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# Comparative safety and effectiveness of vedolizumab to tumour necrosis factor antagonist therapy for Crohn's disease

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## Summary

**Background:** Direct comparisons are lacking between vedolizumab and tumour necrosis factor (TNF)-antagonist therapy in Crohn's disease (CD).

**Aim:** To compare safety and effectiveness of vedolizumab and TNF-antagonist therapy in adult CD patients.

**Methods:** Retrospective observational cohort (May 2014–December 2017) propensity score-weighted comparison of vedolizumab vs TNF-antagonist therapy (infliximab, adalimumab, certolizumab) in CD. Propensity scores were weighted for age, prior treatments, disease complications, extent and severity, steroid dependence, and concomitant immunosuppressive drug use. The primary outcome was comparative risk for infections or non-infectious serious adverse events (requiring antibiotics, antivirals, antifungals, hospitalisation, or treatment discontinuation, or resulting in death). Secondary comparative effectiveness outcomes were clinical remission (resolution of CD-related symptoms), steroid-free clinical remission and endoscopic remission (absence of ulcers/erosions).

**Results:** We included 1266 patients (n = 659 vedolizumab). Rates of non-infectious serious adverse events (odds ratio [OR] 0.072, 95% confidence interval [CI] 0.012–0.242), but not serious infections (OR 1.183, 95% CI 0.786–1.795), were significantly lower with vedolizumab vs TNF-antagonist therapy. Safety comparisons for non-infectious serious adverse events remained significant after adjusting for differences in

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Matthew Bohm and Ronghui Xu equally contributed as first author.

See Appendix A for list of Collaborators.

The complete list of authors' affiliation are listed in Appendix B.

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duration of exposure. No significant difference was observed between vedolizumab and TNF-antagonist therapy for clinical remission (hazard ratio [HR] 0.932, 95% CI 0.707-1.228), steroid-free clinical remission (HR 1.250, 95% CI 0.677-2.310) or endoscopic remission (HR 0.827, 95% CI 0.595-1.151). TNF-antagonist therapy was associated with higher treatment persistence compared with vedolizumab.

**Conclusions:** There was a lower risk of non-infectious serious adverse events, but not serious infections, with vedolizumab vs TNF-antagonist therapy, with no significant difference for achieving disease remission.

## 1 | INTRODUCTION

Crohn's disease (CD) is an inflammatory bowel disease that can affect the entire intestinal tract and is characterised by mucosal ulcerations, diarrhoea, and abdominal pain. Over time a subset of patients can progress to development of stricturing or penetrating disease complications. Treatment with biologics has been shown to prevent hospitalisation and progression to surgery, with tumour necrosis factor (TNF) antagonists representing the mainstay of biologic therapy.<sup>1</sup> Although effective, TNF antagonists can be associated with serious and sometimes life-threatening treatment-related adverse events, including serious or opportunistic infections, and malignancy.<sup>2</sup> Alternative biologic therapies with more targeted mechanisms of action would potentially be advantageous to help avoid these off-target risks of TNF antagonists.

Vedolizumab, a monoclonal anti-integrin antibody that targets the  $\alpha 4\beta 7$  integrin receptor, is approved for the treatment of moderately to severely active CD. The integrated safety analysis of the phase 3 clinical trial programmes and long-term safety extension studies observed no increased risk for serious infections with vedolizumab compared to placebo,<sup>3</sup> and our own clinical practice experiences have similarly observed vedolizumab to be well tolerated, with a low rate of serious infections or serious adverse events.<sup>4</sup> The mechanism of action, combined with its observed safety profile in routine practice, has led to the consideration that vedolizumab is potentially safer than TNF-antagonist therapy in CD. However, indirect comparisons of phase 3 clinical trials have suggested that vedolizumab is the least effective treatment option for achieving disease remission in CD,<sup>5</sup> and no high-quality head-to-head comparisons have been done to specifically assess the theoretical comparative safety advantage.

We therefore studied the comparative safety and effectiveness of vedolizumab and TNF-antagonist therapy in adult CD patients using a multicentre propensity score (PS)-weighted cohort study. Using patient-level data from medical records, we compared the relative safety for developing serious infections or serious adverse events, as well as the comparative effectiveness assessment for achievement of disease remission.

## 2 | METHODS

We followed Good ReseArch for Comparative Effectiveness (GRACE) principles and good practice recommendations from the

joint International Society for Pharmacoeconomics and Outcomes Research and the International Society for Pharmacoepidemiology for real-world data comparative effectiveness studies.<sup>6,7</sup> The study protocol was posted to the Health Services Research Project website ([https://wwwcf.nlm.nih.gov/hsr\\_project/home\\_proj.cfm](https://wwwcf.nlm.nih.gov/hsr_project/home_proj.cfm)), and the results are reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cohort studies and reporting guidelines for PS analyses.<sup>8,9</sup>

### 2.1 | Study design and data source

This is a retrospective review of a North American-based consortium registry.<sup>10</sup> In brief, this is a multicentre collaborative research group in which outcomes are pooled for consecutive CD patients treated with biologics. Institutional review board approval was obtained from each site for ongoing data collection and transfer. Data were collected individually by sites using a standardised data collection form and transferred (after de-identification) to the coordinating site (University of California, San Diego) for data compilation and analysis. The current analysis represents data collected between May 2014 and December 2017.

### 2.2 | Participants

Patients from the consortium registry were included in the current analysis if they had (a) a confirmed diagnosis of CD based on clinical, endoscopic or histologic data; (b) active clinical symptoms attributed to CD prior to biologic therapy; and (c) at least one clinical or endoscopic follow-up after biologic initiation irrespective of response status after induction.

### 2.3 | Variables

Data on variables of interest were collected from sites, including patient characteristics (age at diagnosis, age at biologic initiation, gender, smoking status, body mass index [BMI]), disease characteristics (prior hospitalisations, disease-related complications, extraintestinal manifestations, and phenotype classified according to Montreal sub-classifications), and treatment history (steroids, immunomodulators and TNF $\alpha$  antagonists; duration of use; indication for discontinuation; and complications).

