Interstitial lung disease in patients with connective tissue disease: Subtypes, clinical features and comorbidities in the Western Cape, South Africa

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Background. Interstitial lung disease (ILD) is highly prevalent in patients with connective tissue disease (CTD) and is poorly characterised in South Africa.

Objective. To describe the clinical, serological and radiological features of CTD-ILD and their associations in patients attending a tertiary referral hospital.

Method. A cross-sectional study collating clinical, serological and radiological features of CTD-ILD in patients attending rheumatology and respiratory outpatient clinics in a tertiary referral hospital.

Results. Of 124 CTD-ILD patients, 37 (29.8%) had rheumatoid arthritis (RA), 32 (25.8%) systemic sclerosis (SSc) and 55 (44.4%) other autoimmune connective tissue diseases (OCTD). Most patients were female (86.3%), of mixed racial ancestry (75.0%), and the median age was 55 years. Nonspecific interstitial pneumonia (NSIP) was the most common ILD pattern (63.7%), followed by usual interstitial pneumonia (UIP) (26.6%). Overall, 60.5% were current or past smokers, 33.1% had previous pulmonary tuberculosis infection, and 75.6% had gastro-oesophageal reflux disease. Patients with RA were older, had similar frequencies of NSIP and UIP, and had significantly better pulmonary function tests than the SSc and OCTD groups. Within three years of CTD diagnosis, two-thirds of the SSc and OCTD patients and almost half of the RA patients had developed ILD. Clinical features, chest X-rays and pulmonary function tests correlated poorly with high-resolution computerised tomography (HRCT). No case of acute pneumonitis was documented in CTD-ILD patients treated with methotrexate (MTX).

Conclusions. We suggest routine HRCT in all newly diagnosed CTD patients, particularly those with SSc and OCTD, where more than two-thirds of the patients had developed ILD within three years of their CTD. The use of MTX was not associated with the development of acute pneumonitis in patients with ILD.

Keywords. Interstitial lung disease, connective tissue disease, sub-Saharan Africa.

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Key points
- Clinical features, chest X-rays and pulmonary function tests correlated poorly with high-resolution computerised tomography (HRCT).
- Smoking, environmental toxins, gastro-oesophageal reflux and previous pulmonary tuberculosis infection were significant comorbidities in CTD-ILD patients.
- Early screening of ILD with HRCT is recommended, particularly in SSc.
- Use of MTX before and after ILD diagnosis was not associated with acute pneumonitis.

Interstitial lung disease (ILD) is highly prevalent in patients with connective tissue disease (CTD), leads to significant morbidity and mortality, and is difficult to treat owing to its variable presentation, progression and response to therapy, with a relative lack of guidelines to assist clinicians.5 In CTD, ILD is classified according to pathological and radiological features into six subtypes: nonspecific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP), organising pneumonia (OP), lymphocytic interstitial pneumonia (LIP) and diffuse alveolar damaged (DAD)/acute interstitial pneumonia (AIP) and, rarely, desquamative interstitial pneumonia (DIP). These subtypes occur in different frequencies in the various CTDs, with distinct treatment and prognosis. The most common types are NSIP and UIP. The prevalence of ILD differs between CTDs: in systemic sclerosis (SSc), 70 - 90% of patients are diagnosed with ILD; in idiopathic...
inflammatory myopathies (IIM) 15 - 70%; in mixed connective tissue disease (MCTD) 20 - 85%; in rheumatoid arthritis (RA) 4 - 68%; in primary Sjögren’s syndrome (pSS) 10 - 30%; and in systemic lupus erythematosus (SLE) 2 - 10%. Risk factors for the development and progression of ILD in CTD include older age, male sex, smoking, disease duration (early in SSc, MCTD and IIM; advanced in RA, SLE and pSS), silica exposure in Ssc, gastro-oesophageal reflux disease (GORD) and the presence of autoantibodies including anti-topoisomerase 1, rheumatoid factor (RF) and anti-tRNA synthetase antibodies such as anti-Jo1 antibodies.[13-15] It has been consistently reported that oesophageal dilatation and the presence of a high degree of GORD is associated with more severe lung impairment and more rapid decline of pulmonary function values in SSc patients.[15]

To date there are few published studies from sub-Saharan Africa examining ILD among all CTDs. A recent cross-sectional study from Nigeria showed CTD-ILD in 10% of patients, and highlights the importance of screening for ILD in all CTD patients.[15]

The present study describes the clinical, serological and radiological features of CTD-ILD and their associations in patients attending a tertiary referral hospital. The University of Cape Town Faculty of Health Sciences Human Research Ethics Committee approved the study (ref. no. HREC 594/2019).

