



# Association between disease activity measured by RAPID3 and health-related quality of life in patients with rheumatoid arthritis

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Received: 10 January 2019 / Accepted: 14 February 2019 / Published online: 7 March 2019  
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## Abstract

Routine assessment of patient index data 3 (RAPID3) is a simple, valid and reliable tool designed to measure disease activity in patients with rheumatoid arthritis (RA). RA causes significant disability and diminishes health-related quality of life (HR-QoL). The aim of this study was to investigate how RAPID3 is related to HR-QoL in patients with RA. In this cross-sectional study performed at the tertiary outpatient clinic 68 consecutive patients (58 females, and 10 males) with established RA were enrolled. RAPID3 and EuroQoL-5D-3L (EQ-5D-3L) were used to measure disease activity and quality of life, respectively. Alongside, demographic and clinical data were obtained, as well as HAQ-DI as a measure of physical function, and Steinbrocker's score for radiographic damage. To test the relationships among RAPID3 and study variables we used the Pearson product–moment correlation coefficient, with the significance was set at  $P < 0.05$ . Linear and forward stepwise regression was used to show how variables of interest contributed to RAPID3. The mean value of RAPID3 (standard deviation, SD) was 14.12 ( $\pm 5.21$ ), while the median (IQR) value of EQ-5D-3L was 0.51 (0.62–0.23). There was a high significant correlation ( $r = -0.73$ ) between RAPID3 scores and EQ-5D-3L. Among the other variables of interest, the strongest correlation was found between RAPID3 and intensity of pain ( $r = 0.88$ ), while the EQ-5D-3L and pain were moderately correlated ( $r = -0.68$ ). In evaluating the influence of variables of interest on RAPID3, a forward stepwise regression model was constructed to evaluate whether VAS pain, EQ-5D-3L and EQ-VAS predicted RAPID3. The given variables significantly explained approximately 81% of the variation in RAPID3. Based on the results of this study RAPID3, a simple and practical tool to assess disease activity, reflects well HR-QoL in patients with established RA.

**Keywords** Rheumatoid arthritis · Quality of life · Disease activity · Patient outcome assessment

## Introduction

Rheumatoid arthritis (RA) is a multifacet disease with a large impact on physical, functional, social and emotional well-being [1]. Therefore, the need to measure quality of

life (QoL) in RA has always been of great importance [2]. Disease activity is the crucial element in assessing patients with RA, since it is the main component driving in tailoring our treatments, using “target to treat” concept, to achieve the ultimate goal, which is the improvement in QoL [3].

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Many tools are proposed for measuring RA disease activity in clinical practice, but there is still no “gold standard” in that field.

Routine assessment of patient index data 3 (RAPID3) is a simple measure of disease activity, whose advantage over other similar tools is that it does not include the count of tender and swollen joints or lab findings; therefore, it can be calculated in merely 5–9 s [4, 5]. Studies have shown that RAPID3 is a feasible disease activity measure demonstrating similarity to traditional RA disease activity measurements and fulfilling the required properties of a disease activity instrument (reliability, validity and categorizing patients into various stages of disease activity); also showing its good correlation with other clinical features of RA [4–13]. Recently it was presented that RAPID3 correlates with hand function, so important in patients with RA [13]. It is also proven that RAPID3 can be used to measure disease activity for rheumatic diseases other than RA [14–16].

Knowing that the RA as a disease significantly contributes to overall disability and diminishes QoL [17–20], the novelty of the study is the assessment of the correlation between RAIPD3 and QoL in RA.

