A Diagnostic Model For Chronic Hypersensitivity Pneumonitis

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Supplemental Materials

METHODS

Study Variables

Radiologic evaluation included assessment for the presence and extent of individual radiographic parameters (**Table S1**). These included ground-glass opacity (GGO), reticulation, bronchiectasis (traction and non-traction), honeycombing, airway thickening, nodules, cysts, and mosaic perfusion. Mosaic perfusion was defined as lobular areas of decreased attenuation and vascularity on inspiratory imaging (**Figure S1**). Air trapping was defined as lobular areas of decreased attenuation and vascularity on expiratory imaging. Radiographic variables were scored on their extent and their predominant distribution. The severity of radiographic variables was defined as none, mild (involvement of <10% of the lung), moderate (involvement of 10% to <50% of the lung) or severe (involvement of >50% of the lung). Air trapping was classified as none, mild (involving <3 lobes) or moderate (involving ≥3 lobes). Distribution was defined in the cranio-caudal (upper, middle, lower or diffuse) and axial (peripheral, central or diffuse) planes. GGO, mosaic perfusion and air trapping were further dichotomized into the presence or absence of significant abnormality. The subset of HRCT studies with expiratory images available was also assessed for the presence and extent of air trapping. Air trapping was considered significant if scored as moderate.

Statistical Analysis

Two diagnostic models were developed, both including demographic and clinical variables. Model 1 also includes selected radiographic findings, while Model 2 instead adds the radiologist's level of confidence in the HP diagnosis (dichotomized into low vs. moderate or

high). Model performance was then tested in the validation cohort, as well as among derivation cohort patients with either chronic HP or IPF. Using coefficient estimates based on the derivation cohort, we used Models 1 and 2 to calculate predicted probabilities of HP diagnosis for each validation cohort patient. Finally, we evaluated an HP score, with range 0-100, defined as the model-based probability of chronic HP, then identified a cutoff value for the risk score estimated to provide 90% specificity in diagnosing HP. Values of the HP score at or above the suggested cutoff achieve an estimated 90% specificity, thus misdiagnosing at most 10% of non-HP patients as HP, in our view an adequate level of diagnostic certainty. We also performed LASSO modeling as an alternate model derivation strategy.

RESULTS

Exploratory Models Distinguishing HP vs. IPF

In the subgroup of patients with either chronic HP or IPF, Model 1 (including age, a history of down feather and/or bird exposure, the presence of diffuse cranio-caudal ground-glass opacity on HRCT, and the presence of mosaic perfusion on HRCT) demonstrated excellent performance in discriminating HP from IPF (CV-C=82.4 and H-L GOF p-value <0.005). Model 2 (including age, history of down feather and/or bird exposure and a moderate-high confidence in the radiographic diagnosis of HP) also demonstrated excellent performance discriminating HP from IPF (CV-C=84.6 and H-L GOF p-value <0.005.)

LASSO Models

Using LASSO, we derived a reduced and full model to predict a diagnosis of chronic HP. The reduced model included only the presence of mosaic perfusion on HRCT with good discriminant performance (C-statistic = 0.71; 95% CI 0.62, 0.79). The full model included sex, smoking history, exposure history (birds, down and/or hot tub) plus the HRCT presence of any GGO, diffuse axial GGO, mosaic perfusion, air-trapping and an interaction term for severe fibrosis in the axial plane with any one of the 7 exposures. This model demonstrated good performance with a C-statistic of 0.81 (95% CI 0.73, 0.89).