Variables of interest specific to biologic agent use were baseline disease severity or activity (endoscopic, radiographic, biochemical or clinical assessments), concomitant treatments (steroids or immunomodulators: azathioprine, 6-mercaptopurine, methotrexate) and follow-up assessments (endoscopic, radiographic or clinical assessments).

## 2.4 | Outcomes

Comparative safety outcomes were serious infections and serious adverse events. Serious infection was defined as any infection occurring after biologic initiation that required antibiotics, antifungals or antivirals or resulted in discontinuation of biologic therapy, hospitalisation or death. Serious adverse events were defined as having any infectious or noninfectious adverse event after biologic initiation that required antibiotics, antifungals, or antivirals or resulted in discontinuation of biologic therapy, hospitalisation or death.<sup>11</sup> Post-hoc comparisons were made for noninfectious serious adverse events because of the observed differences in event rates for this outcome in our population, and for the safety outcome of serious infections, limited to vedolizumab and TNF-antagonist monotherapy subgroups, because of the known risk of infections with concomitant immunosuppressive use.

Comparative effectiveness outcomes were clinical remission, steroid-free clinical remission, endoscopic remission and treatment persistence. Clinical remission was defined by complete resolution of CD-related symptoms based on the physician global assessment. Steroid-free remission was only assessed in those patients on either prednisone or budesonide at the initiation of biologic therapy and was defined as achieving clinical remission, tapering off steroids, and the absence of a subsequent steroid prescription within 1 month of achieving remission. Endoscopic remission was defined as absence of ulcers or erosions, and was limited to patients with confirmed ulcerations and/or erosions at baseline prior to treatment initiation. Treatment persistence took into consideration the occurrence of surgery, and patients were censored at the time of surgery irrespective of whether they continued therapy post-operatively because this was considered a treatment failure. The coordinating site used de-identified endoscopy reports to confirm endoscopic remission status, and any discrepancies were resolved through consensus between the study sites and the coordinating site.

## 2.5 | Statistical analyses

Because of the nonrandomised nature of this study, inverse probability weighting (IPW) with PS was used to estimate the average treatment effect (ATE) of vedolizumab vs TNF antagonist in our population. The PS provides an estimate of the individual probability of being treated with the intervention based on information available for that individual, to help account for treatment selection bias inherent in routine practice.<sup>12-14</sup>

For effectiveness outcomes, a Cox proportional cause-specific hazards model was used, with time to surgery treated as a competing

risk for effectiveness.<sup>15,16</sup> For the safety outcomes, a logistic regression model was used. Sensitivity analyses were done using optimal full match to assess for consistency in estimates across methodologies.<sup>13,17-19</sup> Safety data were further reported based on patient years of exposure and after limiting the cohort to patients with at least 12 months of follow-up.

### 2.5.1 | Propensity score model

Propensity score were calculated using R package “twang” (Toolkit for Weighting and Analysis of Nonequivalent Groups),<sup>20</sup> which estimates PS using boosted regression as the predicted probability of starting treatment with vedolizumab vs TNF-antagonist therapy, conditioned on the measured baseline variables thought to be confounders or predictors for the outcome of interest. Investigators used a combination of prior published literature, clinical experience and data availability within the current data set to generate a list of potential prognostic variables for consideration. An investigator-driven approach for confounding evaluation was chosen based on causal knowledge.<sup>21</sup> In addition, care was taken not to include those variables that were strongly correlated with exposure but only weakly correlated with the outcome.<sup>22-24</sup>

The final set of variables included for the clinical remission PS model was prior TNF-antagonist exposure and number of prior TNF antagonists to which the patient was exposed, disease extent (isolated small bowel, ileocolonic, isolated colonic), history of fistulising disease, prior bowel surgery, disease phenotype (stricturing/penetrating or not), clinical disease severity (severe vs nonsevere based on the physician global assessment), CD-related hospitalisation within the preceding 1 year, baseline steroid dependency or refractoriness, concomitant steroid use or concomitant immunomodulator use. Baseline C-reactive protein (CRP), albumin and BMI were not included because >25% of the cohort had missing baseline data for these variables. Post-hoc assessment of these variables revealed that they had no prognostic significance for the primary safety outcomes (serious infection or serious adverse events) or the primary effectiveness outcome (clinical remission), and therefore were unlikely to create an unmeasured confounder bias on the comparative estimates.

Stabilised weights were obtained and further trimmed to be within (0.1, 10), if necessary, before they were used for IPW approaches.<sup>14</sup> Adequacy of the PS model was examined by plotting the PS distributions in the vedolizumab vs TNF-antagonist groups and by the standardised mean difference of each covariate before and after weighting. The PS model was fit separately for all comparisons of effectiveness and safety between vedolizumab and TNF antagonists<sup>25</sup> and for subgroup analyses.<sup>25,26</sup>

## 2.6 | Subgroup analyses

A priori subgroup analyses were specified for the comparison of vedolizumab to TNF-antagonist therapy in TNF-antagonist-naïve

and -exposed patients and for vedolizumab vs infliximab and vedolizumab vs subcutaneous TNF antagonists (adalimumab or golimumab) separately. Subgroup comparison in TNF-antagonist-naïve and -exposed groups was conducted given prior evidence supporting an increased risk of serious infections and reduction in effectiveness with vedolizumab in TNF-antagonist-exposed individuals.<sup>3,27,28</sup> Subgroup comparisons to infliximab and subcutaneous TNF antagonists were performed separately to assess for the potential influence of medical (vedolizumab or infliximab) or pharmacy (subcutaneous TNF antagonists) benefits and market access as a determinant of treatment choice and comparative estimates.<sup>29</sup>

Exploratory post-hoc subgroup analyses were performed for the comparison of vedolizumab to TNF-antagonist therapy stratified by disease location and disease duration. Disease duration has been observed to significantly impact the achievement of disease remission with vedolizumab,<sup>30</sup> and ileal disease location has been observed to significantly impact the achievement of disease remission across all biologics.<sup>31</sup> To compare whether the hazard ratio (HR) of vedolizumab vs TNF-antagonist therapy was significantly different across disease location and disease duration subgroups, we performed the Wald test with 2 degrees of freedom in the PS-weighted analysis.

