CHEST Online Supplement

Outcomes and Mortality Prediction Model of Critically Ill Adults With Acute Respiratory Failure and Interstitial Lung Disease

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e-Appendix 1.

Definitions, classification criteria, and/or characteristics of interstitial lung disease subtypes

Idiopathic pulmonary fibrosis:
Definition: A progressive, fibrosing interstitial pneumonia of unknown cause limited to the lung and associated with a key histopathological and/or radiological pattern of usual interstitial pneumonia.[1]
Classification criteria[1]:

I. Exclusion of other known causes of interstitial lung disease (e.g. domestic and occupational environmental exposures, connective tissue disease, and drug toxicity)

II. The presence of usual interstitial pneumonia on high resolution computed tomography in patients not subjected to surgical lung biopsy

III. Specific combinations of high resolution computed tomography and surgical lung biopsy pattern in subjects subjected to surgical lung biopsy

Connective tissue disease related interstitial lung diseases:
Definition: Interstitial lung disease associated with an underlying connective tissue disease, most commonly systemic sclerosis, rheumatoid arthritis, and inflammatory myositis.[2]

Rheumatoid arthritis (classification criteria)[3]:
Score based algorithm for diagnosis of categories I-IV (score of ≥6 points):

I. Joint involvement
    1. One large joint (0 points)
    2. Two to ten large joints (1 point)
    3. One to three small joints (with or without involvement of large joints) (2 points)
    4. Four to ten small joints (with or without involvement of large joints) (3 points)
    5. More than ten joints (at least one small joint) (5 points)

II. Serology
    1. Negative rheumatoid factor (RF) and negative anti-cyclic citrullinated peptide antibody (APCA) (0 points)
    2. Low positive RF or APCA (≤3 times the upper limit of normal (2 points)
    3. High positive RF or ACPA (>3 times the upper limit of normal (3 points)

III. Acute phase reactants
    1. Normal C-reactive protein and normal erythrocyte sedimentation rate (0 points)
    2. Abnormal C-reactive protein or abnormal erythrocyte sedimentation rate (1 point)

IV. Duration of symptoms
    1. <6 weeks (0 points)
    2. ≥6 weeks (1 point)

Systemic sclerosis (classification criteria)[4]:
One major criterion or at least two minor criteria:

I. Major criterion: Proximal scleroderma

II. Minor criteria
1. Sclerodactyly
2. Digital pitting scars of fingertips or loss of substance from distal finger pad
3. Bibasilar pulmonary fibrosis

Systemic lupus erythematosus (classification criteria)[5]*:*
At least one clinical and one immunological criteria or a histologic diagnosis of lupus nephritis in the presence of antinuclear antibody (ANA) or anti-double stranded DNA (anti-dsDNA)

I. Clinical criteria
1. Acute cutaneous lupus (including lupus malar rash, bullous lupus, maculopapular lupus rash, photosensitive lupus rash)
2. Chronic cutaneous lupus (including classic discoid rash, localized rash above the neck, generalized rash above and below the neck, hypertrophic lupus, lupus panniculitis, mucosal lupus)
3. Oral ulcers (palate, buccal, tongue) or nasal ulcers
4. Non-scarring alopecia
5. Synovitis (≥ 2 joints) or tenderness on palpation (≥ 2 joints) and morning stiffness (≥ 30 min)
6. Serositis (pleurisy or pericardial pain for more than 1 day)
7. Renal involvement
8. Neurological involvement (including seizures, psychosis, myelitis, peripheral or cranial neuropathy)
9. Hemolytic anemia
10. Leukopenia (<4,000/uL) or lymphopenia (1,000/uL)
11. Thrombocytopenia (<100,000/uL) at least once

