Original article

Shielding reduced incidence of COVID-19 in patients with inflammatory arthritis but vulnerability is associated with increased mortality

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Abstract

Objectives. Investigate whether individuals with inflammatory arthritis (IA), their treatments and shielding status affect the risk of adverse outcomes from COVID-19 for the entire population of Wales, UK.

Methods. Retrospective, population-based cohort study using linked, anonymized electronic health data from SAIL Databank, including primary/secondary care, rheumatology, Office for National Statistics Mortality and COVID-19 laboratory data. Individuals aged 18 years and over testing positive for COVID-19 between March 2020 and May 2021 with READ Codes present for rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis formed the study cases.

Results. A total of 1966 people with IA and 166 602 without tested positive for COVID-19. The incidence rate was 3.5% (1966/56 914) in IA, *vs* 6% in the general population (166 602/2 760 442), (difference: 2.5%, 95% CI: 2.4%, 2.7%, $P \leq 0.001$). In an adjusted Cox proportional hazard model, IA was not associated with higher mortality (HR: 0.56, 95% CI: 0.18, 1.64, $P=0.286$). Significant risk factors included shielding (HR: 1.52, 95% CI: 1.40, 1.64, $P \leq 0.001$), hospitalization for previous infections (HR: 1.20, 95% CI: 1.12, 1.28, $P \leq 0.001$), hospitalizations one year pre-pandemic (HR: 1.34, 95% CI: 1.25, 1.44, $P \leq 0.001$) and glucocorticoid use (HR: 1.17, 95% CI: 1.09, 1.25, $P \leq 0.001$).

Conclusions. Individuals with IA had a lower incidence of COVID-19, probably due to shielding. IA was not associated with increased mortality following COVID-19 infection; being vulnerable (shielded), comorbidities and other factors were associated with increased risk. These key risk factors can identify individuals with IA at greater risk from COVID-19 and advised to shield during high community prevalence.

Key words: inflammatory arthritis, RA, PsA, AS, COVID-19, electronic health records

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Rheumatology key messages

- COVID-19 incidence was lower in individuals with IA and shielding was associated with reduced COVID-19.
- Key risk factors including age, smoking and comorbidities were associated with increased COVID-19 related mortality.
- These factors can identify individuals to shield during times of high COVID-19 prevalence and pre-vaccination.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has caused over 10 million deaths. The lives of individuals with rheumatic diseases have been greatly affected with concerns regarding the risk of infection and severe outcomes, causing great anxiety, depression and reduced wellbeing [1]. Having inflammatory arthritis (IA) and treatment with anti-rheumatic medication increases the risk of infections in general [2] and comorbidities common in individuals with IA are also associated with increased mortality from COVID-19 [3–5].

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CLINICAL SCIENCE

A small primary care cohort and the global rheumatology registry found an increased risk of severe disease and mortality in individuals with rheumatic diseases [3, 6, 7]. A large-scale cohort study conducted on English routinely-collected primary care data has also found an increased risk of COVID-19 related death (HR: 1.23, 95% CI: 1.20, 1.27) and hospitalization (HR: 1.32, 95% CI: 1.29, 1.35) in people with immune-mediated inflammatory diseases, including inflammatory arthritis, bowel or skin disease.

No increased risk of adverse COVID-19 outcomes were observed in individuals on DMARDs used to treat the immune-mediated inflammatory diseases, with the exception of rituximab, which the authors explain may be related to confounding [8]. However, this study did not examine susceptibility to serious infection or vulnerability to poor outcome. It has, however, been documented that previous serious infections are predictive of increased risk of serious infection in biologic-treated rheumatoid arthritis patients [9].

Previous studies have shown that comorbidities and medications, particularly in people with RA with active disease, increase the risk of serious infection, morbidity and mortality which may confound the association between IA and COVID-19 related outcomes [2].

In addition, a moderate to a high dose of glucocorticoids has been associated with a higher risk of people with rheumatic disease being hospitalized [6]. One biologic in particular, rituximab has been associated with more severe COVID-19 [10].

In the UK, including Wales, the government advised vulnerable individuals, including many people with IA, to follow shielding practices which included self-isolating at home, avoiding face-to-face contact, and mask wearing, social distancing and quarantining when necessary. Individuals deemed as high risk from COVID-19 were contacted by mail issued by the National Health Service and provided with guidance on shielding [11]. Shielding, however, has also been associated with negatively affecting physical and emotional wellbeing among patients with rheumatic diseases in the UK [12], which has implications for the large number of rheumatic patients advised to shield during the pandemic. In the UK and US, The British BSR [13] treatment guidelines and National Institute for Health and Care Excellence (NICE) [14] and the ACR [15], respectively, recommended the continuation with DMARD treatment and following shielding practices during the pandemic; however, pausing DMARD treatment in the case of COVID-19 infection. The EULAR produced guidelines at the beginning of the pandemic and updated these recently with more evidence-based recommendations. Findings were similar to UK and US guidelines; however, EULAR suggests continuing with the treatment regimen even in the case of suspected or confirmed COVID-19, with the exception of rituximab [16, 17].

