Title

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Journal

Inflammatory Bowel Diseases, 27(10)

ISSN

1078-0998

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Publication Date

2021-10-18

DOI

10.1093/ibd/izaa327

Peer reviewed

Frailty and Risk of Serious Infections in Biologic-treated Patients With Inflammatory Bowel Diseases

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Background: Identifying biologic-treated patients with inflammatory bowel diseases (IBDs) at higher risk of serious infections is a priority. We conducted a retrospective cohort study evaluating frailty and risk of serious infections in biologic-treated patients with IBD.

Methods: Using an administrative claims database, we identified biologic-treated patients with IBD between 2014 and 2018 with follow-up 1 year before and after treatment initiation. Using a validated claims-based hospital frailty risk scoring system, patients were classified as frail and nonfrail. We compared the risk of serious infections (infections requiring hospitalization) between frail and nonfrail patients using Cox proportional hazard analysis adjusting for age, comorbidities, disease characteristics, health care utilization, use of corticosteroids, immunomodulators, and opiates.

Results: We included 5987 biologic-treated patients with IBD (4881 on TNFα antagonists, 1106 on vedolizumab), of whom 2350 (39.3%) were classified as frail; over 7115 person-years of follow-up was included, and 520 patients developed serious infection. Frailty was not associated with increased risk of serious infection (adjusted hazard ratio [aHR], 1.12; 95% CI, 0.93–1.36), whereas advanced age (older than 60 years), high comorbidity burden, corticosteroid use, opiate use, and prior serious infection were associated with increased risk of serious infection. On stratified analysis, frailty was associated with increased risk of serious infections in vedolizumab-treated patients (aHR, 1.69; 95% CI, 1.03–2.79) but not in TNFα antagonist-treated patients (aHR, 1.03; 95% CI, 0.83–1.27).

Conclusions: In biologic-treated patients with IBD, frailty assessed using a claims-based frailty index was not independently associated with increased risk of serious infections. Future studies evaluating objective and biological measures of frailty are warranted to risk-stratify older patients with IBD.

Key Words: debility, infestation, enteritis, colitis, immune suppression

INTRODUCTION

As treatment options for inflammatory bowel diseases (IBDs) are expanding, personalized treatment approaches that balance risk of disease- vs treatment-related complications are critical. Although there has been considerable emphasis on identifying patients at high risk for disease-related complications, risk stratification strategies to identify patients at high risk of treatment-related complications such as serious infections are limited.[1] Conventional risk factors for serious infections include use of combination therapy with biologic agents

Received for publications September 1, 2020; Editorial Decision November 13, 2020.

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Author Contribution: SS contributed to the study concept and design. HCH contributed to the acquisition of data. SS and HCH contributed to the analysis and interpretation of data. SS drafted the manuscript. HCH, LS, NDS, JCL, WJS, and AAM critically revised the manuscript for important intellectual content. SS, HCH, LS, NDS, JCL, WJS, and AAM approved the final manuscript.

Supported by: This project was supported by the NIH/NIDDK K23DK117058 (SS), IOIBD Operating Grant 2019 (SS), NIH R01AG059183 (JL), P30 DK120515 (WS), and P30 AG059299 (AM). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Conflicts of Interest: SS reports research grants from AbbVie and Janssen. WS reports research grants from Atlantic Healthcare Limited, Amgen, Genentech, Gilead Sciences, Abbvie, Janssen, Takeda, Lilly, Celgene/Receptos,Pfizer, Prometheus Biosciences; consulting fees from Abbvie, Allergan, Amgen, Arena Pharmaceuticals, Avexegen Therapeutics, BeiGene, Boehringer Ingelheim, Celgene, Celltrion, Conatus, Cosmo, Escalier Biosciences, Ferring, Forbion, Genentech, Gilead Sciences, Gossamer Bio, Incyte, Janssen, Kyowa Kirin Pharmaceutical Research, Landos Biopharma, Lilly, Oppilan Pharma, Otsuka, Pfizer, Progenity, Prometheus Biosciences, Reistone, Ritter Pharmaceuticals, Alimentiv (formerly Robarts Clinical Trials, owned by Health Academic Research Trust, HART), Series Therapeutics, Shire, Sienna Biopharmaceuticals, Sigmoid Biotechnologies, Sterna Biologicals, Sublimity Therapeutics, Takeda, Theravance Biopharma, Tigenix, Tillotts Pharma, UCB Pharma, Ventyx Biosciences, Vimalan Biosciences, Vivelix Pharmaceuticals; and stock or stock options from BeiGene, Escalier Biosciences, Gossamer Bio, Oppilan Pharma, Prometheus Biosciences, Progenity, Ritter Pharmaceuticals, Shoreline Biosciences, Ventyx Biosciences, Vimalan Biosciences; spouse is a consultant for and has stock options in Iveric Bio and Oppilan Pharma, has stock in Progenity, Escalier Biosciences, Ventyx Biosciences, Vimalan Biosciences, and Ventyx Biosciences, and is an employee for and has stock options in Prometheus Biosciences. All other authors report no conflicts of interest.

