

Analysis of risk factors of Mortality in Rheumatoid Arthritis

Patients with Interstitial Lung Disease: A Nationwide, Population-based, Cohort Study

Table A. Selected comorbidities and their corresponding ICD-9-CM codes.

Comorbidities	ICD-9-CM
Hypertension	401–405
Hyperlipidaemia	272
Myocardial infarction	410,412
Congestive heart failure	428
Peripheral vascular disease	441, 443.9, 785.4, V43.4
Cerebrovascular disease	430-438
Dementia	290
COPD	490-505,506.4
Connective tissue disease	710.0, 710.1, 710.4, 714.0, 714.1, 714.2,714.81,725
Peptic ulcer disease	531-534
Mild liver disease	571.2, 571.4-571.6
Diabetes mellitus	250.0-250.3, 250.7
DM with end-organ damage	250.4-250.6
Hemiplegia	342, 344.1
Moderate to severe renal disease	582, 583.0-583.7, 585, 586, 588
Tumor	140-195, 200-208
Metastatic solid tumor	196-199

Abbreviations: ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification;

COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus.

Table 1 Baseline characteristics in ILD group and non-ILD group

	Before PSM (1:10 sex, age and disease duration-matched population)				1:1 PSM population			
	None ILD n=1,640	ILD n=164	P- value	ASD	None ILD n=155	ILD n=155	P- value	AS D
Gender			1.000	0.000			1.000	0.00 0
Female	1,280 (78.0)	128 (78.0)			123 (79.4)	123 (79.4)		
Male	360 (22.0)	36 (22.0)			32 (20.6)	32 (20.6)		
Age at RA diagnosis, years (mean ± SD)	58.8 ± 11.6	58.8 ± 11.7	1.000	0.000	59.3 ± 11.8	59.2 ± 11.5	0.950	0.00 7
Age at ILD diagnosis, years	62.3±11.7	62.3±11.8	1.000	0.000	62.7±12.1	62.7±11. 7	0.973	0.00 4
Disease duration, years (mean ± SD)	3.5±2.8	3.5±2.8	1.000		3.5±2.8	3.5±2.9	0.904	
Urbanisation			0.122				0.269	
Urban	447 (27.3)	57 (34.8)			40 (25.8)	53 (34.2)		
Suburban	716 (43.7)	63 (38.4)			69 (44.5)	60 (38.7)		
Rural	477 (29.1)	44 (26.8)			46 (29.7)	42 (27.1)		
Low income	843 (51.4)	81 (49.4)	0.623		77 (49.7)	75 (48.4)	0.820	
Comorbidities[†]								
Hypertension	515 (31.4)	44 (26.8)	0.227	0.101	46 (29.7)	41 (26.5)	0.527	0.07 2
Hyperlipidaemia	179 (10.9)	14 (8.5)	0.348	0.080	13 (8.4)	12 (7.7)	0.835	0.02 4
Myocardial infarction	6 (0.4)	0 (0.0)	0.438		0 (0.0)	0 (0.0)	NA	
Congestive heart failure	33 (2.0)	12 (7.3)	<0.00 1	0.254	9 (5.8)	9 (5.8)	1.000	0.00 0
Peripheral vascular disease	14 (0.9)	0 (0.0)	0.235	NA	0 (0.0)	0 (0.0)	NA	

Cerebrovascular disease	67 (4.1)	8 (4.9)	0.628	0.038	5 (3.2)	6 (3.9)	0.759	0.035
Dementia	13 (0.8)	2 (1.2)	0.566	0.043	2 (1.3)	2 (1.3)	1.000	0.000
COPD	133 (8.1)	42 (25.6)	<0.001	0.481	36 (23.2)	36 (23.2)	1.000	0.000
Connective tissue disease	1,313 (80.1)	154 (93.9)	<0.001	0.420	147 (94.8)	145 (93.5)	0.627	0.055
Peptic ulcer disease	300 (18.3)	42 (25.6)	0.023	0.177	43 (27.7)	39 (25.2)	0.607	0.059
Mild liver disease	85 (5.2)	7 (4.3)	0.612	0.043	7 (4.5)	7 (4.5)	1.000	0.000
Diabetes mellitus	191 (11.6)	17 (10.4)	0.624	0.041	13 (8.4)	14 (9.0)	0.840	0.023
DM with end-organ damage	43 (2.6)	1 (0.6)	0.111	0.160	2 (1.3)	1 (0.6)	0.562	0.066
Hemiplegia	6 (0.4)	1 (0.6)	0.632	0.035	1 (0.6)	0 (0.0)	0.317	NA
Moderate to severe renal disease	36 (2.2)	2 (1.2)	0.407	0.075	1 (0.6)	2 (1.3)	0.562	0.066
Tumor	61 (3.7)	10 (6.1)	0.135	0.110	5 (3.2)	8 (5.2)	0.395	0.097
Metastatic solid tumor	9 (0.5)	2 (1.2)	0.293	0.072	1 (0.6)	2 (1.3)	0.562	0.066
Use of medication at baseline†								
NSAID	1,530 (93.3)	159 (97)	0.067		149 (96.1)	150 (96.8)	0.759	
Corticosteroid	1,166 (71.1)	146 (89.0)	<0.001		130 (83.9)	138 (89.0)	0.184	
Methotrexate	771 (47)	114 (69.5)	<0.001		93 (60.0)	110 (71.0)	0.042	
Sulfasalazine	787 (48)	97 (59.1)	0.006		83 (53.5)	93 (60.0)	0.252	
Leflunomide	154 (9.4)	36 (22.0)	<0.001		15 (9.7)	36 (23.2)	0.001	
Hydroxychloroquine	941 (57.4)	121 (73.8)	<0.001		111 (71.6)	113 (72.9)	0.800	