## Methods

### Patients and methods

This was a cross-sectional study performed at the tertiary health-care university center during the period between September 2013 and July 2014. We have included 68 consecutive RA patients at the Rheumatology Clinic, University Clinical Center of Kosovo during their outpatient visit. These patients were enrolled according to inclusion criteria out of 253 patients with RA. The inclusion criteria were as follows: diagnosis of RA established by the ACR/EULAR 2010 criteria [21], patients of both genders aged 18–75 years, disease duration of at least 6 months; and no change in disease-modified anti-rheumatic drugs (DMARDs) and glucocorticoids within the 3 months before the inclusion in the study. Regarding disease-modified anti-rheumatic drugs (DMARDs), patients have been treated with conventional synthetic DMARDs—as methotrexate, sulfasalazine, (hydroxy)chloroquine, and leflunomide. As for the dose of glucocorticoids, patients were treated with prednisone up to 10 mg/daily, or equivalent. The exclusion criteria were: patients with previous trauma, skin conditions or congenital malformation significantly compromising overall function and well-being; fractures or surgical interventions with detrious consequences, severe neurologic disease, severe psychiatric disease; severe renal or hepatic insufficiency; severe cardiac insufficiency (NYHA III or IV), malignant disease with the exception of non-melanoma skin cancer,

and patients who attended physical therapy treatment within the previous 1 month period.

The study was approved by the Ethics Committee of the University Clinical Center of Kosovo, Pristina, Kosovo (protocol number: 2577) obtained on 03.05.2013, and the Ethics Committee of the University of Zagreb, School of Medicine, Zagreb, Croatia, (protocol number: 380-59-10106-18-111/223) obtained on 19.11.2013. It was conducted in accordance with the principles of the Declaration of Helsinki and its later revision [22]. Prior to data inception, the purpose of the research was explained to each patient, and after obtaining consent from the patients to participate in the research, each participant signed an informed consent.

Demographic and clinical data were recorded on an examination sheet and thereafter put into Excel table.

The clinical data consisted of the duration of the disease, morning stiffness, intensity of pain, disease activity, quality of life and structural damage.

Duration of the disease related to the beginning of the articular symptoms consistent with rheumatoid arthritis was recorded in years. Morning stiffness was assessed for its duration, and recorded in minutes [23]. Regarding the duration of morning stiffness for the purpose of statistical analysis the patients were divided into two categories: less or equal or more than 60 min.

The intensity of pain in the last 24 h was evaluated by using a horizontal visual analogue pain scale (VAS) [23]. It is a 100 mm straight line anchored by mark “no pain” on the left-hand end and “the worst pain” on the right-hand end and the patients were asked to assess their pain intensity by marking on the line between these endpoints. The distance between the anchor “no pain” and the patient’s mark was the obtained result [24].

To assess disease activity, we used RAPID3 and Disease Activity Score 28 using ESR (DAS28-ESR). RAPID3 is a pure patient-reported outcome instrument that measures physical function, level of pain and patient global assessment of health during the previous week. The sum of the three parts of the RAPID3, ranging from 0 to 30, was recorded. The RAPID3 score is categorized as follows: high disease activity (greater than 12), moderate disease activity (6.1–12), low disease activity (3.1–6) and near-remission disease activity (3 or less) [4, 5].

The functional ability was measured using Health Assessment Questionnaire-Disability Index (HAQ-DI), as the most widely described functional disability instrument used in RA patients [25]. Its results can range from 0 to 3, higher score meaning worse physical function [25]. To measure health-related QoL (HR-QoL) we used EuroQoL questionnaire (EQ-5D), which is the most commonly used generic tool for rheumatic diseases, capturing a patient’s health across five domains [26]. The instrument is widely used and validated in RA patients [27–33]. It consists of

two parts: a descriptive system with five domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and global health captured on VAS. In our study, we used three “problem” levels for each domain (EQ-5D-3L). In total, there are 243 health states, which range from  $-0.594$  to  $1$ , the latter being full health. The EQ-VAS scale consists of one vertical line anchored at the bottom end with “the worst health one can imagine” marked as  $0$  and the “best health one can imagine” at the top end marked as  $100$ , and the patient was asked to mark the line to describe his/her health [34]. Since there is no local EQ-5D-3L algorithm score, scoring in our patients was carried out according to the UK TTO 3L value set, which is the most widely used [34].