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doi: 10.1093/ibd/izaa327
Published online 16 December 2020

and antimetabolites, with or without corticosteroids, moderate to severe disease activity, and older age.[2–5] However, these factors are not particularly helpful in risk stratification; baseline disease activity is intrinsically linked to need for combination therapy, and with roughly 30% patients with IBD expected to be older by 2030, using "old age" to characterize treatment risks is inadequate and potentially detrimental.[6, 7] Older adults with IBD experience high rates of surgery and hospitalization when compared with younger patients, yet they are less likely to be treated with immunosuppressive agents.[8, 9] In fact, older adults with IBD are more likely to be treated with chronic corticosteroids rather than biologic agents, which have been associated with higher risk of mortality and major adverse cardiovascular events compared with tumor necrosis factor-α (TNFα) antagonists, without any difference in the risk of serious infections.[10, 11] In selected older patients, early combined immunosuppression was effective and safe as compared with conventional management to decrease risk of CD-related complications, similar to observations in younger patients.[12] Hence, more accurate assessment of treatment-related risks is warranted to inform immunosuppressive therapy decision-making for patients with IBD.[13]

Beyond age, a more comprehensive assessment of biologic reserve and functional status may be more predictive of risks of adverse health outcomes. Frailty represents a dynamic state with vulnerability to external and internal stressors and has been associated with increased risk of hospitalization, serious infections, and mortality in several chronic diseases.[14] There has been very limited assessment of frailty using performance-based measures of functional activity and muscle strength or biological markers of frailty and aging in patients with IBD. In a recent nationwide study, we identified that frailty, measured using a validated, administrative claims-based index, the Hospital Frailty Risk Score, was associated with higher burden and costs of hospitalization and increased risk of readmissions and mortality in hospitalized patients with IBD.[15] Using an electronic health record–based cohort of 1299 patients with IBD treated with TNFα antagonists, Kochar and colleagues observed a 2-fold higher risk of all infections in patients classified as frail; however, their study was underpowered to detect a difference in risk of serious infections (ie, infection-related hospitalization).[16]

To better understand the association between frailty and risk of serious infections in biologic-treated patients with IBD, we conducted a retrospective cohort study using a large de-identified administrative claims database. The presence of frailty was determined using the Hospital Frailty Risk Score.[17]

METHODS

Data Source

We conducted a retrospective analysis of de-identified medical and pharmacy administrative claims from a large database, OptumLabs Data Warehouse, which includes commercially insured and Medicare Advantage enrollees throughout the United States.[18] The database contains data more than 100 million enrollees from geographically diverse regions across the United States, with greatest representation from the South and Midwest. Medical claims include International Classification of Diseases, Ninth Revision and Tenth Revision, Clinical Modification (ICD-9-CM; ICD-10-CM) diagnosis codes; ICD-9 and ICD-10 procedure codes; Current Procedural Terminology, Fourth Edition (CPT-4) procedure codes; Healthcare Common Procedure Coding System (HCPCS) procedure codes; site of service codes; and provider specialty codes. All study data were accessed using techniques compliant with the Health Insurance Portability and Accountability Act of 1996, and because this study involved analysis of preexisting de-identified data, it was exempted from institutional review board approval.

