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UNIVERSITY OF ZAGREB
SCHOOL OF MEDICINE

Merita Qorolli

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DISSERTATION

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This dissertation was completed at the Rheumatology Clinic, University Clinical Centre of Kosovo.

Mentor: Professor Simeon Grazio, MD, PhD

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ABBREVIATIONS:

ACPA	Anti-Citrullinated Peptide Antibody
ACR	American College of Rheumatology
AIMS	Arthritis Impact Measurement Scales
BMI	Body Mass Index
CDAI	Clinical Disease Activity Index
CRP	C- Reactive Protein
DAREA	Disease Activity Index for Reactive Arthritis
DAS	Disease Activity Measure
DAS28	Disease Activity Measures 28
EGA	Examiner's Global Assessment
ESR	The Erythrocyte Sedimentation Rate
EQ-VAS	EQ Visual Analogue Scale
EQ-5D-3L	EUROQOL-5D-3L
GAT	Grip Ability Test
GDP	Gross Domestic Product
HAQ	Health Assessment Questionnaire
HAQ-DI	Health Assessment Questionnaire-Disability Index
HRQOL	Health Related Quality of life
HUI	Health Utility Index
JAM scale	Joint Alignment and Motion scale
J-HAQ	Japanese Health Assessment Questionnaire
MCP	MetaCarpo-Phalangeal
MDHAQ	Multidimensional Health Assessment Questionnaire
MHQ	Michigan Hand Questionnaire
MRI	Magnetic Resonance Imaging
NHP	Nottingham Health Profile
OMERACT	Outcome Measures in Rheumatology
PAS	Patient Activity Scale
PGA	Patient Global Assessment
PIP	Proximal Inter-Phalangeal
PrGA	Provider Global Assessment

PROM	Patient-Report Outcome Measure
PROMIS	Patient Reported Outcomes Measurement Information System
RA	Rheumatoid Arthritis
RAPID3	Routine Assessment of Patient Index Data 3
RADAI	Rheumatoid Arthritis Disease Activity Index
RCT	Randomized Control Trial
SDAI	Simplified Disease Activity Measure
SIP	Sickness Impact Profile
SOFI	Signals of Functional Impairment
UKTTO	UK Time Trade Off
US	UltraSound
VAS	Visual Analogue Scale
WHOQOL	World Health Organization Quality Of Life

1. INTRODUCTION

Although progress in the field of medicine is quite common currently, rheumatoid arthritis (RA) remains a challenging disease due to its nature. Since RA is a progressive and destructive disease (1), it is necessary to adequately assess it in order to control it (2). However, certain procedures are sometimes neglected in busy clinical settings (3), which have led researchers to develop instruments that are more feasible in everyday clinical practice.

As there is still no “gold standard" tool that is appropriate for measuring RA disease activity, the need for such an instrument to capture essential features is obvious. There are different examination procedures for RA patients, which are often quite time consuming both for the patient and for the examiner. Our interest involved routine assessment of patient index data 3 (RAPID3), which is a simple, valid and reliable disease activity measure whose application is well-documented (3,4). RAPID3 does not include either the number of tender and swollen joints or lab findings; therefore, it can be calculated in merely 5-9 sec (5). The instrument's contents challenged us to investigate how RAPID3 is related to hand function and quality of life, knowing that the hands are ubiquitously affected in patients with RA, and impairment associated with their function significantly contributes to overall disability and diminishes quality of life.

We hope that this study will encourage the utilization of RAPID3 and will persuasively raise interest in the task of finding a reliable, quick, easy method to perform a questionnaire to measure RA disease activity that also encompasses the main features of the disease.

1.1 Definition and basic epidemiology

RA is an autoimmune, progressive, chronic disease characterized by synovial inflammation and damaged cartilage and bone that causes significant disability (1,6). Any joint can be affected, but the most common are the small joints of the hands and feet, the wrists, and the knee and elbow joints, all of which can lead to functional limitation and consequently to increased difficulty in performing daily activities (7,8). Rheumatoid arthritis is also a systematic disease, meaning that it affects other parts of the body including internal organs such as the lungs, heart and eyes (9). The prevalence of RA differs among different populations and geographic regions, varying between 0.5% and 1% (10), with some studies citing 0.24%, and it is two to three times higher among women than men (11). Although prevalence increases with age, RA can develop at any time; the usual onset is between 30 and 50 years (10,11).

1.2 Clinical presentation

Clinically, RA occurs after the actual onset of the disease (12). The onset of the disease is slow and subtle in up to 70% of patients, with wide-ranging symptoms (13). These include synovial inflammation, joint pain and morning stiffness, which are usually accompanied by general symptoms such as fatigue, malaise and shivers (14,15,16). The upper extremities are affected in more than half of patients, while hand involvement is evident in approximately 25% of patients, even during early disease (13). The most frequently affected joints are the wrists, the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints of the hand, elbows, shoulders, knees and the small joints of the feet (15). Although symmetrical joint manifestation is one of the hallmarks of RA, patients often identify the involvement of only one joint at the beginning of the clinical course (15,16).

1.3 Pathophysiology

As previously mentioned, the main pathophysiological feature of RA is inflammation of the synovium. The inflammatory process leads to the proliferation of synovial cells, subsequently forming a pannus that invades and destroys cartilage, periarticular bone and the joint capsule along with surrounding soft tissues (i.e., ligaments, tendons), progressing into the destruction stage. This is the main factor underlying deviations in biomechanical forces, causing different irreversible deformities such as wrist radial deviation, MCP ulnar deviation, “swan-neck” deformity, “boutonniere” deformity, “Z thumb” deformity, and others (17,18). In addition to articular involvement, 30-40% of patients experience extra-articular manifestations.

The most common extra-articular features are RA subcutaneous nodules, mostly in the elbows and fingers. Keratoconjunctivitis sicca or xerostomia, with secondary Sjögren's syndrome, develops in 10% of RA patients. Other systems, such as the pulmonary, cardiovascular, neurologic, hematologic, and renal systems as well as the skin, may also be involved (19-21).

1.4. Classification and diagnostic criteria in RA

The main challenge in rheumatology involves the differentiation of diseases with similar signs and symptoms. Similarities in the manifestation of rheumatic diseases have caused researchers to establish criteria that differentiate such diseases (22). To differentiate patients with RA, the American Rheumatology Association first time proposed classification criteria for rheumatoid arthritis in 1956, which were revised in 1958 (23-25). The next set of revised criteria, established by the American College of Rheumatology (ACR) in 1987, consisted of seven components combining clinical, serological and radiological characteristics. The criteria include: 1) morning stiffness in and around joints lasting at least 1 hour before maximal improvement; 2) soft tissue swelling (arthritis) of 3 or more joint areas observed by a physician; 3) swelling (arthritis) of the proximal interphalangeal, metacarpophalangeal, or wrist joints; 4) symmetric swelling (arthritis); 5) rheumatoid nodules; 6) the presence of rheumatoid factor; and 7) radiographic erosions and/or periarticular osteopenia in hand and/or wrist joints. Criteria 1 through 4 must have been present for at least 6 weeks. RA is defined by the presence of 4 or more criteria (26). The downside of the 1987 ACR criteria is their insufficient sensitivity to identify cases of early disease (27,28).

Progress in basic science regarding the inflammatory processes underlying RA (29), as well as the need to identify patients with early RA, resulted in the new 2010 ACR and European League Against Rheumatism (EULAR) classification criteria (Table 1). A new biomarker, anti-citrullinated peptide antibody (ACPA), has enabled the identification of patients with early symptoms, enabling early treatment and thus improvements in disease outcomes. According to 2010 ACR classification, RA is defined if the score is 6 or more (30). Notably, these classification criteria are only to be used as guidelines to establish common approaches for clinical research worldwide, to classify patients with or without RA, and to establish clinical diagnoses. Also, the guidelines are not to be used to determine severity of the disease (31). Further assessments include clinical measures that capture all RA disease signs and symptoms to guide the care of individual patients (22,32). In 1992, researchers (established by ACR) from different world regions at the international meeting of Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) presented a core set of disease activity measures, "ACR

core data set", which were accepted after slight revision (33,34). This core data set consists of: swollen and tender joint count, physician global status, erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), physical function, and patient global pain (33,34). Since then, OMERACT meetings have continued, working to establish a framework and recommending the "core outcome measurement set" appropriate for randomized control trials (RCTs), including detailed steps to determine "what to measure" and "how to measure" in RA patients. Moreover, OMERACT emphasizes the importance of patient-report outcome measures (35).

Table 1. The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis (30).

Target population (Who should be tested?): Patients who 1) have at least 1 joint with definite clinical synovitis (swelling) 2) with the synovitis not better explained by another disease†	
Classification criteria for RA (score-based algorithm: add score of categories A–D; a score of is needed for classification of a patient as having definite RA)	6/10
A. Joint involvement	
1 large joint	0
2-10 large joints	1
1-3 small joints (with or without involvement of large joints)	2
4-10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)**	5
B. Serology (at least 1 test result is needed for classification)	
Negative RF *and* negative ACPA	0
Low-positive RF *or* low-positive ACPA	2
High-positive RF *or* high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)	
Normal CRP *and* normal ESR	0
Abnormal CRP *or* abnormal ESR	1
D. Duration of symptoms	
< 6 weeks	0
≥ 6 weeks	1

1.5. Disease activity

Disease activity is the crucial parameter to measure since it best reflects RA inflammation. In practical terms, the most important parameters that encompass disease activity include pain, stiffness, and swelling, which are the main signs and symptoms of the disease (36). Consequently, disease activity is responsible for structural damage, eventual disability, and deterioration in quality of life (36,37). Scot D et al. proposed that disease activity assessment as part of the core assessment should include joint counts (tender and swollen joint counts), doctor's and patient's global assessments, pain score and assessment of disability, as well as laboratory assessment (ESR or CRP) (1). Additional assessments include fatigue; as well as, radiological damage, a consequence of disease activity (1). According to Scot D et al., the most commonly employed combined indices in clinical trials are the Disease Activity Index based on 28 joint counts (DAS28), the Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI) (1).

Joint count of swollen and tender joints is an important disease activity measure, mirroring synovial inflammation (38). Joint swelling, defined as soft tissue swelling caused by synovial effusion, is detectable along the joint margins and does not involve bony enlargement or deformity, meaning that fluctuation of the effusion is its key feature. Joint tenderness is pain at rest that is triggered by the exertion of pressure during the examination of certain joints (39). There are several systems to determine the number of counted joints; one of them includes 66 swollen and 68 tender joints (40). Given that examination of all of these joints in everyday clinical practice is rather impractical over time, the joint count has been simplified to the 28-joint count, which has been shown to be a valid and reliable measure of RA disease activity (41,42). Although both measures are usually undertaken by training professionals, some studies have demonstrated that self-assessment of swollen and tender joints is also as valuable as a joint count done by a physician (43). In clinical practice, joint counts are generally components of composite disease activity measures (44-46). However, despite the fact that one of the most specific ways to assess RA is by measuring the number of tender and swollen joints, this method is very often disregarded in daily clinical practice (3).

Even today, with notable advances in our understanding of RA, pain is the cardinal symptom that plays a major role in RA diagnosis because it remains a patient's most serious symptom (47,48). Inflammation contributes to pain, but one should bear in mind that pain may also be caused by other non-inflammatory components (47,49). This is indicated by the fact that some

people experience great pain even if the disease activity is low or the disease is in remission (50,51). Therefore, a patient's perception of pain also plays a large role in the disease process. Pain is a multidimensional subjective category; therefore, there are different ways to evaluate it (47,52). In RA, pain intensity is still the predominant component; most often assessed using the 100-mm horizontal visual analogue scale (VAS) ("patient's assessment of pain"), which measures pain for the past week, or within the last 24 hours (36,53). Even that pain is subjective outcome, the contribution to functional disability, disease activity and quality of life is elaborately explained (54,55).

Similar to pain, the patient's global assessment (PtGA) is also a widely applied disease activity measure, and its utility has been reaffirmed by several studies (56-58). This instrument assesses a patient's global health or disease activity by self-assessment (59), largely recorded on the 100-mm VAS scale (60). Additionally, the physician's global assessment (PhGA), sometimes called the examiner's global assessment (EGA), is another valuable disease activity instrument that differs from the PtGA because it is administered by an examiner (61). Logically, there might be a discordance between the PtGA and the PhGA/EGA because variables that influence the examiner assessment differ from those involved in the patient self-assessment (57).

Biomarkers are objective indicators of biological and pathological processes that can be measured in patients to make a diagnosis, monitor the disease process and develop a prognosis (62). Currently, numerous biomarkers, specific and non-specific, are used for RA disease determination. ESR and CRP are general inflammation indicators, but they are most often used in RA patients (63).

In conclusion, all the above-mentioned assessment methods for RA disease activity can be evaluated separately, but they are usually part of composite indices (36).

1.5.1. Composite indices

Given the nature of RA, there is still no diagnostic RA "gold standard" to assess disease activity. This is the major factor that has motivated researchers to develop composite indices by combining different single disease activity measures summarizing the results into one number. These indices have been shown to be very useful in clinical trials and for patient follow-up as well; additionally, indices have demonstrated similarity with each other and have been selected as traditional measures of disease activity in clinical trials and clinical practice (4,36,44,64-68).

In 1990, Van der Heijde et al. developed the Disease Activity Score (DAS), which is the most commonly used index in routine clinical practice, merging joint count, acute phase reactants and PtGA (69). The reduced variant with the 28-joint count has been shown to be valid and as reliable as the original DAS, which is based on a 44-joint count (44). Currently, DAS28 is broadly accepted as a disease activity measure, showing correlations with other RA disease dimensions such as physical function, radiological damage, and quality of life (70-75). However, there are some obstacles to using DAS28 in everyday clinical practice, especially in situations when ESR or CRP is not available. Thus, in the search for simpler RA disease activity measures, researchers have continued to develop other composite indices (3,67,76,77). The Disease Activity Index for Reactive Arthritis (DAREA) was the first index shown to be valid and sensitive to change in patients with reactive arthritis for which the summary of different single disease activity measures is done without the need for a computer or calculator (76). Later, this concept was applied to RA patients, and SDAI, based on DAREA, was developed, consisting of the linear sum of 28 tender and swollen joints, PtGA of disease activity, PhGA, and CRP (45). However, given that laboratory analysis results are not available in certain settings, and the contribution of CRP to SDAI was shown to be only 21%, another composite instrument, the CDAI, was developed in 2005 (46). The CDAI is similar to the SDAI but does not involve lab tests, i.e., ESR or CRP (46). Nevertheless, joint counts remained in the CDAI, and it was argued that this instrument remains unsatisfactory for application in clinical practice (78).

Therefore, in recent years, and particularly in very busy clinical settings, the need for less time-consuming disease activity measures has increased. Moreover, consideration of the patient's perspective of their disease, measured via Patient-report outcome (PRO) measures, which are obtained without any input from healthcare professionals or other personnel, has greatly increased in the past decade (35). PRO measures are usually obtained through questionnaires, symptom ratings, treatment effects, or measurement of the impact of the disease on patient quality of life (QoL) (79). For RA, PRO measures include different components of RA disease, such as pain, fatigue, quality of life, morning stiffness, and others (80). In terms of measuring disease activity, PRO measures have drawn attention, and their application in clinical practice is increasing and becoming more feasible (77,81). In addition, some instruments better predict mortality than other instruments (82). One must bear in mind that certain instruments were developed to monitor patients in everyday clinical practice and not as a substitution for traditional measures of disease activity (35). Although in most cases these measures include

patient-oriented evaluation of pain, physical function and overall disease, the challenge of determining which instrument should be applied to an individual patient in clinical practice remains (80). The criteria for an effective instrument are generally that it must be easy to administer and score and it must provide results that can be interpreted simply, enabling its use in both clinical trials and everyday practice (83). In addition, the instrument must fulfil psychometric properties such as being reliable, able to be validated and responsive to change (35).

Recently, Hendrix et al identified 17 PRO measures of disease activity identified by consensus-based standards for the selection of health measurement instruments. Among them, RAPID3, Rheumatoid Arthritis Disease Activity Index-5 (RADAI-5), Rheumatoid Arthritis Disease Activity Index (RADAI) and Patients'-Disease Activity Index 28 (Pt-DAS28) are the most suitable PRO measurements of disease activity since they had the best measurement properties (77).

ACR also recommended measures that best reflect disease activity (84). Following a multistep process, the ACR working group identified disease activity instruments that categorize the level of a patient's disease activity as remission, low, moderate and high. The 2012 ACR core data included: patient-reported indices - Patient Activity Scale (PAS, PAS-II9 and Routine Assessment of Patient Index Joint (RAPID3)); patient-reported with the addition of provider assessment - CDAI; and patient-reported, provider assessment and laboratory exams - DAS and DAS28 (84).

Among these disease activity measures, RAPID3, is the only instrument proposed by both the ACR2012 core data set and by the systematic review from Handrix et al. (77,84). Numerous 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 an instrument (reliability, validity and categorizing patients into various stages of disease activity) (3,4,68,85-91). Other studies have shown that RAPID3 can also be used to measure disease activity for rheumatic diseases other than RA (92-95). Moreover, the correlation of RAPID3 with other clinical features is evident (96), and a recent study showed that RAPID3 is a good predictor of radiographic changes (85).

Morning stiffness is one of the earliest RA symptoms (80), but it is also a characteristic of other rheumatic diseases. Therefore, it was not included in 2010 ACR RA classification criteria (30). The pathway underlying morning stiffness, which includes many biological processes and

immune responses explained elsewhere, causes the accumulation of fluid in the joints and periarticular structures affected by inflammation. “Gel phenomenon” is a term that is often used to describe morning stiffness because the fluid inside the joint becomes dense, resulting in limited joint movement (14). Patients usually refer to stiffness as pain, limited range of motion or even weakness. Therefore, the clinician must be very clear in asking questions to gain precise information regarding the dimension of morning stiffness the patient refers to in terms of duration, intensity, timing or/and localization. Although the inclusion of morning stiffness in research has been questionable, the OMERACT 11 conference reached a consensus that morning stiffness is a symptom that must be measured in RA patients (97). Moreover, studies have shown an association between morning stiffness and other RA measurements, based either on intensity or duration (96,98).

Thus, once a patient is diagnosed with RA, further quantification is needed, including clinical measures (32), and the assessment of disease activity, pain, physical function, global health, quality of life, fatigue, and other parameters (64).

1.6. Assessment of physical function

According to PROMIS as cited by Bruce B *et al*, “*Physical function is ability to carry out various activities that require physical capability, ranging from self-care (basic activities of daily living (ADL)) to more –vigorous activities that require increasing degree of mobility, strength or endurance*” (99). Bearing in mind that RA has a large impact on all components of physical function, causing functional limitation and disability, the ACR has listed physical function assessment as one of the main outcomes in RA patients (34). The physical function can be assessed by performance-based measures, observation and PRO measures. The performance-based measures are tasks which the patients have to fulfill in the given period of time, while observation is a method in which clinician carry out formal evaluation of performing given tasks (100). Performance-based measurements have not been shown to be sensitive in RA patients and therefore are not listed in the ACR core data set (100), while PRO measures are the most extensive measures for assessing functional disability in patients with RA because these measurements best reflect a patient’s physical (dis)ability (101).

In RA, function can be measured in a disease-specific manner or in general; both measurements are valuable in clinical trials and sensitive to change (100). The literature provides various instruments. However, the most widely described functional disability instrument used in RA patients is the Stanford Health Assessment Questionnaire (HAQ), which is reliable and a valid

self-report. The HAQ was developed in 1978 (102). At the beginning, this instrument was developed as a generic instrument, but it was validated in RA patients, and its multiple uses as mentioned above have resulted in its classification as a disease-specific instrument; the HAQ remains the instrument of choice in assessing RA patient functional status (103). Initially, the instrument consisted of 41 questions, which made it rather impractical for use. This led researchers to shorten the instrument and use only the components that refer to disability, comprising 20 questions in 8 domains. This new Health Assessment Questionnaire - disability index (HAQ-DI) has become feasible for everyday clinical practice and currently is often referred to only as the "HAQ" (104). The reliability and validity of the HAQ-DI have been broadly documented, showing correlations with other RA measures (72,75,105-108). Although use of the HAQ-DI is accepted, other instruments have occasionally been developed as derivatives of the HAQ. The most common measurements originating from the HAQ are the Modified HAQ, Multidimensional HAQ (MDHAQ) and HAQII. All three instruments involve a reduced number of questions: the Modified HAQ contains only eight questions, specifically one question for each of eight domains, while the MDHAQ and HAQ II each consist of 10 questions (109). The MDHAQ is two-sided instrument, in which the first page is RAPID3 (110).

1.7. Assessment of quality of life

Bearing in mind that RA is a multidimensional disease with a large impact on physical, functional, social and emotional well-being, the need to measure QoL in RA has always been of great importance (111,112). To quantify a patient's perception of the disease in terms of their QoL, a variety of Health-related quality of life (HRQoL) instruments are used. Some of these instruments are generic, e.g., the Sickness Impact Profile (SIP), Short Form-36 (SF-36), EUROQOL-5D (EQ-5D) or the Nottingham Health Profile (NHP), while some are disease-specific, but both types usually assess different health dimensions (111). One characteristic of generic instruments is that they can be used across different diseases as well as in the normal population. Generic instruments encompass a wider range of health issues but are sufficient to reflect the impact of disease on an individual's health (113). Moreover, generic instruments are categorized as general health status instruments, such as SF-36, SIP, and NHP, which assess each health dimension (114), or as health utility measures, such as EQ-5D, HUI, and SF-6D, which summarize different health domains into a single value (115). SF-36, the most widely used generic instrument, assesses physical and mental health using 36 questions across eight health subscales and was validated in RA patients (112). The SIP questionnaire, which covers

14 health domains in 189 questions, is less frequently used, as well as NHP, a six-dimension instrument, is not often used in RA patients (116).

Given its short administration time and ease of use, the EQ-5D is the most commonly used HRQoL instrument for rheumatic diseases, capturing a patient's health across five domains (117). This instrument is also widely used and validated in RA patients (75,118-123). The main feature of this instrument is that it can be used either as a HRQoL or as a utility measure (122).

In addition to general instruments, disease-specific quality of life instruments such as the Arthritis Impact Measurement scales (AIMS2) and the Rheumatoid Arthritis Quality of life Questionnaire (RAQoL) are commonly used, describing specific and important concerns of patients (124).

1.8. Structural damage

In RA, joint damage and disability increase with disease progression (125). Plain radiography of the hands and feet is a standardized technique used to assess structural damage to follow disease progress and to assess treatment effects. To quantify this information, different scoring methods, both global and detailed, have been developed (126). Radiographic scoring, which involves global changes as classified by Steinbrocker et al., is acceptable for assessing damage in trials with non-radiological primary outcomes (127). Published evidence indicates a link between joint damage disease activity and functional disability: an increase in joint damage is associated with an increase in disability over time (71,72,85,128-131). In addition to classical radiography, other techniques such as magnetic resonance imaging (MRI) and ultrasound (US) are used to assess structural changes in RA patients (132).

1.9. Assessment hand function in RA

The hand has a complex anatomical structure, enabling functional multiplicity. Given its complexity, sensitivity and motor perfection, hand use in everyday life is unavoidable. Hence, hand dysfunction, an important component of disability, truly compromises a person's well-being (133).

In RA, hand involvement is evident in the early stages of the disease (134). Disease manifestations such as pain, stiffness, and swelling, especially at the MCP, PIP and wrist, can occur, causing functional limitations in hand movement. Throughout the course of the disease, in addition to the destruction of the joints, the surrounding tissue including the ligaments, tendons and muscles is also affected, causing irreversible joint deformities such as ulnar

deviation of the MCP joints, “button whole” deformity, and “swan neck” deformity (134). Therefore, to assess RA progression, it is highly important to complete a proper hand examination measuring all necessary components of hand function (135).

According to their research, Horsten et al. proposed that hand assessment should be carried out during early disease, even when patients do not report problems with their hands (136). Similar to the examination of other parts of the body, the first step of hand assessment is a detailed physical examination. A patient’s history, hand inspection focusing on joint deformities, skin condition and nodules, palpation to assess tender and swollen joints, examination of the active joint range of motion, joint stability, grip strength, and the examination of daily activities are the components of a hand assessment in RA patients (134,137).

Based on the hand’s complexity and the consequences of functional loss in RA disease, the literature provides a range of valid and sensitive measurement tools for each component of hand function that are being used in clinical trials and everyday practice. It is difficult to choose the best assessment method; however, clinicians and researchers should base their choice on the fulfillment of instrument properties that have been adequately tested and presented in the literature (35,138).

Based on a patient’s history, we can evaluate the presentation of a patient pain and morning stiffness, as described previously. Pain is usually measured by the VAS scale, while the duration of morning stiffness is the component that is most frequently reported (36,97). Moreover, joint examination is one of the core clinical outcomes in RA patients, providing us with disease activity based on counting the number of tender and swollen joints (42). However, further examination should be performed to obtain a full clinical picture of RA.

