Association between Immunosuppression and Risk of New Onset Interstitial Lung Disease in Systemic Sclerosis

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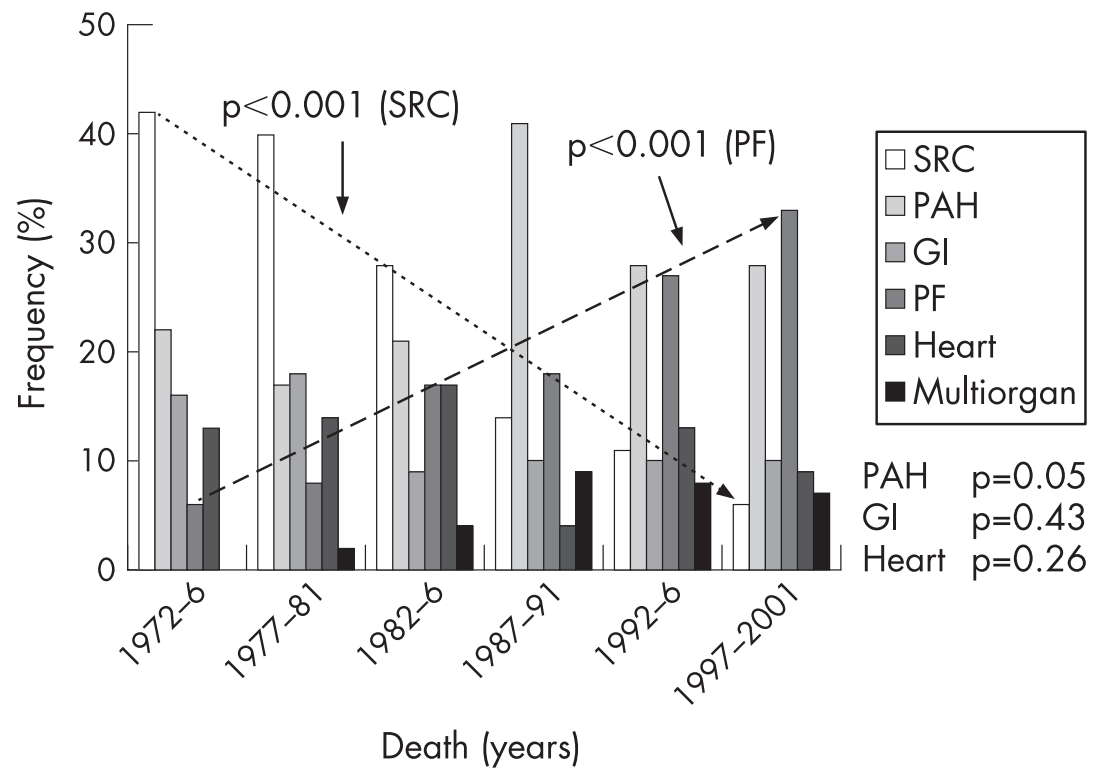Laurentian Conference of Rheumatology, May 11, 2018

