SYSTEMATIC REVIEW AND META-ANALYSES

Siddharth Singh, Section Editor

HLA-DQA1*05 Genotype and Immunogenicity to Tumor Necrosis Factor-α Antagonists: A Systematic Review and Meta-analysis

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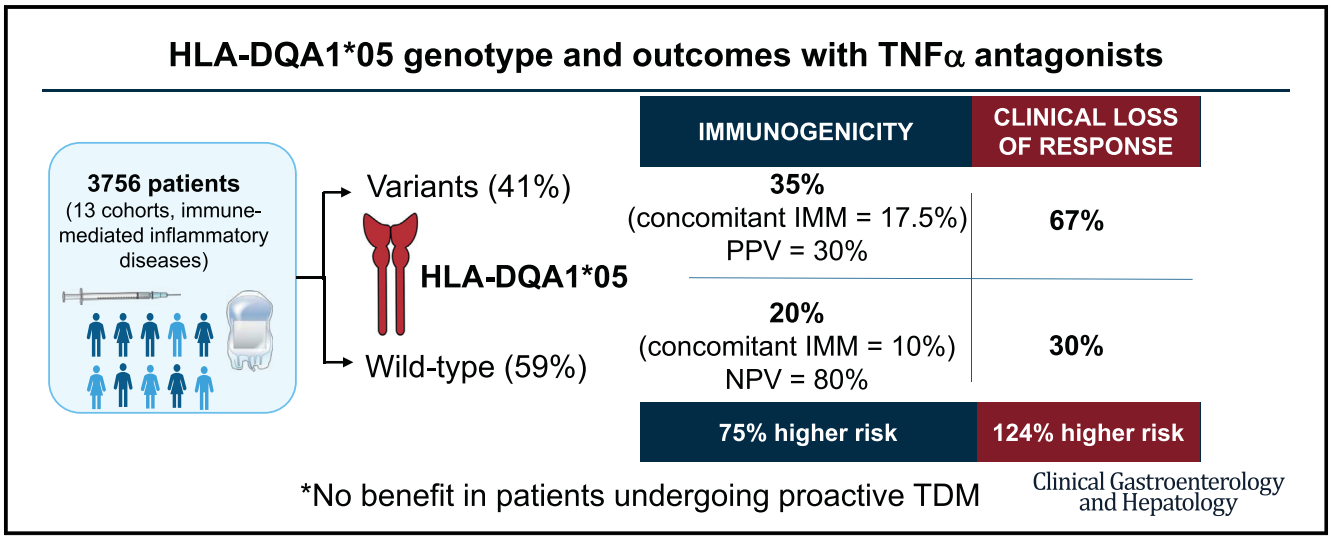
This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e45. Upon completion of the CME activity, successful learners will be able to deal with immunogenicity in patients with immune mediated inflammatory disorders, including inflammatory bowel disease, who are treated with tumor necrosis factor (TNF)α antagonists. They will also learn how to identify patients at high risk of immunogenicity and adopt measures to mitigate it.



Abbreviations used in this paper: ADAs, anti-drug antibodies; CI, confidence interval; GRADE, Grading of Recommendations, Assessment, Development and Evaluations; IBD, inflammatory bowel disease; IMID, immune-mediated inflammatory disease; IMMs, immunosuppressives; IQR, interquartile range; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PSA, psoriatic arthritis; PSO, psoriasis; QUIPS, Quality In Prognosis Studies; RA, rheumatoid arthritis; RCTs, randomized controlled trials; RR, relative risk; SpA, spondyloarthritis; TDM, therapeutic drug monitoring; TNF, tumor necrosis factor.

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BACKGROUND & AIMS: **Identifying patients at high risk of immunogenicity is important when selecting tumor necrosis factor (TNF)-α antagonists in patients with immune-mediated inflammatory diseases (IMIDs). We evaluated the association HLA-DQA1*05 genotype and risk of immunogenicity with TNF-α antagonists.**

METHODS: **Through a systematic review through July 14, 2022, we identified studies in patients with IMIDs treated with TNF-α antagonists, which reported the risk of immunogenicity and/or secondary loss of response in patients with HLA-DQA1*05 variants. Primary outcome was risk of immunogenicity. We performed random effects meta-analysis and used GRADE to appraise certainty of evidence.**

RESULTS: **On meta-analysis of 13 studies (3756 patients; median follow-up, 12 months; 41% with variants), HLA-DQA1*05 variants were associated with 75% higher risk of immunogenicity compared with non-carriers (relative risk, 1.75; 95% confidence interval, 1.37-2.25) with considerable heterogeneity (I^2 = 62%) (low certainty evidence). Positive and negative predictive values of HLA-DQA1*05 variants for predicting immunogenicity were 30% and 80%, respectively. Proactive therapeutic drug monitoring, but not concomitant use of IMMs, IMIDs, and TNF-α antagonist-type, modified this association. Patients with HLA-DQA1*05 variants experienced 2.2-fold higher risk of secondary loss of response (6 cohorts; relative risk, 2.24; 95% confidence interval, 1.67-3.00; I^2 = 0%) (moderate certainty evidence).**

CONCLUSION: **Variants in HLA-DQA1*05 are associated with an increased risk in immunogenicity and secondary loss of response in patients with IMIDs treated with TNF-α antagonists. However, the positive and negative predictive value is moderate, and decisions on concomitant use of IMMs to prevent immunogenicity should be individualized based on all factors that influence drug clearance.**

Keywords: Biologics; Crohn's Disease; Pharmacogenomics; Rheumatoid Arthritis.

