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Original Article

Severe infections remain common in a real-world rheumatoid arthritis cohort: A simple clinical model to predict infection risk

Dorothy Wang[1], Ai Li Yeo[1-3], Claire Dendle[1, 3], Susan Morton[2], Eric Morand[1, 2], Michelle Leech[1, 2]

Abstract

Objective: This study aimed to investigate the incidence of severe infections in patients of a dedicated rheumatoid arthritis (RA) clinic, identify the associated risk factors, and derive an infection risk screening tool.

Methods: Between January and July 2019, 263 eligible patients with a diagnosis of RA were recruited retrospectively and consecutively from an RA clinic of an Australian tertiary hospital. The primary outcome was severe infection (requiring hospital admission) between January 2018 and July 2019. We collected data from medical records and pathology results. We used validated scores, such as the disease activity score of 28 joints (DAS28) and the Charlson comorbidity index, to assess the disease activity and comorbidity burden. Multivariable logistic regression was used for statistical analysis.

Results: A total of 45 severe infection episodes occurred in 34 (13%) patients, corresponding to 10.8 infections per 100 patient-years. Respiratory (53%) and urinary (13%) tract infections were the most common. In the multivariable analysis, significant risk factors included low lymphocyte count (odds ratio [OR], 4.08; 95% confidence interval [CI], 1.16-14.29), severe infection in the past 3 years (OR, 3.58; 95% CI, 1.28-9.97), Charlson comorbidity index >2 (OR, 2.69; 95% CI, 1.03-7.00), and higher DAS28 (OR, 1.35/0.5-unit increment; 95% CI, 1.10-1.67). A model incorporating these factors and age had an area under receiver operating characteristic curve of 0.82.

Conclusion: To the best of our knowledge, this was one of the first Australian studies to evaluate severe infection rates in a real-world RA cohort. The rates remained high and comparable with those of the older studies. Lymphopenia, disease activity, comorbidity burden, and previous severe infection were the independent risk factors for infection. A model comprising easily assessable clinical and biological parameters has an excellent predictive potential for severe infection. Once validated, it may be developed into a screening tool to help clinicians rapidly identify the high-risk patients and inform the tailored clinical decision making.

Keywords: Arthritis, rheumatoid, infections, risk factors

ORCID iDs of the authors:
D.W. 0000-0002-9842-2492;
A.L.Y. 0000-0001-6242-1562;
C.D. 0000-0002-6642-5365;
S.M. 0000-0002-6823-3199;
E.M. 0000-0002-9507-3338;
M.L. 0000-0002-7226-7121.

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[1] Centre for Inflammatory Diseases, Monash University, Clayton, Victoria, Australia
[2] Department of Rheumatology, Monash Health, Clayton, Victoria, Australia
[3] Department of Infectious Disease, Monash Health, Clayton, Victoria, Australia

Address for Correspondence:
Dorothy Wang; Centre for Inflammatory Diseases, Monash University, Clayton, Victoria, Australia

E-mail: dorothyjwang@gmail.com

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Introduction

A higher infection risk in patients with rheumatoid arthritis (RA) compared with the general population has been well documented. Case-control studies have shown that patients with RA have approximately twice the risk of developing a severe infection than those without RA (1, 2). Severe infection consistently ranks within the top 3 causes of mortality in patients with RA (3) and remains an ongoing clinical risk in the management of RA, particularly in the era of biologic therapies. In general, the higher risk of infection in patients with RA can be explained by the risk factors associated with the disease itself, the immunosuppressive medications used to treat RA, and the coexisting comorbidities and lifestyle factors (4).

The available literature has provided an enhanced understanding of the inherent immunological dysfunction in RA and the infection risk profiles of immunosuppressive medications. This has led to the development of several infection risk calculators, which use risk factors to estimate the probability of a severe infection in the next 12 months, such as the RA observation of biologic therapy (RABBIT) risk calculator (5, 6). This is a web-based tool (https://biologika-register.de/en/rabbit/rabbit-risk-score-of-infections/), which can be used to evaluate the infection risk and the effect of medication escalation or de-escalation of the infection risk.

