ORIGINAL ARTICLE

Axial spondyloarthritis may protect against poor outcomes in COVID-19: propensity score matched analysis of 9766 patients from a nationwide multi-centric research network

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Abstract

Introduction The outcomes of COVID-19 in patients with axial spondyloarthritis (ax-SpA) have not been explored in detail. Tumour necrosis factor inhibitors (TNFi) are commonly used for ax-SpA patients, and how they influence outcomes may have implications on COVID-19 management.

Methods A nationwide multi-centric research network was queried for patients with ax-SpA, including ankylosing spondylitis (AS) and non-radiographic SpA (nr-SpA) who had developed COVID-19. An equal number of propensity score(PS) matched controls were extracted from the database amongst patients with COVID-19 who did not have any inflammatory arthritis. Outcomes included mortality and others including hospitalization, intensive care unit, ventilation, acute kidney injury (AKI), renal replacement therapy, acute respiratory distress syndrome, cerebral infarction, venous thromboembolism (VTE), and sepsis.

Results We identified 9766 patients with ax-SpA (924 AS and 8842 nr-SpA) and 691,862 without SpA who had COVID-19. In the unmatched comparison, patients with ax-SpA had higher risk ratios (RR) for all outcomes. After matching for demographics and comorbidities, patients with ax-SpA had lower RR for mortality [RR: 0.707 (95% CI: 0.598–0.836), $p < 0.0001$], severe COVID-19 [RR: 0.791 (0.69–0.906), $p = 0.0007$], hospitalization [RR: 0.872 (0.826–0.921), $p < 0.0001$], and AKI [RR: 0.902 (0.816–0.997), $p = 0.044$]. Only the risk of VTE was higher in ax-SpA patients [RR: 1.219 (1.037–1.433), $p = 0.016$]. Amongst the ax-SpA group, males had worse outcomes in 9 out of the 11 domains except for VTE and cerebral infarction, while blacks had worse outcomes in all except for mortality and the need for renal replacement therapy. AS had similar risk ratios for all outcomes compared with nr-SpA except hospitalization [RR: 1.457 (1.03–2.06), $p = 0.0318$]. There was no difference in outcomes in patients who had received TNFi in the year previous to COVID-19 infection. Ax-SpA patients who had been prescribed non-steroidal anti-inflammatory drugs in the 3 months prior to COVID-19 had poorer outcomes.

Conclusion In conclusion, COVID-19 outcomes were better in patients with ax-SpA as compared with PS matched controls except for increased risk for VTE. The use of TNFi is not associated with better or worse outcomes. These apparently protective effects observed need to be validated and explored further.

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Key Points

- *Patients with axial spondyloarthritis have lower mortality and morbidity during COVID-19 infections as compared with propensity score matched controls.*
- *Axial spondyloarthritis is associated with higher risks for venous thromboembolism during COVID-19.*
- *There is no difference in outcomes between ankylosing spondylitis and non-radiographic spondyloarthritis except in rates of hospitalization, which were higher in ankylosing spondylitis.*
- *Use of tumour necrosis factor inhibitors did not influence COVID-19 outcomes.*

Keywords Ankylosing spondylitis · COVID-19 · Multi-centric cohort · Outcomes · Spondyloarthritis

Introduction

In the last 18 months, the COVID-19 pandemic has claimed over 3 million lives and has left no human unaffected. Though vaccination is helping to control the pandemic, new infections are still emerging. Different autoimmune diseases and immunosuppressants are expected to influence the outcomes of COVID-19. To date, most published analyses of the effects of various rheumatic and musculoskeletal diseases (RMD) on COVID-19 outcomes have utilized heterogeneous groups of patients [1, 2]. Overall, inflammatory rheumatic diseases were expected to have higher risks for infections and more severe disease. In-depth analyses of published case series have revealed this to be not true [3]. Having a connective tissue disease like lupus, but not inflammatory arthritis, may be linked to more severe COVID-19 [4, 5]. Thus, with growing numbers of COVID-19 available worldwide, there is a need to study the effect of individual diseases on COVID-19 outcomes. If any disease has protective outcomes, it can be due to the medications used for that disease or due to some intrinsic protection due to the disease itself. One such disease is axial spondyloarthritis, ax-SpA. The outcomes of COVID-19 in spondyloarthritis (SpA) are limited to case reports. Moreover, the literature focusing on outcomes of COVID-19 in ax-SpA patients exclusively is sparse [6, 7].

Tumour necrosis factor inhibitors (TNFi) are commonly used in the treatment of ax-SpA. Thus, exploring outcomes in SpA would also enable us to study the possible associations of TNFi use with COVID-19 outcomes. In the fight against COVID-19, a major thrust has been on the repurposing of existing drugs [8]. The success of steroids in reducing mortality in the RECOVERY trial has provided support for the use of immunosuppressants and anti-inflammatory

agents [9]. Early in the pandemic, the use of TNFi was suggested for severe COVID-19 based on its biological nature [10]. Till date there is no evidence of any adverse effects of TNFi during COVID-19. There is some epidemiological data from psoriasis and inflammatory bowel disease cohorts to support a better outcome in patients using TNFi [11]. At least 3 to 4 randomized controlled trials exploring the role of TNFi in severe COVID-19 are expected to be completed in the latter part of the year 2021 [11, 12].

