Published in final edited form as:
Ann Rheum Dis. 2012 May ; 71(5): 635–637. doi:10.1136/annrheumdis-2011-200473.

The risk of comorbidity

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The field of rheumatology has shown great interest in comorbidity-related risk among patients with rheumatoid arthritis (RA). A recent paper reported that a person with RA has a similar risk of sustaining a myocardial infarction as a person with diabetes mellitus (DM), and this risk is comparable to that of a healthy person 10 years older.[1] Several other papers have also recently reported that people with RA and DM share a similar cardiovascular risk.[23] These findings are strikingly similar to those of the Charlson Index published 25 years ago.[4]

The Charlson Comorbidity Index is the most commonly used prognostic measure of illness bur-den in contemporary clinical research.[5] Cited in nearly 7000 studies, it is considered the gold standard to assess comorbid risk in clinical research.[6] Over time the Charlson Index has increased in use and relevance, likely related to increased rates of chronic disease, supporting the need to measure and adjust for these conditions in research.

REVISITING THE DERIVATION OF THE CHARLSON INDEX

The original objective was to develop a prognostic taxonomy for comorbid conditions that could singly or in combination prognosticate short-term mortality.[4] In order to accomplish this, two cohorts were studied.

In a phase I training cohort, 607 patients admit-ted to a general medicine service over 1 month in 1987 were enrolled and followed for 1 year to calculate adjusted RR of death. A weighted index taking into account the seriousness of disease was developed (table 1). All conditions met two criteria: adjusted RR of death ≥1.3 and independent association ($p<0.1$) with 1-year mortality.

A retrospective phase II validation study was next undertaken with 685 breast cancer patients who had received their initial treatment between 1962 and 1969. Outcomes were assessed at 10 years and it was found that both comorbidity and age predicted mortality.

WHAT DO THE CHARLSON INDEX WEIGHTS MEAN?

The Charlson Index assigns a weight of 1 to the following conditions: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease and diabetes without end organ damage.[4] Other diseases have weights of 2, 3 and 6. The Charlson Index weights and adjusted RR of 1-year mortality are shown in table 1.[4] The Charlson Index is calculated by summing the weights for each condition in the medical history. For example, a person with RA (weight=1) and DM without end organ damage (weight=1) would have a Charlson Index score of 2, while a person with RA (weight=1), DM with end organ damage (weight=2) and a myocardial infarction (weight=1) would have a Charlson Index score of 4. Regardless of whether the conditions are obtained in the con-text of clinical care or outcomes data, the Charlson Index weight for each condition is identical. Index scores range from 0 to 10, although higher scores are possible for severely ill patients.

WHY DO RESEARCHERS USE THE CHARLSON INDEX?

The power of the Charlson Index comes from its ability to predict major morbidity,[7–10] mortality,[711] cost[9] and hospitalisation.[9] Twenty-five years ago it was established that the 1- and 10-year mortality risk for a person with a history of myocardial infarction is comparable to that of a person with DM and also equivalent to that of a person with a connective tissue disease. This is because all conditions with a Charlson Index weight of 1 have similar 1-year adjusted RRs of death. Furthermore, in two publications we have reported that each decade of age ≥50 years is equivalent to a 1-point increase in comorbidity (ie, 50–59 years=1 point; 60–69 years=2 points).[47] Unfortunately, these fundamental and powerful prognostic realities have been forgotten over the years in spite of the expanding use and popularity of the Charlson Index. Clearly, treatments for all of the weighted conditions have advanced since the Index was developed in 1987. However, the predictive validity of the weights relative to one another and the aggregate score remain clinically appropriate, as evidenced by the continued ability of the Index to predict outcomes across a wide range of contemporary clinical populations.[9–13]

WHAT ARE THE IMPLICATIONS OF THESE FINDINGS FOR RHEUMATOLOGY?

