The SSc community – overview of registries and educational opportunities in SSc

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The role of registries in understanding the disease & education opportunities

1. The disease course
2. The Mortality
3. Disease features & Organ manifestations
4. The Gender enigma
5. The challenge of prediction
6. The problem of measuring the outcome
7. Education & opportunities
8. Conclusions

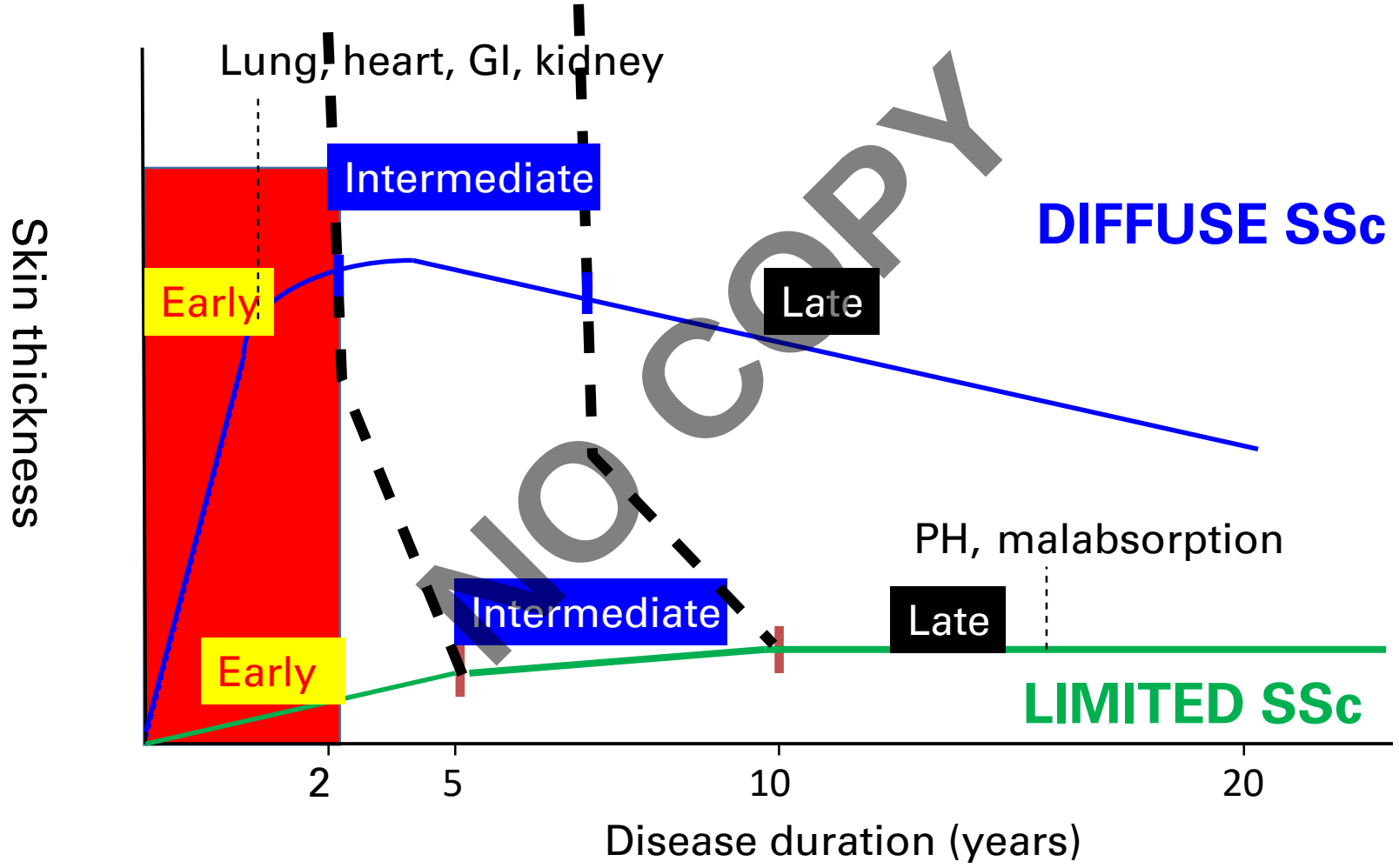
Worldwide estimates of economic burden of SSc