Immunosuppressants	97 (5.9)	23 (14.0)	<0.001	12 (7.7)	22 (14.2)	0.069
TNFi	80 (4.9)	17 (10.4)	0.003	9 (5.8)	17 (11.0)	0.101
Rituximab	8 (0.5)	4 (2.4)	0.003	0 (0.0)	4 (2.6)	0.044
Tocilizumab	0 (0.0)	1 (0.6)	0.002	0 (0.0)	1 (0.6)	0.317
Abatacept	1 (0.1)	0 (0.0)	0.752	0 (0.0)	0 (0.0)	NA

†Comorbidity and medications were identified within one year before index date.

Data are shown as number (%) unless specified otherwise.

Abbreviations: ILD, interstitial lung disease; PSM, propensity score matching; ASD, absolute standardised difference; RA, rheumatoid arthritis; SD, standard deviation; NA, not assessed; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; NSAID, nonsteroidal anti-inflammatory drug; TNFi, tumor necrosis factor inhibitor.

Table 2. Demographics and clinical characteristics in rheumatoid arthritis patients with interstitial lung disease, n = 214

Variable	Number (%), unless specified otherwise
Gender	
Female	138 (64.5)
Male	76 (35.5)
Age at RA diagnosis, years (mean ± SD)	60.6±14.2
Age at ILD diagnosis, years (mean ± SD)	64.2±14.2
Disease duration, years (mean ± SD)	3.6±3.0
Urban	
Urban	77 (36.0)
Suburban	83 (38.8)
Rural	54 (25.2)
Low income	117 (54.7)
Comorbidities[†]	
Hypertension	63 (29.4)
Hyperlipidaemia	20 (9.4)
Congestive heart failure	17 (7.9)
Peripheral vascular disease	1 (0.5)
Cerebrovascular disease	10 (4.7)
Dementia	2 (0.9)
COPD	57 (26.6)
Connective tissue disease	202 (94.4)
Peptic ulcer disease	55 (25.7)
Mild liver disease	9 (4.2)
Diabetes mellitus	21 (9.8)
DM with end-organ damage	1 (0.5)
Hemiplegia	1 (0.5)
Moderate to severe renal disease	5 (2.3)
Tumor	12 (5.6)
Metastatic solid tumor	2 (0.9)

Use of medications at baseline[†]

NSAID	208 (97.2)
Corticosteroid	192 (89.7)
Methotrexate	148 (69.2)
Sulfasalazine	119 (55.6)
Leflunomide	44 (20.6)
Hydroxychloroquine	150 (70.1)
Cyclophosphamide	5 (2.3)
Other immunosuppressant*	26 (12.1)
TNFi	21 (9.8)
Tocilizumab	1 (0.5)
Abatacept	0 (0.0)
Rituximab	5 (2.3)

Time-averaged dose of medications, mean±SD

NSAID (cDDD/day)	0.8±0.6
Corticosteroid (Pd equivalent dose, mg/day)	10.0±14.1
Methotrexate (per 2.5 mg/week)	1.5±1.8
Sulfasalazine (cumulative dose/500mg)/day	0.8±1.1
Leflunomide (cDDD/day)	0.1±0.2
Hydroxychloroquine (cDDD/day)	0.3±0.3
Cyclophosphamide (cumulative dose, mg, / 500mg/month)	0.1±0.3
Other immunosuppressants* (cDDD/day)	0.03±0.1
TNFi (cDDD/day)	0.1±0.2
Tocilizumab (cDDD/day)	0.001±0.01
Abatacept (cDDD/day)	0.0004±0.005
Rituximab (cumulative dose, mg, /500mg/6 months)	0.1±0.6

[†]Comorbidity and medications were identified within one year before index date.

