnosed with celiac disease without a confirmatory duodenal biopsy.[5] A subsequent prospective multicenter study confirmed the reliability of the no-biopsy approach to diagnose celiac disease in children with a positive predictive value (PPV) of >99%.[6]

Despite the evidence supporting the no-biopsy approach in children, applying the same approach to adults remained controversial. Thus, current international guidelines still recommend duodenal biopsies to confirm the diagnosis of celiac disease in adults.[7–9] The aim of this systematic review and meta-analysis was to evaluate the accuracy of the no-biopsy approach in adult patients with suspected celiac disease.

Methods

Registration of Review Protocol

This study was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for diagnostic test accuracy (PRISMA-DTA) guidelines (Supplementary Materials),[10] based on a priori registered protocol (PROSPERO; CRD42023398812).

Search Strategy and Study Selection

We systematically searched MEDLINE, EMBASE, Cochrane Library, and Web of Science for relevant studies from January 1998 to the April 2, 2023, to identify studies evaluating the diagnostic performance of IgA-tTG ≥10×ULN compared with duodenal biopsies in adult patients (age ≥16 years) with suspected celiac disease. We restricted the literature search to start from 1998 following the publication of a landmark study by Dieterich et al,[11] which defined how celiac disease is diagnosed in children and adults using IgA-tTG. There were no language restrictions. The literature search was repeated on the October 3, 2023, with a refined search strategy to ensure that no relevant studies have been missed. Two reviewers (Mohamed G. Shiha and Nicoletta Nandi) independently

Abbreviations used in this paper: **CI, confidence interval; EMA, endomysium antibodies; IgA, immunoglobulin A; NPV, negative predictive value; PPV, positive predictive value; tTG, tissue transglutaminase; ULN, upper limit of normal.**

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screened the titles and abstracts of all citations against the inclusion criteria. The full-text articles of all potentially relevant studies were retrieved and further evaluated in more detail using standardized forms. We also manually searched the bibliographies of the relevant reviews and included studies for any additional eligible studies. The full search strategy is shown in the Supplementary Materials.

We included studies that met the following criteria: (1) included adult patients (age ≥16 years) at risk of celiac disease, (2) reported IgA-tTG cutoff levels of ≥10×ULN, (3) celiac disease diagnosed based on a Marsh ≥2 lesions on duodenal biopsy, (4) published in full-text articles. We excluded studies that included only pediatric patients, conference abstracts, case reports, reviews, editorials, and practice guidelines. Studies with insufficient information to create 2 × 2 contingency tables for the diagnostic accuracy of IgA-tTG ≥10×ULN were also excluded.

Data Extraction

Two reviewers (Mohamed G. Shiha and Nicoletta Nandi) extracted the data from eligible studies using a standardized Excel spreadsheet. The following data were extracted, where available: study country, study design, study period, inclusion criteria, participants' number and characteristics, the prevalence of celiac disease, number of true positives, false positives, false negatives, and true negatives. Disagreements between reviewers were resolved by consensus.

Risk of Bias and Quality Assessment

The risk of bias assessment was independently assessed by 4 reviewers using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS- 2) tool based on the following domains: patient selection, index test, reference standard, and flow and timing.[12] Studies that did not explicitly state whether consecutive or random sampling was made were judged as having a high risk of bias in the patient selection domain of the QUADAS-2 tool. The index test domain of the QUADAS-2 tool was judged as unclear, if the authors did not provide sufficient details of the IgA-tTG assay used. The reference standard domain of the QUADAS-2 tool was judged as having a high risk of bias if the authors did not explicitly state whether duodenal biopsy was interpreted without knowledge of the IgA-tTG results. Finally, the flow and timing domain of the QUADAS-2 tool was judged to have an unclear risk of bias if the authors did not report the exact time interval between IgA-tTG and duodenal biopsy. The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) criteria was used to assess the quality of evidence.[13] Disagreements between reviewers were resolved by consensus.

Study Outcomes

The primary outcome of the meta-analysis was the diagnostic accuracy of IgA-tTG ≥10×ULN in identifying patients with celiac disease, compared with intestinal biopsy as the reference standard.

Data Synthesis and Statistical Analysis

The prevalence of celiac disease and proportion of patients with IgA-tTG ≥10×ULN in the included studies were pooled and estimated with 95% confidence interval (CI) using a random effects model. We used 2 × 2 tables to calculate the summary estimates of sensitivity, specificity, and positive and negative likelihood ratio of IgA-tTG ≥10×ULN using a bivariate random effects model. Summary estimates of the sensitivity and specificity of the included studies were presented in forest plots. A summary receiver operating characteristic curve was constructed and the area under the curve was calculated.[14]

The unconditional PPV and negative predictive value (NPV) were assessed based on a uniform prior distribution of celiac disease. However, the prevalence of celiac disease varies according the studied population, and it is estimated to be approximately 1% of the general population,[15] 4% of patients with irritable bowel syndrome type symptoms,[16] and 10% of people with a family history of celiac disease.[17] Therefore, we used these common pretest probabilities of celiac disease to estimate the posttest probabilities if the test is positive or negative, using Fagan's nomograms.[18]

We assessed heterogeneity by visual inspection of the forest plot, bivariate box plot, and using Cochran Q χ^2 test and the I^2 statistics.[19] To identify potential outliers and estimate the influence of individual studies, we used Cook's distance (Cook's D). In addition, we evaluated the risk of publication bias using Deek's funnel plot asymmetry test.[20] A P value of $< .05$ was considered statistically significant. All statistical analyses were performed with Stata version 17 (StataCorp, College Station, TX), using the "metaprop," "midas," and "metadta" commands.

