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Comparative Risk of Serious Infections with Biologic and/or Immunosuppressive Therapy in Patients with Inflammatory Bowel Diseases: A Systematic Review and Meta-analysis

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Abstract

Background and Aims: We performed a systematic review and meta-analysis to evaluate the comparative risk of serious infections with tumor necrosis factor-α (TNFα) antagonists, biologic agents that do not inhibit TNFα, tofacitinib, and immunosuppressive agents in inflammatory bowel diseases (IBD).

Methods: Through a systematic search until March 18, 2018, we included 15 observational studies (>500 person-years) in patients with IBD treated with TNFi, non-TNFi biologics, tofacitinib and/or IS monotherapy (thiopurines, methotrexate), reporting the risk of serious infections. Studies reporting active comparators were included, to allow appropriate comparative synthesis. We performed random effects meta-analysis and estimated relative risk (RR) and 95% CIs.

Results: Compared to monotherapy with a TNFα antagonist, risk of serious infection increased with the combination of a TNFα antagonist and an immunosuppressive agent (in 6 cohorts; RR, 1.19; 95% CI, 1.03–1.37), with a TNFα antagonist and corticosteroids (in 4 cohorts; RR, 1.64; 95% CI, 1.33–2.03), or with all 3 drugs (in 2 cohorts; RR, 1.35; 95% CI, 1.04–1.77); there was minimal heterogeneity among studies. In contrast, monotherapy with an immunosuppressive agent

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Author Contribution

- Study concept and design: SS, AF
- Acquisition of data: SS, AF
- Analysis and interpretation of data: SS
- Drafting of the manuscript: SS
- Critical revision of the manuscript for important intellectual content: AF, PSD, VJ, WJS
- Approval of the final manuscript: SS, AF, PSD, VJ, WJS
- Guarantor of Article: SS

was associated with a lower risk of serious infections than monotherapy with a TNFα antagonist (7 cohorts; RR, 0.61; 95% CI, 0.44–0.84) or a TNFα antagonist with an immunosuppressive agent (2 cohorts; RR, 0.56; 95% CI, 0.39–0.81). Infliximab-based therapy was associated with lower risk of serious infections as compared to adalimumab-based therapy in patients with ulcerative colitis (4 cohorts; RR, 0.57 [0.33–0.97]), but not Crohn's disease (4 cohorts; RR, 0.91 [0.49–1.70]). Few data are available on the comparative safety of biologic agents that do not inhibit TNFα and tofacitinib.

Conclusion: Combination therapies for IBD that include TNFα antagonists, especially with corticosteroids, are associated with higher risk of serious infection, whereas monotherapy with an immunosuppressive agent is associated with lower risk, compared to monotherapy with a TNFα antagonist. Studies are needed to evaluate the comparative safety of biologic agents that do not inhibit TNFα and tofacitinib for treatment of IBD.

Keywords

UC; Crohn's disease; vedolizumab; ustekinumab

INTRODUCTION

Inflammatory bowel diseases (IBD) are associated with significant morbidity, high burden of hospitalization, surgery and need for corticosteroids and biologic and/or immunosuppressive agents in a subset of patients with moderately to severely active disease. In a nationally representative cohort study, we estimated that high-need, high-cost patients with IBD spend approximately 3.7 days in the hospital/month, and serious infections are one of the leading causes for hospitalization.[1, 2] Both underlying active disease, as well as treatment with immune suppressing therapy contributes to an increased risk of serious and opportunistic infections in these patients.[3–6]

Comparative risk of treatment-related complications is an important attribute during shared decision-making regarding treatment choice in patients with IBD. However, to date, there has been limited comparative synthesis of the risk of serious infections with different biologic and/or immunosuppressive agents in patients with IBD, when used as monotherapy or in combination with each other. Most prior studies and meta-analyses on the topic have several inherent limitations, including (1) selective evaluation of participants in clinical trials or open-label extension of trials pre-selected for patients with clinical response to treatment of interest, (2) non-comparative studies, evaluating risk of serious infections with exposure to specific medications vs. no treatment, (3) heterogeneous studies, comparing particular exposure to a diverse and heterogeneous group of comparators (non-exposure to medication of interest, 5-aminosalicylates), (4) combined a variety of outcomes under the umbrella of serious infections, and (5) inclusion of studies that may not adequately adjust for important confounders related to risk factors for serious infections, IBD disease activity and concomitant medication use. Moreover, these meta-analyses have not evaluated the comparative risks of serious infections with newer non-tumor necrosis factor inhibitor (TNFi) biologics such as vedolizumab, ustekinumab and small molecule inhibitors like tofacitinib. Network meta-analysis of clinical trials are not powered to detect differences in

risk of serious infections due to their relative rare occurrence and short-term follow up, are highly selective and provide indirect comparisons.[7–9]

Hence, we evaluated the comparative effect of TNFi, non-TNFi biologic agents, tofacitinib, and/or immunosuppressive agents (thiopurines, methotrexate) on the risk of serious infections in patients with IBD. By focusing on comparative studies, using TNFi as a common reference, we sought to minimize conceptual heterogeneity across studies to more optimally inform evidence.

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.[10]

Selection Criteria

We screened cohort studies that met the following inclusion criteria: (1) patients with IBD, (2) treated with TNFi, non-TNFi biologics (vedolizumab, ustekinumab), tofacitinib and/or immunosuppressive (IS) agents (thiopurines, methotrexate), (3) reporting risk of serious infections (requiring hospitalization and/or intravenous antibiotics), with (4) minimum follow-up of 500 person-years (to improve generalizability and minimize risk of selection bias). From these, only studies that reported comparative risk estimates with different medications were included, i.e., comparator group included patients treated with IS, TNFi, and/or non-TNFi biologics. If studies reported results from multiple databases in same study, each database was treated as an independent cohort if feasible.