Tumor necrosis factor (TNF)-α antagonists are the most widely used biologics for treating immune-mediated inflammatory diseases (IMIDs) including inflammatory bowel diseases (IBDs), rheumatoid arthritis (RA), psoriasis and psoriatic arthritis (PsO/PsA) and spondyloarthritis (SpA). Although TNF-α antagonists are highly effective across indications, approximately 40% to 50% of patients experience secondary loss of response, primarily due to the development of anti-drug antibodies (ADAs), often referred to as "immunogenicity."[1-3] Immunogenicity is associated with increased clearance of TNF-α antagonists. Thus, identifying patients at high risk of immunogenicity and adopting measures to mitigate this risk are important. Besides immunogenicity, patient and clinical factors associated with high drug clearance include male sex, high body mass index, high burden of inflammation, low albumin, diagnosis, and smoking, among others.[4-6] However, the predictive value of these factors is low. Concomitant use of immunosuppressives (IMMs) (eg, thiopurines, methotrexate) decreases the risk of immunogenicity, and consequently TNF-α antagonists are frequently used in combination with IMMs; however, the use of combination therapy is associated with increased risk of long-term side effects including lymphoma and serious infections.[7,8]

Pharmacogenetic factors that predispose to immunogenicity of TNF-α antagonists have been explored. Recently, genetic variants at HLA-DQA1*05, particularly one 'tagged' by rs2097432, have been identified as predictors of immunogenicity to TNF-α antagonists, and a commercial test is available for routine use.[9-11] If these variants are highly predictive, then pharmacogenetic testing may help identify patients at high vs low risk of immunogenicity and can influence patient counseling regarding the choice of biologic (whether to use TNF-α antagonists vs non-TNF biologics) and facilitate discussion regarding use of concomitant IMMs.

We conducted a systematic review and meta-analysis to evaluate and quantify the association between HLA-DQA1*05 variants and risk of immunogenicity and secondary loss of clinical response in patients with IMIDs treated with TNF-α antagonists. We used the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework to critically appraise the certainty of evidence.[12]

Methods

This systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement and was conducted following a priori established protocol (available upon request).

Selection Criteria

We included randomized controlled trials (RCTs) and cohort studies that met the following inclusion criteria: (1) Patients: pediatric and adult patients with IMIDs who were treated with TNF-α antagonists (eg, infliximab, adalimumab, etanercept, certolizumab pegol, golimumab); (2) Exposure and comparator: variants in

HLADQA1*05 allele (including rs2097432 and others) vs wild type (non-carriers); and (3) Outcome: development of ADAs and/or secondary loss of response in patients with HLA-DQA1*05 variants vs wild-type (non-carriers). We excluded genome-wide studies focusing only on genotype-phenotype correlation in all patients with IBD regardless of TNF-α antagonist exposure, studies reporting on non-HLA-DQA1*05 pharmacogenetic factors, or studies that did not report on specific outcomes by HLA-DQA1*05 genotype (and such data could not be obtained from study investigators).

Search Strategy, Data Abstraction, and Risk of Bias Assessment

We conducted a comprehensive search of MEDLINE, Embase, and the Cochrane Library (CENTRAL), from inception to July 14, 2022, with no language restrictions, and limited to human studies. The online Supplementary Appendix and Supplementary Table 1 detail the search strategy. A targeted search of PubMed on March 10, 2023, did not identify any new unique studies. After study selection, 2 authors (VS, AF) independently abstracted data on study and patient characteristics, exposure variables, outcomes, confounding variables, and statistical analyses, using a standardized data abstraction form. For studies that met inclusion criteria but did not provide sufficient data for meta-analysis, we contacted corresponding authors for additional information. Details of data abstraction are reported in the Supplementary Appendix. Risk of bias in individual studies was assessed by 2 investigators (VS, AF) independently, using the Quality In Prognosis Studies (QUIPS) tool for prognosis.[13]

Outcomes Assessed

The primary outcome of interest was the risk of immunogenicity in patients with HLA-DQA1*05 variants; secondary outcome of interest was loss of clinical response (relapse in clinical symptoms after initial clinical response to TNF-α antagonists and/or treatment discontinuation). In order to evaluate stability of the association between HLA-DQA1*05 variants and risk of immunogenicity, and to examine potential sources of heterogeneity, we performed several a priori subgroup analyses, based on concomitant use of immunosuppressives, routine use of proactive therapeutic drug monitoring (TDM) to maintain adequate drug exposure, study design (RCT vs cohort), type of TNF-α antagonist (primarily infliximab vs predominantly non-infliximab TNF-α antagonist), type of IMID (IBD [higher prevalence of immunogenicity] vs predominantly non-IBD cohorts), and analysis approach (multivariable vs only univariable analysis). A priori, we hypothesized that HLA-DQA1*05 variants will be associated with increased risk of immunogenicity in those treated with vs without concomitant IMMs but this association will not be clinically significant when proactive TDM to maintain adequate serum trough concentration is routinely used.

What You Need To Know

Background

Identifying patients at high risk of immunogenicity is important when selecting tumor necrosis factor-α antagonists in patients with immune-mediated inflammatory diseases.

Findings

On meta-analysis of 13 studies, HLA-DQA1*05 variants were associated with 75% higher risk of immunogenicity, and 124% higher risk of secondary loss of response. Positive and negative predictive values of HLA-DQA1*05 variants for predicting immunogenicity were 30% and 80%, respectively.

Implications for patient care

HLA-DQA1*05 may inform decision to use or withdraw concomitant immunomodulators when using tumor necrosis factor-α antagonists.

Statistical Analysis

We used the random-effects model described by DerSimonian and Laird to calculate summary relative risks (RRs) and 95% confidence intervals (CIs).[14] Maximally adjusted risk estimates were used for analysis to account for confounding variables. Additional details are reported in the Supplementary Appendix.

Besides evaluating RRs, we also calculated sensitivity and specificity of HLA-DQA1*05 variants in identifying patients who develop immunogenicity. The paired values of sensitivity and specificity were pooled using a bivariate regression random-effects model proposed by proposed by Reitsma et al as implemented in the R package 'mada.'[15] Using pooled prevalence of immunogenicity in all cohorts of patients with IMIDs treated with TNF-α antagonists, we examined the positive predictive value and negative predictive value of HLA-DQA1*05 variants and risk of immunogenicity.

Certainty of Evidence

We ascertained certainty of evidence for the primary outcomes using the GRADE approach.[16] In this approach, observational studies on prognosis start at high quality and can be rated down based for risk of bias in the body of evidence (assessed using the QUIPS tool), indirectness (addressing a different but related population, intervention, or outcome from the one of interest), imprecision (either wide 95% CI, or not meeting optimal information size of 200 events), inconsistency (or heterogeneity, both conceptual and/or statistical), and/or publication bias to levels of moderate, low, and very low quality.

