

## Rheumatoid Arthritis Comorbidity Index (RACI): Development and Validation of a New Comorbidity Index for Rheumatoid Arthritis Patients

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### Abstract

**Objective:** Classify comorbidities with greatest impact on Rheumatoid Arthritis (RA) patients. Develop and validate a prospectively applicable comorbidity index for classifying RA patients according to their comorbid disorders which might impact alter their hospitalization and mortality risk.

**Methods:** A weighted index which considers the number and impact of comorbid conditions was developed based on clinical registry of a cohort of 2029 patients with early RA monitored over 10-years. Logistic and Cox Regression analyses were implemented to estimate the risk of mortality. Regression coefficients were used to develop the index score. ROC curve for the invented index was used to evaluate the discriminating ability of the index and identify different cutoff values that can delineate patients at different stages for risk of death. Disease activity parameters were considered.

**Results:** Comorbidities (18 conditions) were strongly associated with the 10-year death risk, and composed the RA-comorbidity index, include Cardiovascular (7 comorbidities), infection, osteoporotic fractures, falls risk, Depression/anxiety, functional status (HAQ >2), diabetes mellitus, steroid therapy >5 mg, DAS-28 >3.6), renal/liver/lung disease and tumors. Considering the comorbidities number, the comorbidities adjusted relative risk were employed as weights to develop a weighted index. Validation using ROC curve revealed AUC of 97%.

**Conclusion:** The RA-comorbidity index is a valid method for assessing risk of death in RA patients. The index enables the treating physician to include comorbidities valuation and treatment in their standard practice. It can be used to identify targets, predict resource utilization, and detect the potential targets for lowering high costs, by prospectively recognizing RA patients at high risk.

**Keywords:** Comorbidity; Index; RA; Early rheumatoid arthritis; PROMs

### Introduction

Following the advances in rheumatoid arthritis (RA) management and the growing role of biologic therapy, the assessment of its associated comorbidity (ies) in clinical practice has become a hot topic. Although RA patients are now living longer than decades ago, in comparison to the general population, mortality rates remains higher amongst people living with RA. Published studies reported that an RA patient are comparable to diabetes mellitus, is that both of them have similar risk of having myocardial infarction, and this risk is comparable to that of a 10-years older healthy person [1]. In spite of the recognition of higher mortality rates and shorter survival in RA patients, this finding remains not fully elucidated. Unfortunately, population death registry databases have not been of any help. This has been attributed to the finding that RA is not often stated as a primary death cause in death certificates in contrast with other major disorders

such as malignancies, infections, cardiovascular diseases, or trauma [2]. This was supported by the results of recent cross-sectional, international, study (COMORA), which revealed a gap in standard clinical practice between current recommendations for identifying, treating or averting comorbidities [3].

In addition to the complex clinical nature of RA, the interaction of the active inflammatory process and its accompanying medical conditions may lead to increased morbidity as well as mortality risk. The concept of comorbidity index has attracted the attention the researchers as early as 1980s. However, whilst earlier trends considered RA as one of the co-factors for mortality, other studies looked at RA as the index disease with the other disorders regarded consequential [4, 5]. However, the available comorbidity tools, when applied to RA patients, face some tough challenges. Good percentage (nearly half) of the studies included in the EULAR recommendations for cardiovascular risk (CV) assessment in RA patients, were from cohorts assembled in 1955–1973 [6-11]. Bearing in mind the vast development in RA management both in pharmacotherapy (Methotrexate

introduced into clinical practice in 1986 [11] and biologic therapy introduced in late 1990s [12]), as well as management strategies (the new ACR/EULAR diagnostic criteria [13], Window of Opportunity and Treat to Target guidelines [14]), a query could be asked regarding whether employment of these earlier indices in standard practice will reflect appropriately on the modern disease management provided to the patient; and whether these studies may exemplify a bias towards poor outcomes. On another front, the recently introduced patient centered approach mandated a shift of the rheumatologists' understanding towards placing the RA disease itself, its associated comorbidities as well as the possible interactions at equal distance. This highlighted the need to address the full clinical expression of this myriad of parameters in standard clinical practice with views towards prevention or early management.