When shielding practices were investigated in a cross-sectional study of nearly 500 RA individuals from Boston, USA, the use of DMARDs and glucocorticoids were both associated with increased adherence to shielding practices in the United States [18]. However, non-compliance with DMARDs has been shown to slightly increase during the pandemic in a study conducted in Switzerland [17].

Using the complete COVID-19 test data for the entire nation of Wales, UK, we compared the incidence and mortality of COVID-19 in people with IA to the general population for an entire nation with a 3 million population while controlling for shielding status, comorbidities, history of serious infections, previous hospitalization, medications used to treat IA and susceptibility to severe outcomes of COVID-19.

To our knowledge, this is the first study to use data for an entire population that uses linked, routinely collected health data from multiple health sources to include individuals' shielding status in analyses.

Method

A population-based cohort was derived from multiple data sources comprising deidentified data held in the Secured Anonymised Information Linkage (SAIL) databank for the population of Wales. Linkage fields are used to anonymously link data sources using a multiple encryption system with a trusted third party, NHS Wales Informatics Service (NWIS). Using a split-file approach, identifiable data is removed from data and NWIS uniquely matches identities to an Anonymised Linkage Field (ALF). Data can then be recombined using the unique ALF while protecting anonymity [20, 21] which has been used to respond to the COVID-19 pandemic in Wales, previously [22]. Individuals who tested positive for COVID-19 sourced from COVID-19 laboratory testing data formed the population.

COVID-19 laboratory testing data between March 2020 and May 2021 dataset was included in the analysis. Individuals with READ Codes present for rheumatoid arthritis, psoriatic arthritis and snkylosing spondylitis ($n = 1966$) on 1 March 2021 in primary care health data comprised the individuals with IA (Supplementary Table S1, available at *Rheumatology* online), while those without these codes formed the general population ($n = 166\,602$). Individuals who were under 18 years of age when tested for COVID-19 were excluded from analysis to exclude people with juvenile inflammatory arthritis. A flow diagram of the cohort creation is available in Supplementary Fig. S1, available at *Rheumatology* online.

Shielding status data was available in COVID-19 related datasets and provided whether an individual was advised to shield in Wales during the initial outbreak of the pandemic, between March and August 2020 [11].

Primary and secondary care data was linked at the person level and used to follow up individuals through the health system, prospectively and retrospectively from date of a positive COVID-19 test for diagnosis codes for IA, comorbidities, medications and healthcare visits

(Codelist libraries are found in Supplementary Tables S2–S4, available at *Rheumatology* online). Previous hospitalizations due to infections were investigated from secondary care data as a surrogate of susceptibility to serious infection. All hospitalizations within one year prior to the COVID-19 pandemic (between 1 March 2019 and 1 March 2020) were also investigated as a surrogate of vulnerability. Mortality data was obtained by linking to the Annual District Death Daily dataset from the Office of National Statistics. The researchers had full access to the relevant datasets following application to and approval from the SAIL databank governance panel.

COVID-19 positive cases were defined as individuals with a positive COVID-19 test during the study period. Individuals who did not have a COVID-19 test were considered as COVID-19 negative. The relationship between shielding status and COVID-19 incidence was investigated for all individuals using a χ^2 test [23]. This was repeated for extrapolated figures for individuals in Wales with IA and separately for individuals without IA. Death within 28 days of COVID-19 test positive was counted as due to COVID-19 infection. A Cox proportional hazard model was used to generate hazard ratios of mortality following COVID-19 positive test result for people with IA compared with those without IA. Univariable analysis informed the significant candidate variables ($P \leq 0.05$ level of significance) added as covariates to the final model.

Individuals with positive COVID-19 tests in the laboratory testing data without Anonymised Linkage Fields were excluded from analysis as these could not be linked to primary and secondary healthcare records. Age was missing for a small number of individuals with IA but were included in analysis. Supplementary Fig. S1, available at *Rheumatology* online, outlines the cohort creation and handling of missing data.

All data analysis was conducted using STATA Version 16.

Ethical approval

Data held in the SAIL databank are anonymised and therefore, no ethical approval is required. All data contained in SAIL has the permission from the relevant Caldicott Guardian or Data Protection Officer. This study has been approved by the SAIL databank Information Governance Review Panel.

