EUROPEAN CLINICAL RESPIRATORY JOURNAL
2025, VOL. 12, 2449270
https://doi.org/10.1080/20018525.2024.2449270

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RESEARCH ARTICLE

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Detecting respiratory impairment in newly diagnosed rheumatoid arthritis by MRC dyspnoea scale and microfibrillar-associated protein 4

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ABSTRACT

Objectives: To evaluate the Medical Research Council (MRC) dyspnoea scale and serum Microfibrillar-associated protein 4 (MFAP4) levels for the detection of respiratory impairment in newly diagnosed rheumatoid arthritis (RA).

Methods: Patients underwent blood tests, pulmonary function tests (PFT) and dyspnoea assessment using the MRC scale. Respiratory impairment was defined as a diffusion capacity of the lungs for carbon monoxide (DLCO) <80% predicted or FEV1/FVC <70%. The primary outcomes were the MRC and MFAP4's sensitivity, specificity, and diagnostic odds ratio (DOR) with 95% confidence intervals (CI).

Results: One hundred and thirty-one patients had available baseline tests. Mean age was 57.7 years (SD: 10.9), 61% were female, and 45% had respiratory impairment. For MRC score ≥ 2, the sensitivity was 39.0% (95% CI 26.5; 52.6), specificity 76.4% (95% CI 64.9; 85.6), and DOR 2.07 (95% CI 0.97; 4.40). For MFAP4 > 29.0 U/mL, the sensitivity was 62.7% (95% CI 49.1; 75.0), specificity 56.9% (95% CI 44.7; 68.6), and DOR 2.22 (95% CI 1.10; 4.50). The DOR was 3.01 (95% CI 1.27; 7.16) for MFAP4 detecting respiratory impairment when adjusted for age, sex and smoking status.

Conclusion: The MRC dyspnoea score and unadjusted MFAP4 levels were poor predictors of respiratory impairment in patients with early treatment-naïve rheumatoid arthritis.

ARTICLE HISTORY
Received 23 August 2024
Accepted 30 December 2024

KEYWORDS
Rheumatoid arthritis; respiratory impairment; MRC; MFAP4; Early detection

Background

Rheumatoid arthritis (RA) is a chronic inflammatory disease, and all-cause mortality in RA is highest within the first 7 years following the diagnosis [1]. Preclinical and clinical lung disease, such as interstitial lung disease (ILD), chronic obstructive pulmonary disease (COPD) and bronchiectasis, are highly prevalent in RA [2,3]. ILD and (COPD), are associated with increased mortality in RA [4,5]. This emphasises the importance of early diagnosis and treatment of both rheumatoid arthritis and concomitant lung disease. A recent consensus statement on screening for RA-associated ILD, a serious type of pulmonary manifestation of RA, states that currently, no credible patient-reported outcome measures (PROMS) exist for detection of lung disease in RA [6]. IgM rheuma factor (RF) and anti-citrullinated protein antibody (ACPA) are associated with an increased risk of ILD [7]. However, the sensitivity and specificity are not high, and another recent systematic review states that studies on biomarkers, other than IgM RF and ACPA, for the detection of ILD are needed [8].

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/20018525.2024.2449270

The Medical Research Council (MRC) dyspnoea scale has been used for many years to grade the effect of breathlessness on daily activities, mainly in COPD [9,10]. It is easy to administer and reflects the walking test performance [11]. MRC grade 1–2 is regarded within the normal range. However, patients with COPD and self-reported MRC grade 2 have lower exercise tolerance than healthy individuals with self-reported MRC grade 2 [12]. RA is associated with an increased risk of lung disease. This cohort was initially designed to map co-morbidities in treatment naïve RA patients; the MRC dyspnoea score was included as a simple tool for symptom characterisation that complements pulmonary function testing. The MRC dyspnoea score has not previously been tested as a screening tool in treatment naïve patients with newly diagnosed RA.