Range of motion is another parameter in the measurement of hand function in RA patients. Active and passive range of motion can be measured, but in RA patients, the assessment of active range of motion is recommended, although this measurement has not been demonstrated to be reliable for hand function in RA patients (139,140). There are different measurement tools (e.g., goniometer, ruler/tape measure, solder wire, etc.) and methods (goniometry, composite range of motion, pulp-to-palm distance), of which we emphasize pulp-to-palm distance as a simple, valuable and quick measurement that gives us useful information related to function (139,141). Moreover, other range of motion measures include the Joint Alignment and Motion scale (JAM scale), which is based on the percentage of loss of normal range of motion and alignment, ranging from 0-4, given as a single number, by calculating the average value of the

joints. The JAM scale has shown good correlation with disease activity, radiological damage and function (142). In addition, Eberhardt et al. presented another measurement method for functional impairment called Signals of Functional Impairment (SOFI). SOFI is based on a patient's performance and consists of three parts: upper limb, hand and lower limb. This instrument is reliable, valid and sensitive to change, and it can be used with all three designated parts or separately (143).

Hand function is primarily influenced by grip strength, and given the frequency of hand involvement in RA patients, diminished grip strength in these patients is expected compared to that of a healthy population (144). Therefore, in RA patients, assessment of grip strength is part of the clinical evaluation, regardless of disease stage (145,146). Moreover, the literature provides sufficient evidence of correlation between grip strength and disease activity measurements, showing that disease activity impacts grip strength (72,74,128,147-151), whereas grip strength impacts functional disability (72,74,108,146,148,150-152). Several instruments are used to measure grip strength, such as hydraulic, pneumatic and digital dynamometers. The most commonly used instrument is the hydraulic dynamometer (Jamar, North Coast), while pneumatic dynamometers actually measure grip pressure, not grip strength (153). In addition to muscle strength, hand thermography measurements can be added to provide additional physiological information (154).

Taking into consideration that ROM and grip strength do not capture all the functional abilities of the hand, and given that the key interest of clinicians is to improve function and quality of life, further assessment of hand function is needed (155). In everyday practice, standardized performance (observational)-based functional instruments or patient-report-based instruments can measure the functional ability of the hand. Observational instruments assess the performance of specific tasks, with or without any equipment, while patient-report-based functional instruments assess a patient's interpretation of hand function (156,157). Poole has summarized hand functional tests, both performance and patient-reported, in RA patients, describing the main characteristics of test measurements, number of items, reliability, validity and responsiveness of each test (134). The only test not listed by Poole is SOFI, a performance-based test that has been validated in RA patients (143,149,158).

In addition, studies have described anthropometric measurements of the hand, although there have been controversial conclusions regarding the relationships between simple anthropometric measures and grip strength (146,159).

According to Dellhag et al., measurements of grip strength and ROM deficits as well as measurements of activities of daily living (ADL) ability are useful in predicting a patient's actual hand function and self-estimated hand function (160). Furthermore, when presenting SOFI, Eberhardt et al. stated that SOFI could not be used without HAQ for complete hand functional assessment (143). Another author suggested that grip strength and pinch measurements should be included in the follow-up of patients with RA (147). Therefore, there is still no consensus regarding which instrument is optimal for hand evaluation in RA patients, particularly if we desire to include all components of the hand.

Nevertheless, the factors that influence RA outcome cannot be overlooked. Gender differences are obvious in RA patients: the disease has a somewhat different impact in women compared to men (148,161,162). Moreover, there are differing opinions relating to age, which is another indicator of RA severity (163,164). Disease duration has a large impact on outcome. The cumulative effects of disease activity are accompanied by worsening functional disability and quality of life (165,166). Other factors that impact RA are socioeconomic status, which correlates with disease activity and gross domestic product (GDP), and level of education, which has a great impact on the clinical outcome of RA (167-169).

Currently, overweight status and obesity are general health issues, and some researchers have included body mass index (BMI) as a factor that influences RA, although debatable results have been presented (170-174). Naturally, other factors such as genetics and the environment contribute to RA disease severity (175).

Therefore, given differing conclusions related to outcome measures in RA patients, the need for an instrument that provides fulfilling and significant information on RA disease is increasing; specifically, disease activity is the essential measurement in RA that affects all other outcomes (36). We hypothesize that disease activity measured by simple disease activity index RAPID3 is a valuable tool that reflects physical function of the hand and quality of life in patients with RA, since RAPID3 consists of the physical function part which embraces 7 tasks that require hand use (194), as well as parts for pain assessment and patient estimate of global health, dimensions of health which are also usually assessed by quality of life instruments. Thus, the aim of this work is to explore whether RAPID3, a novel, simple disease activity index, can measure both hand function and quality of life.

1. AIMS OF THE STUDY

The general aim is to evaluate a simple test for disease activity (RAPID3) and determine its association with hand functional ability and quality of life in patients with (RA).

Specific aims are:

To determine the validity of RAPID3 as an index that reflects the level of functional disability measured by a disease-specific questionnaire (Health Assessment Questionnaire-Disability Index – HAQ-DI) in patients with RA.

To determine the validity of RAPID3 as an index that reflects a hand-related instrument (SOFI), grip strength, and fist formation (pulp-to-palm distance) in patients with RA.

To determine how well a simple disease activity measure, RAPID3, reflects quality of life (QoL) in patients with RA.

Additionally, it will be possible to determine the impacts of hand functional ability, grip strength and pulp-to-palm distance on quality of life in patients with RA.

2. PATIENTS AND METHODS

3.1. Patients

The study was approved by the Ethics Committee of the University Clinical Center of Kosovo and was conducted in accordance with the principles of the Declaration of Helsinki. The study is cross-sectional study.

During the period between September 2013 and July 2014, sixty-eight consecutive RA patients participated in the study during their outpatient visit at the Rheumatology Clinic, University Clinical Center of Kosovo. Experienced physiotherapists, always in the presence of the same rheumatologist, conducted the research. The rheumatologist also introduced the researcher to the patient. RA patients who fulfilled inclusion criteria were invited to take part in the study. The inclusion criteria were: patients of both genders aged 18-75 years, with a diagnosis established by the ACR/EULAR 2010 criteria for RA; disease duration of at least 6 months; and no change in disease-modified anti-rheumatic drugs (DMARDs) and glucocorticoids within the last 3 months. The exclusion criteria were: patients who had previous hand surgical interventions; present or previous fractures of the hand; patients who attended physical therapy within the previous month; severe neurologic disease; severe renal or hepatic insufficiency; severe cardiac insufficiency (NYHA III or IV); malignant disease with the exception of non-melanoma skin cancer; severe psychiatric disease; congenital physical malformation of the hand; and psoriasis or other skin defect of the hand compromising hand function. 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.

3.1.2 Healthy controls

As we did not have normative data for grip strength in the Albanian population and to support previous findings regarding grip strength in RA patients, we compared the grip strength of our patients with selected age and gender matched participants. The latter were employees from the Labor Institute or were drawn from a circle of friends, age subgroups being as follows: <40 years, 40-59 years and ≥60years. Normative matches were selected if they did not report any type of hand problem or other health conditions listed in the exclusion criteria. In table 2 are presented mean values and standard deviations of grip strength in RA patients and healthy controls, stratified by gender and age groups.

Table 2. Grip strength characteristics of RA patients and healthy controls stratified by gender and age-groups.

		RA patients	SD	Healthy controls	SD
Total	n	mean grip strength (kg)		mean grip strength (kg)	
	68	16.55	8.38	30.26	5.21
Gender					
Female	58	14.86	7.23	29.50	4.69
Male	10	26.35	8.17	34.85	5.83
Age-groups (years)					
<40	10	16.15	7.13	33.35	7.18
40-49	12	18.41	6.96	32.41	3.67
50-59	21	18.41	9.11	30.83	3.84
≥60	25	14.26	8.68	27.54	6.21

n, number of subjects; RA, rheumatoid arthritis; SD, standard deviation; kg, kilograms;

3.2. Methods

Patient data consisting of demographic and clinical characteristics were recorded on an examination sheet. Demographic data consisted of information on gender (female/male), age (year when the patient was born), employment status, marital status, education level, family history regarding RA, duration of the disease, and hand dominance.
The clinical data consisted of duration of morning stiffness, disease activity data, pain assessment, hand function data, quality of life data, level of deformity, level of structural changes and drug intake. Specific anthropometric parameters such as body height, body weight, hand length and hand circumference were measured as well.

We used patient-reported outcome measures to assess different RA disease components. RAPID3 (176) was the main questionnaire used for disease activity, HAQ-DI (106) for functional ability and EQ-5D-3L (177) for QoL. For each questionnaire, the researcher obtained the authors' approval. The EUROQOL group supplied us with the Albanian version of the EQ-5D-3L questionnaire, while RAPID3 and HAQ-DI were translated into Albanian by professional translators. The translation process was as follows: two professional translators, native in Albanian, translated the original questionnaires from English into Albanian. The interpreters/translators and researcher went through the translations to integrate the two translated questionnaires in one (producing one common translation). Afterwards, two individuals, native in English and unfamiliar with the questionnaires, translated the obtained common questionnaire from Albanian into English. An expert committee consisting of one rheumatologist, one doctor of Physical Medicine and Rehabilitation and two experienced physiotherapists reviewed all translations, comparing the back translations with the original questionnaires to confirm the consistency between them. Pre-final versions were created with the following minor change: in the HAQ-DI questionnaire, in the question "Are you able to: Reach and get down a 5-pound object (such as a bag of sugar) from above your head?", the measurement unit was changed from pound to kg and recalculated accordingly (178). Therefore, we used "2-kg" instead of "5-pound".
Additionally, a pre-test was performed with 12 patients who were native in Albanian (9 f, 3 m) and recruited at the Rheumatologic Clinic University Clinical Centre of Kosovo one month before the study began. Data were collected through face-to-face interviews (179). The patients were asked to read the questions carefully, and if they came across any obscurity, they were invited to point it out and comment on it. Each patient was asked: "Do you understand the questions?" and "Do you have any difficulties in understanding the response options?" Since

all questions and response options were clearly understood, there was no need for further modifications, and we decided to use the translated questionnaires for our study. We decided to collect our data face-to-face because our patients are not very familiar with PROs and to minimize any missing information or unclear questions during the research interview. It has been shown that face-to-face interviews reduce the probability of unanswered questions, and the quality of the responses is quite good. Furthermore, face-to-face interviews are a good method for data collection among illiterate and elderly populations (179). During the examination, the interviewer reads each question and the reply options out loud, recording the responses that are most suitable for the patient.
The questionnaires used in the study were attached to examination sheet and are presented in Appendix 1.

3.2.1 Morning stiffness

Morning stiffness, a common symptom in patients with inflammatory rheumatic diseases, was assessed for its duration recorded in minutes by asking the question: "Do you experience stiffness in your joint from the time of waking up? If so, how long does morning stiffness last until full functioning (as much as you can)?" (96,180). For statistical analysis, the patients were divided into two categories according the duration of morning stiffness: less (<) or (>) than 60 minutes.

3.2.2. Disease activity

To assess disease activity, we used the number of swollen and painful joints (42), DAS28 (44) and RAPID3 (5).

Number of swollen and painful joints generally serves as a common measure in patients with RA and is usually assessed by experienced professionals (38). In our study, the same rheumatologist ascertained the number of swollen and painful joints in six joint areas, specifically the shoulder, elbow, wrist, MCP, PIP and knee, on both sides for a total of 28 joints. To assess a tender joint, the examiner palpated the joint with enough pressure until the examiner's thumb and index finger nail blanched. During the assessment of swollen joints, the examiner recorded only the joints that had soft tissue swelling or fluctuance, while bony deformities and hypertrophy were excluded (41,42).

Disease Activity Score (DAS) and the DAS28 modification are the most commonly used tools for measuring disease activity. Since DAS 28 is the most frequently used disease activity

measure in everyday clinical practice, we used it in our research. DAS28 consists of 28 tender joint counts, 28 swollen joint counts, erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) and the patient's global health assessment (45). The number of tender and swollen joints was ascertained by the same rheumatologist. In view of the fact that each patient at his/her visit provided us with recent (not more than one month old) ESR, DAS28 was calculated using this laboratory measure. A visual analog scale, consisting of a 100-mm horizontal line anchored with "Very well" on the left-hand side and "Very poor" on the right hand-side, was used to assess global health. The study participants were asked to mark the VAS between these endpoints, representing their general health today (44). The formula for DAS28 calculation is quite complicated, but in recent years different electronic calculators have been developed. In our study, DAS28 calculation was performed with the online calculator available at: http://www.das-score.nl/das28/DAScalculators/dasculators.html (181). The obtained result was recorded on the examination sheet. The range of values is from 0 to 10. The cut-off points are classified as remission < 2.6, low disease activity from ≥ 2.6 to < 3.2, moderate disease activity ≥ 3.2 to ≤ 5.1, and high disease activity > 5.1 (44).

Routine Assessment of Patient Index Data 3 (RAPID3) is a pure patient-reported outcome instrument that measures physical function, level of pain and patient global assessment of health. These are three of seven patient-reported measures from the American College of Rheumatology core data set. All questions include the state of the patient during the previous week. The physical function part consists of 12 questions on a 4-grade Likert scale ranging from "without difficulties" rated as zero (0) up to "unable to do it" rated as three (3). The researcher read the questions and the response options. Patients were asked to choose the option that best describes their condition. The answers were recorded on the structured questionnaire sheet. The scores of the physical function questions were added up, and the sum was converted using the formula in the right column and recorded. The questions regarding psychological distress were not included in the final score. The second part, assessment of pain, was presented in the form of 21 circles, and each circle had endpoints: no pain (0) up to pain as bad as it could be. Patients were asked about their pain using the questions presented in the circles, and they answered the question by filling in the circle that best represents their level of pain. The number below the marked circle was transcribed onto the determined spot on the right. To evaluate the third section, the patient's global assessment, patients were asked to answer the questions of how he/she was doing with illness and how the illness was affecting her/him within a given period of time by filling in one of 21 circles anchored with very well up to very bad. As with

pain evaluation, the number below the marked circle was transcribed onto the determined spot on the right for patient's global assessment. The sum of the three parts of the RAPID3, which can be determined in 5 seconds, ranging from 0 to 30, was recorded on the right side at the bottom of the page. The RAPID3 score is categorized as follows: high disease activity (greater than 12), moderate disease activity (6.1 to 12), low disease activity (3.1 to 6) and near-remission disease activity (3 or less) (4,5).

3.2.3. Pain evaluation

The intensity of pain in last 24 hours was evaluated by using a VAS scale (180) which is a 100-mm horizontal line defined from no pain (0) to pain as bad as it can be (100) as the anchors (53). The examiner explained the VAS scale components, and then the patients were asked to assess their pain intensity by marking on the line between the endpoints. The researcher measured the distance between the anchor "no pain" and the patient's mark with a ruler, and obtained result was recorded on the examination sheet (182).

3.2.4 Physical function

The *HAQ (Health Assessment Questionnaire)* is a patient-based instrument focused on five health dimensions: disability, pain and discomfort, drug side effects, costs and death. For the study, we used the most common version, a short version of the HAQ or the 2-page HAQ - Disability Index (HAQ-DI), the HAQ visual analogue (VAS) pain scale, and the VAS patient global health scale. The HAQ-DI assesses a patient's functional disability of the upper and lower extremities with 20 questions classified in eight categories applicable to the previous week: functioning - dressing; rising standing up; eating, walking; hygiene; reach; grip; and usual activities. The response options for each question are scaled from zero (without any difficulty) to three (unable to do). The HAQ-DI score ranges from 0 to 3: mild to moderate disability if the overall result is 0-1, moderate to severe disability from 1-2, and severe disability from 2-3. The HAQ VAS pain and VAS-GH scales are presented as separate horizontal lines, anchored with no pain (0) and (100) severe pain for VAS pain and best (0) and worst (100) for general health. Patients were asked to mark on the lines to describe their pain on the VAS pain line and general health on the GH VAS line, over the previous week. HAQ-DI scoring was carried out as presented in a paper by Bruce B and Fries J. The worst scores for each domain were summed, and the final result was obtained by dividing this sum by the number of domains that was addressed (104,106).

3.2.5. Hand function data

Grip strength was measured by a standardized technique to evaluate hand function (183). Grip strength measures the total of the static force that the hand produces while gripping, and the measurement units are kg. In our patients, grip strength was evaluated by using a hydraulic hand dynamometer (North Coast™ hydraulic hand dynamometer, North Coast Medical, Inc., Morgan Hill, CA, USA) (184). Instructions regarding the measurement technique were followed according to the American Association of Hand Therapy. During the examination, patients were in a sitting position with the arm in adduction, the elbow flexed to 90 degrees, and the forearm and wrist in neutral position (between supination and pronation). The hand dynamometer has five adjustable handle positions, of which the second one is the most reliable. Therefore, the handle on the dynamometer was placed in the second position. The examiner asked the patient to squeeze the dynamometer as much as he/she could, firstly with the dominant hand. Each hand was tested three times, with a one-minute time gap in between. The averages of three grips measured for the dominant hand and three grips for the non-dominant hand were documented (in kg) (185,186). To better understand the method used to measure grip strength, a photo illustration was given on the examination sheet (Appendix I).

Pulp-to-palm distance was used to measure the active ROM of total finger flexion. This is a quick, simple and valuable method to evaluate overall finger flexion. During the procedure, the distance between the pulp of fingers II-V and the palm is measured. For more accurate measurement, the palmar landmark was defined as a line that merges the ulnar end of the distal palmar crest with the radial end of the proximal palmar crest. During the evaluation, patients sat with their hands on a table, the arm in adduction, the elbow 90 degrees in flexion, and the forearm in a supine position. The examiner asked the patients to make a fist, aiming to touch the palm of the hand at a precise landmark, as previously explained. The distance between the pulp/fingertips and the palmar landmark was measured with a ruler, and the averages for the right and for the left hand were recorded in cm (187).

Signals of Functional Impairment (SOFI) was used to measure hand function. Altogether, this test consists of 11 items: four items relating to hand function, three items relating to arm function and four items relating to leg function. Each item is rated as follows: no impairment (0), slight to moderate impairment (1), and severe impairment (2), and the overall SOFI scores ranges from 0-44. In our study, we used items relating to hand function (SOFI-hand). The tasks for this part of the test involved asking our patients to grip a plastic tube, bend fingers around a

pencil, make a round pincer grip, and oppose the thumb to the base of the 5th finger. The overall results for the left and right hands ranged from 0-16. The original article contains an illustration of each item, and to better understand the tasks after verbal explanations, we showed illustrations of the items to patients (143).

The Joint Alignment and Motion (JAM) scale was used to measure joint ROM in a more structured manner. The JAM scale is a 0-4 point scale that measures the percentage of decrease in joint range of motion as well as joint misalignment; 0 indicates normal range of motion and alignment, 1 indicates 0-5% diminished range of motion, 2 indicates 6-25%, 3 indicates 26-75%, and 4 indicates a decrease in ROM of 76-100% or joint fusion or joint dislocation (142). Overall, the JAM scale includes the evaluation of 44 joints (upper and lower extremity bilaterally) for which the examiner visually determines the limitation of joint range of motion and joint alignment in approximately 5 minutes, providing a single numerical score (142). In our study, the examiner evaluated each hand joint (bilateral wrist, thumb IP joints, and proximal IP joints 2-5). The mean of 22 joints was added and recorded. For statistical analyses, our patients were stratified according to the JAM scale.

3.2.6. Quality of life

EUROQOL-5D-3L (EQ-5D-3L) was used to measure quality of life (QoL). EQ-5D-3L is a health-related quality of life (HRQoL) instrument developed by the EuroQoL group in 1990 and is also used as a utility measure (177). EQ-5D-3L is a generic HRQoL instrument that is used widely for different heath conditions (122,120,121). EQ-5D-3L consists of two parts: a descriptive system and a VAS scale. The descriptive system includes five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Under each domain, three "problem" levels are presented as answer options: level one, no problems; level two, moderate problems; and level three, extreme problems. Therefore, a health state for one patient measured by this instrument is a combination of a given level for each domain, resulting in a three-digit value. In total, there are 243 health states, which range from -0.594, defined as worse than death, to 1, defined as full health, according to the UK TTO value set (188). The patients were asked to value their health state today by marking the box for the most appropriate answer. The VAS scale consists of one vertical line anchored at the end with the worst health you can imagine marked as 0 and the best health you can imagine marked as 100. The examiner described the scale to the patients, and then the patient was asked to mark the line to describe their health (118).

EQ-5D-3L data can be presented as EQ-5D-3L health states, which are converted to a single EQ-5D-3L index value. There are various evaluation methods, among which time-trade-off (TTO) is the most widely employed. Since there is no EQ-5D-3L algorithm score in our country, EQ-5D-3L scoring in our patients was carried out according to the UK TTO 3L value set, which is the most widely used (188).

3.2.7. Anthropometric measures

Different measurement tools measure hand anthropometry. In our patients, forearm length, forearm circumference, hand length, and hand circumference were measured by using a standardized 1000-mm flexible measuring tape (189).

Hand length and hand circumference were measured from the midpoint of the distal wrist crease to the tip of the middle finger, while hand circumference was measured across the hand at the level of the MCP joints (189). During the measurement of hand length and hand circumference, patients were in a sitting position with hands on a table, the arm in adduction, elbow 90 degrees in flexion, forearm in a supine position, fingers II-IV extended and adducted, and the thumb in abduction.

Forearm length and forearm circumference were measured from the most prominent point of the olecranon to the processes styloideus radii and across the point at the level of 10 cm distal to the olecranon, respectively. Patients were in a sitting position with hands on a table, the arm in adducted to the trunk, elbow 90 degrees in flexion, and the forearm in a neutral position. The results obtained for the left and right hands were recorded on the examination sheet (190). The average value of both forearms was reported.

Patient height and weight were measured by conventional measures. Patient height was measured by a measuring tape, while patient weight was measured by weighting scales. Body mass index was then calculated using a patient's height and weight by the following formula: BMI=weight (kg)/height^2 (m) (191).

3.2.8. Radiographic evaluation

To assess structural damage in our patients, plain hand radiographs (posterior-anterior view) were performed at the Radiology Clinic, University Clinical Center of Kosovo. Eight patients have refused to do hand radiography, so that out of 68 patients, hand radiographs were performed for 60 patients. The radiographs were read by an experienced radiologist specializing

in skeletal radiology (Matej Mustapić, MD, PhD), who was blinded to all clinical data, at the University Clinical Centre Sestre Milosrdnice, Zagreb, Croatia. Although several radiographic scoring methods have been developed to quantify stages of structural damage, the Steinbrocker scale (method) was used in our study. This is a simple scoring method comprising four stages: stage I - minimal damage, or no destructive changes, but periarticular osteoporosis may be present; stage II - osteoporosis and minor damage of cartilage and subchondral bone; stage III - bone destruction and osteoporosis; and stage IV - severe damage, characterized with bony ankylosis. The stage was determined by the most severe change in any hand joint (127).

3.3. Statistical analysis

Sample size calculation

According to the last population census in 2011 Kosovo's total population is 1,739,825, and population older than 18 years is 1,147,779 (192). Table 3 presents determination of sample size necessary for this study. The required sample size was 136 (approximately 8.5% margin of error with 95% confidence), comprising of both RA patients and non-RA controls. Finally, data were collected from 68 RA patients and 68 age- and sex-matched healthy controls for the grip strength measurements.

Table 3. Determination of sample size.

Confidence level	95%	95%	95%
Confidence interval("Margin of Error")	10%	5%	8.4%
Sample size	96	383	136

Grouping the data

We grouped the variables into four groups: 1- socio-demographic and disease data; 2- hand function survey data (grip strength, pulp-to-palm distance, SOFI-hand) and overall functional data (HAQ-DI); 3- disease activity data (RAPID3, DAS28); and 4- quality of life data (EUROQOL-5D-3L). The relationship between any given data group was determined, and we evaluated how the first or second group predicts disease activity measured by RAPID3.

For statistical analysis, data were stratified by age, gender, disease duration, JAM scale, Steinbrocker scale, and morning stiffness.

Statistical techniques

We used the following descriptive statistics: mean, standard deviation, maximum, minimum, 25th and 75th percentile, for selected demographic and clinical characteristics of the patients. Correlation tests were performed between RA groups and controls for grip strength, between certain demographic data and clinical data, and between disease activity data, hand function data, and quality of life data. In some instances multiple regression was performed to assess the relationships between a number of selected variables and RAPID3 and EQ-5D-3L values.

For the correlation analysis between RAPID3 and other variables, the Pearson product-moment correlation coefficient was used, and inferred significance was based on the Student's t-test.

Then the correlation was used to test the relationships among RAPID3, DAS28, HAQ-DI, grip strength, SOFI-hand, pulp-to-palm distance and EQ-5D-3L in each of the subgroups stratified by gender, age, disease duration, JAM scale, Steinbrocker's scale and morning stiffness. The correlation analysis was also performed to compare selected anthropometric measures and grip strength between two subgroups stratified by gender. Moreover, multivariate regression analysis was performed to evaluate the relationships between a number of selected variables and RAPID3 and EQ-5D-3L values. STATA version 11 software was used for statistical analyses, and a STATA code was prepared for the conversion of QoL scores from the questionnaire into their respective EQ-5D-3L values. The significance level was set at 0.05.