The following studies were excluded: (1) non-comparative studies (in which infection risk was reported in patients exposed vs. not exposed to medication of interest), (2) studies in which comparator group included only 5-aminosalicylate-treated patients (to avoid confounding by disease severity and focus analyses on patients with moderate-severe disease severity), (3) studies reporting risk of any infection or opportunistic infections that do not result in hospitalization and/or need for intravenous antibiotics (i.e., do not meet definition of serious infections, regardless of etiology), and (4) studies performed in patients with other, non-IBD, autoimmune diseases. We also excluded open-label extension of clinical trials that were often non-comparative, and selected patients with response to medication of interest. Placebo-controlled, randomized clinical trials were excluded due to highly selective inclusion of patients, short duration of induction studies, selective nature of trials of maintenance therapy (generally including patients with clinical response to induction therapy). Meta-analyses of risk of serious infections from these clinical trials have previously been published. Findings from active comparator trials of immunosuppressive therapy with minimum follow-up of 6 months are discussed qualitatively.

Data Sources, Search Strategy and Study Selection

The search strategy was designed and conducted by an experienced medical librarian with input from study investigators, utilizing various databases from inception to March 18, 2018. The databases included Ovid Medline, Ovid EMBASE, Scopus, Web of Science, Ovid

Cochrane Central Register of Controlled Trials, and Ovid Cochrane Database of Systematic Reviews. Controlled vocabulary supplemented with keywords was used to search for studies reporting infection risk in patients with IBD. Details of the search strategy are shown in the online supplement. Two authors (SS, AF) independently reviewed the title and abstract of studies identified in the search to exclude studies that did not answer the research question of interest, based on pre-specified inclusion and exclusion criteria. The full text of the remaining articles was independently reviewed, to determine whether it contained relevant information. Next, we manually searched the bibliographies of the selected articles, as well as review articles on the topic for additional articles. In addition, we searched clinical trial registries (www.clinicaltrials.gov and www.clinicaltrialsregister.eu), and abstracts from conference proceedings between 2014–18 (Digestive Diseases Week, American College of Gastroenterology annual meeting, European Crohn's and Colitis Organization annual meeting) for additional studies.

Data Abstraction and Risk of Bias Assessment

After study selection, two authors (SS, AF) independently abstracted data on study and patient characteristics, exposure variables, outcomes, confounding variables and statistical analyses, using a standardized data abstraction form. The following data were collected from each study: (a) study characteristics: primary author, time period of study including period of recruitment and follow-up/year of publication, country of origin, study design (clinical registries vs. administrative claims-based vs. medical record review; prospective vs. retrospective; new-user vs. prevalent user design), study duration (timing of outcome assessment), factors pertinent to risk of bias assessment; (b) patient characteristics: approach to identifying patients with IBD, age, sex, smoking status, comorbidities, prior infections and/or treatment with antibiotics, disease characteristics (severity, phenotype, duration, etc.), concomitant medications (corticosteroids, IS); (c) exposure characteristics: classification of medication exposures (TNFi, non-TNFi biologics, tofacitinib and IS), whether patients could be included only once vs. multiple times with different exposures, timing of occurrence of event in relation to exposure ('on-treatment' [event occurs during active therapy with exposure], 'as-treated' [event occurring either on-treatment or within 1–4 month period after drug discontinuation] or 'ever-exposed' [event occurring any time after initiation of therapy, regardless of whether patient is on- or off-therapy at time of event], how medication exposures, outcome and covariates were ascertained; (d) outcomes studied: type and definition of outcomes, incident events; (e) potential confounding variables accounted for in analysis including IBD disease activity (objectively or via surrogates), disease duration, infection risk factors including prior infections, and use of IBD- and other medications; and (f) statistical approach: unadjusted and adjusted hazard ratio (HR), relative risk (RR) or odds ratio (OR) and 95% confidence intervals (CI), incidence rate of events in each exposure group, and methods to control for bias including use of propensity score methods and inclusion of time-varying covariates.

Risk of bias was assessed by 2 investigators (SS, AF) independently, using the Quality In Prognosis Studies tool, which evaluates validity and bias in studies of prognostic factors across six domains: participation, attrition, prognostic factor measurement, confounding measurement and account, outcome measurement, and analysis and reporting.[11]

Outcomes Assessed

The primary outcomes of interest were comparative risk of serious infections in patients exposed to TNFi-based combination therapy (TNFi+IS, TNFi+corticosteroids, TNFi+IS +corticosteroids), non-TNFi biologic therapy or IS monotherapy, using TNFi monotherapy as reference medication (for ease of comparability). From studies comparing different TNFi, we compared risk of serious infections between infliximab vs. adalimumab.

In order to evaluate stability of the association between different medication exposures and risk of serious infections, and to examine potential sources of heterogeneity, we performed several *a priori* subgroup analyses for comparisons informed by >5 studies, based on: adjustment for IBD disease severity, prior infections (only incident infectious events vs. prior serious infections included); study design (claims-based analysis vs. registry studies vs. medical record review); and analysis approach (propensity score-matched or -adjusted analysis vs. only multivariable or univariable analysis). When different studies used the same databases but over different time periods with partial overlap, sensitivity analysis was performed after excluding overlapping cohorts.

Statistical Analysis

We used the random-effects model described by DerSimonian and Laird to calculate summary RR and 95% confidence intervals (CI).[12] Maximally adjusted risk estimates were used for analysis to account for confounding variables. To estimate what proportion of total variation across studies was due to heterogeneity rather than chance, an I^2 statistic was calculated.[13] An I^2 value of <30%, 30%−60%, 60%−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 <0.10 was considered statistically significant. Publication bias was assessed qualitatively using funnel plots when >10 studies were identified for a comparison.[14] All analyses were performed using Comprehensive Meta-Analysis version 2.0 (Englewood, New Jersey).