Study Population

Between January 1, 2014, and December 31, 2018, we identified all patients who filled a prescription (or received an infusion) for TNFα antagonists (infliximab, adalimumab, certolizumab pegol, and/or golimumab) and/or vedolizumab. From this cohort, we included adult patients (18–89 years) with (1) at least 1 diagnosis code for IBD (CD, ICD-9 555.x or ICD-10 K50; UC, ICD-9 556.x or ICD-10 K51) before index date for receipt of candidate biologic agent, either from an inpatient or outpatient visit; (2) continuous health plan enrollment with pharmacy benefits, with no prescription for candidate biologic in the 12 months before index date (new user design), and minimum 12-month enrollment in health plan after index date; patients who received candidate for <12 months and discontinued due to intolerance or nonresponse but still remained in the health plan were included. In case a patient received diagnostic codes for both CD and UC, then the patient was classified as having CD if the majority of diagnostic codes were for CD. We excluded patients with (1) human immunodeficiency virus infection, congenital immunodeficiency, or organ transplantation, or (2) concomitant diagnosis of rheumatoid arthritis, ankylosing spondylitis, psoriasis, or psoriatic arthritis within the baseline 12-month period before prescription of TNFα antagonists.

Exposure

Patients' frailty risk score was calculated using the Hospital Frailty Risk Score in the baseline 1 year before initiation of biologic therapy.[17] This frailty score was developed and validated in 1.04 million hospitalized older adults age 75 years and older to screen for frailty and identify a group of patients who are at greater risk of adverse outcomes (mortality, readmission, length of stay). This score based on International Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) codes can be readily implemented in hospital

information systems and performs as well as existing frailty and risk stratification tools. For patient records between 2014 and 2016, we translated the ICD-10 codes used in the study to corresponding ICD-9-CM codes and used them to assign patients as "nonfrail" (frailty risk score <5) or "frail" (frailty risk score 5 or higher). Details of risk score calculation are shown in Supplementary Table 1.[16]

Outcome

The primary outcome of interest was time to serious and/or opportunistic infections, defined as infection requiring hospitalization. These infections were identified based on principal discharge diagnoses (ICD-9 or ICD-10 codes) and included infections of the respiratory tract, skin and soft tissue, genitourinary tract, gastrointestinal tract, central nervous system, and septicemia/sepsis.[19] In prior studies considering medical chart reviews as the reference, our definitions for serious infection requiring hospitalization have consistently shown positive predictive values of 80% or higher.[20, 21] Due to low event rate for opportunistic infections requiring hospitalization, we did not perform separate analyses for opportunistic infections. We opted to focus only on hospitalized infection because these infections are severe and are significantly more likely to have adverse outcomes including treatment discontinuation; in contrast, there is considerably more heterogeneity in severity of outpatient infections.

Covariates

Baseline covariates (at time of biologic exposure or in preceding 12 months) included demographics: age, sex, race (gathered routinely by the database used), census region, calendar year, comorbidity burden measured using the Elixhauser index (12-month baseline period), unplanned health care utilization (defined as all-cause inpatient hospitalization or emergency department visits in 12-month baseline period for each exposure), serious and/or opportunistic infections (12-month baseline period), IBD phenotype (CD or UC), abdominal surgery (12-month baseline period), and receipt of endoscopy and/or abdominal imaging (12-month baseline period).[22] Additionally, we captured recent use of corticosteroids and immunomodulators in the 3 months before biologic initiation and opiates in the 12 months before biologic initiation. We did not have access to individual patient medical records, endoscopy reports, or biochemical parameters.

Statistical Analysis

We used descriptive statistics to compare baseline demographic, clinical, and treatment characteristics in frail vs nonfrail patients with IBD. We used Pearson $\chi 2$ test to analyze categorical variables and Student *t* test for continuous variables. Categorical variables are expressed as percentages and continuous variables as median with an interquartile range (IQR). All hypothesis testing was performed using a 2-sided *P* value with a statistical significance threshold of <0.05.