Patients and methods

This cross-sectional study included patients with CTD-ILD attending a South African tertiary-level state hospital. Patients from the rheumatology and respiratory outpatient clinics seen between October 2018 and September 2019 were included if they met the following criteria: age ≥18 years, CTD diagnosed according to classification criteria for each disease, ILD diagnosed on high-resolution computerised tomography (HRCT), and pulmonary function tests (PFTs). Patients with non-parenchymal lung disease (including pleural disease, airway disease or tumours) were excluded.

Clinical details, autoantibody status, PFTs, current and previous medications, and smoking status (ever/current at the time of ILD diagnosis) were collated. Plain chest radiographs (CXRs) and HRCT images were reviewed by a rheumatologist (EP), pulmonologist (GC) and radiologist (QSH), and ILD was classified into subtypes. Chronic obstructive pulmonary disease (COPD) was defined either by PFT or emphysema seen on HRCT images.[14] GORD was defined by reflux symptoms and/or barium swallow and/or a dilated oesophagus on HRCT.

Patients were divided into 3 groups: RA, SSc and ‘other’ CTD (OCTD), which included 14 patients with IIM, 10 with MCTD, 10 with SLE, 3 with pSS and 16 patients with overlap syndrome (majority with overlap SLE and SSc).

The ANOVA, Kruskal-Wallis and chi-squared tests were used to test the associations depending on the distribution of data and types of variables. Sporadically missing covariates data were managed using multiple imputation if the proportion of missing data was less than 50%. Analyses were performed with STATA 14.0 (Stata Corp., USA) and p-values ≤0.05 were considered significant.

Results

Of 124 patients with ILD-CTD, 37 (29.8%) had RA, 32 (25.8%) SSc (24 diffuse cutaneous and 8 limited cutaneous disease) and 55 (44.4%) OCTDs (Table 1). Most patients were female (86.3%), of mixed racial ancestry (75.0%) and the median time to develop ILD after CTD diagnosis was 2 years. The median (IQR) age at CTD symptom onset and ILD diagnosis was 45 (35-55) years and 55 (46-66 years) respectively. Within three years of CTD diagnosis, two-thirds of the SSc and OCTD patients and almost half of RA patients had developed ILD. Compared with the SSc and OCTD groups, RA patients were older at CTD diagnosis (p <0.001), had longer disease duration before onset of ILD (p=0.06) and were older at ILD diagnosis (p<0.001).

ILD features

Thirteen patients (10%) were asymptomatic and the ILD diagnosis was made based on images requested for other reasons (Table 2). The most frequent CXR abnormalities were reticular, reticulonodular or nodular infiltrates. Of note, 5 out of 124 (4.0%) had no parenchymal abnormalities on CXR, but HRCT revealed NSIP. The most common pattern was NSIP and, in the RA group, the frequency of NSIP and UIP was similar. Patients in the SSc and OCTD groups had worse PFTs with significantly lower FVC, and lower diffusion capacity for carbon monoxide (DLCO). The percentage of patients with severe disease (FVC <70%) was greater in the SSc and OCTD groups (50.0% and 58.2%) in contrast with 32.4% of RA patients (p=0.05).

Usual interstitial pneumonia

To demonstrate the predictors associated with the most serious ILD pattern, UIP, we compared patients with and without UIP (Table 3). As expected, RA was associated with UIP (odds ratio (OR) 3.8, 95% confidence interval (CI) 1.5 - 9.5). Other associated variables were older age (OR 1.1, 95% CI 1.0 - 1.1), COPD (OR 3.2 (95% CI 1.4 - 8.0), and longer CTD-ILD intervals (OR 1.0, 95% CI 1.0 - 1.2). Interestingly, the PFTs in the UIP group were better overall than those in the non-UIP group, particularly the median %FVC at UIP diagnosis (79 v. 71, OR 1.6, 95% CI 0.8 - 3.0).