The simplest scheme to assess comorbidity is to use the summation of each comorbid illness to produce a total comorbidity value, identified as "comorbidity count". However, as not all comorbid diseases have the same impact on the outcome of interest, more complex comorbidity indices were developed [15-22]. The aim was to select and weight specific comorbid illnesses, to measure, more accurately, the burden and impact of overall comorbidity. However, most of these indices are broadly nonspecific tools, as they did not address the early inflammatory arthritic factor or carried out any assessment of RA disease activity and its directly related comorbidities. With the substantial impact that comorbidity exerts on health outcomes in RA patients, and given the lack of a standardized comorbidity index for clinical or research use, there is an unmet need for an accurate tool to measure the burden of comorbidity in RA patients which can be implemented in the standard clinical practice. This study was carried out aiming at

1. Identify comorbidities with greatest impact on RA patients' health status.
2. Develop and validate a prospectively applicable comorbidity index for classifying RA patients according to their comorbid conditions which might alter their risk of hospitalization and mortality.

## Methods

### Study design

This was a retrospective cohort analysis multicenter of RA patients in a clinical rheumatology registry assessing the prevalence and impact of comorbidities recorded at the patients' regular monitoring in the outpatient clinic over 10-years period.

### Ethical considerations

The study was carried out following the approved local ethical and methodological protocols. All patients who shared in this study agreed for their data to be used and signed an informed consent per Helsinki declaration (at the General Assembly in October 2008).

### Patients recruitment

Based on "Early arthritis" referral pathway, patients suspected to have inflammatory arthritis were referred to a specialized early arthritis clinic (EAC) [23]. Arthritis diagnosis was considered based on both clinical and sonographic assessment using US (Mylab 25 esaote, Italy). If further confirmation was needed, MRI scan of the affected joint was performed. X-ray of the affected joints was also carried out.

Lab investigations were carried out to assess for inflammatory markers (ESR and CRP), full blood count, as well as liver and kidney functions, bone profile, thyroid functions, and hepatitis markers. Immunological profile testing included assessment of Rheumatoid factor, anti-CCP, anti-nuclear antibodies (ANA), and extractable nuclear antigen (ENA).

### Inclusion criteria

Adult subjects >18-years old, diagnosed to have early RA with disease duration <3-months and eligible for DMARDs and/or biologic therapies were invited to share in this study. Exclusion criteria: 1. Subjects with past-history of psoriasis, intestinal, urogenital, or other forms of infection with clinical manifestations suggestive of spondyloarthritis. 2. Patients treated with oral steroids for other, non-arthritic, medical conditions. 3. Patients who have past-history of hepatitis, cancer, HIV, or who have any other reason to contradict biologic or DMARDs therapy.

### Data collection

Prior to baseline assessment in the outpatient clinic and each follow up visit; every patient completed a copy of the patient reported outcome measures (PROMs) questionnaire for inflammatory arthritis [24]. Body mass index (BMI) was calculated from measures (body weight and height) recorded during the patients' clinic visits. The BMI figures were classified, according to WHO criteria, as 'normal', 'overweight' and 'obese'. Smoking status was recorded.

### Treatment protocol

Initially, all patients were treated according to local treatment protocols, then starting from 2009, all the patients were treated following NICE guidelines [25], consistent with treat-to-target approach [26]. Unless contraindicated, the patients started their synthetic DMARDs therapy once the diagnosis was ascertained. A one-off steroid injection was given intra-muscularly as a bridge therapy on starting synthetic DMARD therapy. For those whose disease remained highly active i.e. DAS-28 >5.1, after receiving synthetic DMARD(s) therapy for 6-month (either as mono- or combined therapy), biologic therapy, in combination with synthetic DMARDs medication, was commenced. For those whose disease activity remained in the moderate range i.e. DAS-28 score of 3.2-5.1, switching to, or adding, another synthetic DMARDs therapy was considered. Should the patient show no significant response (a change of DAS-28 score by <1.2) or sustain any side effects, switching biologic therapy was considered. Every patient had an access to the arthritis advice line and whenever indicated, earlier clinic visits were arranged.

### Database recording

The "Electronic Outcome Measures for Inflammatory arthritis and spondylo-Arthritis/ EROMIA) [27] was used to record, each patient's clinical outcomes as well as comorbidities present.