Increased serum Microfibrillar-associated protein 4 (MFAP4) has been shown to reflect disease-induced processes and has low heritability and limited basal variation [13]. MFAP4 has exceptionally high expression in the heart and small intestine, and increased MFAP4 have been correlated to liver cirrhosis as well as diabetic neuropathy [14,15]. Further, MFAP4 has been localised in the pulmonary arterioles and interalveolar walls, and studies have found that MFAP4 may have a role in healthy tissue remodelling of the lungs [16,17].

The overall aim of the present study was to explore the diagnostic accuracy of the MRC dyspnoea score and serum MFAP4 in detecting respiratory impairment in early RA using pulmonary functional testing (PFT) as the reference standard. Furthermore, other RA-associated co-morbidities, such as cardiovascular diseases (CVDs) [18], may present with dyspnoea or abnormal PFT. The secondary aim is to assess the MRC or MFAP4 reflected underlying CVD, using the available transthoracic echocardiography (TTE) assessed left ventricular ejection fraction (LVEF) as a proxy.

Methods

This study is based on baseline data from a prospective cohort study, where treatment-naive patients with newly diagnosed RA, according to the European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) criteria [19], were included at the Department of Rheumatology, Silkeborg Regional Hospital, Denmark. Inclusion took place in the period from 2011 to 2019. To be eligible, patients had to be a minimum of 18 years of age, newly diagnosed with RA, naïve to treatment for RA, and able to understand and sign informed consent. The pre-specified statistical analysis plan (SAP) for for this study was initiated after the first results from this cohort had been published [20] but before accessing and analysing data regarding the MRC dyspnoea scale and serum MFAP4. Reporting of this diagnostic test accuracy study follows the STARD 2015-guideline (the *Standards for the Reporting of Diagnostic Accuracy Studies*) [21].

Patients answered the MRC dyspnoea questionnaire within 6 months after inclusion. Serum samples were collected at the time of inclusion, and serum MFAP4 levels were detected using the AlphaLISA technique, as described in Wulf-Johansson, H. et al. [16]. The Department of Molecular Medicine, University of Southern Denmark, Odense, Denmark, was responsible for MFAP4 measurements.

PFTs (forced expiratory volume in one second (FEV1), forced vital capacity (FVC), total lung capacity, residual volume, diffusing capacity of the lungs for carbon monoxide (DLCO)), and Six-Minute Walk Test, were performed according to the European Respiratory Society recommendations [22–25] as previously reported [20]. All tests were performed within 6 months after the RA diagnosis. DLCO measurements were corrected for haemoglobin in the case of anaemia. Respiratory impairment was defined as DLCO < 80% and/or index (FEV1/FVC) <70%.

Other RA-associated co-morbidities, such as cardiovascular diseases (CVDs) [18], may present with dyspnoea or abnormal PFT. Patients underwent transthoracic echocardiography (TTE). Left ventricular (LV) dimensions, volumes, and ejection fraction (LVEF) were measured offline using standard methods. The LVEF was calculated by a modified biplane Simpson´s method from apical 4- and 2-chamber views, as previously reported [26]. The lung parenchyma was evaluated using CT imaging, obtained as part of a cardiac CT performed within 6 months after the RA diagnosis (baseline). Except the very apical parts of the upper lobes, which are not included on cardiac CT, whole-lung CT imaging was available, and the imaging quality allowed systematic evaluation of the lung parenchyma for pulmonary disease, as previously reported on this cohort [20].

Statistical methods

Descriptive data are presented as mean and standard deviation (SD) or median and interquartile range (IQR) if continuous and as frequencies if categorical. We calculated the standardised differences to compare the distribution of baseline covariates between groups

[27]: a standardised difference above 0.5 SD-units indicated a potentially significant imbalance and difference between exposure groups. The comparison was made using a t-test, Wilcoxon rank sum, or chi-squared test, as appropriate.