Results

The systematic literature review identified 2857 unique articles, of which full texts of 39 articles were reviewed in detail. Thirteen published studies were included.[9-11,17-26] Supplementary Figure 1 shows the study selection flowsheet.

Characteristics of Included Studies

Table 1 details key characteristics of the studies included in this systematic review and meta-analysis. Nine studies reported on the primary outcome of immunogenicity,[9-11,17-19,21,23,24] and 6 studies reported on risk of secondary loss of clinical response.[11,20-22,25,26] Overall, these studies included 3756 patients with IMIDs treated with TNF-α antagonists. The median prevalence of HLA-DQA1*05 variants was 41% (interquartile range [IQR], 39%–46%) in the included studies. Five studies specifically focused on the rs2097432 variant.[9,11,17,18,20] After a median follow-up of 12 months (IQR, 12–29 months), 24% of patients (range in included studies, 11%–65%) with IMIDs in the included studies developed immunogenicity to TNF-α antagonists.

Three studies were conducted in North America,[10,11,17] and 10 in Europe.[9,18-26] Eleven studies were cohort studies (4 prospective, 7 retrospective); one RCT (NOR-DRUM), designed to compare efficacy of proactive TDM vs usual care, was also treated as a prospective cohort study in this synthesis. Studies did not routinely report the ancestry of participants. Ten studies were conducted exclusively in patients with IBD (7 studies including both Crohn's disease and ulcerative colitis, 3 studies exclusively in patients with Crohn's disease, and 1 exclusively in patients with ulcerative colitis), 2 studies in patients with RA, including 1 study on mixed population of patients with rheumatic IMIDs. Infliximab was the most commonly studied TNF-α antagonist, being the sole agent in 7 studies. Ten studies overall reported results adjusted for concomitant IMM therapy.

Overall, the studies were at low-moderate risk of bias. Supplementary Table 1 shows detailed risk of bias assessment.

Risk of Immunogenicity

Nine studies (3394 patients; median prevalence of HLA-DQA1*05 variants, 40% [range, 33%–58%]) were included.[9-11,17-19,21,23,24] Five studies reported risk adjusted for concomitant use of IMMs.[9,11,17,18,23] On meta-analysis, presence of HLA-DQA1*05 allele was associated with a 75% higher risk of immunogenicity, compared with non-carriers, in patients with IMIDs treated with TNF-α antagonists (RR, 1.75; 95% CI, 1.37–2.25) with considerable heterogeneity ($I^2 = 62\%$) (Figure 1). Exclusion of one study with a very large effect size decreased the heterogeneity without a substantial change in effect estimate (RR, 1.68; 95% CI, 1.38–2.04; $I^2 = 41\%$).[11] In 4 studies that specifically examined the rs2097432 variant, the overall risk of immunogenicity was similar (RR, 2.02; 95% CI, 1.12–3.65). With an observed incidence of immunogenicity in HLA-DQA1*05 non-carriers of 20%, within 12 months of starting TNF-α antagonists, the estimated risk of immunogenicity to TNF-α antagonists in patients with HLA-DQA1*05 variants would be 35.0% (95% CI, 27.2%–45.0%). With an observed incidence of immunogenicity in HLA-DQA1*05 non-carriers in patients on concomitant IMMs of 10% within 12 months, the estimated risk of immunogenicity with HLA-DQA1*05 variants would be 17.5% (95% CI, 13.6%–22.5%). The overall certainty of evidence was rated as low, being rated down for risk of bias and inconsistency.

Summary sensitivity and specificity of HLA-DQA1*05 variant for predicting risk of immunogenicity was 51% (95% CI, 47%–54%) and 62% (95% CI, 55%–69%), respectively. With a pooled prevalence of immunogenicity to TNF-α antagonists of 24%, the positive predictive value of HLA-DQA1*05 variants in predicting immunogenicity was 30% (ie, 30% patients who carry HLA-DQA1*05 variants would develop immunogenicity within 12 months of starting TNF-α antagonists). Corresponding negative predictive value of HLA-DQA1*05 non-carrier was 80% (ie, 80% patients who do not carry HLA-DQA1*05 variants will not develop immunogenicity within 12 months of starting TNF-α antagonists).

Subgroup Analyses

Concomitant IMM use. The risk of immunogenicity was similar in 5 cohorts which adjusted for concomitant IMM use (RR, 1.97; 95% CI, 1.36–2.86; $I^2 = 69\%$) vs 5 cohorts which did not adjust for concomitant IMM use (RR, 1.48; 95% CI, 0.96–2.29; $I^2 = 61\%$) (P-value for difference between groups = .33) (Table 2).

Use of proactive TDM. The risk of immunogenicity with HLA-DQA1*05 variants was only significant in cohorts were routine proactive TDM was not performed (8 cohorts; RR, 1.96; 95% CI, 1.60–2.42; $I^2 = 46\%$); in 2 cohorts where proactive TDM was routinely performed, presence of HLA-DQA1*05 variants was not associated with risk of immunogenicity to TNF-α antagonists (RR, 0.74; 95% CI, 0.42–1.31; $I^2 = 0\%$).[10,17] This difference in subgroups was significantly explaining some of the heterogeneity observed in the overall analysis (P-value for difference between groups = .002).

Other subgroups. There were no significant differences in the risk of immunogenicity with HLA-DQA1*05 variants based on study design (retrospective vs prospective; $P = .35$), TNF-α antagonist type (predominantly infliximab cohorts vs mixed; $P = .88$), IMID type (IBD vs mixed IMIDs; $P = .60$), or drug measurement assay (drug-tolerant vs drug-sensitive assay; $P = .24$). On sensitivity analysis, focusing on 4 studies that reported risk of immunogenicity within 12 months, overall

