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# Proposal of a radiation-free screening protocol for early detection of interstitial lung involvement in seropositive and ACPA-positive rheumatoid arthritis

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## Abstract

**Background** Seropositive rheumatoid arthritis (RA) is associated with significant cardiovascular and pulmonary morbidity. However, screening for early detection of pulmonary involvement especially interstitial lung disease (ILD) is not established in RA.

**Methods** We propose a non-invasive radiation-free approach to screen for interstitial lung involvement (ILI) by means of pulmonary function tests (PFT) and pleuro-pulmonary transthoracic ultrasound (LUS) with additional cardiopulmonary exercise tests (CPET) with ECG, and echocardiography. We included patients with confirmed diagnosis of seropositive RA according to ACR criteria, but without symptoms for or known cardiopulmonary disease. ILD was suspected when significant LUS abnormalities and additional PFT changes were present.

**Results** We included 67 consecutive patients (78% female, mean age 61 ± 12 years, 48% active or previous smokers), who fulfilled the inclusion criteria and gave written informed consent.

We found 48% of patients with suspected changes in PFT with a diffusion capacity (DLCOc-SB) ≤ 80%, among them 7% with forced vital capacity (FVC) ≤ 80%.

In 40% of patients, we found noticeable changes in LUS, 24% with an ILD compatible pattern. In 16% of cases, LUS abnormalities and additional PFT changes were present, and ILI was suspected. Additional findings included obstructive lung disease ($n = 11$), subpleural consolidation ($n = 6$) including one confirmed lung cancer, minimal pleural effusion ($n = 6$), and ischemic cardiac disease ($n = 2$). None of the patients showed signs of pulmonary vascular involvement.

**Conclusions** ILI was suspected in 16% of cases using a new radiation-free screening protocol in asymptomatic RA patients.

**Trial registration** German Register of Clinical Studies (DRKS00028871).

**Keywords** Interstitial lung disease, Seropositive rheumatoid arthritis, Non-invasive, Pulmonary function test, Lung ultrasound, PFT, LUS, ILD, RA

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## Background

According to the World Health Organization (WHO), rheumatoid arthritis (RA) is the most common inflammatory rheumatic disorder with a prevalence of 0.8–5.5% and an annual incidence between 25–60 per 100,000 adults per year. About 65–80% of RA patients have a positive (IgM) rheumatoid factor (seropositive RA). Detection of anti-citrullinated peptide antibodies (ACPA) are highly specific for RA (sensitivity approximately 70%, specificity 95%) and indicate a more severe and destructive disease course with higher serological inflammatory activity [1].

Pulmonary manifestation in RA is well known and present with different forms, such as obstructive lung disease (1–21%), bronchiectasis (3–62%), pleural manifestation (up to 70% postmortem), pulmonary nodules (up to 30% of patients), or treatment related pulmonary complications [2]. Interstitial lung disease is the most frequent pulmonary manifestation of RA (RA-ILD) with about 3–6% of RA patients affected. It may present as usual interstitial pneumonia (UIP), non-specific interstitial pneumonia (NSIP), organizing pneumonia, or diffuse alveolar damage [3]. Each pattern bears the potential to turn into progressive disease in RA [4]. RA-ILD is associated with increased morbidity and mortality and serves as a determinant for poorer RA prognosis [3, 5]. The course of ILD in RA is highly variable. RA-ILD may develop at any stage of RA and may precipitate even before joint manifestation [6, 7]. However, many patients are diagnosed late at an advanced stage of the disease. So far, several risk factors for the development of RA-ILD have been suggested such as presence of specific RA antibodies, longer disease duration, high disease activity, active smoking, and male gender [2, 3]. Early diagnosis of ILD- RA is warranted especially in the advent of effective treatment strategies [8].

Screening for ILD in RA has been previously reported and suggested [9]. In current practice, clinical assessment and PFT with diffusion capacity are mainly used. However, PFT is technically demanding and has only moderate sensitivity and specificity for detection of ILD [9–11]. High-resolution thoracic computed tomography scans (HRCT) have recently been proposed in several screening studies for RA-ILD [3, 12, 13] with a detection rate between 20–60% [12]. While HRCT is the current gold standard for diagnostic imaging in ILD, it is associated with procedural issues, mild radiation exposure, and medical expenses [3].