The multi-centric research network TriNetX compiles electronic information from multiple centres across the USA, with minor contributions from other countries. It includes diagnoses, therapies used, infections like COVID-19, and clinically meaningful outcomes. Previously, the multi-centric health network, TriNetX, had been used to find out the outcomes of 8540 patients with RMDs [2]. Thus, we took the opportunity provided by TriNetX to explore outcomes of COVID-19 in patients with ax-SpA and also to analyse the effects of TNFi.

Methods

The study was designed along the lines of previous publications [2, 13–15] as a retrospective cohort derived from the TriNetX network. Ankylosing spondylitis (AS) and non-radiographic SpA (nr-SpA) who had COVID-19 were included, and one-to-one matched controls were selected using propensity score (PS).

The TriNetX database contains anonymized data. It was queried based on either the International Classification of Diseases tenth revision (ICD-10), Current Procedural Terminology (CPT) codes, or Logical Observation Identifiers Names and Codes (LOINC). These extracted data included demographics, diagnoses, drugs, and clinical outcomes.

Patient selection

The SpA with COVID-19 cohort included all patients who were 18 years of age or older, had a pre-existing diagnosis of ax-SpA (AS or nr-SpA), and were diagnosed with COVID-19 anytime from January 20, 2020, to April 30, 2021. ICD-10 codes were used for the diagnosis of ankylosing spondylitis (M45.x) or axial spondyloarthritis (M46.1, M46.8, M46.9). Diagnosis of COVID-19 was based on ICD-10 codes (U07.1, U07.2, J12.81, B34.2, B97.21, B97.29) augmented by polymerase chain reaction (PCR) for SARS-CoV-2 results when available. The control cohort was extracted from all the other COVID-19 patients excluding known ankylosing spondylitis or axial spondyloarthritis (M45.x, M46.x) or any other form of inflammatory arthritis (M05.x, M06.x, L40.53).

Data extracted

Demographic characteristics (age, sex, race, body mass index), presence of comorbidities (hypertension [ICD10 code: I10], chronic lower lung disease [ICD10 codes: J40–J47], diabetes mellitus [ICD10 codes: E08–E13], ischemic heart disease [ICD10 codes: I20–I25], chronic kidney disease [ICD10 code: N18], heart failure [ICD10 code: I50], cerebrovascular disease [ICD10 codes: I60–I69], nicotine dependence [ICD10 code: F17], and alcohol-related disorders [ICD10 code: F10]), and medication used preceding the diagnosis of COVID-19 were extracted. TNFi included were etanercept, adalimumab, infliximab, certolizumab, and golimumab. Also, the use of non-TNFi biologicals like interleukin 17 inhibitors (namely secukinumab, ixekizumab) were included.

Outcomes

COVID-19 clinical outcomes included mortality, hospitalization, intensive care unit (ICU) admission, mechanical ventilation, acute kidney injury, renal replacement therapy (RRT) including haemodialysis, acute respiratory distress syndrome (ARDS), cerebral infarction, venous thromboembolism (VTE), and sepsis. Severe COVID-19 was defined in this study as the composite of mechanical ventilation and mortality. All these outcomes were assessed within 30 days from the date when the diagnosis of COVID-19 had been made.

Statistical analysis

A one-to-one PS-based matching was carried out to identify a control group. The demographic and comorbidity variables mentioned above were used as factors or covariates in the PS matching that utilized a greedy nearest-neighbour algorithm with a calliper of 0.1 pooled standard deviations. Risk ratios (with 95% confidence intervals) were calculated for the outcomes mentioned above, comparing with both unmatched and matched controls. The detailed methodology is provided elsewhere [13, 15]. Two-sided tests of significance were used. Statistical significance was fixed at a p-value of less than 0.05. For visualization of results, R statistical program (Ver 4.0.3) was used along with the ggplot2 package and its dependencies.

Ethics statement

Due to its status as a federated network providing de-identified data with aggregated counts and statistical summaries, the TriNetX has been granted a waiver by the Western Institutional Review Board.

Results

We identified 9766 patients with ax-SpA who had COVID-19 infection. Of these, 924 were coded as having AS and the other 8842 as nr-SpA. The mean age was 60.3 ± 15.3, 66.2% were females, and the majority (74.3%) were white. After

Table.1 Baseline characteristics of axial spondyloarthritis (ax-SpA) versus the rest (unmatched and matched)