Results

Study Selection and Characteristics

The search strategy identified 17,576 citations from 4 electronic databases, of which 82 articles appeared to be relevant and eligible for full-text screening (Figure 1). A total of 18 studies comprising 12,103 participants from 15 countries met the criteria for inclusion in the meta-analysis.[21–38] The main characteristics of the included studies are summarized in Table 1.

All the studies were conducted in secondary and tertiary care settings and excluded patients with known celiac disease or on a gluten-free diet. All studies included adult patients with suspected celiac disease who underwent serology and duodenal biopsy. The inclusion and exclusion criteria of each study are summarized in the Supplementary Materials. Three studies included repeated measurements of IgA-tTG assays across different commercial kits.[22,28,36] The PPV of IgA-tTG ≥10×ULN to identify patients with celiac disease was similar across the different IgA-tTG assays in all 3 studies. In our primary analyses, we included the Celikey IgA assay results as the shared assay among the 3 studies and reported the results of the other assays in separate sensitivity analyses. Three studies were published as letters,[23,31,32] including Sugai et al,[23,39] which was a post hoc analysis of an earlier study. We have decided to include these studies in our primary analysis and conducted a sensitivity analysis excluding them to estimate their influence on the results. The prevalence of biopsy-proven celiac disease in the included studies was 62% (95% CI, 40%–83%) with a high heterogeneity between studies (I^2 = 99.9%) (Supplementary Figure 1). The proportion of patients with IgA-tTG ≥10×ULN was 32% (95% CI, 24%–40%) with a high heterogeneity between studies (I^2 = 99.3%) (Supplementary Figure 2).