II. Immunological criteria
1. ANA level above laboratory reference range
2. Anti-dsDNA antibodies
3. Anti-Smith antibodies
4. Antiphospholipid antibody positivity as determined by any of the following:
    a. Positive test result for lupus anticoagulant
    b. False-positive test result for rapid plasma reagin
    c. Medium- or high-titer anticardiolipin antibody level (IgA, IgG, or IgM)
    d. Positive test result for anti–β_2-glycoprotein I (IgA, IgG, or IgM)
5. Low complement (C3, C4, or CH50)
6. Direct Coombs test in the absence of hemolytic anemia

Primary Sjögren Syndrome (classification criteria)[6]*:*
Any four of six criteria, provided that either histopathology (IV) or autoantibodies (VI) is positive
Any three of the following four objective criteria: ocular signs (III), histopathology (IV), salivary gland involvement (V), autoantibodies (VI)

I. Ocular symptoms: at least one
1. Daily persistent, dry eyes > 3 months

2. Recurrent sensation of sand or gravel in the eyes
3. Use of tear substitutes > 3 times/day

II. Oral symptoms: at least one
1. Daily feeling of dry mouth > 3 months
2. Recurrent or persistently swollen salivary glands
3. Frequent consumption of liquid to swallow dry food

III. Ocular signs: at least one
1. Positive Schirmer test
2. Rose bengal score or other ocular dye score 4

IV. Histopathology: In minor salivary glands (obtained through normal-appearing mucosa) focal lymphocytic sialadenitis, evaluated by an expert histopathologist, with a focus score >1, defined as a number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4 mm^2 of glandular tissue

V. Salivary gland involvement: at least one
1. Decreased salivary flow
2. Parotid sialography demonstrating diffuse sialectasias
3. Abnormal salivary scintigraphy

VI. Autoantibodies: Antibodies to Ro (Sjögren syndrome antigen A), La (Sjögren syndrome antigen B), or both

Myositis (classification criteria)[7]*:*

I. Symmetric weakness of proximal muscles with or without dysphagia or respiratory muscle involvement

II. Characteristic histopathologic findings on skeletal muscle biopsy sample

III. Elevation of skeletal muscle enzymes: creatine kinase, aldolase, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase

IV. Characteristic findings on electromyography

V. Dermatologic features, including
1. Heliotrope discoloration of the eyelids with periorbital edema
2. Scaly, erythematous dermatitis over the dorsa of hands, especially metacarpophalangeal and proximal interphalangeal joints
3. Involvement of the knees, elbows, medial malleoli, face, neck, and upper torso

Mixed connective tissue disease (characteristics)[8]*:*

I. Overlapping features between ≥ 2 systemic autoimmune diseases

II. Presence antibodies against the U1 small nuclear ribonucleoprotein autoantigen

Unclassifiable idiopathic interstitial pneumonia:

Definition: A heterogeneous collection of interstitial lung diseases and a type of idiopathic interstitial pneumonia characterized by inadequate clinical, radiologic, or pathologic data and/or major discordance between clinical, radiologic, and pathologic findings.[9,10]

Idiopathic non-specific idiopathic pneumonia:

Definition: An interstitial lung disease that is idiopathic and a distinct clinical entity from other idiopathic interstitial pneumonias.[11]

I. Clinical characteristics

1. Breathlessness and cough of typically 7 months' duration
2. Predominantly in women, never smokers, and sixth decade of life
3. Restrictive ventilator defect

II. Radiologic characteristics

1. Bilateral, symmetric, predominantly lower lung reticular opacities with traction bronchiectasis and lower lobe volume loss

III. Histopathologic characteristics

1. Interstitial involvement with a spectrum from a cellular to fibrosing process

Hypersensitivity pneumonitis:

Definition: An immunologically mediated response to an inhaled antigen that results in inflammation and/or fibrosis of the lung parenchyma. A number of features are similar to those seen in other fibrotic interstitial lung diseases, though there are no universally accepted classification criteria. A detailed search for potential exposures is crucial for those under suspicion.[9]

I. Clinical characteristics[12]

1. Cough
2. Progressive dyspnea
3. Hypoxemia
4. Restriction with reduced diffusion capacity seen on pulmonary function tests