To assess structural damage in our patients, standard plain hand radiographs (posterior–anterior view) were performed and were available in 60 out of 68 patients. The radiographs were read by an experienced radiologist (MM) specialized in skeletal radiology, who was blinded to all clinical data. Although several radiographic scoring methods have been developed to quantify stages of structural damage, for the purpose of this study we used the Steinbrocker staging system (range  $0 =$  normal to  $4 =$  total joint destruction, either lysis or ankylosis), as a simple and well known one [35].

## Statistical analysis

Descriptive statistics median, interquartile range (IQR), mean and standard deviation (SD), were presented according to the normal distribution of the variables. For the correlation analysis between RAPID3 and variables of interest, the Pearson product-moment correlation coefficient was used. Given that our correlation analyses identified significant relationships between variables, the next step was to evaluate the effect of various factors on the relationship between the two, showing how independent variables (EQ-5D-3L, EQ-VAS, VAS-pain) contributed to a single dependent variable (RAPID3) using linear regression equation. Each of the independent variables were regressed on RAPID3 and the relevant  $R^2$  ( $R$ -squared coefficients) show the percentage of contribution, while the results of a  $t$  test on the significance of the relationship between the two variables is shown by the  $P$  value (which if less even than  $0.01$ ), showing that the factors are significantly related to RAPID3. Moreover, to show the size effect, Beta coefficient values are presented. Finally, we used forward stepwise regression analyses in which EQ-5D-3L, EQ-VAS and VAS-pain are input in the initial model, and significance level less than  $0.05$  was set for addition of the variables to the model. For statistical analysis STATA version 11 software (StataCorp, College Station, TX) was used.

## Results

The sample consisted of 68 patients (58 females and 10 males); the median age was  $56.5$ , IQR ( $62.50$ – $47.00$ ) years. The median duration of the disease was  $7.00$ , IQR ( $14.50$ – $3.00$ ) years. The main descriptive data of the clinical variables of interest are presented in Table 1.

The correlations between RAPID3 scores and EQ-5D-3L scores were calculated as crude values. There was a negative significant correlation between disease activity measure (RAPID3) with quality of life (EQ-5D-3L) and with pain (on VAS), i.e. the patients’ quality of life and pain worsen with higher disease activity (Table 2). The correlation between RAPID3 scores and EQ-5D-3L scores was somewhat stronger than the correlation between EQ-5D-3L scores and HAQ-DI scores, and EQ-5D-3L scores with pain scores.

Correlations between RAPID3 components (RAPID3 physical function, RAPID3 pain and RAPID3 global health) with EQ-5D-3L, EQ-VAS and pain on VAS are shown in Table 3. We found a significant correlation between all study variables, the strongest being between RAPID3 physical function with VAS pain. In investigating whether each component of RAPID3 scores performs well in predicting QoL measures a significant correlation between each component of RAPID3 and EQ-5D-3L was shown, with the strongest correlation being between RAPID3 physical function and EQ-5D-3L.

**Table 1** Descriptive statistic of demographic and clinical data ( $n=68$ )

Variables ( $n=68$ )	
Gender	
Female $n$ (%)	58 (85.3%)
Male $n$ (%)	10 (14.71%)
Age (years), median (IQR)	56.50 (62.50–47.00)
Disease duration (years), median (IQR)	7.00 (14.50–3.00)
Morning stiffness duration (min), median (IQR)	45.00 (75.00–20.00)
Tender joint count (0–28), mean (SD)	14.26 ( $\pm 7.36$ )
Swollen joint count (0–28), mean (SD)	9.21 ( $\pm 5.74$ )
RAPID3 (0–30), mean (SD)	14.12 ( $\pm 5.21$ )
DAS28-ESR, mean (SD)	5.88 ( $\pm 1.28$ )
HAQ-DI, mean (SD)	1.83 ( $\pm 0.74$ )
VAS pain (0–100 mm), mean (SD)	59.47 ( $\pm 20.09$ )
EQ-5D-3L, median (IQR)	0.51 (0.62–0.23)
EQ-VAS, mean (SD)	47.23 ( $\pm 21.51$ )
Steinbrocker scale, median (IQR)	1.50 (2.50–1.00)