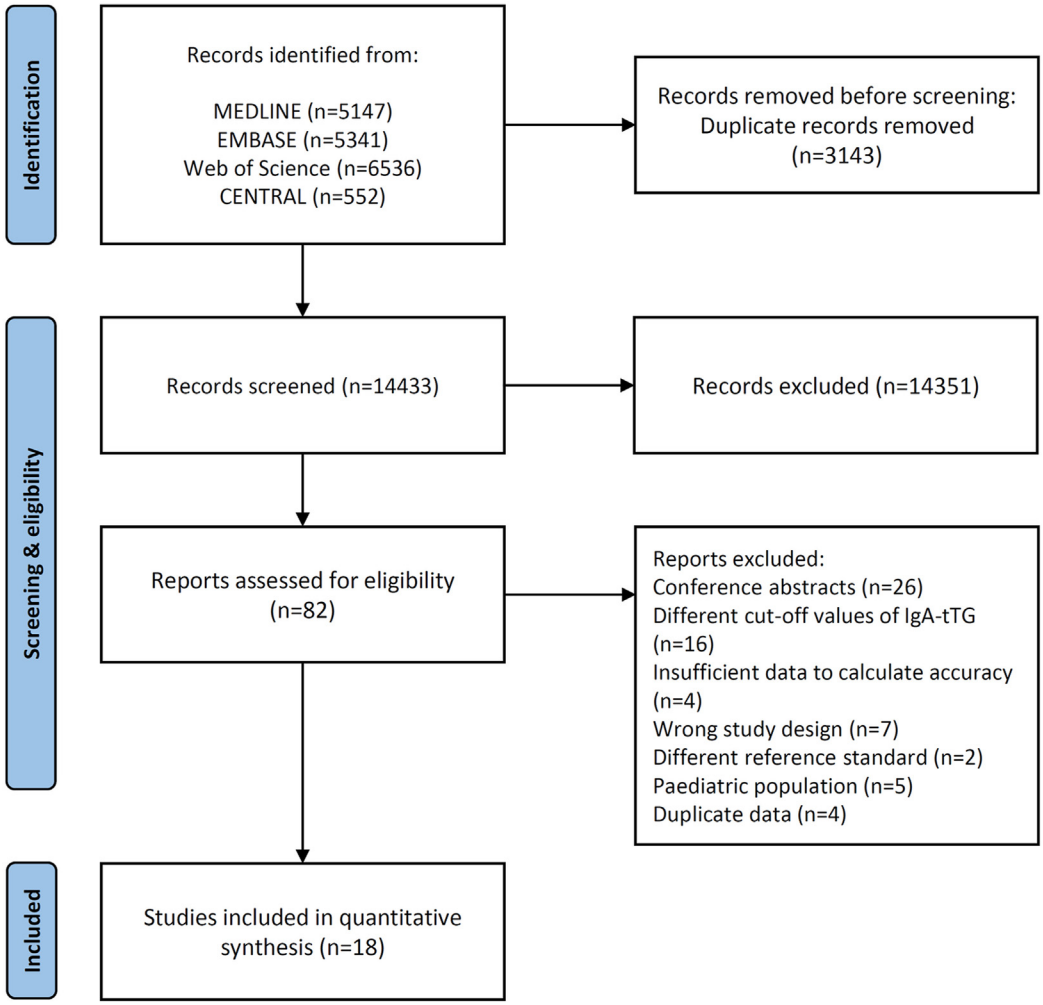

Figure 1. PRISMA flow diagram of study selection.

Diagnostic Performance of the No-Biopsy Approach

The summary sensitivity of IgA-tTG ≥10×ULN was 51% (95% CI, 42%–60%), and the summary specificity was 100% (95% CI, 98%–100%) for the diagnosis of celiac disease (Figure 2). The positive and negative likelihood ratios were 183.42 (95% CI, 30.1–1114.6) and 0.49 (95% CI, 0.34–0.59), respectively. The diagnostic odds ratio was 373 (95% CI, 60–2314). The area under the summary receiver operating characteristic curve was 0.83 (95% CI, 0.77–0.89) (Figure 3). The unconditional PPV was 98% (95% CI, 96%–99%), and the unconditional negative NPV was 62% (95% CI, 61%–63%) (Figure 4).

The PPV of the no-biopsy approach to identify patients with celiac disease was 65%, 88%, 95%, and 99% if celiac disease prevalence was 1%, 4%, 10%, and 40%, respectively (Figure 5). The prevalence of 40% represents the lower CI of the pooled prevalence from the included studies. The PPV and NPV of the no-biopsy approach across different celiac disease prevalences are shown in Supplementary Figure 3. The diagnostic accuracy results and downstream consequences of testing 4 hypothetical adult cohorts with different pretest probabilities of celiac disease are presented in absolute terms per 1000 patients tested in Supplementary Figure 4.[40]

Heterogeneity Assessment and Sensitivity Analyses

Between-study heterogeneity for sensitivity was high (I^2 = 92.3%), and there was low heterogeneity for specificity (I^2 = 1.5%). The generalized between-study heterogeneity was moderate (I^2 = 30.3%). The bivariate box plot showed that most studies clustered within the median distribution and 95% confidence bound of the data points, with only 2 outliers[27,29] (Figure 6). Further influence analysis using Cook's distance confirmed that both outlier studies had a significant influence on the results (Supplementary Figure 5). Excluding both outlier studies did not significantly alter the results with a summary sensitivity of 49% (95% CI, 42%–57%) and a summary specificity of 99% (95% CI, 98%–100%) (Supplementary Figure 6).

Sub-group analysis of 13 studies reporting Marsh 3 lesions on duodenal biopsies yielded similar diagnostic performance of IgA-tTG ≥10×ULN with a summary sensitivity of 51% (95% CI, 40%–62%) and summary specificity of 100% (95% CI, 98%–100%) (Supplementary Figures 7 and 8). Excluding the 3 studies published in letters did not significantly alter the results with a summary sensitivity of 54% (95% CI, 44%–63%) and a summary specificity of 100% (95% CI, 98%–100%) (Supplementary