Results

Over 3 million COVID-19 tests had been administered in Wales at the time of analysis. The incidence of positive cases was crudely calculated based on data available within the SAIL primary care dataset for the study period between 1 March 2020 to 12 May 2021. Of those individuals aged 18 years or over testing positive for COVID-19, 1966 had a diagnosis of IA in their primary care record compared with 166 602 individuals, without diagnosis codes for IA. For people with IA, the crude COVID-19 incidence was 3.5% (3.2% for RA individuals alone), compared with 6% for the general population (difference: 2.5%, 95% CI: 2.4%, 2.7%) (Table 1).

Among individuals who tested positive for COVID-19, those with IA were significantly older than those without IA; mean age 62.6 and 46.1 years, respectively (difference: 16.5, 95% CI: 15.7, 17.3). The individuals with IA were 36.2% female compared with 55.4% in the general population (difference: 19.3, 95% CI: 17.1, 21.4). A significantly larger proportion of individuals with IA were shielding (49.4%) compared with the general population group (4.6%) (difference: 44.8%, 95% CI: 42.6, 47) (Table 2). A significantly higher proportion of the IA individuals smoked (42%) compared with general population (27.4%) (difference: 14.6%, 95% CI: 12.5, 16.9). The IA population had more comorbidities than the general population including cardiovascular disease, diabetes, hyperlipidaemia, hypertension, chronic kidney disease, respiratory disease, cancer and depression and anxiety (Table 2).

Significantly more individuals with IA had been hospitalized with serious infection prior to having COVID-19 compared with those without IA (34.1% and 17.5%, respectively; difference 16.6%, 95% CI: 14.6, 18.8). More individuals with IA (33.9%) were hospitalized 1-year pre-COVID-19 pandemic (between 1 March 2019 to 1 March 2020 to exclude those who may have been admitted to hospital as a result of COVID-19) compared with those without IA (16.6%) (difference: 17.3%, 95% CI: 15.3, 19.4) (Table 2).

As expected, IA individuals took significantly more DMARDs than those without IA. Glucocorticoid use was also significantly higher in those with IA (57.8%) compared with those without (17.9%) (difference: 39.9%, 95% CI: 37.7, 42.1) (Table 2).

Post-COVID-19 infection, significantly more people with IA (24.4%) were admitted to hospital compared with

TABLE 1 Individuals testing positive for COVID-19 aged 18 years and over and residents of Wales, UK with data contributing to the SAIL Databank

	Percentage positive	COVID-19 positive per 100 000 population
Inflammatory arthritis	3.5% (1966/56 914)*	3454.3
Rheumatoid arthritis only	3.2% (1283/40 723)	3150.5
Non-inflammatory arthritis	6% (166 603/2 760 442)	6035.3

*$P < 0.0001$ by χ^2 compared with general population.

Table 2 Characteristics of individuals, with and without inflammatory arthritis who tested positive for COVID-19 from March to May 2021

	Inflammatory arthritis (n = 1966)	General population (n = 166 602)	Difference (95% CI)
Mean age at test,[a] years (S.D.)	62.6 (16.4)	46.1 (18.9)	16.5 (15.7, 17.3)
Female, % (n)	36.2% (711)	55.4% (92 263)	19.3 (17.1, 21.4)
Rheumatoid arthritis, % (n)[d]	65.3% (1283)	—	—
Psoriatic arthritis, % (n)[d]	26.1% (514)	—	—
Ankylosing spondylitis, % (n)[d]	12.5% (246)	—	—
Shielding, % (n)	49.4% (972)	4.6% (7689)	44.8 (42.6, 47)
Ever smoked, % (n)	42% (826)	27.4% (45 601)	14.6 (12.5, 16.9)
Mean BMI (S.D.)	29.2 (7.1)	28.4 (67 965)	0.8 (0.4, 1.2)
Comorbidities			
Cardiovascular disease, % (n)	16% (315)	4.4% (7349)	11.6 (10.1, 13.3)
Diabetes, % (n)	15.7% (308)	6.3% (10 505)	9.4 (7.8, 11)
Hyperlipidaemia, % (n)	15.2% (298)	5.1% (8482)	10.1 (8.6, 11.7)
Hypertension, % (n)	40.6% (799)	15% (25 035)	25.6 (23.5, 27.8)
Chronic kidney disease, % (n)	4.1% (81)	0.01% (13)	4.1 (3.3, 5.1)
Orthopaedic surgery, % (n)	5.8% (113)	0.01% (19)	5.7 (4.8, 6.9)
Respiratory Disease, % (n)	87.5% (1721)	72.3% (120 376)	15.3 (13.7, 16.7)
Cancer, % (n)	14.8% (290)	5.8% (9610)	9 (7.5, 10.6)
Depression/Anxiety, % (n)	49.9% (980)	36.7% (61.140)	13.2 (10.9, 15.4)
Serious infections (hospitalized), % (n)	34.1% (671)	17.5% (29 151)	16.6 (14.6, 18.8)
Hospitalized within 1 year pre-pandemic,[c] % (n)	33.9% (666)	16.6% (28 138)	17.3 (15.2, 19.4)
Medication			
cDMARDs, % (n)	34.2% (672)	0.6% (1007)	33.6 (31.5, 35.7)
Antimalarial only, % (n)	12.8% (251)	0.2% (408)	12.5 (11.1, 14.1)
Biologics,[e] % (n)[b]	9.3% (182)	0.03% (47)	9.2 (8, 10.6)
Glucocorticoids, % (n)	57.8% (1, 137)	17.9% (29 869)	39.9 (37.7, 42.1)
Colchicine, % (n)	8.9% (175)	2.8% (4586)	6.2 (5, 7.5)
Outcomes			
Admitted to hospital, % (n)	24.4% (479)	10.5% (17 448)	13.9 (12, 15.8)
Median hospital stay duration, days (IQR)	14 (37)	8 (35)	
Sick notes post COVID, % (n)	2.5% (50)	1.8% (2957)	0.8 (0.2, 1.6)
Deceased following testing positive for COVID-19, % (n) (within 28 days of positive test)	11.2% (221)	3.2% (5345)	8 (6.7, 9.5)
Median time to death from positive test, days (IQR)	10 (9)	9 (9)	
Mean age deceased following COVID-19, years (S.D.)	78.1 (9.4)	80.1 (11.8)	2 (0.4, 3.6)
Proportion females (deceased), % (n)	59.3% (131)	44.9% (2402)	5.2 (4.2, 6.4)