RESULTS

From 11,947 unique studies identified using our search strategy, full text of 115 studies were reviewed in detail, and eventually 15 studies were included in the quantitative analysis;[15–29] in addition, three studies comparing TNFi-based therapy vs. chronic corticosteroids and non-TNFi biologics vs. TNFi-based therapy were evaluated qualitatively.[30–32] Figure 1 shows the study selection flowsheet. Of these 15 studies, nine utilized administrative claims databases (using a collaborative multi-database study including Medicaid Analytic Extract linked to Medicare, Tennessee Medicaid, two US states' Medicare, Kaiser Permanente, nationwide population-based cohorts from France and Denmark, regional population-based cohorts from British Columbia and Lazio, Italy, and claims analyses from OptumLabs data warehouse),[18–26] three were sponsored post-marketing registry studies,[15–17] and three involved single- or multicenter cohorts.[27–29]

Table 1 shows the study-level characteristics of included studies. Eight studies were conducted in Europe and four studies were conducted in North America. Nine studies adjusted for IBD disease activity or severity; six studies adjusted for prior serious infections and/or antibiotic use. The minimum median follow-up across included studies was 6 months; 14/15 studies had median follow-up ≥12 months. Claims-based studies relied on validated international classification of diseases, version 9 or 10 (ICD-9/10) algorithms to identify patients with IBD, generally including two outpatient codes or single inpatient ICD-9 code for IBD, in combination with use of IBD-related medications. Likewise, most administrative claims studies relied on validated claims-based diagnostic criteria for identification of patients with serious infections (requiring inpatient hospitalization). All studies except one attributed outcomes to exposure only if they occurred 'on-treatment' or within 4 months of drug discontinuation.[17] Overall, most included studies were at moderate risk of bias (Supplementary Table 1). Due to the limited number of studies for each comparison (<10), formal evaluation of publication bias was not performed.

Etiology of serious infections by organism and organ system, where reported, is summarized in Supplementary Table 2. Respiratory, skin and soft tissue and gastrointestinal infections including intra-abdominal and perianal abscess were the most common sites of infections. While clinical trials were not included in quantitative synthesis, findings from three pivotal active comparator clinical trials comparing TNFi monotherapy vs. IS monotherapy vs. TNFi combination therapy are summarized in Supplementary Table 3.[33–35] Of the three trials, risk of serious infections was reported in only one trial, SONIC.[33] In this study, rate of serious infections was 4.9%, 5.6% and 3.9% in patients treated with infliximab monotherapy, thiopurine monotherapy and combination therapy with infliximab and thiopurines, respectively.

Tumor necrosis factor inhibitors vs. immunosuppressive agents

Five studies (7 cohorts) reported comparative risk of serious infections with TNFi monotherapy vs. IS monotherapy.[16, 18–21] Across studies, median (range) of serious infections with TNFi monotherapy and IS monotherapy was 3.9 (0.4–11.1) and 2.2 (0.9–11.2) per 100 patient-years, respectively. On meta-analysis, TNFi monotherapy was associated with 64% higher risk of serious infections, as compared to IS monotherapy (RR, 1.64 [1.19–2.27]), with moderate heterogeneity (I^2=59%) (Figure 2). Overall results were consistent in subgroup analysis based on adjustment for IBD disease severity, prior infections, study design and analysis approach (Table 2). In two cohorts reporting risk of TNFi+IS vs. IS monotherapy, combination therapy was associated with 78% higher risk of serious infections (RR, 1.78 [1.24–2.57]).[15, 20]

Tumor necrosis factor inhibitors vs. other non-TNFi biologic agents

No full text articles comparing risk of serious infections between patients treated with TNFi vs. non-TNFi biologic agents were identified. In a multi-center consortium, Lukin and colleagues reported a trend towards lower risk of serious infections in patients treated with vedolizumab-based therapy vs. TNFi-based therapy (6.9% vs. 10.1%; odds ratio [OR], 0.67 [0.41–1.07]), particularly amongst patients treated with monotherapy (4.1% vs. 10.1%; OR, 0.37 [0.13–1.02]), but not amongst patients treated with biologic therapy in combination

with IS and corticosteroids (11.5% vs. 13.9%; OR, 0.81 [0.31–2.07]).[31] In contrast, in an administrative claims-based analysis, Osterman and colleagues did not any significant difference in the risk of serious infections in adalimumab- vs. vedolizumab-treated patients after adjusting for covariates (incidence rate ratio, 0.82 [0.49–1.37]).[32]

We did not identify any studies comparing either TNFi or vedolizumab with either ustekinumab or with tofacitinib. Amongst TNFi, six cohorts compared risk of serious infections between infliximab vs. adalimumab.[22–27] In patients with ulcerative colitis, risk of serious infections in infliximab-treated patients was lower as compared to adalimumab-treated patients (4 cohorts; OR, 0.57 [0.33–0.97]) with minimal heterogeneity (I^2=0%); in contrast, in patients with Crohn's disease, there was no significant difference in risk of serious infections in infliximab- vs. adalimumab-treated patients (4 cohorts; OR, 0.91 [0.49–1.70]), with moderate heterogeneity (I^2=40%).

Tumor necrosis factor inhibitors vs. chronic corticosteroids

In a single retrospective cohort study among Medicaid and Medicare beneficiaries from 2001 to 2013, Lewis and colleagues compared risk of serious infections in new users of TNFi vs. patients treated with chronic corticosteroids (>3000 mg prednisone or equivalent) over 12 months.[30] There was no significant difference in the risk of serious infections in patients treated with TNFi vs. those treated with chronic corticosteroids in patients with Crohn's disease (incidence rate, 6.6 vs. 7.7 per 100py; OR, 0.98 [0.87–1.10]) or in patients with ulcerative colitis (incidence rate, 4.7 vs. 5.5 per 100py; OR, 0.99 [0.78–1.26]).

Tumor necrosis factor inhibitor-based combination therapy vs. TNF inhibitor monotherapy

On meta-analysis of 6 cohorts, TNFi+IS was associated with 19% higher risk of serious infection as compared to TNFi monotherapy (RR, 1.19 [1.03–1.37]), with minimal heterogeneity (I^2=8%) (Figure 3).[15–17, 20, 21, 28] Overall results were consistent in subgroup analysis based on adjustment for IBD disease severity, prior infections, study design and analysis approach (Table 2).