Lung ultrasound (LUS) has been suggested as an easy-to-use radiation-free imaging method. It can detect subpleural interstitial changes using several ultrasound criteria [13–15]. Some studies have evaluated the use of LUS in several forms of ILD diseases with a reported sensitivity between 73.5–100% and a specificity of 53–97.3% compared to HRCT [16]. However, it might be influenced by several factors, such as severe infection or pulmonary congestion in cardiac disorders [17].

In this prospective study, we used PFT and LUS as a screening tool in consecutive RA patients without known cardiopulmonary disease to detect interstitial lung involvement (ILI).

## Methods

In this prospective study, we included patients with seropositive and ACPA-positive RA for screening of ILI.

Inclusion criteria were:

- Patients with diagnosis of seropositive and ACPA-positive RA according to Aletaha-EULAR/ACR classification criteria [18] regardless of time of diagnosis and current or previous disease-modifying anti-rheumatic drugs (DMARDs) such as conventional synthetic csDMARDs (e.g. methotrexate, leflunomide), targeted synthetic tsDMARDs (e.g. small molecules tofacitinib, baricitinib, upadacitinib), and biological bDMARDs (e.g. TNF alpha blockers, rituximab, tocilizumab)
- No known or previously diagnosed cardiopulmonary disease
- No symptoms of cardiopulmonary impairment, especially no cough, sputum production, breathlessness on exertion / at rest, or thoracic discomfort / chest pain
- No lung function screening in the last six months before inclusion in the study.
- Written informed consent sheet consistent with the International Conference on Harmonization Harmonized Tripartite Guideline for Good Clinical Practice (ICH-GCP) and local legal requirements must be signed prior to the start of the study
- Male or female patients $\geq$ 18 years at baseline
- No signs of active infection, especially negative test for SARS-CoV 2 infection (PCR or antigen test)

Exclusion criteria are shown in the supplement.

After informed consent patients underwent a screening protocol including:

- History and physical examination including smoking status and medication, especially DMARDs time since diagnosis,
- RA-specific questionnaires of disease activity (CDAI, SDAI, DAS28-CRP [19–22]),
- Inflammatory activity based on CRP, BKS, RF, ACPA antibodies

- PFTs including spirometry, body plethysmography, and diffusion capacity with Methan-CO method and correction for hemoglobin using global lung initiative GLI normal values.
- Transthoracic echocardiography TTE according to routine clinical protocol to rule out significant cardiac comorbidities.
- 12 lead ECG at rest and during exercise
- CPET on a treadmill in erect body position including 12 lead ECG, analysis of expiratory gas samples using a CPET mask, blood gas analysis at rest and during exercise from the arterialized earlobe, oxygen saturation and non-invasive blood pressure measurement. For exercise, we used a ramp protocol with a 1-min preload phase and a maximum workload considering the patient's physical condition to be reached after 10 min. The anaerobic threshold (AT) was determined using the V slope method.
- For transthoracic pleuropulmonary ultrasound (LUS) we used a convex 3.5 MHz probe (Hitachi Aloka ProSound Alpha 6 or Hitachi Arietta V70). The patient sat in an erect position. Using a prespecified protocol according to [13] and [23], the investigation was performed examining dorsal, lateral, and ventral views at 14 prespecified scanning points including the whole thorax. LUS was performed by 2 of 3 investigators (F.R, M.H., W.v.W.) in mutual agreement.
  For assessment of ILI, we used established sonographic markers based on changes in the pleural line, such as fragmentation and thickening [14] and the presence of hyperechoic vertical artefacts (B lines) >5 per field of view [15].

ILI was suspected if impaired PFT with DLCOc-SB / KCOc-SB < 80% pred or FVC < 80% pred and signs of interstitial changes on LUS in the absence of other abnormal cardiopulmonary findings at the time of screening were detected.

Patients with conspicuous findings on LUS, e.g. signs of ILD or consolidations, were recommended to undergo further evaluation including HRCT.