*Significant at $P \leq 0.05$. [a]Age was missing for 0.3% (499/166 602) of the individuals without IA. [b]Rheumatology data was unavailable for 66% (1298/1966) of individuals with IA. [c]Including hospitalizations from 1 March 2019 to 1 March 2020. [d]Some individuals were positive for multiple IA conditions. [e]Biologics included: adalimumab, infliximab, certolizumab, golimumab, abatacept, rituximab, tocilizumab, ustekinumab, secukinumab.

general population (16.9%) (difference: 13.9, 95% CI: 12, 15.8). Mortality rate within 28 days of COVID-19 positive test was significantly higher in individuals with IA (11.2%) compared with general population (3.2%) (difference: 8%, 95% CI: 6.7, 9.5) (Table 2).

When comparing the characteristics of individuals hospitalized following COVID-19, those with IA were significantly older, with a higher proportion of females, increased proportion of shielded individuals and a higher rate of smokers compared with individuals without IA. Of those hospitalized, a significantly larger proportion of people with IA died (22.5%) compared with general population (13.1%) (difference: 9.4%, 95% CI: 5.9, 13.4, $P \leq 0.001$) (Table 3).

Mortality was investigated using the Cox proportional hazard ratio to explore risk factors associated with time to death within 28 days of COVID-19 infection. While IA was associated with over a three and a half-fold increased risk in the univariable analysis, when adjusted for confounding variables, IA was not associated with an increased risk of death compared with general population in the adjusted multivariable analysis (HR: 0.56, 95% CI: 0.18, 1.64, $P = 0.286$) (Table 4). However, the significant factors associated with increased risk of death compared with general population in adjusted analysis included shielding status (HR: 1.52, 95% CI: 1,40, 1.64, $P \leq 0.001$). Age was also associated with an increased risk of death with 8% higher rate per additional year in

TABLE 3 Characteristics of individuals hospitalized following COVID-19

	Inflammatory arthritis (*n* = 479)	General population (*n* = 17 448)	Difference (95% CI)
Mean age at test years (S.D.)	71.1 (13)	61.4 (20.5)	9.7 (7.9, 11.6)*
Female, % (*n*)	61.2% (293)	54.5% (9, 482)	6.8 (2.3, 11.2)*
Rheumatoid arthritis, % (*n*)	74.3% (356)	—	—
Psoriatic arthritis, % (*n*)	20.5% (98)	—	—
Ankylosing spondylitis, % (*n*)	9.8% (47)	—	—
Shielding, % (*n*)	60.8% (291)	17.1% (2983)	43.7 (39.2, 48)*
Ever smoked	54.3% (260)	43.1% (2983)	11.2 (6.6, 15.6)*
BMI	29.2 (6.8)	29.5 (7.3)	0.3 (−1.1, 0.5)
Outcomes following hospitalization			
Deceased following testing positive for COVID-19, % (*n*) (*within 28 days of positive test*)	22.5% (108)	13.1% (2, 290)	9.4 (5.9, 13.4)*
Median hospital stay duration, days (IQR)	10 (15.5)	9 (16)	

*Significant at *P* ≤0.05.