Table 1. Characteristics of Patients Participating in the Included Studies

Author, year of publication; location	Design; follow-up, months (mean ± SD)	No. of patients, overall and by TNF-α type	Disease distribution (CD, UC, RA, PsO/PsA, AS, others)	% of patients who were HLA-DQA1*05 carriers (hetero/homozygous) vs non-carriers	Age, years; % female; Concomitant IMM	% of patients with immunogenicity; assay type	Other outcomes reported
Bangma, 2020; the Netherlands	Case-control; 29 ± 45	376 (IFX, 284; ADA, 92)	CD, 74%; UC, 23%; IBD-U, 3%	60% vs 40% (33%/6%); specifically examined rs2097432	47 (21); 65%; 47%	22.6% (20% in WT vs 27% in variant); Drug-tolerant	–
Brun, 2023; Norway	Secondary analysis of RCT	612 (IFX, 612)	RA, 20%; AS, 29%; Ps/PsA, 19%; UC, 19%; CD, 13%	67% vs 33% (28%/5%)	45 (14); 49%; 54%	24% (19% in WT vs 35% in variant); Drug-sensitive	–
Colman, 2022; USA	Prospective cohort; 12	78 (IFX, 78); 51 patients with data on HLA type	CD, 100%	51% vs. 49% [NR]	13 (9–15); 36%; 6.4%	65% (69% in WT vs 60% in variant); Drug-tolerant	–
Fuentes-Valenzuela, 2023; Spain	Retrospective cohort; 17 (9–31)	112 (IFX or ADA); 100% with proactive TDM	CD, 80%; UC, 20%	54% vs. 46% [NR]; specifically examined rs2097432	39 (25–50); 42%; 36%	NR; Drug-sensitive	Treatment persistence; clinical remission
Gonzalez, 2021; UK	Retrospective cohort; 15 (9–29)	94 (IFX, 94)	UC, 100%	61% vs. 39% [NR]	NR; NR; 52%	36.2% (24% in WT vs 59% in variant); NR	Treatment persistence
Guardiola-Capon, 2020; Spain	Retrospective cohort; 51 (35–74)	53 (ADA 53)	CD, 100%	55% vs. 45% [NR]	NR; NR; NR	NR; NR	Loss of response
Hassler, 2020; Europe	Prospective cohort; 12	338 on TNF-α antagonists [IFX, 101; ADA, 153; ETA, 84]	IBD, 54%; RA, 46%	NR	IBD: 37 (14); 48%; NR RA: 54 (14); 77%; NR	IFX, 16%; ADA, 42%; ETA, 3%; Drug-tolerant	NR
Lopez-Blanco, 2022; Spain	Retrospective cohort; 12	208 (IFX or ADA)	IBD, 100%	42% vs 58% [NR]	NR; NR; NR	11% (10% in WT vs 12% in variant); NR	NR
Angulo McGrath, 2021; Spain	Retrospective cohort; 35 (58)	88 (IFX, 88)	CD, 72%; UC, 28%	58% vs 42% [NR]	39 (20); 48%;	NR; NR	Loss of response
Sazonovs 2020; UK	Prospective cohort; 12	1240 (IFX 742, ADA 498)	CD, 100%	61% vs 39% [33%/6%]; specifically examined rs2097432	IFX: 31 (21–46); 52%; 60% ADA: 38 (29–50); 53%; 51%	44% at 12m (@12m: 38% in WT vs 58% in variant); Drug-tolerant	NR
Spencer, 2022; US	Prospective cohort; 12	186 (IFX, 186)	CD, 70%; UC, 27%; IBD-U, 2%	54% vs 46%; specifically examined rs2097432	17 (14–20); 48%; 10%	12% at 12m (13% in WT vs 12.5% in variant); Drug-tolerant	NR

Table 1. Continued

Author, year of publication; location	Design; follow-up, months (mean ± SD)	No. of patients, overall and by TNF-α type	Disease distribution (CD, UC, RA, PsO/PsA, AS, others)	% of patients who were HLA-DQA1*05 carriers (hetero/homozygous) vs non-carriers	Age, years; % female; Concomitant IMM	% of patients with immunogenicity; assay type	Other outcomes reported
Suris Marin, 2021; Spain	Retrospective cohort; >6	99 (IFX, 99)	CD, 66%; UC, 34%	61% vs 39% [NR]	NR; NR; NR	NR; NR	Loss of response; treatment persistence
Wilson, 2019; Canada	Retrospective cohort; 36	262 (IFX, 262)	CD, 58%; UC, 42%	60% vs 40% (30%/10%); specifically examined rs2097432	40 (18–79); 52%; 90%	13% (4.4% in WT vs 26% in variant); NR	Loss of response

ADA, Adalimumab; AS, ankylosing spondylitis; CD, Crohn's disease; IMM, immunosuppressives; IFX, infliximab; NR, not reported; PsO/PsA, psoriasis/psoriatic arthritis; RA, rheumatoid arthritis; SD, standard deviation; TNF, tumor necrosis factor; UC, ulcerative colitis; UK, United Kingdom; US, United States; WT, wild-type (non-carriers).

findings were unchanged (RR, 1.44; 95% CI, 0.97–2.13). Risk of immunogenicity stratified by disease severity was not reported.

Risk of Secondary Loss of Clinical Response

Six cohort studies (708 patients; median prevalence of HLA-DQA1*05, 41% [range, 39%–46%]) reported risk of secondary loss of clinical response in patients with HLA-DQA1*05 variants.[11,20-22,25,26] Five studies adjusted for concomitant use of IMMs.[11,20-22,25] On meta-analysis, presence of HLA-DQ A1*05 variants was associated with an increased risk of secondary loss of response compared with non-carriers (RR, 1.74; 95% CI, 1.03–2.94) with substantial heterogeneity ($I^2 = 68\%$) (Figure 2). In one study in which proactive TDM was performed, there was no association between presence of HLA-DQ A1*05 variants and risk of loss of response.[20] Exclusion of this study made the effect estimate larger (RR, 2.24; 95% CI, 1.67–3.00), and eliminated heterogeneity ($I^2 = 0\%$). There was moderate certainty of evidence in the overall body of evidence for loss of response outcome, with evidence being rated down for risk of bias; evidence was not rated down for heterogeneity because it was attributable to one study in which proactive TDM was performed. With a baseline risk of secondary loss of response of TNF-α antagonists in those without HLA-DQ A1*05 of 30%, the estimated risk of loss of response with HLA-DQ A1*05 variant is 67.2% (95% CI, 50.1%–90.0%).