3. RESULTS

4.1. Patient's demographic and clinical data

4.1.1. Demographic data.

The demographic characteristics of the patients are shown in Table 4. The study comprised 68 patients, 58 of which were female (85.30%), with a total mean age of 53.50 years and a mean disease duration of 9.60±7.90 years. Family history of RA was reported by 31.00% of patients. Dominant right handedness described 97.00% of RA patients. Regarding education level, 18.00% of RA patients were illiterate, 44.00% had an elementary education, 29.00% had a high-school education and 9.00% had a university education. Regarding employment, 84.00% of patients were unemployed.

Table 4. Demographic characteristics of the patients.

Variables (n=68)	n	%	Mean	SD	Median	Min	Max	p25	p75
Gender									
Female	58	85.30%							
Male	10								
Age (years)			53.50	11.60	56.50	21.00	71.00	47.00	62.50
Disease duration (years)			9.60	7.90	7.00	0.50	35.00	3.00	14.50
Dominant hand									
Right		97.00%							
Left		3.00%							
Employment status									
Employed		16.00%							
Unemployed		84.00%							
Education Level									
Functional illiterate		18.00%							
Elementary school		44.00%							
High school		29.00%							
University		9.00%							
Family History of RA									
Yes		31.00%							
No		69.00%							

n, number of participants; %, percentile of subjects; SD, standard deviation; min, minimum; max, maximum; p25, 25th percentile; p75, 75th percentile;

The mean ages of the RA patients included in the study stratified by gender are shown in figure 1. The mean age of female participants was 52.53 years, and the mean age of male participants was 58.90 years.

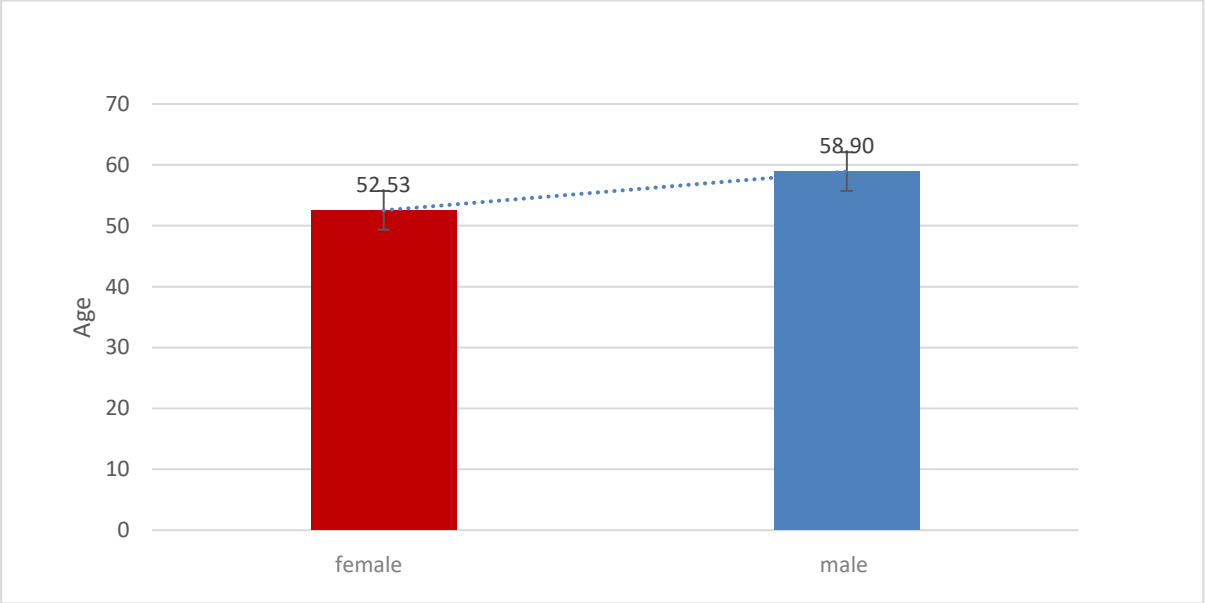


Figure 1. Average patient's age stratified by gender.

Average RAPID3 and DAS28 values stratified by employment status are shown in figure 2. The average RAPID3 and DAS28 values were lower in employed patients then in unemployed patients.

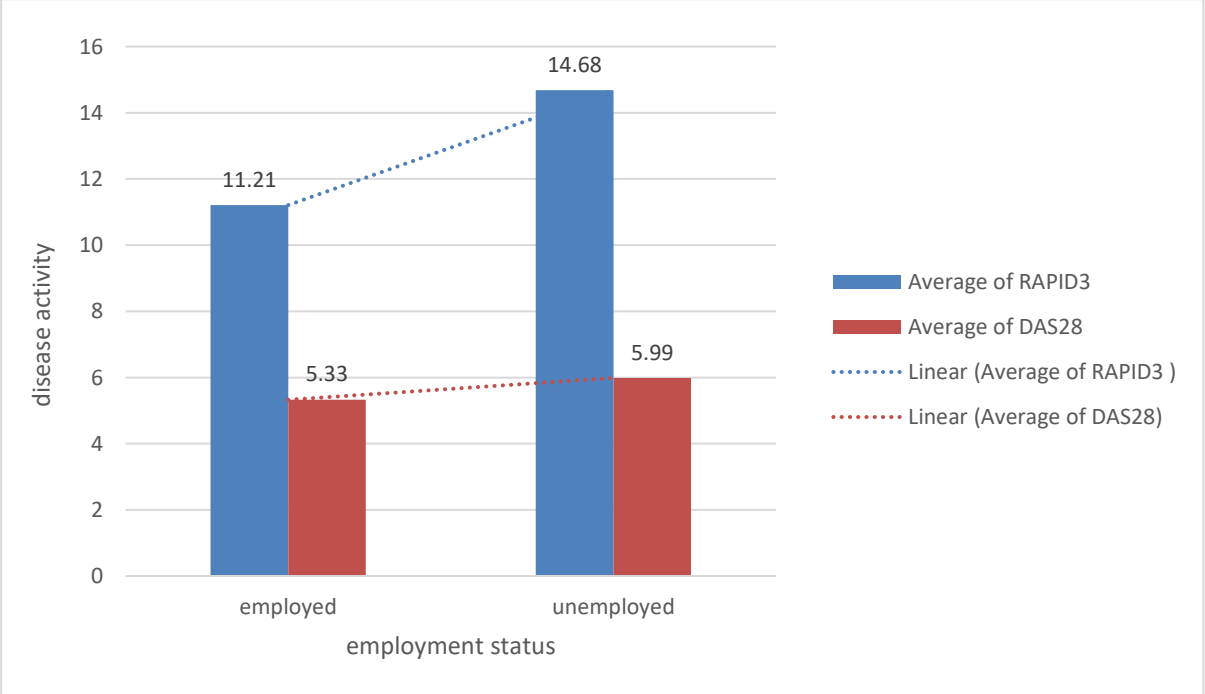


Figure 2. Average RAPID3 and DAS28 values stratified by employment.

Regarding education level, patients with a higher level of education had lower disease activity measured by RAPID3, as presented in figure 3. Additionally, disease activity measured by DAS28 was lowest in patients with a university degree compared to other educational levels.

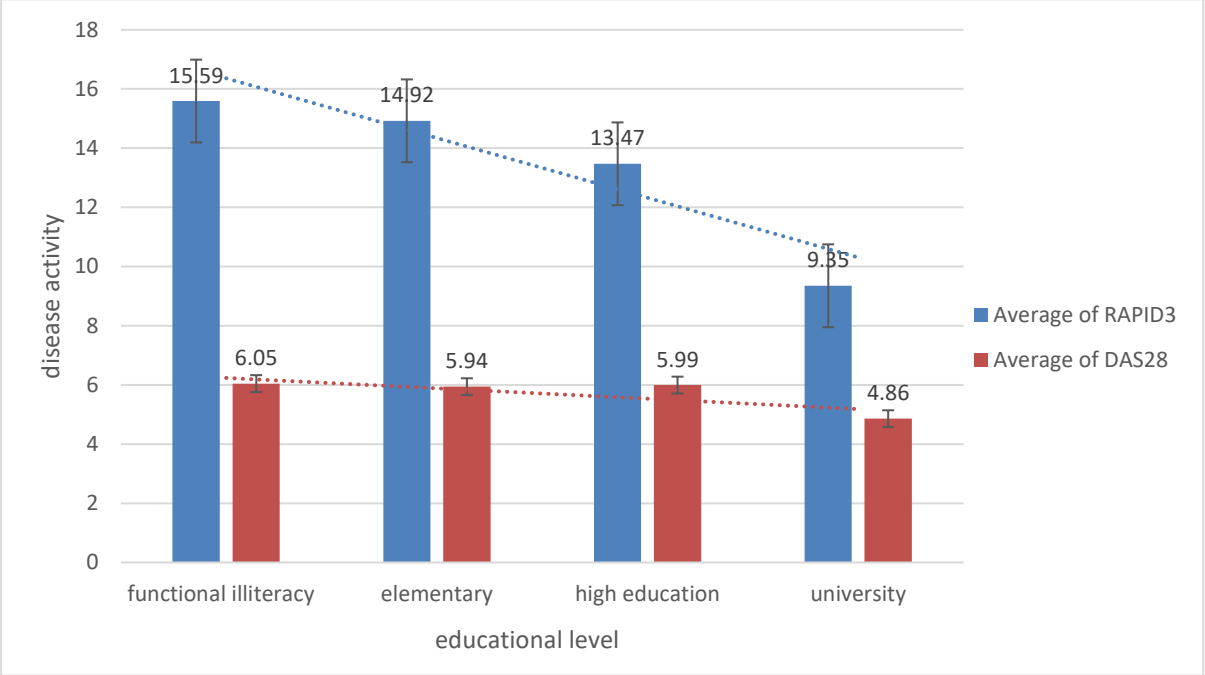


Figure 3. Average RAPID3 and DAS28 values stratified by educational level.

4.1.2 Clinical data

The clinical characteristics of the patients are shown in Table 5. Patient clinical data consisted of disease activity data, hand function data, quality of life data, radiological evaluation, and pain evaluation. The mean values and standard deviations (shown in brackets) of RAPID3 disease activity, DAS28 disease activity, number of tender joints (TJC), number of swollen joints (SJC), morning stiffness, and VAS pain were as follows: 14.12 (± 5.21), 5.89 (±1.28), 14.26 (±7.36), 9.21(±5.74), and 59.47 (±20.09), respectively. The mean values of hand outcome measures were: grip strength, 16.55 (±8.38); HAQ-DI, 1.83(±0.74); SOFI hand, 4.58 (±3.90); and pulp-to-palm distance, 1.72 (±0.96). The mean EQ-5D-3L value was 0.44 (±0.22). The mean value of the JAM scale was 1.70 (±1.04), and the mean value of the Steinbrocker scale was 1.90 (±1.10).

Table 5. Clinical characteristics of the patients.

Variables (n=68)	Mean	SD	Median	Min	Max	p25	p75
Morning stiffness duration (minutes)	55.14	54.00	45.00	0.00	300.00	20.00	75.00
Tender joint count (0-28)	14.26	7.36	14.50	2.00	28.00	8.00	18.50
Swollen joint count (0-28)	9.21	5.74	8.00	2.00	28.00	4.50	13.00
RAPID3 (0-30)	14.12	5.21	13.75	1.50	24.50	11.10	18.40
DAS 28	5.89	1.28	6.11	2.69	8.21	5.08	6.77
HAQ-DI	1.83	0.74	1.94	0.25	3.00	1.32	2.38
VAS Pain (0-100mm)	59.47	20.09	55.00	10.00	95.00	45.00	74.50
Grip strength (kg)	16.55	8.38	15.00	2.00	41.00	10.50	22.50
Pulp-to-palm distance (cm)	1.72	0.96	1.80	0.25	4.40	1.10	2.05
SOFI-hand	4.58	3.90	4.00	0.00	15.00	2.00	6.00
EQ-5D-3L	0.44	0.22	0.51	0.06	0.80	0.23	0.62
EQ-VAS	47.23	21.51	50.00	7.00	94.00	30.50	59.75
JAM scale	2.10	1.04	2.00	1.00	4.00	1.00	3.00
Steinbrocker scale	1.90	1.10	1.50	1.00	4.00	1.00	2.50

n, number of subjects; SD, standard deviation; min, minimum; max, maximum; p25, 25th percentile; p75, 75th RAPID3, Routine Assessment of Patient Index Data 3; DAS28, Disease Activity Score 28; VAS, Visual Analog Scale; HAQ-DI, Health Assessment Questionnaire-Disability Index; EQ-5D-3L, EUROQOL-5D-3L; JAM scale, Joint Alignment and Motion scale;

Table 6 shows forearm and hand anthropometric measures, of which the mean values, standard deviations (shown in brackets) of forearm length, forearm circumference, hand length, and hand circumference were: 24.47 (±2.29) cm, 23.90 (±2.87) cm, 17.74 (±1.66) cm, and 20.41 (±1.48) cm, respectively.

Body mass index was calculated using each patient's weight (kg) height (m), and the mean value (standard deviation) was 26.89 (± 3.87) kg/m^2.

Table 6. Anthropometric measures.

Variables (n=68)	Mean	SD	Median	Min	Max	p25	p75
BMI (kg/m^2)	26.89	3.87	27.20	17.24	39.54	24.98	29.16
Forearm length (cm)	24.47	2.29	25.00	19.00	30.00	23.00	26.00
Forearm circumference (cm)	23.90	2.87	23.91	16.25	29.50	22.50	26.06
Hand length (cm)	17.74	1.66	18.00	10.25	21.00	17.00	19.00
Hand circumference (cm)	20.41	1.48	20.00	18.00	24.50	19.50	21.25

n, number of subjects; SD, standard deviation; min, minimum; max, maximum; p25, 25th percentile; p75, 75th percentile, BMI, body mass index;

Systemic pharmacological intake is presented in Table 7. Eighty-one percent of RA patients used disease-modifying anti-rheumatic drugs (DMARDs), 69% used oral glucocorticoids, 68% used non-steroidal anti-rheumatic drugs (NSAIDs) and 51% used plain analgesics.

Table 7. Use of pharmacological treatment.

Treatment drug	n=68	100%
Simple analgesics	35	51%
Non-steroidal antirheumatic drugs	46	68%
Disease modifying anti-rheumatic drugs	55	81%
Glucocorticoids (orally)	47	69%

n, number of subjects; %, percentage of patient use of pharmacological treatment;

Table 8 shows the mean values and standard deviations of the study variables adjusted for gender, age and disease duration. Considering gender, females (n=58) demonstrated higher

disease activity, greater pulp-to-palm distance and SOFI, worse quality of life, and greater reported pain, whereas men (n=10) had greater grip strength. The largest number of RA patients was found in the age group over 59 years (n=25); these patients had the highest values for disease activity, deteriorated function, greater reported pain and worse quality of life. Although mean RAPID3, DAS28, HAQ-DI and VAS pain values increased with patient age; this was not the case for mean SOFI, pulp-to-palm distance, grip strength and EQ-5D-3L values. Regarding disease duration, increased disease duration was accompanied by worsening hand function (SOFI-hand, grip strength and pulp-to-palm distance), pain (VAS) and quality of life (EQ-5D-3L). Patients with a disease duration over 20 years had the highest values for given clinical study parameters, while the highest mean RAPID3 and DAS28 values were in RA patients with a disease duration of 6-10 years; the mean HAQ-DI values for patients with disease durations of 6-10 years and more than 20 years were 2.06 and 2.09, respectively.

Table 8. RAPID3, DAS28, HAQ-DI, SOFI-hand, Grip strength, Pulp-to-palm distance, EQ-5D-3L and VAS pain stratified by gender, age, and disease duration.

		RAPID3		DAS28		HAQ-DI		SOFI-hand		Grip strength		Pulp-to-palm		VAS pain		EQ-5D-3L	
	n	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Total	68	14.12	5.21	5.89	1.28	1.83	0.74	4.58	3.90	16.55	8.38	1.72	0.96	59.47	20.09	0.44	0.22
Gender																	
Male	10	11.17	4.40	5.65	0.82	1.36	0.79	2.90	2.33	26.35	8.17	1.62	1.07	49.30	14.30	0.57	0.22
Female	58	14.63	5.20	5.92	1.35	1.91	0.71	4.88	4.03	14.86	7.23	1.74	0.95	61.22	20.50	0.42	0.22
Age (years)																	
<40	10	13.05	6.49	5.37	1.37	1.54	0.87	4.50	4.27	16.15	7.13	1.65	0.67	54.30	17.71	0.53	0.67
40-59	33	13.15	5.20	5.66	1.30	1.75	0.76	3.97	3.66	18.41	8.28	1.56	0.97	58.21	21.89	0.45	0.19
>59	25	15.83	4.37	6.30	1.14	2.05	0.62	5.44	3.99	14.26	8.68	1.97	1.05	63.32	18.32	0.38	0.25
Disease duration (years)																	
0-1	9	13.30	5.46	5.71	1.22	1.73	0.79	2.67	1.32	21.80	9.12	1.18	0.43	55.67	19.21	0.43	0.30
1-5	18	11.34	4.84	5.48	1.43	1.44	0.74	3.50	3.43	18.14	7.56	1.53	0.90	49.22	20.05	0.53	0.20
6-10	18	16.02	4.76	6.24	1.32	2.06	0.68	4.39	2.79	15.64	6.46	1.78	0.84	67.78	18.24	0.40	0.24
11-20	17	15.01	5.16	6.03	1.17	1.96	0.69	5.65	5.07	14.70	9.78	1.87	1.17	59.53	19.34	0.45	0.20
>20	6	15.50	5.24	5.83	1.13	2.09	0.71	8.33	4.23	11.92	8.19	2.48	1.12	70.83	17.00	0.29	0.19

n, number of participants, SD, standard deviation; RAPID3, Routine Assessment of Patient Index Data 3; DAS28, Disease Activity Score based on 28 joint evaluation; HAQ-DI, Health Assessment Questionnaire-Disability Index; SOFI-hand, Signal of Functional Impairment- hand; VAS, Visual Analog Scale; EQ-5D-3L, EUROQOL-5D-3L;

Table 9 shows the mean values of study variables adjusted for the JAM scale, Steinbrocker scale and duration of morning stiffness. No patient had a full range of motion (JAM scale=0). With decreased range of motion or alignment (JAM scale), disease activity measures (RAPID3 and DAS28) increased, an HAQ-DI functional disability deteriorated with decreased movement amplitude. Hand assessment measures indicated the deterioration of hand function with decreased ROM. In addition, QoL measured by EQ-5D-3L decrease. Regarding VAS pain over the previous 24 hours, there was a small difference between JAM scale 3 and JAM scale 4, and patients with limited ROM (JAM scale stage 3 or 4) reported more pain than patients with less ROM limitations (JAM scale stage 1 and 2).

Out of 68 patients, hand radiographs were performed for 60 patients. Among them, 30 patients were radiographic stage 1 according to the Steinbrocker classification, and the mean value and (standard deviations shown in brackets), of disease activity was higher RAPID3=14.31 (±4.84); DAS28=5.90 (±1.29) than in patients with radiographic stage 2; RAPID3=11.61 (±3.68); Das28=5.22 (±1.27). The mean RAPID3 value (standard deviations shown in brackets) for Steinbrocker scale 3 patients was 17.33 (±5.39), while patients who were Steinbrocker scale stage 4 had a mean RAPID3 value of 19.26 (±4.42). Moreover, the HAQ-DI mean value of patients with radiographic stage 1 was higher than that of patients with radiographic scale 2, while patients classified as Steinbrocker scale stage 3 and 4 reported HAQ-DI mean values (standard deviations shown in brackets) of 2.21 (±0.44) and 2.57 (±0.38), respectively. Regarding hand outcome measures (SOFI, grip strength, pulp-to-palm distance) and QoL measures (EQ-5D-3L), hand function and QoL deteriorated with increased radiologic stage. Regarding pain, patients with Steinbrocker stage 3 and 4 reported more pain than patients with Steinbrocker stage 1 and 2. Therefore, patients with Steinbrocker scale stage 1 demonstrated deteriorated disease activity, functional disability, pain and QoL compared to patients with Steinbrocker scale stage 2.

Regarding duration of morning stiffness, 42 patients reported a duration of morning stiffness less than 60 minutes. Patients with a duration of morning stiffness ≥ than 60 min had the highest disease activity and the worst quality of life. Furthermore, in addition to pulp-to-palm distance, HAQ-DI, SOFI-hand and grip strength values indicated that these patients had the most highly deteriorated hand function. Patients who reported a morning stiffness duration of < than 60 minutes also reported less pain VAS=55.19 (±20.17) in comparison to patients with morning stiffness ≥ than 60 minutes VAS=66.38 (±18.13).

Table 9. RAPID3, DAS28, HAQ-DI, SOFI-hand, Grip strength, Pulp-to-palm distance and EQ-5D-3L stratified by JAM scale, Steinbrocker's scale, and morning stiffness.

		RAPID3		DAS28		HAQ-DI		SOFI-hand		Grip strength		Pulp-to-palm		VAS pain		EQ-5D-3L	
	n	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Total	68	14.12	5.21	5.89	1.28	1.83	0.74	4.58	3.90	16.55	8.38	1.72	0.96	59.47	20.09	0.44	0.22
JAM scale																	
1	23	11.47	4.91	5.31	1.09	1.35	0.70	1.61	1.50	23.04	7.36	0.99	0.56	50.65	18.05	0.55	0.20
2	25	13.47	4.26	5.85	1.33	1.80	0.67	3.80	1.53	16.52	5.91	1.60	0.39	57.80	18.58	0.44	0.22
3	10	16.71	4.59	6.41	1.38	2.27	0.39	6.30	2.41	12.55	5.42	2.45	0.84	71.70	16.08	0.36	0.25
4	10	19.28	4.17	6.72	0.88	2.56	0.36	11.70	3.23	5.70	3.42	2.99	1.16	71.70	21.86	0.28	0.15
Steinbrocker scale																	
1	30	14.31	4.84	5.90	1.29	1.80	0.73	2.90	2.35	17.67	6.23	1.53	0.73	61.3	19.91	0.41	0.23
2	15	11.61	3.68	5.22	1.27	1.61	0.61	4.07	1.58	16.80	5.66	1.51	0.47	51.47	16.49	0.51	0.20
3	6	17.33	5.29	6.87	1.06	2.21	0.44	6.50	1.87	11.09	4.18	2.30	0.84	71.50	16.67	0.35	0.25
4	9	19.26	4.42	6.67	0.92	2.57	0.38	12.33	2.69	5.17	3.15	3.10	1.17	71.60	23.18	0.29	0.16
Morning stiffness																	
<60 min	42	12.84	4.99	5.54	1.26	1.69	0.73	3.95	3.49	18.11	8.24	1.54	0.91	55.19	20.17	0.50	0.21
≥60 min	26	16.19	4.95	6.43	1.14	2.04	0.73	5.62	4.30	14.04	8.14	2.02	1.00	66.38	18.13	0.34	1.22

n, number of subjects; RAPID3, Routine Assessment of Patient Index Data 3; DAS28, Disease Activity Score based on 28 joint evaluation; HAQ-DI Health Assessment Questionnaire-Disability Index; SOFI, Signal of Functional Impairment; VAS, Visual Analog Scale; JAM scale, Joint Alignment and Motion scale;

Average RAPID3 and DAS28 values stratified by gender and Steinbrocker scale are presented in figure 4, showing that the highest RAPID3 levels were observed in female patients classified as Steinbrocker stage 4. The highest RAPID3 levels in male patients were observed in those categorized as Steinbrocker stage 3, although there were no male patients categorized as Steinbrocker stage 2 or 4.