We explored the best fit for the cut-off value for MRC and MFAP4 for detection of respiratory impairment, using receiver operating characteristic (ROC) curves. These plots consist of two parameter estimates: True Positive Rate (sensitivity) and False Positive Rate (1- Specificity), i.e. two primary measures of quantifying the diagnostic accuracy of a test. Sensitivity is defined as the ability of the index tests to detect respiratory impairment when it is truly present, i.e. the probability of a positive test index test result, given that the patient has respiratory impairment. Specificity is the ability of the tests to exclude the condition in RA patients who do not have respiratory impairment, i.e. the probability of a negative index test result, given that the patient does not have respiratory impairment [28]. The associated 95% confidence intervals (CI) were also calculated for all diagnostic outcome measures. The optimal cut-off was calculated using Youden's Index. Finally, we tested the sensitivity and specificity of combining MRC and MFAP4 by applying c-statistics [29]. Since all patients underwent both diagnostic tests, we used statistical methods appropriate for paired data accounting for the correlated binary outcomes (McNemar's test).

Deviations from the original SAP: We initially planned to also evaluate the New York Heart Association (NYHA) classification score as a diagnostic test. However, due to many missing NYHA scores and TTE examinations, they were excluded from the primary analysis, and TTE data is presented as supplementary material.

Missing index tests (MRC score or MFAP4 measurements) led to exclusion from the primary analysis. The reference standard was dichotomised into DLCO < 80% of predicted or FEV1/FVC <70. Missing PFTs or serum samples led to the exclusion of the patient from the primary analysis population. Analyses were performed using Stata statistical software (version 15; StataCorp, College Station, TX, USA).

Results

Of the 150 patients with treatment naïve RA included in the study, 19 had missing PFT, MRC, or blood samples and were excluded from the primary analysis population (Figure 1). Of the 131 included patients, 61% were female, and the mean age was 57.7 years. Forty-five percent were categorised as having respiratory impairment, of whom 46% were male and 39% were current smokers (Table 1). There was a significant difference between the MRC score (p-value 0.042), age (p-value 0.015), smoking pack years (p-value <0.001), current smoking status (p-value 0.002), LVEF (p-value

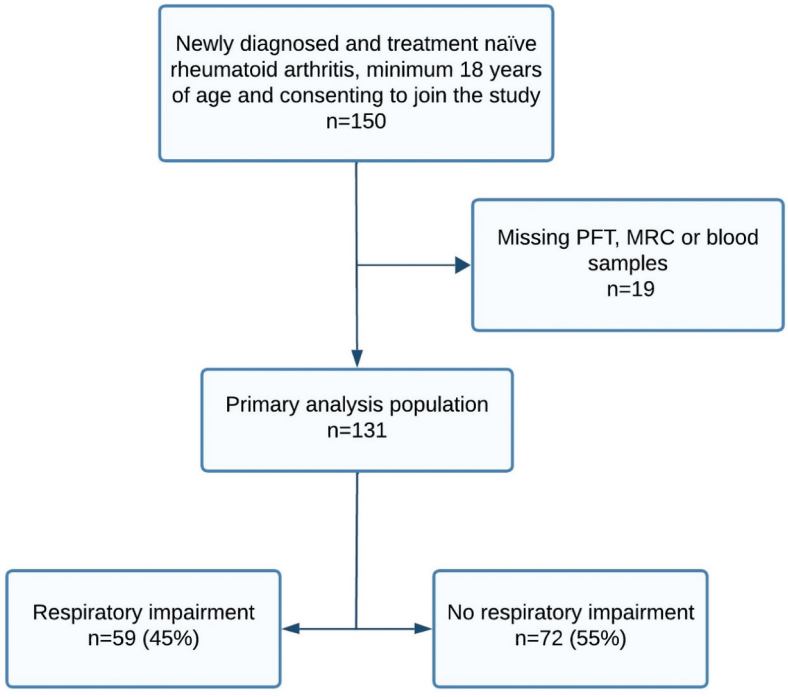

Figure 1. n = number, PFT = Pulmonary function test, MRC = Medical Research Council dyspnoea scale

Table 1. Patient characteristics.