$n$  number of subjects,  $SD$  standard deviation,  $IQR$  interquartile range,  $RAPID3$  routine assessment of patient index data 3,  $DAS28$  Disease Activity Score 28,  $HAQ-DI$  Health Assessment Questionnaire-Disability Index,  $VAS-pain$  Visual Analog Scale-pain,  $EQ-5D-3L$  EuroQol-5D-3L,  $EQ-VAS$  EuroQol-Visual Analog Scale

**Table 2** Correlations between RAPID3 scores, HAQ-DI scores, EQ-5D-3L scores, EQ-VAS scores and pain on VAS scores

Variables	RAPID3 scores	HAQ-DI scores	EQ-5D-3L scores	EQ-VAS scores	VAS pain scores
RAPID3 scores					
<i>r</i>	1.00				
<i>P</i> value	< 0.001				
EQ-5D-3L scores					
<i>r</i>	− 0.73*	− 0.71*	1.00		
<i>P</i> value	< 0.001	< 0.001			
EQ-VAS scores					
<i>r</i>	− 0.72*	− 0.67*	0.67*	1.00	
<i>P</i> value	< 0.001	< 0.001	< 0.001		
VAS pain scores					
<i>r</i>	0.86*	0.72*	− 0.68*	− 0.65*	1.00
<i>P</i> value	< 0.001	< 0.001	< 0.001	< 0.001	

*r* correlation coefficient, *RAPID3* routine assessment of patient index data 3, *HAQ-DI* Health Assessment Questionnaire-Disability Index, *EQ-5D-3L* EuroQol-5D-3L, *EQ-VAS* EuroQol-Visual Analog Scale, *VAS* Visual Analog Scale

\**P* < 0.05

**Table 3** Correlations between different components of RAPID3 (RAPID3 physical function score, RAPID3 pain score, and RAPID3 global health score) with EQ-5D-3L scores and pain on VAS scores

Variables	RAPID3 physical function	RAPID3 pain	RAPID3 global health
EQ-5D-3L scores			
<i>r</i>	− 0.70*	− 0.69*	− 0.64*
<i>P</i> value	< 0.001	< 0.001	< 0.001
EQ VAS scores			
<i>r</i>	− 0.70*	− 0.62*	− 0.67*
<i>P</i> value	< 0.001	< 0.001	< 0.001
VAS pain scores			
<i>r</i>	0.74*	0.88*	0.75*
<i>P</i> value	< 0.001	< 0.001	< 0.001

*r* correlation coefficient, *RAPID3* routine assessment of patient index data 3, *EQ-5D-3L* EuroQol-5D-3L, *EQ VAS* EuroQol-Visual Analog Scale, *VAS* Visual Analog Scale

\**P* < 0.05

In linear regression analysis for EQ-5D-3L, EQ-VAS and VAS-pain, on RAPID3 as a dependent variable (Table 4), we found that EQ-5D-3L significantly predicted RAPID3 (*P* = 0.00) and was able to explain 53% of the variability in RAPID3. EQ-VAS and VAS-pain also significantly predicted RAPID3. EQ-VAS was able to explain 52% of the variability in RAPID3, while VAS-pain was able to explain 74% of the variability in RAPID3.

In a forward stepwise regression model constructed to evaluate whether VAS pain, EQ-5D-3L and EQ-VAS predicted RAPID3 (Table 5) it was demonstrated that these variables significantly explained (approximately 81%) of the variation in RAPID3. All variables had significant positive regression weights, indicating persons with lower values of EQ-5D-3L and EQ-VAS were expected to have higher RAPID3, while higher values VAS pain was expected to have higher RAPID3 values, after controlling for the other variables in the model.