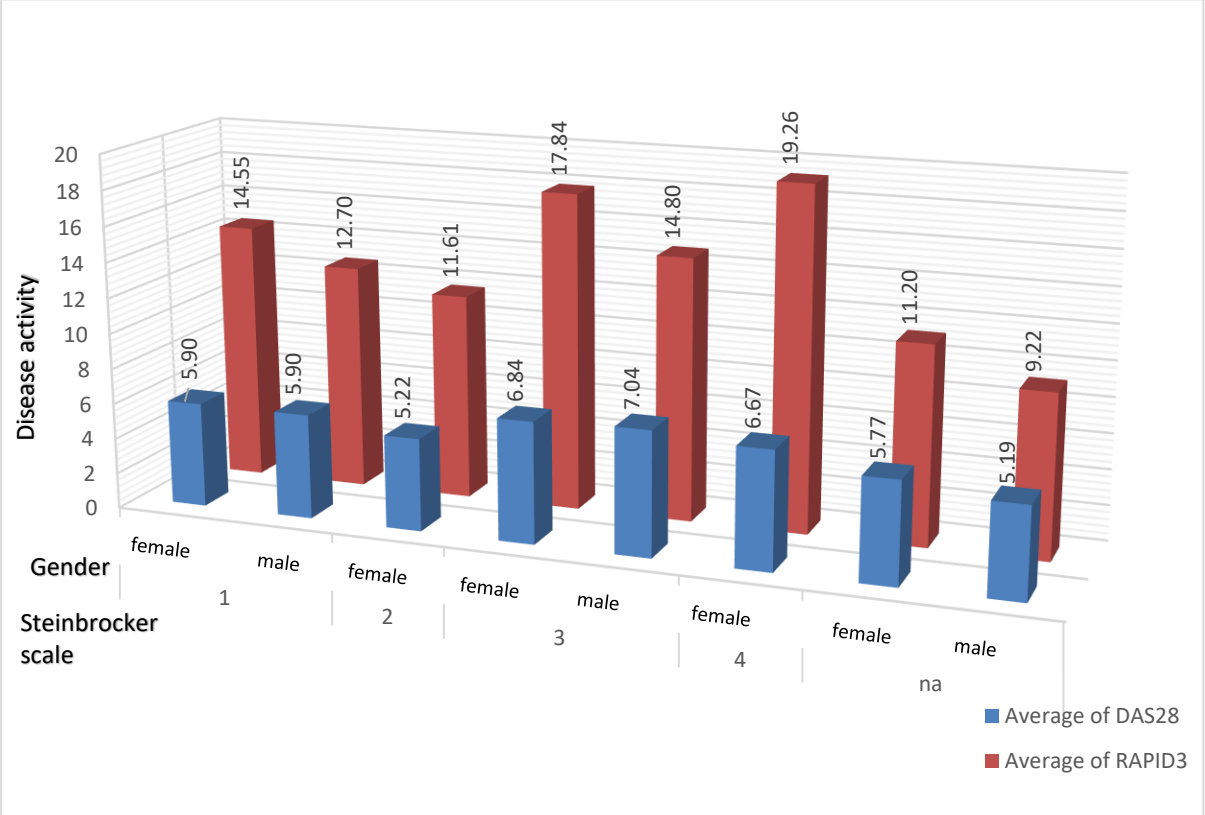


Figure 4. Average RAPID3 and DAS28 values stratified by Steinbrocker's scale and gender.

Average EQ-5D-3L and HAQ-DI values stratified by gender and Steinbrocker's scale are presented in Figure 5, showing that female patients classified higher on the Steinbrocker scale reported very severe functional disability, while the same patients also demonstrated the most deteriorated quality of life.

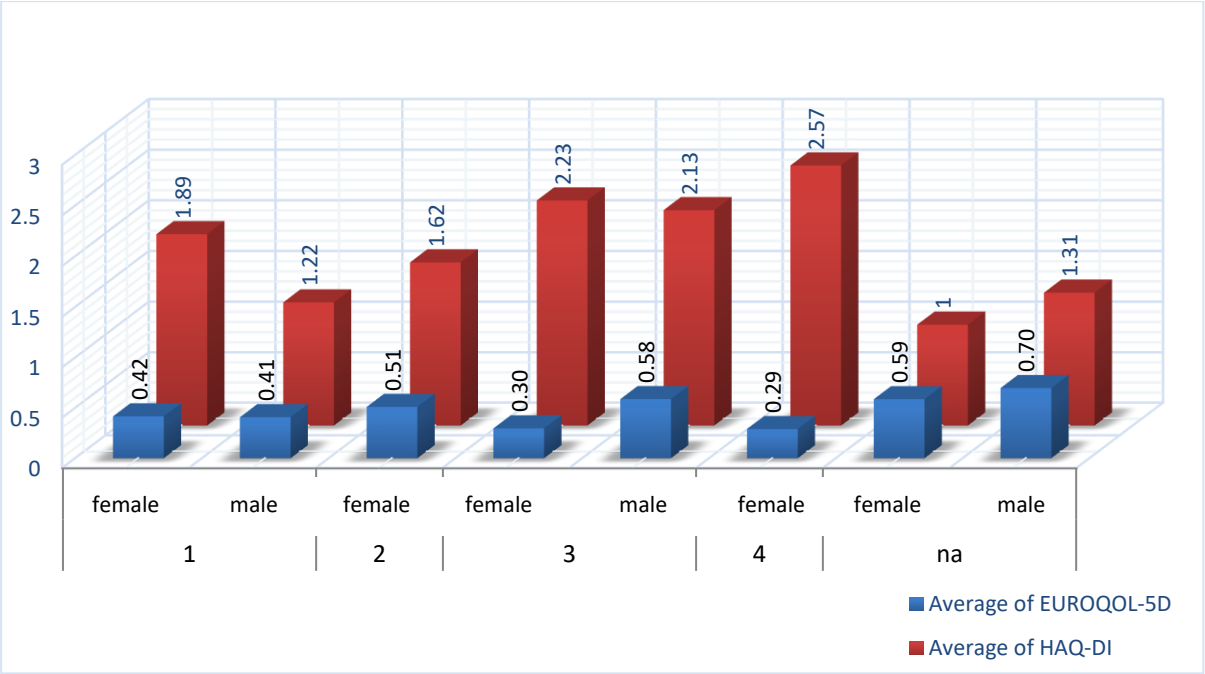


Figure 5. Average of EQ-5D-3L and HAQ-DI by Steinbrocker's scale and gender.

The mean values for hand function data (grip strength, SOFI-hand and pulp-to-palm distance) stratified by gender and Steinbrocker's scale are shown in figure 6. Male participants had better grip strength and SOFI-hand results than females, while pulp-to-palm distance was better in female patients than in male patients.

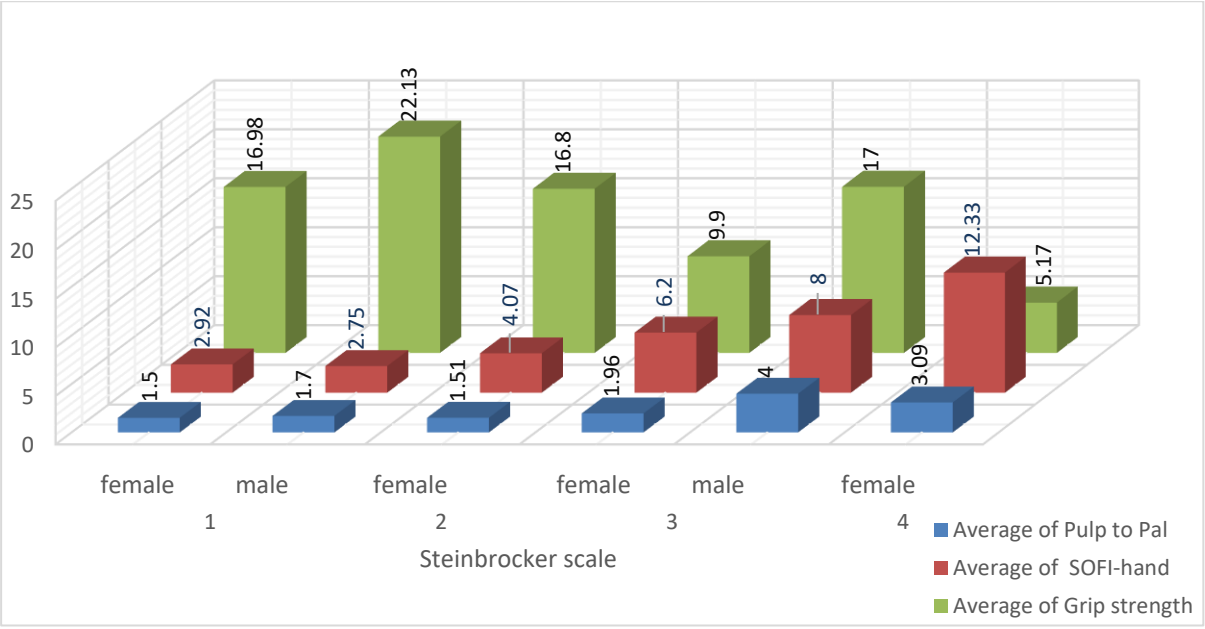


Figure 6. Average grip strength, SOFI-hand and pulp-to-palm distance values stratified by gender and Steinbrocker's scale.

4.2. Correlations analysis

Correlation analyses between disease activity data, hand function data, quality of life, and pain with age, gender, educational level, disease duration, JAM scale, and morning stiffness are presented in table 10. We analyzed relationships between disease activity measured by RAPID3 and DAS28, functional disability (HAQ-DI), hand function (grip strength, SOFI-hand, pulp-to-palm distance), QoL (EQ-5D-3L) and pain (VAS) as crude results and presented in table 11. We analyzed relationships between the components of RAPID3 (RAPID3 physical function, RAPID3 pain and RAPID3 global health) and hand function (grip strength, SOFI-hand, pulp-to-palm distance), quality of life (EQ-5D-3L) and pain on VAS and presented in table 12. We also analyzed relationships between disease activity measured by RAPID3, functional disability (HAQ-DI), hand function (grip strength, SOFI-hand, pulp-to-palm distance), quality of life (EQ-5D-3L) and pain (VAS), and the data are stratified by age, gender, disease duration, JAM scale, Steinbrocker scale and morning stiffness presented in table 13,14, 15 and 16.

Correlations between disease activity data, hand function data, and quality of life and pain with age, gender, disease duration, Jam scale, and morning stiffness are shown in table 10. There was a significant positive correlation between RAPID3 and JAM scale, Steinbrocker scale and morning stiffness, while significant negative correlation between RAPID3 and educational level, demonstrating how higher RAPID3 is related to lower educational level. Correlation between RAPID3 and age has significance on p=0.08. DAS28 showed a significant positive correlation with age, JAM scale and morning stiffness. HAQ-DI significantly positively correlated with age, JAM scale, Steinbrocker scale and morning stiffness, while the negative correlation is observed between HAQ-DI and educational level. EQ-5D-3L showed significant positive correlation with gender, while negative correlation with JAM scale, and morning stiffness. Correlation with age has significant at p = 0.05.

Pain showed significant positive correlation with JAM scale and morning stiffness, while significant negative correlation with educational level. Hand function data revealed significant correlations between grip strength and the study variables, although there was no correlation between grip strength and age. The strongest correlation was observed between grip strength and JAM scale (r= -70), demonstrating how limited range of motion, as evaluated by JAM scale, is related to decreased grip strength. Both SOFI-hand and pulp-to-palm distance showed significant positive correlations with disease duration, JAM scale, Steinbrocker scale and morning stiffness, of which we have emphasized the correlation between SOFI-hand and JAM scale, which is the strongest correlation among all given study parameters (r=0.85).

Table 10. Correlations between RAPID3, DAS28, HAQ-DI, SOFI-hand, Grip strength, pulp-to-palm distance, EQ-5D-3L and age, gender, disease duration, JAM scale, Steinbrocker's scale and morning stiffness.

Variables	n=68	RAPID3	DAS28	HAQ-DI	SOFI-hand	Grip Strength	Pulp-to-palm	EQ-5D-3L	VAS-pain
Age									
r		0.21	0.29*	0.27*	0.12	-0.09	0.14	-0.26	0.19
p-value		0.08	0.02	0.03	0.33	0.47	0.26	0.05	0.12
Gender									
r		-0.24	-0.07	0.26	0.18	0.49*	-0.04	0.24*	-0.21
p-value		0.05	0.55	0.03	0.13	0.00	0.71	0.04	0.08
Educational level									
r		-0.29*	-0.16	-0.35*	-0.35*	0.47*	-0.21	0.21	-0.24*
p-value		0.03	0.19	0.00	0.01	0.00	0.08	0.08	0.04
Disease duration									
r		0.20	0.06	0.22	0.39*	-0.29*	0.33*	-0.19	0.23
p-value		0.11	0.61	0.07	0.00	0.02	0.01	0.12	0.05
JAM scale									
r		0.52*	0.39*	0.58*	0.85*	-0.70*	0.73*	-0.41*	0.43*
p-value		0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Steinbrocker scale									
r		0.33*	0.24	0.37*	0.80*	-0.61*	0.56*	-0.19	0.20
p-value		0.01	0.07	0.00	0.00	0.00	0.00	0.14	0.13
Morning stiffness									
r		0.39*	0.45*	0.35*	0.31*	-0.27*	0.32*	-0.46*	0.34*
p-value		0.00	0.00	0.00	0.01	0.02	0.01	0.00	0.00

*p<0.05; n, number of subject; RAPID3, Routine Assessment of Patient Index Data 3; DAS28, Disease Activity Score based on 28 joint evaluation; HAQ-DI, Health Assessment Questionnaire- Disability Index; SOFI-hand, Signal of Functional Impairment; VAS, Visual Analog Scale;

The correlations between study variables were investigated further and are presented in tables 11, 12, 13, 14, 15 and 16, and in figures 7, 8, 9 and 10. Correlations between crude variables, all significant, are shown in table 11.

Correlations between disease activities measured by RAPID3 and hand function data

Positive correlations were found between RAPID3 and HAQ-DI, SOFI-hand, and pulp-to-palm distance, while negative correlation were found between RAPID3 and grip strength. The strongest correlation was found between RAPID3 and HAQ-DI (r=0.81), followed by grip strength (r=-0.69), SOFI-hand (r=0.57) and pulp-to-palm distance (r=0.44).

Correlations between disease activities measured by DAS28 and hand function data

Positive correlations were found between DAS28 and HAQ-DI, SOFI-hand, and pulp-to-palm distance, while a negative correlation was found between DAS28 and grip strength. The strongest correlation was found between DAS28 and HAQ-DI (r=0.60), followed by grip strength (r=-0.52), SOFI-hand (r=0.37) and pulp-to-palm distance (r=0.37). Hand assessment data demonstrated a stronger correlation with RAPID3 than with DAS28.

Correlations between EQ-5D-3L and hand function data

A positive correlation was found between EQ-5D-3L and grip strength (r=0.60), while the strongest correlation was found between EQ-5D-3L and HAQ-DI (r=-0.71), followed by SOFI-hand (r=-0.46) and pulp-to-palm distance (r=-0.30).

Correlations between disease activity measures (RAPID3 and DAS28) and EQ-5D-3L

Table 11 also shows the negative correlation between disease activity measures (RAPID3 and DAS28) and EQ-5D-3L. The correlation between RAPID3 and EQ-5D-3L (r=-0.73) is stronger than the correlation between DAS28 and EQ-5D-3L (r=-0.60).

Correlations between hand function data

As illustrated in table 11, hand function data also demonstrated correlations. The strongest correlation was between SOFI-hand and pulp-to-palm distance (r=0.77), followed by the correlations between HAQ-DI and grip strength (r=-0.76), SOFI and grip strength (r=-0.69), and grip strength and pulp-to-palm distance (r=-0.64).

Correlations between VAS pain, disease activity measures, hand function data and EQ-5D-3L

VAS pain demonstrated statistically significant correlations with all study parameters. The strongest correlation was found between VAS pain and RAPID3 (r=0.86). A significant correlation was also found between VAS pain and hand function data, as well as between VAS pain and EQ-5D-3L.

Table 11. Correlations between RAPID3, DAS28, HAQ-DI, Grip strength, SOFI-hand, Pulp-to-palm distance, EQ-5D-3L and VAS pain.

Variables	n=68	RAPID3	DAS28	HAQ-DI	Grip strength	SOFI-hand	Pulp-to-palm	EQ-5D-3L	EQ-VAS	VAS pain
RAPID3										
r		1.00								
p-value		0.00								
DAS28										
r		0.73*	1.00							
p-value		0.00								
HAQ-DI										
r		0.81*	0.60*	1.00						
p-value		0.00	0.00							
Grip strength										
r		-0.69*	-0.52*	-0.76*	1.00					
p-value		0.00	0.00	0.00						
SOFI-hand										
r		0.57*	0.37*	0.59*	-0.69*	1.00				
p-value		0.00	0.00	0.00	0.00					
Pulp-to-palm										
r		0.44*	0.37*	0.54*	-0.64*	0.77*	1.00			
p-value		0.00	0.00	0.00	0.00	0.00				
EQ-5D-3L										
r		-0.73*	-0.60*	-0.71*	0.60*	-0.46*	-0.30*	1.00		
p-value		0.00	0.00	0.00	0.00	0.00	0.01			
EQ-VAS										
r		-0.72*	-0.52*	-0.67*	0.59*	-0.55*	-0.43*	0.67*	1.00	
p-value		0.00	0.00	0.00	0.00	0.00	0.00	0.00		
VAS pain										
r		0.86*	0.60*	0.72*	-0.56*	0.42*	0.30*	-0.68*	-0.65*	1.00
p-value		0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.00	

*p< 0.05; n, number of subjects; r, correlation coefficient; RAPID3, Routine Assessment of Patient Index Data 3; DAS28, Disease Activity Score based on 28 joint; VAS, Visual Analog Scale; HAQ, Health Assessment Questionnaire; SOFI-hand, Signal of Functional Impairment; JAM scale, Joint Alignment and Motion scale;

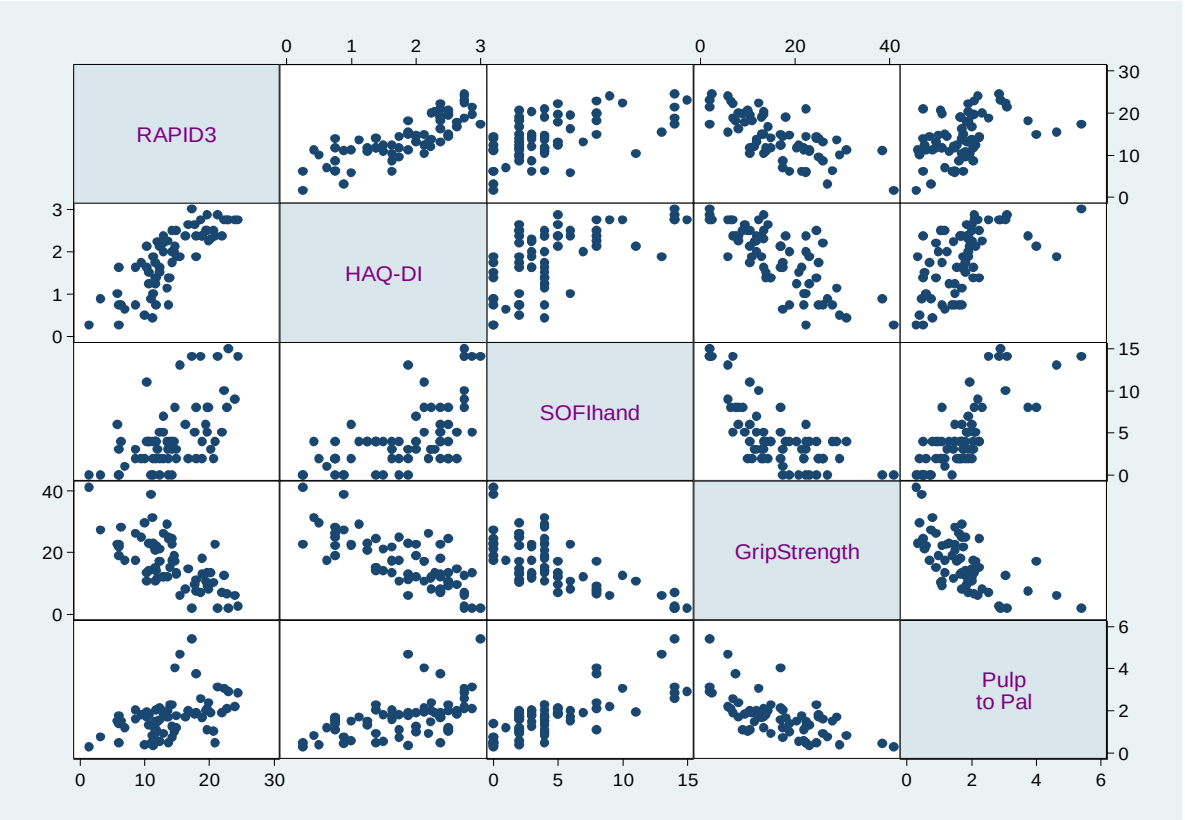


Figure 7. Scatterplots of RAPID3, HAQ-DI, SOFI-hand, Grip strength and pulp-to-palm distance.

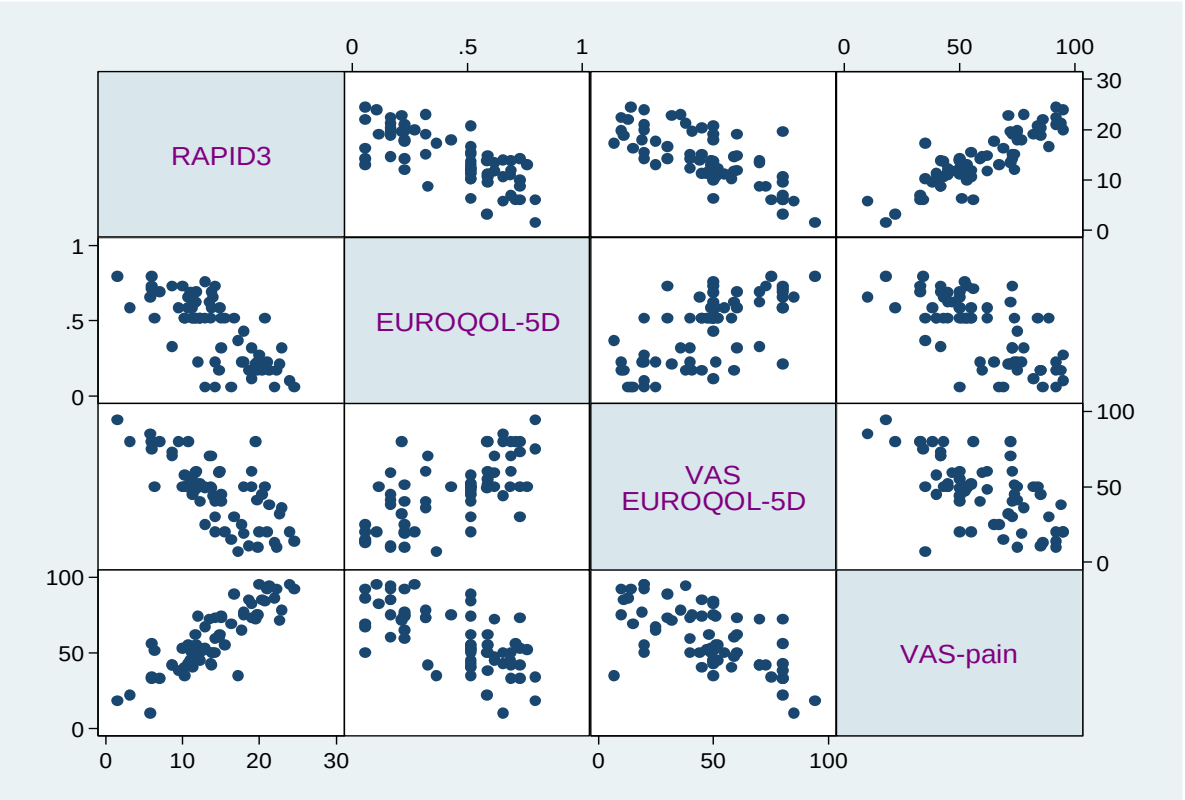


Figure 8. Scatterplots of RAPID3, EQ-5D-3L, EQ-5D-3L VAS and VAS pain.

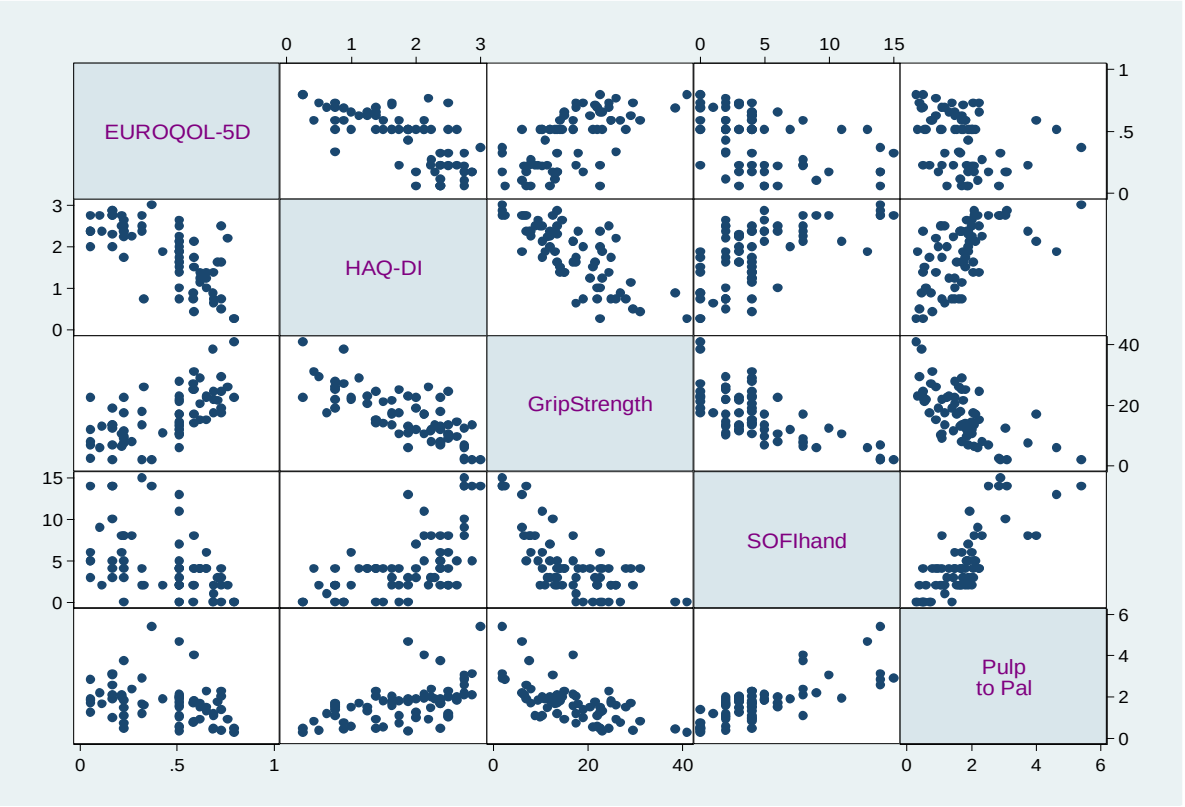


Figure 9. Scatterplots of EQ-5D-3L, HAQ-DI, grip strength, SOFI-hand and pulp-to-palm distance.