In contrast, combination therapy of TNFi+corticosteroids was associated with 64% higher risk of serious infection as compared to TNFi monotherapy (4 cohorts; RR, 1.64 [1.33–2.03]), with minimal heterogeneity (I^2=8%).[15, 17, 28, 29] Similarly, the combination of TNFi +IM+corticosteroids was associated with 35% higher risk of serious infection as compared to TNFi monotherapy (2 cohorts; RR, 1.35 [1.04–1.77]).[15, 28]

DISCUSSION

In this systematic review and meta-analysis of 15 cohort studies on the comparative risk of serious infections with TNFi, non-TNFi biologics and immunosuppressive agents in patients with IBD, we made several key observations. First, combination therapy with TNFi + IS associated only with a modestly higher risk (19%) of serious infections as compared to TNFi monotherapy. Second, TNFi monotherapy is associated with a 64% higher risk of serious infection as compared to immunosuppressive monotherapy; risk of serious infections may be comparable between TNFi-based therapy and chronic corticosteroids. Third, there is considerable paucity of comparative safety studies between TNFi and newer non-TNFi

biologics and targeted small molecules in patients with IBD, which is a key knowledge gap. Taken together, this data suggests that risk of serious infections may be lower with immunosuppressive agents, followed by TNFi monotherapy and chronic corticosteroids, and the risk is only modestly higher with combination therapy of TNFi + IS. The comparative safety of newer non-TNFi biologics while promising remains to be studied comprehensively. Interpreting these data in the context of comparative efficacy in inducing and maintaining corticosteroid-free remission and minimizing the risk of disease-related complications of surgery and hospitalization may inform shared decision-making.

Besides biologic and/or immunosuppressive therapy, most consistent disease-related factors associated with risk of serious infections in patients with IBD include severe disease activity, advanced age, exposure to corticosteroids and narcotic use.[3–6, 36] Underlying severely active disease may increase risk of serious infections through impaired immune surveillance, increased risk of abdominal infections (for example, intra-abdominal or perianal abscesses in patients with penetrating Crohn's disease), malnutrition or through need for repeated courses of corticosteroids to temporarily improve inflammation-driven symptoms. We observed that combination therapy with TNFi + IS has only a modestly higher risk of serious infections as compared to TNFi monotherapy. In a multi-center cohort study on the safety of vedolizumab published since this literature search, Meserve and colleagues observed that the incidence of serious infections was comparable in patients treated with vedolizumab monotherapy vs. vedolizumab + IS (5.2 per 100py exposed vs. 5.8/100py, respectively).[37] However, with the addition of corticosteroids to either vedolizumab monotherapy (9.5/100py) or vedolizumab + IS (12/100py), risk of serious infections was significantly higher. This probably reflects more severe disease in patients needing corticosteroids. Combination therapy is the most effective treatment strategy in inducing and maintaining corticosteroid-free remission, and decreasing the risk of IBD-related complications such as surgery and hospitalization.[33, 38, 39] Similarly, in the active comparator SONIC trial in biologic- and immunosuppressive-naïve patients with CD, risk of serious infections was numerically lower in patients treated with combination of infliximab and thiopurines (3.9%), as compared to patients treated with infliximab monotherapy (4.9%) and thiopurine monotherapy (5.6%).[33] It is conceivable that combination therapy, by effectively controlling disease activity and maintaining corticosteroid-free remission, may offset a theoretically higher risk of serious infections, particularly those directly related to IBD. Gastrointestinal infections, in particular intra-abdominal and perianal abscesses were one of the most causes of serious infections in this synthesis, and may be disease-related. However, available data did not permit further testing of this hypothesis, which merits further evaluation.

We also observed a higher risk of serious infections with TNFi monotherapy as compared to immunosuppressive agents. While TNFi and corticosteroids are associated with excess risks of all types of infections, thiopurines are primarily associated with excess risk of opportunistic viral infections, some of which may be serious, requiring hospitalization.[36] In a recent comprehensive nationwide French cohort study, Kirchgesner and colleagues observed a lower risk of opportunistic viral infections with TNFi monotherapy vs. thiopurine monotherapy, and no significant difference in risks between combination therapy vs. thiopurine monotherapy.[20] This may be attributed to thiopurine-induced lymphopenia.[40] Our findings on the magnitude of excess risks of serious infections with TNFi monotherapy over

thiopurine monotherapy were stable when limited to studies that indirectly adjusted for disease severity, suggesting that it may be true excess risks rather than confounding by disease severity. Chronic corticosteroids are frequently, excessively and often chronically used in the management of IBD, due to an under-appreciation of risks associated with this therapy and unwillingness or providers and patients to wean them in a timely manner. In a matched study in patients on Medicare/Medicaid, Lewis and colleagues observed that the risk of serious infections was comparable with chronic corticosteroid use and TNFi-based therapy.[30] In this study, chronic corticosteroid use was associated with an increased risk of death and major adverse cardiovascular events as compared to TNFi-therapy, particularly in patients with Crohn's disease. Similarly, in a retrospective study using the Veterans Affairs database, Waljee and colleagues observed that 17% patients with IBD received prolonged treatment with corticosteroids, which was associated with a higher risk of serious infections, thromboembolic events and pathologic fractures.[41]

There has been a considerable expansion in treatment options for patients with IBD over the last 5 years, with availability of non-TNFi biologic agents (vedolizumab, ustekinumab) and targeted small molecules like tofacitinib. Some of these medications premise a superior safety profile over TNFi by virtue of more targeted immunosuppression. In clinical trials of vedolizumab, there was no significant increase in risk of serious infections compared to patients treated with placebo, attributed to its gut selectivity.[42] However, there has been limited real-world comparative safety assessment with other biologics and immunosuppressive agents. In a preliminary study using VICTORY consortium, Lukin and colleagues observed a trend towards lower risk of serious infections with vedolizumab vs. TNFi, this benefit was most apparent in patients treated with monotherapy; combination therapy, particularly with addition of corticosteroids seemed to mitigate any potential safety benefit of vedolizumab over TNFi.[31] In a network meta-analysis of clinical trials of biologic agents, Bonovas and colleagues did not observe any significant difference in risk of serious infections between anti-integrin agents and TNFi on indirect comparison.[7] However, clinical trials have highly restrictive inclusion criteria not adequately representative of real-world clinical practice, and by design, trials of maintenance therapy include patients who respond to induction therapy and may be at lower risk of serious infections.