Risk calculators may help to stratify risk and identify high-risk patients for tailored treatment measures, such as treatment de-escalation, temporary breaks in immunosuppressive therapy, vaccinations, use of primary and secondary antimicrobial prophylaxis, and more intensive laboratory monitoring. However, tools, such as the RABBIT risk calculator, may be difficult to integrate into routine clinical care. Parameters required in the calculator include the Health Assessment Questionnaire (HAQ), a lengthy questionnaire used to evaluate functional status, and the number of previously used disease-modifying anti-rheumatic drugs (DMARDs), which may be difficult to assess in the clinical setting owing to time constraints. In contrast to the risk calculators, there is a lack of simple screening tools for RA that are useful for rapidly identifying a subset of patients with a high infection risk, in whom more advanced risk stratification tools, such as the RABBIT risk calculator, could be applied.

In this study, we aimed to investigate the incidence of severe infections in a real-world RA cohort, identify the risk factors associated with infection, and develop a prototype screening tool to predict infection risk in everyday clinical practice.

Methods

Setting

A retrospective observational cohort study was performed at the RA clinic of a tertiary hospital in Melbourne, Australia. Patients were recruited consecutively at routine clinic visits between January 2018 and July 2019. The study was approved by the Monash Health Human Research Ethics Committee (Approval Date: February 16, 2018; Approval Number: Project 13019A), and all patients provided written informed consent.

Main Points

- In this observational cohort study of 263 patients with rheumatoid arthritis, the incidence of severe infections was high at 10.8 severe infections per 100 patient-years.
- This study yielded a multivariable model with 5 parameters: 1) age ≥50 years; 2) disease activity; 3) Charlson comorbidity index of ≥2; 4) lymphopenia; and 5) severe infection in the last 3years.
- This model has an excellent predictive ability for severe infection (area under receiver operating characteristic curve, 0.82). Once validated, it may be used for identifying the patients at risk of infection and guide the clinical decisions targeting risk reduction measures.

Inclusion and exclusion criteria

Patients were eligible to participate if they were aged 18 years or older, consented to the study, and met the American College of Rheumatology/European League against Rheumatism (ACR/EULAR) classification criteria for RA (7). Patients who did not provide consent or meet the ACR/EULAR classification criteria were excluded.

Data collection

The consenting eligible patients completed a questionnaire. The collected data included baseline demographics and the number of severe infections, which is defined as infections requiring hospital admission and occurring over a 1.5-year study period (January 2018 to July 2019). Severe infection episodes were confirmed, and the details were corroborated with hospital records and discharge summaries. At subsequent visits, we documented all the recurrent or incident infection episodes occurring within the study period. We also documented whether the patients had an up-to-date influenza vaccination (within the last year) or pneumococcal vaccine (within the last 5 years). Medical records were used to obtain details of the medical and medication history. We used the Charlson comorbidity index (8) to calculate a comorbidity score (excluding age). We assessed RA disease activity using the disease activity score of 28 joints (DAS28) (9) with 3 variables derived from the tender and swollen joint counts and most recent erythrocyte sedimentation rate (ESR). We obtained ESR, C-reactive protein levels, and blood counts as part of routine care. Two additional non-routine tests, including lymphocyte subsets (T cells [CD3+], T-helper cells [CD3+/CD4+], cytotoxic T cells [CD3+/CD8+], B cells [CD19+], and natural killer cell counts) measured by flow cytometry and immunoglobulin (Ig) concentrations (IgG, IgA, and IgM) were performed at the time of recruitment. For patients with multiple laboratory results over the study period, the mean of each parameter was used in the analysis. We defined immune biomarkers as low if they were below the normal reference range at any time within the study period before an infection episode. Data were recorded using research electronic data capture REDCap version 8.10.5 (Vanderbilt University; Nashville, TN, USA).

