

Editorial

Multimorbidity Accrual After Incident Rheumatoid Arthritis: A Wolf at the Door

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Rheumatoid arthritis (RA) has long been recognized to have serious extraarticular manifestations such as interstitial lung disease (ILD).¹ Consequences of immunosuppressive medications used to treat RA include serious infections, liver toxicity, and osteoporosis leading to fracture.^{2,3} Patients with RA are known to have increased risk for other autoimmune conditions such as thyroid disease.⁴ Over the last 2 decades, the relationship between RA, articular disease activity, systemic inflammation, and cardiovascular disease (CVD) has been elucidated as an important contributor to morbidity and mortality.⁵ RA and its treatments may possibly affect cancer risk.⁶ Recently, RA has been associated with non-ILD pulmonary diseases such as asthma and chronic obstructive pulmonary disease.^{7,8} Since RA is a painful, long-term condition, it can also lead to mental health and substance abuse disorders.^{9,10} Thus, almost any condition could in theory be attributed to RA. The specter of these morbidities looms like a wolf at the door for patients with RA. Indeed, nearly all of them seem to have been investigated separately, resulting in numerous publications. How do clinicians and researchers integrate these many conditions when considering patients with RA? The concept of “multimorbidity” may be the answer.

Simply stated, multimorbidity is the co-occurrence of 2 or more chronic conditions.¹¹ On the surface, this may seem similar to the traditional concept of comorbidity.¹² However, the emerging concept of multimorbidity places the patient at the center of a complex, holistic framework that takes into account

the total burden of morbidities. Therefore, the multimorbidity concept recasts chronic conditions from sideline actors to an ensemble cast, each contributing uniquely to the plot.

In this issue of *The Journal of Rheumatology*, Gunderson and colleagues investigated multimorbidity burden in RA.¹³ They used the Rochester Epidemiology Project (REP) to identify 597 patients with incident RA and 594 subjects without RA matched by age, sex, and calendar year at the index date of RA diagnosis. The REP links all medical records in Olmsted County, Minnesota, to provide an entire picture of each individual's medical history. Thus, this study provided the opportunity to construct a timeline related to multimorbidity and RA, including morbidities prior to clinical RA onset and accrual after diagnosis. They compiled a list of 25 morbidities from 3 indices: the Charlson Comorbidity Index, the Elixhauser Comorbidity Index, and the Rheumatic Disease Comorbidity Index (RDCI). Presence of each morbidity in the medical record required at least 2 diagnosis codes (extracted by the REP) separated by 30 days. Multimorbidity was considered as 2+ morbidities occurring after index date, and “substantial” multimorbidity was 5+ morbidities. They then investigated the association of RA, overall and by serologic phenotypes, with multimorbidity accrual compared to matched non-RA subjects, adjusting for matching factors, smoking, and obesity. They also investigated each morbidity separately (sparing readers from 25 separate papers on each topic!).

The investigators found that patients with RA had slightly more morbidities at baseline than comparators (38% vs 32%, $P = 0.02$).¹³ Patients with RA had higher odds for developing incident multimorbidity than comparators (OR 1.39, 95% CI 1.14–1.69).¹³ However, there was no association for substantial multimorbidity (OR 1.17, 95% CI 0.93–1.47).¹³ When considering either prevalent or incident morbidity, the patients with RA also tended to have more multimorbidity, though the findings were less striking for substantial multimorbidity. There were no differences in incident multimorbidity when comparing seropositive RA to seronegative RA. Interestingly, patients who

This work was not funded. Dr. Sparks is supported by the National Institutes of Health (grant numbers R03 AR075886, K23 AR069688, and L30 AR066953), the Rheumatology Research Foundation K Supplement Award, and the Brigham Research Institute.

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JAS has consulted for Bristol Myers Squibb, Gilead, Inova Diagnostics, Optum, and Pfizer, unrelated to this work.

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went on to develop seropositive RA than seronegative RA were less likely to have substantial multimorbidity at baseline. This finding is somewhat unexpected since seropositive patients with RA are traditionally thought to have a more severe disease course. It could be related to diagnostic delay or the intrinsic heterogeneity of seronegative RA. When considering individual morbidities, patients with RA had statistically higher odds than comparators for incident anemia, depression, hypertension, and liver disease. Hypothyroidism and chronic pulmonary disease were more likely to be present at baseline in patients with RA than comparators.