Parameters		Ax-SpA patients	Unmatched non-ax-SpA		Matched non-ax-SpA controls	
			Data	Standardized difference	Data	Standardized difference
Total numbers		9,766	691,862	-	9,766	-
Age (years)		60.3 ± 15.3	47.8 ± 18.7	0.73	60.5 ± 15.3	0.014
Body mass index		31.9 ± 7.4	30.5 ± 7.4	0.19	31.9 ± 74	0.006
Female		6,461 (66.16%)	381,609 (55.16%)	0.23	6401 (65.54%)	0.013
Race	White	7,252 (74.26%)	427,956 (61.86%)	0.27	7360 (75.36%)	0.025
	African Americans	1,538 (15.75%)	115,341 (16.67%)	0.02	1474 (15.09%)	0.018
	Asian	121 (1.24%)	17,537 (2.54%)	0.09	115 (1.18%)	0.006
Comorbidities	Hypertension	6,403 (65.56%)	177,330 (25.63%)	0.87	6,475 (66.3%)	0.016
	Chronic lung disease	4,292 (43.95%)	104,401 (15.09%)	0.67	4,262 (43.64%)	0.006
	Diabetes mellitus	3,220 (39.97%)	87,055 (12.58%)	0.50	3,183 (32.59%)	0.008
	Ischemic heart diseases	2,584 (26.46%)	52,989 (7.66%)	0.52	2,533 (25.94%)	0.012
	Heart failure	1,521 (15.57%)	29,999 (4.34%)	0.38	1,455 (14.90%)	0.019
	Chronic kidney disease	1,766 (18.08%)	36,962 (5.34%)	0.40	1,708 (17.49%)	0.015
	Cerebrovascular accident	1,746 (17.88%)	32,117 (4.64%)	0.43	1,637 (16.76%)	0.029
	Nicotine dependence	1,879 (19.24%)	51,486 (7.44%)	0.35	1,826 (18.70%)	0.014
	Alcohol-related disorders	605 (6.19%)	17,303 (2.50%)	0.18	518 (5.30%)	0.038

Table.2 Risk ratios comparing outcomes of axial spondyloarthritis (ax-SpA) using the unmatched cohort

Parameter	Ax-SpA with COVID ($n = 9{,}841$)	Non-ax-SpA with COVID ($n = 704{,}456$)	Risk ratio (95% CI)	p
Mortality	227 (2.31%)	12065 (1.71%)	1.35 (1.18, 1.53)	< 0.0001
Hospitalization	1933 (19.64%)	103704 (14.72%)	1.33 (1.28, 1.39)	< 0.0001
Acute kidney failure	677 (6.88%)	27332 (3.9%)	1.77 (1.65, 1.91)	< 0.0001
Renal replacement therapy	53 (0.55%)	2216 (0.32%)	1.73 (1.32, 2.27)	< 0.0001
Acute respiratory distress syndrome	192 (1.95%)	8285 (1.18%)	1.66 (1.44, 1.91)	< 0.0001
Critical care services	401 (4.07%)	18006 (2.56%)	1.59 (1.45, 1.76)	< 0.0001
Mechanical ventilation	228 (2.32%)	12695 (1.80%)	1.29 (1.13, 1.46)	0.0001
Severe COVID-19 (mortality + ventilation)	356 (3.62%)	19233 (2.7%)	1.32 (1.19, 1.47)	< 0.0001
Cerebral infarction	140 (1.42%)	4497 (0.64%)	2.23 (1.89, 2.63)	< 0.0001
Venous embolism and thrombosis	320 (3.25%)	10869 (1.54%)	2.11 (1.89, 2.35)	< 0.0001
Secondary sepsis	461 (4.68%)	21590 (3.1%)	1.53 (1.40, 1.67)	< 0.0001
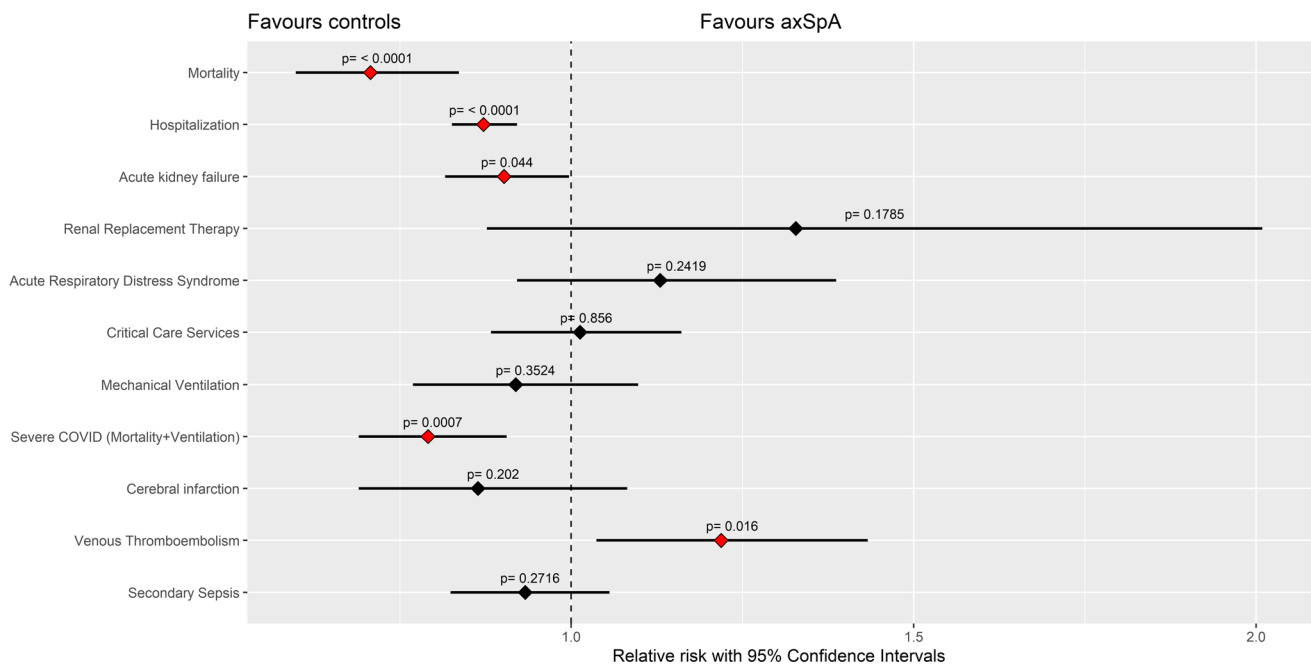
Fig. 1 Relative risk of outcomes of COVID-19 in patients with axial spondyloarthritis as compared with propensity score matched controls. Matching has been carried out for demographic characteristics (age, sex, race, body mass index) and the presence of comorbidities (hypertension, chronic lower lung disease, diabetes mellitus, ischemic heart disease, chronic kidney disease, heart failure, cerebrovascular disease, nicotine dependence, and alcohol-related disorders)