We performed survival analysis using Kaplan-Meier curves to evaluate the association between frailty and risk of serious infections in all biologic-treated patients with IBD and by subgroups (disease phenotype, CD vs UC; age at time of biologic initiation, <30 years [reference], 30–40 years, 41–60 years and >60 years; index biologic: TNFα antagonists vs vedolizumab; comorbidity burden, Elixhauser index score 0–1 vs 2 vs 3 vs >3). Subsequently, to evaluate the independent effect of frailty on risk of serious infections, we performed multivariable Cox proportional hazard analysis using backward variable selection, adjusting for age, sex, race/ethnicity, disease phenotype, index biologic agent, comorbidity burden, abdominal surgery, hospitalization, or emergency department (ED) visit in baseline 12 of months, hospitalized infection in baseline 12 of months, in addition to use of corticosteroids and immunomodulators within 3 months and opiates within 12 months before biologic initiation. We also performed stratified analysis by index biologic (TNFα antagonists vs vedolizumab) and evaluated risk factors for serious infections in those with vs without frailty. All statistical analyses were performed with Stata MP (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, Texas, USA).

Data Availability Statement

The data underlying this article were provided by OptumLabs by permission. Data will be shared on request to the corresponding author with permission of OptumLabs.

RESULTS

Our cohort included 5987 patients with IBD who were new users of TNFα antagonists or vedolizumab, of whom 2350 (39.3%) were classified as frail based on claims diagnostic codes in the 12 months before initiation of biologics. Baseline characteristics of patients classified as frail based on the hospital frailty risk score are shown in Table 1. Overall, frail patients were slightly older at biologic initiation (frail vs nonfrail: 44 years vs 40 years), had higher rates of ED visits (68% vs 35%), hospitalization (45% vs 19%), abdominal surgery (14% vs 10%), serious infections (15% vs 3%), and higher burden of comorbidities (Elixhauser index score, 4 or more: 29% vs 8%) in the 12 months before initiation of biologic therapy. Frail patients were more likely to be exposed to opiates (53% vs 35%) and corticosteroids (81% vs 70%) in the baseline 12 of months without significant difference in rates of use of TNFα antagonists (79% vs 83%) and vedolizumab (21% vs 17%). From the hospital frailty risk score, the most common codes that contributed to the diagnosis of frailty (with variable weights) were hypokalemia (9.4%), urinary tract infection (8.2%), constipation (7.8%), dehydration (7.3%), and joint pain (4.7%).

TABLE 1. Baseline Demographic Characteristics, Health Care Utilization, and IBD-related Medication Use in the 12 Months Before Initiation of Index Biologic in the Entire Cohort

Variable	Frail (n = 2350)	Not frail (n = 3637)
Demographic variables		
Mean age ± SD, years	44 ± 17	40 ± 14
Sex (% males)	43.6	54.9
Race/Ethnicity (%)		
White	71.0	73.1
African American	13.6	11.3
Asian	3.5	3.7
Hispanic	6.9	7.4
Unknown	5.1	4.6
IBD phenotype		
Crohn's disease (%)	57.2	58.7
Ulcerative colitis (%)	42.8	41.3
Mean (± SD) follow-up after starting biologic	11.6 ± 10.2	16.3 ± 14.7
Health care utilization and comorbidities (baseline 12 months before biologic initiation)		
Emergency department visits (% pts with ≥1)	67.5	35.0
Inpatient visits (% pts with ≥1)	44.6	18.7
Abdominal Imaging (% of pts with ≥1)	66.5	46.7
Endoscopic procedures (% pts with ≥1)	79.1	71.1
Abdominal surgery (% pts with ≥1)	14.4	9.6
Mean (± SD) Elixhauser score	2.7 ± 2.2	1.3 ± 1.5
Elixhauser score 2–3	36.1	25.6
Elixhauser score 4 or more	28.8	7.8
Major comorbidities		
Chronic obstructive lung disease	16.2	10.3
Diabetes with or without complication	15.8	6.2
Hypertension with or without complication	32.4	16.6
Obesity	12.2	6.4
Anemia	32.3	19.9
Serious infection (% pts with ≥1)	15.1	3.2
IBD-related medication use		
TNFα antagonists (at index date; %)	79.1	83.1
Vedolizumab (at index date; %)	20.9	16.9
Oral corticosteroids (in baseline 12 m), %	80.7	70.4
Opiates (in baseline 12 m), %	53.3	34.7