Secondary post-hoc analyses were also performed to understand if observed differences in duration of treatment exposure had an effect on observed differences in adverse events and comparisons between vedolizumab and TNF-antagonist therapy.

## 2.7 | Power calculation

In this observational nonrandomised cohort study, we used the observed event rates in the control group (TNF-antagonist-treated CD patients) to determine power calculations for unweighted comparisons of safety and effectiveness outcomes using the methodology described by Cohen et al.<sup>1,32</sup> For serious infections and serious adverse events we would need an observed event rate of 4% and 7% respectively in the vedolizumab treatment group to be powered for the comparison. For clinical remission we would need 256 observed events to achieve 90% power if the HR was 1.5 or higher between the two groups. If the HR of the effectiveness event were 2.0 or higher, we would need 88 events to achieve 90% power.

## 3 | RESULTS

### 3.1 | Baseline demographics

A total of 1266 patients were included, of whom 659 were treated with vedolizumab, 305 with infliximab and 302 with subcutaneous TNF-antagonist agents. Baseline demographics are reported in Table 1. The median duration of exposure was higher in the

TNF-antagonist group (508 days, interquartile range [IQR] 311-786; 932 patient years) vs the vedolizumab group (316 days, IQR 194-454; 603 patient years). The median duration of treatment persistence without the need for surgery was higher in the TNF-antagonist group (539 days, IQR 324-818) vs the vedolizumab group (340 days, IQR 213-483). At 6 and 12 months, after accounting for the occurrence of surgery as a censoring event, a larger number of TNF-antagonist-treated patients remained (531 and 417) compared with vedolizumab-treated patients (506 and 261). (Figure 1).

There was a slight female predominance among patients treated with vedolizumab compared with infliximab or subcutaneous TNF antagonist (57.8% vs 53.0% vs 46.6%) and a longer mean disease duration (12 vs 6 vs 3 years). Baseline mean CRP was higher in vedolizumab-treated patients (4.6 vs 0.7 vs 1.4 mg/L), and vedolizumab-treated patients more often had prior bowel resection (60.7% vs 47.0% vs 42.0%). Only 9.1% of vedolizumab-treated patients were TNF-antagonist naïve compared with 43.0% of subcutaneous TNF-antagonist-treated patients and 52.8% of infliximab-treated patients. Vedolizumab-treated patients were more often steroid dependent at baseline (37.5% vs 15.4% vs 19.9%) and more often taking concomitant steroids (45.8% vs 27.2% vs 26.5%). Prior TNF-antagonist exposure and number of prior TNF antagonists used constituted the most imbalanced variables at baseline between groups, but after weighting these were both well balanced, along with all other variables as assessed by standardised mean difference (Figure 2).

## 3.2 | Safety outcomes

### 3.2.1 | Serious infection rates and events

A total of 47 vedolizumab-treated and 47 TNF-antagonist-treated patients developed serious infections, with one death in each group due to serious infections. This equates to an unadjusted rate of 7.8 per 100 patient years for vedolizumab-treated patients and 5.1 per 100 patient years for the TNF-antagonist treated patients. When limiting the cohort to patients with at least 12 months of follow-up, the rate of serious infections was comparable between vedolizumab-treated (n = 24; 9.2%, 6.5 per 100 patient years) and TNF-antagonist treated (n = 39; 9.7%, 4.2 per 100 patient years) patients.

The most common serious infections were abscess (n = 8/47 vedolizumab, n = 6/47 TNF antagonist), *Clostridium difficile* (n = 7/47 vedolizumab, n = 5/47 TNF antagonist), other enteric infections (n = 5/47 vedolizumab, n = 7/47 TNF antagonist), skin infections (n = 3/47 vedolizumab, n = 2/47 TNF antagonist), upper and lower respiratory tract infections (n = 5/47 vedolizumab, n = 5/47 TNF antagonist) and shingles (n = 2/47 vedolizumab, n = 2/47 TNF antagonist). Two vedolizumab-treated patients developed gram-negative rod bacteraemia, one of whom died. One TNF-antagonist-treated patient died of Gram-negative rod bacteraemia.