Discussion

Risk of immunogenicity is a key factor in treatment decisions for patients with IMIDs regarding class of biologic agent and concomitant use of IMMs. Through a systematic review and meta-analysis of 13 studies involving 3756 patients with IMIDs treated with TNF-α antagonists, we made several key observations. First, we observed a 75% higher risk of immunogenicity in patients with at least 1 HLA-DQA1*05 allele, which was observed in approximately 40% of the studied population. These variants were associated with 2.2-fold higher risk of loss of clinical response to TNF-α antagonists. Second, even though the overall risk of immunogenicity was lower in patients who received concomitant IMMs, the increased risk of immunogenicity in patients with HLA-DQA1*05 variants persisted even after adjusting for concomitant use of IMMs. However, this increased risk of immunogenicity with HLA-DQA1*05 variants was not observed in cohorts where proactive TDM was routinely performed to maintain a target serum drug concentration. Type of IMID or TNF-α antagonist type did not significantly impact risk of immunogenicity, although most patients in the included studies had IBD and were treated with infliximab or adalimumab. Third, although the risk of immunogenicity is increased in HLA-DQA1*05 carriers, the positive predictive value of the test is

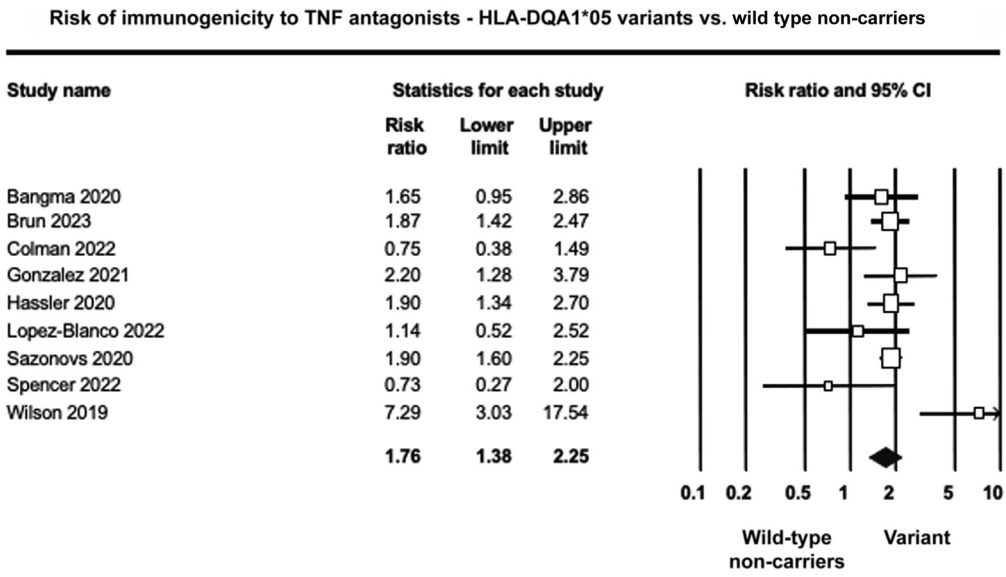

Figure 1. Forest plot comparing the risk of immunogenicity to TNF-α antagonists in patients with variants of HLA-DQA1*05 vs wild-type (HLA-DQA1*05-non carriers).

modest at 30%, implying a majority of patients who have these variants will not develop ADA within 12 months. In contrast, a high negative predictive value of 80% implies a low likelihood of immunogenicity in patients who do not carry HLA-DQA1*05. Overall, these findings identify the HLA-DQA1*05 genotype as a significant factor predicting risk of immunogenicity with TNF-α antagonists. However, it should be used in conjunction with other

Table 2. Subgroup Analyses Comparing Risk of Immunogenicity With HLA-DQA1*05 Variants vs non-carriers in Patients With IMIDs Treated With TNF-α Antagonists

Subgroup	No. of cohorts	RR (95% CI)	I^2	*P*-value for difference between subgroups
Study design				.35
• Prospective	5	1.63 (1.25–2.11)	60%	
• Retrospective	4	2.25 (1.19–4.25)	72%	
Concomitant IMM use				.33
• Adjusted	5	1.97 (1.36–2.86)	69%	
• Not adjusted for	4	1.48 (0.96–2.29)	61%	
Use of proactive TDM				.002
• Yes	2	0.74 (0.42–1.31)	0%	
• No	7	1.96 (1.60–2.42)	46%	
Type of IMID				.60
• IBD only	7	1.67 (1.11–2.50)	72%	
• Mixed	2	1.88 (1.52–2.34)	0%	
Type of TNF-α antagonist				.88
• Predominantly infliximab	5	1.77 (0.97–3.22)	80%	
• Mixed	4	1.85 (1.60–2.14)	0%	
Type of drug measurement assay				.24
• Drug-tolerant	5	1.52 (1.11–2.08)	44%	
• Drug-sensitive	2	3.46 (0.92–13.01)	80%	

CI, Confidence interval; IBD, inflammatory bowel disease; IMID, immune-mediated inflammatory disease; IMM, immunosuppressive; RR, relative risk; TDM, therapeutic drug monitoring; TNF, tumor necrosis factor.

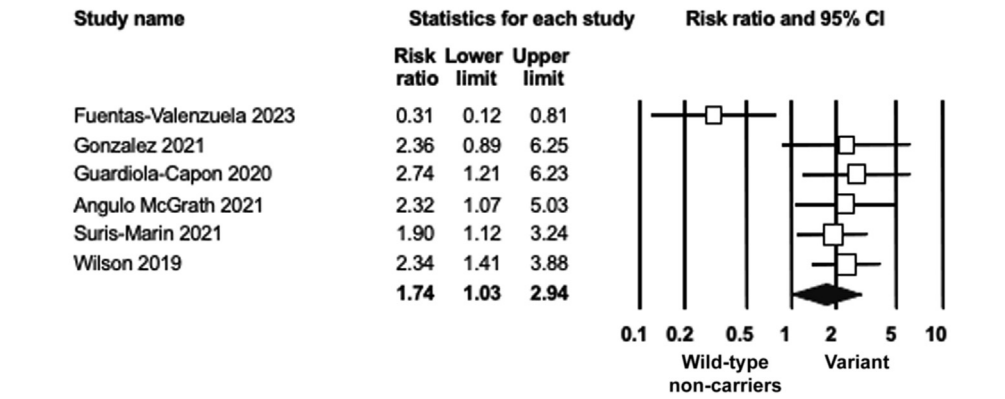

Figure 2. Forest plot comparing the risk of secondary loss of response to TNF-α antagonists in patients with variants of HLA-DQA1*05 vs wild-type (non-carriers).