### Comorbidity assessment

The PROMs self-administered questionnaire [24] was used to screen for comorbidities. Participants were identified to have one comorbidity or more if they answered 'yes' to the following question: 'Has a doctor ever told you that you have any of these conditions?' The patient's answers were checked against the patients' medical notes, ICD-10 record, as well as both lab and sonographic/radiologic outcomes. If the

patient passed away, the cause of death was recorded. Similarly, have the patient been hospitalized, the cause of admission was recorded.

### Protocol of comorbidity monitoring and risk factors

**CV disease:** Optimum monitoring was considered if all measurable CV risk factors, namely: blood pressure, serum glucose, lipids and creatinine were evaluated and recorded at least once over the past year.

**Infections:** Optimum monitoring was considered if (a) dental check was carried out for the patient once in the past year; (b) for patients aged >65 years or receiving biological DMARDs, if a pneumococcal vaccination was administered within the last 5-years and influenza vaccination in the last 12-months; and (c) for patients ever received biological DMARDs, if viral hepatitis screen (HBV and HCV) had ever been carried out. **Cancer:** optimum monitoring was considered (bearing in mind the patient's gender and age) for the population at high risk, and following each cancer's screening recommendations. For breast cancer, subjects at risk include (a) women >50-years old without breast cancer history and (b) women of all ages who do not have any personal history of breast cancer but have a positive family history of breast cancer; for both groups, optimum monitoring was considered if they had a mammogram done during the past 2-years. Regarding cancer cervix screening, population at high risk included women of all ages without history of cervix cancer; optimum monitoring was considered a cervical smear test was carried out within the last 3-years. For colon cancer, patient at high risk included: all patients >50-years. Optimum monitoring was considered if testing for faecal occult blood was carried out at least once during the last 2-years. The patients, who had at least one risk factor for colorectal cancer including history of inflammatory bowel disease, positive family history of cancer colon or adenomatous polyposis, were identified as optimally monitored if colonoscopy was at least carried out once. For skin cancer, high risk patients included those with >40 naevi or those had ever received biologic DMARDs. Optimum monitoring was considered if the patient was reviewed by a dermatologist at least once in the last year.

**Outcomes of interest:** The rheumatoid arthritis comorbidity index (RACI) was evaluated and weighed based on impact on four main outcomes: hospitalization, death, health related quality of life namely functional ability and quality of life, as well as complications induced by medications. Linear regression was carried out based on functional disability as the dependent variable.

### Validation and comparative assessment

**Content validity:** This denotes the scope to which a tool covers all aspects of a given construct. This was assessed by using clinical data as well as the outcomes of interest to predict mortality based on evaluation of the relative risk measures of the proportional regression model

**Criterion validity:** This assesses the level of correlation between the new index and existing ones having the same construct. The developed rheumatoid arthritis comorbidity index was evaluated in correlation with the Charlson comorbidity index [15], rheumatic diseases comorbidity index (RDCI) [20], multimorbidity index [28], as well as functional comorbidity index [29].

**Predictive validity:** This evaluates to the degree the new index is able to predict hospitalization/death as well as quality of life and functional ability in the future. Using linear regression and comparison of the predicted versus observed measures, the developed rheumatoid

arthritis comorbidity index was correlated to both quality of life functional ability at year 3, 5 and 10. External validation of the RACI was evaluated in a cross sectional observational study which included 451 RA patients.

### Statistical Analysis

All statistical analyses and manipulation were carried out using the 20th version of SPSS. Comorbidity burden was defined as frequency and 95% confidence intervals of the comorbidities recorded among the RA patients cohort. Chi-squared test student t-test were used for categorical and continuous and data respectively. The relationship between the variable comorbidities and disease activity parameters, drug associated comorbidities as well as hospitalization/death was assessed using univariate analysis. Over the 10-years follow up period, emerging comorbidities were recorded and included in this research database. Cox regression analysis was used to assess the contribution of each of the identified comorbidities and disease activity status in survival. Regression coefficient of each of those variables was rounded to the nearest 0.5 number, to give the weight of each of those predictors in the form of a score. If the comorbid condition or the disease parameter was not present, the assigned score was multiplied by 0; and by 1 if it was present. Summing up all the assigned score for different comorbidities and disease activity, per patient, would give the total comorbidity score. ROC curve was used for internal validation of the proposed comorbidity score. Different coordinates of ROC curve were revised, to select the cutoff point giving the highest specificity and sensitivity. Spearman correlation coefficient was calculated, in order to test the relationship between the developed RACI score and the comparator comorbidity indices scores. Critical p-value was set at 0.5.

