INTERSTITIAL LUNG DISEASE

Radiological versus histological diagnosis in UIP and NSIP: survival implications


Background: High resolution computed tomography (HRCT) has an important diagnostic role in idiopathic interstitial pneumonia (IIP). We hypothesised that the HRCT appearance would have an impact on survival in patients with IIP.

Methods: HRCT scans from patients with histological usual interstitial pneumonia (UIP; n=73) or histological non-specific interstitial pneumonia (NSIP; n=23) were characterised as definite UIP, probable UIP, indeterminate, probable NSIP, or definite NSIP. Cox regression analysis examined the relationships between histopathological and radiological diagnoses and mortality, controlling for patient age, sex, and smoking status.

Results: All 27 patients with definite or probable UIP on HRCT had histological UIP; 18 of 44 patients with probable or definite UIP on HRCT had histological NSIP. Patients with HRCT diagnosed definite or probable UIP had a shorter survival than those with indeterminate CT (hazard ratio [HR] 2.43, 95% CI 1.06 to 5.58; median survival 2.08 v 5.76 years) or HRCT diagnosed definite or probable NSIP (HR 3.47, 95% CI 1.58 to 7.63; median survival 2.08 v 5.81 years). Patients with histological UIP with no HRCT diagnosis of probable or definite UIP fared better than patients with histological UIP and an HRCT diagnosis of definite or probable UIP (HR 0.49, 95% CI 0.25 to 0.98; median survival 5.76 v 2.08 years) and worse than those with a histological diagnosis of NSIP (HR 5.42, 95% CI 1.25 to 23.5; median survival 5.76 v 9 years).

Conclusions: Patients with a typical HRCT appearance of UIP experience the highest mortality. A surgical lung biopsy is indicated for patients without an HRCT appearance of UIP to differentiate between histological UIP and NSIP.

Severa...
High resolution computed tomography (HRCT)

HRCT was performed with 1.0 or 1.5 mm thick sections taken at 1 cm intervals throughout the entire lung during inspiration in the supine position and through the caudal 10 cm of the lung at 2 cm increments in the prone position. Images were reconstructed using a high spatial frequency reconstruction algorithm. Two thoracic radiologists (EAK, BHG) independently reviewed each HRCT scan and recorded each case as either definite UIP, probable UIP, indeterminate (equal probability of UIP or NSIP), probable NSIP, or definite NSIP. The algorithm reflects a theoretical continuum of distribution, degree of reticular/honeycomb change, and degree of ground glass opacity illustrated below the algorithm. Generally, patients with a more basilar/subpleural distribution, more reticular infiltrates, and less ground glass were felt to have UIP. Patients with a more diffuse distribution, less reticular infiltrates, and more ground glass were felt to have NSIP.

Figure 1  Diagnostic algorithm used to classify the HRCT pattern as definite UIP, probable UIP, indeterminate (equal probability of UIP or NSIP), probable NSIP, or definite NSIP. The algorithm reflects a theoretical continuum of distribution, degree of reticular/honeycomb change, and degree of ground glass opacity illustrated below the algorithm. Generally, patients with a more basilar/subpleural distribution, more reticular infiltrates, and less ground glass were felt to have UIP. Patients with a more diffuse distribution, less reticular infiltrates, and more ground glass were felt to have NSIP.

Table 2  Baseline characteristics for patients with a histological diagnosis of UIP or NSIP