**TABLE 1** Baseline patient characteristics

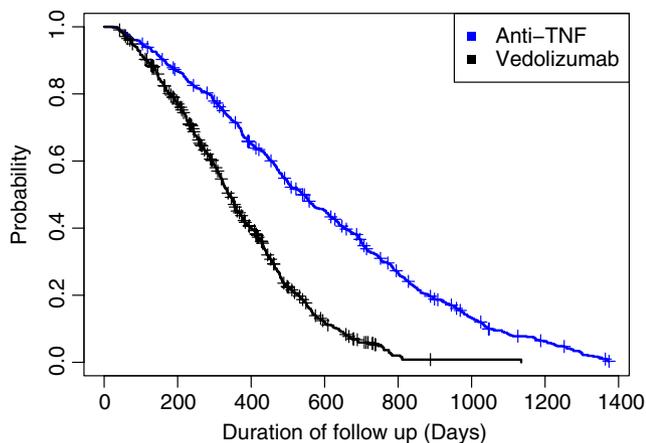
	Infliximab (n = 305)	Subcutaneous TNF antagonists (n = 302)	Vedolizumab (n = 659)
Patient years of exposure	477	458	602
Age (diagnosis), mean years (SD)	36.34 (15.11)	39.07 (16.21)	39.80 (15.39)
Age (biologic initiation), mean years (SD)	28.99 (14.53)	27.80 (13.76)	25.59 (13.81)
Gender (female), n (%)	142 (46.6)	160 (53.0)	381 (57.8)
BMI, mean kg/m <sup>2</sup> (SD)	25.19 (6.00)	25.25 (5.89)	25.48 (6.87)
Smoking status, n (%)			
Current	28 (9.2)	36 (11.9)	69 (10.5)
Former	54 (17.7)	58 (19.2)	112 (17.0)
Never	223 (73.1)	208 (68.9)	478 (72.5)
Disease duration, mean years (SD)	3 (10)	6 (17)	12 (13)
Ever hospitalised? n (%)			
Never	119 (39.0)	128 (42.4)	139 (21.1)
Yes (in the last year)	119 (39.0)	60 (19.9)	240 (36.4)
Yes (not in the last year)	67 (22.0)	114 (37.7)	280 (42.5)
CRP, mean mg/L (SD)	1.4 (6.6)	0.7 (1.9)	4.6 (15.83)
Albumin, mean g/dL (SD)	3.87 (0.60)	4.09 (0.50)	3.87 (0.54)
Rheumatic EIM (yes), n (%)	54 (17.7)	62 (20.5)	143 (21.7)
Ophthalmologic EIM (yes), n (%)	8 (2.6)	6 (2.0)	15 (2.3)
Dermatologic EIM (yes), n (%)	17 (5.6)	19 (6.3)	47 (7.1)
Hepatic EIM (yes), n (%)	1 (0.3)	4 (1.3)	11 (1.7)
Disease extent, n (%)			
L1	73 (23.9)	73 (24.2)	104 (15.8)
L2	71 (23.3)	57 (18.9)	140 (21.2)
L3	160 (52.5)	167 (55.3)	413 (62.7)
L4	1 (0.3)	5 (1.7)	2 (0.3)
Phenotype, n (%)			
B1	115 (39.1)	89 (29.6)	214 (32.6)
B2	43 (14.6)	59 (19.6)	161 (24.5)
B3	136 (46.3)	153 (50.8)	282 (42.9)
Fistulising disease history (yes), n (%)	138 (47.1)	111 (37.0)	240 (36.5)
Disease severity, n (%)			
Mild	30 (9.8)	48 (15.9)	101 (15.3)
Moderate	171 (56.1)	164 (54.3)	330 (50.1)
Severe	104 (34.1)	90 (29.8)	228 (34.6)
Endoscopic severity, n (%)			
Mild	48 (21.0)	57 (25.9)	102 (22.3)
Moderate	93 (40.6)	77 (35.0)	184 (40.3)
Severe	88 (38.4)	86 (39.1)	171 (37.4)
Prior surgery (yes), n (%)	128 (42.0)	142 (47.0)	400 (60.7)
Concomitant IM (yes), n (%)	145 (47.5)	136 (45.0)	272 (41.3)
Concomitant steroid (yes), n (%)	83 (27.2)	80 (26.5)	302 (45.8)
Steroid dependency (yes), n (%)	47 (15.4)	60 (19.9)	247 (37.5)
Prior TNF antagonist (yes), n (%)	144 (47.2)	172 (57.0)	598 (90.7)

(Continues)

TABLE 1 (Continued)

	Infliximab (n = 305)	Subcutaneous TNF antagonists (n = 302)	Vedolizumab (n = 659)
Number of prior TNF antagonists, n (%)			
0	161 (52.8)	130 (43.0)	60 (9.1)
1	116 (38.0)	130 (43.0)	161 (24.4)
2	25 (8.2)	36 (11.9)	253 (38.4)
3	3 (1.0)	5 (1.7)	183 (27.8)
4	0 (0.0)	1 (0.3)	2 (0.3)

Abbreviations: BMI, body mass index; CRP, C-reactive protein; EIM, extraintestinal manifestation; IM, immunomodulator; SD, standard deviation; TNF, tumour necrosis factor.



**FIGURE 1** Treatment persistence. Kaplan Meier plot for duration of follow-up. TNF, tumour necrosis factor. Y-axis is proportion of patients still on therapy and X-axis is time point of follow-up

### 3.2.2 | Non-infectious serious adverse event rates and events

Three vedolizumab-treated and 25 TNF-antagonist-treated patients developed non-infectious serious adverse events. This equates to an unadjusted rate of 0.5 per 100 patient years for vedolizumab-treated patients and 2.7 per 100 patient years for the TNF-antagonist treated patients. When limiting the cohort to patients with at least 12 months of follow-up, the rate of non-infectious serious adverse events was lower in vedolizumab-treated patients ( $n = 2$ ; 0.8%, 0.54 per 100 patient years) as compared to TNF-antagonist-treated patients ( $n = 14$ ; 3.5%, 1.7 per 100 patient years).

For vedolizumab-treated patients, these events were severe arthralgias requiring therapy discontinuation ( $n = 3$ ). For TNF-antagonist-treated patients, events included hypersensitivity or infusion reactions ( $n = 6$ ), drug-induced psoriasis ( $n = 6$ ), drug-induced lupus ( $n = 5$ ), severe liver function test abnormalities ( $n = 3$ ), skin rash ( $n = 2$ ), lung cancer ( $n = 1$ ) and jaw or hip necrosis ( $n = 2$ ).