TABLE 4 Factors related to time to death within 28 days of a positive COVID-19 test from March 2020 to May 2021

	Univariable analysis HR (95% CI)	Adjusted multivariable analysis HR (95% CI)
Inflammatory arthritis	3.64 (3.18, 4.16)*	0.56 (0.18, 1.64)
Rheumatoid arthritis, % (*n*)	3.07 (2.13, 4.42)*	1.90 (0.64, 5.62)
Psoriatic arthritis, % (*n*)	0.30 (0.20, 0.48)*	0.81 (0.28, 2.30)
Ankylosing spondylitis, % (*n*)	0.61 (0.38, 0.98)*	1.67 (0.55, 5.02)
Shielding	5.52 (5.17, 5.89)*	1.52 (1.40, 1.64)*
Mean age at test, years (S.D.)	1.10 (1.10, 1.10)*	1.08 (1.08, 1.09)*
Female, % (*n*)	0.60 (0.62, 0.69)*	0.56 (0.52, 0.60)*
Ever smoked	3.27 (3.10, 3.45)*	1.27 (1.17, 1.38)*
BMI	0.99 (0.99, 0.99)*	1.01 (1.01, 1.02)*
Cardiovascular disease	8.48 (7.99, 8.99)*	1.05 (0.98, 1.13)
Diabetes	5.78 (5.45, 6.13)*	1.38 (1.28, 1.48)*
Hyperlipidaemia	4.21 (3.93, 4.51)*	1.06 (0.98, 1.15)
Hypertension	7.36 (6.97, 7.76)*	1.19 (1.11, 1.28)*
Chronic kidney disease	4.62 (3.22, 6.64)*	1.25 (0.82, 1.91)
Orthopaedic surgery	1.49 (0.93, 2.38)	
Respiratory disease	1.14 (1.07, 1.21)*	0.95 (0.87, 1.04)
Cancer	6.21 (5.85, 6.59)*	1.10 (1.02, 1.18)*
Depression/Anxiety	1.00 (0.95, 1.06)	
Serious infections prior to COVID-19 (hospitalized)	4.48 (4.25, 4.72)*	1.20 (1.12, 1.28)*
Hospitalized within 1 year pre-pandemic[a]	17.61 (16.54, 18.76)*	1.34 (1.25, 1.44)*
cDMARDs	2.73 (2.31, 3.22)*	1.22 (0.98, 1.51)
Antimalarial only	2.22 (1.75, 2.82)*	1.22 (0.91, 1.63)
Biologics	0.75 (0.46, 1.22)	
Glucocorticoids	2.81 (2.66, 2.97)*	1.17 (1.09, 1.25)*
Colchicine	4.15 (3.81, 4.52)*	1.07 (0.97, 1.18)

*Significant at *P* ≤0.05. [a]Including hospitalizations from 1 March 2019 to 1 March 2020.

age compared with the general population (HR: 1.08, 95% CI: 1.80, 1.09, *P* ≤0.001). Each BMI point incremental increases were associated with a 1% increase in risk of death in people with IA compared with those without IA (HR: 1.01, 95% CI: 1.01, 1.02, *P* ≤0.001). Smoking was associated with 27% increased risk of death, (HR: 1.27, 95% CI: 1.17, 1.38, *P* ≤0.001).

Significant comorbidities associated with increased risk of death included diabetes (HR: 1.38, 95% CI: 1.28, 1.48, *P* ≤0.001), hypertension (HR: 1.19, 95% CI: 1.11, 1.28, *P* ≤0.001), cancer (HR: 1.10, 95% CI: 1.02, 1.18, *P* ≤0.01). Susceptibility to infection as assessed by serious infection requiring hospitalizations prior to COVID-19 infection and vulnerability as having been hospitalized

within one year pre-COVID-19 pandemic (between 1 March 2019 and 1 March 2020) were strongly associated with an increased risk of death by 20% (HR: 1.20, 95% CI: 1.12, 1.28, $P \leq 0.001$) and 34% (HR: 1.34, 95% CI: 1.25, 1.44, $P \leq 0.001$), respectively. Finally, use of glucocorticoids was associated with an increased risk of death (HR: 1.17 95% CI: 1.09, 1.25, $P \leq 0.001$) (Table 4).

A total of 13 255 individuals testing positive for COVID-19 were excluded from analysis due to no available anonymised linkage field, preventing follow-up through linked healthcare records. For gender, 0.3% (6/1966) of individuals with IA had missing gender codes but were included in analysis. Supplementary Fig. S1, available at *Rheumatology* online describes the cohort creation and handling of missing data.