### Statistics

As the data were normally distributed, they are displayed in mean ± standard deviation (SD). Subgroup comparisons were performed in the context of t-tests for independent samples, or frequency distribution comparisons with the chi-square test and ROC analysis.

### Data management and ethics

Patients' data were pseudonymized, collected, and stored in a password protected file on a non-internet-enabled computer.

The study was registered in the German Register of Clinical Studies (DRKS00028871) and approved by the ethics committee of the University of Munich, Germany (21–1138).

## Results

### Patients

Between April 2022 and December 2023, we included 67 consecutive RA patients, who fulfilled the inclusion criteria and gave written informed consent. None of the patients complained of respiratory symptoms, especially no dyspnea at rest or exercise, cough, or chest pain. The mean age was 61 ± 12 years, 78% of patients were female. A total of 40% were active or previous smokers with a smoking history of 20 ± 20 mean pack years.

The mean duration of RA disease since diagnosis was 9.3 ± 8.5 years. Regarding RA disease activity, patients showed a mean DAS 28-CRP of 2.3 ± 0.9 (equivalent to remission of RA), a mean CDAI 6.2 ± 6.6 (indicating low RA disease activity), a mean SDAI 6.7 ± 6.6 (indicating low disease activity). Forty-one patients were treated with csDMARDs, 13 patients with tsDMARDs, and 33 patients with bDMARDs, while 7 patients were treated with steroids at the time of the examination (see Table 1).

Fourteen patients (20%) experienced a COVID 19 infection within the last 2 years prior to study inclusion. None of the patients had an active COVID 19 infection.

### PFT

All participants underwent PFT. In the total cohort, the mean FEV1 was 2.6 ± 0.6 l [97(18) %pred], mean FVC 3.5 ± 0.7 l [105(17) %pred], mean TLC 5.9 ± 1.2 l [107(16) %pred], mean DLCOCc-SB was 77 (18) %pred, and mean KCOc-SB 88 (17) %pred.

Eleven patients showed an obstructive airway pattern (FEV1/FVC < 70%), 2 patients a combined obstructive-restrictive pattern, and 1 patient a restrictive pattern (TLC < 80% pred). An impaired diffusion capacity was measured in 32 patients with DLCOc-SB < 80% and in 23 patients with KCOc-SB < 80%.

### LUS

LUS was performed in all patients. It showed a normal pleuropulmonary imaging in 40 patients (60%). Six patients (9%) presented with minimal pleural effusions (not amenable for pleurocentesis), in 6 patients (9%) subpleural consolidations were detected. Further findings included unilateral B lines in previous pleural trauma ($n = 2$) and unilateral diaphragm dysfunction ($n = 2$ patients).

One patient showed bilateral fragmentation, pleural thickening, and B lines as well as pleural effusion, impaired renal function, and impaired cardiac function

**Table 1** Comparison of nonILI and susILI groups with respect to clinical, rheumatological, and functional parameters[a]

| Characteristics | Total patients ($n=67$) | No ILI signs ($n=56$) | Suspected ILI ($n=11$) |
|---|---|---|---|
| Female | 52 (78%) | 43 (77%) | 9 (82%) |
| Age | 60.8 ± 11.7 | 60.0 ± 11.3 | 64.8 ± 13.1 |
| BMI | 25.4 ± 4.5 | 25.1 ± 4.5 | 26.5 ± 4.8 |
| Active or previous smoking | *N* = 27 (40%) | *N* = 19 (33%) | *N* = 8 (73%)* |
| Pack years | 20 ± 20 | 17 ± 19 | 33 ± 21 |
| DAS 28-CRP | 2.3 ± 0.9 | 2.3 ± 0.9 | 2.2 ± 0.8 |
| CCP titer | 219 ± 100 | 221 ± 101 | 223 ± 100 |
| csDMARDs | *N* = 41 (61%) | *N* = 33 (59%) | *N* = 8 (73%) |
| tsDMARDs | *N* = 13 (19%) | *N* = 12 (21%) | *N* = 1 (9%) |
| bDMARDs | *N* = 33 (49%) | *N* = 27 (48%) | *N* = 6 (55%) |
| DLCOc-SB (%pred) | 78 ± 19 | 80 ± 17 | 66 ± 15* |
| KCOc-SB (%pred) | 88 ± 18 | 91 ± 17 | 72 ± 10* |
| FVC (%pred) | 105 ± 17 | 106 ± 17 | 99 ± 17 |
| CPET Watt max | 131 ± 41 | 135 ± 41 | 114 ± 37 |
| VO2max ml/kg/min | 22.6 ± 8.2 | 23.6 ± 8.4 | 18.3 ± 5.8* |
| VO2- AT ml/kg/min | 16.8 ± 6.8 | 17.5 ± 7.0 | 13.5 ± 5.3* |
| EQCO2 slope | 27.3 ± 5.7 | 26.7 ± 5.6 | 29.9 ± 5.2 |