Table 1. Study Characteristics

Author, year (Ref)	Country	Study design	Total participants	Patients with celiac disease	IgA-tTG assay
Hill et al, 2008[21]	UK	Single center, retrospective	146	139	Celikey ELISA (Phadia, Freiburg, Germany)
Oyaert et al, 2015[22]	Belgium	Single center, prospective	662	90	EliA Celikey IgA (Thermo Fisher, Uppsala, Sweden) & QUANTA Flash (Inova Diagnostics, San Diego, USA)
Sugai et al, 2015[23]	Argentina	Dual center, prospective	161	63	QUANTA Lite (Inova Diagnostic, San Diego, CA, USA)
Di Tola et al, 2016[24]	Italy	Single center, retrospective	671	633	QUANTA Lite (Inova Diagnostic, San Diego, CA, USA)
Previtali et al, 2018[25]	Italy	Single center, retrospective	549	199	QUANTA Flash (Inova Diagnostics, San Diego, USA)
Gülseren et al, 2019[26]	Turkey	Single center, prospective	21	39	SIEMENS BNProSpec device and Siemens serum IgA kit (Siemens, Munich, Germany)
Fuchs et al, 2019[27]	Finland	Multicenter, retrospective	5500	274	Celikey ELISA & QUANTA Flash
Ylönen et al, 2020[28]	Finland	Multicenter, retrospective	836	207	Multiple assays[a]
Sinha et al, 2020[29]	India	Single center, prospective	122	112	Celikey IgA Immunoassay (Thermo Fischer, Waltham, MA, USA)
Penny et al, 2021[30]	International[b]	Multicenter, prospective and retrospective cohorts	1417	861	Multiple assays[c]
Paul et al, 2021[31]	UK	Single center, retrospective	101	89	Not specified
Tashtoush et al 2021[32]	UK	Single center, retrospective	479	388	Not specified
Baykan et al, 2022[33]	Turkey	Single center, retrospective	269	77	ELISA kit (Orgentec, Mainz, Germany) and an Alisei QS (SEAC Group, Italy)
Johnston et al, 2022[34]	UK	Single center, retrospective	265	213	Orgentec IgA-tTG ELISA (Orgentec Diagnostika, Mainz, Germany) and QUANTA Flash tTG IgA assay (Inova-Werfen, San Diego, USA)
Beig et al, 2022[35]	New Zealand	Single center, retrospective	144	77	BioRad Autoimmune EIA Anti-tTG-IgA immunoassay
Castelijn et al, 2023[36]	Netherland	Multicenter, retrospective	89	85	Multiple assays[d]
Deane et al, 2023[37]	Ireland	Single center, retrospective	217	184	EliA Celikey IgA assay (Thermo Scientific, Uppsala, Sweden)
Ciacci et al, 2023[38]	International[e]	Multicenter, prospective	636	359	Multiple assays[f]

[a]Celikey (Phadia, Freiburg, Germany), Orgentec (ORG 540A, Orgentec Diagnostika, Mainz, Germany), Inova (QUANTA Lite h-tTG, Inova Diagnostics, San Diego, CA), and Eurospital (Eu-tTG, Trieste, Italy).
[b]UK, USA, Argentina, Iran, Netherlands, Italy, Romania, Turkey.
[c]ARUP Laboratories (Utah), QuantaLite (Inova Diagnostics, San Diego, CA), Eu- tTG (Eurospital, Italy), Euroimmune (Luebeck, Germany) and Celikey ELISA (Thermo Fisher, Freiburg, Germany).
[d]EliA Celikey IgA FEIA (Phadia AB, Thermo Fisher Scientific, Uppsala, Sweden), QUANTA Flash h-tTG IgA CLIA (Werfen/Inova Diagnostics), and Anti-Tissue Transglutaminase ChLIA (IgA) (EUROIMMUN Medizinische Labordiagnostika AG, Lübeck, Germany).
[e]Italy, UK, Spain, Netherland, Romania, Israel, New Zealand, Argentina, India.
[f]QUANTAFLASH, QUANTA Lite ELISA R-tTG IgA, QUANTA Lite ELISA h-tTG IgA, BioPlex 2200 system, Phadia, Diamicron, Multiplex CytoBead CeliAK, Eurospital, IDS Diagnostica, AESKULISA tTg-A, Orgentec Diagnostika, IDS iSYS laboratories, Diasorin Liaison XL, Invitrogen.

Figure 9).[23,31,32] Furthermore, there were no significant differences in the summary sensitivity and specificity between retrospective and prospective studies (Supplementary Figure 10). The results were also not significantly altered after sensitivity analyses using the different assays in Oyaert et al[22] (Supplementary Figure 11),