**Table 4** Factor linear regression results for each variable on RAPID3 as dependent variable

	<i>R</i> <sup>2</sup>	<i>β</i> value	Standard error	<i>t</i> value	<i>P</i> value	95% confidence interval	
EQ-5D-3L	0.53	− 17.17	1.96	− 8.76	< 0.001	− 21.08	− 13.25
EQ-VAS	0.52	− 0.17	0.02	− 8.53	< 0.001	− 0.22	− 0.13
VAS-pain	0.74	0.22	0.02	13.69	< 0.001	0.19	0.25

*R*<sup>2</sup> squared correlation coefficient, *RAPID3* routine assessment of patient index data 3, *EQ-5D-3L* EuroQol-5D-3L, *EQ-VAS* EuroQol-Visual Analog Scale, *VAS-pain* Visual Analog Scale-pain

\**P* < 0.05

**Table 5** Stepwise regression analysis of VAS pain, EQ-5D-3L and EQ-VAS with RAPID3 as a dependent variable

	$\beta$ value	Standard error	<i>t</i> value	<i>P</i> value	95% confidence interval	
Constant	9.37	2.07	4.54	< 0.001	5.26	13.24
VAS-pain	0.15	0.02	7.34	< 0.001	0.11	0.20
EQ-VAS	− 0.06	0.02	− 2.72	0.008*	− 0.09	− 0.01
EQ-5D-3L	− 4.26	1.86	− 2.28	0.026*	− 8.24	− 0.53

$R^2=0.81$ ; \* $P < 0.05$

$R^2$  squared correlation coefficient, RAPID3 Routine Assessment of Patient Index Data 3, EQ-5D-3L EuroQol-5D-3L, EQ-VAS EuroQol-Visual Analog Scale, VAS-pain Visual Analog Scale-pain

\* $P < 0.05$

## Discussion

In our study, we explored the correlation between RAPID3, a simple disease activity tool and HR-QoL in patients with RA. We hypothesized that RAPID3 embodied EQ-5D-3L because it reflects the patient's perspective of physical function, disease activity and pain, which are factors that greatly impact QoL [27, 28]. This was confirmed in our study, as well as that EQ-5D-3L significantly influence RAPID3 score.

To quantify a patient's perception of the disease in terms of their QoL, a variety of HR-QoL instruments are proposed. In our study, EQ-5D-3L was used to assess HR-QoL [34]. It is one of the most commonly used generic QoL instrument that addresses the main aspects of RA [28]. Moreover, in the recent study of Dritsaki et al. showed that EQ-5D-3L had the best acceptance by study participants out of several instruments that measure HR-QoL [32]. Numerous studies have explored the correlation between disease activity and QoL in patients with RA [17–20, 27–33], using tools other than RAPID3 in disease activity assessment., which is understandable because compared to other instruments RAPID3 has been developed rather recently. It is proved that disease activity impacts HR-QoL, mostly in the sense that low HR-QoL correlates with high disease activity [20, 27]. Overall, our results showed a strong correlation between RAPID3 scores and both EQ-5D-3L scores and EQ-VAS scores; the correlation with EQ-5D-3L scores being even stronger than that reported between DAS28 and EQ values [28]. Hurst et al. performed a study establishing the reliability, validity and responsiveness of EQ-5D-3L in RA patients [28]. Another study used Clinical Disease Activity Index (CDAI), Simplified Disease Activity Index (SDAI) and DAS28 as disease activity measures, with the aim to compare RA outcomes, including HR-QoL in patients with low disease activity and remission, and demonstrated significant but moderate correlations between disease activity and HR-QoL [19]. The authors reported on a stronger correlation between QoL and functional disability measured by HAQ than with DAS28 indices, while in our correlation

analysis the strongest correlation occurred between EQ-5D-3L scores and disease activity measured by RAPID3 scores. This might be the consequence of the difference in disease activity measures between two studies. Although in both studies the patients had a long-standing disease with the assumption of irreversible joint damage, the most obvious difference is that in our study the majority of patients had a high disease activity, while the majority of patients in the above-mentioned study were in the remission/low disease activity stage [19]. Also, there is a study presenting a correlation between EQ-5D-3L and clinical data in RA patients, showing significant correlations regardless of gender, age, disease duration [27].

Al-Fadl et al. used Short-Form-36 (SF-36) to assess HR-QoL in patients with early RA, finding that RA greatly influenced HR-QoL and there was a very strong correlation between DAS28 and SF-36 [18]. The same conclusion was reached by other authors such as West et al. [17], and similar results were obtained in the study of Gamal et al. [20], in which the disease duration was similar to our sample of patients with RA.