Discussion

To our knowledge, this is one of the first studies that has shown shielding is associated with reduced incidence of COVID-19 in both IA individuals and the general population. The incidence rate of COVID-19 infections was lower in individuals with IA compared with the general population, which was associated with a higher proportion of individuals who have been advised to shield. Although there is general agreement on the need to shield in individuals who are vulnerable, there is a debate on the exact criteria used for risk stratification with some authors proposing that shielding is unnecessary in people with rheumatic diseases [24]. Data from this study would support that individuals with RA, in particular those who have risk factors associated with poor outcomes from COVID-19 should be advised to 'shield'. Most importantly, previous serious infection leading to hospitalization and hospitalization within the previous 12 months should be included as risk factors for severe outcome.

The disparity in proportion of females testing positive for COVID-19 between IA and the general population may be explained by the greater level of shielding in IA patients. In addition, RA were predominantly female (72.2%) while PsA and AS were 54.3% and 38.2% female, respectively.

Our findings were consistent with a previous study in England [8], showing that individuals with IA were more likely to be hospitalized and had an increased mortality with similar hazard ratio. However, our findings differed from this previous study [8], which found increased mortality in individuals with IA, particularly in those receiving rituximab, independent of other risk factors such as age and gender.

Our data suggested that higher mortality in IA is due to confounders rather than disease. There are several potential explanations for these differences. First, in the previous study, the study duration was March to September 2021, while our study was from March 2020 to May 2021. New and more contagious COVID-19 variants emerged between May to September 2021 (delta). Second, the previous study has addressed some confounders such as age and some comorbidities, whereas in our study, we included additional comorbidities: hyperlipidaemia and hypertension. Third, the previous study did not assess susceptibility to infection and vulnerability.

In this study, prior history of serious infections requiring hospitalization, shielding status and hospitalization within 1 year prior to the pandemic were included as covariates. Shielding status and hospitalization within 1 year prior to the pandemic were included as surrogates of vulnerability. All these were found to be independently associated with increased in mortality. Previous studies in RA have shown that some individuals have higher risk of infections and hospitalization leading to the development of risk calculators such as the RABBIT risk score [25].

A novel finding of this study is the fact that individuals with IA who had been hospitalized for serious infections prior to COVID-19 were over 20% more likely to die following COVID-19 infection compared with those without IA.

Shielding status was associated with over 50% increased risk of mortality in people with IA compared with people without IA. This was probably due to these individuals having multiple features that are classified as 'vulnerable' by the UK government and so having more complex disease. Because shielded individuals have a lower incidence of COVID-19–19 in both IA and the general population, data from this study validates and supports the criteria and recommendation for shielding.

Another novel finding from this study is IA individuals who were hospitalized within one year prior to the pandemic had over 34% increase in mortality. This may reflect on the severity of comorbidities and disease. Hospitalization either due to infection or general admission one year prior to the pandemic should be included as criteria to define vulnerability for shielding. This will improve risk stratification for shielding.

Despite vaccination, shielding may still be necessary for the unvaccinated or those who may not be able to access subsequent vaccinations or boosters. In fact, hesitance to receive the COVID-19 vaccinations have been reported with waning uptake of vaccination observed in the UK and other countries [26]. In addition, a global study demonstrates the hesitancy of individuals with autoimmune and rheumatic diseases [27].

Furthermore, as with many RNA viruses, COVID-19 is prone to genetic adaptations, which may have implications for future vaccine efficacy [28] and shielding may be necessary to protect those most at risk of severe outcome from COVID-19. In common with previous research, our findings demonstrate that only treatment with glucocorticoids was associated with increased risk of death in individuals with IA compared with the general population. All other IA-related medications included in the model were not associated with severe outcome post-COVID-19 treatment. However, only 9.3% of people with IA contracted COVID-19 were taking biologics, the negative association may be due to small sample size so

definitive conclusions should not be drawn. In the aforementioned English study [8], no association between mortality from COVID-19 with biologics and Janus kinase inhibitors apart from rituximab was observed.

Strengths

A considerable strength of our study is that it draws findings on the entire population of Wales, UK, demonstrating that IA alone is not the cause of poor outcomes following COVID-19 infection. This study links data from various sources and provides comprehensive large-scale detail follow-up of clinical events for individuals seen in primary and secondary care including rheumatology department data in Wales. Furthermore, we are also able to capture the shielding status of individuals tested for COVID-19.

By highlighting from clinical data that secondary health care admissions one year prior to the pandemic and also a history of serious infections is associated with an increased risk of death in individuals with IA compared with the general population adds insight into those at severe risk of COVID-19 and can help inform shielding advice given, tailored to those who need it rather than the entire IA patient group. This is of particular importance since physical and mental adverse effects associated with shielding in rheumatology patients have been observed [12]; therefore, identifying only high-risk patients requiring to shield can help mitigate the negative aspects.