known risk factors for high drug clearance and low drug concentrations such as high inflammatory burden, low albumin, male sex and obesity, and the patient's overall clinical status (disease phenotype and behavior, prior failure of other biologic therapies) to make informed decisions on use of TNF-α antagonists in combination with immunosuppressives, and with close monitoring of serum drug concentrations.[4-6]

An exposure-response relationship has been consistently observed with TNF-α antagonists.[27,28] Neutralizing ADAs are not infrequently observed with TNF-α antagonists, particularly infliximab and adalimumab, and significantly increase drug clearance, increase loss of response, decrease treatment persistence, and increase risk of infusion or injection reactions.[4] In this study, we have identified specific variants in HLA DQA1*05 that independently influence the risk of immunogenicity and loss of response to TNF-α antagonists, across different agents and different IMIDs. This genotype test, which is commercially available, can be used as an adjunct to inform clinical decision-making. The high prevalence of these variants in the population suggests routine testing may be valuable. However, given modest positive predictive value, and with low certainty of evidence in effect estimates, in isolation, it may not inform whether to use TNF-α antagonists vs non-TNF-targeting biologics, because the risk of immunogenicity to TNF-α antagonists is not prohibitive in patients who carry these variants.

Pharmacogenomic testing is frequently utilized in patients with IMIDs who are being treated with thiopurines. Mutations in *TPMT* gene that influence thiopurine methyl transferase enzyme activity have been associated with thiopurine-induced leukopenia, and testing for these is recommended prior to starting thiopurines in patients with IBD.[29] In Asian populations, mutations in *NUDT15* have been associated with increased risk of thiopurine-induced leukopenia.[30-32] However, to date, no pharmacogenetic factor has been utilized to inform optimal utilization of TNF-α antagonists in patients with IMIDs. In extended analysis of the PANTS study, Powell Doherty and colleagues identified 2 distinct variants variably associated with immunogenicity to infliximab and adalimumab. HLA-DQA1*05:01 and its extended haplotype were significantly associated with immunogenicity against infliximab but not adalimumab, whereas HLA-DQA1*05:05 and its extended haplotype were significantly associated with immunogenicity against adalimumab and, less strongly, infliximab.[33] Besides HLA-DQA1*05 allele, other pharmacogenetic factors have also been identified that influence risk of immunogenicity and loss of response to TNF-α antagonists. In the NOR-DRUM trial, other HLA-DQ variants, particularly the DQ2 molecule encoded by 2 HLA-DQ haplotypes DQB1*02:01∼DQA1*05 and DQB1*02:02∼DQA1*02 were associated with increased risk of immunogenicity, and not DQA1*05 allele alone. HLA-DRB1*03 variants have been associated with increased risk of immunogenicity in patients treated with infliximab and adalimumab.[34,35] Similarly, a single nucleotide polymorphism in FCGR3A, rs396991, has also been associated with increased risk of immunogenicity, lower serum drug concentration, and loss of response to infliximab in pediatric IBD.[36] However, these observations have been inconsistent, and testing for these is not currently commercially available.

Our systematic review and meta-analysis has important strengths, including a comprehensive literature search including conference proceedings, a priori hypotheses with planned subgroup analyses, application of GRADE to critically appraise body of evidence, and contextualizing risk of immunogenicity with use of absolute risk and positive and negative predictive value using observed prevalence. This approach allows ready adoption of our findings in clinical guidelines. However, there are important limitations that should be acknowledged. First, since this was a study-level synthesis, we were unable to accurately estimate attributable risk of HLA-DQA1*05 variants to risk of immunogenicity after accounting for all known factors that may influence drug clearance. No significant differences were observed in effect estimates in studies that adjusted vs did not adjust for key covariates. Of note, the largely pediatric-based

cohorts in which proactive TDM is commonly used did not identify a higher risk of immunogenicity among HLA-DQA1*05 variants. However, dosing strategies were not uniformly reported in the studies that did find a higher risk of immunogenicity and that did not use proactive TDM, suggesting that it is difficult assess the true effect of dosing practices. Second, the studies did not uniformly assess neutralizing vs all ADAs and had different thresholds and assays for ADA measurement. Third, as observational studies only examine associations, it is difficult to ascertain the true impact of measuring HLA-DQA1*05 genotype on clinical management. Ideally, a clinical trial comparing HLA-DQA1*05-informed management decisions vs routine care would inform role of pharmacogenetic testing in the management of patients with IMIDs. Fourth, this meta-analysis was dominated by cohorts of patients from Europe and North America. Prevalence and impact of HLA-DQA1*05 variants on risk of immunogenicity and secondary loss of response in subjects of other races and ethnicities might be different from those in European ancestry populations. In a retrospective cohort from Miami with a predominantly Hispanic population, prevalence of HLA-DQA1*05 variants was comparable to those observed in Caucasian cohorts.[37]

Our findings have important implications for practice. In our opinion, based on the current evidence, the presence or absence of HLA-DQA1*05 variants should not be the sole reason to guide choice of TNF-α antagonists vs non-TNF biologics. When TNF-α antagonists are used, concomitant use of IMMs is routinely recommended for most patients based on clinical guidelines, particularly those with unfavorable pharmacokinetics. However, when patients and/or providers are hesitant to use IMMs due to concern for adverse events, then HLA-DQA1*05 may be helpful. In fact, in patients in whom genetic variants are not detected, the high negative predictive value suggests low risk of developing immunogenicity with TNF-α antagonist monotherapy. In contrast, if these patients are positive for HLA-DQA1*05 variants, then combination therapy may be preferred; alternatively, proactive TDM may be helpful to minimize risk of developing immunogenicity. Another area where testing for HLA-DQA1*05 may be informative is during decisions for de-escalation of combination therapy and withdrawal of IMMs. In this situation, the absence of HLA-DQA1*05 variants increases confidence in decision-making supporting de-escalation. However, presence of HLA-DQA1*05 variants may suggest higher risk of immunogenicity with TNF-α antagonist monotherapy; in these instances, continuing combination may be preferred, or if decision is made to de-escalate, proactive TDM may be helpful for monitoring.