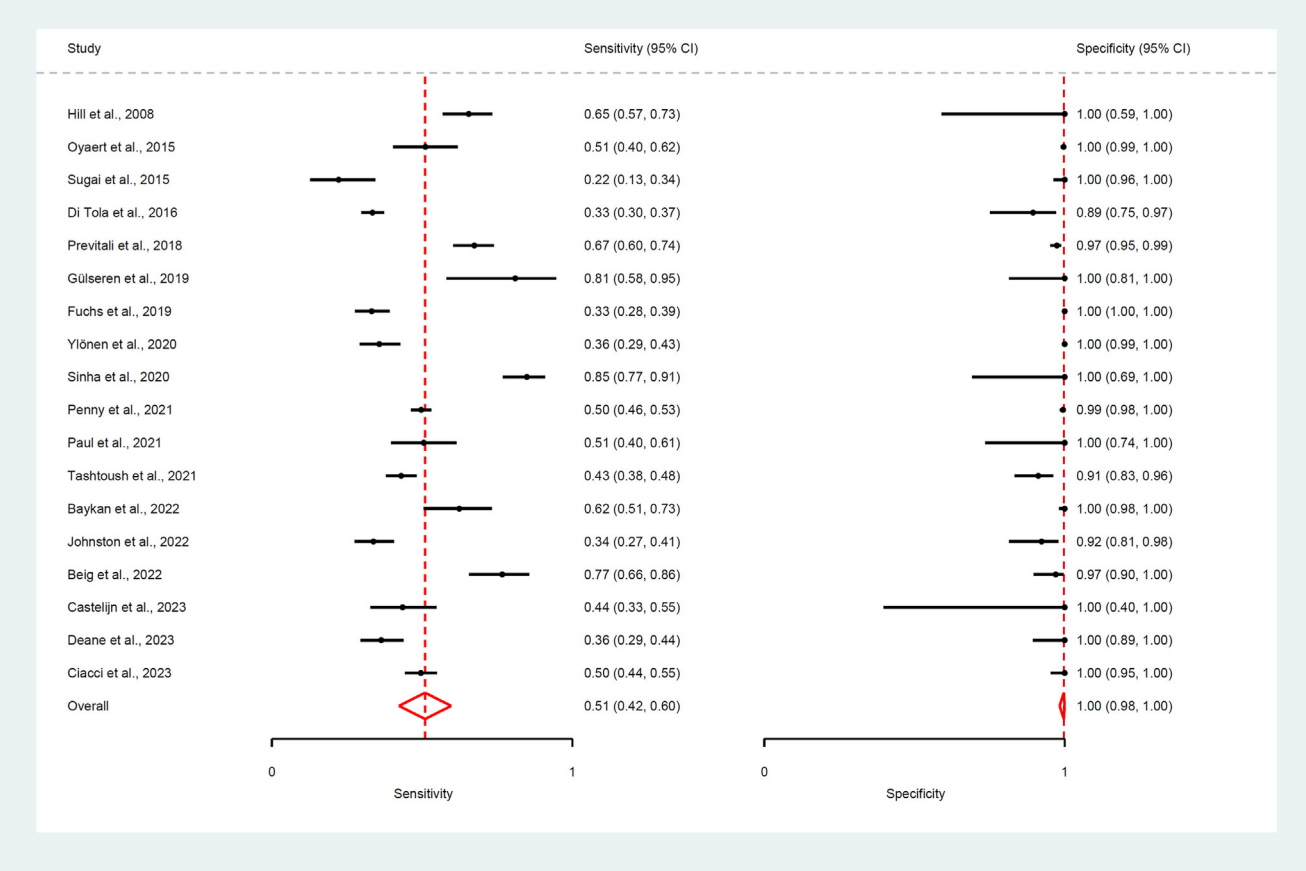

Figure 2. Forest plot of summary sensitivity and specificity of IgA-tTG ≥10×ULN to identify patients with celiac disease.

Ylönen et al[28] (Supplementary Figures 12–14), and Castelijn et al[36] (Supplementary Figure 15). There was no evidence of Deek's funnel plot asymmetry to suggest publication bias ($P = .05$) (Supplementary Figure 16).

Risk of Bias and Quality Assessment

The outcomes of the methodological quality assessment of the included studies using the QUADAS-2 tool are summarized in the Supplementary Materials. There was only 1 study with a low risk of bias in all domains.[25] However, there were no concerns regarding applicability as all the studies reflected real-life clinical practice. The overall certainty of evidence was downgraded to moderate because of serious risks of bias (Supplementary Table 1).

Discussion

This is the first systematic review and meta-analysis to evaluate the accuracy of the no-biopsy approach for the diagnosis of celiac disease in adults. A total of 18 studies with 12,103 participants from 15 countries were included in this meta-analysis. Summary data showed that IgA-tTG ≥10×ULN has an overall sensitivity of 51% (95% CI, 42%–60%) and an overall specificity of 100% (95% CI, 98%–100%) for detecting celiac disease. The PPV of IgA-tTG ≥10×ULN to identify patients with celiac disease was 98% (95% CI, 96%–99%); however, this high predictive value varied according to the pretest probability of celiac disease in the studied population. We provided PPV estimates of IgA-tTG ≥10×ULN for common pretest probabilities of celiac disease to aid clinicians and patients in reaching an informed decision on a no-biopsy diagnosis based on the best available evidence.

The results of this study demonstrate that the no-biopsy approach, which has been incorporated in pediatric practice to diagnose celiac disease for more than a decade, can be safely extrapolated to select adult patients in secondary care settings. This has significant implications for clinical practice by reducing the diagnostic delays, risks, and health care costs associated with endoscopy. In a recent study, we estimated that the cost of diagnosis in adults could be reduced by more than 75% if endoscopy and biopsy were avoided.[41]

Despite the consistent evidence supporting the no-biopsy approach in diagnosing adult patients with celiac disease, there have been some concerns regarding its applicability. One potential concern with relying on serology testing alone is the possibility of false-positive diagnosis of celiac disease.[9] This could lead to unnecessary dietary restriction and negative effects on patients' quality of life. Although our results did not show that the PPV of IgA-tTG ≥10×ULN to identify patients with celiac disease was 100%, it is important to note that no diagnostic test for celiac disease is 100% accurate, even duodenal biopsy, which is considered the gold standard. Studies have shown that adherence to recommended biopsy guidelines occurs in