Comorbidities

A high prevalence of smoking (>60%) and previous PTB (33.1%) were observed. A significant number of patients (22.6%) had COPD in addition to their ILD. No patient was HIV positive. All SSc patients and more than two-thirds of other patients had GORD. In the SSc group, 8 (72.7%) patients had significant environmental or occupational exposure, including gold mining-related silica exposure (2 patients), organophosphates (1 patient), biomass fuels (1 patient), sand (2 patients), cotton (1 patient) and 1 patient with multiple exposures (printing fumes, spray paint and metal dust).

Autoantibodies

The majority (74.2%) of patients were antinuclear antibody positive, including 86.4% of RA patients. Regarding SSc, 9 patients had positive anti-topoisomerase antibodies, and 1 patient had anticentromere antibodies. Eight of 14 IIM patients had anti Jo-1 antibodies.

Methotrexate exposure

Regarding methotrexate (MTX) exposure, 37.1% of patients were prescribed MTX before ILD diagnosis, and 33.9% continued, started or restarted after ILD diagnosis (59.5% of RA, 25.0% of SSc and
### Table 1. Demographic, clinical and serological characteristics of patients with CTD-ILD, N=124

| Characteristics                                      | All, n (%) | RA (N=37), n (%) | SSc (N=32), n (%) | OCTD (N=55), n (%) | p-value  |
|------------------------------------------------------|------------|------------------|-------------------|-------------------|----------|
| Female                                               | 107 (86.3) | 31 (83.8)        | 27 (84.4)         | 49 (89.1)         | 0.719    |
| Age at CTD symptoms onset, years (median (IQR))      | 45 (35 - 55) | 54 (45 - 62)    | 42 (34 - 52)      | 40 (29 - 49)      | <0.001  |
| Ethnic background (self-reported)                     | 0.768      |
| Mixed ancestry                                       | 93 (75.0)  | 29 (78.4)        | 26 (81.3)         | 38 (69.1)         |          |
| Black                                                | 26 (21.0)  | 6 (16.2)         | 5 (15.2)          | 15 (27.3)         |          |
| White                                                 | 3 (2.4)    | 1 (2.7)          | 1 (3.1)           | 1 (1.8)           |          |
| Other                                                 | 2 (1.6)    | 1 (2.7)          | 0                 | 1 (1.8)           |          |
| Ever smoker                                           | 75 (60.5)  | 28 (75.7)        | 17 (53.1)         | 30 (54.5)         | 0.078    |
| Current smoker                                        | 28 (22.6)  | 13 (35.1)        | 6 (18.8)          | 9 (16.4)          | 0.090    |
| Past smoker                                           | 47 (37.9)  | 15 (40.5)        | 11 (34.4)         | 21 (38.2)         | 0.869    |
| Previous pulmonary tuberculosis                       | 41 (33.1)  | 13 (35.1)        | 12 (37.5)         | 16 (26.1)         | 0.688    |
| Environmental or occupational exposure                | n=21/35 (60.0) | n=4/5 (80.0)  | 8/11 (72.7)       | 9/19 (47.4)       | 0.242    |
| GORD                                                 | 94 (75.8)  | 25 (67.6)        | 32 (100.0)        | 37 (67.3)         | 0.001    |
| COPD                                                 | 28 (22.6)  | 13 (35.1)        | 6 (18.7)          | 9 (16.4)          | 0.090    |
| HIV                                                  | 0          | 0                | 0                 | 0                 |          |
| RF                                                   | 79 (63.7)* | n=36 (97.3)      | 12 (37.5)         | 31 (56.4)         | <0.001   |
| ACPA                                                 | n=22/46 (47.8) | n=16/20 (80.0) | n=1/5 (20)        | n=5/21 (23.8)     | 0.001    |
| ANA                                                  | 92 (74.2)* | n=30 (86.5)      | 20 (62.5)         | 40 (72.3)         | 0.072    |
| ATA                                                  | n=12/45 (27.0) | -              | n=9/27 (33.3)     | n=3/18 (16.7)     | 0.215    |
| ACA                                                  | n=3/37 (8.0) | -              | n=1/22 (4.5)      | n=2/15 (13.3)     | 0.336    |
| Anti-Jo1                                              | n=8/17 (47.1) | 0(0)            | n=0/1 (0)         | n=8/16 (50.0)     | <0.001   |