exclusion of all inflammatory arthritis, 691,862 patients who had COVID-19 were identified. Demographics and prevalence of different comorbidities in ax-SpA and the others are presented in Table 1. After matching, 9766 controls were identified with a standardized difference of all matched parameters less than 0.04 (Table 1).

In the unmatched comparison, patients with ax-SpA had higher risk ratios (RR) for all 11 outcomes (Table 2). When compared with the PS matched controls (Fig. 1),

patients with ax-SpA had lower RR for mortality [RR: 0.71 (95% CI: 0.60–0.84), $p < 0.0001$], severe COVID-19 [RR: 0.79 (0.69–0.91), $p = 0.0007$], hospitalization [RR: 0.87 (0.83–0.92), $p < 0.0001$], and AKI [RR: 0.90 (0.82–0.997), $p = 0.044$]. Only the risk of VTE was higher in ax-SpA patients [RR: 1.22 (1.04–1.43), $p = 0.016$].
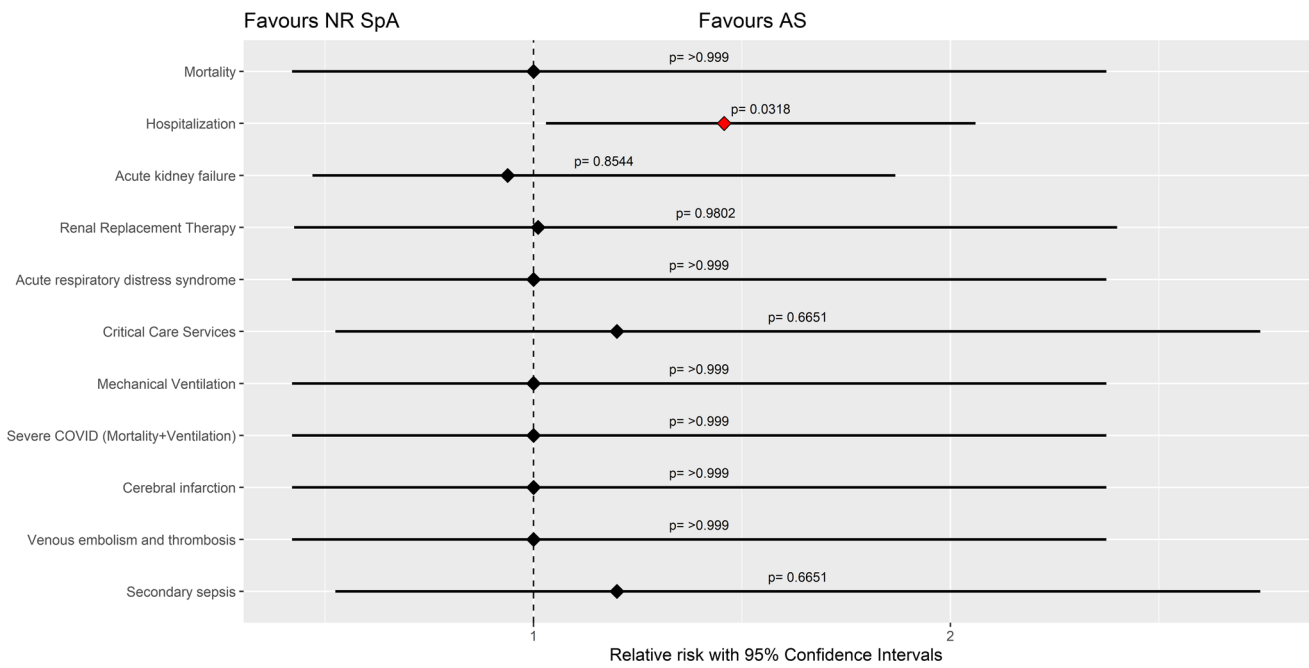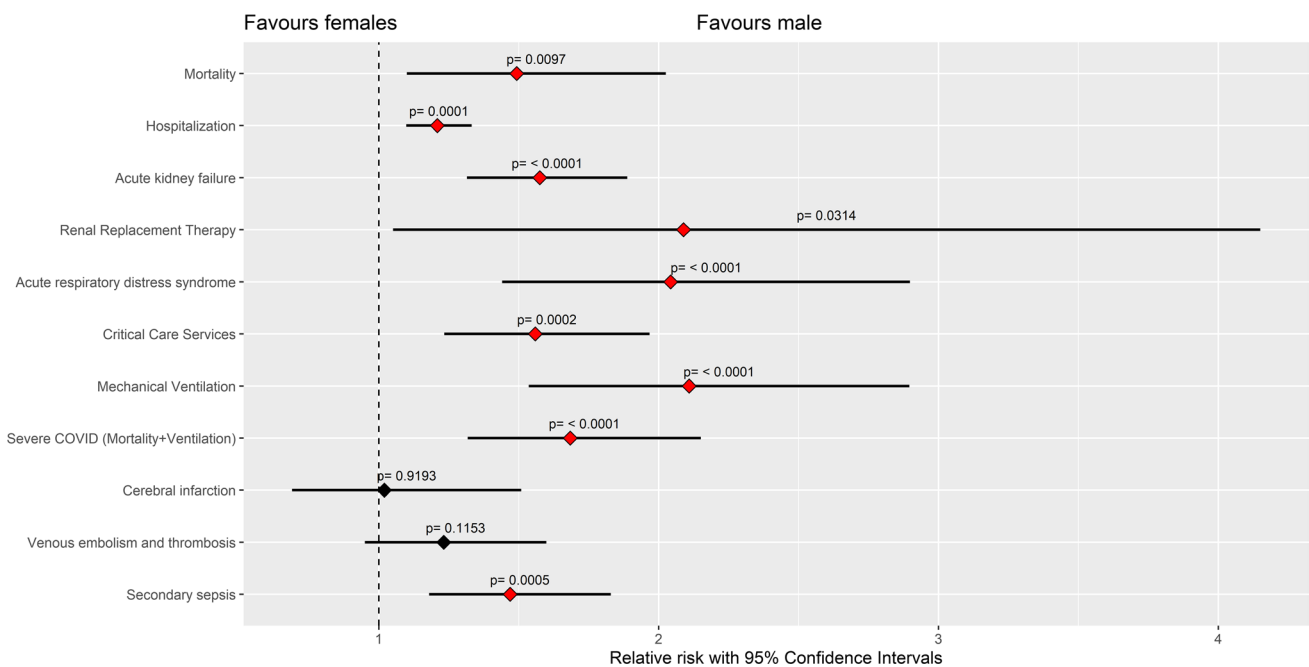
Fig. 2 Relative risk of outcomes of COVID-19 in patients with ankylosing spondylitis as compared with non-radiographic axial spondyloarthritis. PS-based matching has been carried out for demographic characteristics (age, sex, race, body mass index) and the presence of comorbidities (hypertension, chronic lower lung disease, diabetes mellitus, ischemic heart disease, chronic kidney disease, heart failure, cerebrovascular disease, nicotine dependence, and alcohol-related disorders)
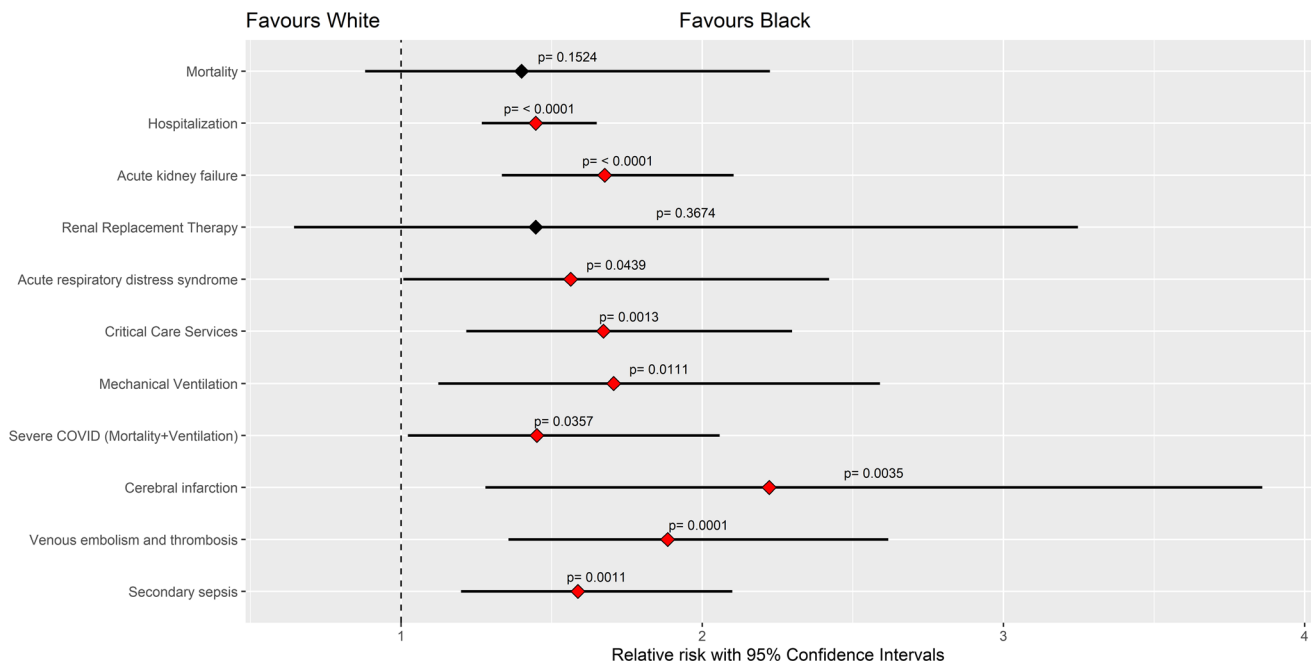