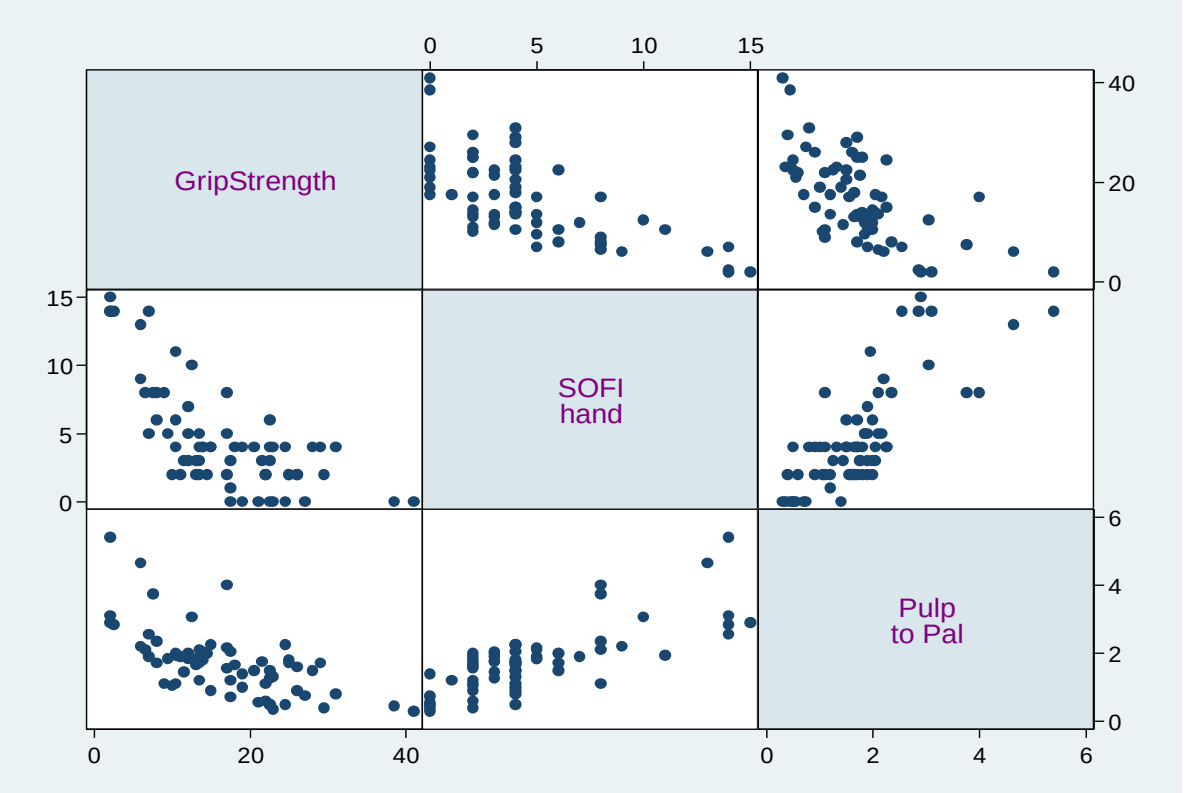


Figure 10. Scatterplots of EQ-5D-3L, HAQ-DI, grip strength, SOFI-hand and pulp-to-palm distance.

Correlations between RAPID3 components (RAPID3 physical function, RAPID3 pain and RAPID3 global health) and DAS28, HAQ-DI, grip strength, SOFI-hand, pulp-to-palm distance, EQ-5D-3L, VAS pain and EQ-VAS are shown in Table 12. We found significant correlations between all study variables. RAPID3 physical function demonstrated the strongest correlation with HAQ-DI (r=0.86), RAPID3 pain with VAS pain (r=0.88), and RAPID3 global health with VAS pain (r=0.75).

Table 12. Correlation between RAPID3 physical function, RAPID3 pain, RAPID3 global health and DAS28, HAQ-DI, Grip strength, SOFI-hand, pulp-to-palm distance, EQ-5D-3L and VAS pain.

Variables	n=68	RAPID3 physical function	RAPID3 pain	RAPID3 global health
DAS28				
r		0.66*	0.65*	0.68*
P vale		0.00	0.00	0.00
HAQ-DI				
r		0.86*	0.71*	0.67*
p value		0.00	0.00	0.00
Grip Strength				
r		-0.70*	-0.60*	-0.62*
p value		0.00	0.00	0.00
SOFI-hand				
r		0.67*	0.43*	0.47*
p value		0.00	0.00	0.00
Pulp-to-palm				
r		0.56*	0.31*	0.33*
p value		0.00	0.01	0.00
EQ-5D-3L				
r		-0.70*	-0.69*	-0.64*
p value		0.00	0.00	0.00
EQ-VAS				
r		-0.70*	-0.62*	-0.67*
p value		0.00	0.00	0.00
VAS Pain				
r		0.75*	0.88*	0.75*
p value		0.00	0.00	0.00

*p< 0.05; n, number of subject; r, correlation coefficient; RAPID3, Routine Assessment of Patient Index Data 3; DAS28, Disease Activity Score based on 28 joint; VAS, Visual Analog Scale; HAQ, Health Assessment Questionnaire; SOFI-hand, Signal of Functional Impairment-hand;

Correlations between RAPID3 and HAQ-DI, grip strength, pulp-to-palm distance, EQ-5D-3L, EQ-VAS and VAS pain are shown in table 13, adjusted by gender, age and disease duration. The correlations between RAPID3 and HAQ-DI were significant regardless of gender, age or disease duration such that an increase in disease activity was accompanied by an increase in functional disability. In terms of gender analysis, we found a stronger correlation in females, while age analysis indicated that the strongest correlation was in patients younger than 40 years. However, this correlation is doubtful due to the small sample size. Interestingly, regarding disease duration, patients with disease duration 6-10 years showed the strongest correlation between disease activity and functional disability (r=0.82). The correlations between RAPID3 and hand function measured by SOFI-hand and pulp-to-palm distance did not demonstrate significance when accounting for all stratification. The correlations between RAPID3 and grip strength was significant regardless of gender, age or disease duration; correlations ranged from r=-0.51 to r=-0.87. We found a stronger correlation in males than in females, while in age and disease duration analysis, if we omit correlations in patients younger than 40 year and in patients with disease duration less than one year, the strongest correlation was found in patients with disease duration more than 11 years (r=-0.74). Hence, we can say that RAPID3 mirrors functional disability and grip strength, which is not the case for pulp-to-palm distance in patients older than 59 years. Both the correlations between RAPID3 and SOFI-hand and RAPID3 and pulp-to-palm distance did not reach significance in groups with insufficient sample sizes (male, age group <40 years and disease duration <1 year). However, the correlation between RAPID3 and SOFI-hand in patients older than 59 years was also significant.

Similarly, the correlations between RAPID3 and EQ-5D-3L was significant for the abovementioned factors. However, overall we found a strong correlation between RAPID3 and EQ-5D-3L (r=-0.73), especially in female patients. The correlations between RAPID3 and EQ-5D-3L was significant regardless of gender and age, with the strongest correlation in patients with disease duration 6-10 years (r=-0.81), while there was no significant correlation in male and in patients with a disease duration of up to one year which is reasonable due to a small sample size. The correlations between RAPID3 and pain was significant regardless of gender, age, and disease duration. The strongest correlation was found in patients aged 40-59 years, while we did not find a significant correlation between RAPID3 and EQ-VAS in patients with a longstanding disease.

Table 13. Stratified correlations among RAPID3, HAQ-DI, Grip strength, SOFI-hand, Pulp-to-palm distance, EQ-5D-3L, EQ-VAS and VAS pain, for gender, age and disease duration.

	n		RAPID3 vs HAQ-DI	RAPID3 vs Grip strength	RAPID3 vs Pulp-to-palm	RAPID3 vs SOFI-hand	RAPID3 vs EQ-5D-3L	RAPID3 vs EQ-VAS	RAPID3 vs VAS pain
Total	68	r	0.81*	-0.69*	0.44*	0.57*	-0.73*	-0.72*	0.86*
		p	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Gender									
Male	10	r	0.76*	-0.74*	0.56	0.50	-0.20	-0.76*	0.79*
		p	0.01	0.01	0.09	0.14	0.58	0.01	0.00
Female	58	r	0.81*	-0.67*	0.41*	0.56*	-0.79*	-0.72*	0.86*
		p	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Age (years)									
<40	10	r	0.86*	-0.79*	0.73*	0.82*	-0.92*	-0.83*	0.86*
		p	0.00	0.00	0.02	0.00	0.00	0.00	0.00
40-59	33	r	0.82*	-0.65*	0.40*	0.37*	-0.71*	-0.77*	0.89*
		p	0.00	0.00	0.02	0.03	0.00	0.00	0.00
>59	25	r	0.73*	-0.70*	0.34	0.68*	-0.71*	-0.57*	0.84*
		p	0.00	0.00	0.09	0.00	0.00	0.00	0.00
Disease duration (years)									
0-1	9	r	0.79*	-0.82*	0.61	0.56	-0.46	-0.61	0.88*
		p	0.01	0.00	0.08	0.11	0.21	0.07	0.00
2-5	18	r	0.78*	-0.73*	0.56*	0.63*	-0.72*	-0.88*	0.83*
		p	0.00	0.00	0.01	0.00	0.00	0.00	0.00
6-10	18	r	0.82*	-0.51*	0.18	0.65*	-0.81*	-0.77*	0.86*
		p	0.00	0.03	0.47	0.00	0.00	0.00	0.00
>11	23	r	0.77*	-0.74*	0.45*	0.57*	-0.77*	-0.16	0.82*
		p	0.00	0.00	0.03	0.00	0.00	0.47	0.00

*p< 0.05; n, number of subject; r, correlation coefficient; RAPID3, Routine Assessment of Patient Index Data 3; HAQ, Health Assessment Questionnaire; SOFI-hand, Signal of Functional Impairment; EQ-5D-3L, EUROQOL-5D-3L; VAS, Visual Analog Scale;

The correlations between RAPID3 and HAQ-DI, grip strength, pulp-to-palm distance, pulp-to-palm distance, SOFI-hand, EQ-5D-3L, VAS pain, EQ-VAS stratified by JAM scale, Steinbrocker scale, and morning stiffness are shown in table 14. Due to a small number of patients belonging to Steinbrocker scale stage 3, we joined patients with radiological stage 3 (n=6) and stage 4 (n=9) and presented the correlation between study variables accordingly. For the same reason in stratification according to JAM scale, we joined patients with JAM scale stage 3 (n=10) and stage 4 (n=10).

The positive correlation between RAPID3 and HAQ-DI ranged from r=0.65 to r=0.81, in which correlations of r=0.81 can be found, besides in overall, in different patients group as in patients with JAM scale stage 1, Steinbrocker scale stage 1 and in patients with duration of morning stiffness ≥60 minutes.

Regarding hand function data, the significant negative correlations between RAPID3 and grip strength ranged from r=-42 to r=-0.76. The strongest correlation is seen in patients with duration of morning stiffness ≥ than 60 minutes.

Correlations between RAPID3 and SOFI-hand were significant in patients stratified by duration of morning stiffness, whereas significance was not found in patients stratified by JAM scale. A significant correlation was found in patients with Steinbrocker stage 1. Regarding the correlation between RAPID3 and pulp-to-palm distance, significance was found in patients who experienced less than 60 minutes of morning stiffness and in patients classified as Steinbrocker scale stage 1.

The negative correlation between RAPID3 and EQ-5D-3L was significant regardless of ROM, radiological damage and duration of morning stiffness. Very strong correlation is seen in patients classified as Steinbrocker scale stage 3 and 4 (r=-0.88) and in patients classified as JAM scale stage 2 (r=-0.80).

Remarkably, the correlation between RAPID3 and VAS pain was significant regardless of ROM, radiological damage and duration of morning stiffness. Looking at the results, there was a correlation between RAPID3 and VAS pain ranging from a strong correlation (r=0.73) to a very strong correlation (r=0.91); the latter occurred in patients categorized as JAM scale stage 1. This was the strongest correlation among all variables. In the same patients, a very strong correlation was found between RAPID3 and HAQ-DI while hand function data indicated a strong correlation between RAPID3 and grip strength.

Table 14. Stratified correlations between RAPID3 and HAQ-DI, Grip strength, Pulp-to-palm distance, SOFI-hand, EQ-5D-3L, VAS pain, EQ-VAS for JAM scale, Steinbrocker scale and morning stiffness.

	n		RAPID3 vs HAQ-DI	RAPID3 vs Grip strength	RAPID3 vs Pulp-to-palm	RAPID3 vs SOFI-hand	RAPID3 vs EQ-5D-3L	RAPID3 vs VAS pain	RAPID3 vs EQ-VAS
Total	68	r	0.81*	-0.69*	0.44*	0.57*	-0.74*	0.86*	-0.72*
		p	0.00	0.00	0.00	0.00	0.00	0.00	0.00
JAM scale									
1	23	r	0.81*	-0.64*	0.14	0.39	-0.51*	0.91*	-0.72*
		p	0.00	0.00	0.52	0.07	0.01	0.00	0.00
2	25	r	0.72*	-0.42*	0.18	0.23	-0.80*	0.80*	-0.73*
		p	0.00	0.03	0.38	0.28	0.00	0.00	0.00
3 and 4	20	r	0.72*	-0.59*	0.09	0.41	-0.72*	0.76*	-0.75*
		p	0.00	0.00	0.69	0.07	0.00	0.00	0.01
Steinbrocker scale									
1	30	r	0.81*	-0.58*	0.41*	0.58*	-0.63*	0.90*	-0.71*
		p	0.00	0.00	0.02	0.00	0.00	0.00	0.00
2	15	r	0.65*	-0.54*	-0.14	0.49	-0.71*	0.74*	-0.90*
		p	0.01	0.04	0.62	0.06	0.00	0.00	0.00
3 and 4	15	r	0.76*	-0.68*	-0.03	0.28	-0.88*	0.77*	-0.34
		p	0.00	0.00	0.89	0.31	0.00	0.00	0.20
Morning stiffness									
< 60 min	42	r	0.80*	-0.61*	0.43*	0.54*	-0.77*	0.88*	-0.85*
		p	0.00	0.00	0.00	0.00	0.00	0.00	0.00
≥60 min	26	r	0.81*	-0.76*	0.33	0.55*	-0.59*	0.79*	-0.43*
		p	0.00	0.00	0.09	0.00	0.00	0.00	0.02

*p< 0.05; n, number of subjects; r, correlation coefficient; RAPID3, Routine Assessment of Patient Index Data 3; VAS, Visual Analog Scale; HAQ, Health Assessment Questionnaire; SOFI-hand, Signal of Functional Impairment; EUROQOL-5D-3L, EQ-5D-3L;

Correlations between EQ-5D-3L functional disability hand outcome measures (grip strength, SOFI-hand, pulp- to-palm distance) and VAS pain are shown in Table 15. There was no significant correlation between study parameters in male patients and in patients with a disease duration of less than one year. This may be due to a small sample number in both groups. Noticeable there is no significant correlation also between EQ-5D-3L and pulp to palm distance in patients with disease duration of more than 11 years. Additionally, there was no correlation between EQ-5D-3L and pulp-to-palm distance in patients with a duration of RA from 6 to 10 years. While, if we look at correlation between EQ-5D-3L and SOFI-hand, omitting stratified groups with small sample sizes (males, disease duration less than one year, and patients younger than 40 years) we can found a significant negative correlation ranging from r=-0.36 to r=-0.51. Regardless of patient age and disease duration, the negative correlation between EQ-5D-3L and HAQ-DI was significant. EQ-5D-3L and grip strength demonstrated moderate correlations, and the positive significant correlation range from r=0.55 to r=0.70.

Table 15. Stratified correlations between EQ-5D-3L and HAQ-DI, Grip strength, Pulp-to-palm distance, SOFI-hand, VAS pain, for gender, age and disease duration.

	n		EQ-5D-3L vs HAQ-DI	EQ-5D-3L vs Grip strength	EQ-5D-3L vs Pulp- to-palm	EQ-5D-3L vs SOFI-hand	EQ-5D-3L vs VAS pain
Total	68	r	-0.71*	0.60*	-0.30*	-0.45*	-0.68*
		p	0.00	0.00	0.01	0.00	0.00
Gender							
Male	10	r	-0.07	0.31	-0.08	-0.15	-0.06
		p	0.85	0.38	0.82	0.67	0.86
Female	58	r	-0.80*	0.64*	-0.33*	-0.47*	-0.73*
		p	0.00	0.00	0.01	0.00	0.00
Age (years)							
<40	10	r	-0.93*	0.79*	-0.67*	-0.74*	-0.80*
		p	0.00	0.00	0.03	0.01	0.00
40-59	33	r	-0.71*	0.55*	-0.36*	-0.36*	-0.71*
		p	0.00	0.00	0.04	0.04	0.00
>59	25	r	-0.61*	0.66*	-0.12	-0.46*	-0.61*
		p	0.00	0.00	0.55	0.02	0.00

Table 15. continued

Disease duration (years)							
0-1	9	r	-0.54	0.57	-0.43	-0.61	-0.49
		p	0.13	0.11	0.25	0.08	0.18
2-5	18	r	-0.66*	0.56*	-0.47*	-0.51*	-0.69*
		p	0.00	0.03	0.04	0.01	0.00
6-10	18	r	-0.69*	0.70*	-0.01	-0.48*	-0.59*
		p	0.00	0.00	0.96	0.04	0.00
>11	23	r	-0.80*	0.66*	-0.35	-0.46*	-0.78*
		p	0.00	0.00	0.09	0.02	0.00

*p< 0.05; n, number of subjects; r, correlation coefficient; EUROQOL-5D-3L, EQ-5D-3L; HAQ-DI, Health Assessment Questionnaire-Disability Index; SOFI-hand, Signal of Functional Impairment-hand; VAS, Visual Analog Scale;

Correlations between EQ-5D-3L and study variables stratified by JAM scale, Steinbrocker scale and morning stiffness are shown in Table 16. A significant negative correlations were found only between EQ-5D-3L and pain, regardless of radiological damage, JAM scale, or duration of morning stiffness. The strongest correlation was found in patients with Steinbrocker scale stage 3 and 4 (r=-0.77). The correlations between EQ-5D-3L and HAQ-DI was significant in all stratified groups, presenting the strongest correlation in patients with morning stiffness < 60 minutes (r=-0.76) The correlations between EQ-5D-3L and hand function data were significant, including a positive correlation with grip strength, taking into account the duration of morning stiffness, and in patients with JAM scale stage 2 and stage 3 and 4 and Steinbrocker scale stage 1 and stage 3 and 4. Significant correlations between EQ-5D-3L, SOFI hand and pulp-to-palm distance were found only in patients with a duration of morning stiffness of < than 60 minutes, while significant correlation between EQ-5D-3L, SOFI hand was found in patients with Steinbrocker scale stage 1. We can conclude that EQ-5D-3L cannot mirror total finger flexion as measured by pulp-to- palm distance or SOFI-hand.

Table 16. Stratified correlations between EQ-5D-3L and HAQ-DI, Grip strength, Pulp-to-palm distance, SOFI-hand, VAS pain for JAM scale, Steinbrocker's scale and morning stiffness.

	n		EQ-5D-3L vs HAQ-DI	EQ-5D-3L vs Grip strength	EQ-5D-3L vs Pulp-to-palm	EQ 5D-3L vs SOFI-hand	EQ-5D-3L vs VAS pain
Total	68	r	-0.71*	0.58*	-0.32*	-0.46	-0.67*
		p	0.00	0.00	0.01	0.00	0.00
JAM scale							
1	23	r	-0.57*	0.38	-0.17	-0.30	-0.53*
		p	0.00	0.07	0.44	0.16	0.01
2	25	r	-0.74*	0.58*	-0.05	-0.31	-0.66*
		p	0.00	0.00	0.80	0.31	0.00
3 and 4	20	r	-0.60*	0.62*	-0.10	-0.27	-0.70*
		p	0.00	0.01	0.67	0.26	0.00
Steinbrocker scale							
1	30	r	-0.74*	0.53*	-0.33	-0.51*	-0.61*
		p	0.00	0.00	0.08	0.00	0.00
2	15	r	-0.66*	0.43	-0.10	-0.50	-0.61*
		p	0.01	0.11	0.72	0.05	0.01
3 and 4	15	r	-0.73*	0.62*	-0.24	-0.17	-0.77*
		p	0.00	0.01	0.38	0.53	0.00
Morning stiffness							
< 60 min	42	r	-0.76*	0.60*	-0.33*	-0.48*	-0.73*
		p	0.00	0.00	0.03	0.02	0.00
≥60 min	26	r	-0.57*	0.57*	-0.11	-0.35	-0.50*
		p	0.00	0.00	0.59	0.08	0.01

*p< 0.05; r, correlation coefficient; n, number of subjects; EQ-D-3L, EUROQL-5D-3L; HAQ, Health Assessment Questionnaire; SOFI-hand, Signal of Functional Impairment; VAS, Visual Analog Scale;

Correlations between RAPID3, grip strength and anthropometric measures

Table 17 shows correlations between anthropometric measures, RAPID3 and grip strength. There were no significant correlations between RAPID3, grip strength and BMI. Significant, but week negative correlations were found between RAPID3 and forearm circumference (r=-0.25), RAPID3 and forearm length (r=-0.44), hand circumference (r=-0.32), and RAPID3 and hand length (r=-0.44). Additionally, a significant correlation was found between grip strength and forearm circumference (r=0.35), between grip strength and forearm length (r=0.59), between grip strength, hand circumference (r=0.50) and between grip strength and hand length (r=0.52), with the strongest correlation between grip strength and forearm circumference, followed by the correlation between grip strength and hand length.

Table 17. Correlation between RAPID3 and Grip strength and BMI, Hand circumference and Hand length.

Variables	n=68	RAPID3	Grip strength
BMI			
r value		-0.08	0.12
p value		0.51	0.32
Forearm circumference			
r value		-0.25*	0.35*
p value		0.04	0.00
Forearm length			
r value		-0.44*	0.59*
p value		0.00	0.00
Hand circumference			
r value		-0.32*	0.50*
p value		0.00	0.00
Hand length			
r value		-0.44*	0.52*
p value		0.00	0.03

*p<0.05; n, number of subjects; RAPID3, Routine Assessment of Patient Index Data; BMI, body mass index;

Correlations between RAPID3 and forearm length, RAPID3 and forearm circumference, RAPID3 and hand length, and RAPID3 and hand circumference are shown in Figures 11, 12, 13 and 14.

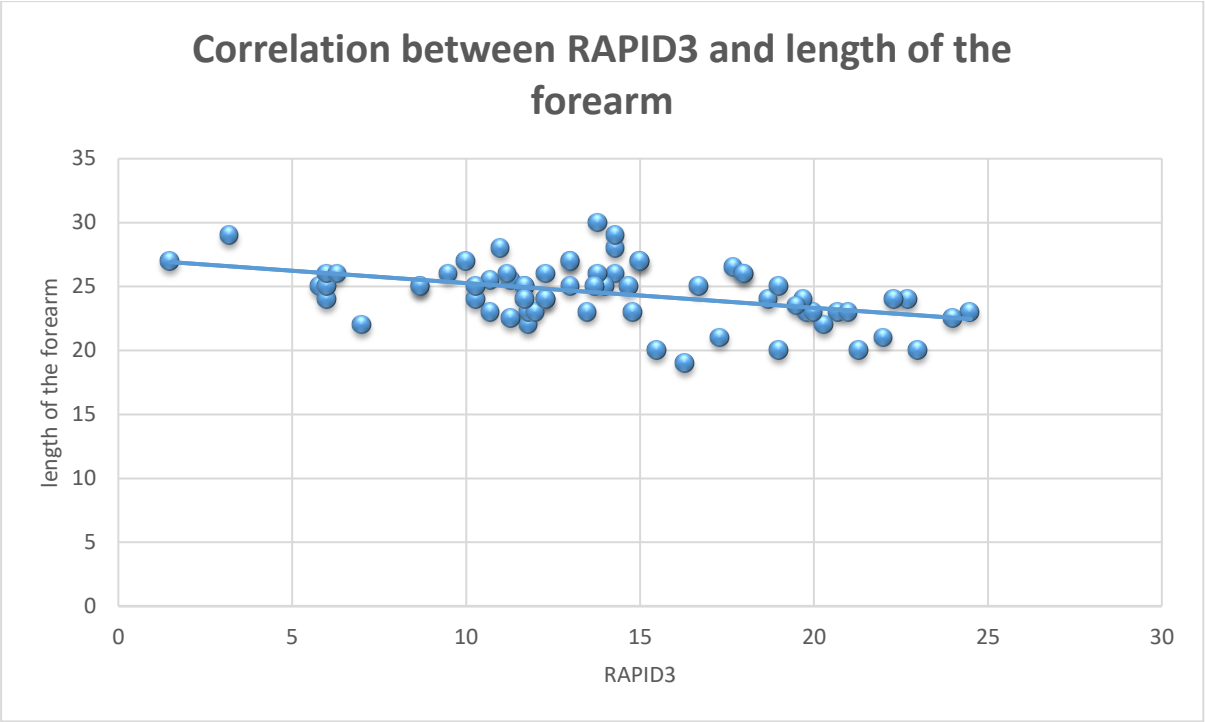


Figure 11. Correlation between RAPID3 and forearm length.