OCTD = other connective tissue diseases; RA = rheumatoid arthritis; SSc = systemic sclerosis; IQR = interquartile range; GORD = gastro-oesophageal reflux; COPD = chronic obstructive pulmonary disease; HIV = human immunodeficiency virus; RF = rheumatoid factor; ACPA = anti-cyclic citrullinated peptide antibodies; ANA = anti-nuclear antibody; ATA = anti-topoisomerase antibody; anti-Jo1 = anti-histidyl transfer RNA synthetase antibody; ACA = anti-centromere antibody; Ever smoker = having positive smoking history either current or past; Current smoker = patients still smoking at the time of review.

*Unless otherwise specified.

1 Multiple imputation was performed.

### Table 2. Details of interstitial lung disease in patients with CTD-ILD, N=124

| Details                                               | All patients, n (%) | RA (N=37), n (%) | SSc (N=32), n (%) | OCTD (N=55), n (%) | p-value  |
|-------------------------------------------------------|---------------------|------------------|-------------------|-------------------|----------|
| Symptomatic at ILD Dx                                 | 111 (89.5%)*        | 34 (91.9)        | 29 (90.6)         | 48 (87.3)         | 0.756    |
| Age at ILD symptoms onset, years (median (IQR))      | 49 (40 - 61)        | 62 (55 - 68)     | 49 (38 - 56)      | 42 (33 - 56)      | <0.001   |
| CTD-ILD interval years (median (IQR))                 | 2 (0 - 7)           | 5 (1 - 13)       | 2 (0 - 7.5)       | 1 (0 - 4)         | 0.058    |
| CTD-ILD interval <1 y                                 | 56 (45.2)           | 12 (32.4)        | 15 (46.9)         | 29 (52.7)         | 0.155    |
| CTD-ILD at presentation                               | 39 (31.5)           | 7 (18.9)         | 12 (37.5)         | 20 (36.4)         | 0.213    |
| CTD-ILD interval <3 y                                 | 76 (61.3)           | 17 (45.9)        | 20 (62.5)         | 39 (70.9)         | 0.054    |
| Disease subtype                                       |                     |                  |                   |                   |          |
| NSIP                                                  | 79 (63.7)           | 19 (51.3)        | 26 (81.2)         | 34 (61.8)         | <0.001   |
| UIP                                                   | 33 (26.6)           | 18 (48.6)        | 4 (12.5)          | 11 (20.0)         |          |
| Other*                                                | 12 (9.7)            | 0 (0.0)          | 2 (6.3)           | 10 (18.2)         |          |
| FVC at ILD Dx, absolute (litres), median (IQR)        | 2.1 (1.8 - 2.4)*    | 2.1 (1.8 - 2.6)  | 2.1 (1.9 - 2.5)   | 2.1 (1.6 - 2.3)   | 0.217    |
| FVC at ILD Dx, (% expected), median (IQR)             | 74 (60 - 85)*       | 83 (70 - 100)    | 71 (64 - 82)      | 68 (56 - 82)      | <0.001   |
| FVC ≤70%                                              | 60 (48.4)*          | 12 (32.4)        | 16 (50.0)         | 32 (58.2)         | 0.052    |
| DLCO at ILD Dx, median (IQR)                          | 48 (38 - 54)*       | 51 (42 - 58)     | 50 (41 - 59)      | 44 (35 - 50)      | 0.020    |
| MTX before ILD onset                                  | 46 (37.1)*          | 24 (65.9)        | 8 (25.0)          | 14 (25.5)         | <0.001   |
| MTX after ILD onset                                   | 42 (33.9)*          | 22 (59.5)        | 8 (25.0)          | 12 (21.8)         | <0.001   |
| MTX exposure before ILD diagnosis, months, (SD)       | 21.7 (46.2)*        | 46.9 (63.1)      | 12.0 (35.3)       | 9.9 (29.2)        | <0.001   |
| MTX exposure after ILD diagnosis, months, (SD)        | 14.8 (29.1)*        | 19.7 (33.2)      | 15.1 (34.4)       | 11.4 (22.3)       | 0.049    |
| LEF before                                            | 2 (1.6)*            | 2 (5.4)          | 0 (0.0)           | 0 (0.0)           | 0.092    |
| LEF after                                            | 7 (6.3)*            | 5 (13.5)         | 1 (3.1)           | 1 (1.8)           | 0.045    |
| LEF exposure after ILD diagnosis, months, (SD)        | 0.4 (2.4)*          | 1.1 (4.2)        | 0 (0)             | 0.02 (0.1)        | 0.545    |