Disclosure
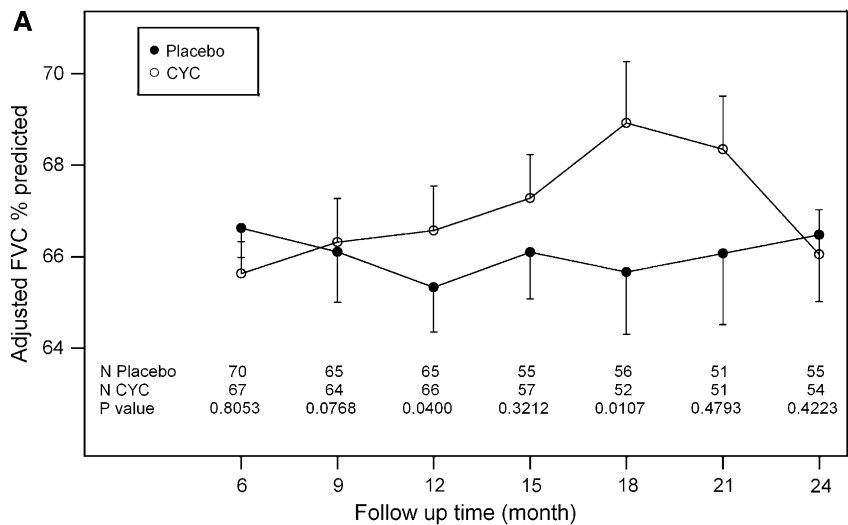
- No conflict of interest

Interstitial lung disease in SSc
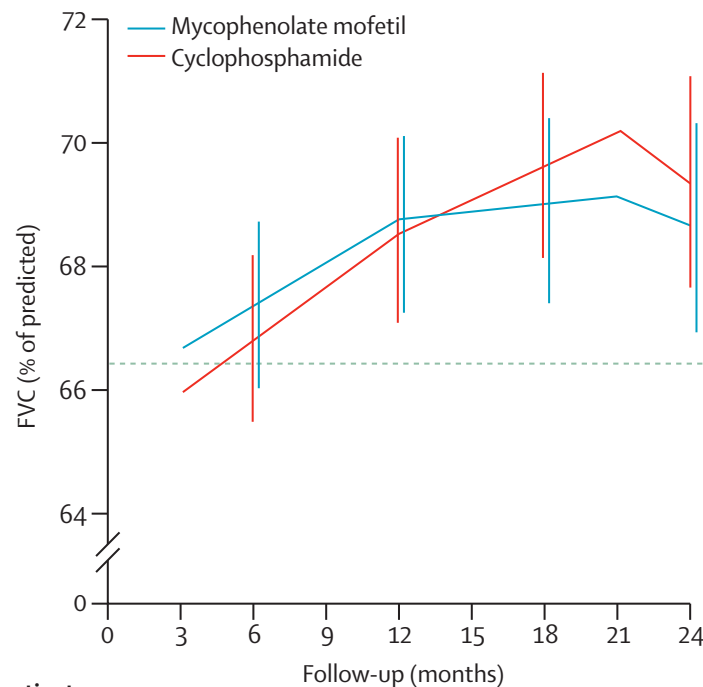

Causes of death in scleroderma

Steen VD, Medsger TA, Ann Rheum Dis 2007;66:940–944.

Treatment of SSc-ILD

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PREVENTION?

Tashkin DP et al. Scleroderma Lung Study I and II