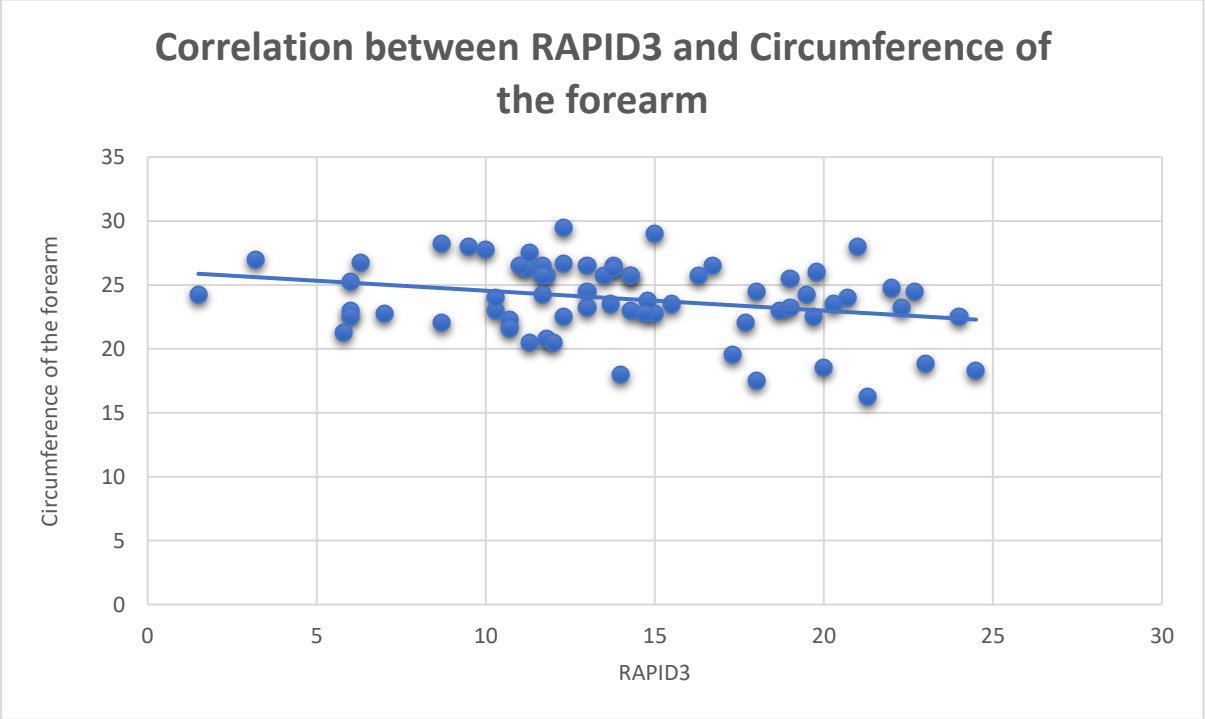


Figure 12. Correlation between RAPID3 and forearm circumference.

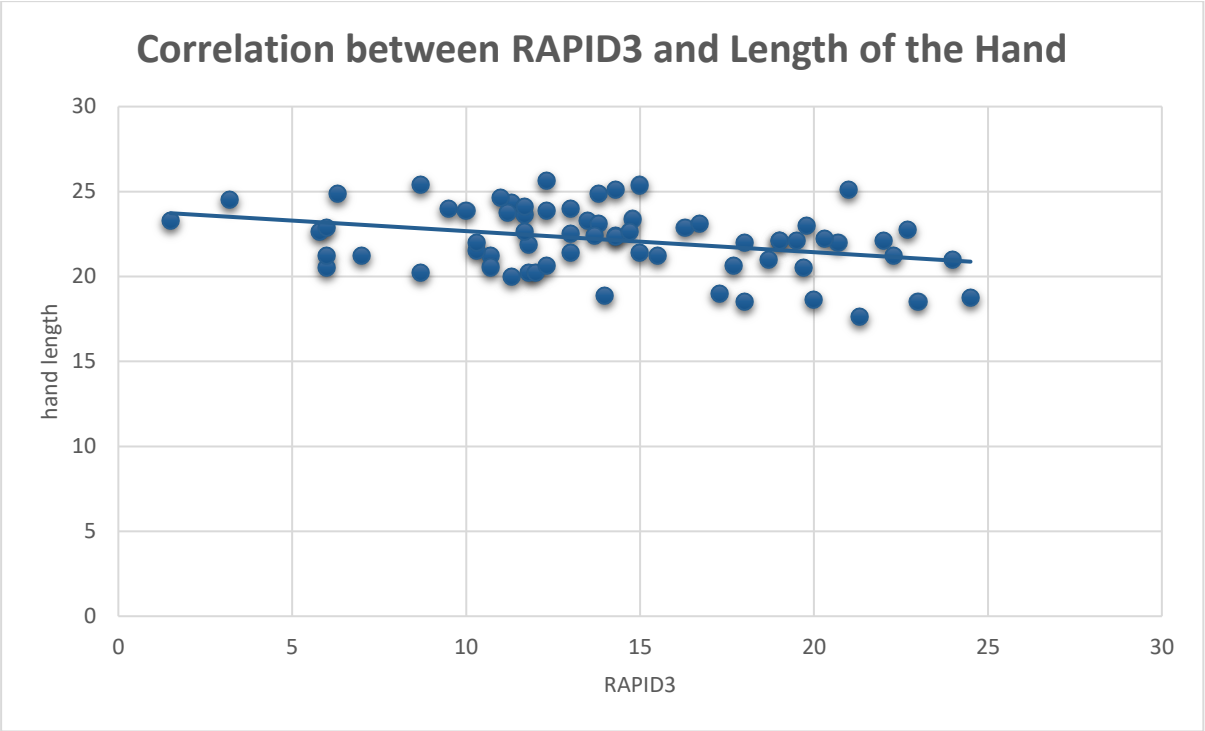


Figure 13. Correlation between RAPID3 and hand length.

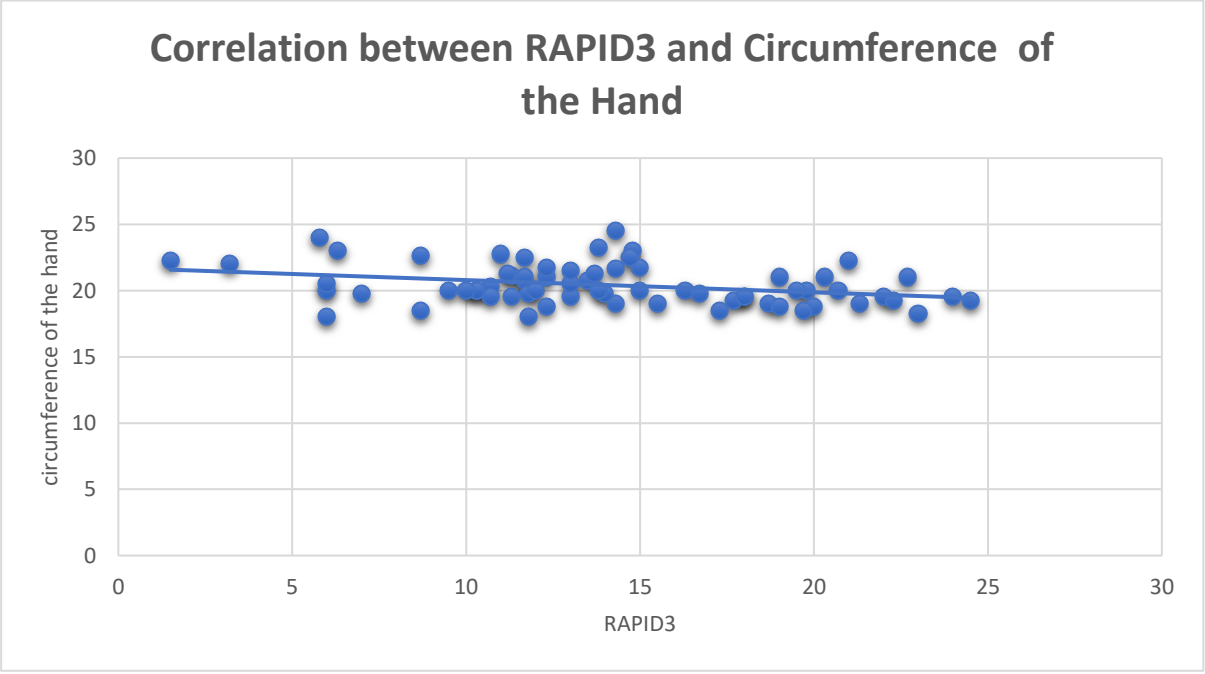


Figure 14. Correlation between RAPID3 and hand circumference.

Table 18 demonstrates correlations between anthropometric measures and RAPID3 stratified by gender. There was no significant correlation between RAPID3 and BMI regardless of gender, while significant and weak negative correlation was found between RAPID3 and hand circumference while moderate positive correlation between RAPID3 and hand length, only in females.

Table 18. Correlation between RAPID3 and BMI, Hand circumference and Hand length in female and male.

Variables	RAPID3	
	Female n=58	Male n=10
BMI		
r value	-0.12	-0.15
p value	0.39	0.68
Hand circumference		
r value	-0.26*	-0.05
p value	0.04	0.89
Hand length		
r value	0.47*	-0.08
p value	0.00	0.82

*p<0.05; n, number of subjects; r, correlation coefficient; RAPID3, Routine Assessment of Patient Index Data; BMI, body mass index;

Table 19 shows correlations between anthropometric measures and grip strength stratified by gender. In males, there were no significant correlations between grip strength and any of the given measures, while in females we found a significant correlation only between grip strength and hand circumference.

Table 19. Correlation between grip strength and BMI, Hand circumference and Hand length in women and men.

Variables	Grip strength	
	Female n=58	Male n=10
BMI		
r value	0.18	0.45
p value	0.17	0.19
Hand circumference		
r value	0.32*	0.27
p value	0.01	0.44
Hand length		
r value	-0.39*	-0.08
p value	0.00	0.81

*p<0.05; n, number of subjects; r, correlation coefficient; BMI, body mass index;

4.3. Regression analysis

Given that our correlation analyses identified significant relationships between variables, the next step was to show how independent variables contributed to a single dependent variable. In this context, we used multiple regression analyses to determine how clinical data in the form of hand function data, functional disability, quality of life and pain contributed to RAPID3, as well as how disease activity, hand function data, functional disability, and pain contributed to quality of life. Variables were regressed on RAPID3 and EQ-5D-3L and relevant R-squared coefficients showed the percentage of respective contribution. Furthermore, the results of t-tests to determine the significance of the relationships between two variables are shown by p-values, representing factors significantly related to RAPID3 and EQ-5D-3L as well. Additionally, to show the effect size, we added beta coefficient values.

Thus, we studied the effects of more than one variable on RAPID3. Variables were selected based on the characteristics of the instrument. Therefore, we constructed two models; the first model included hand outcome measurements, whereas second model included PRO measurements. A multiple regression analysis testing the relationship between independent variables such as grip strength, SOFI-hand and pulp-to-palm distance and RAPID3 is shown in Table 20. The regression provided an explanation for approximately 50% of the variation in RAPID3; grip strength was significant at the 5% level, while SOFI-hand and pulp-to-palm distance were not. An increase in grip strength decreased RAPID3 by 0.37 when holding all other variables constant.

Table 20. Multiple regression analysis of Grip strength, SOFI-hand, Pulp-to-palm distance with RAPID3 as a dependent variable.

	β coefficient	Stand Error	t value	p value
Constant	20.11	2.20	9.09	0.00
Grip strength	-0.37	0.08	-4.77	0.00
SOFI-hand	0.37	0.20	1.79	0.07
Pulp-to-palm distance	-0.87	0.76	-1.09	0.26

$R^2 = 0.50$; $p<0.05$

As shown in Table 21, a multiple regression model was constructed to evaluate whether HAQ-DI, VAS pain, EQ-5D-3L and VAS EQ-5D-3L predicted RAPID3. The given variables significantly explained approximately 84% of the variation in RAPID3. As seen in Table 21,

HAQ-DI and VAS pain had significant positive regression weights, indicating persons with higher values of HAQ-DI or VAS pain were expected to have higher RAPID3 values after controlling for the other variables in the model. EQ-5D-3L and EQ-VAS did not contribute to the multiple regression model.

Table 21. Multiple regression analysis of HAQ-DI, VAS pain, EQ-5D-3L and EQ-VAS with RAPID3 as a dependent variable.

	β value	Stand Error	t value	p value
constant	5.25	2.19	2.40	0.02
HAQ-DI	2.17	0.57	3.84	0.00
VAS pain	0.13	0.02	6.29	0.00
EQ-5D-3L	-1.95	1.80	-1.09	0.28
EQ-VAS	-0.04	0.02	-2.12	0.03

R^2= *0.84; p<0.05*

A multiple regression analysis testing the relationship between the independent variables of grip strength, SOFI-hand and pulp-to-palm distance and EQ-5D-3L is presented in Table 22. The regression provided an explanation for 42% of the variation in EQ-5D-3L; grip strength was significant, while SOFI-hand and pulp-to-palm distance were not significant in explaining the variation in EQ-5D-3L scores. An improvement in grip strength increased EQ-5D-3L by 0.02, holding all other variables constant.

Table 22. Multiple regression analysis of Grip strength, SOFI-hand and Pulp-to-palm distance with EQ-5D-3L as dependent variable.

	β value	Stand Error	t value	p value
constant	0.10	0.11	0.98	0.30
Grip strength	0.02	0.04	4.49	0.00
SOFI-hand	-0.01	0.01	-1.41	0.16
Pulp-to-palm distance	0.07	0.04	1.83	0.07

R^2=*0.42; P<0.05*

A multiple regression analysis testing the relationship between the independent variables of HAQ-DI and RAPID3 to EQ-5D-3L is shown in Table 23. The regression provided an explanation for 58% of the variation in EQ-5D-3L, with both HAQ-DI and RAPID3 being

significant. An increase in HAQ-DI decreased EQ-5D-3L by 0.09, while an increase in RAPID3 decreased EQ-5D-3L by 0.02, holding all other variables constant.

Table 23. Multiple regression analysis of HAQ-DI and RAPID 3 with EQ-5D-3L, as a dependent variable.

	β value	Stand Error	t value	p value
constant	0.90	0.05	16.95	0.00
HAQ-DI	-0.09	0.04	-2.28	0.02
RAPID3	-0.02	0.01	-3.42	0.00

R^2 = *0.58; p<0.05*

A multiple regression analysis testing the relationship between the independent variables of grip strength, SOFI-hand, pulp-to-palm distance and EQ-5D-3L and RAPID3 is presented in Table 24. The regression provided an explanation for 63% of the variation in RAPID3, with both grip strength and EQ-5D-3L being significant. In this model, an improvement in grip strength decreased RAPID3 by 0.24, while an increase in EQ-5D-3L decreased RAPID3 by 11.50, holding all other variables constant.

Table 24. Multiple regression analysis of Grip strength and EQ-5D-3L with RAPID3 as a dependent variable.

	β value	Stand Error	t value	p value
Constant	23.15	0.93	24.80	0.00
Grip strength	-0.24	0.06	-4.14	0.00
EQ-5D-3L	-11.50	2.15	-5.35	0.00

R^2 = *0.63; p<0.05*

A multiple regression analysis testing the relationship between the independent variables of RAPID3 and grip strength to EQ-5D-3L is presented in table 25. The regression provided an explanation for 56% of the variation in EQ-5D-3L, with RAPID3 being significant. In this model, an increase in RAPID3 decreased EQ-5D-3L by 0.05, holding all other variables constant.

Table 25. Multiple regression analysis of RAPID 3 and Grip strength with EQ-5D-3L, as a dependent variable.

	β value	Stand Error	t value	p value
constant	0.73	0.11	6.46	0.00
RAPID3	-0.03	0.005	-5.35	0.00
Grip strength	0.05	0.003	1.59	0.16

R^2 = *0.56; p<0.05*

A multiple regression analysis testing the relationship between the independent variables of RAPID3 and EQ-5D-3L to grip strength analysis is presented in table 26. The regression provided an explanation for 50% of the variation in grip strength, with RAPID3 being significant. In this model, an increase in RAPID3 decreased grip strength by 0.86, holding other variables constant.

Table 26. Multiple regression analysis of RAPID3 and EQ-5D-3L with grip strength as a dependent variable.

	β value	Stand Error	t value	p value
constant	25.43	4.77	5.33	0.00
RAPID3	-0.86	0.20	-4.14	0.00
EQ-5D-3L	7.65	4.78	1.59	0.11

R^2 = *0.50; p<0.05*

4.4 Comparison of grip strength values between RA patients and reference values

An independent t-test was performed to determine whether there was a significant difference between the mean values of grip strength for the reference controls and RA patients.

The mean values of grip strength for the reference controls and RA patients, stratified by gender, are presented in table 27, demonstrating significantly lower grip strength in females than in males among both groups: non-RA controls and in RA patients.

Table 27. Grip strength (kg) in females and males in the healthy (non-RA) population and RA population.

	Female			Male				
	n	Mean grip strength (kg)	SD	n	Mean grip strength (kg)	SD	t value	p value
Reference controls	58	29.50	4.69	10	34.85	5.83	-2.75	0.02*
RA patients	58	14.86	7.23	10	26.35	8.17	-4.17	0.00*

*p<0.05; n, number of subjects; SD, standard deviation; GS, grip strength; RA, rheumatoid arthritis;

Differences between the mean values of hand grip strength in RA patients and healthy controls in females and in males are presented in Table 28. For both genders, we found significantly lower grip strength in RA patients than in healthy controls.

Table 28. Grip strength in RA populations and the healthy controls, stratified by gender.

Gender	n	RA mean grip strength (kg)	SD	Healthy controls mean grip strength (kg)	SD	t value	p value
total	68	16.55	8.38	30.26	5.21	-11.42	0.00*
Females	58	14.86	7.23	29.50	4.69	-12.92	0.00*
Males	10	26.35	8.17	34.85	5.83	-2.68	0.01*

*p<0.05; SD, standard deviation; n, number of subjects; RA, rheumatoid arthritis;

Differences between the mean values of hand grip strength in RA patients and healthy controls stratified by age are presented in Table 29. Regardless of age, RA patients showed significantly lower grip strength than healthy references.

Table 29. Grip strength in RA patients and the healthy controls, stratified by age.

Age (years)	n	RA mean grip strength (kg)	SD	Healthy controls mean grip strength (kg)	SD	t value	p value
<40	10	16.15	7.13	33.35	7.18	-5.37	0.00*
40-49	12	18.41	6.96	32.41	3.67	-6.16	0.00*
50-59	21	18.41	9.11	30.83	3.84	-5.76	0.00*
≥60	25	14.26	8.68	27.54	6.21	-6.22	0.00*

*p<0.05; n, number of subjects; SD, standard deviation; kg, kilograms; RA, rheumatoid arthritis;

4.5. Clinical measures stratified by use of therapy

Table 30 shows disease activity measures, hand outcome measures and QoL measures stratified by use of therapy. The largest percentage of patients (81%) used disease-modifying anti-rheumatic drugs (DMARDs). The mean values of SOFI-hand in patients who used glucocorticoids drugs were significantly worse than those in patients who did not.

Table 30. RAPID3, DAS28, HAQ-DI, Grip strength, Pulp-to-palm distance and EQ-5D-3L, stratified by drugs usage.

		RAPID3		DAS28		HAQ-DI		SOFI-hand		Grip strength		Pulp-to- palm		EQ-5D-3L	
	%	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Total	100%	14.12	5.21	5.89	1.28	1.83	0.74	4.58	3.90	16.55	8.38	1.72	0.96	0.44	0.22
Simple analgesics															
Used	51%	14.07	5.70	5.98	1.4	1.89	0.74	4.86	3.89	16.36	7.75	1.72	0.97	0.43	0.23
Not used	49%	14.18	4.72	5.78	1.16	1.76	0.75	4.30	3.90	16.76	9.12	1.72	0.96	0.45	0.22
Non-steroidal anti-rheumatic drugs															
Used	68%	14.57	5.02	5.90	1.29	1.83	0.76	4.57	3.94	16.34	8.83	1.72	0.96	0.44	0.24
Not used	32%	13.19	5.59	5.83	1.30	1.82	0.71	4.64	3.82	17.00	7.52	1.72	0.96	0.44	0.20
Disease modifying anti-rheumatic drugs															
Used	81%	14.39	5.12	5.80	1.29	1.87	0.74	4.91	4.11	15.76	8.50	1.75	0.99	0.45	0.22
Not used	19%	13.02	5.66	6.22	1.23	1.65	0.72	3.23	2.27	19.88	7.23	1.60	0.88	0.38	0.25
Glucocorticoids (orally)															
Used	69%	14.80	5.41	5.98	1.21	1.92	0.76	5.23*	4.24	15.34	8.34	1.88	1.00	0.44	0.21
Not used	31%	12.60	4.47	5.64	1.43	1.62	0.67	3.14	2.41	19.26	8.00	1.37	0.79	0.43	0.25

*p<0.05; %, percent of subjects; RAPID3, Routine Assessment of Patient Index Data 3; DAS28, Disease Activity Score based on 28 joint evaluation; VAS, Visual Analog Scale; HAQ-DI, Health Assessment Questionnaire-Disability Index;; SOFI, Signal of Functional Impairment;

4. DISCUSSION

Given that RA is very complex disease, various objective and subjective instruments have been proposed to capture all consequences of RA. Disease activity is a crucial parameter to measure, but considering that RA is a destructive disease that consequently has a large impact on QoL, assessment of the interplay of various evaluation instruments is necessary to collect optimal information regarding a patient's condition and to initiate proper therapy accordingly (36,37). Since RA disease mostly affects the small joints of the hand (17,134,193), the aim of our study was to investigate the relationship between RAPID3 and hand function and QoL. To our knowledge, this relationship has not previously been studied. Thus, we do not argue that RAPID3 is a substitute for the direct measurement of hand function and quality of life or vice versa, but we sought to explore to what degree RAPID3 encompasses the components of hand function and QoL, potentially representing additional value for this novel disease activity index (194).

So far various disease activity measurements have been presented, and there is growing interest in the use of PROs to capture the patient's perspective on RA disease (36,65,38,77). The use of PROs is increasing in both clinical practice and research studies, since the limitations of composite indices such as joint count or time to compute in busy clinical settings are noticeable (77). RAPID3 is a novel PRO tool to assess disease activity with documented reliability and ongoing confirmation, highlighting its advantages (88,86,91,87,3,68). Clinical trials have confirmed that RAPID3 provides similar information as DAS28, CDAI and SDAI and correlates with these disease activity measurements at very significant levels (3,5,87,89,195,196). Pincus et al. demonstrated a strong correlation between RAPID3, DAS28 and CDAI (3,5,87,89), while Amaya-Amaya et al. performed a correlation analysis showing moderate correlation between SDAI and DAS28 and between RAPID3 and DAS28, as well as a strong correlation between RAPID3, CDAI and SDAI (195). In line with the abovementioned studies, Bossert et al. confirmed the validity of RAPID3 as a disease activity measurement by comparing it with DAS28, CDAI and SDAI (196). Our work contributes to these efforts, revealing a very strong correlation between RAPID3 and DAS28. Moreover, to confirm that RAPID3 is a valuable disease activity, we showed a very strong correlation between DAS28 and components of RAPID3 (RAPID3 pain, physical function and global assessment) (194). Although Leeb et al. demonstrated that RAPID3 and RADAI are more reliable instruments than DAS28 and CDAI, contrary to our results, they reported a lower correlation between RAPID3

and DAS28, thus highlighting the advantages of RAPID3 and encouraging further studies (197).

So, based on our results and also confirming previous reports, we can state that RAPID3 is a well-established disease activity measurement tool showing similarity with DAS28 (194).

Grip strength is a simple and reliable measurement of muscle strength and is a great predictor of disability under different health conditions (198). A large body of evidence has presented grip strength normative data stratified by age and gender, which serve as reference values for clinical use and investigations (108,198,199). There are no grip strength reference values for the Kosovo population. Therefore, to show that RA patients have lower grip strength than the healthy population, we compared RA patients with a healthy age- and sex-matched reference population at a 1:1 ratio.