[a] Given are mean ± SD

* $p < 0.05$

on TTE. Therefore, changes were related to fluid overload in cardiorenal compromise and not suspicious for ILI.

In 16 patients (24%), LUS revealed bilateral pleural fragmentation ($n=12$), pleural thickening ($n=6$), and > 5 B lines ($n=9$) as signs of possible ILI.

### TTE

TTE was performed in all participants to rule out significant cardiac comorbidities, with a mean systolic LV function of 64 ± 7%, the mean sPAP corrected for CVP was 26 ± 6 mm Hg, and the mean RV-TAPSE was 23 ± 4 mm. One patient presented with severe aortic stenosis due to bicuspid aortic valve requiring further intervention. Other findings included mild diastolic left ventricular dysfunction ($n=16$), left ventricular hypertrophy ($n=6$), septal and anterior hypokinesia ($n=2$), minimal mitral valve prolapse ($n=1$), and minimal aortic insufficiency ($n=53$). None of the patients showed signs of pulmonary vascular involvement.

### CPET

Sixty-five patients were able to perform CPET with a peak VO2 of 22.6 ± 8.2 ml/kg/min (95 ± 27%pred) and a maximum workload of 131 ± 41 Watt (111 ± 27%pred). The AT was detected at 16.8 ± 6.8 ml/kg/min (70 ± 26%pred VO2 peak). Slope of breathing equivalent for CO2 was 27.3 ± 5.7. None of the patients developed hypoxemia or signs of cardiac ischemia during or after exercise. Two patients did not undergo exercise due to severe aortic stenosis and withdrew consent for CPET.

### Assessment of ILD-suspicion

In 16 patients an ILI compatible pattern was detected on LUS (24%). Among them, 11 patients showed impaired PFT with DLCOc-SB/KCOc-SB ≤ 80% pred ($n=10$) and FVC < 80% ($n=2$). This group was suspected of having ILI (susILI), which was 16% of patients.

### Comparison between non-ILI group (nonILI) and ILI suspected group (susILI)

Comparing the patients in the susILI ($n=11$) and nonILI group ($n=56$) (see Table 1), patients in the susILI group included significantly more active or previous smokers with a tendency towards higher pack years. They had a lower diffusion capacity, and a reduced exercise capacity measured by VO2 peak at maximum exercise and VO2 at AT during CPET. Both groups showed comparable gender and age distribution, lung volumes, as well as rheumatic disease activity indices. Patients with susILI were more often on treatment with csDMARDs in combination with bDMARDs, while the nonILI group was more often on monotherapy with tsDMARDs. Data is shown in Table 1.

### HRCT

In the follow-up, 11 patients underwent HRCT outside the study for further evaluation of suspicious test results (16%).

In the susILI group, 4/11 patients underwent HRCT (36%). Three patients demonstrated signs compatible with ILD: 2 with subpleural reticular changes and 1 patient with basal lung scaring. One patient with moderate reduced diffusion capacity presented with bilateral upper lobe emphysema.

In the nonILI group, 7/56 patients underwent HRCT (12%). Two patients showed ILI with reticular changes but also bronchi(olo)ectasis. Both exhibited normal PFT including diffusion capacity although both had possible ILI signs on LUS. One patient with normal PFT but possible ILI signs on LUS had minimal pericardial effusion on HRCT.