Do immunosuppressive drugs prevent incident ILD in SSc?

Our study

Patients without lung disease

Treated with immunosuppressors

Methotrexate
Mycophenolate
Azathioprine
Cyclophosphamide

Not treated with immunosuppressors

New lung disease?
Follow-up: 3.6 (0-11.4) years
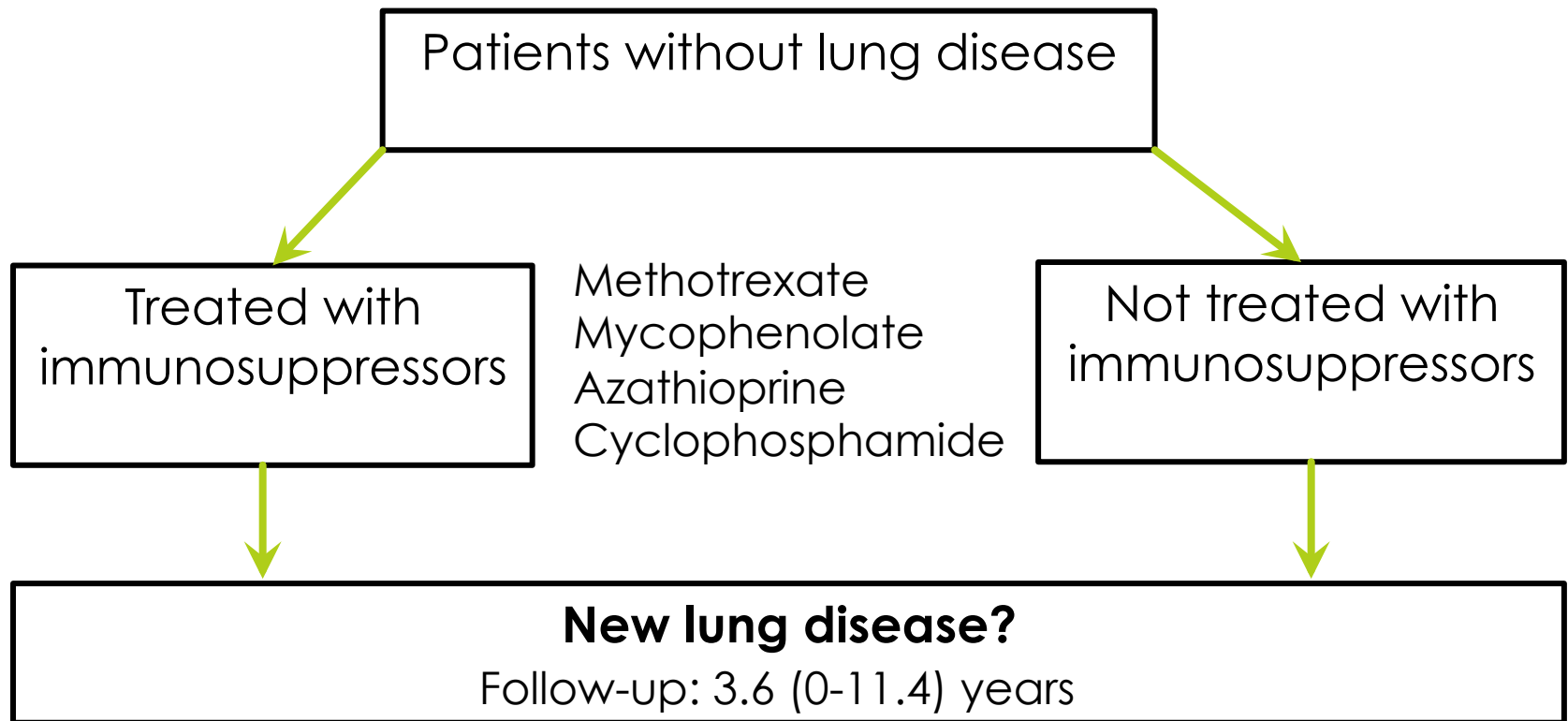
By HRCT or, if unavailable, by CXR and/or velcro-like crackles (Steele et al, 2012)