Clinical outcomes

The primary outcome of this study was a severe infection episode occurring within the study period (January 2018 to August 2019). We defined a severe infection as any infection requiring hospital admission. We classified infections as microbiologically defined (wherein the microorganism related to the clinical presentation was isolated) or clinically defined (wherein no microorganism related to the clinical presentation was isolated). For each infection episode, we documented antimicrobial use during admission as well as the admission duration, organ system and infection site, organisms isolated, imaging findings, and changes made to RA medications during admission.

Statistical analysis

All continuous variables followed a non-parametric distribution, confirmed by the Shapiro-Wilk test of normality. Differences between patients with and without severe infections were analyzed using the Mann-Whitney U and chi-squared tests. Univariable logistic regression was used to determine the factors associated with a severe infection. Variables with a p value <0.10 were used in the multivariable analysis, unless they were collinear with another variable. In the case of collinearity, the most statistically significant or clinically appropriate variable was included in the multivariable analysis. Age was included in the multivariable analysis because of an *a priori* decision about its clinical relevance. The area under the receiver operating characteristic (AUROC) curve was used to evaluate the utility of the multivariable model for predicting the infection risk. For all analyses, results with $p<0.05$ was considered statistically significant. All analyses were performed using the Stata version 15 (StataCorp; College Station, TX, USA).

Results

Cohort characteristics

Between January 2018 and July 2019, 292 consecutive patients were recruited. A total of 29 patients did not meet the ACR/EULAR classification criteria, leaving a cohort of 263 patients (68% of the total patients regularly attending the clinic). Baseline demographics of these 263 patients are presented in Table 1. The mean age of the cohort was 59 years. The median duration of RA was 9 years, and 77% of patients were seropositive (rheumatoid factor or anti-citrullinated protein antibodies). Of the patients included in the cohort, 50 (19%) had coexisting fibromyalgia, 252 (96%) were on DMARDs, and 106 (38%) were receiving biologic therapies or targeted synthetic DMARDs. Etanercept (22% of biologic users), tocilizumab (15% of biologic users), and adalimumab (12% of biologic users) were the most commonly prescribed biologics; 61 (23%) patients were on glucocorticoids. The median (interquartile range) DAS28 was 2.6 (2.0-3.3), indicating an overall low disease activity. Disease activity measures and laboratory data are presented in Table 2.

Severe infections

Between January 2018 and July 2019, 45 severe infections were recorded in 34 (13%) patients, equating to an incidence of 10.8 infections per 100 patient-years (/100py). Of these 34 patients, 25 (73%) experienced 1 severe infection, 7 (21%) experienced 2, and 2 patients (6%) experienced 3 severe infections. Over the study period, 2 (6%) patients died from a severe infection of the respiratory tract. Within the group of patients experiencing a severe infection, the most common infection sites were the respiratory tract (53%), urinary tract (13%), and skin and soft tissue (11%). Community-acquired pneumonia (31%) and infective exacerbation of chronic obstructive pulmonary disease (11%) were the most common severe infection types (Table 3). The median (range) length of admission was 4 days (2-40). At least 1 dose of antimicrobial therapy was administered to 30 (88%) patients. The 4 (12%) patients who did not receive antimicrobials were diagnosed with viral chest infections or viral meningitis. A total of 16 (36%) infections had abnormalities on imaging, and 20 (44%) infections were microbiologically proven (Table 4). At the time of the severe infection, 40% of patients were on glucocorticoids and 40% on biologics. The majority of patients (83%) using glucocorticoids were on a dose of 5 mg or lesser. In 42% of patients, immunosuppressive therapy was not altered or withheld during the hospital admission.

Table 1. Patient demographics of the RA cohort.