In one patient with moderate impaired diffusion capacity but normal LUS, HRCT revealed bronchi(olo)ectasis.

Three patients underwent HRCT due to consolidations on LUS. This was confirmed as minimal nodular changes ($n=1$), postinfectious changes ($n=1$), and a tumor- suspected lesion, which was diagnosed as non-small lung cancer during bronchoscopy. The patient underwent curative lung resection in stage I disease.

#### Comparison of susILI and ILD on HRCT

We compared the screening results for ILI with the HRCT findings in the 11 susILI patients.

Using the LUS/PFT criteria for detection of ILI compared to ILD on HRCT, the sensitivity was 0.6 with a specificity of 0.83 and a positive predictive value (ppv) of 75% and negative predictive value (npv) of 71%.

Using only the LUS positive criteria for ILI compared to ILD on HRCT, the sensitivity was 0.71 with a specificity of 0.6 and a ppv of 71% and npv of 75%.

When analyzing reduced DLCOc-SB compared to presence of ILD on HRCT, we found a low AUC of 0.257 like the analysis DLOC vs susILI assessment with AUC 0.269 (Fig. 1). Due to the small sample size further analysis was not performed.

## Discussion

The development of ILD in RA is rare but a clinically meaningful manifestation of therapeutic relevance [3].

Undoubtedly, HRCT is the gold standard for imaging in ILD diagnosis and established for screening in diseases with high prevalence for ILD, such as systemic sclerosis [24]. However, this might be different in diseases with a high population prevalence but a relatively low ILD prevalence as in RA.

The combination of functional and imaging studies for screening of ILD in rheumatic disease has been recently recommended [10]. Our approach is to substitute HRCT by LUS in the screening but not the diagnosis of ILD in RA.

In this study, we used a new radiation-free screening approach for lung manifestation in 67 consecutive seropositive and ACPA-positive RA patients based on PFT and LUS as an easy-to-use imaging tool. Using these combined techniques, we found a pattern suggestive of ILI in 11 patients (16% susILI). Four of these patients underwent HRCT, where ILI was confirmed in 3 patients. This accounts for 75% ppv with a sensitivity of 0.6, specificity of 0.83 and npv 71%. The frequency is lower than in previous screening studies probably due to low rates and selection bias of HRCT performed in our study. However, the percentage of ILI detected with our approach is compatible with the preliminary results of a very recent RA-ILD HRCT based screening study [25].

The clinical relevance of our findings is clinically supported, as patients with susILI had a lower exercise performance with significantly lower VO2 at peak exercise and AT compared to nonILI.

In our small cohort, there was no gender difference between the susILi and the nonILI group. However, there were significantly more previous and active smokers in the susILD group. Smoking is an established risk factor for ILD in RA [3].

We found no significant difference between both groups with respect to clinical and serological activity of RA as displayed by DAS-28, CDAI, SDAI, inflammation markers, and CCP level. Whether tsDMARD therapy has a positive impact on lung involvement in RA cannot be assessed in this study due to the small number of cases. Notably, 2 patients with normal PFT presented with ILI changes on LUS, which were confirmed by HRCT. This indicates that imaging changes might precede PFT changes in ILD.

Using LUS only, we found a npv of 75% (sensitivity 0.71, specificity 0.6, ppv of 71%), which is lower than recently reported in asymptomatic RA patients [26]. That might be due to the small percentage of patients receiving a confirmatory HRCT in our cohort.

LUS findings have a broad differential diagnosis and should be interpreted according to the clinical situation [17]. Indeed, one patient with ILD compatible signs on LUS presented with bilateral pleural effusions and an impaired cardiac function on TTE consistent with cardiac failure and pulmonary congestion. Among PFT, diffusion capacity is traditionally used to detect early lung involvement in rheumatic disease although technically demanding. When analyzing only reduced DLCOc-SB compared to HRCT, we found a low AUC of 0.257 similar to the analysis DLOC vs susILI assessment (Fig. 1).