Our findings agree with the results obtained by Steiner et al. who showed that grip strength in a healthy female population was lower than males and that grip strength diminishes with age (198). The above-mentioned study presented its results stratified by age, gender and body height, providing grip strength thresholds that are useful for clinical purposes (198). Packer et al. compared different components of hand function, including pain, between healthy references and RA patients and found that grip strength is lower in RA patients and is not a consequence of aging but is attributable to inflammatory disease itself (199). In line with the Packer et al. study, we have also shown that grip strength in RA patients is decreased compared to that of healthy references, both overall and when stratified by age and gender.

Although our main goal was to investigate the correlation between RAPID3 and hand function, in addition to the correlation between hand outcome measures and RAPID3, we also analyzed the correlation between DAS28 and hand outcome measurements as a control for disease activity measurement (194). Interestingly, we showed a stronger correlation between RAPID3 and hand outcome measurements than between DAS28 and hand outcome measurements (194). Since hand (dis)function is almost inevitable, assessment of RA patients should include different hand components using valid and sensitive functional measurements (149,194,200,). Although various assessment tools have been developed (201) grip strength measurement remains the basis of hand function evaluation in RA patients (72,128,150) serving as one of the main indicators of disease activity (128,194). The relationships between DAS28 scores and different hand outcome measurements were confirmed by other studies (72-74,128,150,202).

Dedeoglur et al. investigated the correlation between grip strength and other RA outcome measures, identifying negative correlations with DAS28, HAQ, VAS pain and SOFI (72). Additionally, the study found correlations between DAS28 with SOFI and HAQ, (72) and these results are in accordance with our findings (194). Nevertheless, we found that the correlation between RAPID3 and grip strength was stronger than that described in the Dedeoglur study. Similarly, our study identified the strongest correlation between DAS28 and HAQ-DI, followed by that correlation between grip strength and SOFI-hand (194). Furthermore, Hallert et al. used a generalized estimated equation to investigate which factors are stronger predictors of disease activity and HAQ-DI and found that grip strength and SOFI were significant predictors of disease activity (73). We established that all hand outcome measurements correlates with RAPID3, and among them, HAQ-DI had the greatest impact, followed by grip strength, SOFI-hand and pulp-to-palm distance (194).

Moreover, given that RA is a disease without a known etiology, we must always consider other factors that may influence the disease outcome, such as gender, age, and disease duration, and stratify accordingly. In our study, although the number of females was notably higher than the number of males, the average age did not differ between either gender, nor did the duration of disease. In line with previous reports (73,74,203,168) our results show that females have higher disease activity, reduced grip strength, increased values of HAQ-DI and pulp-to-palm distance compared to males. SOFI-hand results in our patients did not agree with the findings of some other studies showing that females had better hand performance than men (73,108,146). Thus, females had a worse SOFI-hand index than males, potentially attributable to the large difference in numbers between genders. In addition, regarding possible gender differences, significant correlations were found between study variables for both genders, with the exception of RAPID3 and pulp-to-palm distance in males. In terms of disease duration, our results showed that longer disease duration does not always mean worsening of disease outcome measures. Sheehy et al. investigated correlations between study variables in early RA and found a strong correlation between DAS28 and grip strength in patients with a disease duration of less than 2 years, emphasizing the importance of assessing grip strength, which acts as a disease activity measurement in RA patients (150). These results are in accordance with our findings. Specifically, our patients with disease durations of 2-5 years showed significant correlation between RAPID3 and grip strength, as well as between RAPID3 and other hand measures. Eberhard et al. examined patients over the course of one year and showed significant correlations between hand outcome measurements (SOFI, grip strength and Grip Ability Test

(GAT)) and HAQ at the end of the study, while there were no correlations between hand outcome measurements and DAS28; the authors reasoned that the majority of RA patients exhibited disturbed hand function (149). Our overall results showed significant correlations between disease activity (RAPID3 and DAS28) and hand outcome measurements. This might be attributable to the long average disease duration (15 years) in the previous study, while the average disease duration of our patients was 9.6 years. Moreover, when we analyzed correlations between RAPID3 and hand outcome measurements in patients with longer disease duration (>11 years), we found a seemingly strong correlation between RAPID3, HAQ-DI, and grip strength, while in patients with a disease duration of 6-10 years the correlation between RAPID3 and grip strength demonstrated a moderate correlation. Also, the correlation between RAPID3 and SOFI-hand in patients with a disease duration of more than two years was significant. This finding, in which we identify a significant correlation between RAPID3 and SOFI-hand in patients with RA duration larger than 11 years, are not in accordance with the findings of Erbehard et al (149). Welsing et al. showed that in early disease functional capacity measured by HAQ-DI reflects disease activity but not radiological damage, while in late disease, HAQ-DI mostly reflects joint radiological damage (130). In our results, a significant correlation was found between RAPID3 and HAQ-DI regardless of the disease duration, with the strong correlation in patients with long disease duration (> 11 years) (194). Strong correlations between RAPID3 and HAQ-DI are also presented elsewhere. This is expected because RAPID3 is part of the modified MD-HAQ, which is the variance of HAQ (5). Kapetanovic et al. used DAS28 as a disease activity measurement, showing the contribution of disease activity to HAQ-DI over a 20-year period by following up the same patients over that period (158). These findings are also in accordance with results of other authors (204,205). Furthermore, Kapetanovic et al. demonstrated the contribution of disease activity to impairment (SOFI) at all disease durations, with the highest contribution at a disease duration of 5 years (158). In our study, we found a moderate correlation between RAPID3 and SOFI-hand (194). Another study did not use SOFI-hand for hand evaluation but did use pulp-to-palm distance and found significant correlations between DAS28, grip strength, and pulp-to-palm distance (206). Overall, our results are in accordance with that of Tastekin et al (206).

Considering different opinions regarding the influence of age at RA onset on disease outcomes (163,164), we distinguished RA onset in young and older patients. Truly in young onset group (<40 years) there were only 10 patients and perhaps, these obtained correlation results are not representative enough. However, they can provide a scientific track for further researches. Our

results showed the worsening of disease activity and function measured by HAQ with increasing age. Older patients (>60 years) had worse disease activity and hand function relative to younger patients, which appears reasonable, and is in accordance with the study by Arnold et al., although these authors evaluated patients with early RA (164). Notably, our results strengthen available evidence regarding the correlation between HAQ-DI and disease activity (usually measured by DAS28 in other studies) (72,75,107,130) our results showed a significant correlation between another measure of disease activity, RAPID3, and HAQ-DI, regardless of gender, age, disease duration and duration of morning stiffness. However, in patients with severe ROM and in patients with severe joint destruction, high disease activity does not mean the worsening of functional disability. Hakkinen et al. analyzed their data without considering factors that impact RA disease (74). Overall, their findings support our study by presenting correlations between disease activity measured by DAS28, grip strength and HAQ, indicating that pain, disease activity and grip strength impact disability (74). In a large European cohort study, Salaffi et al evaluated the validity of another PRO's disease activity measure, the rheumatoid arthritis impact of disease (RAID) score, showing a high correlation between HAQ-DI and RAID (81). However, an article by Bircan et al. demonstrated a significant, although weak, correlation between hand function and disease activity, wherein hand function was evaluated by GAT (70). Notably, the same study indicated a moderate correlation between GAT and HAQ as well as between GAT and grip strength and flexion deficit in the dominant hand (70).

Other clinical factors influence RAPID3. Traditionally, disease activity is related to radiological damage in RA patients (72,207). To date, the relationship between radiological damage in RA, scored by different assessment methods, and disease activity in cross-sectional or longitudinal studies have been demonstrated in several studies, with the annotation that disease activity has largely been measured by DAS28 (147,207,208). Of course, some papers have used other disease activity measurements, such as CDAI and SDAI, indicating that the progression of radiological damage is accompanied by an increase in disease activity (209,210). In line with these reports, our study analyzed the correlation between RAPID3 and radiological damage classified by Steinbrocker and found a significant relationship between these two variables. The recent longitudinal study of Katayama K et al., which applied RAPID3 in remission, showed that RAPID3 predicts radiological damage (211). Moreover, Keystone E et al. showed that RAPID3 better predicted radiological damage than CDAI and SDAI over time (129,212). Therefore, we can state that our results are in line with the abovementioned studies.

Various studies have focused on the relationship between radiological damage, disability and QoL in patients with RA (72,131,208,213). The correlation between radiological damage and functional disability has been demonstrated in several studies (72,131,208,213). In their longitudinal study, Navarro-Compan V et al. presented a correlation between functional disability and radiological damage by using HAQ and evaluated grip strength and dexterity as disability measures (213). In accordance with our results, they found a significant correlation between HAQ and radiological damage (213). Although the influence of radiological damage on QoL is evident, it is of a lower magnitude than that of other RA clinical measures (214). In accordance with these results, our study supports previous reports by emphasizing that the influence of radiological damage on QoL is obvious but not on the same scale as disease activity, pain or functional disability.

Although the new ACR/EULAR 2010 classification criteria do not include morning stiffness as a classification criterion for patients with RA, we consider it an outcome measurement in our study because there are reports supporting morning stiffness as a valuable measurement in the management of RA patients (105). We showed a significant correlation between RAPID3 and the duration of morning stiffness. Our results are in line with the study of Khan et al., who previously investigated the relationship between duration of morning stiffness and RAPID3 and found a better correlation between morning stiffness and RAPID3 than between morning stiffness and other variables (96). Similar to our findings, Boers et al used DAS28 as a disease activity measurement (105).

Aside from clinical measures, we investigated RAPID3 in relation to anthropometric measures, and our results are not consistent with the findings of other authors (170,172,173). Since overweight status and obesity are currently major health issues, some researchers have included BMI as a factor that influences RA. Therefore, some studies have presented a correlation between obesity and RA, mostly in women (170,172,173), although other studies did not find a correlation between BMI and RA (171,174). For example, in the QUEST-RA multi-centre study, Jawaheer et al. presented a relationship between BMI and disease activity, finding that high BMI (>30 kg/m^2) influenced disease activity among women (170). Overall, we did not find any significant contribution of BMI to the results obtained with RAPID3.

To the best of our best knowledge, this is also the first study to analyze the correlation between RAPID3 and hand anthropometric measurements we found a significant correlation between RAPID3 and hand anthropometric measurements in females, which in our opinion is influenced

by the correlation in overall findings. We have reinforced previous results regarding the correlation between grip strength and hand anthropometric measures (159,215), such as the weak to moderate correlation obtained by Fraser et al (159).

Moreover, it is known that socio-economic factors influence RA disease outcomes, including disease activity (168). In our correlation analysis, we found a significant correlation between employment status and disease activity. As Kosovo is listed among the lower middle-income countries of the world (216), and 87% of our patients were unemployed, the findings of previously mentioned authors support our results, in that patients in countries with lower GDPs are likely to have higher disease activity (168). The QUEST–RA study demonstrated a link between disease activity and GDP, and the authors concluded that disease activity levels appeared to be much more highly associated with the wealth of the country than with current medications (168).

Additionally, we found a significant correlation between education level and disease activity, with lower disease activity levels in patients with higher education. Our findings are supported by other authors such as Putrik et al., who showed that a low education level correlates with high disease activity in a large multicentric study (167). Considering that the majority of our patients (62%) fell within the elementary/no education group, we believe this factor influenced disease activity in our patients.

Studying QoL in RA patients is another crucial parameter because all RA disease components have a large impact on patient QoL (111,112). Quality of life is diminished in RA patients in comparison with the healthy population and has a negative impact on everyday function across each health domain (217), in both early disease (217,218) and established RA (219-221). The literature provides us with different findings regarding factors that influence QoL, including clinical and demographic characteristics (123,222). Disease activity is one major predictor of QoL in RA patients (123). We have shown that RAPID3, a simple tool to assess disease activity in everyday clinical practice, also encompasses hand function (194). Moreover, we found a significant correlation between components of RAPID3 and hand function data, which strengthened our findings and the value of RAPID3 (194). Furthermore, QoL is another important parameter assessed in RA patients, and the other purpose of our study was to explore whether there is a correlation between RAPID3 and QoL as measured by EQ-5D-3L. We believed that RAPID3 influences QoL because RAPID3 reflects the patient's perspective of

physical function as well as global assessment of disease activity and pain, which are clinical factors that greatly impact QoL in RA patients (75,123).

In our study, we measured our patients' QoL by using EQ-5D-3L (177), which is one of the most commonly used generic QoL instruments addressing the main aspects of RA disease (118). EQ-5D-3L is practical, has been validated elsewhere, and captures eight health domains (75,118-123,222,223). In recent years, the use of EQ-5D-3L has increased considerably, not only for RA but also for numerous other health problems (75,118-123,223). In addition to being a quality of life indicator, EQ-5D-3L is also a well-known utility measure that is used to analyze quality adjusted life years (QALY) (117). Moreover, 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 HRQoL (122).

Numerous studies have explored the correlation between disease activity and QoL (55,75,118,217,219,220). The literature provides us with information regarding the relationship between disease activity measures and EQ-5D-3L, but in general, instruments other than RAPID3 have been used to measure disease activity. As we stipulated above, this is reasonable because DAS28 has been the most widely used instrument of choice for disease activity, showing that disease activity impacts QoL in the sense that low HRQoL correlates with high disease activity (75,219). Overall, our results showed a strong correlation between RAPID3 and both EQ-5D-3L and EQ-VAS; the correlation with EQ-5D-3L is even stronger than that between DAS28 and EQ values. In 1997, Hurst et al. performed a study establishing the reliability, validity and responsiveness of EQ-5D-3L in RA patients. The authors found a significant correlation between both the EQ-5D-3L descriptive system and disease activity, which was evaluated by ACR disease activity measures (118). Radner et al. used CDAI, SDAI and DAS28 as disease activity measures with the aim to compare RA outcomes, including HRQOL, between low and remission disease activity (219). In this study HRQOL was measured by EQ-5D, SF-36 and Short Form 6 dimensions (SF-6D), which is the revised form of SF36 (219). Similar to our study, the authors showed that increased levels of disease activity were accompanied by decreased QoL (219). In addition, they found significant but moderate correlations between disease activity measurements and measurements of HRQoL (219). Notably, and unlike our study in which the majority of patients were in the moderate/high disease activity stage, the majority of patients in the above-mentioned study were in the remission/low disease activity stage (219). The similarity between our study and that of Radner et al. (219) is the disease duration, as both sets of study participants were characterized by long-

lasting disease duration, with the assumption that there was irreversible joint damage present. Moreover, Radner et al. presented a stronger correlation between QoL and functional disability measured by HAQ than with DAS28 (219), while in our correlation analysis the strongest correlation occurred between EQ-5D-3L and disease activity measured by RAPID3. In their cross-sectional study, Hoshi et al. presented a correlation between EQ-5D-3L and clinical data in RA patients, showing significant correlations regardless of gender, age, disease duration or level of disease activity (75). Overall, our results are in line with Hoshi's results (75), but if we take into consideration age, gender, disease duration, joint destruction, ROM and morning stiffness, we find certain differences between these two studies. For example, if we consider gender, we did not find a significant correlation between RAPID3 and the EQ-5D-3L descriptive system in male participants, while the correlation between RAPID3 and EQVAS in the same patients was very strong; thus, high disease activity did not impact QoL, assessed by the EQ-5D-3L descriptive system, in our male participants. We believe that this discrepancy might be attributable to the fact that Hoshi's study (75) sample was more representative than ours because it had a larger sample size. It has been established that there is a discrepancy in disease course between men and women with RA (224) as well as psychological variances between them, suggesting that needs and coping required to manage RA disease in the male population are different than those required by women (162). Thus, there is a need for further studies to explore how patients and particularly men cope with RA (162).

Another discrepancy between Hoshi's study and our study is in relates to factors that mostly contribute to EQ-5D-3L. In Hoshi's study, the most influential factor for EQ-5D-3L was J-HAQ; of note, these authors considered with explanation that dimensions of EQ-5D-3L such as mobility, self-care and usual activities are to be components of HAQ (75). In our study, the most influential factor for EQ-5D-3L was RAPID3, which is acceptable since dimensions of EQ-5D-3L are also components of the physical part of RAPID3, albeit across fewer questions. Likewise to Hoshi's study, Anyfanti et al. has have showed shown that HAQ is as the most influential factor for EQ-5D-3L; however, yet data regarding disease activity were not included in the study (123).

Regarding disease duration, we found a significant correlation in patients with a disease duration from two to twenty years, which is in line with a number of studies. Al-Fadl et al. used SF-36 to assess QoL in patients with early RA, presenting a very strong correlation between DAS28 and SF-36 and showing that RA greatly influences QoL (217). Also, the same conclusion was reached by other authors such as West et al. (218) and Aggarwal et al. (225),

who also used SF-36 as a HR-QoL instrument, identifying a significant correlation between SF-36 and DAS28.

Similar results are presented in the study of Gamal et al., in which the average disease duration was 11.2 years (220). Although we found a significant correlation in patients with a disease duration of 2 to 5 years, it is notable that we did not find a significant correlation in patients with a disease duration of less than one year. This might be because the consequences of the disease in the first year are not strong enough to decrease QoL, or, in our opinion, the sample size for that disease duration group is too small to draw any conclusion. These patients in disease duration 2-5 years are also characterized by the low QoL values, indicating that other factors, such as psychosocial factors, influence QoL in patients with RA disease (221).

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 (222). We found the strongest significant correlation between EQ-5D-3L and RAPID3, while the Cho study found significant correlations between EQ-5D-3L and study variables; there was a moderate correlation with DAS28 and a stronger correlation between EQ-5D-3L and HAQ-DI. In the Cho et al. study, as well as others, patients were stratified by level of disease, and to our surprise, functional disability did not influence QoL in moderate/high disease activity patients (222). Since our patients had high disease activity, this finding is not in line with the results of our study because functional disability is, after RAPID3, the most influenced factor of EQ-5D-3L. If we look at the study of Salaffi et al., whose purpose was to compare the QoL instruments EQ-5D-3L and SF36 and determine which was more highly correlated with RA disease parameters, we find moderate correlation between EQ-5D-3L and DAS28, showing that DAS28 is a significant predictor of QoL (226). Additionally, in accordance with these reports is a study by Fukuda et al., who showed that disease activity strongly contributes to QoL (227).

Furthermore, other studies have presented pain as the strongest predictor of QoL, showing that pain is an accompanying symptom at each RA stage and impacts QoL (55). We found a strong correlation between QoL and pain, similar to the findings of Wan et al., whose study evaluated pain in the past month (55). Nevertheless, focusing on disease activity and functional disability, our correlation analyses between RAPID3, HAQ-DI and EQ-5D-3L were stronger than those in the aforementioned study because, in regards to disease activity in our opinion, disease activity was measured by TJC and SJC. Rupp et al (214) included DAS28, pain and QoL in

their study, measuring QoL with the Dutch version of the RAND-36, and found that pain had a greater influence on the RAND36 physical health component by using standardized coefficients (b-values). Although Rupp et al. did not include either HAQ-DI or RAPID3 in their correlation analyses with HR-QoL (214), we conclude that these results are in line with our findings because we found a stronger correlation between HR-QOL and pain than between HR-QoL and DAS28.

With the exception of SF-36, there are other instruments that are used to measure QoL in RA patients (165,228). Chiu et al. used The World Health Organization Quality of Life (WHOQOL) instrument to analyze the relationship between WHOQOL, DAS28 and HAQ, aiming to define how disease activity influences QoL; they found that disease activity impacts all QoL domains, although the same cannot be said for functional disability (165). The explanation of the authors was that regardless of functional disability, improved disease activity would have been accompanied by improved QoL (165,228). In our study, RAPID3 was shown to influence QoL, both overall and in a stratified analysis. Generally, we can also state the same for HAQ-DI, both overall and in a stratified analysis. Thus, we can say that we expect worsening QoL with worsening functional disability. Additionally, other researchers have confirmed the findings of Chiu et al., who used the same instruments to measure disease activity and QoL (165). Harron et al. used another QoL instrument, WHOQOL-BREF, and found a significant correlation between this tool, DAS28 and HAQ, emphasizing that only HAQ independently affected QoL in RA patients (228), which contrasts the findings of Chui's study but is in line with our results if we only consider functional disability. Sunar et al. (229) used RA QoL scale, a disease-specific QoL instrument, demonstrating that high disease activity diminished QoL. Garip et al. evaluated QoL using one generic (Nottingham health profile - NHP) and one disease-specific instrument (RAQoL) and found a strong significant correlation between QoL and disease activity (230). A strong correlation was also found between QoL, pain, and functional disability, which agrees with the results of our study (230). The difference between our study and that of Garip et al. (230) lies in the correlation between QoL and radiological progression; we did not find a significant correlation between these two variables. Of course, others studies have found a weak correlation between radiological damage and QoL, suggesting that apart from structural changes, PRO measures must be incorporated in everyday clinical practice (214). Notably, in our study, there was a correlation between QoL, disease activity, functional disability and pain at a very significant level, regardless of a patient's joint damage.

Hence, the literature provides us with different conclusions regarding which factors have the greatest influence on QoL. It is well known that disease activity, pain and functional disability are clinical factors that largely influence QoL (75,123). Our identification of a significant correlation between only the female gender and EQ-5D-3L is in line with the studies of Anyfanit et al. and Hoshi et al., who also presented the impact of female gender on QoL (75,123). Unlike our results, a study by Rupp et al. did not find a significant relationship between gender and all components of their investigated QoL tools (214).

Although women experience more pain, they also demonstrate deteriorated functional disability, higher disease activity, and worse QoL than men (161,203,231). Therefore, we must always consider gender differences that include not only biomedical but also psychosocial and epidemiological differences (231). Age is another factor to consider because aging in RA patients is accompanied by a deterioration in QoL (123,232). This was confirmed by our study as well because we identified a significant correlation between age and QoL. On the other hand, some studies did not find any relationship between age and QoL (217).

BMI is another factor that has drawn research attention in studies aiming to investigate its influence on QoL in RA patients. As shown by Anyfanti et al., there was no significant correlation between QoL and BMI (123). Fukida et al. also explored the relationship between BMI, QoL and functional disability levels, finding that low BMI worsens QoL (227). A study by García-Poma et al. found a significant correlation between obesity in RA patients and QoL measured by SF-36 (233). The authors concluded that HRQoL was significantly reduced in obese patients with RA (233). The mean value of our patients categorizes them as overweight, but we do not have a true explanation for why there was no correlation between BMI and QoL in our patients.

In everyday life, it is necessary to have full hand function to accomplish everyday activities such as self-care, work activity, and social life. In other words, hand function has a large influence on an individual's QoL (234). The deterioration of hand function is one of the main consequences of RA, considering that the hands are involved in RA disease across almost all stages; first, swollen and painful joints act as signs of inflammation, and then later the destruction ruins the biomechanism, hand function and finally other deformities, all hindering individuals from performing daily life activities and impacting QoL (134,147). Although our main aim was to investigate the relationship between RAPID3, hand function and QoL, knowing that hand function seriously influences a person's QoL, we also sought to explore the

relationship between EQ-5D-3L and hand function. As we indicated previously, hand function was measured by valid and reliable assessment instruments in our patients, which provided us with various components of hand function (194). Overall, our results showed significant, strong to moderate correlations between EQ-5D-3L and hand function data, among which the strongest correlation was between EQ-5D-3L and HAQ-DI, followed by the correlation between EQ-5D and grip strength. Our findings are in line with other reports that have presented correlations between hand function and QoL in RA patients, and used different instruments to assess hand function and QoL. Durmus et al. used the Michigan hand questionnaire (MHQ), a reliable and valid instrument for hand function, and found a significant correlation between MHQ and all aspects of HR-QoL measured by SF-36 (235). Moreover, Waljee et al. used the MHQ but measured QoL by AIMS and found a weak correlation between MHQ and certain AIMS social domains (236). A recent study also used MHQ to explore the correlation between MHQ and preference-based quality of life measures in RA patients, showing the strongest correlation between MHQ and EQ-5D-3L and at the same time highlighting the use of EQ-5D-3L (122). However, the above-mentioned studies did not include factors that greatly impact the disease, such as gender, age, disease duration, and also impact the quality of life in RA disease (123). There is little evidence showing the correlation between grip strength and QoL in RA patients, adjusted for different factors. Sayer A et al. conducted a study to investigate the correlation between grip strength and quality of life, measured by SF36, in an older healthy population (237). In their unadjusted analysis, they found a significant correlation between grip strength and QoL in women and men, while grip strength in women was correlated with more factors of SF-36, such as physical role, vitality and bodily pain, than in men after adjustment for age and other factors (237). To strengthen our findings, we adjusted our analysis by gender, showing a non-significant correlation between hand function data and EQ-5D-3L in male patients, similar to disease activity. We can compare our results with those of Sayer et al (237), even though they included a healthy population in their study. The other factor we considered in our study was disease duration, and we found a significant correlation in patients with more than two years of disease duration. To explore quality of life in a Swedish population, West E et al. performed a longitudinal study including patients with recent onset of RA (less than 12 months duration), with follow-up for 24, 48 and 72 months (218). Their results contrast our findings because they found a significant correlation between grip strength and QoL for a disease duration of less than one year (at the inclusion), while in patients with a disease duration of two years, the correlation was not meaningful. If we look at the Dritsaki study, the mean value of

disease duration was 10 years, and a correlation was evident as mentioned above (122), is in accordance with our results.