	Total (*N*=131)	Respiratory impairment (*n*=59)	No respiratory impairment (*n*=72)	StdD	P-value
MRC, median (IQR):	1.0 (1.0; 2.0)	1.0 (1.0; 2.0)	1.0 (1.0; 1.0)	0.4	0.042*
MFAP4, median (IQR)	30.1 (22.3; 40.8)	32.1 (24.4; 42.1)	27.5 (20.8; 36.6)	0.1	0.101
Age, years, mean (SD)	57.7 (10.9)	60.2 (9.8)	55.6 (11.4)	0.4	0.015*
Female, n (%)	80 (61%)	32 (54%)	48 (67%)	−0.3	0.155
BMI (kg/m2) (SD)	26.4 (5.1)	25.9 (4.9)	26.7 (5.3)	−0.2	0.476
ACPA, median (IQR)	86.0 (1.0; 340.0)	35.0 (1.0; 250.0)	141.5 (1.0; 340.0)	−0.4	0.063
IGM-RF, median (IQR)	14.0 (2.0; 74.0)	11.0 (1.0; 50.0)	18.5 (3.5; 76.0)	−0.1	0.189
Packyears, median (IQR)	8.0 (0.0; 25.0)	20.0 (3.0; 36.0)	0.0 (0.0; 14.5)	0.6*	<0.001
Current smoking status					0.002*
Never smoker, n (%)	55 (42%)	16 (27%)	39 (54%)	−0.6*	
Former smoker, n (%)	42 (32%)	20 (34%)	22 (31%)	0.1	
Current smoker, n (%)	34 (26%)	23 (39%)	11 (15%)	0.6*	
CRP, median (IQR)	4.5 (1.6; 12.2)	4.8 (1.6; 10.7)	4.4 (1.6; 13.6)	0.0	0.804
DAS28CRP, mean (SD)	4.8 (4.1; 5.3)	4.8 (4.2; 5.3)	4.7 (4.1; 5.3)	0.0	0.839
FEV1% predicted), mean (SD)	99.8 (18.2)	91.5 (16.2)	106.7 (17.0)	N/A	N/A
FVC (% predicted), mean (SD)	106.6 (18.3)	102.8 (15.4)	109.7 (20.0)	N/A	N/A
FEV1/FVC (%), mean (SD)	77.6 (9.1)	73.1 (10.0)	81.3 (6.1)	N/A	N/A
TLC (% predicted), mean (SD)	104.9 (15.3)	105.6 (16.4)	104.4 (14.4)	0.1	0.647
DLCO (% predicted), mean (SD)	84.3 (15.8)	72.5 (10.5)	94.0 (12.6)	N/A	N/A
**6MWD, meters, mean (SD)	616.0 (169.0)	604.4 (180.0)	625.4 (160.2)	−0.1	0.503
**6MWD, Δ-Desat, mean (SD)	0.0 (0.0; 1.0)	0.0 (0.0; 2.0)	0.0 (0.0; 1.0)	0.0	0.531
**LVEF, %, mean (SD)	56.0 (6.7)	54.4 (6.7)	57.4 (6.4)	−0.5*	0.025*
**LVEF <50%, n (%)	19 (20%)	12 (26%)	7 (14%)	0.3	0.202
FEV1/FVC <70%, n (%)	25 (19%)	25 (42%)	0 (0%)	N/A	N/A
**Emphysema, n (%)	28 (22%)	18 (32%)	10 (14%)	0.4	0.019*
**Bronchiectasis, n (%)	38 (30%)	21 (38%)	17 (24%)	0.3	0.122
**ILD, n (%)	2 (2%)	1 (2%)	1 (1%)	0.0	1.000

StdD = Standardized difference, SD = standard deviation, IQR = Interquartile range, BMI = Body mass index, ACPA = Anti-citrullinated protein antibody, IgM RF = IgM rheumatoid factor, CRP = C-Reactive protein, DAS28CRP = Disease activity score-28 for rheumatoid Arthritis with CRP, FEV1 = Forced expiratory volume in 1 second, FVC = Forced vital capacity, TLC = Total lung capacity, DLCO = Diffusing capacity for carbon monoxide, 6MWD = 6-min walk distance, Desat. = Desaturation, LVEF = Left ventricular ejection fraction, n = number, PFT = pulmonary function test, MRC = medical research council dyspnoea scale. *StdD = Moderate effect size, *p-value <0.05, **= data not complete. **LVEF data on 97 patients. **emphysema, bronchiectasis and ILD based on cardiac CT on 126 patients.