Characteristic	Median (IQR) or number (%)
Age (years)	62 (50-70)
Sex (female)	191 (73)
Length of RA diagnosis (years)	9 (5-18)
Seropositivity (RF or ACPA)	192 (77)
Extra-articular manifestations (any)	38 (15)
Biologic use (over study period)	106 (40)
Glucocorticoid use (over study period)	77 (29)
Cigarette smoking	
Current	41 (16)
Ex-smoker	84 (32)
Never	134 (52)
Up-to-date vaccinations	
Influenza	189 (72)
Pneumococcal	83 (32)
Neither	58 (22)
Charlson comorbidity index	0 (0-1)
Comorbidities	
Chronic lung disease	27 (10)
Diabetes mellitus	41 (15)
Chronic kidney disease	15 (6)
Number of regular medications (all)	4 (3-7)
Number of RA medications	2 (1-3)
Number of comorbidity medications	2 (0-4)
Number of regular pain medications	0 (0-1)

RA: rheumatoid arthritis; IQR: interquartile range; RF: rheumatoid factor; ACPA: anti-citrullinated protein antibodies.

Factors associated with severe infection

Univariable analysis identified several factors, which were significantly associated with severe infection ($p<0.05$). Clinical factors associated with infection included the Charlson comorbidity index (excluding age), chronic lung disease, number of regular medications, disease activity, and having a previous severe infection in the past 3 years. Immunological risk factors for severe infection included low (below the normal reference range) lymphocyte, T cell (CD3+), and cytotoxic T cell counts (Table 5).

Table 2. Disease activity and laboratory data.

Clinical or biological parameters	Median (IQR) or number (%)
DAS28	2.6 (2.0-3.3)
Swollen joint count	0.5 (0.0-2.0)
Tender joint count	0.0 (0.0-2.0)
CRP (mg/L)	4.4 (1.9-10.5)
ESR (mm/h)	15.0 (6-25)
White blood cell count ($\times10^9$/L)	6.9 (5.7-8.5)
Neutrophil count ($\times10^9$/L)	4.2 (3.3-5.2)
Lymphocyte count ($\times10^9$/L)	1.7 (1.3-2.3)
CD3+ number (cells/µL)	1,189.5 (845-1,654)
CD3+/CD4+ number (cells/µL)	868 (611-1,130)
CD3+/CD8+ number (cells/µL)	341 (210-490)
CD19+ number (cells/µL)	162 (111-281)
NK cell count number (cells/µL)	205 (136-307)
IgG (g/L)	11.1 (9.3-13.6)
IgA (g/L)	2.4 (2.0-3.5)
IgM (g/L)	1.1 (0.8-1.8)

IQR: interquartile range; DAS28: disease activity score of 28 joints; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; CD3+: T cell; CD3+/CD4+: T-helper cell; CD3+/CD8+: cytotoxic T cell; CD19+: B cell; NK: natural killer, Ig: immunoglobulin.

Table 3. Types of severe infection.

Infection type	Frequency (%)
Community-acquired pneumonia	14 (31)
Infective exacerbation of COPD	5 (11)
Cellulitis	4 (9)
Cystitis	4 (9)
Osteomyelitis	2 (4)
Pyelonephritis	2 (4)
Influenza	2 (4)
Hospital-acquired pneumonia	2 (4)
Abscess	1 (2)
Cholangitis	1 (2)
Encephalitis	1 (2)
Epididymo-orchitis	1 (2)
Meningitis	1 (2)
Septic arthritis	1 (2)
Salivary gland	1 (2)
Gastroenteritis	1 (2)
Tuberculosis	1 (2)
Tonsillitis	1 (2)

COPD: chronic obstructive pulmonary disease.

Table 4. Microbiology of severe infections.

Microorganism isolated	Number
Staphylococcus aureus	3
Escherichia coli	2
Pseudomonas aeruginosa	2
Influenza A	2
Legionella pneumophila	1
Staphylococcus lugdunesis	1
Streptococcus agalactiae	1
Streptococcus pyogenes	1
Bordertella pertussis	1
Human metapneumovirus	1
Rhinovirus	1

Table 5. Univariable and multivariable logistic regression models for severe infection.