Abbreviations: RA, rheumatoid arthritis; ILD, interstitial lung disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation; cDDD, cumulative defined daily dose; TNFi, tumor necrosis factor inhibitor.

*Other immunosuppressants: cyclosporin, azathioprine, mycophenolate mofetil, mycophenolic acid.

Table 3. Cox proportional hazard regressions for estimation of adjusted HRs with 95% CIs in RA patients with ILD, n = 214

Variable	Univariable		Multivariable	
	HR (95% CI)	P value	HR (95% CI)	P value
Male (reference: female)	2.69 (1.70–4.25)	<0.001	0.90 (0.53–1.54)	0.700
Age at ILD diagnosis	1.04 (1.02–1.06)	<0.001	1.05 (1.03–1.08)	<0.001
Disease duration, years	1.01 (0.92–1.10)	0.869		
Urbanisation				
Urban	Ref.			
Suburban	1.36 (0.79–2.35)	0.273		
Rural	1.28 (0.70–2.33)	0.417		
Low income	1.45 (0.90–2.33)	0.123		
Comorbidities[†]				
Hypertension	1.37 (0.85–2.20)	0.201		
Hyperlipidaemia	1.04 (0.45–2.41)	0.921		
Congestive heart failure	1.70 (0.73–3.95)	0.218		
Peripheral vascular disease	210.50 (13.17–3365.37)	<0.001	Cannot estimate	
Cerebrovascular disease	1.75 (0.64–4.81)	0.281		
Dementia	1.88 (0.26–13.60)	0.530		
COPD	3.52 (2.22–5.59)	<0.001	2.12 (1.25–3.58)	0.005
Connective tissue disease	1.03 (0.38–2.83)	0.950		
Peptic ulcer disease	0.90 (0.53–1.53)	0.691		

Mild liver disease	0.77 (0.24–2.47)	0.662		
Diabetes mellitus	1.46 (0.75–2.85)	0.264		
DM with end-organ damage	15.41 (2.02–117.78)	0.008	33.85 (3.72–308.24)	0.002
Hemiplegia	4.33 (0.60–31.56)	0.148		
Moderate to severe renal disease	0.55 (0.08–3.97)	0.555		
Tumor	1.26 (0.46–3.47)	0.650		
Metastatic solid tumor	3.25 (0.45–23.78)	0.245		
Use of medications at baseline†				
NSAID	0.87 (0.21–3.53)	0.840		
Steroid	2.72 (0.86–8.65)	0.090		
Methotrexate	0.86 (0.53–1.40)	0.548		
Sulfasalazine	1.06 (0.66–1.68)	0.819		
Leflunomide	0.99 (0.55–1.76)	0.958		
Hydroxychloroquine	0.90 (0.54–1.49)	0.668		
Cyclophosphamide	0.27 (0.04–1.93)	0.190		
Other immunosuppressant*	0.92 (0.46–1.85)	0.820		
TNFi	0.12 (0.02–0.88)	0.037	0.42 (0.06–3.15)	0.395
Rituximab	1.99 (0.49–8.17)	0.339		
Time-averaged dose of medications				
NSAID (cDDD/day)	1.11 (0.70–1.75)	0.657		

Corticosteroid (Pd equivalent dose, mg/day)	1.07 (1.05–1.08)	<0.001	1.09 (1.07–1.11)	<0.001
Methotrexate (per 2.5 mg/week)	0.77 (0.65–0.91)	0.002	0.94 (0.77–1.13)	0.504
Sulfasalazine (cdose/500mg/day)	1.10 (0.90–1.34)	0.371		
Leflunomide (cDDD/day)	0.39 (0.10–1.48)	0.166		
Hydroxychloroquine (cDDD/day)	2.55 (0.99–6.60)	0.053		
Cyclophosphamide (cumulative dose, mg, /500mg/month)	2.02 (1.21–3.37)	0.007	1.41 (0.86–2.30)	0.177
Other immunosuppressants* (cDDD/day)	5.62 (0.83–38.14)	0.077		
TNFi (cDDD/day)	0.07 (0.01–0.77)	0.030	0.18 (0.01–2.41)	0.195
Rituximab (cumulative dose, mg, /500mg/6 months)	0.28 (0.04–2.00)	0.204	0.53 (0.09–3.23)	0.493

†Comorbidity and medical utilisation identified within 1 year before index date.

Abbreviations: RA, rheumatoid arthritis; ILD, interstitial lung disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; NSAID, nonsteroidal anti-inflammatory drug; cumulative defined daily dose; TNFi, tumor necrosis factor inhibitor.

*Other immunosuppressants: cyclosporin, azathioprine, mycophenolate mofetil, mycophenolic acid