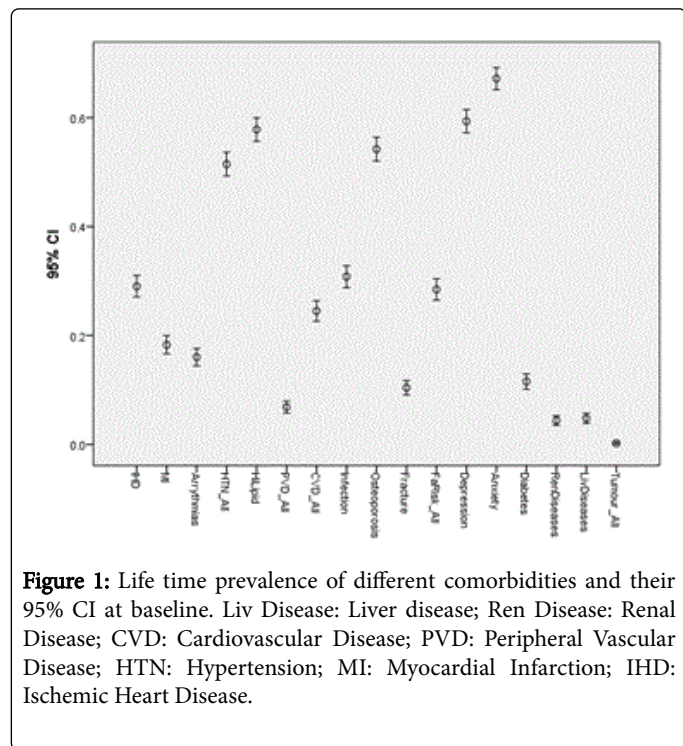
### Results

A total of 2029 RA patients were reviewed as retrospective cohort group. Their average age was  $47.5 \pm 16.5$  years ranging between 28 and 74 years. 1136 (56%) were females. 66.2% of patients receiving biologic after 3 years from the disease onset achieved disease remission ( $DAS-28 < 2.6$ ) whereas only 11% of those who started biologic at 5 years from the disease onset achieved disease remission and 31% achieved  $DAS-28$  score  $< 3.2$ .

### Prevalence of comorbidities

The life time prevalence of different comorbidities was calculated over this 10-years follow up period. Figure 1 error bar chart demonstrates the frequency of these comorbidities with their 95% CI. The comorbidities prevalence varied significantly ( $p < 0.01$ ) on comparing the frequencies at baseline and 3-years in contrast to 5- and 10-years disease duration. 69% of patients (1401/2029) had associated comorbidities of 1 to 2 and about 12% had more than 10 comorbidities associated with RA. On comparing the non-hospitalized patients to the hospitalized cohort, the incidence of comorbidities was significantly higher in the hospitalized cohort ( $p < 0.01$ ). Controlling for age of onset of the disease, and comparing the 2 groups; binary regression analysis revealed that male gender, disease activity, diseases, diabetes/metabolic syndrome, life time cerebrovascular or cardiovascular, infection, osteoporosis, evident fall risk, anxiety/depression, as well as lung, liver, GIT and renal diseases were independent factors affecting, significantly, the disease 10-years outcome. The identified comorbidities, whether raw or categories, were significantly higher in the patient cohort who reported medication

associated problems ( $p < 0.01$ ). In the first 3-years, the most frequently reported comorbidities were depression (67.2% 95% CI 65–69%), anxiety (59.3% 95% CI 57–61%), whereas hyperlipidemia (57.8% 95% CI 55–60%), osteoporosis (54.2% 95% CI 52–56%), hypertension (51.5% 95% CI 49–53%) were more prevalent after 5-years of disease onset. Diabetes frequency ranged between 7.9% and 11.3% of patients (95% CI 10–13%).