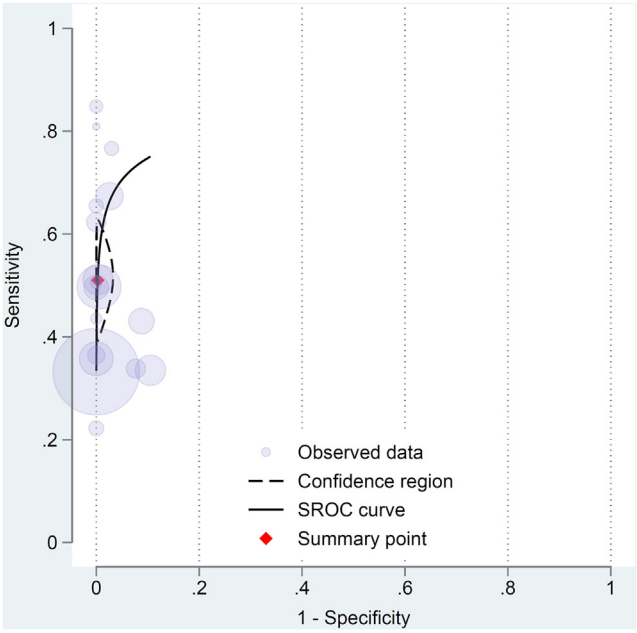

Figure 3. A summary receiver operating characteristic (SROC) plot of the study estimates of IgA-tTG ≥10×ULN sensitivity and specificity.

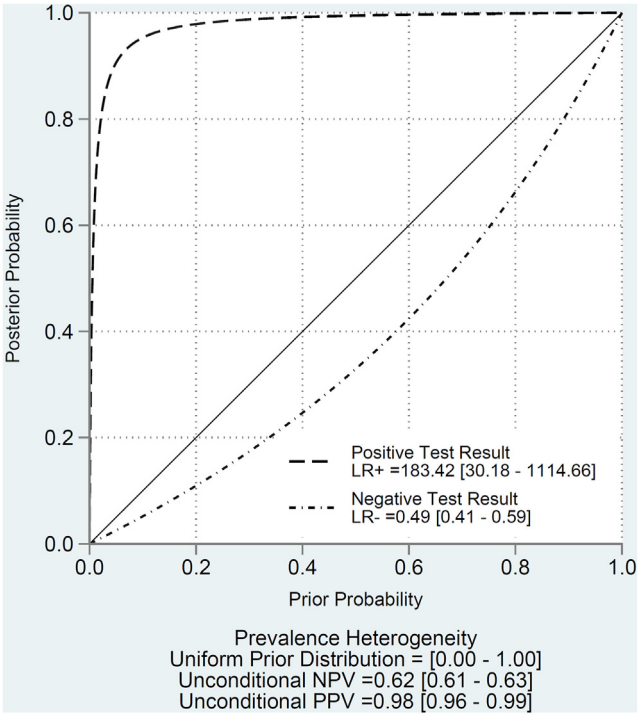

Figure 4. Probability modifying plot showing the unconditional PPV and NPV of IgA-tTG ≥10×ULN to identify patients with celiac disease. LR, likelihood ratio.

only 40% of cases,[42,43] indicating that the diagnosis could be missed despite duodenal sampling. Furthermore, interpretation of histopathological changes can be subjective and substantial interobserver variability exists between different pathologists.[6] Therefore, the results interpreted as "false-positive" serology could have been false-negative histology.[27] The no-biopsy diagnosis of celiac disease in patients with IgA-tTG ≥10×ULN could mitigate the risk of potential false-negative histology results. This is particularly relevant in cases in which the histopathological findings are not diagnostic for celiac disease due to inadequate sampling.

The lack of standardization of IgA-tTG assays across different laboratories is another concern.[44] However, studies directly comparing different IgA-tTG assays showed that a cutoff level ≥10×ULN had a consistent PPV for celiac disease close to 100%.[28,36] This is in line with our results showing high diagnostic performance of IgA-tTG ≥10×ULN across different commercial kits, laboratories, and countries. Yet, local validation of this pathway is recommended to ensure the accuracy and applicability of the no-biopsy approach. Concerns also have been raised regarding the possibility of missing concurrent pathology in patients avoiding endoscopy and biopsy. Although recent evidence suggests that patients with celiac disease, including older patients, had no significant co-pathology that would have been missed if they avoided endoscopy,[38,45,46] the decision to avoid endoscopy should be made on a case-by-case basis. Factors such as the patient's age, comorbidities, risk factors, and preferences should all be considered when making the decision of a no-biopsy diagnosis.