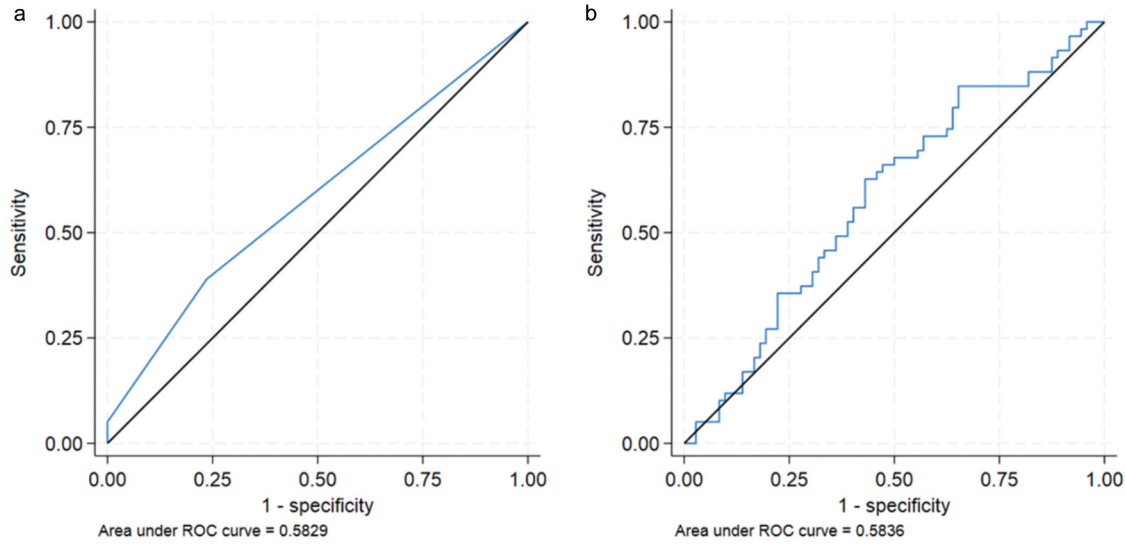

Figure 2. a. ROC curve for MRC detecting lung impairment. b: ROC curve for unadjusted MFAP4 detecting lung impairment.

0.025), and radiological presence of emphysema (P-value 0.019) on being categorised as having respiratory impairment.

The ROC curves for the detection of respiratory impairment had an AUC of 0.583 for MRC and 0.584 for MFAP4 (Figure 2). The cut-off value for MRC was 2,

Table 2. Diagnostic outcome measures.

	MRC ≥ 2 n=40 (30.5%)	MFAP4 ≥ 29.0 n=68 (52.0%)	Combined* n=84 (64.1%)
Diagnostic OR (95% CI)	2.07 (0.97; 4.40)	2.22 (1.10; 4.50)	1.76 (0.85 to 3.67)
Sensitivity, % (95% CI)	39.0 (26.5; 52.6)	62.7 (49.1; 75.0)	71.2 (57.9 to 82.2)
Specificity, % (95% CI)	76.4 (64.9; 85.6)	56.9 (44.7; 68.6)	41.7 (30.2 to 53.9)
Positive predictive value, % (95% CI)	57.5 (40.9; 73.0)	54.4 (41.9; 66.5)	50.0 (38.9 to 61.1)
Negative predictive value, % (95% CI)	60.4 (49.6; 70.5)	65.1 (52.0; 76.7)	63.8 (48.5 to 77.3)