Upon follow-up including over 7115 person-years, 520 patients developed serious infection. On univariate analysis, frail patients had 1.9-times higher risk of serious infections compared with nonfrail patients (hazard ratio [HR], 1.90; 95% CI, 1.60–2.27; Table 2, Fig. 1). This higher rate of serious infections in frail patients was observed in multiple subgroups, in patients with CD and UC, in patients starting TNFα antagonists and vedolizumab, in younger adults (younger than 60 years), and in patients with or without major comorbidities. However on Cox proportional hazard analysis, after adjusting for covariates including age, sex, race/ethnicity, disease phenotype, index biologic agent, comorbidity burden, abdominal surgery, hospitalization or ED visit, serious infections, and medications, *frailty was not associated with increased risk of serious infections* (HR, 1.12; 95% CI, 0.93–1.36; Table 3). Advanced age (older than 60 years vs younger than 30 years as reference), Hispanic (vs white as reference), multimorbidity (Elixhauser index, 4 or more vs 0–1 score), recent corticosteroid exposure, opiate use, ED visit, and serious infection in the preceding 12 months were associated with increased risk of serious infections.

Upon stratified analyses by type of biologic exposure, frailty was independently associated with 1.7-times higher risk of serious infections (HR, 1.69; 95% CI, 1.03–1.79), besides advanced age and ED visits, in vedolizumab-treated patients with

TABLE 2. Association Between Frailty and Risk of Serious Infections in Biologic-treated Patients With Inflammatory Bowel Diseases Overall and by Predefined Strata (Univariate Analysis)

Subgroup Analysis	Hazard Ratio (95% CI)	*P*
Overall	1.90 (1.60–2.27)	<0.01
Disease phenotype		
Crohn's disease	1.75 (1.30–2.21)	<0.01
Ulcerative colitis	2.11 (1.62–2.74)	<0.01
Age		
>60y	1.29 (0.92–1.80)	0.14
60y or less	1.87 (1.52–2.30)	<0.01
Index biologic		
TNFα antagonists	1.80 (1.48–2.18)	<0.01
Vedolizumab	2.57 (1.65–3.99)	<0.01
Elixhauser index		
0–1	1.42 (1.04–1.96)	<0.01
2 or more	1.64 (1.31–2.05)	<0.01

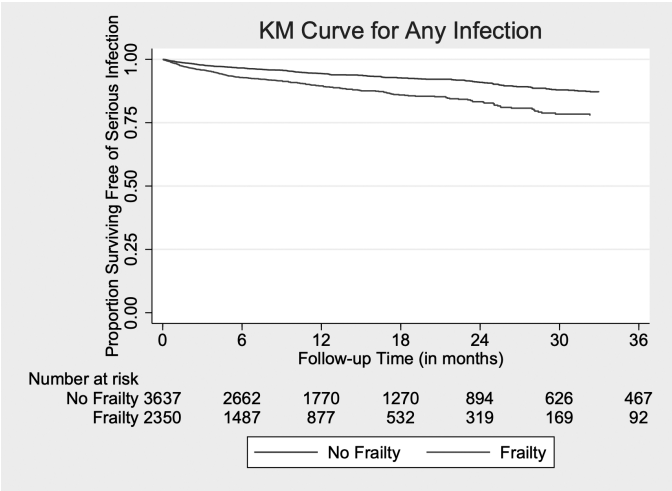

FIGURE 1. Frailty and risk of serious infection in biologic-treated patients with inflammatory bowel diseases on Kaplan-Meier time-to-event analysis.

IBD (Table 4A). In contrast, in new users of TNFα antagonists, frailty was not associated with increased risk of serious infections (HR, 1.03; 95% CI, 0.83–1.27; Table 4B). Advanced age, high comorbidity burden, recent corticosteroid use, opiate use, ED visit, and prior serious infections were associated with increased risk, and abdominal surgery was associated with decreased risk of serious infections in TNFα antagonist-treated patients with IBD.