Country (patient number)	**Annual direct cost per patient** (healthcare, ambulatory, pharmaceutical)	**Total annual indirect cost per patient** (productivity loss)	**Total annual cost per patient (US $) per year**
Australia	**AUD$11,622 (USD$8,554)**	**$8,024 (USD$6,178)**	**$15,127**
Canada	$3,879	$10,341	**$14,208**
USA	$17,365	not measured	**$17,365**
Spain	$9,372	$14,571	**$23,948**

Estimated cost of SSc in Australia per year	**AUD**
Direct	**64 Million**
Indirect	**44 Million**
Total	**108 Million**

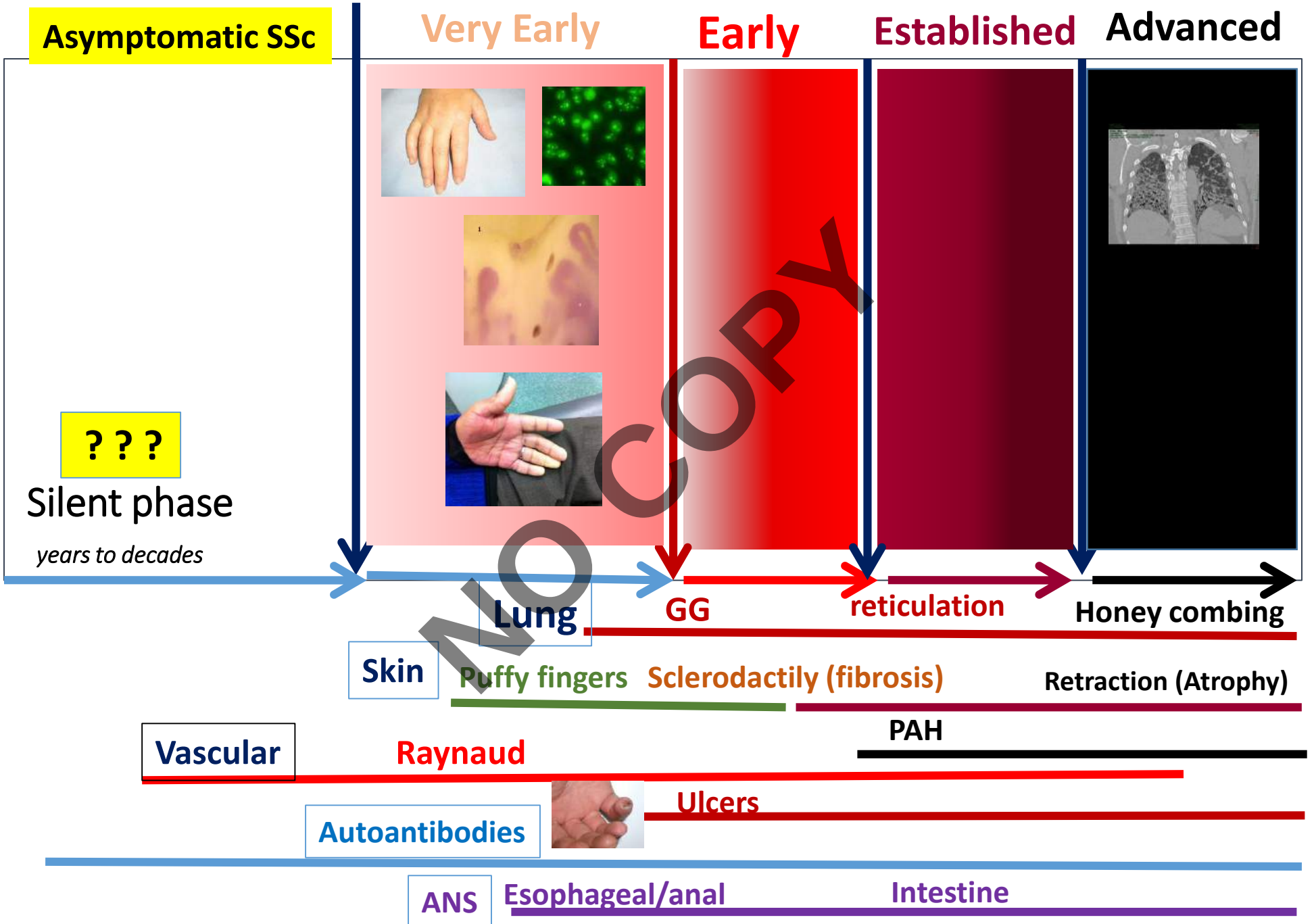
[1] AIHW 2014. Health-care expenditure on arthritis and other musculoskeletal conditions 2008-2009. *Arthritis series 20 Cat no PHE 177 Canberra: AIHW* 2014.