There are several strengths of this systematic review including: (a) direct comparative assessment of risk of serious infections with TNFi, non-TNFi biologics, tofacitinib and immunosuppressive agents; (b) minimal heterogeneity across all analyses, through well-defined inclusion and exclusion criteria, carefully excluding studies where the exposure was compared to a diverse and heterogeneous group of comparators, and (c) multiple subgroup analyses confirmed the stability and consistency of findings, including those that adjusted for risk factors for infection and disease activity. Our findings are generally comparable to findings from large drug-specific registries like TREAT, attesting to the validity of these findings. There are several limitations in our study. First, the meta-analysis included only observational studies. Observational studies lack the experimental random allocation of the intervention necessary to test exposure-outcome hypotheses optimally. Despite adjusting for several covariates, it is not possible to eliminate the potential of residual confounding, especially with regard to factors that go into prescribing specific medications to patients through factors not easily captured via claims or registry-based analyses. We excluded

clinical trials from quantitative synthesis due to highly restrictive inclusion criteria not adequately representative of real-world clinical practice, and by design, trials of maintenance therapy include patients who respond to induction therapy and may be at lower risk of serious infections. Second, there were subtle differences in the definition of exposures, particularly of combination therapy. In several studies, on-treatment, time-varying exposure to corticosteroids was not well characterized. However, as noted above, there was minimal heterogeneity in our analysis, and results were stable on multiple subgroup analyses, including analytic approach. Third, there were several differences between studies that we could not adequately account for, such as duration of IBD, objective assessment of disease behaviour and activity, concomitant medications, including dose of corticosteroids and use of narcotics. Fourth, we were unable to rule out the presence of a publication bias. With the limited number of studies, statistical testing for publication bias assessment is not recommended. We tried to minimize the potential for this by carefully examining published abstracts, as well as reviewing clinical trial websites.

In conclusion, based on a systematic review and meta-analysis of cohort studies, we estimated the comparative risk of serious infections with commonly used immune suppressing therapies in patients with IBD. We observed a modestly higher risk of serious infections with combination therapy over TNFi monotherapy, and a higher risk of TNFi monotherapy over immunosuppressive monotherapy. With the availability of several newer non-TNFi biologics and targeted small molecules, well-designed comparative real-world studies are warranted to optimally inform risks associated with these agents, especially over longer-term horizons which are not captured within the confines of clinical trials. While awaiting such studies, patients at high risk of disease-related complications ought to be treated aggressively as appropriate with combination therapy, rather than conservatively due to fear of serious infections. In contrast, patients at high risk of treatment-related complications such as serious infections and low risk of disease-related complications should be treated cautiously weighing risk and benefit of therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of Interest

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AF - None

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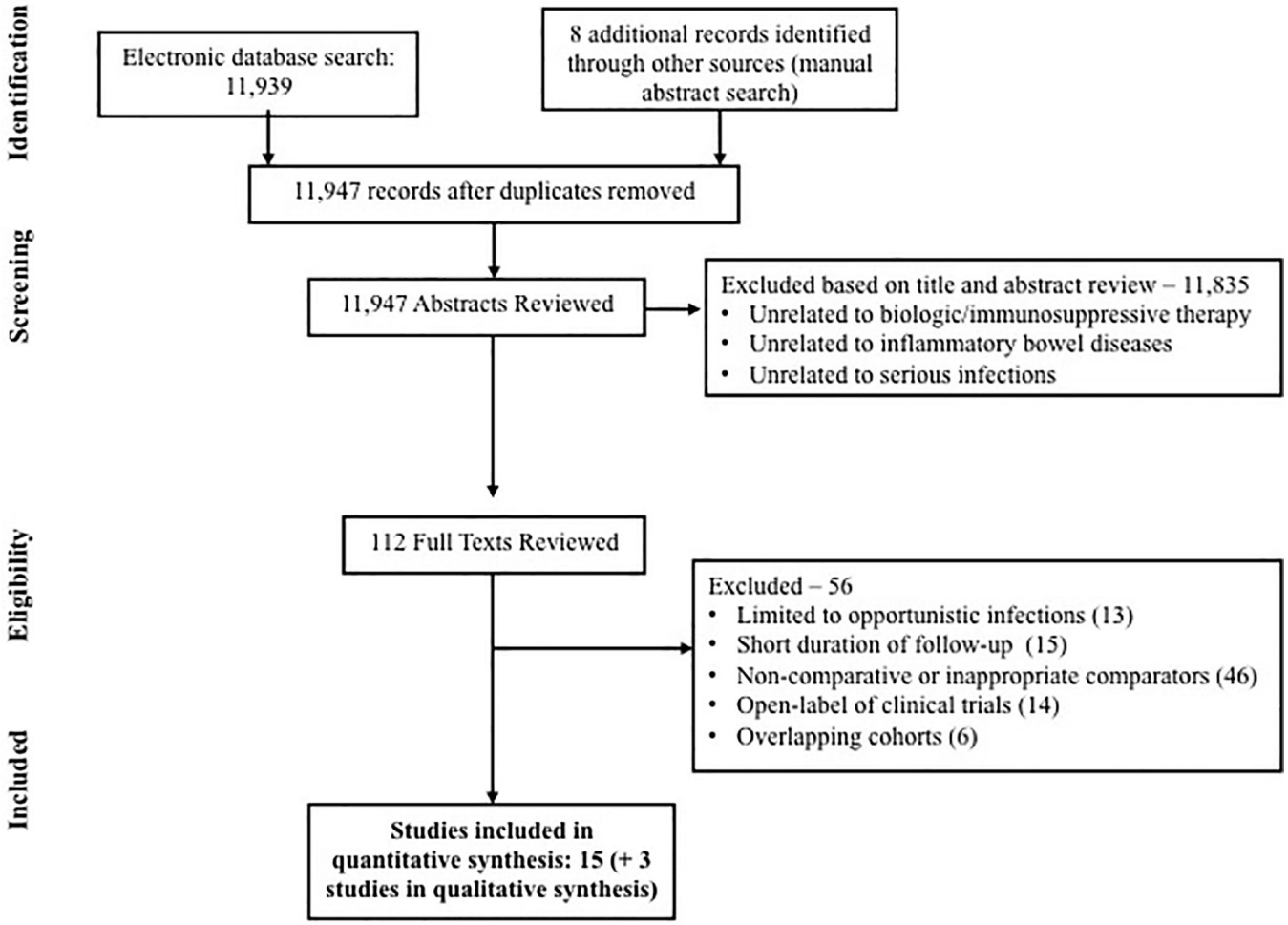