Table 2 legend: MRC = The Medical Research Council dyspnoea scale (range 1–5), MFAP4=Microfibrillar-associated protein 4, n = number, CI = confidence interval, OR = Odds ratio. *MRC ≥ 2 or MFAP4 ≥ 29.0

and the cut-off value for MFAP4 was 29.0 U/ml. The corresponding diagnostic odds ratio (DOR) of the MRC score was 2.07 (0.97; 4.40), with a sensitivity of 39.0 (26.5; 52.6), a specificity of 76.4 (64.9; 85.6), a PPV of 57.5 (40.9; 73.0) and NPV of 60.4 (49.6; 70.5) (Table 2). MFAP4 ≥ 29.0 U/mL had a DOR of 2.22 (95% CI: 1.10 to 4.50), a sensitivity of 62.7 (49.1; 75.0), a specificity of 56.9 (44.7; 68.6), a PPV of 54.4 (41.9; 66.5), and an NPV of 65.1 (52.0; 76.7). C-statistics for combining MRC and MFAP4 had a c-index of 0.612 (95% CI: 0.514 to 0.710). A logistic regression analysis on MFAP4 ≥ 29.0, adjusted for age, sex, and smoking status, showed a DOR of 3.01 (95% CI 1.27 to 7.16) for respiratory impairment.

In this cohort, 97 patients underwent echocardiography, with an assessment of LVEF, which was significantly lower among patients with respiratory impairment (Table 1). The proportion of patients with low LVEF (<50%) was higher among patients with respiratory impairment, where 12/19 (63%) had respiratory impairment and 7/19 (37%) did not (Table 1). Cohen's D was 0.5 for LVEF and 0.3 for LVEF < 50%, indicating reduced LVEF as having a moderate to small effect size on patients classified as having lung impairment, i.e. data-driven confounder. Exploratory analysis of MRC and MFAP4 in detecting reduced LVEF showed no correlation (see supplementary Figure S1 and Table S1).

Discussion

This is the first study to evaluate MRC for detecting respiratory impairment in treatment naïve RA patients. In the pre-specified and crude analysis, MRC dyspnoea score ≥ 2 was more prevalent among patients with respiratory impairment. However, the sensitivity was low and specificity moderate, at 39% and 76%, respectively. The minimal but significant difference in MRC levels between patients with and without respiratory impairment might indicate that the MRC dyspnoea score has potential as a detection method. However, median MRC values were similar, with a broader IQR in the respiratory impairment group and few patients in this cohort reported an MRC > 2, corresponding to a relatively low dyspnoea burden in this cohort.

MFAP4 levels were higher among patients with lung impairment, although insignificant. For serum MFAP4 ≥ 29.0 U/mL the DOR was 2.22, and the sensitivity and specificity were low, indicating that unadjusted MFAP4 is not a good fit for detecting respiratory impairment in newly diagnosed RA. However, when adjusted for known confounding factors (age, sex, and smoking status), MFAP4 had an improved DOR of 3.01 for detecting respiratory impairment. Our findings support the idea that when evaluating circulating MFAP4 levels, these variables should be considered for diagnostic or prognostic purposes in clinical studies [30]. Combining the tests (MRC and unadjusted MFAP4) did increase sensitivity slightly with a corresponding decrease in specificity. The AUC for MRC and MFAP4 were <0.6, indicating a low correlation for the tests detecting respiratory impairment.

Increased circulating MFAP4 has been associated with increased extracellular matrix (ECM) turnover, which can occur as part of active inflammation or active fibrosis [30,31]. Issa et al., (2020) found MFAP4 to be increased in manifest RA, but not significantly increased in early RA and not associated with RA disease activity or synovitis [32]. Since RA typically involves smaller joints, the inflamed areas may be small and thus, circulating MFAP4 May not increase in RA, which primarily affects the joints. An increase in circulating MFAP4 may be due to comorbidities, such as active pulmonary involvement, where lung tissue remodelling and fibrotic activity due to active RA in the lungs could increase circulating MFAP4. Similar findings have been reported in asthma [33,34].

Dyspnoea, impaired DLCO, and increased MFAP4 may also be caused by underlying cardiovascular disease [32,35]. In this cohort, 97 patients underwent echocardiography, with an assessment of LVEF. Patients with respiratory impairment seemed to have a lower LVEF; however, clinically reduced LVEF (<50%) showed no difference between the groups, and there was no correlation between MRC or MFAP4 and reduced LVEF.