	Univariable			Multivariable			
Variables	OR	95% CI	p	Coefficient	OR	95% CI	p
Age ≥50 years	1.83	0.85-3.94	0.120	-0.50	0.60	0.20-1.81	0.368
Sex (male)	1.32	0.61-2.86	0.487				
Length of RA diagnosis (per 1-year increase)	1.00	0.99-1.00	0.815				
Seropositivity (RF or ACPA)	1.69	0.68-4.24	0.260				
Erosions on X-ray	1.22	0.58-2.59	0.599				
Extra-articular manifestations	1.69	0.68-4.24	0.260				
Fibromyalgia	0.52	0.18-1.56	0.247				
Charlson comorbidity index (≥2)	1.39	1.12-1.73	0.003	0.99	2.69	1.03-7.00	0.043
Chronic lung disease	2.71	1.05-7.00	0.040				
Diabetes mellitus	1.32	0.61-2.86	0.487				
Number of regular medications (per 1 increase)	1.24	1.11-1.37	<0.001				
Previous severe infection in last three years	6.02	2.48-14.62	<0.001	1.27	3.58	1.28-9.97	0.015
DAS28 (per 0.5-unit increase)	1.31	1.24-2.42	0.001	0.30	1.35	1.10-1.67	0.005
Low white blood cell counts (<4)	0.91	0.11-7.63	0.930				
Low lymphocyte counts (<1)	3.64	1.27-10.48	0.016	1.41	4.08	1.16-14.29	0.028
Low neutrophil counts (<1)	1.16	0.35-5.50	0.847				
Low T-cell (CD3+) counts (<688)	4.56	1.26-15.53	0.021				
Low T-helper cell (CD3+/CD4+) counts (<389)	2.66	0.45-15.74	0.282				
Low cytotoxic T-cell (CD3+/CD8+) counts (<309)	5.67	1.84-17.45	0.002				

Variables with a p<0.10 were included in the multivariable analysis. In cases of collinearity between variables, the most statistically significant or clinically relevant factor was selected. Age was included in the multivariable model regardless of its significance because of an a priori decision about its clinical relevance.
OR: odds ratio; CI: confidence interval; RF: rheumatoid factor; ACPA: anti-citrullinated protein antibodies; DAS28: disease activity score of 28 joints.

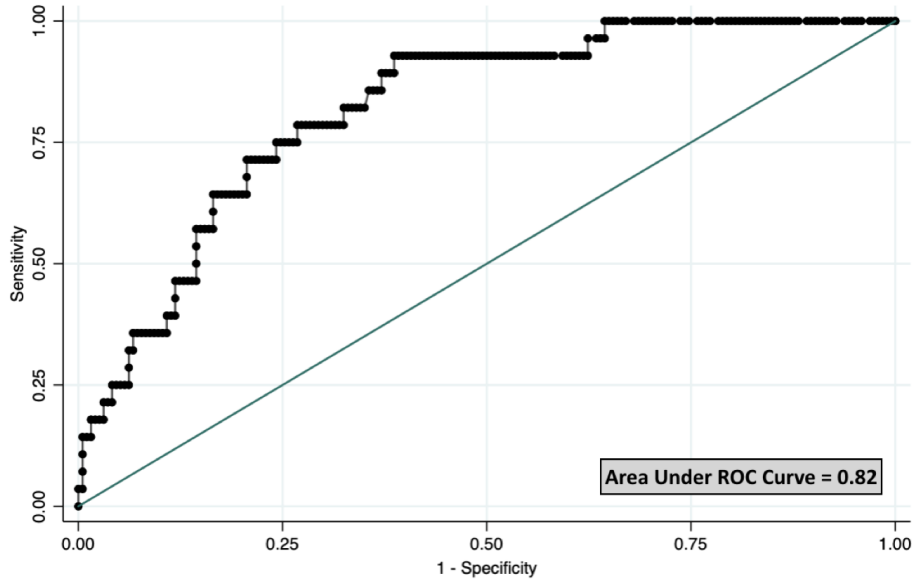

Figure 1. The area under the receiver operating characteristic curve for the multivariable model is 0.82 (95% confidence interval, 0.75-0.89). The multivariable model includes age ≥50 years, low lymphocyte count, previous severe infection, disease activity score of 28 joints (per 0.5-unit increase), and Charlson comorbidity index >2.