In this study, we did not find any evidence of more severe outcome in PsA and AS so only RA patients have more severe outcome because they are older and more likely to have more comorbidities. Even within the RA population, we have shown previous admission with serious infection and hospitalisation within 12 months are significant risk factors. These have not been shown previously.

Limitations

Limitations of the study relate to the use of routinely collected health data for secondary research purposes, such as misclassification bias. Access to routine healthcare was also hugely disrupted throughout the country and so latent or new comorbidities may be missed causing misclassification. Also, a record of a prescribed medication does not necessarily mean that the medication has been taken.

There are a small proportion of individuals receiving DMARD treatment in the general population, which likely means that other inflammatory conditions, such as psoriasis and inflammatory bowel disease are included in this population; however, this study was interested in IA conditions only. Furthermore, our findings and others [8] show that DMARD use is not associated with adverse outcome from COVID-19.

Similarly, it is impossible to know the extent to which shielding recommendations have been adhered to. However, a study using data from the UK demonstrated

that shielding advice was followed by 81% of those who were advised to shield [12]. Conversely, some individuals with IA who have not been advised to shield might do so out of concern. Research from the US has demonstrated that the perception of COVID-19 risk among individuals with RA varies substantially, with greater perceived risk associated with greater adherence to shielding practices [16].

Rheumatology data was not available for all individuals with IA as at present, data from only two centres in Wales are available. This means that care must be taken in interpreting the findings regarding biologics that are administered by rheumatologists in the UK. It is likely that we may be underpowered to draw conclusions on the effect of biologics on COVID-19 because we have aggregated data of different biologics due to low numbers for some of the drugs, especially because rituximab, for instance, is known to increase the risk of severe COVID-19 [10]. However, as more rheumatology data is contributed, this can be explored further.

While data reported here is for an entire population of Wales, the handling of the pandemic, healthcare delivery in general and COVID-19 related healthcare disruption is likely to be unique across different countries. Therefore, this should be borne in mind when generalizing these findings.

Lastly, we assumed individuals who were not tested for COVID-19 did not have the virus. Some individuals may have asymptomatic/mild disease and COVID-19 testing was restricted, most notably during the first wave. However, we have included data for over a year of the pandemic to help overcome this.

In summary, individuals with IA, particularly RA, are older and more vulnerable to severe effects of COVID-19. We have identified key risk factors associated with a poorer outcome from COVID-19: older, male, vulnerable/shielding individuals, with a history of serious infections or hospitalizations, smoking, increased BMI, comorbidities and glucocorticoid use. These can be used to stratify individuals with IA who are at greater risk from severe effects of COVID-19 and advise them to shield at times of high community prevalence of COVID-19 infection and prior to vaccination.

Data availability statement

The data underlying this article were provided by SAIL Databank by permission. Data will be shared on request to the corresponding author with permission of SAIL Databank (http://saildatabank.com).

Supplementary data

Supplementary data are available at *Rheumatology* online.

References

1 D'Silva KM, Wallace ZS. COVID-19 and rheumatoid arthritis. Curr Opin Rheumatol 2021;33:255–61.

2 Listing J, Gerhold K, Zink A. The risk of infections associated with rheumatoid arthritis, with its comorbidity and treatment. Rheumatology 2013;52:53–61.

3 Chen L, Yu J, He W *et al.* Risk factors for death in 1859 subjects with COVID-19. Leukemia 2020;34:2173–83.

4 Williamson EJ, Walker AJ, Bhaskaran K *et al.* OpenSAFELY: factors associated with COVID-19 death in 17 million patients. Nature 2020;584:430–6.

5 D'Silva KM, Serling-Boyd N, Wallwork R *et al.* Clinical characteristics and outcomes of patients with coronavirus disease 2019 (COVID-19) and rheumatic disease: a comparative cohort study from a US hot spot. Ann Rheum Dis 2020;79:1156–62.

6 Gianfrancesco M, Hyrich KL, Hyrich KL *et al.* Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. Ann Rheum Dis 2020;79:859–66.

7 Liu M, Gao Y, Zhang Y *et al.* The association between severe or dead COVID-19 and autoimmune diseases: a systematic review and meta-analysis. J Clean Prod 2020;doi:10.1016/j.jinf.2020.05.065.

8 Mackenna B, Kennedy NA, Mehkar A *et al.* Risk of severe COVID-19 outcomes associated with immune-mediated inflammatory diseases and immune modifying therapies: a nationwide cohort study in the OpenSAFELY platform. medRxiv 2021090321262888. 2021.