Figure 1.
Study selection flowsheet

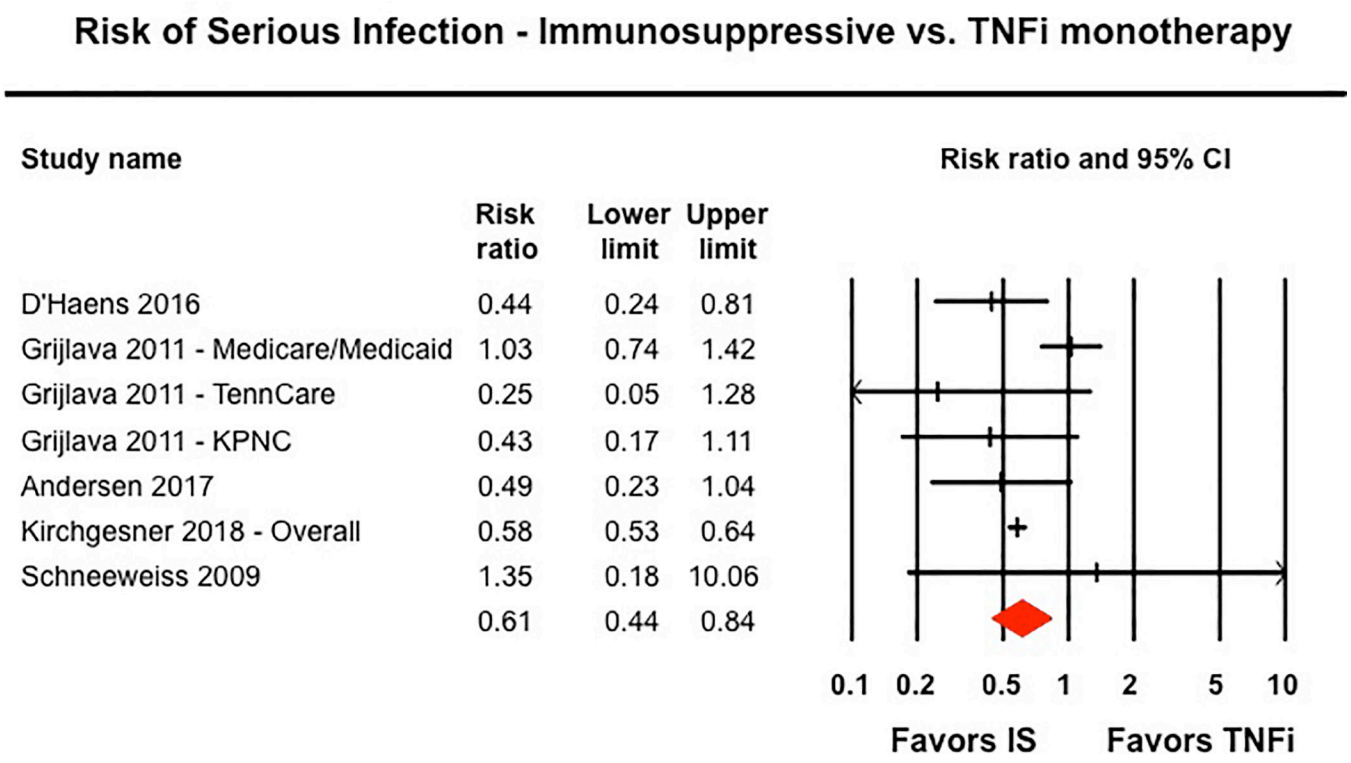

Figure 2.
Comparative risk of serious infections with immunosuppressive monotherapy vs. tumor necrosis factor inhibitor monotherapy