DISCUSSION

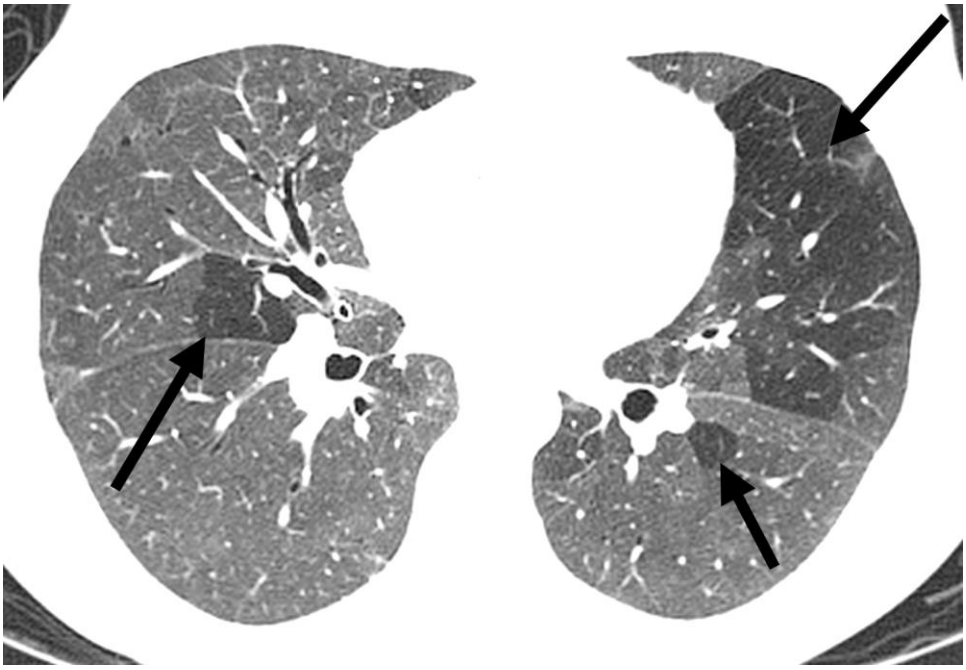
Case Examples

The following three case examples illustrate how this diagnostic model approach could be used in practice. Case 1 is a 55 year-old woman with two parrots at home and an HRCT demonstrating diffuse cranio-caudal ground-glass opacity and mosaic perfusion. Based on this presentation, the HP score based on Model 1 is 87, well above the cutoff of 63 providing specificity of 91%. Case 2 is a 50 year-old man with no history of exposure to birds or down feathers. His HRCT demonstrates diffuse cranio-caudal ground-glass opacities and mosaic perfusion. For this case, the HP score is 68, also above the test cutoff of 63. Case 3 is a 44 year-old woman with no bird or down exposures, mild lower lobe predominant reticulation with no ground-glass opacities or mosaic perfusion. For this patient, the HP score is only 8, well below the cutoff of 63. We suggest that in cases 1 and 2, the diagnosis of chronic HP can be made with a high degree of confidence and surgical lung biopsy is unnecessary. In case 3, the patient is

highly unlikely to have chronic HP, and the decision to pursue surgical biopsy would depend on the other conditions in the differential diagnosis.

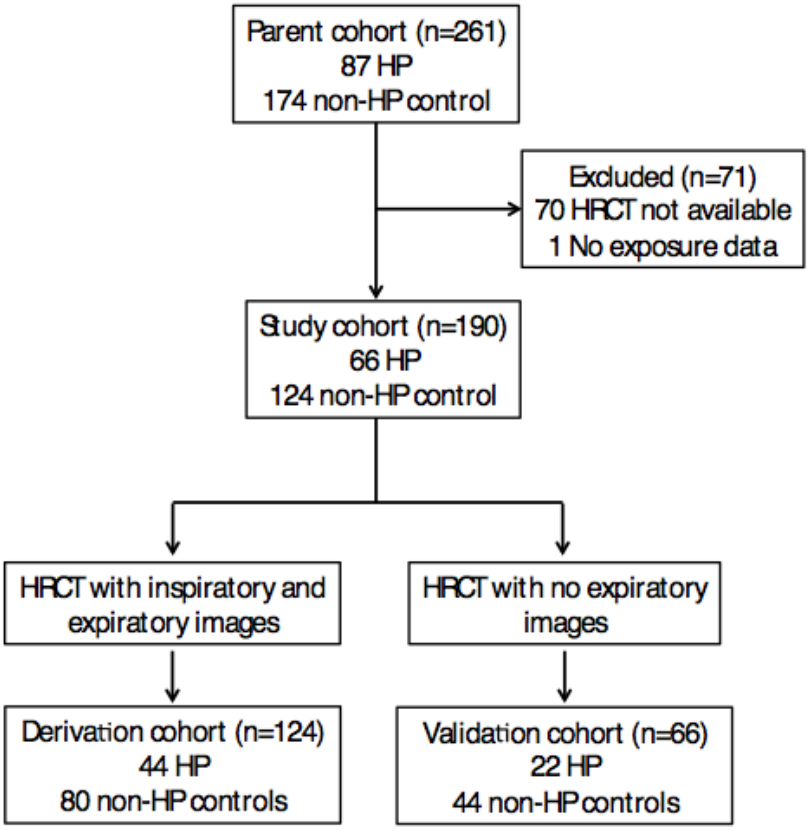
The case examples also highlight a few important aspects of risk prediction modeling. First, each variable in the model is not required to be present (or elevated) to classify a patient as high-risk for chronic HP, and variables are not equally weighted (**Tables S3a and S3b**). For example, in the absence of a positive exposure history, a young age and the presence of key HRCT features are adequate for confident classification. Second, different sets of candidate predictors may have similar discriminatory ability, a pragmatic and verifiable criterion. Thus omission from the final prediction model does rule out a potentially strong association with type of ILD. For example, the absence of radiographic fibrosis from the models does not mean that it is not an important clinical finding that may be more common in one form of ILD or another. It only means that in the patient population with chronic ILD, it was outperformed by other candidate variables in discriminating HP from other fibrotic lung diseases.