We must emphasize that we found a significant correlation between QoL and hand function regardless of a patient's age. In our opinion, this finding is important because aging in RA patients is not consistent with physiological aging. Roma I et al. performed a study comparing QoL between adults and elderly individuals and found no difference in QoL between these age groups (238). In our patients, QoL diminished with age; however, we cannot confirm whether this trend was applicable to hand function, although a correlation between QoL and grip strength was evident.

Level of pain is one of the main outcomes in RA patients and is the most concerning for patients, who want improvement in that segment (47,48). In our study, level of pain was measured by VAS based on reporting pain intensity in the previous week (36). In general, our patients reported moderate/severe levels of pain, which was similar to the results of other studies such that of Hakkinen et al. but dissimilar to other studies presenting higher levels of pain (239,240). Moreover, in line with other studies, we reported gender differences associated with the level of pain, in that females report more pain than males, which is currently not understood (161). 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 (54,72,89). We reported that pain, RAPID3 and DAS28 worsened with age and limited ROM, as well as in patients with longer duration of morning stiffness. Moreover, our results are in accordance with other reports showing a very strong correlation between pain and disease activity (54,72,89). Andersson et al. showed that chronic widespread pain was correlated with DAS28 (54). Additionally, by analyzing general and hand pain, Thyberg et al. found moderate to strong correlation between DAS28 and pain (161), in both genders. Pincus et al. showed a very strong correlation between RAPID3 and pain (89), which is in line with our study, in which we showed that the most important factor contributing to RAPID3 was pain. This is because pain is a component of RAPID3. However, studies indicating that pain continued despite low DAS28 values should not be overlooked (50,51). Apart from correlation with disease activity, pain has been shown to influence another component, disability, as measured by HAQ. Our results are in line with previous reports demonstrating a significant correlation between pain and HAQ-DI (54,74,161).

A study by Wan et al. presented predictors of QoL in RA patients, of which the strongest

correlation was between pain and QoL (55). In addition, the same study demonstrated that pain was the most influential factor for QoL, such that patients who have greater levels of pain were expected to have worse QoL (55). Additionally, Hoshi et al. presented results indicating that pain was the second most influential factor on QoL (75). Our results confirmed these reports because we found a strong correlation between QoL and pain, not only in all patients but also following stratification by age, ROM, radiological damage and duration of morning stiffness. Similar to the relationship between RAPID3 and EQ-5D-3L, we did not find a significant correlation between pain and QoL in males or in patients at the beginning of the disease and during the late disease stage. Interestingly, at the beginning of the disease, our patients reported more pain and simultaneously had higher disease activity than patients with established disease.

Starting in early disease, hand function in RA patients is diminished, and pain is one of the main symptoms that influences the limitations of hand function (128). The results of our study strengthen these previous findings (72), because we found a significant correlation between pain and hand function data, specifically with the strongest correlation between pain and grip strength. In our opinion, the findings of Parker et al., while weakly dissimilar to our findings because Parker et al. used the MHQ to evaluate level of pain, are in line with those of our study, which identified a significant correlation between pain and grip strength (199).

Our results showed considerable correlations between different hand outcome measurements, with the strongest correlation between SOFI-hand and pulp-to-palm distance, which is understandable as the SOFI-hand index actually measures ROM (148,149). Additionally, we found a strong correlation between grip strength and functional disability, which is in line with other findings regarding the correlation between functional disability and grip strength in both early and longer disease duration (72,74,108,148,152) indicating that grip strength has a major impact on disability. A correlation between grip strength and SOFI was identified in a study by Eberhard et al., who found similar results to ours (149). In addition, the findings of our study are in accordance with those of other studies that presented significant correlations between HAQ and SOFI (149,158). In contrast to our study, Bjork et al. found a weak correlation between hand outcome measurements (grip strength, GAT and SOFI-hand), providing the plausible explanation that they measured different aspects of hand function (grip force, grip ability and ROM) (108).

The present study has a few limitations that are worth mentioning. The cross-sectional design was the most noticeable limitation (194). Although we obtained healthy controls for grip

strength at a proportion of 1:1, it is desirable to have a larger proportion of healthy controls in relation to RA patients. Additionally, the lack of a control group for HR-QoL in the Kosovar population is another shortcoming. There was an imbalance between genders, with a larger number of females (approx. 6:1), which might have influenced the hand function results since hand performance has been shown to be better in men than in women (73,148). Moreover, the limited number of patients, especially male participants may have influenced the significance of our statistical analyses when gender was taken into consideration. Another limitation was that the majority of patients demonstrated moderate to high disease activity; thus, it would be desirable to incorporate patients across the spectrum of disease activity (194). Furthermore, due to the small number of patients in particular stratified groups, as for the disease duration less than 1 year, even that we have found significant and strong correlation, in order to confirm our results further research with a larger sample size is needed.

5. CONCLUSIONS

1. In this study it was proven that RAPID3 is a simple and very attractive questionnaire for the measurement of disease activity in clinical practice. Based on the results of our study, RAPID3 appears to be a simple tool to assess disease activity in everyday clinical practice, which encompasses the function of the hand, and simultaneously reflecting QoL, despite of the patient's gender, age, disease duration, ROM, radiological damage or duration of morning stiffness.
2. A strong to moderate correlation was found between RAPID3 scores and various measurements of hand function in patients with early and established RA. Additionally, we found grip strength to be a patient's strongest predictor of disease activity. By compiling hand outcome measures together to analyze the effects of these variables on RAPID3, we found that this model provided an explanation for 50% of the variation in RAPID3; only grip strength was significant.

2.1. Also a strong correlation was found between RAPID3 and QoL measured by EQ-5D-3L, regardless of age, ROM, radiological damage, and morning stiffness, indicating that QoL is a strong predictor of disease activity measured by RAPID3.

2.2. This study added knowledge regarding the importance of different clinical RA indicators, such as functional disability and pain, to disease activity, too. Disability is one of the main predictors of RAPID3, which is expected because RAPID3 is derived from HAQ.

2.3. Although current research has confirmed that pain is one of the most common symptoms affecting disease activity, this study contributed by showing that pain is highly and meaningfully correlated with RAPID3.

2.4. The present study also explored other factors that may influence disease activity and found that gender and educational level significantly correlated RAPID3.

2.5. It has been shown that QoL is seriously diminished in RA patients. We showed that EQ-5D-3L influenced disease activity as measured by RAPID3. Conversely, we also explored the impact of disease activity on QoL and found that RAPID3 was the leading factor influencing EQ-5D-3L.

2.6. By identifying a significant relationship between hand function data and EQ-5D-3L, we showed that among hand function parameters, grip strength was the most influential factor for EQ-5D-3L.

Our results increase the value of RAPID3. With our findings, we support the application of RAPID3 in busy clinical settings where medical professionals do not regularly perform joint counts and do not even measure acute phase reactants. Although the relationship between RAPID3, hand function and QoL were, for the first time explored in this study, larger sample size and longitudinal follow-up of patients, including those with low disease activity, are needed to further evaluate our findings.

6. ABSTRACT IN CROATIAN

Reumatoidni artritis (RA) je autoimuna, kronična i progresivna bolest, koja je karakterizirana upalom sinovije, oštećenjem zglobne hrskavice i kosti, te uzrokuje značajnu onesposobljenost. Routine Assessment of Patient Index Data 3 (egl. skr. RAPID3) je mjerni pokazatelj izvještavan od strane bolesnika za aktivnost bolesti, koji uključuje fizičku funkciju, bol i ukupnu ocjenu bolesnika, a bez formalnog brojanja zahvaćenih zglobova. Kako su zahvaćenost šake i njezina smanjena funkcija važna obilježja RA, cilj ovog istraživanja bio je odrediti odnos svojstava RAPID 3 instrumenta u odnosu na funkciju šake i kvalitetu života.

U ovo istraživanje uključeno je šezdeset-osam konsekutivnih bolesnika iz reumatološke ambulante koji imaju RA (85% žene), dobi 18-75 godina. Osim demografskih i kliničkih podataka, prikupljeni su sljedeći parametri: mjere aktivnosti bolesti, RAPID3 i DAS28, mjere funkcije šake, specifično Signal of functional impairment (SOFI)-hand, snaga stiska šake, mjera stupnja zatvaranja šake (udaljenost jagodica prst-dlan), kao i mjera funkcije, Health Assessment Questionnaire-Disability Index (HAQ-DI) i kvalitete života, EUROQOL-5D-3L (EQ-5D-3L),. Pearsonova kolorelacija, Studentov t-test te i multipla regresijska analiza. Statistička značajnost je postavljena na $p < 0.05$.

Pozitivna korelacija nađena je između rezultata RAPID3 i HAQ-DI, SOFI-hand i udaljenosti između jagodica prsta i dlana, a negativna korelacija između rezultata RAPID3 i snage stiska šake. Nadalje, pozitivna korelacija je nađena između RAPID3 i EQ-5D-3L. Osim toga, utvrđena je i značajna korelacija između EQ-5D i rezultata testova funkcije šake.

Ovo istraživanje je pokazalo da su rezultati RAPID 3, vrlo praktičnog instrumenta za mjerenje aktivnosti bolesti, u snažnoj korelaciji prema mjerama funkcijske sposobnosti šake i kvalitete života. Stoga, RAPID3 se može u kliničkoj praksi primijeniti kao mjera aktivnosti bolesti koja u sebi karakterizira i funkciju šake, kao i kvalitetu života bolesnika s RA.

7. ABSTRACT

Rheumatoid arthritis (RA) is an autoimmune, chronic and progressive disease characterized by synovial inflammation, damaged cartilage and bone, causing significant disability. The Routine Assessment of Patient Index Data 3 (RAPID3) is a patient-reported disease activity measure which encompasses physical function, pain, and global health in patients with rheumatoid arthritis (RA), without formal joint counts. Since hand involvement and its decreased function are hallmarks of RA, the aim of our study was to investigate the performance of RAPID3 scores with regard to hand function and quality of life.

Sixty-eight consecutive patients with RA (85% female), aged 18-75 years, were included in the study and were recruited during their rheumatology outpatient visit. Apart from demographic and clinical data, the obtained parameters of interest included disease activity measurements, RAPID3, Disease activity score 28 (DAS28), assessments of the function of the hand, specifically, the Signal of functional impairment (SOFI)-hand, grip strength, and pulp-to-palm distance, as well the measure of functional ability, Health Assessment Questionnaire-Disability Index (HAQ-DI), and quality of life instrument, EUROQOL-5D-3L(EQ-5D-3L). Pearson's correlation coefficient, Student's t test and multiple regression were used in the statistical analysis of the results. The significance was set to $p < 0.05$.

A positive correlation was found between RAPID3, scores and HAQ-DI scores, SOFI-hand scores, and pulp-to-palm distance, and negative correlation was observed between RAPID3 scores and grip strength. The positive correlation was also found between RAPID3 and EQ-5D-3L. In addition, we have found significant correlation between EQ-5D and hand function data.

This study showed that RAPID3, as a very practical tool to assess disease activity, was strongly correlated with measurements of the functional ability of the hand, and quality of life. Therefore, RAPID3 can be used as a measure of disease activity in clinical practice characterizing hand function and quality of life in patients with RA.

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9. CURRICULUM VITAE

Merita Qorolli, maiden name Martinaj, was born on October 12, 1976 in Belgrade, Republic of Serbia. In 2005 she obtained the Bachelor degree in Physiotherapy from the University of Pristina, Republic of Kosovo. She graduated at the University of Pristina, Faculty of Medicine, Department of Physiotherapy, and received the title Master of Science in Physiotherapy, in April 2011.

In July 2011 she enrolled into the PhD program Biomedicine and Health Sciences at the University of Zagreb, School of Medicine.

Merita is currently employed as a regular teaching assistant at the Department of Physiotherapy, Faculty of Medicine, University of Pristina. After completing the continuing education for hand rehabilitation at Lund University Sweden, she has been working as a Hand Therapist, within the Department of Physical Medicine and Rehabilitation at University Clinical Center of Kosova.

She is married and has a son.

10. APPENDIX

Appendix I- Examination sheet

EXAMINATION SHEET

Association of disease activity measured by RAPID3 with physical function of the hand and quality of life in patients with rheumatoid arthritis

Name and surname: _____
Address: _____
Date of birth: _____

Gender: M ☐ F ☐

Education level: no education ☐ elementary school ☐ secondary school ☐

bachelor or equivalent ☐ master or equivalent ☐ doctoral ☐

Occupation: _____

Marriage status: Married ☐ Single ☐ Divorced ☐

Family history of Rheumatoid Arthritis: Yes ☐ No ☐

If yes, who in the family: .....

Duration of disease (in years): .....

Drug intake: Yes ☐ No ☐

If yes which (circle the corresponding number):
1. Simple analgesics 2. Non-steroidal antirheumatic
3. Disease modifying anti-rheumatic 4. Glucocorticoids (orally)

Hand dominance: left ☐ right ☐

Morning stiffness: Yes ☐ No ☐ If yes, how long (in minutes): ..... ☐

Number of painful joints (28) ..... ☐

Number of swollen joints (28) ..... ☐

How much pain did you have during the last 24h VAS (mm)..... ☐
(Mark on the given Visual Analog Scale –VAS and results put in the box)



0 100
no pain pain as bad as it can be

JAM SCALE ..... ☐

STEINBROCKER SCALE ..... ☐

RAPID3* ..... ☐

EUROQOL-5D* ..... ☐

DAS 28 ..... ☐

HAQ-DI* ..... ☐

SOFI-hand ..... ☐

*Complete given questionnaire, and obtained results put in the box

Anthropometric measures:

Body height (cm) .....
Body weight (kg) .....

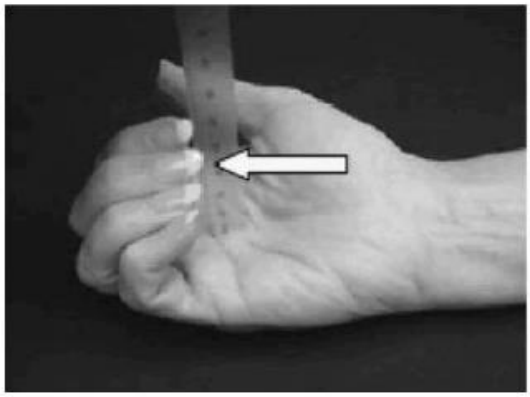
	Right hand	Left hand
Length of the forearm (cm)		
Circumference of the forearm (cm)		
Length of the hand (cm)		
Circumference of the arm (cm)		

	Right hand				Left hand			
a. Grip strength (kg)								
b. Pulp to palm distance (mm)	II	III	IV	V	II	III	IV	V

a. measurement of grip strength using Jamar dynamometer



b. measurement of pulp to palm distance



Hand Physiotherapy in last three months: Yes □ No □
If Yes how many times during this period: _____
If Yes which physiotherapy (circle the corresponding number, multiple choices are possible):

1. Therapeutic exercises
2. Electrotherapy
3. Thermotherapy
4. Splinting

Date: Examiner:

....

Note: During the evaluation, the same rheumatologist will be present

RAPID3
ROUTINE ASSESSMENT OF PATIENT INDEX DATA

The RAPID3 includes a subset of core variables found in the Multi-dimensional HAQ (MD-HAQ). Page 1 of the MD-HAQ, shown here, includes an assessment of physical function (section 1), a patient global assessment (PGA) for pain (section 2), and a PGA for global health (section 3). RAPID3 scores are quickly tallied by adding subsets of the MD-HAQ as follows:

1. PLEASE CHECK THE ONE BEST ANSWER FOR YOUR ABILITIES AT THIS TIME:

OVER THE LAST WEEK, WERE YOU ABLE TO:	WITHOUT ANY DIFFICULTY	WITH SOME DIFFICULTY	WITH MUCH DIFFICULTY	UNABLE TO DO
a. Dress yourself, including tying shoelaces and doing buttons?	___ 0	___ 1	___ 2	___ 3
b. Get in and out of bed?	___ 0	___ 1	___ 2	___ 3
c. Lift a full cup or glass to your mouth?	___ 0	___ 1	___ 2	___ 3
d. Walk outdoors on flat ground?	___ 0	___ 1	___ 2	___ 3
e. Wash and dry your entire body?	___ 0	___ 1	___ 2	___ 3
f. Bend down to pick up clothing from the floor?	___ 0	___ 1	___ 2	___ 3
g. Turn regular faucets on and off?	___ 0	___ 1	___ 2	___ 3
h. Get in and out of a car, bus, train, or airplane?	___ 0	___ 1	___ 2	___ 3
i. Walk two miles or three kilometers, if you wish?	___ 0	___ 1	___ 2	___ 3
j. Participate in recreational activities and sports as you would like, if you wish?	___ 0	___ 1	___ 2	___ 3
k. Get a good night's sleep?	___ 0	___ 1.1	___ 2.2	___ 3.3
l. Deal with feelings of anxiety or being nervous?	___ 0	___ 1.1	___ 2.2	___ 3.3
m. Deal with feelings of depression or feeling blue?	___ 0	___ 1.1	___ 2.2	___ 3.3

1. a-j FN (0-10):

1=0.3 16=5.3
2=0.7 17=5.7
3=1.0 18=6.0
4=1.3 19=6.3
5=1.7 20=6.7
6=2.0 21=7.0
7=2.3 22=7.3
8=2.7 23=7.7
9=3.0 24=8.0
10=3.3 25=8.3
11=3.7 26=8.7
12=4.0 27=9.0
13=4.3 28=9.3
14=4.7 29=9.7
15=5.0 30=10

2. PN (0-10):

3. PTGE (0-10):

RAPID3 (0-30)

2. HOW MUCH PAIN HAVE YOU HAD BECAUSE OF YOUR CONDITION OVER THE PAST WEEK? PLEASE INDICATE BELOW HOW SEVERE YOUR PAIN HAS BEEN:

NO PAIN — PAIN AS BAD AS IT COULD BE

0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0 8.5 9.0 9.5 10

3. CONSIDERING ALL THE WAYS IN WHICH ILLNESS AND HEALTH CONDITIONS MAY AFFECT YOU AT THIS TIME, PLEASE INDICATE BELOW HOW YOU ARE DOING:

VERY WELL — VERY POORLY

0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0 8.5 9.0 9.5 10

CONVERSION TABLE

Near Remission (NR): 1=0.3; 2=0.7; 3=1.0
Low Severity (LS): 4=1.3; 5=1.7; 6=2.0
Moderate Severity (MS): 7=2.3; 8=2.7; 9=3.0; 10=3.3; 11=3.7; 12=4.0
High Severity (HS): 13=4.3; 14=4.7; 15=5.0; 16=5.3; 17=5.7; 18=6.0; 19=6.3; 20=6.7; 21=7.0; 22=7.3; 23=7.7; 24=8.0; 25=8.3; 26=8.7; 27=9.0; 28=9.3; 29=9.7; 30=10.0

HOW TO CALCULATE RAPID 3 SCORES

1. Ask the patient to complete questions 1, 2, and 3 while in the waiting room prior to his/her visit.
2. For question 1, add up the scores in questions A-J only (questions K-M have been found to be informative, but are not scored formally). Use the formula in the box on the right to calculate the formal score (0-10). For example, a patient whose answers total 19 would score a 6.3. Enter this score as an evaluation of the patient's functional status (FN).
3. For question 2, enter the raw score (0-10) in the box on the right as an evaluation of the patient's pain tolerance (PN).
4. For question 3, enter the raw score (0-10) in the box on the right as an evaluation of the patient's global estimate (PTGE).
5. Add the total score (0-30) from questions 1, 2, and 3 and enter them as the patient's RAPID 3 cumulative score. Use the final conversion table to simplify the patient's weighed RAPID 3 score. For example, a patient who scores 11 on the cumulative RAPID 3 scale would score a weighed 3.7. A patient who scores between 0–1.0 is defined as near remission (NR); 1.3–2.0 as low severity (LS); 2.3–4.0 as moderate severity (MS); and 4.3–10.0 as high severity (HS).

The STANFORD HEALTH ASSESSMENT QUESTIONNAIRE©
Stanford University School of Medicine, Division of Immunology & Rheumatology

HAQ Disability Index:
In this section we are interested in learning how your illness affects your ability to function in daily life. Please feel free to add any comments on the back of this page.

Please check the response which best describes your usual abilities OVER THE PAST WEEK:

	Without ANY difficulty [0]	With SOME difficulty [1]	With MUCH difficulty [2]	UNABLE to do [3]
DRESSING & GROOMING				
Are you able to:				
-Dress yourself, including tying shoelaces and doing buttons?	☐	☐	☐	☐
-Shampoo your hair?	☐	☐	☐	☐
ARISING				
Are you able to:				
-Stand up from a straight chair?	☐	☐	☐	☐
-Get in and out of bed?	☐	☐	☐	☐
EATING				
Are you able to:				
-Cut your meat?	☐	☐	☐	☐
-Lift a full cup or glass to your mouth?	☐	☐	☐	☐
-Open a new milk carton?	☐	☐	☐	☐
WALKING				
Are you able to:				
-Walk outdoors on flat ground?	☐	☐	☐	☐
-Climb up five steps?	☐	☐	☐	☐

Please check any AIDS OR DEVICES that you usually use for any of these activities:

- ☐ Cane
- ☐ Walker
- ☐ Crutches
- ☐ Wheelchair
- ☐ Devices used for dressing (button hook, zipper pul long-handled shoe horn, etc.)
- ☐ Built up or special utensils
- ☐ Special or built up chair
- ☐ Other (Specify:_____)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

- ☐ Dressing and Grooming
- ☐ Arising
- ☐ Eating
- ☐ Walking

Please check the response which best describes your usual abilities **OVER THE PAST WEEK:**

	Without ANY difficulty [0]	With SOME difficulty [1]	With MUCH difficulty [2]	UNABLE to do [3]
HYGIENE				
Are you able to:				
-Wash and dry your body?	☐	☐	☐	☐
-Take a tub bath?	☐	☐	☐	☐
-Get on and off the toilet?	☐	☐	☐	☐
REACH				
Are you able to:				
-Reach and get down a 5-pound object (such as a bag of sugar) from just above your head?	☐	☐	☐	☐
-Bend down to pick up clothing from the floor?	☐	☐	☐	☐
GRIP				
Are you able to:				
-Open car doors?	☐	☐	☐	☐
-Open jars which have been previously opened?	☐	☐	☐	☐
-Turn faucets on and off?	☐	☐	☐	☐
ACTIVITIES				
Are you able to:				
-Run errands and shop?	☐	☐	☐	☐
-Get in and out of a car?	☐	☐	☐	☐
-Do chores such as vacuuming or yardwork	☐	☐	☐	☐

Please check any AIDS OR DEVICES that you usually use for any of these activities:

☐ Raised toilet seat
☐ Bathtub seat
☐ Jar opener (for jars previously opened)
☐ Bathtub bar
☐ Long-handled appliances for reach
☐ Long-handled appliances in bathroom
☐ Other (Specify:_____)

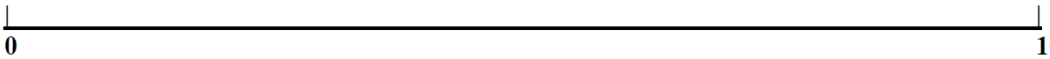
Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

☐ Hygiene
☐ Reach
☐ Gripping and opening things
☐ Errands and chores

We are also interested in learning whether or not you are affected by pain because of your illness.
How much pain have you had because of your illness IN THE PAST WEEK:

PLACE A VERTICAL (|) MARK ON THE LINE TO INDICATE THE SEVERITY OF THE PAIN

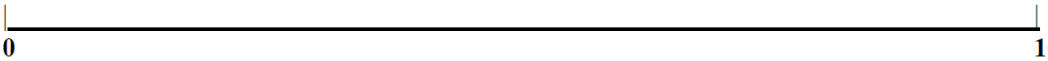
No Pain — **Severe Pain**



0 — **100**

Considering all the ways that your arthritis affects you, rate how you are doing on the following scale by placing a vertical mark on the line.

Very Well — **Very Poor**



0 — **100**



Health Questionnaire

English version for the UK

(Validated for Ireland)

Sample

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By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities *(e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain / Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety / Depression

I am not anxious or depressed ❑

I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

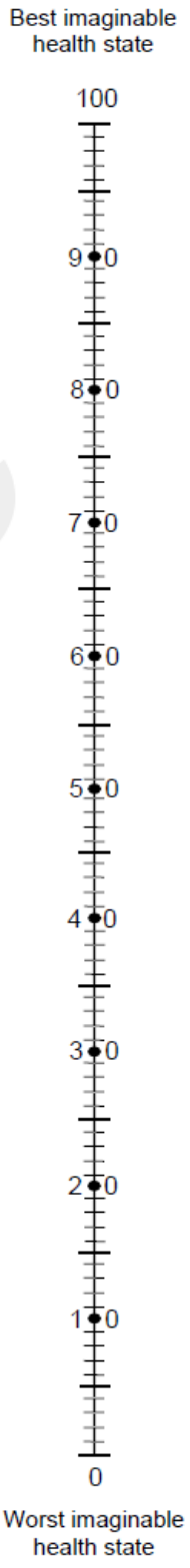
Sample

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To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Sample

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