The course of the disease



Modified from Medsger T & Steen V, *Systemic Sclerosis,* 1995, p 51, Williams & Wilkins.

Matucci Cerinic M. Kahaleh B, Wigley F: «Scleroderma i a vascular disease», A&R



International observational cohorts

JSRD
ISSN 2397-1983

J Scleroderma Relat Disord 2017; 2(3): 169-182
DOI: 10.5301/jsrd.5000256

ORIGINAL RESEARCH ARTICLE

What have multicentre registries across the world taught us about the disease features of systemic sclerosis?

Susanna M. Proudman[1,2], Molla Huq[3,4], Wendy Stevens[3], Michelle E. Wilson[3], Joanne Sahhar[5,6], Murray Baron[7], Marie Hudson[7], Janet Pope[8], Yannick Allanore[9], Oliver Distler[10], Otylia Kowal-Bielecka[11], Marco Matucci-Cerinic[12], Andrea H.L. Low[13], Gim Gee Teng[14], Weng Giap Law[15], Amelia Santosa[13], Mandana Nikpour[3,4]; Australian Scleroderma Interest Group (ASIG)*; Canadian Scleroderma Research Group (CSRG)*; EULAR Scleroderma Trials and Research group (EUSTAR)*; Singapore Scleroderma Workgroup (SCORE)*

Largest meta-cohort analysis in SSc to date, reporting on frequency of disease manifestations and mortality in 17,838 SSc patients from ASIG, CSRG, EUSTAR ad SCORE cohorts

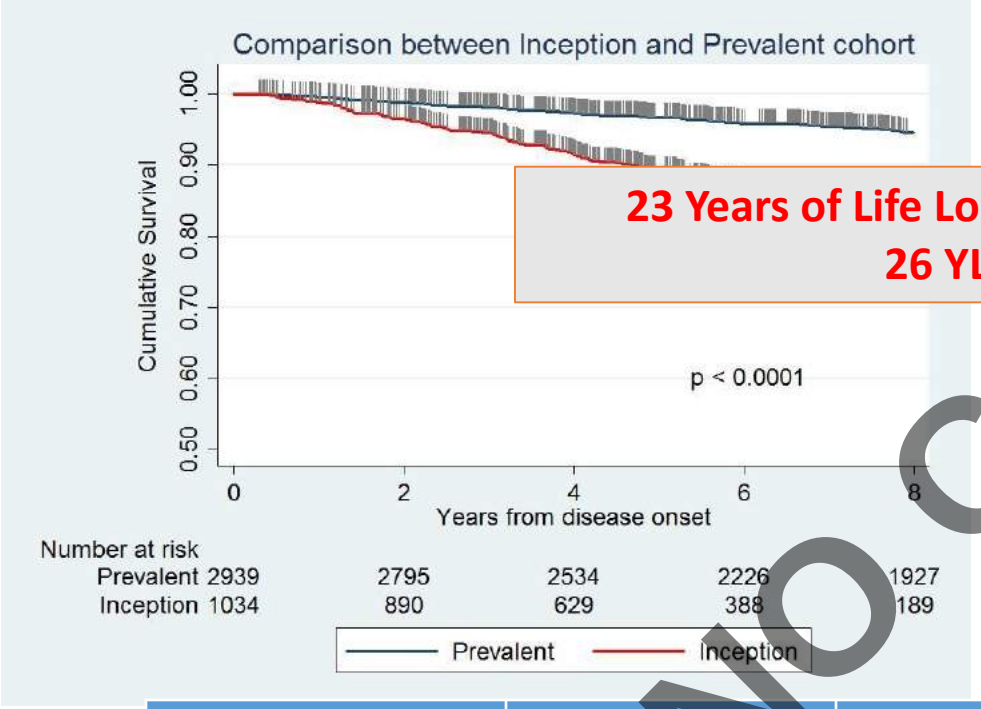
Kaplan-Meier analysis of survival following disease onset in each cohort.