**Figure 1:** Life time prevalence of different comorbidities and their 95% CI at baseline. Liv Disease: Liver disease; Ren Disease: Renal Disease; CVD: Cardiovascular Disease; PVD: Peripheral Vascular Disease; HTN: Hypertension; MI: Myocardial Infarction; IHD: Ischemic Heart Disease.

### Validation and comparative assessment

The weight of each of the predictors included in the RACI index is shown in Table 1 in the form of a score. The RACI score ranges from 0-36. The probability of a rheumatoid arthritis patient to get hospitalized goes up as the score goes higher. Using the DAS-28 as a disease activity measure, all comorbidities recorded associated significantly ( $p < 0.01$ ) with the RA disease activity score (DAS-28 > 3.6).

RACI	Regression Coefficient		P-value	Assigned Score
	B	Std. Error		
31 Comorbidities				0-36
DAS-28 score > 3.6	5.47	0.26	0.001	5
Metabolic Syndrome	1.06	0.28	0.001	1
Myocardial Infarction	2.33	0.32	0.001	2
Ischemic Heart Disease	2.11	0.27	0.001	2
Depression	2.08	0.25	0.001	2
Diabetes Mellitus	2.48	0.24	0.001	2
Fracture	2.47	0.26	0.001	2
Hypertension	1.24	0.23	0.001	1

Hyperlipidaemia	1.16	0.21	0.002	1
Arrhythmia	1.25	0.23	0.001	1
CVD	1.28	0.27	0.001	1
PVD	1.23	0.25	0.005	1
Fall	1.14	0.25	0.002	1
Liver disease	1.35	0.26	0.001	1
Pulmonary disease	1.28	0.24	0.001	1
Endocrine	1.25	0.27	0.001	1
GIT	1.38	0.27	0.002	1
Renal	1.37	0.26	0.005	1
Tumour	1.23	0.27	0.003	1
Infection	1.28	0.26	0.001	1
Anxiety	1.19	0.25	0.001	1
Smoking	1.47	0.23	0.001	1
Osteoporosis	1.36	0.28	0.001	1
Periodontitis	0.73	0.26	0.001	0.5
Osteoarthritis	0.64	0.26	0.001	0.5
Fibromyalgia	0.69	0.26	0.001	0.5
Eye inflammation/uveitis	0.61	0.28	0.001	0.5
Vasculitis	0.64	0.29	0.001	0.5
Amyloidosis	0.57	0.24	0.001	0.5
Carpal Tunnel Syndrome	0.49	0.25	0.001	0.5
Atlanto-axial subluxation	0.48	0.24	0.001	0.5

**Table 1:** The beta-coefficients and p-values of the different comorbidities identified by linear regression analyses and its assigned weights in accordance to the beta-coefficients.

On applying the developed RACI adjusted for age and gender, and using multivariate linear regression analysis for prediction of the functional ability score; there was significant correlation at 1-, 3-, 5- and 10-years shown (Table 2).

	1-year	3-year	5-year	10-year
F-value	0.645	0.712	0.825	0.879
p-value	<0.001	<0.001	<0.001	<0.001
R2	0.743	0.767	0.908	0.835
Adjust R2	0.741	0.765	0.916	0.834

**Table 2:** Multivariate linear regression analysis for functional disability score prediction using Comorbidities adjusted for age and gender.

Similarly, there was significant correlation depicted with Quality of life ( $p < 0.001$ ). The assessment of the developed RACI performance in



contrast to the 4 tested comorbidity Indices at 1, 3, 5 and 10 years is shown in Table 3.

Comorbidity Index	RACI at 1-year	RACI at 3-years	RACI at 5-years	RACI at 10-years
CCI	0.325*	0.436*	0.558*	0.784*
FCI	0.861*	0.585*	0.843*	0.879*
RDCI	0.872*	0.689*	0.886*	0.929*
MMI	0.756*	0.732*	0.786*	0.913*

**Table 3:** Correlation of the RACI score with the comparator Comorbidity indices at 1, 3, 5 and 10-years. RACI: Rheumatoid arthritis comorbidity index; CCI: Charlson comorbidity index; FCI: Functional comorbidity index; RDCI: Rheumatic Diseases comorbidity index; MMI: Multimorbidity index. \*p<0.01.