Glucocorticoid and biologic use were not significantly associated with severe infection. Although a greater proportion of patients with severe infections were on glucocorticoids and biologics, the difference between users and non-users of these medications did not reach statistical significance. Diabetes mellitus, smoking status, vaccination status, and other immunobiological parameters (total white blood cell and neutrophil count, immunoglobulin concentrations, and number of B cells and natural killer cells) were not found to be significantly associated with severe infections.

Age-adjusted multivariable analysis revealed 4 factors that were independently associated with severe infection (Table 5). These included low lymphocyte count (odds ratio [OR], 4.08; 95% confidence interval [CI], 1.16-14.29), severe infection in the past 3 years (OR, 3.58; 95% CI, 1.28-9.97), Charlson comorbidity index (excluding age) ≥2 (OR, 2.69; 95% CI, 1.03-7.00), and higher DAS28 (OR, 1.35/0.5-unit increment; 95% CI, 1.10-1.67). The age-adjusted model in-

corporating these factors demonstrated an excellent predictive potential, with an AUROC curve of 0.82 (95% CI, 0.75-0.89) (Figure 1).

Discussion

Infections constitute a significant comorbidity and are associated with significant mortality in RA. Methods for identifying the patients at high risk for severe infection in routine clinical practice are lacking. Our results identified a high incidence of severe infections in a single-center RA clinic cohort. The risk factors that were significantly associated with severe infection included the Charlson comorbidity index, disease activity, previous infection, and lymphopenia. An algorithm incorporating these factors and age had a high predictive ability with an AUROC of 0.82. These findings indicate the potential for routinely available clinical data to be used as a screening tool to identify patients at high risk of severe infection.

More than 1 in 10 patients were hospitalized for severe infection in the 1.5 years studied, equating to an incidence of 10.8 infections/100py. These findings are comparable with a 2016 study conducted at 2 tertiary centers in the United Kingdom, which found that 7.8% of their RA cohort had experienced a hospitalized infection within the preceding year (10). A 2002 case-control study by Doran et al. (1) found that the incidence of infections that required hospitalized in patients with RA was 9.6/100py. This study by Doran et al. (1) was conducted in the pre-biologic era, whereas 45% of our cohort had used biologics. Other observational studies conducted in the biologic era have shown lower rates of severe infection. Crowson et al. (6) found an incidence of 7.2/100py, whereas Smitten et al. (2) found a considerably lower incidence of 4.5/100py. Both these studies used population-based medical record databases for patient recruitment, whereas our cohort was recruited consecutively at a tertiary center RA clinic. Furthermore, our cohort had a higher comorbidity burden than the cohorts in the studies of Crowson et al. (6) and Smitten et al. (2). Our cohort also had a greater proportion of patients using biologic therapies, reflecting the recency of our study. Although registry-based studies have the advantage of large sample size, they can underestimate the infection rates by relying on self-reporting. Real-world studies, in contrast, may provide a better snapshot of a population.

In addition to the infection rates, this study also yielded a simple multivariable model with an excellent predictive ability for severe infections. The model incorporates 4 clinical factors (age, previous infection, Charlson comorbidity index, and disease activity) and 1 biological risk factor (lymphopenia). Although age ≥50 years was not statistically significant on multivariable analysis, it was included in the model because of an *a priori* decision about its clinical relevance. Most factors in this model have been identified individually in the literature as factors associated with infection risk in RA, lending face validity to their inclusion in our model. A 2018 study by Subesinghe et al. (11) showed that the annual rate of severe infections in patients with RA with a previous severe infection was almost 3-fold higher. Having a previous severe infection within the last 3 years is also included in the RABBIT risk calculator, with an infection within the previous year contributing the highest risk (12). Widdifield et al. (13) found that in a cohort of older patients with RA (≥65 years), those with a Charlson comorbidity index of ≥2 had 1.44 times higher odds of a severe infection. Au et al. (14) and Emery et al. (15) also found linear associations of infection and increase in the DAS28.