A crucial aspect of the successful implementation of the no-biopsy approach is that it should not be interpreted as a "no-referral" approach. Despite current guidelines mandating referral for biopsy in all patients with positive celiac serology, reports from the United Kingdom, Israel, and the United States showed that almost a third of patients were never referred from primary care.[34,45,47,48] Therefore, a close collaboration and dialogue between primary and secondary care is necessary to implement the no-biopsy approach safely, and to promote adherence to the serology-biopsy guidelines. This would avoid overdiagnosis of celiac disease in primary care, which could have detrimental effects on patients' quality of life.[49] Importantly, it should be stressed that endoscopy would still be required for patients with <10-fold elevation of IgA-tTG, patients with red flag signs or symptoms, and for those who wish to have a confirmatory biopsy before adhering to a lifelong gluten-free diet.[50] The development of clear clinical guidelines, educational initiatives, and local diagnostic pathways would ensure that clinicians are well-informed and capable of appropriately assessing the pretest probability of celiac disease in different clinical settings.

The current European pediatric guidelines recommend that children with IgA-tTG ≥10×ULN require a positive EMA test in a separate blood sample before confirming the diagnosis of celiac disease.[5] The same approach has been adopted in the Finnish guidelines for the diagnosis of adult celiac disease as well as in the interim guidance issued by the British Society of Gastroenterology during the COVID-19 pandemic.[51,52] However, our results suggest the possibility of reevaluating the necessity of confirmatory EMA testing, as IgA-tTG ≥10×ULN alone has an excellent predictive power for celiac disease. EMA testing requires indirect immunofluorescence, which is costly, labor intensive, and subject to

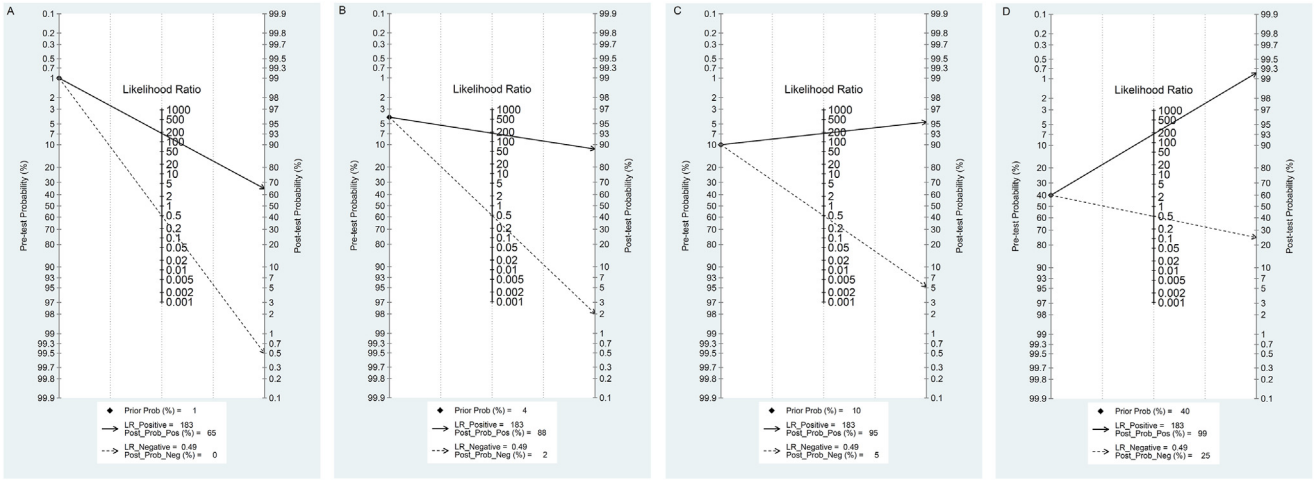

Figure 5. Fagan's nomograms showing the PPV (*solid line*) and NPV (*dashed line*) of IgA-tTG $\geq$10$\times$ULN if the pretest probability of celiac disease is 1% (*A*), 4% (*B*), 10% (*C*), and 40% (*D*).

interobserver variability. Consequently, many clinical laboratories have stopped performing EMA tests and their availability has progressively decreased over time.[22] Therefore, including EMA testing in the no-biopsy diagnostic pathway may hinder its implementation without having a clear added value.

This meta-analysis has important strengths. First, we conducted a comprehensive systematic literature search following a priori registered protocol and predefined inclusion and exclusion criteria. Second, we performed extensive sensitivity analyses to explore causes of heterogeneity and to assess the robustness of our results. Third, we used the validated QUADS-2 tool to assess the risk of bias and applicability concerns in the included studies. Fourth, all the included studies used serology as the index test and Marsh $\geq$2 on duodenal biopsies as the reference