Fig. 3 Relative risk of outcomes of COVID-19 in males with axial spondyloarthritis as compared with females. PS-based matching has been carried out for demographic characteristics (age, sex, race, body mass index) and the presence of comorbidities (hypertension, chronic lower lung disease, diabetes mellitus, ischemic heart disease, chronic kidney disease, heart failure, cerebrovascular disease, nicotine dependence, and alcohol-related disorders)
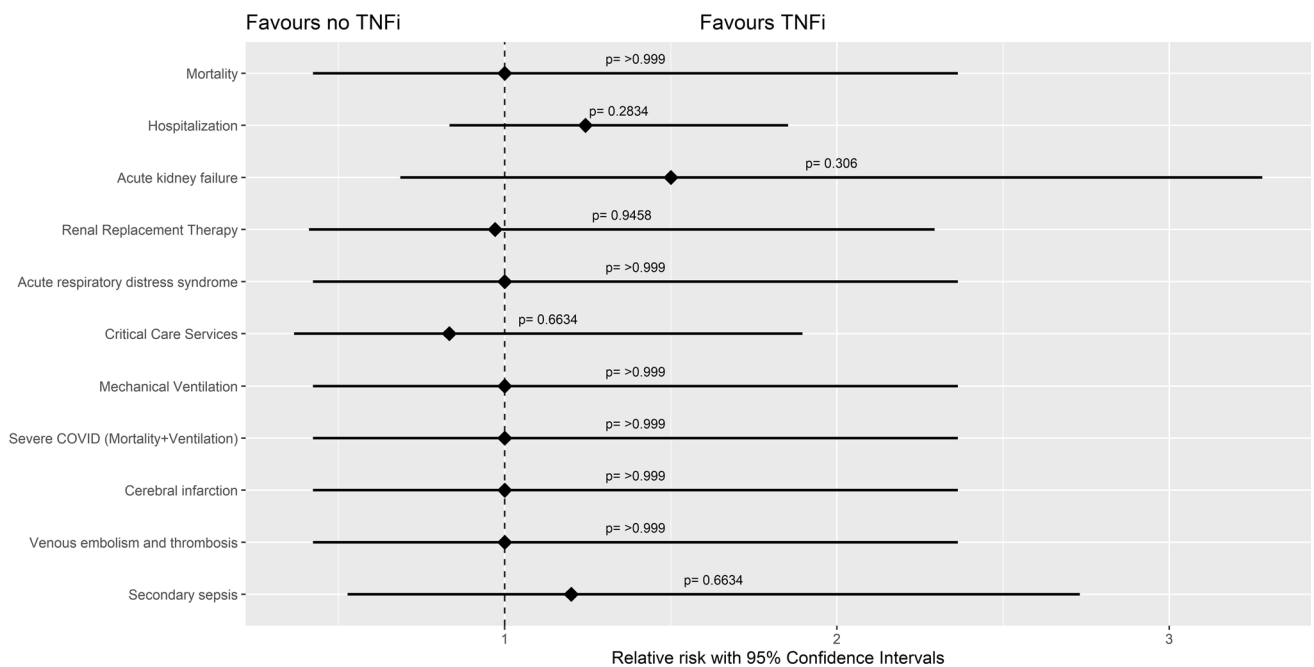
Fig. 4 Relative risk of outcomes of COVID-19 in black patients with axial spondyloarthritis as compared with white patients. PS-based matching has been carried out for demographic characteristics (age, sex, race, body mass index) and the presence of comorbidities (hypertension, chronic lower lung disease, diabetes mellitus, ischemic heart disease, chronic kidney disease, heart failure, cerebrovascular disease, nicotine dependence, and alcohol-related disorders)

Fig. 5 Relative risk of outcomes of COVID-19 in patients with axial spondyloarthritis who received tumour necrosis factor inhibitors in previous 12 months as compared with others. PS-based matching has been carried out for demographic characteristics (age, sex, race, body mass index) and the presence of comorbidities (hypertension, chronic lower lung disease, diabetes mellitus, ischemic heart disease, chronic kidney disease, heart failure, cerebrovascular disease, nicotine dependence, and alcohol-related disorders)

Sub-group analysis

Firstly, the difference in outcomes between AS and nr-SpA was compared. Both had a similar risk ratio except for hospitalization [RR: 1.457 (1.03–2.06), $p = 0.0318$], which was higher in patients with AS (Fig. 2). Second, the effects of sex and race were explored. Males had worse outcomes in 9 out of the 11 domains except for VTE and cerebral infarction (Fig. 3). Blacks had worse outcomes in all domains except for mortality and the need for RRT as compared with whites (Fig. 4).