Surprisingly, no biomarkers or clinical laboratory parameters have previously been statistically linked to infection risk in the RA context (16). Although Crowson et al. (6) found that low lymphocyte, neutrophil, and total white blood cell counts trended toward an association with increased infection, these did not reach statistical significance. The multivariable model presented here found that lymphopenia was one of the most significant risk factors for severe infection (OR, 4.08). This association is intuitive, given the crucial role of lymphocytes in the adaptive immune response. Lymphopenia may result from RA itself or the immunosuppressive therapy used. RA is associated with inherent immune dysfunction and accelerated immunosenescence, resulting in lower lymphocyte and T cell counts (17, 18). Immunosuppressive medications, such as glucocorticoids, can deplete the lymphocyte counts by reducing the receptor signals, promoting apoptosis (19). Although confirmation in independent cohorts is required to confirm this association, lymphocyte count may be a novel routinely available biological parameter predictive of infection risk.

The utility of simple clinical and laboratory data in infection prediction tools has been increasingly recognized in other clinical contexts. For example, we have previously demonstrated the utility of such an approach in a renal transplant cohort (20). The factors revealed in our modeling are all assessable during standard clinical practice and may be developed for rapid screening purposes. This model is unique in the RA literature, combining simple clinical and laboratory parameters to predict a severe infection risk. Although there are currently no infection prediction tools combining both clinical and biological parameters, there are existing infection risk calculators. These aim to objectively estimate severe infection risk in RA. The RABBIT risk score was developed and validated in a large sample (n=8,000 patients with RA) from German biologics registry data, and it measures the impact of patient and time-dependent factors (for example, non-biologic and biologic DMARD use, glucocorticoid dose, functional status, and previous severe infections) on infection risk in RA (5, 12). However, this score requires a more extensive data, such as functional status measured by the HAQ and previous DMARD/medication use, which limits its routine use. Our simpler model could be used as a screening tool to facilitate the identification of patients for a more detailed analysis.

This study has a number of limitations. Although it was a real-world cohort study that retrospectively recruited consecutive patients, it was limited by sample size. This may explain why we did not detect significant associations with some previously described risk factors for severe infection, such as glucocorticoid and biologic exposure, diabetes mellitus, and smoking (21-23). Glucocorticoids and biologic therapies are well-known risk factors for infection, despite our study not demonstrating a significant association. Notably, glucocorticoid use throughout the study period was low (29% of patients). Of the patients using glucocorticoids, the doses were also relatively low, with the majority (83%) of these patients being on doses less than 5 mg. As with all observational studies, channeling bias is a possibility. Experienced practitioners may have de-escalated RA therapy in individual patients after a previous severe infection or be reluctant to prescribe immunosuppressive medications, such as biologic therapies, to patients perceived to be high risk. Similarly, patients with the highest risk of infection may already have been targeted by practitioners for interventions, such as vaccinations or smoking cessation, leading to an underestimation of the effect of certain factors on the infection risk. Finally, the death from infection of very high-risk patients before the study observation period could result in survival bias, wherein those that remain in the study have a different risk profile with different associations with infection. Balanced against these limitations, a major strength of this study was that it was conducted consecutively in a real-world setting with patients with a comorbidity burden that reflects real-world practice.

Despite these limitations, our study identified a high rate of severe infections in a real-world

RA cohort, similar to the infection rates documented in the past 2 decades (1, 2, 6). As more broad-spectrum immunosuppressive drugs continue to emerge for RA, it is essential to evaluate personalized risk reduction. Our study yielded a multivariable model that would be easy to apply in a clinical setting and has an excellent predictive potential. Although validation of the model in independent cohorts is required, such a screening tool may facilitate the shared and personalized decision making in RA care.

Ethics Committee Approval: Ethics committee approval was received for this study from the Monash Health Human Research Ethics Committee (Approval Date: 16 February 2018; Approval Number: Project 13019A).

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

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