Figure S1: Mosaic Perfusion in Chronic Hypersensitivity Pneumonitis



Mosaic perfusion on high-resolution computed tomography of the chest. Arrows demonstrate lobular areas of decreased attenuation and vascularity on inspiratory imaging.

Figure S2: Flow scheme of patients



Abbreviations: HP=hypersensitivity pneumonitis, ILD=interstitial lung disease, HRCT=high resolution computed tomography scan of the chest.

Table S1: Variables for Radiographic Scoring of HRCT Scan

Feature	Scoring
1. Ground glass opacity	
Extent	None, mild, moderate, severe
Cranio-caudal distribution	Upper, middle, lower, diffuse
Axial distribution	Peripheral, central, diffuse
2. Consolidation	
Extent	None, mild, moderate, severe
Cranio-caudal distribution	Upper, middle, lower, diffuse
Axial distribution	Peripheral, central, diffuse
3. Fibrosis	
Cranio-caudal distribution	Upper, middle, lower, diffuse
Axial distribution	Peripheral, central, diffuse
Irregular reticulation	None, mild, moderate, severe
Traction bronchiectasis	None, mild, moderate, severe
4. Honeycombing	
Distribution	Upper, middle, lower, diffuse
Cranio-caudal distribution	Anterior, posterior, both
5. Airways disease	
Mosaic perfusion	None, mild, moderate, severe
Air-trapping (expiratory)	None, mild, moderate, severe
Airways inflammation	None, mild, moderate, severe
Non-traction bronchiectasis	None, mild, moderate, severe

6. Nodules	
Extent	None, mild, moderate, severe
Type	Ground-glass, dense
Size	<5, 5-10, 10-30, >30 mm
Calcification	Yes/No
Predominance	Upper, middle, lower, diffuse
Distribution	Perilymphatic, centrilobular, random
7. Emphysema	
Pattern	Centrilobular, paraseptal, panlobular
8. Miscellaneous findings	
Cysts	Yes/No
Intra-lobular septal thickening	Yes/No
Sub-pleural sparing	Yes/No
9. Pleura	
Pleural plaques	Yes/No
Pleural effusion	Yes/No
10. Leading Diagnosis	---
11. Confidence in Diagnosis	Low, moderate, high

Table S2: Diagnoses Included in the Control Population

Diagnosis	Derivation cohort (n=80) Number (%)	Validation cohort (n=44) Number (%)
Idiopathic pulmonary fibrosis	27 (33.75)	19 (43.18)
Scleroderma	15 (18.75)	2 (4.55)
Sarcoidosis	14 (17.5)	3 (6.82)
Uncharacterized connective tissue disease	6 (7.5)	6 (13.64)
Rheumatoid arthritis	4 (5.0)	1 (2.27)
Nonspecific interstitial pneumonia	3 (3.75)	3 (6.82)
Polymyositis	0 (0)	2 (4.55)
Lymphocytic interstitial pneumonia	2 (2.5)	1 (2.27)
Sjögren's syndrome	2 (2.5)	0 (0)
Acute interstitial pneumonia	1 (1.25)	0 (0)
Amiodarone toxicity	0 (0)	1 (2.27)
Antisynthetase syndrome	1 (1.25)	1 (2.27)
Asbestosis	0 (0)	1 (2.27)
Bronchiolitis, idiopathic	1 (1.25)	0 (0)
Cryptogenic organizing pneumonia	0 (0)	1 (2.27)
Dermatomyositis	1 (1.25)	1 (2.27)

Desquamative interstitial pneumonia	0 (0)	1 (2.27)
Hard metal pneumoconiosis	1 (1.25)	0 (0)
Mixed connective tissue disease	1 (1.25)	0 (0)
Pulmonary Langerhans cell histiocytosis	0 (0)	1 (2.27)
Radiation pneumonitis	1 (1.25)	0 (0)

Table S3a: Equation for calculating the probability of HP (HP score) using individual radiographic variables

Step 1: Use patient's age to determine coefficients for Agesp1 and Agesp2 in the equation

Step 2: Plug coefficient values into equation for X

Step 3: Calculate probability of HP (0.0-1.0)

Step 4: Convert probability to HP score (range 0-100) using probability x 100

With an HP score ≥63, the specificity of HP diagnosis is 91%.