European League against Rheumatism (EULAR) patient care guidelines recommend a 1.5 multiplication factor for cardiovascular risk when two or more of the following risks exist: disease duration >10 years; rheumatoid factor or anticyclic citrullinated peptide antibody positivity; or presence of extra-articular manifestations.[14] However, half of the studies used to estimate this risk were from cohorts assembled in 1955–1973.[15–19] Longitudinal studies that include patients with RA who were diagnosed before the introduction of methotrexate into clinical practice in 1986[20] bias the results towards poor outcomes not representative of modern disease management or the cur-rent clinical presentation of RA. Inception cohorts of patients with RA assembled after 1986 report RRs that are similar to those of conditions with a Charlson Index score of 1.[21]

Several recent longitudinal studies of patients with RA have shown that baseline comorbidity is a more powerful predictor of mortality than biomarkers or RA disease severity indices.[22 23] Patients with RA are clinically complex, and the interplay of their prognostically important conditions leads to morbidity and mortality. The Charlson Index addresses the full clinical expression of a defined disease or combination of diseases, whereas a biomarker is one of a myriad of components of a potential disease that may or may not become clinically apparent and/or require treatment.

Antitumour necrosis factor α (anti-TNFα) therapy has changed the lives of hundreds of thousands of patients with RA, reduces inflammation and may reduce cardiovascular risk. The American College of Rheumatology (ACR)/EULAR has recently defined RA ‘remission’ as: tender joint count ≤1; swollen joint count ≤1; C reactive protein ≤1 mg/dl; and patient global assessment ≤1.[24] We agree that tightening the definition of remission is an important advance in the care of patients with RA and may well lead to reductions in joint damage and cardiovascular disease. While early studies that have applied the new ACR/EULAR definition of remission to retrospective cohorts show that patients in remission demonstrate joint progression,[25 26] its long-term significance is unknown. It is possible that patients in remission will have an ongoing increased cardiovascular risk, either by the same mechanisms that currently cause joint progression in remission or due to the impact of biological therapies used in combination with methotrexate, non-steroidal anti-inflammatory medications and steroids employed in a large proportion of RA treatment regimens. Nevertheless, tight management holds the greatest promise for improving short-

and long-term RA out-comes. An important hurdle may be the fact that remission is not commonly achieved in routine clinical care.[27]

Patients with DM who are taking insulin are not considered in remission even if glycaemic control is excellent, they continue to have an increased risk of poor outcomes.[28] No total remission of a chronic illness currently exists because the aetiology of chronic disease is unknown and thus the disease cannot be completely 'turned off' with current management. In actuality, overly aggressive control in both DM and RA can lead to diminishing returns and poor outcomes (ie, hypoglycaemia, sepsis and death).[29] We appreciate that, in the current RA treatment paradigm, there is a difference between remission and full health. In other areas of medicine remission is total absence of disease, a point that can lead to confusion for patients with RA and other healthcare providers. Nonetheless, the ACR/EULAR remission criteria are an important step until more powerful and safer medications are available or an aetiology is found. Patients with RA continue to have an increased risk of overall morbidity and mortality, albeit seemingly lower since the introduction of anti-TNF agents.

In order to determine the cardiovascular and mortality risk in patients with RA, inception cohorts diagnosed after 1986 and treated with contemporary strategies should be carefully followed, particularly patients achieving remission according to the 2011 ACR/EULAR definition. At present there are 25 years of potential longitudinal follow-up. Furthermore, studies must account for weighted comorbidity at baseline and address the impact of biological and combination regimens.

In conclusion, recent literature has equated the risk of RA with the risk of DM, which is also equivalent to an additional decade of age.[1] Given currently available data, we believe that this assumption remains true, as the Charlson Index reported in 1987.

RECOMMENDATIONS

We suggest the Charlson Index be used in clinical studies and care as follows:

1. Baseline comorbidity assessment. Overall means are not as clinically meaningful as proportions in low, moderate and high ranges (eg, 0–1, 2–3, ≥4).[30] Cohorts skewed to the right are at higher risk than those skewed to the left.
2. To control for baseline differences in illness burden as a con-founder of outcomes.[31]
3. As an independent predictor of morbidity, mortality, cost and hospitalisation. Comorbidity should be used as a continuous variable in analyses (2) and (3).
4. In the setting of growing interest in disease management, to provide clinicians and potential payers with a clinically powerful measure of disease burden and prognosis (ie, a fifth vital sign).

ADMINISTRATION GUIDELINES

We advise that trained interviewers administer standardised questions to collect components of the Charlson Index. Outcome data can also be used to calculate the Charlson Index using validated adaptations.[32]

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Table 1

Adjusted RR of 1- year mortality and assigned Charlson Index weight

Adjusted RR of 1-year mortality	Index weight
≥1.3–<1.5	1
≥1.5–<2.5	2
≥2.5–<3.5	3
≥6	6