Baseline characteristics (n=1126)

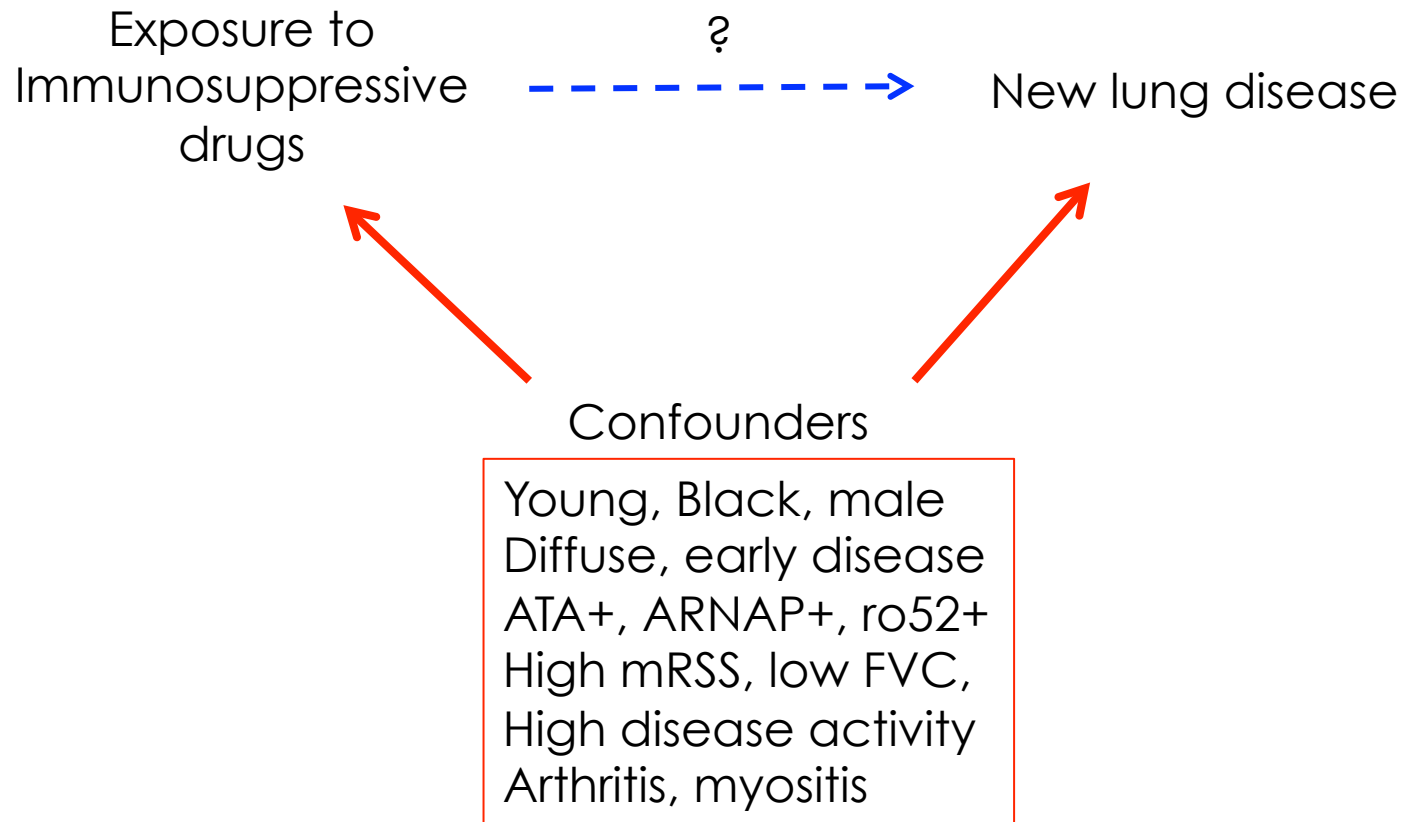|	Never-exposed to treatments (N=864)		Ever-exposed to treatments (N=262)		Standardized differences
	Mean (SD) or N (%)	Missing	Mean (SD) or N (%)	Missing	
* Age, years	55.6 (12.4)	-	51.3 (12.2)	-	-34.5
Female	773 (89.5%)	-	227 (86.6%)	-	-8.7
White	699 (87.6%)	8%	204 (85.0%)	8%	-7.5
Smoking (ever vs. never)	491 (61.5%)	8%	138 (57.0%)	8%	-9.0
* Disease duration from 1st non-RP	10.8 (9.5)	<1%	6.3 (7.2)	-	-53.1
* Diffuse subtype (vs. limited)	205 (23.8%)	<1%	147 (56.1%)	-	69.7
* Modified Rodnan skin score (0-51)	7.4 (8.1)	2%	13.6 (10.7)	2%	65.3
Anti-centromere	369 (51.5%)	17%	61 (30.1%)	23%	-44.6
Anti-topoisomerase	62 (8.6%)	17%	41 (20.2%)	23%	33.3
* Anti-RNA polymerase III	76 (10.6%)	17%	51 (25.1%)	23%	38.5
Anti-Ro52/TRIM21	176 (24.6%)	17%	40 (19.7%)	23%	-11.7
C-reactive protein, mg/L	7.9 (15.8)	21%	9.7 (19.9)	24%	9.9
FVC, % predicted	98.1 (16.8)	15%	93.1 (17.9)	14%	-28.6
* TLC, % predicted	99.6 (15.5)	22%	96.1 (15.9)	21%	-22.1
DLCO, % predicted	75.9 (19.5)	24%	73.7 (19.9)	24%	-10.7
Shortness of breath (0-10)	1.6 (2.4)	8%	1.5 (2.1)	8%	-4.1
* Arthritis	215 (25.7%)	3%	111 (43.9%)	3%	38.9
* Inflammatory myositis	56 (6.5%)	<1%	44 (16.9%)	2%	32.8
* Physician global severity (0-10)	2.3 (2.0)	<1%	3.4 (2.2)	<1%	48.6
Physician global activity (0-10)	2.0 (1.8)	<1%	3.3 (2.3)	<1%	62.8
* Exposure to immunosuppression prior to baseline	71 (8.3%)	<1%	43 (16.4%)	-	25.1