OCTD = other connective tissue diseases; RA = rheumatoid arthritis; SSc = systemic sclerosis; ILD = interstitial lung disease; CTD-ILD = autoimmune connective tissue disease; IQR = interquartile range; FVC = forced vital capacity; DLCO = diffusion lung capacity for carbon monoxide; MTX = methotrexate; LEF = leflunomide.

*Unless otherwise specified.

1 Multiple imputation was performed.

Tymolysic: interstitial pneumonia, organising pneumonia and acute pneumonitis.
21.8% of patients with OCTD). No case of acute pneumonitis was documented.

Discussion

In this study of ILD in CTD, we have shown that ILD is most commonly diagnosed in RA and SSc and, overall, NSIP was the ILD pattern encountered most frequently. This finding is similar to reports from elsewhere.[1,3,5,13]

In the RA group, patients were older at the onset of CTD compared with other groups, and these patients developed ILD later. This pattern is described elsewhere, where age >60 years has been shown to be one of the risk factors for developing ILD.[3,10-17] In the RA group, we found the distribution of NSIP and UIP to be similar, in contrast to other studies that reported higher frequencies of UIP.[2,3,13-16] In the present study, UIP patients had better PFTs than did other ILD subtypes, yet UIP is described as one of the most severe ILD patterns, with poor response to treatment and poor outcomes.[1,13,18] One explanation may be the higher mortality among patients with UIP pattern, where patients with worse PFTs may have already died at the time of this cross-sectional study.

The SSc and OCTD patients tended to have early onset of ILD, with the majority presenting with ILD within the first year of CTD symptoms onset. Pulmonary function tests in these groups were more severe than in the RA group, with lower DLCO scores in reflecting either worse lung disease or concomitant pulmonary hypertension.

Smoking was highly prevalent in this cohort, particularly among RA patients. This factor is an area for intervention, given the evidence that smoking is a risk for ILD in CTD patients.[2,5,15] GORD was a frequent comorbidity, particularly, as expected, in the SSc group, highlighting the importance of aggressive therapy of this problem, given that GORD is associated with more severe ILD in SSc.[19] Almost a third of patients in all groups had a prior history of PTB, reflecting the high prevalence of TB in the general population of South Africa. This issue needs to be taken into account when offering immunosuppressant therapy for CTD and ILD. Elsewhere, a history of TB and COPD needs to be taken into account when offering immunosuppressant therapy for CTD and ILD. Elsewhere, a history of TB and COPD has been identified as a risk factor for ILD, particularly among male smokers.[19] The role of isoniazid prophylaxis on CTD-ILD patients in a TB endemic area such as ours needs to be explored.

Over one-third of our patients were treated with MTX either before or after ILD onset. Among RA patients, 65.9% of the patients were exposed before ILD onset and 59.5% after ILD onset. No case of acute pneumonitis was observed in any patients of our ILD patients exposed to MTX – accounting for 7 605 patient-years of exposure. Elsewhere, acute pneumonitis has been described in ILD patients treated with MTX.[15,18] Nevertheless, there is growing evidence that treatment with conventional disease-modifying antirheumatic drugs including MTX can be used to prevent or delay the onset of ILD, for treating ILD, and can be safely continued in patients with ILD diagnosis without increasing the risk of progression and/or exacerbation of ILD.[10-21]

Neither respiratory symptoms nor chest radiographs were sensitive for identifying ILD, and were normal in 10% and 4% of our cohort, respectively. This is described elsewhere.[15] Similarly, PFT and HRCT severity correlated poorly, with PFTs underestimating the severity of ILD. We suggest routine HRCT in all newly diagnosed CTD patients, particularly those with SSc and OCTD, where more than two-thirds of patients had developed ILD within 3 years of their CTD.