### 3.2.3 | Comparative safety

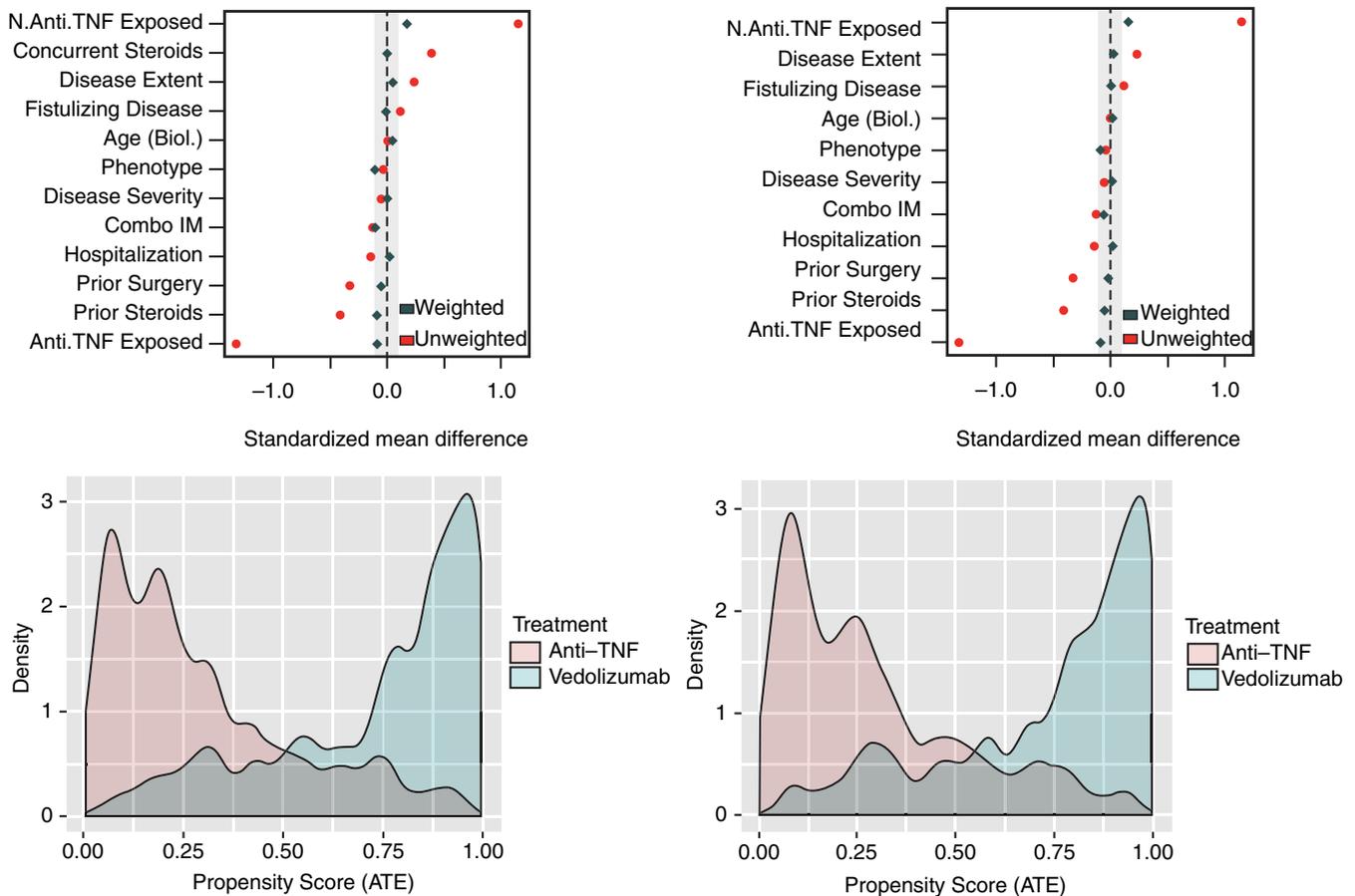
We observed no significant difference in risk of serious infections (OR 1.183, 95% CI 0.786-1.795) or serious adverse events (OR 0.751, 95% CI 0.519-1.086) between vedolizumab- and TNF-antagonist-treated patients (Table 2). The difference in risk of noninfectious serious adverse events specifically was significantly lower with vedolizumab vs TNF-antagonist therapy (IPW ATE: OR 0.072, 95% CI 0.012-0.242; full match: OR 0.150, 95% CI 0.035-0.441). During post-hoc analyses, we observed no significant difference in risk of serious infection between vedolizumab monotherapy and TNF-antagonist monotherapy (IPW ATE: OR 0.759, 95% CI 0.300-1.876; full match: OR 1.426, 95% CI 0.563-3.782).

Post-hoc analyses for duration of treatment exposure observed no significant association between duration of treatment exposure and risk of serious adverse events (OR 1.01, 95% CI 0.99-1.03,  $P = 0.44$ ), serious infections (OR 1.01, 95% CI 0.99-1.03,  $P = 0.39$ ), or noninfectious serious adverse events (OR 1.00, 95% CI 0.96-1.04,  $P = 0.96$ ). After forcing treatment exposure in as an effect modifier for comparisons between vedolizumab and TNF-antagonist therapy, we again observed that vedolizumab-treated CD patients were significantly less likely to develop noninfectious serious adverse events relative to TNF-antagonist-treated CD patients (IPW ATE: OR 0.940, 95% CI 0.892-0.984,  $P = 0.013$ ; IPW ATT: OR 0.915, 95% CI 0.862-0.966,  $P = 0.002$ ; IPW Full Match: OR 0.862, 95% CI 0.802-0.920,  $P < 0.001$ ).

### 3.3 | Comparative effectiveness

We observed no significant difference for achieving clinical remission (HR 0.932, 95% CI 0.707-1.228), steroid-free clinical remission (HR 1.250, 95% CI 0.677-2.310), or endoscopic remission (HR 0.827, 95% CI 0.595-1.151) between vedolizumab and TNF-antagonist-treated patients. Results were consistent when comparing vedolizumab to infliximab and subcutaneous TNF-antagonist agents separately in the entire cohort (Table 3).

Among TNF-antagonist-naïve patients, we observed a significant difference for the achievement of clinical remission (HR 1.861, 95% CI 1.059-3.272) and steroid-free clinical remission (HR 5.608, 95% CI 1.471-21.374) that favoured vedolizumab over subcutaneous



**FIGURE 2** Standardised mean difference of variables included before and after weighting in the full sample. Age (Biol.), age at initiation of treatment with biologic agent; ATE, average treatment effect; IM, immunomodulator; N.Anti. TNF exposed, number of anti-TNF agents to which patient was exposed; TNF, tumour necrosis factor. For SMD plots: SMD before (red) and after (blue) weighting, low absolute value of SMD (usually between 0 and 0.1) means good balance of the distribution of a variable between the treatment and the placebo. For PS distribution plots: Propensity score means: the probability of receiving treatment given the covariates

**TABLE 2** Comparative safety of vedolizumab to TNF-antagonist therapy in Crohn's disease

	Overall cohort	TNF-antagonist naïve	TNF-antagonist exposed
Serious infection			
Unweighted	0.887 (0.581-1.352)	1.526 (0.579-3.594)	0.809 (0.484-1.376)
IPW ATE	1.183 (0.786-1.795)	1.856 (0.681-4.507)	1.111 (0.657-1.944)
Full match	0.970 (0.638-1.474)	2.130 (0.587-9.232)	1.484 (0.905-2.466)
Serious adverse event			
Unweighted	0.591 (0.403-0.862)	1.027 (0.424-2.236)	0.571 (0.357-0.915)
IPW ATE	0.751 (0.519-1.086)	1.082 (0.414-2.478)	0.702 (0.441-1.133)
Full match	0.887 (0.581-1.352)	1.526 (0.579-3.594)	0.809 (0.484-1.376)

Note: Values are odds ratio (95% confidence interval).