<table>
<thead>
<tr>
<th>Histological UIP</th>
<th>Histological NSIP (3)</th>
<th>p value (1)=(2)=(3)</th>
<th>p value (1)=(2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRCT UIP (1)</td>
<td>HRCT not UIP (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>8/19</td>
<td>26/20</td>
<td>13/10</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64 (8)</td>
<td>60 (12)</td>
<td>54 (11)</td>
</tr>
<tr>
<td>Onset (years)</td>
<td>3.6 (2.6)</td>
<td>2.2 (2.6)</td>
<td>2.5 (3.7)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>84 (16)</td>
<td>86 (19)</td>
<td>88 (18)</td>
</tr>
<tr>
<td>Non-smokers (%)</td>
<td>19.2 (39.4)</td>
<td>46.5 (49.9)</td>
<td>39.1 (48.8)</td>
</tr>
<tr>
<td>Pack years</td>
<td>18 (17)</td>
<td>19 (26)</td>
<td>24 (28)</td>
</tr>
<tr>
<td>FVC (l)</td>
<td>2.95 (1.0)</td>
<td>2.36 (0.8)</td>
<td>2.6 (0.8)</td>
</tr>
<tr>
<td>FVC (% pred)</td>
<td>76 (21)</td>
<td>64 (19)</td>
<td>70 (17)</td>
</tr>
<tr>
<td>FEV₁ (l)</td>
<td>2.32 (0.8)</td>
<td>1.93 (0.7)</td>
<td>1.98 (0.6)</td>
</tr>
<tr>
<td>FEV₁ (% pred)</td>
<td>85 (23)</td>
<td>72 (21)</td>
<td>72 (17)</td>
</tr>
<tr>
<td>TLC (l)</td>
<td>4.56 (1.1)</td>
<td>4.05 (1.4)</td>
<td>4.27 (1.9)</td>
</tr>
<tr>
<td>TLC (% pred)</td>
<td>79 (15)</td>
<td>73 (19)</td>
<td>84 (18)</td>
</tr>
<tr>
<td>Tlco (l)</td>
<td>10.31 (5.7)</td>
<td>14.47 (5.5)</td>
<td>13.61 (3.11)</td>
</tr>
<tr>
<td>Tlco (% pred)</td>
<td>40 (20)</td>
<td>56 (16)</td>
<td>57 (14)</td>
</tr>
</tbody>
</table>

Values are mean (SD).
UIP=usual interstitial pneumonia; NSIP=non-specific interstitial pneumonia; onset=duration of symptoms before surgical lung biopsy; FVC=forced vital capacity; FEV₁=forced expiratory volume in 1 second; TLC=total lung capacity; Tlco=carbon monoxide transfer factor.

*Additional comparisons with NSIP that were significant at the p<0.05 level in post hoc analysis were: age (1) v (3), (2) v (3), (1) and (2) v (3), Tlco (% pred) (1) v (3).
differentiate between cellular and fibrotic NSIP. In those cases where initial disagreement was present, a consensus opinion was obtained by re-review of the cases by both radiologists as a consensus panel.

**Pathological classification**

Three pathologists (TVC, WDT, AF) blinded to the clinical and radiological features reviewed the biopsy specimens. Each specimen was assigned a histological diagnosis of UIP or NSIP using defined criteria. A patient received a diagnosis of UIP when one or more biopsy specimens showed UIP. Cases of cellular NSIP (n=3) and fibrotic NSIP (n=20) were collectively classified as NSIP.

**Statistical analysis**

Comparisons between baseline characteristics for continuous measurements were carried out using ANOVA (three group comparisons) and two sample t tests (two group comparisons) allowing for unequal variances. Associations between categorical variables were evaluated using Pearson’s χ² statistics or Fisher’s exact test. Interobserver agreement of the radiological diagnoses was described using kappa and weighted kappa statistics, where weighted kappa statistics confer partial agreement for assignment of adjacent diagnoses—for example, definite and probable UIP, or probable UIP and indeterminate assignments. Interobserver agreement between radiologists was first evaluated across all five diagnostic categories (definite UIP, probable UIP, indeterminate, probable NSIP, and definite NSIP). It was also evaluated between radiologists for three grouped diagnostic categories (definite or probable UIP, indeterminate, and probable or definite NSIP). This later analysis was performed as the survival experience for probable versus definite UIP and probable versus definite NSIP were similar. Survival experiences with patients segregated by histological and radiological diagnoses were compared using the log rank test and displayed using Kaplan-Meier curves. Analyses presented include all cause mortality as of August 2001. Cox regression analysis was used to examine the relationship between histopathological or radiological diagnosis and mortality, controlling for other potential confounders including patient age, sex, and smoking status.

**RESULTS**

**Patients**

The cohort included 73 patients with histological UIP and 23 with histological NSIP. Compared with the 27 patients with histological UIP and a definite or probable HRCT diagnosis of UIP, the 46 with histological UIP without a definite or probable HRCT diagnosis of UIP were more likely to be women (p=0.03), to have a shorter duration of symptoms (p=0.03), to be younger (p=0.06), to be non-smokers (p=0.03), and to have a higher TLCO % predicted (p=0.05). Patients with histological NSIP were younger than patients with histological UIP and had a higher % predicted (p<0.05) and had a higher TLCO % predicted (p<0.05) than patients with histological UIP and an HRCT diagnosis of UIP (table 2). Most of the patients with either UIP (n=58, 79%) or NSIP (n=15, 78%) had a biopsy

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**Table 3** HRCT consensus diagnosis segregated by final histological diagnosis