These findings add to the growing literature investigating multimorbidity after incident RA compared to a non-RA comparator group. A large nationwide study by England, *et al* using MarketScan investigated multimorbidity among 138,891 overall RA cases (30,562 incident during follow-up) and an equal number of matched non-RA comparators.¹⁴ They compiled their own list of 44 conditions using administrative diagnosis codes and also considered the RDCI and Charlson-Deyo Comorbidity Index. As in the Gunderson study, the England study showed that patients with incident RA had higher baseline prevalence and incidence of multimorbidity.¹⁴ Compared to the Gunderson study,¹³ the England study had more obvious differences in faster accrual of multimorbidity in RA cases. RA serostatus was not available in the England study,¹⁴ and the investigators did not focus on individual diseases.

Our group, led by Dr. Kazuki Yoshida, investigated the relationship between RA and mortality considering mediators such as multimorbidity accrual and lifestyle changes after RA diagnosis or matched date for comparators.¹⁵ We analyzed 1007 incident RA cases and 10,070 matched non-RA comparators.¹⁵ We defined multimorbidity using the Multimorbidity Weighted Index (MWI; condensed version freely available online at <https://eprognosis.ucsf.edu/mwi.php>), composed of 61 conditions by self-report on questionnaires administered to the participants (nurses) every 2 years.¹⁵ Unlike Gunderson, *et al*¹³ and England, *et al*,¹⁴ the MWI is weighted by the effect of each condition on physical function as a measure of differential impact. For example, lung cancer is weighted higher than diverticulosis on the MWI.¹⁵ Similar to the other 2 studies, we also found that incident RA cases had more multimorbidity at baseline and more accrual during follow-up than comparators. We examined each domain of the MWI rather than each condition and found that RA cases had accumulation within the musculoskeletal, cardiovascular, pulmonary, and gastrointestinal systems than comparators. Finally, we found that multimorbidity was a substantial mediator between RA and excess mortality, particularly for seropositive RA, emphasizing the clinical importance of multimorbidity accrual. The seropositive RA finding was somewhat contrary to the findings of Gunderson, *et al*, which did not note marked differences in multimorbidity after incident RA.¹³ The Gunderson study had a smaller sample size than the other 2 studies, so it may have been underpowered to detect true associations, particularly for the individual conditions. Overall, the 3 recent studies^{13,14,15} investigating RA and multimorbidity are remarkably consistent in the message that multimorbidity

accrual occurs even before clinical RA onset and that patients with RA have accelerated accrual of multimorbidity after diagnosis.

There is no single method to measure multimorbidity,¹⁶ as evidenced by each of the 3 studies measuring this differently.^{13,14,15} This issue may compromise the ability to incorporate multimorbidity into other research datasets or to be applied clinically. Two of the studies used administrative codes (which may have inherent inaccuracy) to count conditions (treating each individual condition as affecting the individual the same).^{13,14} Those studies came up with a different number and list of conditions in their multimorbidity measures, despite reviewing much of the same literature. While the MWI weighted conditions, this was by self-report (which may have inaccuracy) and despite weighting, there could be substantial differences within each condition. For example, resected/cured early-stage lung cancer and metastatic/refractory lung cancer obviously affect a patient's quality of life and longevity differently.¹⁵ ILD is notably absent from many of the multimorbidity measures since it is uncommon in the general population. Therefore, exclusion of some rare but serious RA manifestations means that the multimorbidity burden may be even higher than estimated in these studies.^{13,14,15} Since all these studies compared RA to non-RA,^{13,14,15} this is somewhat counter to the concept of multimorbidity, where no single condition should take center stage. As rheumatologists caring for patients with RA, these studies do help emphasize the total morbidity burden that our patients experience throughout their disease course. These RA multimorbidity studies also provide a glimpse into the individual diseases and organ systems important in RA pathogenesis and outcomes.

In conclusion, multimorbidity in RA occurs before clinical onset and accrues more rapidly after clinical diagnosis than in the general population. Multimorbidity is a complex and evolving concept¹⁶ that moves beyond the traditional comorbidity construct. RA and other rheumatic diseases in general are ideal conditions to implement the multimorbidity construct due to their chronic involvement of multiple organ systems.^{17,18,19,20} While more progress is needed, the association of RA with multimorbidity offers the possibility of more fully understanding the total effect on a patient, beyond the narrow focus on known RA manifestations or individual comorbidities.

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