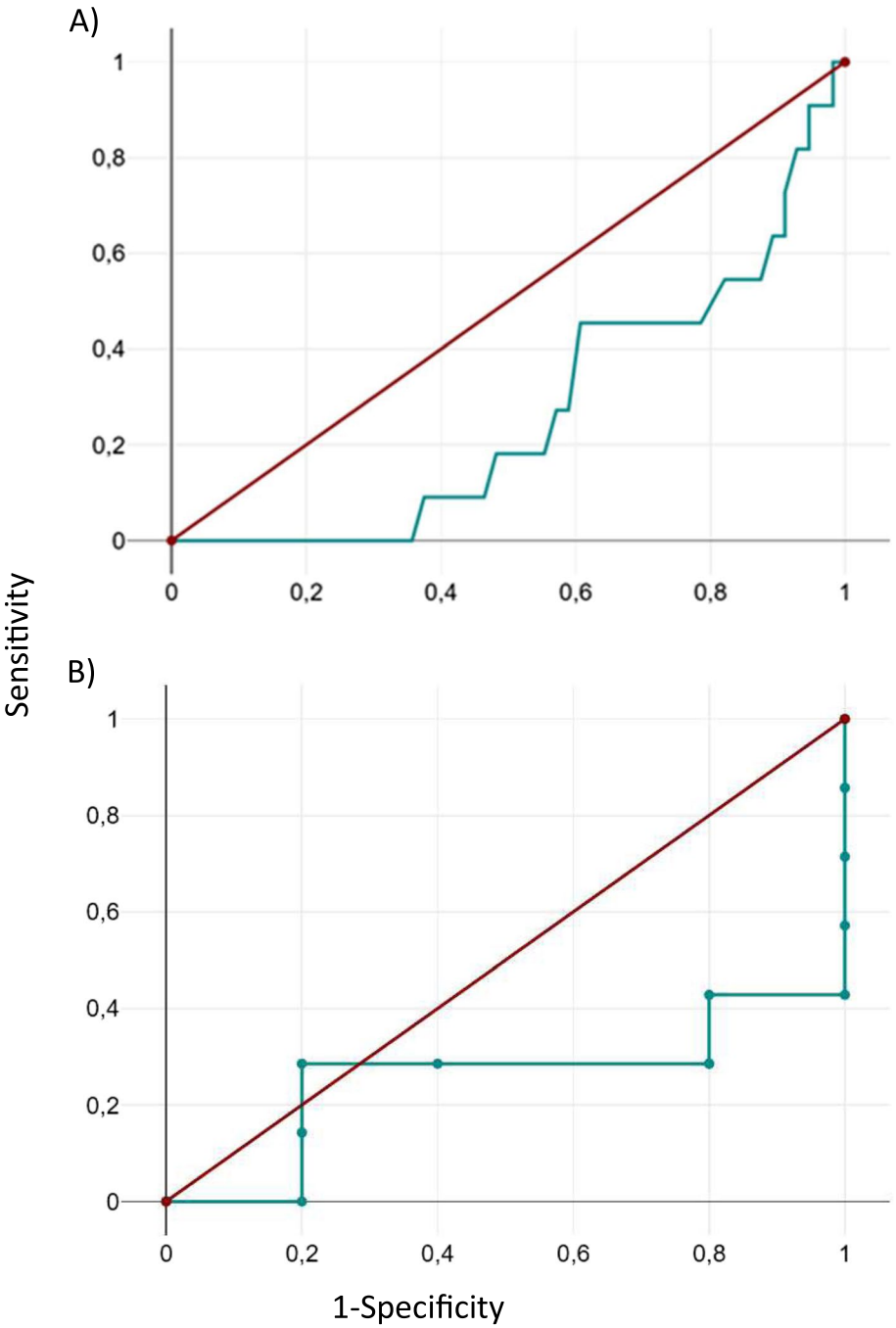


**Fig. 1** ROC analysis for diffusion capacity DLCOc-SB for detection of ILI: **A** compared to assessment by LUS/PFT criteria, AUC 0.269; **B** compared to ILD on HRCT, AUC 0.257

In our cohort, we found 8 patients (12%) with impaired diffusion capacity, among them 5 non-smokers. There were no signs of obstructive lung function, ILI on LUS or pulmonary vascular disease on TTE. This might be due to smoking or RA related lung emphysema in RA. Nevertheless, this phenomenon has been previously described [11]. In the present study, we found several other pulmonary comorbidities, such as obstructive airway patterns in 16%, probably influenced by the high rate of ex- and active smokers [2]. Among the 6 patients with subpleural pulmonary consolidations, 3 underwent HRCT where lung nodules were confirmed. One non-smoking patient was diagnosed with NSCLC amenable for curative surgery. Lung cancer screening is based on

HRCT according to current guidelines and beyond the scope of LUS [27].