There significant variation of the correlation levels reflect the variation of the disease duration amongst patients included in the different comorbidity indices. External validation assessment, (Table 4), revealed similar significant correlations. The proposed RACI score was validated using ROC curve displayed in Figures 2 & 3. The ROC curve revealed an AUC (Area under curve) of 0.967 (95% CI 0.959–0.975). Different coordinate's points yield different sensitivity and specificity. At a cutoff point of 8.2 the proposed score yielded a sensitivity of 91.0% and a specificity of 98.4%.

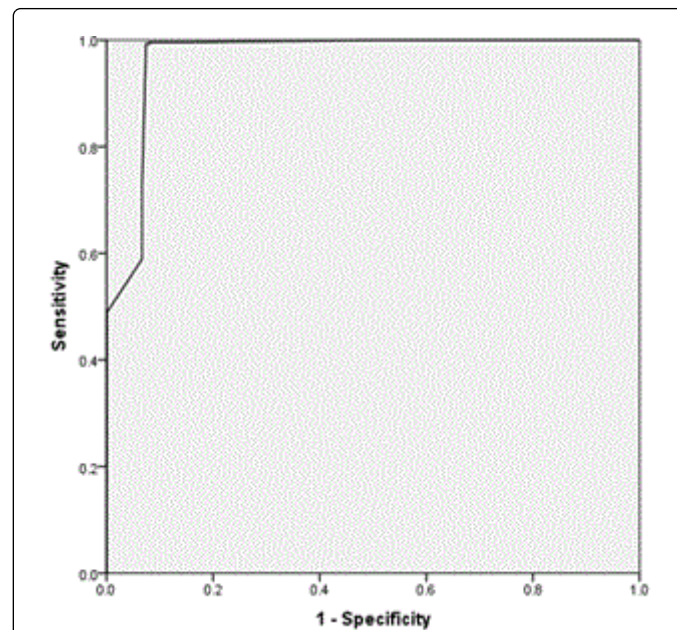
	Spearman Correlation Coefficient	P-value
Functional Disability	0.873	<0.001
Quality of life	0.859	<0.001
Multimorbidity Index	0.916	<0.001
Rheumatic Disease Comorbidity Index	0.961	<0.001
Functional comorbidity index	0.877	<0.001
Charlson Comorbidity Index	0.729	<0.001

**Table 4:** External validation: correlation of the RACI with functional disability, quality of life as well as the comparator comorbidity indices. RACI: Rheumatoid arthritis comorbidity index.

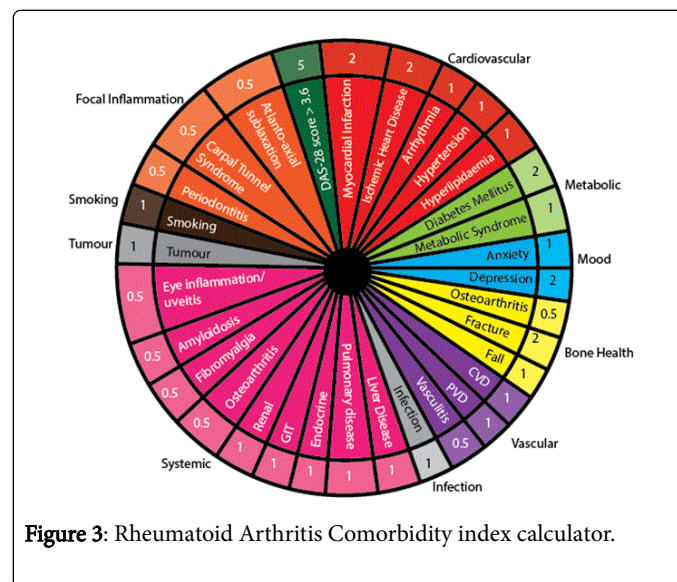
### Comorbidity cross-relationships

About 6% of RA patients who achieved DAS-28 score <3.2 developed IHD while 88% of those experiencing persistent disease activity (DAS-28 >3.6; indicating moderate to high disease activity score) suffered ischemic heart disease comorbidity. Considering biologic therapy, 35.4% of patients receiving biologic after 3 years from the disease onset developed ischemic heart disease whereas 1806/2029 (89%) of the patients who started biologic after 5 years of the disease onset suffered cardiovascular comorbidity (Pearson Chi-Square value was 423.838a). A decrease in physical function was observed and was significantly related (p<0.001) to the number of chronic morbidities. In concordance, 13.6% of RA patients who were in remission got infection in comparison to 75% of those whose disease remained moderately or highly active with Pearson Chi-Square value 726.106a (OR 19.166, CI: 15.049-24.410). Also increase falls risk was correlated

to the disease activity score OR 4.8 (CI: 3.9–5.0). Similarly depression was also correlated to the disease activity score with OR 5.3 (CI 4.2–6.9).