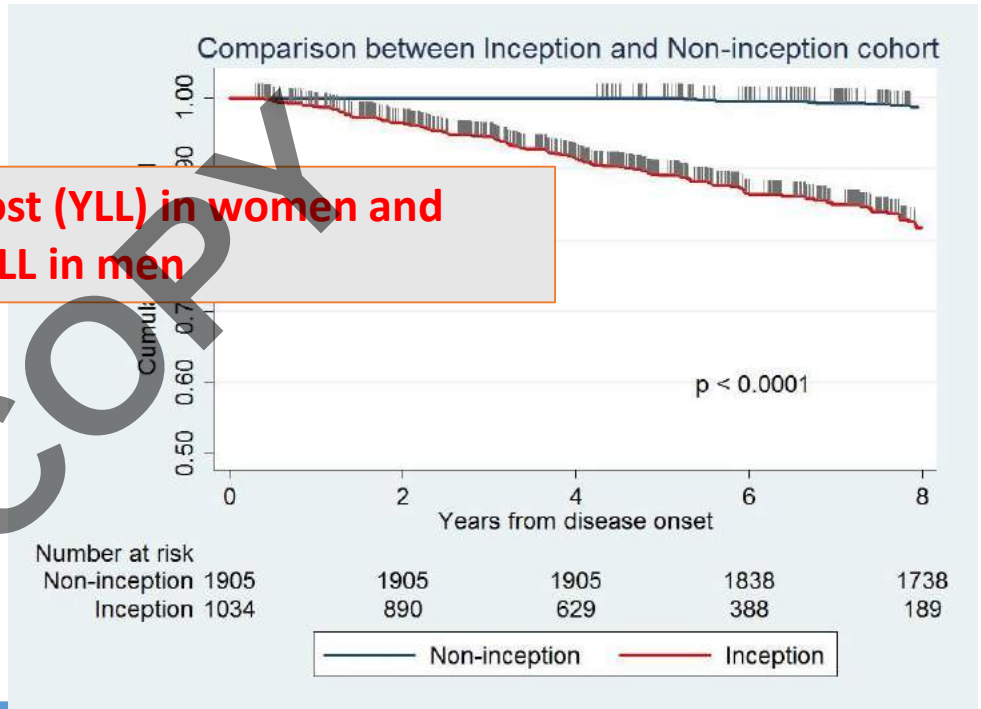
ARTHRITIS & RHEUMATOLOGY
Vol. 69, No. 5, May 2017, pp 1067–1077
DOI 10.1002/art.40027

Early Mortality in a Multinational Systemic Sclerosis Inception Cohort

Yanjie Hao,[1] Marie Hudson,[2] Murray Baron,[2] Patricia Carreira,[3] Wendy Stevens,[4] Candice Rabusa,[4] Solene Tatibouet,[5] Loreto Carmona,[6] Beatriz E. Joven,[3] Molla Huq,[7] Susanna Proudman,[8] Mandana Nikpour,[7] the Canadian Scleroderma Research Group, and the Australian Scleroderma Interest Group

Overall Survival





23 Years of Life Lost (YLL) in women and 26 YLL in men

Survival	1-year	3-year	5-year	8-year
Inception	99.0%	94.8%	88.9%	81.3%
Non-Inception	100%	100%	99.8%	98.8%
Prevalent	99.5%	98.0%	96.7%	94.6%

Causes of deaths-SSc related (62.1% of deaths in inception and 55% deaths in prevalent cohort)

Organ system	Inception Principal cause N=87 n(%)	Prevalent Principal cause N=244 n(%)
Heart and Lung	48 (55.2)	173 (70.9)
PAH	22 (25.3)	88 (36.1)
ILD	18 (20.7)	53 (21.7)
PAH and ILD	8 (9.2)	32 (13.1)
Gut involvement	12 (13.8)	24 (9.8)
Sepsis	1 (1.1)	4 (1.6)
Myocardial involvement	13 (14.9)	22 (9.0)
Renal crisis	12 (13.8)	17 (7.0)
Pericardial effusion	1 (1.1)	4 (1.6)

Clinical determinants of elevated systolic pulmonary artery pressure measured by transthoracic Doppler echocardiography in early systemic sclerosis.