Limitations of this study include missing data (serology, environmental and/or occupational exposure history), but we corrected this hiatus with statistical imputation. In addition, we could not calculate the prevalence or risk factors for ILD in the CTD population because this cross-sectional review focused only on patients with ILD. We did not have echocardiogram, right-heart catheterisation or 6-minute walk test data for the majority of patients. All subjects were seen at a tertiary referral centre, thus introducing referral bias and decreasing the generalisability of these results.

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Table 3. Comparison of CTD-ILD patients features with and without usual interstitial pneumonia

| Patient features                        | UIP (N=33), n (%) | Non-UIP (N=91), n (%) | OR (95% CI)* |
|----------------------------------------|-------------------|-----------------------|-------------|
| Diagnosis                              |                   |                       |             |
| RA                                     | 18 (54.5)         | 19 (20.8)             | 3.8 (1.5 - 9.5) |
| SSc                                    | 4 (12.1)          | 28 (30.8)             | 0.5 (0.1 - 1.9) |
| OCTD                                   | 11 (33.3)         | 44 (48.4)             | 1           |
| Female                                 | 26 (78.8)         | 81 (89.0)             | 0.4 (0.2 - 1.3) |
| Age, median (IQR)                      | 67 (56 - 72)      | 50 (41 - 61)          | 1.1 (1.0 - 1.1) |
| Age at CTD symptoms onset, years (median (IQR)) | 50 (38 - 56)      | 42 (34 - 52)          | 1.0 (0.9 - 1.1) |
| Black ethnicity                        | 5 (15.1)          | 21 (23.1)             | 0.6 (0.2 - 1.7) |
| Ever smoker                            | 25 (75.8)         | 50 (54.9)             | 1.6 (0.7 - 3.8) |
| Concomitant COPD                       | 13 (39.4)         | 15 (16.5)             | 3.2 (1.4 - 8.0) |
| Age at ILD symptoms onset, median (IQR) | 61 (53 - 67)      | 47 (38 - 57)          | 1.1 (1.0 - 1.1) |
| Symptomatic at ILD Dx                  | 30 (90.9)         | 81 (89.0)             | 1.2 (0.3 - 4.8) |
| CTD-ILD interval (years), median (IQR) | 7 (2 - 14)        | 1 (0 - 4)             | 1.0 (1.0 - 1.2) |
| CTD-ILD interval <1 y (%)              | 7 (21.2)          | 49 (53.8)             | 0.2 (0.1 - 0.6) |
| CTD-ILD interval <3 y (%)              | 12 (36.4)         | 64 (70.3)             | 0.2 (0.1 - 0.6) |
| FVC at ILD Dx, percentage (%), median (IQR) | 79 (66 - 100)    | 71 (59 - 82)          | 1.6 (0.8 - 3.0) |
| FVC <70%                               | 13 (39.4)         | 47 (51.6)             | 0.6 (0.3 - 1.4) |

ILM = idiopathic inflammatory myopathy; MCTD = mixed connective tissue disease; SLE = systemic lupus erythematosus; pSS = primary Sjögren’s syndrome; and overlap syndromes. RA = rheumatoid arthritis; SSc = systemic sclerosis; OCTD = other connective tissue diseases; ILD = interstitial lung disease; COPD = chronic obstructive pulmonary disease; FVC = forced vital capacity.

* Odds ratios were calculated by univariable logistic regression analysis.

† Smoking was highly prevalent in this cohort, particularly among RA and SSc and, overall, NSIP was the ILD pattern encountered most frequently. This finding is similar to reports from elsewhere.[1,3,5,13]

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RESEARCH
Conclusion
ILD was most commonly diagnosed in RA and SSc, with NSIP seen most frequently overall, with similar frequencies of NSIP and UIP patterns among RA patients. The use of MTX was not associated with the development of acute pneumonitis in patients with ILD. We believe that, when necessary, we can continue prescribing MTX to ILD patients. Smoking cessation and treatment of GORD may be a valuable consideration and a final decision.

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All authors contributed to the study conception and design. All authors read and approved the final version.

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None.

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GC is a member of the AJTCCM editorial board. This manuscript was not given any priority over other manuscripts and was subjected to the same review process as any other. Another editor assumed responsibility for overseeing the peer review of this submission, and the author’s editorial board member status had no bearing on editorial consideration and a final decision.

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