Abbreviations: IPW ATE, inverse probability weighting average treatment effect; TNF, tumour necrosis factor.

TNF-antagonist agents. This comparison was not significantly different between vedolizumab and infliximab in TNF-antagonist-naïve patients (Table 4).

Among TNF-antagonist-exposed patients, point estimates for the comparison of vedolizumab and infliximab favoured

infliximab for the achievement of clinical remission and steroid-free remission, and this reached statistical significance using full match (clinical remission: HR 0.362, 95% CI 0.169-0.777; steroid-free clinical remission: HR 0.319, 95% CI 0.117-0.871) (Table 4).

	Overall	VDZ vs IFX	VDZ vs SQ TNF antagonist
Clinical remission			
Unweighted	0.812 (0.671-0.982)	0.697 (0.557-0.872)	0.940 (0.743-1.189)
IPW ATE	0.932 (0.707-1.228)	0.692 (0.472-1.014)	1.022 (0.714-1.404)
Full match	0.917 (0.470-1.791)	0.737 (0.301-1.806)	0.926 (0.415-2.066)
Steroid-free clinical remission <sup>a</sup>			
Unweighted	0.953 (0.628-1.446)	0.635 (0.398-1.012)	1.647 (0.861-3.154)
IPW ATE	1.250 (0.677-2.310)	0.695 (0.295-1.641)	1.717 (0.665-4.432)
Full match	1.262 (0.416-3.828)	0.312 (0.126-0.775)	2.365 (0.540-10.358)
Endoscopic remission			
Unweighted	0.727 (0.575-0.918)	0.607 (0.465-0.793)	0.875 (0.660-1.160)
IPW ATE	0.827 (0.595-1.151)	0.696 (0.450-1.076)	1.026 (0.660-1.547)
Full match	1.307 (0.614-2.780)	1.269 (0.472-3.411)	1.159 (0.477-2.815)

Note: Values are hazard ratio (95% confidence interval).

Abbreviations: IFX, infliximab; IPW ATE, inverse probability weighting average treatment effect; SQ, subcutaneous; TNF, tumour necrosis factor; VDZ, vedolizumab.

<sup>a</sup>Steroid-free clinical remission limited to patients taking concomitant steroids at baseline.

Endoscopic remission limited to patients with follow-up assessment of endoscopic disease activity (n = 424 TNF-antagonist; n = 413 vedolizumab).

**TABLE 3** Comparative effectiveness of vedolizumab to TNF-antagonist therapy in Crohn's disease

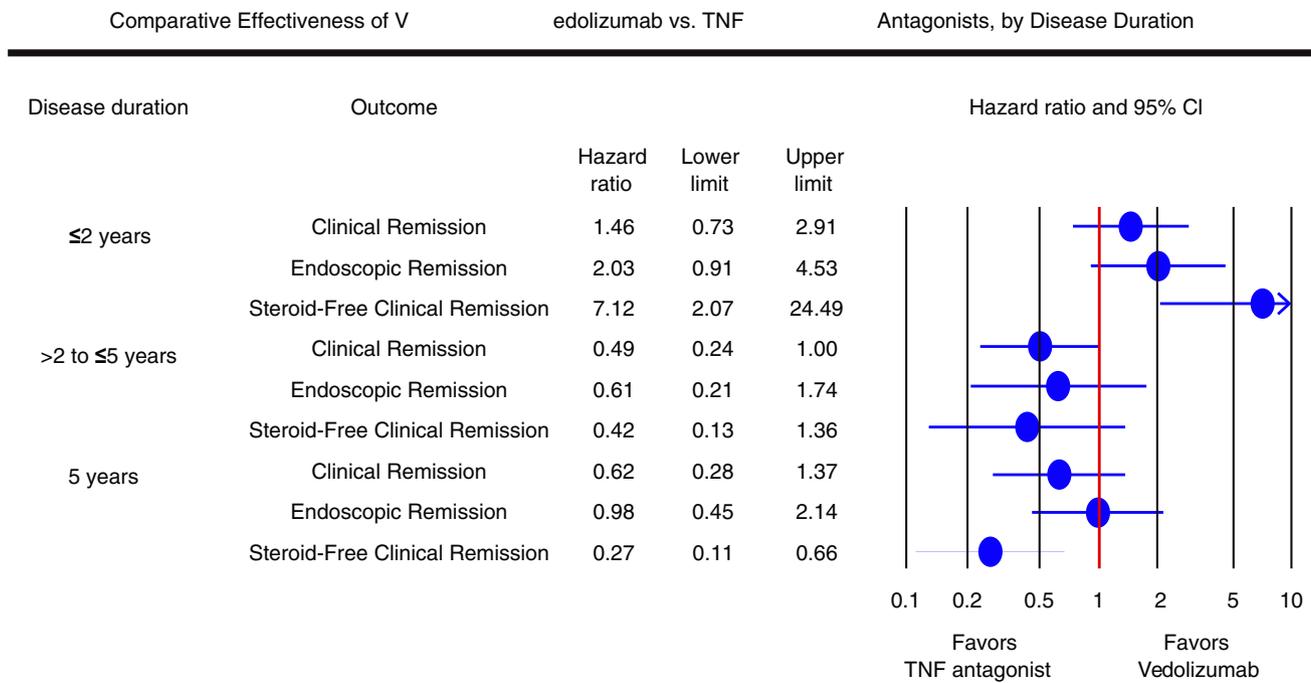
**TABLE 4** Comparative effectiveness of vedolizumab to TNF-antagonist therapy in Crohn's disease stratified by TNF-antagonist exposure