Confounding

Exposure to Immunosuppressive drugs

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New lung disease

Confounders

Young, Black, male
Diffuse, early disease
ATA+, ARNAP+, ro52+
High mRSS, low FVC,
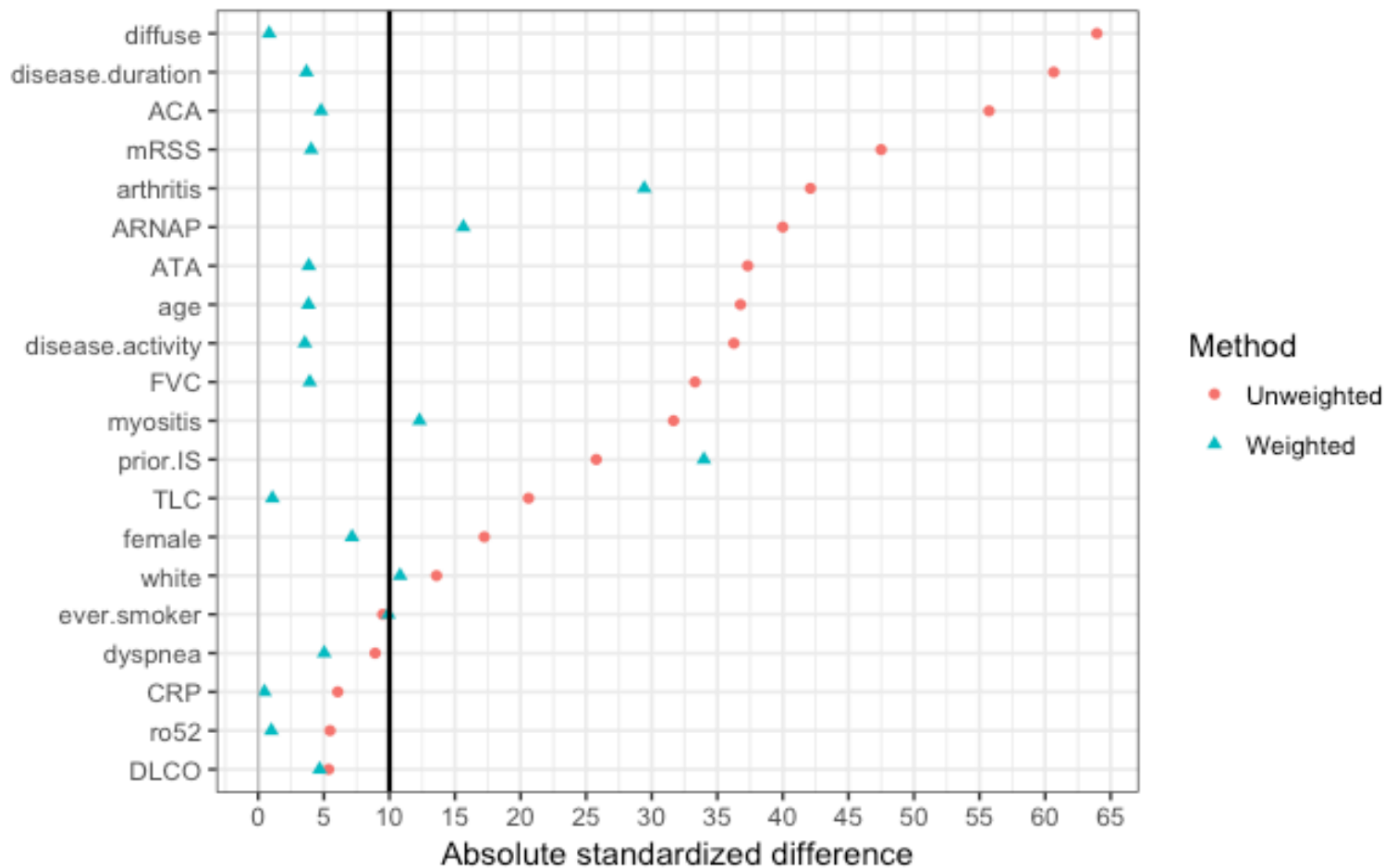High disease activity
Arthritis, myositis

Statistical methods

- Time-dependent Cox proportional hazard regression
  - Adjusted for confounders

- Marginal structural Cox modeling
  - Inverse probability of treatment weighting (IPTW)