Carreira PE et al Clin Exp Rheumatol.2017;35 Suppl 106(4):114-121.

To explore the prevalence and clinical associations of elevated systolic pulmonary artery pressure (sPAP), measured by Transthoracic Doppler-echocardiography (TTE) in patients with early systemic sclerosis (SSc).

- A cross-sectional analysis of the prospective EULAR Scleroderma Trial and Research (EUSTAR) database was performed. **SSc patients with <3 years from the first non-Raynaud's phenomenon (RP) symptom** at baseline EUSTAR visit, were selected. Elevated sPAP was defined as sPAP>40 mmHg on baseline TTE. First visit SSc related variables, including disease subsets, antibodies and visceral involvement, were examined.

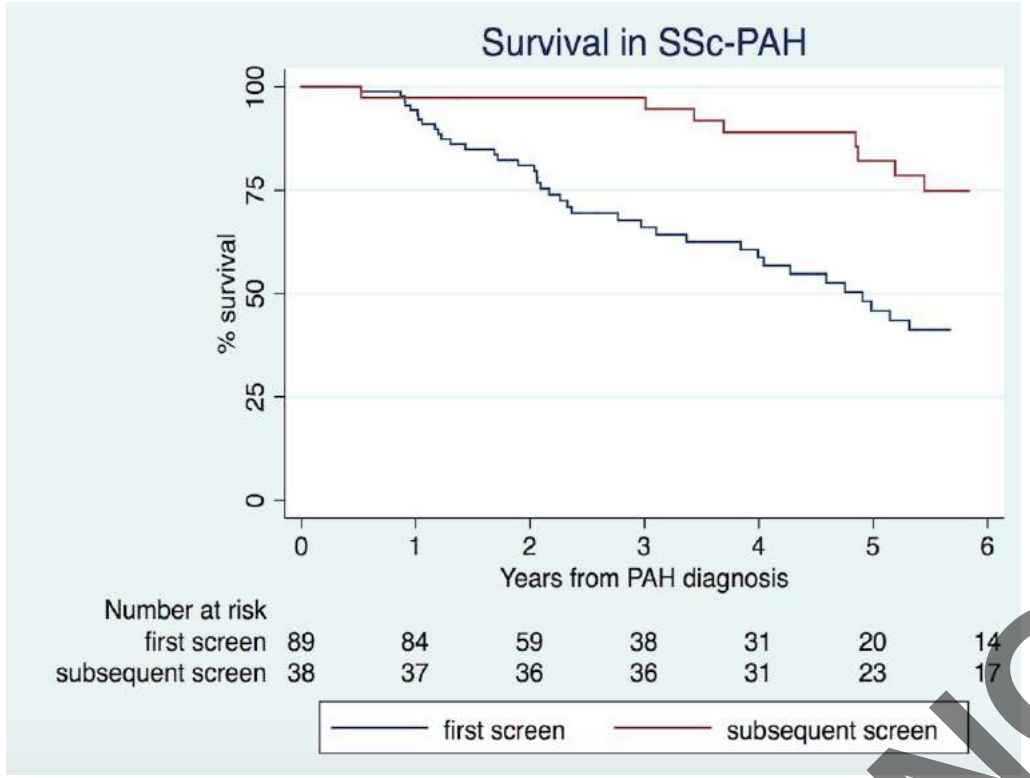
- From 1,188 patients, elevated sPAP was found in **17%** of patients, both lcSSc and diffuse cutaneous SSc (dcSSc).
- In lcSSc, older age at first non-RP symptom, ACA positivity, joint contractures, restrictive defect and lower DLCO, were independently associated with elevated sPAP.
- In dcSSc, older age at first non-RP symptom, longer time between RP onset and first non-RP symptom, digital ulcers, cardiac blocks, and proteinuria were associated with elevated sPAP.