Cho et al. performed an interesting study exploring the correlation between EQ-5D-3L and clinical variables in RA patients as well as correlations of different parameters with each dimension of EQ-5D-3L [36]. They found significant correlations between EQ-5D-3L and variables of interest; the strongest was between EQ-5D-3L and HAQ-DI, while moderate was with the disease activity. If we look at the study of Salaffi et al., whose purpose was to compare the QoL instruments EQ-5D-3L and SF-36 and to determine which was more highly correlated with RA disease parameters, a moderate correlation was shown between EQ-5D-3L and DAS28 [37]. Of note that studies found similar results of RAPID3 to DAS28 and CDAI in clinical trials and clinical care [5]. In our study, a moderate correlation was shown between VAS-pain and EQ-5D-3L, while the strongest correlation was between EQ-5D-3L and RAPID3.

In measuring HR-QoL, instruments other than EQ-5D-3L were used in studies with RA [38, 39]. Chiu et al. used the World Health Organization Quality of Life

(WHOQOL) tool, and analysed the relationship between WHOQOL, DAS28 and HAQ [38]. They found that disease activity was associated with all QoL domains, although the same could not be stated for functional disability. The authors' explanation was that regardless of functional disability, improved disease activity would have been accompanied by improved QoL [38]. Generally, we can also state the same for RAPID3 since we have found significant correlation between EQ-5D-3L and RAPID3 domains (physical function, pain and global health). Garip et al. evaluated 153 patients using RAQoL, Nottingham health profile (NHP), HAQ, DAS28, radiological damage and pain (on VAS) [39]. They found a strong correlation between QoL and disease activity, as well as between QoL, pain, and functional disability, which agrees with the results of our study.

Although pain is a subjective outcome, our results are in line with other reports, showing that pain follows the same patterns of development as other disease activity indices [10, 40]. Pincus et al. found a very strong correlation between RAPID3 scores and pain [10], and we showed that the pain is the most important factor contributing to RAPID3. This is logical because pain is a component of RAPID3 itself. However, sometimes pain remains despite low DAS28 values, which should not be overlooked [41]. In overall, we have found strong correlation between pain and EQ-5D-3L. Similar results were established in study by Wan et al., where the pain was evaluated in the past month [42] and in the study of Rupp et al. who demonstrated that pain had a significant impact on physical health component of the quality of life [43].

The main strengths of our study is that we used a sample of homogenous group of patients using the classification of RA from a contemporary standard care outpatient clinic. For this study, a significant number of well-defined, validated instruments were used, and sufficient data were obtained and taken in account to explore the hypothesis of the study. There are some limitations of our study that invoke some cautions when interpreting the results. The small number of male subjects may have influenced the significance of our statistical analyses. Another limitation is that the majority of patients demonstrated moderate to high disease activity and considerable disability; thus, it would be desirable to incorporate patients across the continuum of disease activity, preferably in the longitudinal way.

In conclusion, in our sample of patients with established RA, RAPID3 reflected HR-QoL measured by EQ-5D-3L. Also, EQ-5D-3L influenced disease activity as measured by RAPID3, indicating that around 50% of RAPID3 depends on EQ-5D-3L. We believe that our findings will encourage the utilization of RAPID3 and will raise interest in further investigations in this field.

**Acknowledgements** We thank our patients for taking part in this research.

**Author contributions** MQ, SR and BR were local investigators who contributed substantially to the acquisition of the data. MQ wrote the first version of the manuscript and undertook the statistical analyses. MQ, SR, BR undertook the data collection. MM and ID undertook the data interpretation and contributed to the writing and editing of the manuscript. SG developed the theoretical framework, supervised the study, and revised the manuscript. All authors participated in the interpretation of the results, editing, and approved the final version of the manuscript.

**Funding** No funding was received for this study.

## Compliance with ethical standards

**Conflict of interest** Authors declare no conflicts of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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