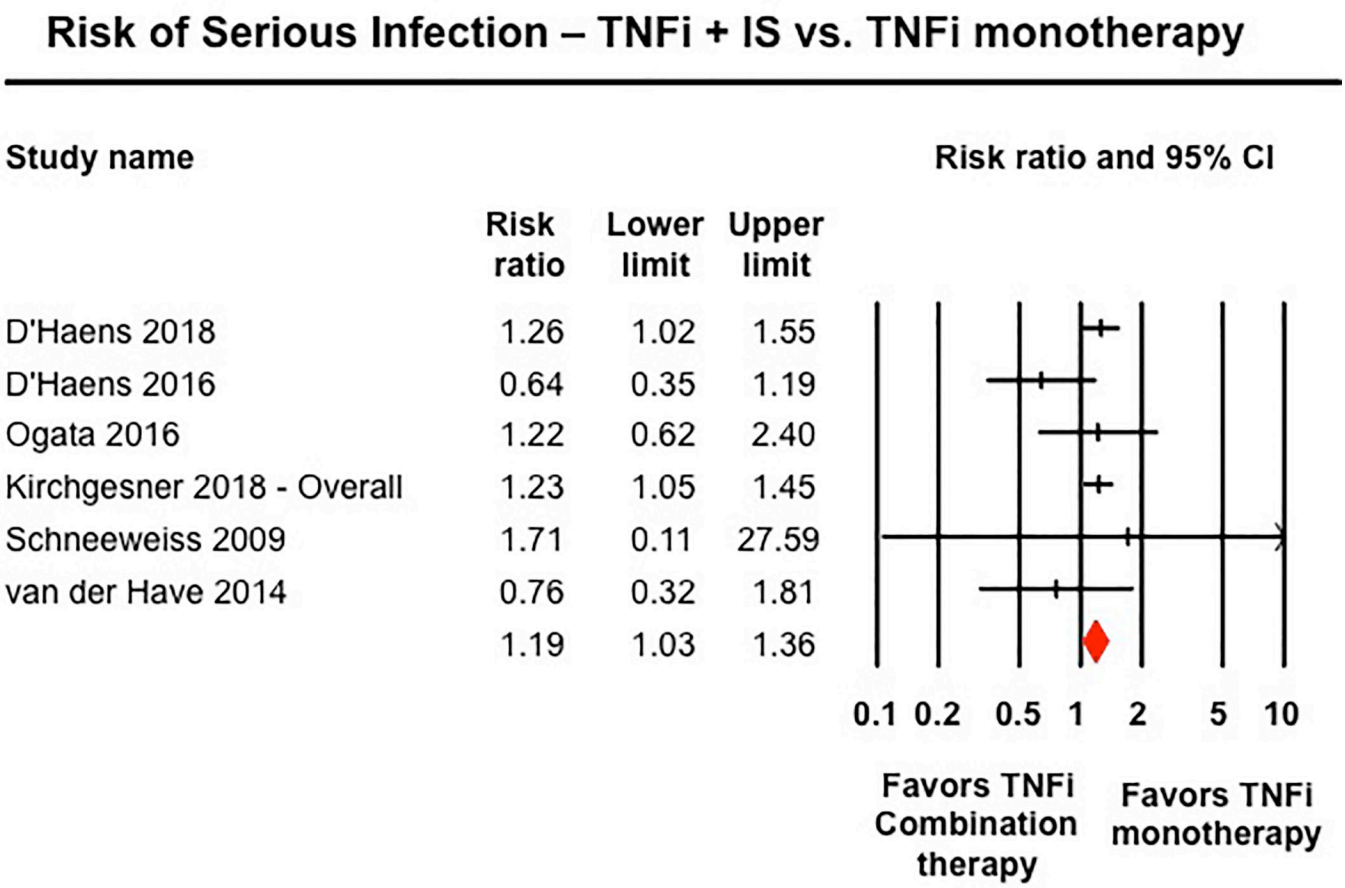

Figure 3.

Comparative risk of serious infections with the combination of tumor necrosis factor inhibitor and immunosuppressive agents vs. tumor necrosis factor inhibitor monotherapy

Table 1.

Characteristics of studies included in the analysis

First author, Year, ref.	Study design, location, setting, # patients	Time period, follow-up	Outcomes; # of events	Medications		Analytical approach	Variables adjusted for
				Exposure, #	Comparator, #		
REGISTRY-BASED STUDIES							
D'Haens 2018; PYRAMID[15]	Multi-center (24 sites); prospective, post-marketing registry of 5025 ADA-treated patients; new-users	Enrolled 2007–09, followed for 6 years (16680py)	Serious infections based on MedDRA v18.1 (N=556, 11.1%); IR=4.7/100py; as-treated (last dose + 70 days)	• ADA+IM (1217 patients): 4.8/100py; • ADA+CS (882 patients): 6.4/100py • ADA+IM+CS (581 patients): 5.0/100py	ADA mono (2345 patients): 4.2/100py	Incidence rate ratio	None
D'Haens, 2017; ENCORE[16]	Europe (9 countries), prospective, post-marketing registry of 1839 IFX-treated patients; new-users	Enrolled 2003–08, followed for 5 years (3687py)	Serious infections (definition NR) (N=98, 5.3%); IR=2.7/100py; as-treated (last dose + 90 days)	• IFX+IM (1276 patients): 2.5/100py; • IFX mono (563 patients): 3.9/100py	IM mono (642 patients): 1.8py	Incidence rate ratio	None
Ogata, 2016[17]	Japan; prospective, post-marketing registry of 1693 ADA-treated patients; new-users	Enrolled 2010–12, followed for 24 weeks (781py)	Serious infections based on MedDRA v15.0; IR=6.6/100py; ever-treated	• IFX+IM: OR, 1.22 (0.62–2.39); • IFX+CS: OR, 2.28 (1.17–4.44)	IFX mono (OR, 1.0)	Multi-variable logistic regression with stepwise model variable selection	4,7
ADMINISTRATIVE CLAIMS-BASED STUDIES							
Grijlava, 2011[18]	USA; SABER including 4 databases: Medicaid Analytic Extract linked to Medicare, Tennessee Medicaid, two US states Medicare, Kaiser Permanente; retrospective cohort of 4646 TNFi or IM-treated patients; new-user design; multiple unidirectional exposures per patient	1998–2007; 12 months (1887py)	Serious infections requiring hospitalization (primary discharge diagnosis), based on ICD-9 codes; IR=10.2/100py; as-treated (last dose + 30 days)	TNFi (2323 patients): 10.9/100py	IM (2323 patients): 9.6/100py	Incidence rate ratio; propensity score adjusted, cox proportional hazard analysis	1–7
Andersen, 2015[19]	Denmark; retrospective nationwide population-based cohort of 3086 TNFi or IM-treated patients; new-user design; single unidirectional exposure per patient	2002–12; 12 months (NR)	Serious infections requiring hospitalization (primary or discharge diagnosis), based on ICD-10 codes (29 events in 536 PS-matched patients); IR=NR; as-treated (last dose + 90 days)	TNFi monotherapy (268 patients): HR, 2.05 (0.97–4.36)	IM monotherapy (268 patients): HR, 1.0	Propensity score matched, cox proportional hazard analysis	1–7
Kirchgesner, 2018[20]	France; retrospective population-based cohort study using national health insurance database of 85,850 TNFi- and/or IM-treated patients; new user design; multiple unidirectional exposures per patient	2009–14; 178,155py	Serious infections requiring hospitalization (primary discharge diagnosis), based on ICD-10 codes; as-treated (last dose + 30–60 days)	• TNFi+IM (12,023 patients): 2.2/100py • TNFi monotherapy (26,255 patients): 1.9/100py	IM monotherapy (47,572 patients): 1.1/100py	Marginal structural Cox proportional hazard models, with time-fixed and time-varying covariates	1–7