**Figure 2:** ROC curve displaying the discriminating ability of the Rheumatoid Arthritis Comorbidity Index (RACI).



**Figure 3:** Rheumatoid Arthritis Comorbidity index calculator.

### Discussion

Comorbidity indices are tools used to quantify the total burden of comorbidity contributing to the patient's overall illness. The development of such indices help in the identification of patients with worse prognosis in terms of heightened mortality, hospitalization risk as well as decline in health-related quality of life. This aim of this work study was to identify comorbidities with greatest impact on RA patients' health status and to develop and validate a prospectively applicable comorbidity index for categorizing patients living with RA

according to their comorbid conditions which might affect their mortality or hospitalization risk.

Results of this work revealed that the chronic, debilitating, active inflammatory autoimmune nature of RA affects the patient both directly as well as indirectly in almost all organ systems. On average, the established RA patient has two or more comorbid conditions. The comorbid frequency, tend to be higher, in RA patients whose disease run a moderate or active course. This agree with earlier published results [30,31] which demonstrated that achieving remission limits disability, improves function, as well as reduce comorbidities commonly reported in RA patients, making it reasonable to implement these targets as a guide for treatment decisions. This is supported by the finding of this work which revealed that the patients who started biologic therapy late in disease course (3- and 5-years disease duration) were more prone to sustain more comorbidities as well as have poor functional ability, in comparison to those who started treatment earlier in the disease course. Similarly, setting DAS-28 cut off points at high levels (DAS-28 >5.1 according to NICE guidelines) for commencing biologic therapy made the patients more prone to comorbidities. This comes in favor of the new treatment guidelines published by the American College of Rheumatology [32] and EULAR [33], and warrants revision of the NICE guidelines for rheumatoid arthritis management. Incorporation of chronological age, long disease duration, comorbidities, drug-related risks and shared physician-patient decision making are clearly important factors that necessitate adjustments of management targets.

The major advantage of comorbidity indices is that it transforms the coexistent disorders, bearing its severity, into one numeric score. This would facilitate the comparison of comorbidity risk amongst patients and pave the way to implementing measures to minimize such risk. The CCI published in 1987 [15], was developed based on the assessment of mortality rates in 607 patients who were admitted under the internal medicine care. The CCI included sixteen diseases which were selected and weighted based on the correlation with 1-year mortality and the strength of that association. Connective tissue diseases were included under one category and an adjust risk of 1 was given regardless of the nature of the underlying rheumatic disease, or disease duration. Elixhauser et al. [20] used administrative data, in acute hospital patients, to recognize the 30 comorbidities (the 17 from CCI + 13 new ones) which had a major impact on short-term outcomes. The score was calculated based on giving 1 point per comorbidity. Adding all points would give the total ECS score. However, taking into consideration the setting of both CCI and ESC, both these indices won't be the best applicable model to assess comorbidities in patients living with RA. The CCI was originally developed to predict death in a sample of hospitalized patients, hence, it won't be applicable for outpatient RA routinely monitored in the standard clinical practice, Similarly, the ECS was developed based on a sample of hospitalized patients to predict hospital charges, length of stay, and the risk of in-hospital death. Therefore, it can be said that both CCI and ECS have been used outside their originally intended scope. On another front, most likely, majority of the RA patients included in the CCI, have not received any form of specific DMARDs therapy and had very long disease duration; whereas most of the patients included in ECS, have not been treated per modern treatment approaches and most likely have missed the biologic therapy era. Therefore, in the current RA management setting, both Charlson and Elixhauser indices can be considered as outdated. In addition, the use of a comorbidity count, such as adopted in the ECS index, is not advisable. This is attributed to the fact that comorbidity counts vary in

