APM ANNALS OF PALLIATIVE MEDICINE
AN OPEN ACCESS JOURNAL FOR HIGH-QUALITY RESEARCH IN PALLIATIVE MEDICINE
IMPACT FACTOR 2.595

Peer Review File
Article Information: https://dx.doi.org/10.21037/apm-21-3974

Reviewer Comments:

Major

1.Line 68, you quoted only one article about 5-year survival rate. 43.4% may be too low for CTD-ILD. I recommend you had better collect more epidemiology study of CTD-ILD and summarize of 5-year survival rate,

Reply 1: I searched the PubMed database (search date 2022.16.02) to collect more data on CTD-ILD epidemiology, most importantly survival rates. The key words included CTD-ILD, survival, survival rates.

Changes in the text: (Page 2, line 43 – page 3, line 64) Kocheril et al (4) revealed 5-year survival rate of 43.4 % of CTD-ILD patients. This statistic varies based on the fibrosis type and comorbidities. A negative tendency of FVC decline was impacted by introduction of anti-fibrotic agents such as nintedanib for patients with non-IPF fibrosing ILD; the effect on long-term survival in CTD-ILD remains to be determined in prospective studies (5). In RA, occurrence of ILD is associated with significantly lower survival years; according to a large database analysis by Raimundo et al, as the mortality rate for RA-ILD patients was found to be 35.9% at 5-years, and the median survival was calculated at 7.8 years (5).

According to Hyldgaard et al, (6) mean survival in RA-ILD is 5-8 years. The occurrence of ILD in Ssc, apart from increased hospitalization rates, is associated with significant morbidity, as 10-year mortality reaches ca. 10 % [Systemic sclerosis-associated interstitial lung disease (7). In fibrotic SSC -ILF, the 9-year cumulative survival rate was calculated at 30% (8). SSC-ILD contributes to approximately 35% of all SSc-related deaths (9).

In inflammative myositis-associated ILDs (PM/DM-ILD) , overall mortality was 7.5% over a median follow-up period of 34 months as reported in a a case series of 107 patients (10). Data on prognosis for SLE-ILD patients is scarce, however, the occurrence of ILD within 1 year is thought to be a death predictor. The death rate is ca. 12.5% at a mean follow-up period of 4.3 years from the time ofinitital SLE diagnosis (11).

2.Regarding PM/DM associated ILD, ARS and MDA-5 have different presentation of clinical and chest HRCT findings. You can demonstrate these findings in this review.

Reply 2: Indeed, these diseases manifest themselves in a different manner both in the clinical and radiological domain. I reviewed the literature on the subject based on database search (PubMed).

Changes in text: (throughout Table 3): cough, erythema, heliotrope rash, Gottron's sign, splinter hemorrhage, subungual erythema seen more often in presence of Melanoma Differentiation-Associated gene 5 antibody (anti-MDA-5) which is also associated with decreased survival (56);

more extensive GGO areas and lung tip consolidation in presence of MDA- 5 (56); rapidly progressing ILD associated with anti-MDA-5 (64); greater extent of GGO, consolidation, and lung tip consolidation associated with decreased diaphragmatic excursion

(56)

3.In terms of ILA progression, could you insist on the importance of subpleural fibrotic pattern is tend to develop definite ILD based on Hatabu et al. ?

Reply 3: subpleural fibrotic ILA can be assessed according to the Fleischner Society Guidelines, a significant percentage of cases of subpleural fibrotic ILA can be classified as UIP pattern. In the text we elaborate further on this topic based on Hatabu et al.

Changes in text: (Page, 26 line 393-399) Follow-up HRCTs of subpleural fibrotic pattern ILA seems of utmost importance, as individuals with subpleural reticulation located predominantly in lower lobes, or traction bronchiectasis (had a ca. six times increase in the risk of HRCT progression than patients with other types of ILAs. This discrepancy remains even after adjusting for significant variables like age and smoking status (116).

Probable UIP or UIP patterns of ILA cases were all associated with profression to ILD over 5 year follow up period.

4.You had better mention about utility and limitation of cryobiopsy for IPAF and CTD-ILD comparison with VATS.

Reply 4: I reviewed literature on the subject and included a large cohort study by

Ravaglia et a comapring the diagnostic yield and safety of these methods and COLDICE comparative study.

Changes in text: (Page 32, Line 555 – page 33, line 566) Ravaglia et al (131) compared safety and diagnostic value of these methods in a large retrospective cohort study (447 ILD patients) and also performed a systematic review with metanalysis of literature. Safety and lower mortaity or complication rates of cryobiopsy in comparison with surgical lung biopsy were confirmed.

These findings were confirmed in a prospective study on accuracy of TBLC in the diagnostic process of ILD (COLDICE) (132).

It was revealed that there is high level of conformity between cryobiopsy and surgical biopsy for both MDD diagnoses and histopathological results.

It may be concluded that cryobiopsy becomes a valid alternative to VATS-LB. However, during cryobiopsy it is more likely to obtain a probable UIP pattern on histopathological examination rather than a definite UIP pattern, due to the restricted access to sub-pleural lung parenchyma (133).

5.You can also add meaning of MDD including rheumatologist for diagnosis and management strategy for IPAF and CTD-ILD.

Reply 5: I searched the impact on MDD, especially in comparison with conventional multidisciplinary teams, on diagnostic work-up of CTD-ILDs.

Changes in text: (Page 31, line 528 – page 32, line 544) Multidisciplinary discussion (MDD) is nowadays seen as the reference standard for ILD diagnosis. In a retrospective observational study on management of 126 ILD (IPF and non-IPF) cases in a tertiary care referral centre, Ageely et al (128) revealed that MDD altered the definitive diagnosis in 37% cases (47/126) and impacted management in 39%. Moreover, MDD also altered management in concordant-pre MDD cases. These observations highlight the importance of MDD in managing ILDs and determining prognosis.

De Lorenzis et al (129) noted that, on average, the agreement between rheumatologists and other specialists during identification of alarming symptoms in the course of CTDs and progression assessment changed over time. The degree of multidisciplinary agreement improved over the six-month observation period. Importantly, it was revealed that the aforementioned agreement increased in MDD of

CTD-ILD cases can lead to an improvement in the diagnostic work-up and the assessment of ILD progression in comparison with single rheumatologist's or conventional multidisciplinay team (two pulmonologists, two radiologists with expertise in ILD assessment and, optionally, a pathologist). These findings may probably be extrapolated for the management of IPAF patients.

Minor

1. Line 61, olymyositis might be changed to polymyositis.

Reply: it was changed

Changes in text: polymyositis/dermatomyositis (PM/DM).

2. Line 75, SSc is better instead of Ssc.

Reply: it was changed

Changes in text: (Ssc),...

3. From Line 87 to Line 93, expression of numbers are discrete such as 1 2 3) 4). I recommend arrange it.

Reply: expression of numbers was arranged

Changes in text: 1. …; 2. …; 3. …; 4. ...

4. Line 130, ?50 is probably mistake.

Reply: a formatting mistake

Changes in text: ≤50

5. Line 153, which group of patients have progression rate of honeycombing 0.07%?

Reply: this is about patients with progressive systemic sclerosis

Changes in text: The median monthly rate of honeycombing progression in patients with UIP pattern in SSc-ILD involved 0.4 % of lung volume, whereas the rate of such progression was calculated at 0.07 % (20).

6. Line 396, you had better add reference about the incidence of ILA in RA.

Reply 6: added a reference

Changes in text: ILD is diagnosed in 2-10 % of patients with RA. However, ILA of

varying degrees occurs in an additional 20-60% of RA patients (117).