	TNF-antagonist naive			TNF-antagonist exposed		
	Overall	VDZ vs IFX	VDZ vs SQ TNF antagonist	Overall	VDZ vs IFX	VDZ vs SQ TNF antagonist
Clinical remission						
Unweighted	1.520 (0.979-2.362)	1.413 (0.879-2.271)	1.660 (1.014-2.719)	0.763 (0.604-0.964)	0.582 (0.435-0.779)	0.960 (0.713-1.292)
IPW ATE	1.654 (1.029-2.659)	1.361 (0.789-2.347)	1.861 (1.059-3.272)	0.821 (0.588-1.146)	0.557 (0.331-0.937)	0.969 (0.612-1.536)
Full match	0.923 (0.459-1.857)	1.087 (0.544-2.173)	1.007 (0.392-2.590)	0.972 (0.520-1.817)	0.362 (0.169-0.777)	1.266 (0.485-3.306)
Steroid-free clinical remission <sup>a</sup>						
Unweighted	1.858 (0.804-4.295)	1.210 (0.504-2.907)	4.637 (1.236-17.390)	0.959 (0.558-1.646)	0.672 (0.349-1.292)	1.394 (0.631-3.080)
IPW ATE	2.002 (0.763-5.255)	1.156 (0.504-3.309)	5.608 (1.471-21.374)	1.014 (0.469-2.192)	0.452 (0.145-1.408)	1.398 (0.424-4.611)
Full match	2.530 (0.971-6.596)	0.930 (0.351-2.463)	11.127 (1.798-68.854)	1.569 (0.374-6.577)	0.319 (0.117-0.871)	6.170 (1.574-24.181)
Endoscopic remission						
Unweighted	0.691 (0.320-1.492)	0.663 (0.301-1.462)	0.728 (0.325-1.632)	0.823 (0.622-1.090)	0.600 (0.424-0.849)	1.033 (0.730-1.460)
IPW ATE	0.900 (0.366-2.213)	0.771 (0.323-1.840)	0.907 (0.364-2.260)	0.864 (0.573-1.301)	0.774 (0.405-1.478)	1.091 (0.640-1.859)
Full match	0.864 (0.321-2.328)	0.418 (0.181-0.965) <sup>b</sup>	1.851 (0.623-5.493)	1.038 (0.427-2.522)	1.278 (0.354-4.616)	1.271 (0.486-3.325)

Note: Values are hazard ratio (95% confidence interval).

Abbreviations: IFX, infliximab; IPW ATE, inverse probability weighting average treatment effect; SQ, subcutaneous; TNF, tumour necrosis factor; VDZ, vedolizumab.

<sup>a</sup>Steroid-free clinical remission limited to patients taking concomitant steroids at baseline. Endoscopic remission limited to patients with follow-up assessment of endoscopic disease activity (n = 424 TNF-antagonist; n = 413 vedolizumab).



**FIGURE 3** Comparative effectiveness of vedolizumab and TNF-antagonist therapy stratified by disease duration subgroups. CI, confidence interval; TNF, tumour necrosis factor

### 3.4 | Impact of disease location and disease duration on effectiveness

Disease location did not significantly impact the comparative effectiveness estimates between vedolizumab and TNF-antagonist-treated patients (Table S1). Using full match, disease duration significantly impacted the comparative effectiveness estimates between vedolizumab and TNF-antagonist-treated patients for the outcomes of clinical remission ( $P = 0.034$ ) and steroid-free clinical remission ( $P = 0.018$ ). Point estimates for comparisons within these subgroups suggested that vedolizumab might be favoured over TNF-antagonist agents in early-disease CD ( $\leq 2$  years) and that TNF-antagonist agents might be favoured over vedolizumab in late-disease CD (Figure 3; Table S1).

## 4 | DISCUSSION

In this routine practice PS-weighted cohort of over 1200 biologic-treated CD patients, we observed no significant difference between vedolizumab and TNF-antagonist therapy for risk of experiencing a serious infection or serious adverse event or for probability of achieving clinical remission, steroid-free clinical remission or endoscopic remission. Exploratory subgroup analyses suggested that vedolizumab might be superior to subcutaneous TNF-antagonist therapy for the achievement of clinical remission and steroid-free clinical remission in TNF-antagonist-naïve patients, and infliximab might be superior to vedolizumab for the achievement of clinical remission and steroid-free clinical remission in TNF-antagonist-exposed patients. During

subgroup analyses, we also observed a significant interaction between disease duration and comparative effectiveness estimates, with vedolizumab potentially being favoured in early-disease CD and TNF antagonists potentially being favoured in later-disease CD.

We observed no significant difference in treatment-related serious infection risks between vedolizumab and TNF antagonists, with a comparable event rate being observed in both groups. The risk of serious infections with biologic therapy is largely driven by disease activity and concomitant use of immunosuppressive agents.<sup>4,11,33-35</sup> The lack of observed difference between vedolizumab and TNF-antagonist therapy for achievement of disease remission and the higher concomitant use of steroids among the vedolizumab-treated patients in our cohort may therefore help to explain the lack of observed difference in risk for serious infections between agents. When limiting the serious infection comparison to patients on biologic monotherapy, however, we observed no significant difference in risk of serious infections, which argues against the concomitant immunosuppressive therapy as a determinant of the comparative safety assessment.

The event rate for noninfectious serious adverse events specifically, however, was significantly lower in the vedolizumab-exposed group ( $n = 3$ ) than in the TNF-antagonist-exposed group ( $n = 25$ ; OR 0.072). This remained significant even after adjusting for differences in treatment exposure between both groups. One of the theoretical advantages of vedolizumab over TNF-antagonist therapy is the potentially lower rate of noninfectious “off-target” adverse events due to differences in mechanism of action. Common noninfectious adverse events observed with TNF-antagonist therapy are hypersensitivity reactions, psoriasis, and

lupus, as well as other dermatological or autoimmune-like disorders.<sup>36</sup> Several of these were observed with TNF-antagonist therapy in our cohort, whereas none were observed with vedolizumab. Larger population-based cohort studies are therefore needed to confirm our observations.