the number as well as types. Also, the count, ignores the weight of the different comorbidities, hence a wide variability in the index predictive ability is expected. The Rheumatic Disease Comorbidity Index (RDCI) was developed based on self-report questionnaires from patients diagnosed to have RA, systemic lupus erythematosus, osteoarthritis or fibromyalgia [22]. Twenty-two comorbidities were assessed for impact on 6 outcomes: hospitalization, death, Health Assessment Questionnaire (HAQ) functional disability, direct medical costs, work disability, and social security disability. The final index encompasses 11 comorbidities. However, the RCDI index has been criticized for having a fixed baseline values for analysis, thus it removed the chronological component of comorbidity during the follow-up period. This reduces the predictive power of comorbidity index over time. Additionally, the RDCI used developed using data collected based on ICD-9-CM codes retrieved from the outpatient visits' notes. The responsibility to maintain an accurate and updated list of comorbid conditions rely on the providers. In the RCDI study, there was a delay of 2-years in data entry, which consequently reflects negatively on the accuracy of the developed index. Lastly, all the patients included in the RDCI were males. This comes in contrast to that fact that RA is more prevalent in women [21,22]. This study presents a comorbidity index developed based on real life scenario of the current clinical practice and the patients were monitored for 10-years. The assessed patient's cohort included both women and men who had short disease duration, and were treated according treat to target approach. Results of this study, revealed the importance of the disease activity state which for the first time, in comparison to the earlier published indices, was included as one of the risk factors.

Results of this work emphasized the importance of for employing the "patient centered approach" in standard clinical assessment and management. Figure 2 is a summary of the index which can be used in standard practice to calculate the patient's comorbidity index. In contrast to comorbidity, the term multimorbidity was introduced recently [28]. The difference is based on "what is the primary index?" For comorbidity, RA is the index disease and all other diseases are mainly regarded consequential. On the other hand, in the multimorbidity concept, the patient is of central concern and all other comorbidities, including RA, are of importance with variable impacts. In the study published in 2014 by Radner et al. [34], the authors stated that for clinicians involved in rheumatology care of an ageing patient population who have multiple diseases, multimorbidity is the rule not the exception. This study demonstrated that the treating rheumatologist should consider the interaction of different diseases and the impact they have, not only on the disease activity, but also on clinical outcomes, such as physical function, quality of life and mortality. Management decisions must be adapted for the patient with multimorbidity, earlier in the disease course; to improve the outcomes, best serve the individual and enhance the overall clinical practice and research focus [28].

When treating RA patients, it is the responsibility of the rheumatologist to assess for the risk of additional conditions. Self-administered questionnaires could be a reliable valid approach to assess comorbidities in standard clinical practice, and a mean to be included in prospective studies. The self-administered comorbidity questionnaire (SCQ) published by Sangha et al. [35], relied on the patients to report their comorbidities. The patients were asked to indicate whether they suffer, at the moment, from 12 medical conditions. These comorbidities were selected by an expert board based on the comorbidities included in the CCI. The SCQ score ranges from 0 to 45 points. Results of this work revealed that self-reported

PROMs questionnaire facilitated the incorporation of comorbidity assessment in the standard practice. In turn, this enabled the treating rheumatologist to link between the patients' comorbidity, the disease activity as well as their functional ability and quality of life scores.

In conclusion, comorbidities are conditions that coexist with a disease of interest, and may lead to a delayed diagnosis, be confounders in analysis of clinical status and course, as well as increase morbidity/mortality risk. Therefore, it appears desirable to sum the disease associated comorbidities into a single score, using self-administered co-morbidity questionnaires. The developed comorbidity index specific for rheumatoid arthritis patients was found to be valid and reliable as well as applicable for use in standard clinical practice for the assessment of comorbidity risk in RA patients. Future directions would involve comorbidity assessment in standard clinical practice in parallel with disease activity assessment. A global patient index including disease activity as well as Comorbidity index scores would be calculated for every RA patient receiving treatment. Getting the disease activity into remission and lowering the comorbidity risk would be the new targets of RA management.

## Competing Interest

The authors have no relevant financial disclosures.

## Contributorship

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. El Miedany had full access to all of the data in the study and Dr. El Gaafary carried out the data analysis.

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## Ethics Approval

Ain Shams University Research Ethics Board.

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