In summary, based on a meta-analysis of 13 studies with 3,756 patients, we observed that variants in HLA-DQA1*05 are associated with increased risk of immunogenicity and secondary loss of clinical response in patients with IMIDs treated with TNF-α antagonists. Although this is an important pharmacogenetic factor, certainty of evidence is low, and positive predictive value of HLA-DQA1*05 genotyping is modest, suggesting it is one of the risk factors to be considered in decision-making regarding the use of TNF-α antagonists in combination with IMMs and monitoring of serum drug concentration with TDM. Future studies examining the clinical impact of HLA-DQA1*05 genotyping in diverse populations, and clinical trials of genotyping-informed decision-making are warranted.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2023.03.044.

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Conflicts of interest

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Supplementary Appendix

Methods

Search Strategy

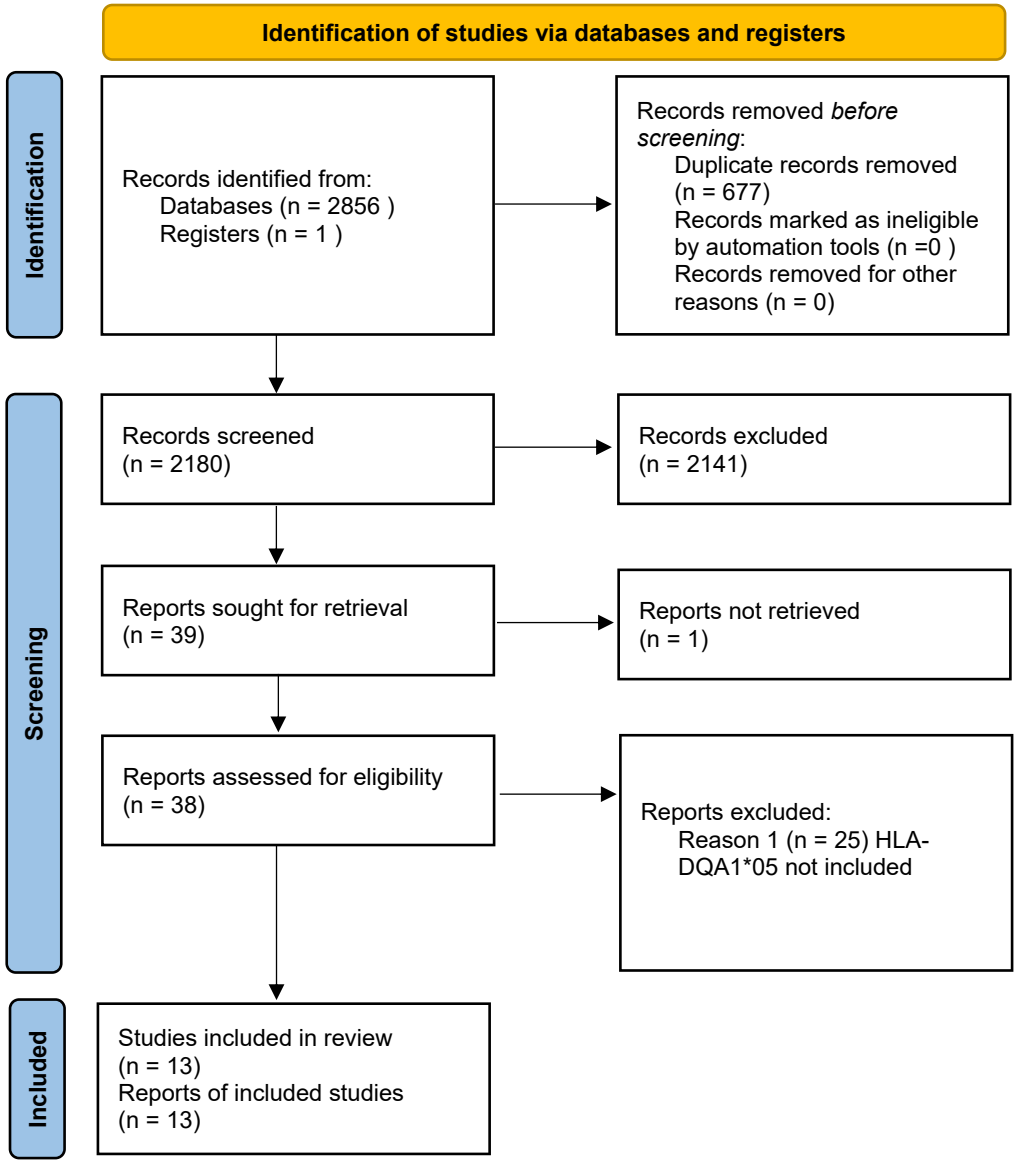
Two investigators (VS, AF) independently reviewed titles and abstracts to exclude studies that did not address the research question of interest. The full text of the remaining articles was examined to determine whether it contained relevant information. Conflicts in study selection at this stage were resolved by consensus, referring back to the original article, in consultation with a third investigator (SS). We searched the bibliographies of these selected articles and systematic reviews on the topic to identify any additional studies. We also conducted a manual search of conference proceedings from major gastroenterology conferences (Digestive Disease Week, American College of Gastroenterology annual meeting, and European Crohn's and Colitis Organization annual meeting) from 2019 to 2022 to identify additional abstracts.

Data Abstraction

The following data were collected from each study: (1) study characteristics: primary author, year of publication, country of origin, study design (randomized controlled trial vs cohort studies vs case-control; prospective vs retrospective), study duration (timing of outcome assessment, follow-up time), factors pertinent to risk of bias assessment; (2) patient characteristics: age, sex, ancestry and ethnicity, immune-mediated inflammatory disease characteristics (phenotype, severity, duration, etc.), baseline disease activity (disease activity index, number in remission, mean scores), type of tumor necrosis factor (TNF)-α antagonists, biologic dose/frequency, comorbidities, concomitant medications (corticosteroids, immunosuppressives); prior immunogenicity to an alternative TNF-α antagonist; (3) exposure characteristics: HLA-DQA1*05 variant type, prevalence and distribution (homozygous vs heterozygous), and assay used; (4) outcomes studied: definition, assay and prevalence of immunogenicity and whether anti-drug antibodies were considered clinically significant, stratified by HLA-DQA1*05 genotype; secondary loss of clinical response; (5) potential confounding variables including concomitant use of immunosuppressives, and whether proactive therapeutic drug monitoring was performed to maintain adequate drug exposure; and (6) statistical approach: unadjusted and adjusted relative risk and 95% confidence intervals, and methods to control for bias.