I. Radiologic characteristics[12]

1. Centrilobular nodules
2. Mosaic air trapping
3. Upper lobe distribution

II. Pathologic characteristics[12]

1. Bronchiolocentric distribution
2. Poorly formed granulomas

Chronic eosinophilic pneumonia:

Definition: A chronic, idiopathic condition characterized by alveolar filling with mixed inflammatory infiltrate consisting predominantly of eosinophils.[13]

I. Clinical characteristics

1. Cough
2. Fever
3. Dyspnea
4. Hypoxia
5. Restrictive defects with a reduced diffusing capacity on pulmonary function tests

II. Laboratory characteristics

1. Peripheral blood eosinophilia (>6% of total white blood cell count)
2. Serum IgE levels can be increased
3. Rheumatoid factors or immune complexes may be found
4. Erythrocyte sedimentation rate usually elevated

III. Radiologic characteristics

1. Peripheral airspace disease

b. Half of patients have mediastinal adenopathy
c. Histologic characteristics
d. Eosinophil and lymphocyte accumulation in alveoli and interstitium with thickened alveolar walls
e. Interstitial fibrosis seen in about half of cases

Drug induced interstitial lung disease (includes the participant with chemotherapy/radiation induced interstitial lung disease and inflammatory bowel disease related interstitial lung disease):
Classification criteria[14]*:*

I. Correct identification of the drug
II. Singularity of the drug
III. Temporal eligibility (onset of symptoms must be temporally associated with drug administration and there should be no evidence of interstitial lung disease prior to treatment)
IV. Characteristic clinical, imaging, bronchial alveolar lavage and pathologic patterns of reaction to the specific drug
V. Exclusion of other causes of interstitial lung disease

Combined pulmonary fibrosis and emphysema:
Definition: The occurrence of both emphysema and pulmonary fibrosis characterized by relatively normal spirometry and lung volumes in the setting of severely impaired gas exchange.[15]

I. Clinical characteristics
1. Smoking history
2. Dyspnea
3. Pulmonary hypertension
4. Hypoxemia

II. Radiographic characteristics
1. Upper lobe emphysema
2. Lower lobe fibrosis

III. Pathologic characteristics
1. Predominance of usual interstitial pneumonia

Idiopathic pleuroparenchymal fibroelastosis:
Definition/characteristics: A rare interstitial lung disease characterized by upper lobe predominant elastotic fibrosis involving the pleura and subpleural lung parenchyma and can be clinically manifested by progressive dyspnea, dry cough, and pneumothorax.[16]

Familial pulmonary fibrosis:
Definition: Accounts for less than 5% of the total patients with idiopathic pulmonary fibrosis and share the same clinical and histological characteristics. Familial forms may develop at an earlier age and may have different patterns of gene transcription.[9]

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e-Table 1: The prediction model and staging system

Predictor	OR 95% CI	Coefficient	Points*
Male gender	2.4 (1.0-5.5)	0.86	2
IPF diagnosis	1.7 (0.4-7.5)	0.55	1
BMI			
<=25	1	0	0
26-30	1.7 (0.7-4.4)	0.53	1
31-35	2.7 (0.8-8.9)	0.99	2
>35	5.4 (0.7-72.0)	1.69	3
Invasive device	3.0 (1.3-7.2)	1.11	2
No ambulation	1.5 (0.6-3.8)	0.4	1
SAPSII score			
<=20	1	0	0
21-30	3.5 (1.1-11.5)	1.25	3
>30	6.2 (0.7-49.3)	1.82	4
Total points			13
Risk category	Low risk	Moderate risk	High risk
Points	0-4	5-8	9-13

*The point score system was developed by multiplying each regression coefficient by 2 and rounding to the nearest integer. This is an established algorithm that has been used to create other regression coefficient-based scoring systems for non-critically ill ILD patients.[34-36]