A strength of this study is the inclusion of newly diagnosed treatment naive RA patients, with respiratory assessment by pulmonary functions testing. It is a limitation to the study that few patients had clinical lung disease, as previously described in this cohort [20]. The MRC questionnaire measures the patient's subjective dyspnoea experience. It is not specific for respiratory disease, and does not include other respiratory symptoms indicating lung disease, such as cough or tightness of the chest. Slight respiratory impairment based on PFTs may not be clinically relevant and is possibly less likely to increase biomarkers originating from active lung inflammation. MFAP4 had a significant DOR for detecting respiratory impairment in the pre-specified unadjusted analysis. However, the sensitivity was low: this could be due to tissue remodelling without significant leak of MFAP4 from ECM in the lungs to the bloodstream, as MFAP4 is primarily upregulated in the affected tissue [36,37]. Likewise, MFAP4 was slightly increased in respiratory-impaired patients, but the difference was insignificant. Patients in this cohort may not have active or possibly limited lung inflammation as the cause of their lung impairment. We report unadjusted OR and sensitivity/specificity/PPV/NPV for our markers. We compared the OR with an adjusted OR to detect how much the adjustment influences the association. We decided not to estimate adjusted sensitivity/specificity/PPV/NPV, as such estimates would correspond to cut-offs varying by covariates, more akin to a full-scale prediction model than our diagnostic analysis. We considered such a model not feasible for the current sample size.

Risk factors associated with lung disease, specifically ILD, in RA are high-titer IgM RF or ACPA, older age at the time of RA onset, current or former smoker, and male sex, and are part of proposed risk scores for ILD in RA [38,39]. Importantly, inquiring about early respiratory symptoms is recommended as part of the routine work-up in RA [7,40]. PROMS may prove helpful in systematically evaluating respiratory symptoms in RA as part of their clinical workup. We recommend prospective studies to test the diagnostic utility of the MRC dyspnoea scale, other relevant PROMS, and biomarkers such as MFAP4 in, e.g. selected RA patients where lung disease is more likely to be present.

Conclusion

The MRC dyspnoea score and MFAP4 levels were poor predictors of respiratory impairment in patients with early treatment-naïve rheumatoid arthritis.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The Region of Southern Denmark's Ph.D.-grant [J.nr.: 19/37084], The funds for Research Support for Highly Specialized and Cross-disciplinary Functions, Odense University Hospital [A4113], The Frontline Centre Fund, Odense University Hospital, Denmark [A5095] and Ph.D.-grant from University of Southern Denmark. Acore grant from the Oak Foundation [OCAY-18-774-OFIL] supports the Section for Biostatistics and Evidence-Based Research, the Parker Institute, Bispebjerg and Frederiksberg Hospital.

Author contributions

Torkell Ellingsen, Christin Isaksen, Brian Bridal Løgstrup, and Grazina Urbonaviciene contributed to the concept and design of the study, Charlotte Hyldgaard, Frank Andersen, Jesper Blegvad-Nissen, Bjørk K Sofíudóttir, Stefan Harders, Brian Bridal Løgstrup, Mette Herly, and Dzenan Masic contributed to data acquisition. Bjørk K Sofíudóttir, Robin Christensen wrote the first draft of the statistical analysis plan and manuscript. Bjørk K Sofíudóttir and Sören Möller analysed the data. All authors contributed to the interpretation of the data and revised the manuscript critically for important intellectual content. The final version to be published was approved by all authors.

Data sharing

The data underlying this article cannot be shared publicly to protect the privacy of the individuals who participated in the study. Data are available on reasonable request from the corresponding author after approval from the Regional Health Authorities of the Central Denmark Region.

Ethical approval

The study was approved by the Regional Committees on Health Research Ethics in the Central Denmark Region (M20100090) and the Region of Southern Denmark (S20140057), and by the Danish Data Protection Agency (2007-58-0010). Each participant signed an informed consent before data collection.

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