- Time-varying, ever/never exposure

- Multiple imputation (for missing data)
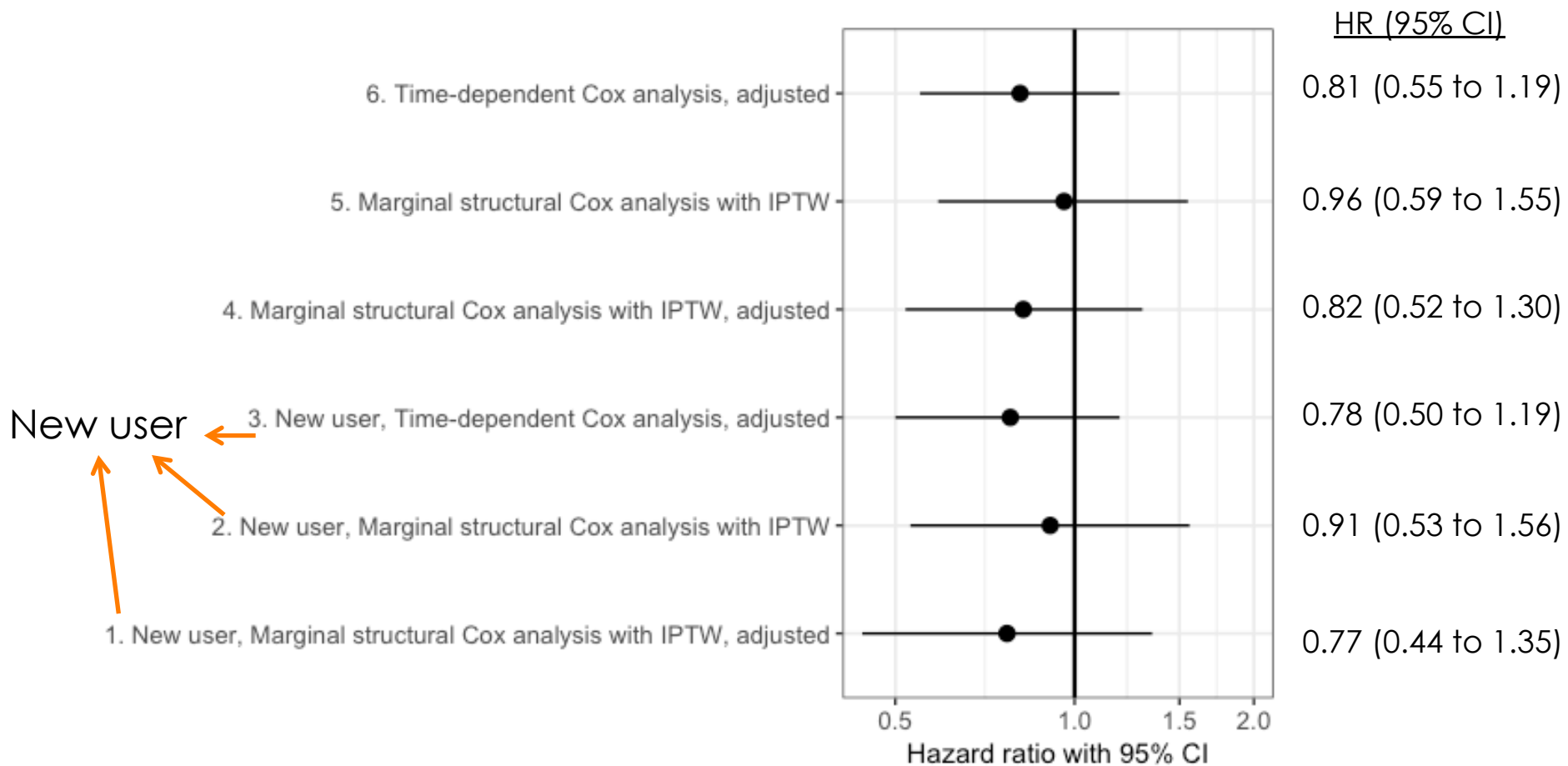
- Inverse probability of censoring weighting (IPCW)

Inverse probability of treatment weighting (IPTW)

Lifewire.com

Covariate balance with IPTW

Results

HR (95% CI)

6. Time-dependent Cox analysis, adjusted — 0.81 (0.55 to 1.19)

5. Marginal structural Cox analysis with IPTW — 0.96 (0.59 to 1.55)

4. Marginal structural Cox analysis with IPTW, adjusted — 0.82 (0.52 to 1.30)

3. New user, Time-dependent Cox analysis, adjusted — 0.78 (0.50 to 1.19)

2. New user, Marginal structural Cox analysis with IPTW — 0.91 (0.53 to 1.56)

1. New user, Marginal structural Cox analysis with IPTW, adjusted — 0.77 (0.44 to 1.35)

New user

Hazard ratio with 95% CI

Limitations

- Survival bias
    - 60% had >5 years of disease duration

- Homogeneity of treatment
    - 79% MTX, 23% MMF, 19% AZA, 11% CYC

- Medication data: yes/no at current visit

- Unmeasured confounding

- Sample size for subgroup analyses

Strengths

- Robust statistical methods to address:
    - Non-randomization
    - Confounding bias
    - Missing data
    - Informative censoring

- Multi-center cohort of well-described patients with SSc

Thanks ☺