First author, Year, ref.	Study design, location, setting, # patients	Time period, follow-up	Outcomes; # of events	Medications		Analytical approach	Variables adjusted for
				Exposure, #	Comparator, #		
Schneeweiss, 2009[21]	British Columbia; retrospective population-based cohort using health insurance database of 10,662 IFX-, IM and/or CS-treated patients with IBD; new user design; multiple unidirectional exposures per patient	2001–06; 8707py	Serious infections requiring hospitalization (primary discharge diagnosis), based on ICD-9 codes; as-treated (last dose + 126 days)	• IFX+IM: 0.73/100py; • IFX+CS: −0/100py • IFX monotherapy: 0.43/100py	IM monotherapy: 0.89/100py	Cox proportional hazard analysis (sensitivity analysis with propensity score matching – results unchanged)	1–7
Singh, 2016[22]	USA; retrospective cohort using OptumLabs clinical data warehouse with 2040 IFX- or ADA-treated patients with Crohn's disease; new-user design; single unidirectional exposure per patient	2006–14; median follow-up, 19m (NR)	Serious infections requiring hospitalization (primary discharge diagnosis), based on ICD-9 codes; on-treatment events	IFX: 0.86/100py	ADA: 0.99/100py	Propensity score matched, Cox proportional hazard analysis	1,2,5,6
Singh, 2016[23]	USA; retrospective cohort using OptumLabs clinical data warehouse with 816 IFX- or ADA-treated patients with ulcerative colitis; new-user design; single unidirectional exposure per patient	2006–14; median follow-up, 19m (NR)	Serious infections requiring hospitalization (primary discharge diagnosis), based on ICD-9 codes; on-treatment events	IFX: 1.3/100py	ADA: 2.6/100py	Propensity score matched, Cox proportional hazard analysis	1,2,5,6
Singh, 2017[24]	Denmark; retrospective nationwide population-based cohort of 1719 IFX- or ADA-treated patients with ulcerative colitis; new-user design; single unidirectional exposure per patient	2005–14; median follow-up 1.3–2.3y	Serious infections requiring hospitalization (primary discharge diagnosis), based on ICD-10 codes; on-treatment events	IFX: 1.9/100py	ADA: 10.3/100py	Propensity score matched, Cox proportional hazard analysis	1,2,5,6
Singh, 2018[25]	Denmark; retrospective nationwide population-based cohort of 2908 IFX- or ADA-treated patients with Crohn's disease; new-user design; single unidirectional exposure per patient	2005–14; median follow-up 2.3y	Serious infections requiring hospitalization (primary discharge diagnosis), based on ICD-10 codes; on-treatment events	IFX: 1.1/100py	ADA: 1.1/100py	Propensity score matched, Cox proportional hazard analysis	1,2,5,6
Domenicantonio, 2018[26]	Italy; retrospective population-based cohort of 1432 IFX- or ADA-treated patients with Crohn's disease; new-user design; single unidirectional exposure per patient	2008–14; follow-up 2 years	Serious infections requiring hospitalization (primary discharge diagnosis), based on ICD-9 codes; 'as-treated' (last dose + 60 days)	CD IFX: 1.4/100py; UC IFX: 1.0/100py	CD ADA: 0.73/100py UC IFX: 1.44/100py	Propensity score adjusted, Cox proportional hazard analysis	1,2,5–7
PATIENT-LEVEL REVIEW OF RECORDS							
Lawrance, 2010[27]	Australia-New Zealand; multi-center prospective cohort of 517 IFX- or ADA-treated patients with IBD; single unidirectional exposure per patient	1999–2009, median follow-up 12m (NR)	Serious infections requiring hospitalization, based on medical record review; 'as-treated' (last dose + 90 days)	CD IFX: 8/339 UC IFX: 2/115	CD ADA: 4/53 UC ADA: 0/10	Univariate logistic regression	None
van der Have, 2014[28]	Netherlands; multi-center retrospective cohort of 611 IFX- or ADA-treated patients with IBD;	2000–10, median follow-up 2y (NR)	Serious infections requiring hospitalization, based on medical record review; 'as-treated' (last dose + 90 days)	• TNFi+IM (461 patients): OR, 0.76 (0.32–1.81) • TNFi+CS (135	TNFi monotherapy (122 patients): OR, 1.0	Univariate logistic regression	None

First author, Year, ref.	Study design, location, setting, # patients	Time period, follow-up	Outcomes; # of events	Medications		Analytical approach	Variables adjusted for
				Exposure, #	Comparator, #		
	new-user design; single unidirectional exposure per patient			patients): OR, 1.86 (0.54–6.37) • TNFi+IM+CS: 1.38 (0.29–6.59)			
Fidder, 2009[29]	Belgium, single-center retrospective cohort of 743 IFX-treated patients; new-user design; single unidirectional exposure per patient	1994–2008, median follow-up 58m (3775py)	Serious infections requiring hospitalization, based on medical record review; 'as-treated' (last dose + 12 weeks)	IFX+CS: OR, 2.69 (1.18–6.12)	IFX monotherapy	Poisson regression	None

[Abbreviations: ADA=Adalimumab; CS=Corticosteroids; IFX=Infliximab; IM=Immunomodulators (including thiopurines, methotrexate); IR=Incidence rate; NR=Not reported; OR=Odds ratio; py=person-years; SABER=The Safety Assessment of Biologic Therapy; TNFi=Tumor necrosis factor inhibitors].

Covariates: 1=Age, 2=Sex, 3=Race, 4=Socioeconomic status, 5=Comorbidities and healthcare utilization, 6=Disease severity, duration and/or behavior, 7=Prior infections or use of anti-bacterial agents

Table 2.

Subgroup analysis for comparison of (A) TNF inhibitor monotherapy vs. immumosuppressive monotherapy and (B) TNF inhibitor + immunosuppressive monotherapy vs. TNF inhibitor monotherapy in modifying the risk of serious infections in patients with inflammatory bowel diseases

Exposures	Subgroup types	Subgroups	# of cohorts	RR (95% CI)	P-value for difference between groups
(A) TNFi vs. IM	Adjusted for IBD disease severity	Yes	3	1.72 (1.57–1.89)	0.69
		No	2	1.50 (0.74–3.03)	
	Adjusted for prior infections	Yes	3	1.72 (1.57–1.89)	0.69
		No	2	1.50 (0.74–3.03)	
	Study design	Registry or medical record review	1	2.27 (1.24–4.15)	0.22
		Claims-based analysis	4	1.47 (1.04–2.08)	
	Analysis involved propensity score methods	Yes	3	1.50 (1.04–2.17)	0.49
		No	2	1.98 (0.98–4.02)	
(B) TNFi + IM vs. TNFi monotherapy	Adjusted for IBD disease severity	Yes	2	1.23 (1.05–1.45)	0.34
		No	4	1.03 (0.73–1.45)	
	Adjusted for prior infections	Yes	2	1.23 (1.05–1.45)	0.34
		No	4	1.03 (0.73–1.45)	
	Study design	Registry or medical record review	4	1.03 (0.73–1.45)	0.34
		Claims-based analysis	2	1.23 (1.05–1.45)	
	Analysis involved propensity score methods	Yes	1	1.23 (1.05–1.45)	0.39
		No	5	1.06 (0.79–1.43)	