To explain the association of ax-SpA with better outcomes, we attempted to analyse the effects of TNFi. After matching for other factors, TNFi usage in the last 1 year did not significantly affect any outcome (Fig. 5). We repeated the analysis matching for TNFi use ever (data not shown), but the apparently protective effects of ax-SpA persisted in this model. The usage of interleukin-17 inhibitors was limited to 45 patients, and thus, we did not analyse the individual effects of this group of drugs. Finally, we attempted to look at how NSAID use was associated with the outcomes. Patients who had documented use of NSAIDs in the 3 months preceding the COVID-19 infection had poorer outcomes in all 11 domains (Fig. 6).

Discussion

Analysing this large cohort of 9766 patients with COVID-19 and ax-SpA, we found that they had poorer outcomes as compared to the unmatched general population. The PS matched analysis revealed that patients with ax-SpA were at lower risk for mortality and morbidity including hospitalization, AKI, or severe COVID-19 (composite of mortality and mechanical ventilation). There was no difference in the rates of renal replacement therapy, ARDS, ICU care, mechanical ventilation, cerebrovascular infarction, or secondary sepsis. Also, the sub-group analysis did not reveal any difference between AS versus nr-SpA patients except for higher hospitalization rates in AS. This may be an effect of longer disease duration or more severe disease in AS (factors like age, BMI, comorbidities, and others were controlled for).

Previous analyses of COVID-19 outcomes in patients with rheumatic diseases have shown neutral effects of the presence of rheumatic disease [16]. Any increased effects are only in univariate analysis [1] and disappear when demographics and comorbidities are adjusted for [3]. One study has reported a possible association of methotrexate, rituximab, and glucocorticoid use with hospitalization [17]. But confounding due to disease activity cannot be ruled out. Our results are in line with other studies that have shown increased risk with male gender and black race [18].
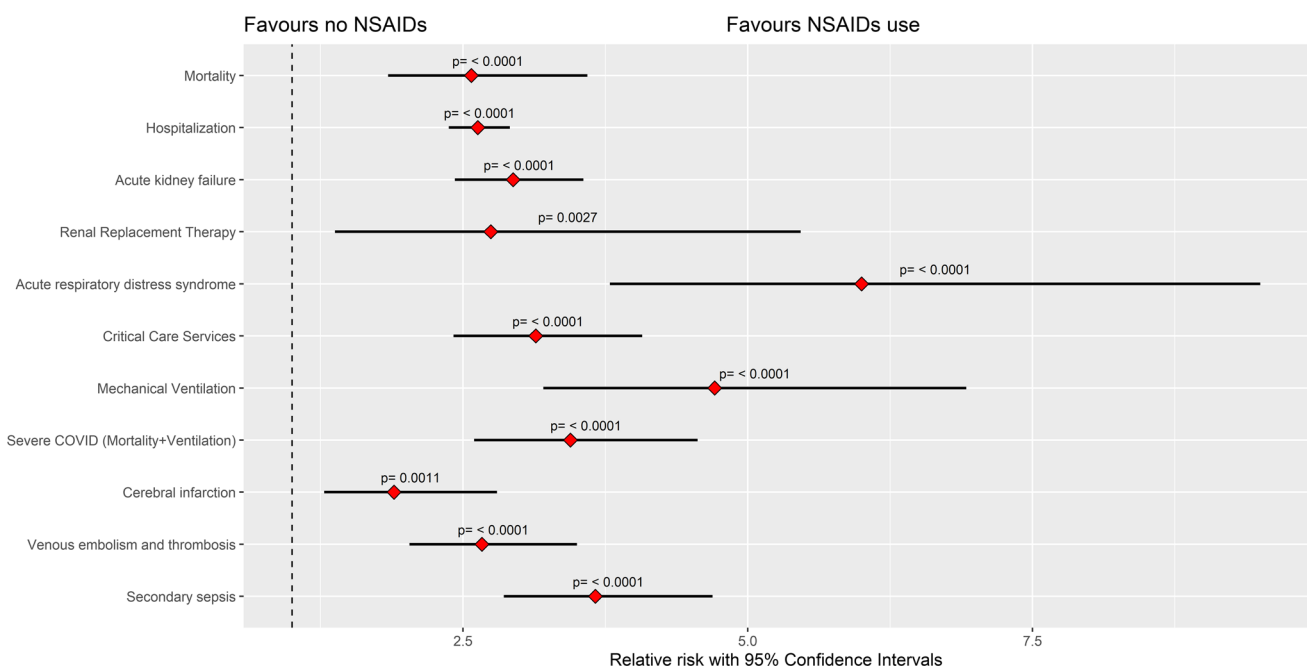