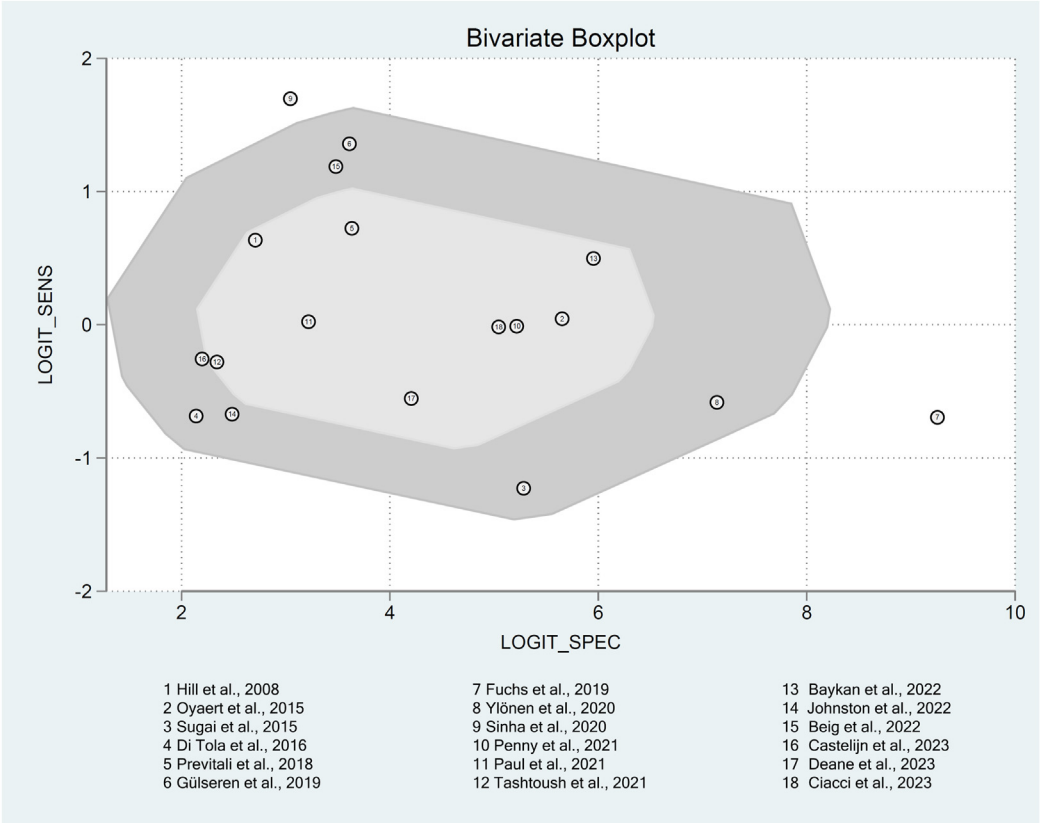

Figure 6. A bivariate box plot of a random effects modeling of the sensitivity and specificity, with the *inner oval* representing the median distribution of the data points and the *outer oval* representing the 95% confidence bound.

standard. Restricting the analysis to only those evaluating the predictive value of IgA-tTG ≥10×ULN for Marsh 3 lesions did not alter the results, adding to the validity of our findings.

Our study also has some limitations that should be considered when interpreting the results. All the included studies were performed in secondary and tertiary care settings with a pooled prevalence of celiac disease of 62%, which is higher than expected in clinical practice. The sensitivity and specificity of any diagnostic test can be influenced by the prevalence of disease in the studied population due to many clinical mechanisms (distorted patient spectrum, referral filter, or reader expectation) or artifactual mechanisms (distorted inclusion of participants including limited-challenge phenomenon, verification bias, or reference standard misclassification). We have adjusted for this by using the likelihood ratios to calculate the predictive values of the no-biopsy approach across different pretest probabilities of celiac disease. The results showed that the no-biopsy approach may have a limited utility in primary care, where the pretest probability of celiac disease is lower than 10%. Another limitation is the retrospective nature of most of the included studies. However, the high predictive value of the no-biopsy approach remained consistent in prospective studies and across different countries and commercial IgA-tTG assays. Finally, only 1 study had a low risk of bias across all domains, as most studies had selection bias, unclear time intervals between serology and histology, which may have introduced misclassification bias, and lack of blinding to serology results, which may have influenced the pathologists' interpretation of the histological findings. To avoid these potential sources of bias, future prospective studies should adhere to predefined protocols and report results according to the Standards for Reporting of Diagnostic Accuracy Studies.[53]

Future research should focus on evaluating the diagnostic accuracy of the no-biopsy approach in primary care settings and in patients with a low-pretest probability of celiac disease. It will also be important to assess the accuracy of lower thresholds of IgA-tTG to predict villous atrophy, and the added value of confirmatory testing with EMA. In addition, given that most studies were conducted in Europe, further studies are needed to determine the generalizability of our findings to regions and countries with limited data on the accuracy of the no-biopsy approach, such as the United States. Importantly, studies exploring patients' preferences, the cost-effectiveness, and the regulatory aspects of implementing the no-biopsy approach are needed to determine its acceptability, feasibility, and impact in clinical practice.

In conclusion, our meta-analysis of 18 studies including more than 12,000 participants provides evidence that IgA-tTG levels ≥10×ULN are highly indicative of celiac disease in adult patients referred to secondary care. Close collaboration between primary and secondary care, and shared decision making between clinicians and patients will be critical in implementing this no-biopsy approach.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2023.12.023.

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Data Availability
Data used in this meta-analysis are publicly available.