<table>
<thead>
<tr>
<th>Consensus HRCT diagnosis</th>
<th>Histological diagnosis</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UIP</td>
<td>NSIP</td>
</tr>
<tr>
<td>Definite UIP</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Probable UIP</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>Probable NSIP</td>
<td>17</td>
<td>8</td>
</tr>
<tr>
<td>Definite NSIP</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>73</td>
<td>23</td>
</tr>
</tbody>
</table>

**Figure 2** Kaplan-Meier survival curves for (A) patients with an HRCT diagnosis of NSIP (n=44, dotted line), indeterminate (n=25, dashed line), and UIP (n=27, solid line), p=0.01; (B) patients with a histopathological diagnosis of NSIP (n=23, dotted line) and UIP (n=73, solid line), p=0.0006; and (C) patients grouped by combining HRCT and histopathological features as follows: histopathological pattern showing NSIP and HRCT was interpreted as indeterminate or NSIP (n=23, dotted line), histopathological pattern showing UIP and HRCT was interpreted as indeterminate or NSIP (n=46, dashed line), and histopathological pattern showing UIP and HRCT was interpreted as UIP (n=27, solid line), p=0.001. + = last follow up visit; ◯ = death.
specimen taken from more than one lobe (Fisher’s exact for association between diagnosis and biopsy in more than one lobe, p=1.0).

**HRCT diagnoses**

The radiologists had complete agreement in 35 (36%) of the cases (kappa=0.20, p<0.0001; weighted kappa=0.43, p<0.0001). When probable or definite UIP were combined and probable or definite NSIP were combined, agreement improved to 61 (64%) of the cases (kappa=0.43, p<0.0001; weighted kappa=0.52, p<0.0001). A consensus diagnosis was reached for all the remaining cases that lacked initial independent agreement. In 25 cases the consensus shift was to radiologist 1, in 27 cases the consensus shift was to radiologist 2, and in nine cases the final consensus diagnosis was between either radiologist’s initial interpretation. Twenty seven patients had a radiological picture which was felt to represent definite or probable UIP; in all of these patients a histological diagnosis of UIP was confirmed (table 3). All 27 were among the 73 patients with histological UIP (37% of UIP cases). In contrast, only 18 of 44 patients with HRCT features suggestive of probable or definite NSIP had histological NSIP. As such, the radiologists demonstrated a high specificity (100%) but a low sensitivity (37 (SD 6)% in identifying UIP and a sensitivity of 78 (SD 9)% and specificity of 64 (SD 6)% for identifying NSIP.

Fifty eight patients with histological UIP had a biopsy specimen taken from at least two lobes, UIP was present in all lobes in 39 patients (67%) and a combination of UIP and NSIP was found between lobes in 19 patients (33%). Patients with histological UIP in all lobes were more likely to have an HRCT appearance of definite or probable UIP (15/39, 38%) than patients with a combination of histological UIP and NSIP between lobes (3/19, 16%, Fisher’s exact test, p=0.05).

**Survival**

Patients with a histological diagnosis of UIP had worse survival (32 deaths/73 patients) than those with a histological diagnosis of NSIP (2 deaths/23 patients) (hazard ratio (HR)=7.24, 95% CI 1.74 to 30.2, log rank p=0.0015). The median follow up was 3.1 years (95% CI 2.3 to 4.4) and 3.3 years (95% CI 3.0 to 4.9) for histological UIP and histological NSIP, respectively. There was no difference in survival when patients with HRCT diagnoses of definite UIP versus probable UIP (HR=1.67, 95% CI 0.60 to 4.64, log rank p=0.32), or when patients with HRCT diagnoses of definite versus probable NSIP (HR=1.31, 95% CI 0.38 to 4.54, log rank p=0.67) were compared. We therefore grouped patients with a definite or probable HRCT diagnosis of UIP as HRCT UIP and those with a definite or probable HRCT diagnosis of NSIP as HRCT NSIP for the remainder of the survival analyses.

The combination of biopsy and HRCT findings allowed for the most discrete separation of patients into groups with different prognoses (fig 2A–C). Patients with an HRCT diagnosis of UIP had the worst survival profile with a higher risk of death than those with an indeterminate HRCT diagnosis (HR=2.45, 95% CI 1.06 to 5.67, log rank p=0.03) and those with an HRCT diagnosis of NSIP (HR=3.5, 95% CI 1.59 to 7.71, log rank p=0.001). Importantly, patients with both an HRCT and histological diagnosis of UIP fared worse than those with a histological diagnosis of UIP in the absence of an HRCT diagnosis of UIP (HR=2.03, 95% CI 1.02 to 4.05, log rank p=0.04; fig 2C). Patients with histological UIP and an HRCT diagnosis of indeterminate or NSIP had a higher risk of death than those with histological NSIP (HR=5.29, 95% CI 1.22 to 23.0, log rank p=0.01; fig 2C). Median survival estimates by diagnostic category are shown in table 4. Survival profiles across treatment groups were not significantly different (log rank p=0.40). Treatment regimens by histopathological diagnosis were not significantly different (Fisher’s exact test, p=0.22).