DISCUSSION

In this large claims-based study of approximately 6000 biologic-treated patients with IBD evaluating risk factors for serious infections (or infection-related hospitalization), we observed that frailty, measured using a claims-based index, was not independently associated with risk of serious infections in biologic-treated patients with IBD, after adjusting for important covariates including age and comorbidity burden. We confirmed prior observations that advanced age, high comorbidity burden, corticosteroid and opiate use, ED visits, and prior infection-related hospitalizations are associated with increased risk of serious infections in biologic-treated patients. Overall, these findings suggest that frailty, as measured using an index of accumulation of health deficits, may not identify biologic-treated patients with IBD at higher risk of serious infections. Future studies focusing on objective functional and biological measures of frailty are warranted to ascertain if it may be helpful to risk-stratify patients with IBD—particularly older patients—at higher risk of serious infections.

Frailty is a complex concept, with 2 dominant paradigms: (1) a biologic syndrome of decreased reserve resulting from cumulative declines across multiple physiologic systems or (2) as a risk index based on accumulation of health deficits.[14, 23, 24] Operationally, in geriatrics and gerontology research, these 2 concepts of frailty have been measured using the frailty phenotype and the frailty index, respectively. The frailty phenotype is based on a biological cycle of frailty that consists of shrinking, weakness, exhaustion, slowness, and low physical activity, relies on patient self-reported and performance-based assessment, is dynamic, lending itself to targeted interventions and monitoring, and can predict adverse outcomes such as hospitalization, falls, disability, and mortality.[25] In contrast, frailty index is measured based on accumulated health deficits from a prespecified number of items (at least 30) of symptoms, signs, diseases, test abnormalities, and disability in physical, psychological, and social domains (such as help with activities of daily living, psychosocioeconomic difficulties, comorbidities, cognition status, etc.).[26] Frailty index and its modifications lend themselves to analyses in administrative claims data as a confounder or treatment effect modifier. The hospital frailty risk score used in this analysis is an administrative claims-based frailty measure based on accumulated deficits.[17] This was developed and validated in 1.04 million hospitalized older adults (75 years and older) to screen for frailty and identify a group of patients who are at greater risk of adverse outcomes (mortality, readmission, length of stay); however, it only had modest agreement with the frailty phenotype. These core differences in what paradigms of frailty are being measured—to examine what outcomes—may explain differences in findings from recent studies of frailty in IBD. In a previous study focused on predicting risk of readmission, hospitalization burden, and mortality in hospitalized patients with IBD, regardless of treatment or cause of initial admission, we observed that hospital frailty risk score–defined frailty was predictive of outcomes.[15] In contrast, in this study, we focused on biologic-treated patients with IBD, only 30% of

TABLE 3. Risk Factors for Serious Infections in Patients With Inflammatory Bowel Diseases Starting Biologic Therapy

Risk Factors	Hazard Ratio (95% CI)	*P*
Frail (vs nonfrail)	1.12 (0.93–1.36)	0.23
Male (vs female)	0.94 (0.79–1.12)	0.47
Age category		
<30 y	1.00	—
30–39 y	0.89 (0.68–1.17)	0.40
40–59 y	0.96 (0.75–1.23)	0.75
60 y or more	2.24 (1.72–2.90)	<0.01
Crohn's disease (vs ulcerative colitis)	0.95 (0.79–1.15)	0.63
Race		
White	1.00	—
African-American	1.10 (0.85–1.42)	0.47
Hispanic	1.54 (1.15–2.06)	<0.01
Asian	0.97 (0.57–1.65)	0.91
Elixhauser index		
0–1	1.00	—
2	1.17 (0.91–1.52)	0.22
3	1.21 (0.91–1.62)	0.19
4 or more	1.52 (1.18–1.96)	<0.01
TNFα antagonists (vs vedolizumab)	1.05 (0.82–1.33)	0.70
Corticosteroid use (in preceding 3 m)	1.30 (1.07–1.59)	<0.01
Immunomodulator use (in preceding 3 m)	0.83 (0.63–1.09)	0.19
Opiate use (in preceding 12 m)	1.24 (1.03–1.50)	0.025
Hospitalization (in preceding 12 m)	1.25 (0.99–1.59)	0.06
Emergency department visit (in preceding 12 m)	1.46 (1.16–1.83)	<0.01
Abdominal surgery (in preceding 12 m)	0.78 (0.58–1.03)	0.08
Serious infection (in preceding 12 m)	1.76 (1.36–2.29)	<0.01