Fig. 6 Relative risk of outcomes of COVID-19 in patients with axial spondyloarthritis who were prescribed non-steroidal anti-inflammatory drugs in previous 3 months as compared with others. PS-based matching has been carried out for demographic characteristics (age, sex, race, body mass index) and the presence of comorbidities (hypertension, chronic lower lung disease, diabetes mellitus, ischemic heart disease, chronic kidney disease, heart failure, cerebrovascular disease, nicotine dependence, and alcohol-related disorders)

An overall increased risk of VTE is expected in COVID-19 [19], and this may be compounded in the presence of inflammatory arthritis that themselves increase the risk of thrombosis. Ax-SpA has been associated with an increased risk of thrombosis per se [20, 21]. This may be due to genetic polymorphisms common to thrombosis and inflammatory arthritides [22]. These genes (such as SERPINE1 and IL-1β) are also implicated in the pathogenesis of thrombosis in COVID-19 [19]. Similar findings of increase VTE risk during COVID-19 has also been reported for rheumatoid arthritis [23]. It can also be due to hyper viscosity, endothelial dysfunction, down-regulation of protein C, and inhibition of fibrinolysis caused by inflammatory cytokines like TNF alpha and IL-1 [24, 25].

TNFi use within the ax-SpA patients did not reveal any reduced risks. In an analysis of an inflammatory bowel disease (IBD) database, the SECURE-IBD registry, TNFi usage was associated with a reduced risk of the composite outcome of death or hospital admission for COVID-19 (adjusted odds ratio: 0·60 [95% CI: 0·38–0·96], $p = 0·03$) [26]. Similarly, in a population-based study of psoriasis patients ($n = 1943$), those receiving TNFi had a lower risk of COVID-19-related hospitalization as compared with those on methotrexate (adjusted HR, 0.10; 95% CI: 0.01–0.82) [27]. In the psoriasis cohort, none of the patients on TNFi died. In a Veterans study, TNFi use in IBD patients was not associated with an increased risk of COVID-19 infection, but the incidence was too low to analyse for severe COVID-19 [28]. In data from the COVID-19 Global Rheumatology Alliance physician-reported registry ($n = 600$), the use of TNFi (alone or in combination) was associated with a lower risk of COVID-19-related hospitalization as compared with patients on no drugs (adjusted OR of 0·40 [95% CI: 0·19–0·81], $p = 0·01$) [1]. In another analysis of 77 patients with rheumatic diseases, none of the patients on TNFi ($n = 16$) needs ventilatory support or died, as opposed to 40% of patients on other therapies [29]. However, all these observational studies did not control for various possible confounders. For example, in the Global Rheumatology Alliance study [1], the comparison was with untreated patients where higher disease activity itself might be the confounding factor.

TriNetX has been previously analysed to explore the effects of TNFi usage on COVID-19 outcomes [30]. However, the number of COVID-19 cases has increased manifold since that study was carried out (total patients in the cohort was 231), and the study design was heterogeneous. Firstly, it clubbed TNFi and methotrexate together during the analysis. Secondly, it clubbed together all diseases that might be a confounding factor in itself. A sub-group analysis looked at all "diseases of the musculoskeletal system" together. However, our study design shows much clearly that TNFi usage in patients of ax-SpA does not reduce the severity of the infection.

A previous study analysing NSAID use in COVID-19 using the OpenSAFELY platform data showed that there was no added risk of the use of NSAIDs. However, in their second analysis that included only patients with rheumatoid arthritis and osteoarthritis, who are expected to be higher users of NSAIDs, current users had a better outcome than non-users [31]. To see if such a phenomenon could explain our results, we explored the association of NSAIDs use in the last 3 months but found that they were associated with poorer outcomes. This can be explained as NSAID use can increase risks of AKI and there would be confounding by higher disease activity.

Our analyses could not pinpoint an explanation why ax-SpA was associated with better COVID-19 outcomes. One hypothesis is that the immune activation in SpA might provide a barrier against certain viral infections. HLA (Human Leukocyte Antigen)-B27 has been reported to be associated with protection against viruses like the human immunodeficiency, hepatitis C, and Epstein Barr viruses [32]. Similar to the 8.1 ancestral haplotype that predisposes to autoimmunity but is protective against certain infections [33], there might be some underlying mechanisms that can minimize certain infection risks in patients with SpA. This may be associated with the HLA class I or ERAP genes, or even some epigenetic or functional changes in immune cells due to the presence of SpA.

The limitations of our analysis include the use of aggregate data that excludes the use of multivariate analysis. The database has minimal data on disease activity, disease duration, or other relevant information like HLA-B27 positivity, insufficient for robust analysis. Also, the possible confounding by unrecognized factors cannot be excluded [34]. We cannot exclude the possibility that some AS patients might have been coded into the system as nr-SpA. However, this should not affect the overall results.

In conclusion, COVID-19 outcomes were better in patients with ax-SpA as compared with PS matched controls except for increased risk for VTE. Amongst individuals with ax-SpA, the use of TNFi does not seem to influence outcomes, but male sex and black race may confer worse COVID outcomes. This possible overall protective effect needs to be validated and explored further.

Declarations

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