Statistical Analysis

To estimate what proportion of total variation across studies was due to heterogeneity rather than chance, an I^2 statistic was calculated.[15] An I^2 value of $<30\%$, 30% to 60%, 60% to 75%, and $>75\%$ were suggestive of low, moderate, substantial, and considerable heterogeneity, respectively. Between-study sources of heterogeneity were investigated using subgroup analyses by stratifying original estimates according to study characteristics (as described above). In this analysis, a *P*-value for differences between subgroups of $< .10$ was considered statistically significant. Publication bias was assessed qualitatively using funnel plots when >10 studies were identified for a comparison.[16] These analyses were performed using Comprehensive Meta-Analysis version 2.0 (Englewood, New Jersey).



Supplementary Figure 1.
Study selection flowsheet.

Supplementary Table 1. Search Strategy

Search Strategy- Pharmacogenomics SR
EMBASE (1947 to Present)
1. (Inflammatory Bowel Disease* or IBD).mp.
2. Ulcerative colitis.mp.
3. Crohn*.mp.
4. Arthritis.mp.
5. Psoriasis.mp.
6. Ankylosing spondylitis.mp.
7. Autoimmune*.mp.
8. Inflammatory*.mp.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. Thiopurine*.mp.
11. (Azathioprine or AZA).mp.
12. (6-mercaptopurine or 6-MP).mp.
13. Methotrexate.mp.
14. Anti-TNF.mp.
15. TNF antagonist*.mp.
16. Biologic*.mp.
17. Vedolizumab.mp.
18. Ustekinumab.mp.
19. Adalimumab.mp.
20. Infliximab.mp.
21. Certolizumab.mp.
22. Natalizumab.mp.
23. Golimumab.mp.
24. 10 or 11 or 12 or 13 or 14 or 15 pr 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25. HLA type*.mp.
26. TPMT.mp.
27. NUDT15*.mp.
28. ACKR1.mp.
29. FCGR3A.mp.
30. (HLA-DRB1* or HLADRB1*).mp.
31. (HLA-DQA1* or HLADQA1*).mp.
32. 25 or 26 or 27 or 28 or 29 or 30 or 31
33. 9 and 24 and 32
Results = 1918 (2000-July 14, 2022)
Medline (1946 to Present)
1. (Inflammatory Bowel Disease* or IBD).mp.
2. Ulcerative colitis.mp.
3. Crohn*.mp.
4. Arthritis.mp.
5. Psoriasis.mp.
6. Ankylosing spondylitis.mp.
7. Autoimmune*.mp.
8. Inflammatory*.mp.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. Thiopurine*.mp.
11. (Azathioprine or AZA).mp.
12. (6-mercaptopurine or 6-MP).mp.
13. Methotrexate.mp.
14. Anti-TNF.mp.
15. TNF antagonist*.mp.
16. Biologic*.mp.
17. Vedolizumab.mp.
18. Ustekinumab.mp.
19. Adalimumab.mp.
20. Infliximab.mp.
21. Certolizumab.mp.
22. Natalizumab.mp.
23. Golimumab.mp.
24. 10 or 11 or 12 or 13 or 14 or 15 pr 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25. HLA type*.mp.
26. TPMT.mp.
27. NUDT15*.mp.
28. ACKR1.mp.
29. FCGR3A.mp.
30. (HLA-DRB1* or HLADRB1*).mp.

Supplementary Table 1. Continued

Search Strategy- Pharmacogenomics SR
31. (HLA-DQA1* or HLADQA1*).mp.
32. 25 or 26 or 27 or 28 or 29 or 30 or 31
33. 9 and 24 and 32
Results = 703 (2000-July 14, 2022)
Cochrane Library (CENTRAL)
1. Inflammatory Bowel Disease* or IBD or Ulcerative colitis or Crohn* or Arthritis or Psoriasis or Ankylosing spondylitis or Autoimmune* or Inflammatory*
2. Thiopurine* or Azathioprine or AZA or 6 mercaptopurine or 6 MP or Methotrexate or Anti TNF or TNF antagonist* or Biologic* or Vedolizumab or Ustekinumab or Adalimumab or Infliximab or Certolizumab or Natalizumab or Golimumab
3. HLA type* or TPMT or NUDT15* or ACKR1 or FCGR3A or HLA-DRB1* or HLADRB1* or HLA-DQA1* or HLADQA1*
4. #1 and #2 and #3
Results = 235 (2000-July 14, 2022)
Total Results = 2856
Duplicates = 676
Results to screen = 2180

Supplementary Table 2. Risk of Bias of studies Included in the Systematic Review According to the QUIPS Tool

Last name of first author, year of publication	QUIPS: Study Participation	QUIPS: Study Attrition	QUIPS: Prognostic Factor Measurement	QUIPS: Outcome Measurement	QUIPS: Study Confounding	QUIPS: Statistical Analysis and Reporting
Bangma, 2022	Low risk	Low risk	Low risk	Low risk	High risk	High risk
Bjorlykke, 2022	Low risk	Low risk	Low risk	High risk	Moderate risk	Low risk
Colman, 2022	Low risk	High risk	Low risk	Low risk	High risk	Low risk
Fuentes-Valenzuela, 2022	High risk	Low risk	High risk	High risk	High risk	High risk
Gonzalez, 2021	High risk	Low risk	High risk	High risk	High risk	High risk
Guardiola, 2020	High risk	Low risk	High risk	High risk	High risk	High risk
Hassler, 2020	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Lopez-Blanco, 2022	Low risk	Low risk	Low risk	Low risk	High risk	High risk
Angula McGrath, 2021	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Sazonovs, 2020	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Spencer, 2022	Low risk	Low risk	Low risk	Low risk	High risk	High risk
Suris Marin, 2021	High risk	Low risk	High risk	High risk	High risk	High risk
Wilson, 2019	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

QUIPS, Quality In Prognosis Studies.