whom were hospitalized in the preceding year before biologic initiation, and evaluated the risk of infection-related hospitalization rather than all-cause hospitalization. In this setting, a claims-based analysis, which relies on accumulated (and documented) deficits, was not predictive of risk of serious infections. We believe these differences may be related to inability to measure the biological phenomenon of frailty with this measure; we hypothesize that it is the loss of complexity of homeostatic mechanisms and vulnerability to stressors which define the biological syndrome of frailty that predisposes immunosuppressed patients to serious infections.

Our findings are ostensibly in contrast to findings from Kochar and colleagues.[16] This may be due to several differences in the 2 studies. First, their cohort was derived from electronic health records, from 1996 to 2010, in contrast to our contemporary administrative claims-based cohort from 2014 to 2018. Second, of their 11,0001 patients with IBD, only 1299 patients received TNFα antagonists, and none of the patients received vedolizumab; in contrast, we focused exclusively on 5987 new users of TNFα antagonists or vedolizumab. Third, to implement the hospital frailty risk score (based on ICD-10 codes), they converted the codes to ICD-9 concepts; however, in their conversion, only 9 ICD-9 codes were used, whereas the original ICD-10-based hospital frailty risk score was based on 140 codes, suggesting under-ascertainment in their cohort. This may explain the lower observed prevalence of frailty in their cohort, with only 5% (n = 68 patients) of 1299 TNFα antagonist-treated patients being classified as frail. In contrast, in our cohort, which relied on full ICD-10 and ICD-9 codes, 39% of patients starting biologic therapy with biologics were classified as frail based on the hospital frailty risk score. Finally, their primary outcome was risk of all infections, including outpatients (n = 14 in TNFα antagonist-treated patients) and infection-related hospitalization (n = 14). This outcome may lend itself to ascertainment bias, where TNFα antagonist-treated patients may have greater frequency of health care exposure, leading to greater documentation of minor infections. Similar to our analysis, they did not observe an increased risk of serious infections in frail vs nonfrail patients in their cohort of TNFα antagonist-treated patients. In contrast, we focused on serious infections or infection-related hospitalizations, which are less prone to ascertainment bias. With a larger sample size, focus

TABLE 4. Risk Factors for Serious Infections in Patients With Inflammatory Bowel Diseases Starting (A) Vedolizumab or (B) TNFα Antagonists