In multivariate analyses, statistically insignificant protective effects were seen for younger patients, smokers, and women. Effect sizes maintained similar magnitude and directions to the unadjusted analysis and also remained statistically significant or marginally significant. The HR for a patient with both histological and HRCT UIP compared with a patient with histological NSIP was 11.40 (95% CI 2.38 to 54.59, p=0.002). The HR of a patient with histological UIP in the absence of HRCT UIP compared with a patient with histological NSIP was 5.58 (95% CI 1.25 to 24.85, p=0.024). The HR of a patient with both histological and HRCT UIP diagnosis compared with histological UIP in the absence of a typical HRCT pattern of UIP was 2.04 (95% CI 0.88 to 4.73, p=0.095). Each of these comparisons was adjusted for age, smoking status, and sex. Similar results were observed when the physiological status was included and when the three patients with cellular NSIP were excluded (data not shown). When treatment categories were added to the multivariate models the parameter estimates did not converge, so reliable conclusions regarding the effect of treatment could not be determined.

**DISCUSSION**

In this study of patients with histologically well defined UIP and NSIP we found that: (1) patients with an HRCT pattern of UIP are likely to have a histopathological pattern of UIP; but patients with an HRCT pattern other than UIP may have either a histological pattern of UIP or NSIP on the surgical lung biopsy specimen; (2) HRCT features add prognostic information to the histological diagnosis of UIP; survival was worse if patients with histological UIP had an HRCT picture felt by...
expert radiologists to be definite or probable UIP compared
with patients with histological UIP but an atypical HRCT pic-
ture for UIP; and (3) HRCT has limited specificity in identify-
ing histological NSIP.

We have quantified the median survival of patients with a
histological diagnosis of UIP and typical HRCT findings. These
patients have a significantly worse prognosis (median survival
2.08 years) than patients with histological UIP but atypical
HRCT findings (median survival 5.76 years). Controversy
exists regarding survival in patients with UIP diagnosed using
biopsy or HRCT criteria. Survival in patients with UIP by clini-
cal and HRCT criteria have been reported to be similar29 30 31 and
worse32 33 than those diagnosed by surgical lung biopsy. Our
findings were strengthened by the large number of patients and
by the application of the latest histological criteria for
diagnosing UIP or NSIP by three pathologists independently.34
In addition, the radiological criteria were applied by two expert radiologists independently who
ultimately achieved consensus diagnoses of UIP or NSIP. Our
data are of particular significance because they document the
potential survival bias depending on the method used to diag-
nose UIP. If the HRCT criteria we describe (and not lung
biopsy) are used to diagnose UIP, later stage UIP appears to be
prevalence is low and so, in some reports35 36 37 and in similar to more
recent data.24 38 The differences may relate to the stringent
radiological criteria used to diagnose UIP in the current study
and the presence of an indeterminate radiological category.
The interobserver agreement in our study was good and simi-
lar to that reported by experienced observers in previous studies.20 21 39

It is important to emphasise that radiologists with differing levels of experience and expertise can interpret
radiographic images differently.40 The radiologists in this study
are specialists in thoracic radiology and have extensive expertise
in the interpretation of HRCT scans from patients with
suspected IIP. The level of agreement and interpretations could
differ if this study was repeated using general radiologists
who may have a more general knowledge of a broader range of
material. Furthermore, agreement between radiologists may
differ if they use different diagnostic criteria or algorithms for
the classification of UIP and NSIP. Further studies are needed to
evaluate radiographic diagnostic criteria and the specificity,
predictive ability, and level of agreement for patients evaluated by
less experienced radiologists.

Our study provides strong support for the concept that no
currently identified single feature or combination of HRCT
features has high specificity for a histological diagnosis of
NSIP.41 42 HRCT findings of ground glass opacity and reticular
abnormality were not accurate predictors of histological NSIP.
In our series most of the patients with typical HRCT findings
of NSIP had a histological diagnosis of UIP at surgical lung
biopsy (26/44, 59%). In addition, patients with histological
UIP who lacked the typical features of UIP on HRCT scanning
experienced a worse survival than those with histological fea-
tures of NSIP. Furthermore, reclassification of NSIP as UIP
risks as indeterminate (having an equal probability of UIP or
NSIP) by two radiologists evaluating HRCT scans using the
radiological criteria shown in fig 1.