The prevalence of elevated sPAP on TTE in early SSc patients is considerable.

***Association with cardiac, lung and renal involvement suggests that, although some patients might have pulmonary arterial hypertension, others may present pulmonary hypertension secondary to lung or heart involvement*.**

Our findings emphasize the need to consider right heart catheterisation in selected early SSc patients with PH suspicion, to clearly determine the cause of PH.

Reducing the burden of SSc: Value of screening for SSc-PAH



Survival	Prevalent PAH	Incident PAH	p-value
3yr	42.7%	94.7%	<0.001

Treatment	Mean time to death (years)	p-value
Prevalent PAH	2.3 (±2.3)	<0.001
Incident PAH	4.7 (±2.4)	

Morrisroe *et al. Arthritis Research & Therapy* (2017) 19:42
DOI 10.1186/s13075-017-1250-z

Arthritis Research & Therapy

RESEARCH ARTICLE Open Access

Epidemiology and disease characteristics of systemic sclerosis-related pulmonary arterial hypertension: results from a real-life screening programme

Kathleen Morrisroe[1,2], Wendy Stevens[2], Joanne Sahhar[3], Candice Rabusa[2], Mandana Nikpour[1,2*†], Susanna Proudman[4,5†] the Australian Scleroderma Interest Group (ASIG)

Causes of deaths-non-SSc related

Han Y et al A&R 2017;60: 1087

Organ system	Inception n=34 n(%)	Prevalent n=148 n(%)
Malignancy	13(38.2)	55(37.2)
Sepsis	5(14.7)	14(9.5)
CVD	4(11.8)	7(4.7)
IHD	3(8.8)	18(12.2)
Liver disease	2(5.9)	3(2.0)
Post operative complications	1(2.9)	9(6.1)
Trauma	1(2.9)	8(5.4)
Sudden death	1(2.9)	4(2.7)

Organ system	Inception n=34 n(%)	Prevalent n=148 n(%)
Renal failure	1(2.9)	1(0.7)
Asthma/COPD	0(0)	6(4.1)
Peripheral vascular disease	0(0)	2(1.4)
Pulmonary embolism	0(0)	1(0.7)
Arrhythmia	0(0)	1(0.7)
Drug related	0(0)	1(0.7)
Other	3(8.8)	18(12.2)

Malignancies in Patients with Anti-RNA Polymerase III Antibodies and Systemic Sclerosis: Analysis of the EULAR Scleroderma Trials and Research Cohort and Possible Recommendationsfor Screening.

Lazzaroni MG et al J Rheumatol. 2017;44(5):639-647

To analyze the characteristics of anti-RNA polymerase III antibodies (anti-RNAP3)- positive patients with systemic sclerosis(SSc) with a focus on the risk of cancer and the characteristics of malignancies, and the aim to provide guidelines about potential cancer screening in these patients.

- Analysis of the EUSTAR database: **4986 patients** with information on their anti-RNAP3 status were included
- **Case-control study**: additional retrospective data, including malignancy history, were queried in 13 participating EUSTAR centers;
- **158 anti-RNAP3+ cases** were compared with 199 local anti-RNAP3- controls, matched for sex, cutaneous subset, disease duration, and age at SSc onset. (3) A Delphi exercise was performed by 82 experts to reach consensus for cancer screening in anti-RNAP3+ patients.