A. Vedolizumab		
Risk Factors	**Hazard Ratio (95% CI)**	***P***
Frail (vs nonfrail)	1.69 (1.03–1.79)	0.039
Male (vs female)	1.10 (0.70–1.73)	0.69
Age category		
<30 y	1.00	—
30–39 y	0.98 (0.45–1.13)	0.96
40–59 y	1.05 (0.55–2.00)	0.89
60 y or more	2.44 (1.29–4.61)	<0.01
Crohn's disease (vs ulcerative colitis)	1.54 (0.97–2.45)	0.07
Elixhauser index		
0–1	1.00	—
2	0.88 (0.47–1.67)	0.70
3	0.92 (0.46–1.85)	0.82
4 or more	0.77 (0.42–1.44)	0.42
Corticosteroid use (in preceding 3 m)	1.16 (0.72–1.87)	0.54
Immunomodulator use (in preceding 3 m)	1.17 (0.61–2.22)	0.64
Opiate use (in preceding 12 m)	0.94 (0.59–1.48)	0.78
Hospitalization (in preceding 12 m)	1.27 (0.72–2.25)	0.41
Emergency department visit (in preceding 12 m)	2.62 (1.52–4.54)	<0.01
Abdominal surgery (in preceding 12 m)	1.11 (0.52–2.35)	0.79
Serious infection (in preceding 12 m)	1.53 (0.70–3.37)	0.29
B. TNFα Antagonists		
Risk Factors	**Hazard Ratio (95% CI)**	***P***
Frail (vs nonfrail)	1.03 (0.83–1.27)	0.81
Male (vs female)	0.92 (0.76–1.11)	0.38
Age category		
<30y	1.00	—
30–39y	0.86 (0.64–1.16)	0.33
40–59y	0.92 (0.70–1.20)	0.53
60y or more	2.15 (1.61–2.87)	<0.01
Crohn's disease (vs ulcerative colitis)	0.88 (0.71–1.08)	0.21
Elixhauser index		
0–1	1.00	—
2	1.24 (0.94–1.64)	0.14
3	1.24 (0.90–1.71)	0.18
4 or more	1.79 (1.29–2.26)	<0.01
Corticosteroid use (in preceding 3 m)	1.31 (1.05–1.63)	0.016
Immunomodulator use (in preceding 3 m)	0.78 (0.57–1.06)	0.11
Opiate use (in preceding 12 m)	1.30 (1.05–1.60)	0.014
Hospitalization (in preceding 12 m)	1.26 (0.97–1.64)	0.09
Emergency department visit (in preceding 12 m)	1.32 (1.03–1.69)	0.031
Abdominal surgery (in preceding 12 m)	0.73 (0.54–0.99)	0.046
Serious infection (in preceding 12 m)	1.85 (1.39–2.46)	<0.01

only on biologic-treated patients with IBD, more comprehensive frailty assessment as intended with the hospital frailty risk score, and a higher outcome rate (n = 520 serious infections), we believe our analysis may provide a less biased estimate of the association between frailty and TNFα antagonist-treated patients with IBD.

The observation of a differential association of frailty and risk of serious infections in TNFα antagonist- and vedolizumab-treated patients with IBD was unexpected. It is possible that biologically frail patients, modestly correlated with (and captured by) the hospital frailty risk score, may have selectively been treated with vedolizumab, rather than TNFα antagonists because the former may portend lower degree of systemic immunosuppression by virtue of its gut-specific mechanism of action.

Although there are important strengths of our study in terms of sample size and event rates, focus on biologic-treated patients with IBD inherently at highest risk of infections, and use of a validated frailty index in a contemporary cohort, there are important limitations. First, as an administrative claims-based database study, we did not have access to subjective or objective measures of disease activity or endoscopy reports and did not have accurate details of disease location and behavior, all of which may modify risk of serious infections. Second, the hospital frailty risk score has not been validated in patients with IBD. Though the frailty risk scoring codes include physical function components, such as hemiplegia, abnormal gait, fracture, and care involving rehabilitation procedures, no objective physical performance measures were assessed to measure frailty phenotype. Moreover, frailty status was determined at a single time point (at time of biologic initiation, examining events occurring in preceding 12 months). Biological frailty is a dynamic, multidomain concept encompassing physical, mental, functional, and social status, that extends along a spectrum rather than being binary. Future prospective studies should focus on examining all these domains of frailty repeatedly over time and evaluate its evolution and impact on adverse health outcomes in patients with IBD. Third, ideally, infections would be adjudicated by medical record review and microbiology data, but this level of data is unavailable in claims databases. However, our definition of serious infections requiring hospitalization has been validated with a high positive predictive value.

In summary, we observed that frailty, measured using a claims-based hospital frailty risk score, is not independently associated with increased risk of serious infections in patients with IBD starting biologic therapy. Future studies focusing on frailty phenotype with objective functional and biological measures of frailty are warranted to determine whether such measures can accurately identify biologic-treated patients at higher risk of serious infections beyond conventional risk factors. If frailty is deemed to be a risk factor for serious infections, then targeted interventions such as physical rehabilitation strategies, nutritional counseling, and supplementation and cognitive training may mitigate frailty and decrease risk of serious infections in these vulnerable patients.

SUPPLEMENTARY DATA

Supplementary data is available at *Inflammatory Bowel Diseases* online.

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