We found several cardiac comorbidities such as valvular disease ($n=7$), signs of ischemic heart disease ($n=2$), and pericardial effusion ($n=1$). None of the patients showed signs of PH which is compatible with the reported low risk of PH in RA [3, 28].

Our study has several limitations. First, we performed a screening study with a non- radiation approach using PFT and LUS. HRCT as the gold standard in imaging of ILD was not routinely performed, but only recommended in patients with suspected screening results. A direct comparison with results of HRCT was only possible in a small subset of patients. This methodological issue was taken into account based on published evidence of the accuracy of detection of ILI by means of LUS.

Second, 14 patients (21%) experienced a diagnosed COVID 19 infection within the last 2 years before inclusion in the study. Although we did not find any direct impact on our study results, an influence on pulmonary function and imaging as well as exercise performance cannot be excluded.

Third, we present the initial results of a monocentric study with potential selection and detection bias. As this is a potentially systematic error, we included consecutive patients who met the inclusion criteria, and we evaluated the LUS imaging with 2 investigators unaware of the additional results.

Finally, data on the long-term consequences of these findings are not yet available and need to be reported in the future.

Our study supports the growing evidence and experience in using LUS for screening for RA-ILD. A combination of functional and imaging methods is suggested in the recent guideline [10]. We propose LUS as an appropriate imaging tool in combination with PFT for ILD screening in RA.

## Conclusions

Screening for ILI by means of LUS and PFT detects changes in 16% of asymptomatic patients with seropositive and ACPA positive RA patients.

### Abbreviations

| | |
|---|---|
| ACPA | Anti-citrullinated peptide antibodies |
| AI | Aortic insufficiency |
| AoSt | Aortic stenosis |
| AT | Anaerobic threshold |
| BMI | Body mass index |
| CCP | Computed cardiopulmonography |
| CPET | Cardiopulmonary exercise test |
| CRP | C-reactive protein |
| CVP | Central venous pressure |
| DLCOc-SB | Diffusion capacity |
| DMARDs | Disease-modifying anti-rheumatic drugs |
| EQCO2 | Ventilatory equivalent of carbon dioxide |
| FVC | Forced vital capacity |
| HRCT | High-resolution thoracic computed tomography |
| ILD | Interstitial lung disease |
| ILI | Interstitital lung involvement |
| KCOc-SB | CO transfer coefficient |
| kg | Kilogram |
| LUS | Lung ultrasound |
| LV | Left ventricular |
| max | Maximum |
| min | Minute |
| ml | Milliliter |
| MVP | Mitral valve prolapse |
| nonILI | No ILI |
| npv | Negative predictive value |
| NSCLC | Non-small cell lung carcinoma |
| PF | Pulmonary function tests |
| PH | Pulmonary hypertension |
| ppv | Positive predictive value |
| pred | Predicted |
| RA | Rheumatoid arthritis |
| SD | Standard deviation |
| susILI | Suspected ILI |
| TTE | Transthoracic echocardiography |
| VO2 | Maximum oxygen consumption |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12890-024-03405-y.

Supplementary Material 1.

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### Authors' contributions

FR, FP, and MW made substantial contributions to the conception and design of the work; FR, MH, WvW, CF, and FP were involved in the acquisition and analysis of the data, FR, FP, WvW, NK, and MW performed the interpretation of data. All authors were involved in the draft and revision of the work. All authors have approved the submitted version and any substantially modified version that involves the author's contribution to the study. All authors have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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### Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Declarations

### Ethics approval and consent to participate

The study was approved by the ethics committee of the University of Munich, Germany, project number 21–1138. Participants signed an informed consent form before the start of the screening process.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare no competing interests.

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