Probability of HP = $1/(1+e^{-X})$, where

X = -6.1121 + 0.0843 x (agesp1) – 0.1099 x (agesp2) + 1.2409 x (down exposure; 0 for no, 1 for yes) + 0.8420 x (bird exposure; 0 for no, 1 for yes) + 0.9656 (diffuse GGO; 0 for no, 1 for yes) + 1.7499 x (mosaicism; 0 for no, 1 for yes)

Age	Agesp1	Agesp2	**Age**	Agesp1	Agesp2
16	16	0.00	**51**	51	0.55
17	17	0.00	**52**	52	0.77
18	18	0.00	**53**	53	1.03
19	19	0.00	**54**	54	1.35
20	20	0.00	**55**	55	1.72
21	21	0.00	**56**	56	2.16
22	22	0.00	**57**	57	2.67

23	23	0.00	**58**	58	3.25
24	24	0.00	**59**	59	3.91
25	25	0.00	**60**	60	4.66
26	26	0.00	**61**	61	5.49
27	27	0.00	**62**	62	6.42
28	28	0.00	**63**	63	7.45
29	29	0.00	**64**	64	8.58
30	30	0.00	**65**	65	9.81
31	31	0.00	**66**	66	11.13
32	32	0.00	**67**	67	12.54
33	33	0.00	**68**	68	14.01
34	34	0.00	**69**	69	15.56
35	35	0.00	**70**	70	17.16
36	36	0.00	**71**	71	18.82
37	37	0.00	**72**	72	20.52
38	38	0.00	**73**	73	22.26
39	39	0.00	**74**	74	24.02
40	40	0.00	**75**	75	25.81
41	41	0.00	**76**	76	27.61
42	42	0.00	**77**	77	29.42
43	43	0.00	**78**	78	31.23
44	44	0.00	**79**	79	33.04
45	45	0.02	**80**	80	34.85

46	46	0.04	**81**	81	36.66
47	47	0.09	**82**	82	38.46
48	48	0.16	**83**	83	40.27
49	49	0.25	**84**	84	42.08
50	50	0.38	**85**	85	43.89

Abbreviations: agesp1=Age Spline 1, agesp2 = Age Spline 2.

Table S3b: Equation for calculating the probability of HP (HP score) using radiologist's level of confidence

Step 1: Use patient's age to determine coefficients for Agesp1 and Agesp2 in the equation

Step 2: Plug coefficient values into equation for X

Step 3: Calculate probability of HP (0.0-1.0)

Step 4: Convert probability to HP score (range 0-100) using probability x 100

With an HP score ≥57, the specificity of HP diagnosis is 91%.

Probability of HP = $1/(1+e^{-X})$, where

X = -4.1329 + 0.0498 x (agesp1) – 0.0761 x (agesp2) + 0.9684 x (down exposure; 0 for no, 1 for yes) + 1.0901x (bird exposure; 0 for no, 1 for yes) + 1.8146 x (moderate-high confidence; 0 for no, 1 for yes).

Age	Agesl1	Agesp2	**Age**	Agesp1	Ag s2
16	16	0.00	**51**	51	0.55
17	17	0.00	**52**	52	0.77
18	18	0.00	**53**	53	1.03
19	19	0.00	**54**	54	1.35
20	20	0.00	**55**	55	1.72
21	21	0.00	**56**	56	2.16
22	22	0.00	**57**	57	2.67

23	23	0.00	**58**	58	3.25
24	24	0.00	**59**	59	3.91
25	25	0.00	**60**	60	4.66
26	26	0.00	**61**	61	5.49
27	27	0.00	**62**	62	6.42
28	28	0.00	**63**	63	7.45
29	29	0.00	**64**	64	8.58
30	30	0.00	**65**	65	9.81
31	31	0.00	**66**	66	11.13
32	32	0.00	**67**	67	12.54
33	33	0.00	**68**	68	14.01
34	34	0.00	**69**	69	15.56
35	35	0.00	**70**	70	17.16
36	36	0.00	**71**	71	18.82
37	37	0.00	**72**	72	20.52
38	38	0.00	**73**	73	22.26
39	39	0.00	**74**	74	24.02
40	40	0.00	**75**	75	25.81
41	41	0.00	**76**	76	27.61
42	42	0.00	**77**	77	29.42
43	43	0.00	**78**	78	31.23
44	44	0.00	**79**	79	33.04
45	45	0.02	**80**	80	34.85

46	46	0.04	**81**	81	36.66
47	47	0.09	**82**	82	38.46
48	48	0.16	**83**	83	40.27
49	49	0.25	**84**	84	42.08
50	50	0.38	**85**	85	43.89

Abbreviations: agesp1=Age Spline 1, agesp2 = Age Spline 2.