Although some studies have suggested predominant
ground glass31 and parenchymal consolidation27 with a
subpleural predominance in NSIP42 others have expanded the
spectrum of radiological abnormalities seen in NSIP.36
Importantly, one multicentre group found HRCT findings
consistent with UIP in 15 of 50 patients with biopsy proven
NSIP. However, in our study all patients with HRCT findings
consistent with UIP had a histological pattern of UIP. These
differences may reflect sampling error inherent in surgical
lung biopsy, evolution in histological criteria, or differential
criteria used by radiologists. Our data support a diagnostic
approach to IIP that incorporates histological and radiological
findings as advocated by expert groups, and indicate that
surgical lung biopsy should be considered for patients with an
HRCT picture which suggests NSIP.

In summary, we have shown that an HRCT diagnosis of UIP
can reliably predict a histological pattern of UIP although
the converse does not apply as many patients with histological
UIP lack stereotypical HRCT features. In those patients with-
out the stereotypical HRCT features of UIP there is a
significant difference in survival between those found to have
histological NSIP and those with histological UIP. Pulmonary and
surgical lung biopsy is therefore required in these patients to provide
accurate prognostic information. Furthermore, among pa-
tients with a histological diagnosis of UIP, there is a
difference in survival between those with HRCT features suggestive of
UIP and those without these HRCT features. Our data provide
further clarification as to which patients will benefit from
surgical lung biopsy and give important information for
stratification of patients in studies where survival is an
outcome variable.

APPENDIX

The University of Michigan Fibrotic Lung Disease Network includes:
University of Michigan, Division of Pulmonary and Critical Care, Ann
Arbor, MI (D Arenberg, C Brennan-Martinez, W Bria, D Dahlgren, S
Gay, C Grum, J Hampton, K Harihar, M Keane, T Ojo, M Peters-Golden,
R Simon, T Sisson, T Standiford, R Stieier); Internal Medicine Clinic,
Alpena, MI (P Bachwitz, C Easton, J Mazur); The Lung Center, Battle
Creek, MI (S Chaperala, G Harrington, N Schilz); Bay City, MI (S
Manawat, J Summer); Clawson, MI (P Hukku, J Sung); Clinton Township,
MI (R Babcock); Pulmonary and Critical Care Medicine Consultants,
Commerce, MI (J Belen, M Dunn, D Maxwell, R Reagle, R Sherman,
S Simecek); Oakland Hospital, Dearborn, MI (L Victor); Henry Ford Hospital,
Detroit, MI (B DiGiovine, M Eichenhorn, R Huyz, J Popovich Jr, D Spizarny);
Botsford General Hospital, Farmington Hills, MI (B Rabinowitz); Pulmonary
and Critical Care Specialists, Farmington Hills, MI (G Ferguson, P
Kaplan, S Sklar, W VanderRoeet); Pulmonary Associates, PC, Flint, MI
(O Filos, V Rao, MV Thomas, J Varghese, J Vyskocil, W Fadenoster);
Grand Valley Internal Medicine, Grand Rapids, MI (J Cantor, W Katz,
R Johnson, Jr., D Listello, J Willi); Michigan Medical Professional
Company, Grand Rapids, MI (L Mathis, T Touwenhoven, T Daum, M
Harrison, M Koets, G Sandman, G Vanotteren); Michigan Medical
PC, Holland, MI (S Kraker); Huntington Woods, MI (M Greenberger,
A O’Neill, D Wu); Pulmonary Clinics of Southern Michigan, Jackson,
MI (RC Albertyon III, J Chauncey, T Murray, G Patten); Associated
Pulmonary and Critical Care Specialists, PC, Kamazoom, MI (T Abra-
ham, J Dirks, B Dykstra, G Granich, B Scholl); Pulmonary and Critical
Care Associates, PC, Kamazoom, MI (R Brush, S Jefferson, J Miller,
S Schuldeiz, M Warlick); Pulmonary and Critical Care Consultants,
Lansing, MI (J Armstrong, A Atkinson, T Kantra, L Ravishore, D
Young); Pulmonary Services, Lansing, MI (A Abbas, CM Gera, G
Kashyap, J Morlock); Respiratory Medicine, Marquette, MI (S Danek,
A Davis); Midland, MI (S Kazam); Central Michigan Healthcare
System, Mi Pleasant, MI (E Obeid); Muskegon Pulmonary Associates,
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