9 Jani M, Barton A, Hyrich K. Prediction of infection risk in rheumatoid arthritis patients treated with biologics: are we any closer to risk stratification? Curr Opin Rheumatol 2019;31:285–92.

10 Avouac J, Drumez E, Hachulla E *et al.* COVID-19 outcomes in patients with inflammatory rheumatic and musculoskeletal diseases treated with rituximab: a cohort study. Lancet Rheumatology 2021;3:e419–26.

11 Welsh Government. Guidance on protecting people defined on medical grounds as clinically extremely vulnerable from coronavirus (COVID-19)- previously known as "shielding." 2020. https://gov.wales/guidance-protecting-people-defined-medical-grounds-clinically-extremely-vulnerable-coronavirus (23 May 2022, date last accessed).

12 Cleaton N, Raizada S, Barkham N *et al.* The impact of COVID-19 on rheumatology patients in a large UK centre using an innovative data collection technique: prevalence and effect of social shielding. Rheumatol Int 2021;41:707–14.

13 British Society for Rheumatology. COVID- 19 guidance. https://www. rheumatology.org.uk/practice-quality/covid-19-guidance (8 March 2022, date last accessed).

14 National Institute for Health and Care Excellence. COVID-19 rapid guideline: rheumatological autoimmune, inflammatory and metabolic bone disorders. https://www.nice.org.uk/guidance/ng167 (8 March 2022, date last accessed).

15 Mikuls TR, Johnson SR, Fraenkel L *et al.* American College of Rheumatology guidance for the management of rheumatic disease in adult patients during the COVID-19 pandemic: version 3. Arthritis Rheumatol 2021;73:e1–12.

16 Landewé RBM, Landewé RBM, MacHado PM *et al.* EULAR provisional recommendations for the management

of rheumatic and musculoskeletal diseases in the context of SARS-CoV-2. Ann Rheum Dis 2020;79:851–8.

17 Landewé RBM, Kroon FPB, Alunno A *et al.* EULAR recommendations for the management and vaccination of people with rheumatic and musculoskeletal diseases in the context of SARS-CoV-2: the November 2021 update. Ann Rheum Dis 2022;doi: annrheumdis-2021-222006.

18 Cook C, Cox H, Fu X *et al.* Perceived risk and associated shielding behaviors in patients with rheumatoid arthritis during the coronavirus 2019 pandemic. ACR Open Rheumatol 2021;3:834–8.

19 Ciurea A, Papagiannoulis E, Bürki K *et al.* Impact of the COVID-19 pandemic on the disease course of patients with inflammatory rheumatic diseases: results from the Swiss Clinical Quality Management cohort. Ann Rheum Dis 2021;80:238–41.

20 Lyons RA, Jones KH, John G *et al.* The SAIL databank: linking multiple health and social care datasets. BMC Med Inform Decis Mak 2009;9:3.

21 Ford D. V, Jones KH, Verplancke JP *et al.* The SAIL Databank: building a national architecture for e-health research and evaluation. BMC Health Services Research 2009;9:157.

22 Lyons J, Akbari A, Torabi F *et al.* Understanding and responding to COVID-19 in Wales: protocol for a privacy-protecting data platform for enhanced epidemiology and evaluation of interventions. BMJ Open 2020;10:e043010.

23 Pearson F.R.S. K. X. On the criterion that a given system of deviations from the probable in the case of a correlated system of variables is such that it can be reasonably supposed to have arisen from random sampling. The London, Edinburgh, and Dublin Philosophical Magazine and Journal of Science 1900;50:157–175.

24 Amani L, Warraich R, Patel N, Tahir H. COVID-19 and rheumatology: is shielding really necessary? Br J Hosp Med 2020;81:1–3.

25 Strangfeld A, Eveslage M, Schneider M *et al.* Treatment benefit or survival of the fittest: what drives the time-dependent decrease in serious infection rates under TNF inhibition and what does this imply for the individual patient? Ann Rheum Dis 2011;70:1914–20.

26 Robinson E, Jones A, Lesser I, Daly M. International estimates of intended uptake and refusal of COVID-19 vaccines: a rapid systematic review and meta-analysis of large nationally representative samples. Vaccine 2021;39: 2024–34.

27 Putman M, Kennedy K, Sirotich E *et al.* COVID-19 vaccine perceptions and uptake: results from the COVID-19 Global Rheumatology Alliance Vaccine Survey. Lancet Rheumatol 2022;4:e237–40.

28 Yuan F, Wang L, Fang Y, Wang L. Global SNP analysis of 11,183 SARS-CoV-2 strains reveals high genetic diversity. Transbound Emerg Dis 2021;68:3288–304.