We observed no significant difference between vedolizumab and TNF-antagonist therapy for the achievement of clinical remission, steroid-free clinical remission, or endoscopic remission, and this was consistent when comparing vedolizumab to infliximab or subcutaneous TNF antagonists separately in the entire cohort or when comparing vedolizumab to TNF-antagonist agents in TNF-antagonist-naïve and -exposed subgroups. We did observe TNF-antagonist therapy to be associated with greater treatment persistence as measured by duration of exposure. It is unclear if this is a function of the time period of observation or if it represents a true difference in treatment persistence between therapies. Prior work from our group has observed that inflammatory bowel disease patients treated with vedolizumab early after its approval and availability in the market were more refractory and had lower persistence rates compared to more recent utilisation.<sup>37</sup> Therefore, it's possible that these differences were related to utilisation patterns in which vedolizumab-treated patients earlier in the period were simply more refractory requiring early discontinuation and those treated later in the observation period had less time to be exposed to the drug.

Our observational cohort study was not designed to be a non-inferiority study, and the safety and effectiveness comparisons were exploratory in nature. Post-hoc power calculations suggested adequate sample size and event rates for the comparisons, and it is interesting to consider the power of our study to make comparisons understanding the limitations of PS analyses relative to randomised controlled trials, and that in observational effectiveness studies the lack of randomisation degrades the ability to demonstrate noninferiority. A trial between vedolizumab and TNF-antagonist therapy with an estimated 30% rate for clinical remission, 90% power and 10% noninferiority limit would require 720 participants with equal distribution between groups. A 7.5% noninferiority limit would require 1280 participants, and a 5% noninferiority limit would require 2880 participants.<sup>38</sup> Our cohort of 1266 patients is therefore relatively robust to explore the overall comparative safety and effectiveness of these agents in routine practice.

In subgroup analyses, we observed a significant interaction between disease duration and comparative effectiveness estimates, with vedolizumab potentially being favoured over TNF antagonists in early CD ( $\leq 2$  years). Disease duration has been observed to significantly impact treatment effectiveness for both vedolizumab and TNF-antagonist therapy.<sup>30,39,40</sup> However, a comparison of effectiveness between these two agents in early CD is lacking. Our exploratory subgroup analysis for this important question suggests that perhaps vedolizumab might be more efficacious than TNF-antagonist therapy in these patients. These results should be interpreted with caution given the relatively small sample size of patients with early CD ( $\leq 2$  years) in our cohort

and the exploratory nature of this comparison. Nonetheless, given the lower risk of noninfectious adverse events with vedolizumab and the incremental risk for noninfectious adverse events with longer duration of use for TNF antagonists, early use of vedolizumab in CD might be an attractive treatment option to optimise disease outcomes while minimising treatment-related risks. This hypothesis will require formal testing with a clinical trial specifically aimed to assess the comparative effectiveness for achievement of disease remission and reduction in disease and treatment-related risks between vedolizumab and TNF antagonists to understand relative trade-offs between efficacy and safety. Furthermore, with the availability of biosimilar agents for TNF antagonists, long-term maintenance costs will also need to be factored into this strategy.

Our study has several strengths, which include the routine practice nature of our cohort, the robustness of our PS-weighting methodology, and the relatively modest sample size for comparison estimates. Several important limitations remain. The retrospective observational nature of data carries limitations, lack of standardised numerical clinical disease activity measurements, and the academic centre nature of sites may impact generalisability to routine community practices. The detailed patient data available allowed for a very granular PS-weighting methodology to be applied that incorporated several markers of disease activity and severity, but residual confounding may still exist which limits the comparison. We also could not adequately account for practice variation with therapeutic drug monitoring or dose escalation during maintenance therapy across sites because of the lack of standardised treatment protocols. Therefore data on dose-intensification were not captured and represents a limitation, however, it may also represent a strength by allowing for routine practice variation when making comparisons across treatments. Caution should also be taken when interpreting comparisons for secondary outcomes and subgroup analyses given the inherent selection bias across these subgroups, limited sample size and event rate, and lack of significance for the primary comparisons.<sup>41</sup> These secondary analyses such as the impact of disease location and disease duration should be considered hypothesis generating as opposed to hypothesis testing, and should be interpreted with caution. Finally, the small number of TNF-antagonist-naïve vedolizumab-treated patients creates a limited common support for the comparative assessment of vedolizumab to TNF-antagonist agents in TNF-antagonist-naïve patients.

In summary, in this large, routine practice, PS-weighted comparative study, we observed no significant differences between vedolizumab and TNF-antagonist therapy for risk of serious infections or serious adverse events or for the probability of achieving disease remission. Post-hoc secondary analyses observed a significant difference between vedolizumab and TNF-antagonist therapy for the risk of noninfectious adverse events specifically, which remained after accounting for differences in duration of follow-up, but not for the risk of serious infections between vedolizumab monotherapy and TNF-antagonist monotherapy. Subgroup analyses also suggested that vedolizumab might be favoured in early-disease CD, but along these same lines TNF-antagonist therapy may be favoured in

later-stage CD. Larger well-powered clinical trials will be needed to confirm the observed impact of disease duration on the comparative effectiveness estimates in our study. In particular, more data are needed on vedolizumab used as a first-line biologic therapy and as true monotherapy to better understand the risk for infectious adverse events.

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*Guarantor of the article:* Parambir S. Dulai, MD.

*Author contributions:* MB and PSD contributed to conceptualisation and planning. RX and PSD contributed to methodology. MB, SV, MF, SK, GT, MR, SA, JM, AW, GK, JLKP, JPC, BB, SS, DF, AW, SC, RH, RU, ES, VP, DH, SC, DL, AS, BES, JFC, SK, EVL, BS, CAS, WJS and PSD contributed to data curation. RX, YZ and PSD contributed to formal statistical analyses. MB, RX, YZ and PSD contributed to manuscript writing. All authors contributed to critical revisions and final approval. PSD contributed to study supervision. All authors approved the final version of the article, including the authorship list.

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## SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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## APPENDIX A

### Collaborators: VICTORY Collaboration

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## APPENDIX B

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