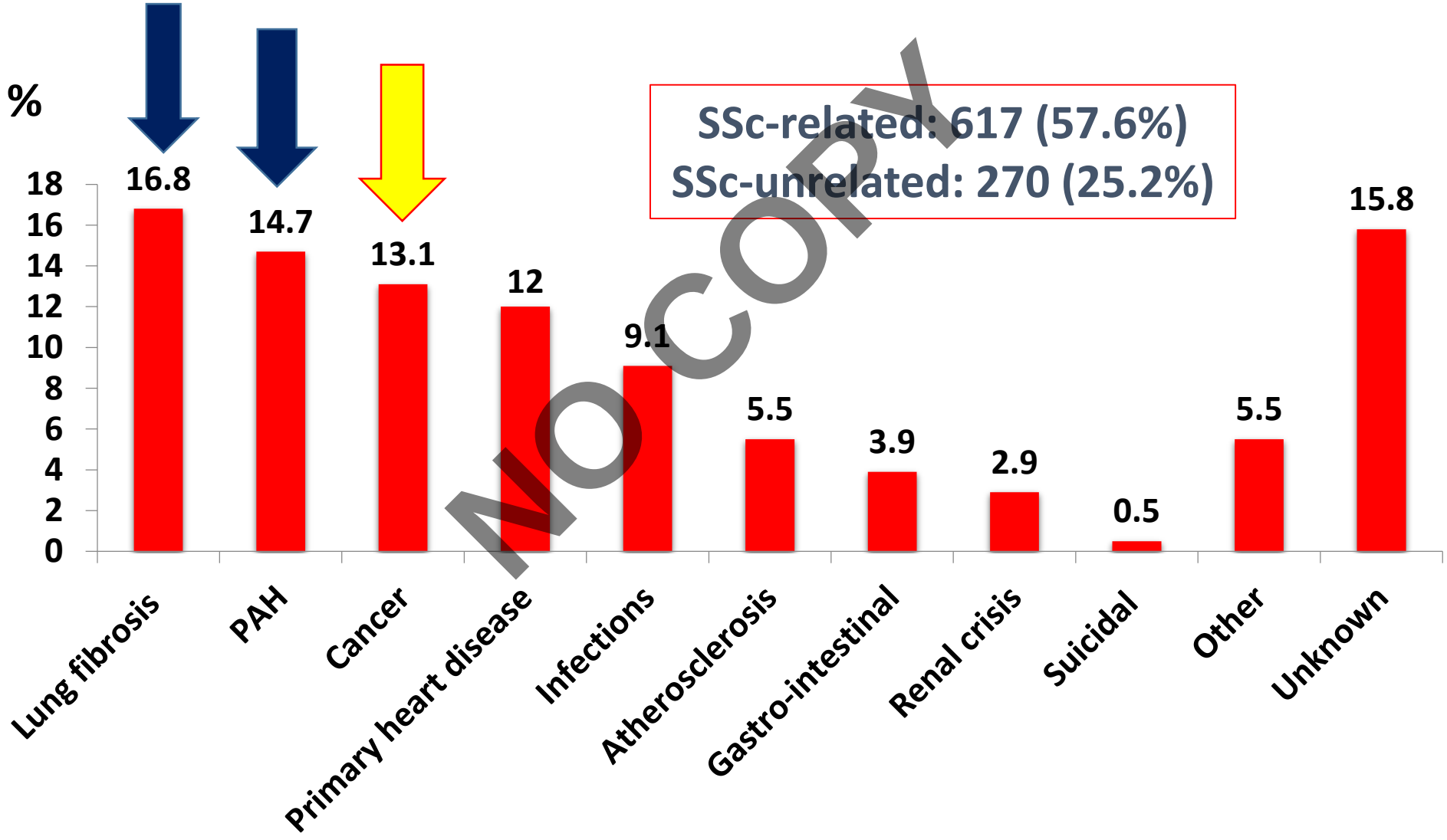
- In the EUSTAR registry, anti-RNAP3 were associated in multivariable analysis with renal crisis and diffuse cutaneous involvement.
- In **the case-control study, anti-RNAP3 were associated with gastric antral vascular ectasia, rapid progression of skin involvement, and malignancies** concomitant to SSc onset (OR 7.38, 95% CI 1.61-33.8). When compared with other anti-RNAP3+ patients, those with concomitant malignancies had older age ($p < 0.001$) and more frequent diffuse cutaneous involvement ($p = 0.008$). The Delphi exercise highlighted the need for malignancy screening at the time of diagnosis for anti-RNAP3+ patients and tight followup in the following years

Anti-RNAP3+ patients with SSc have a high risk of concomitant malignancy.
These results have implications for clinical practice and suggest
regular screening for cancer in anti-RNAP3+ patients.

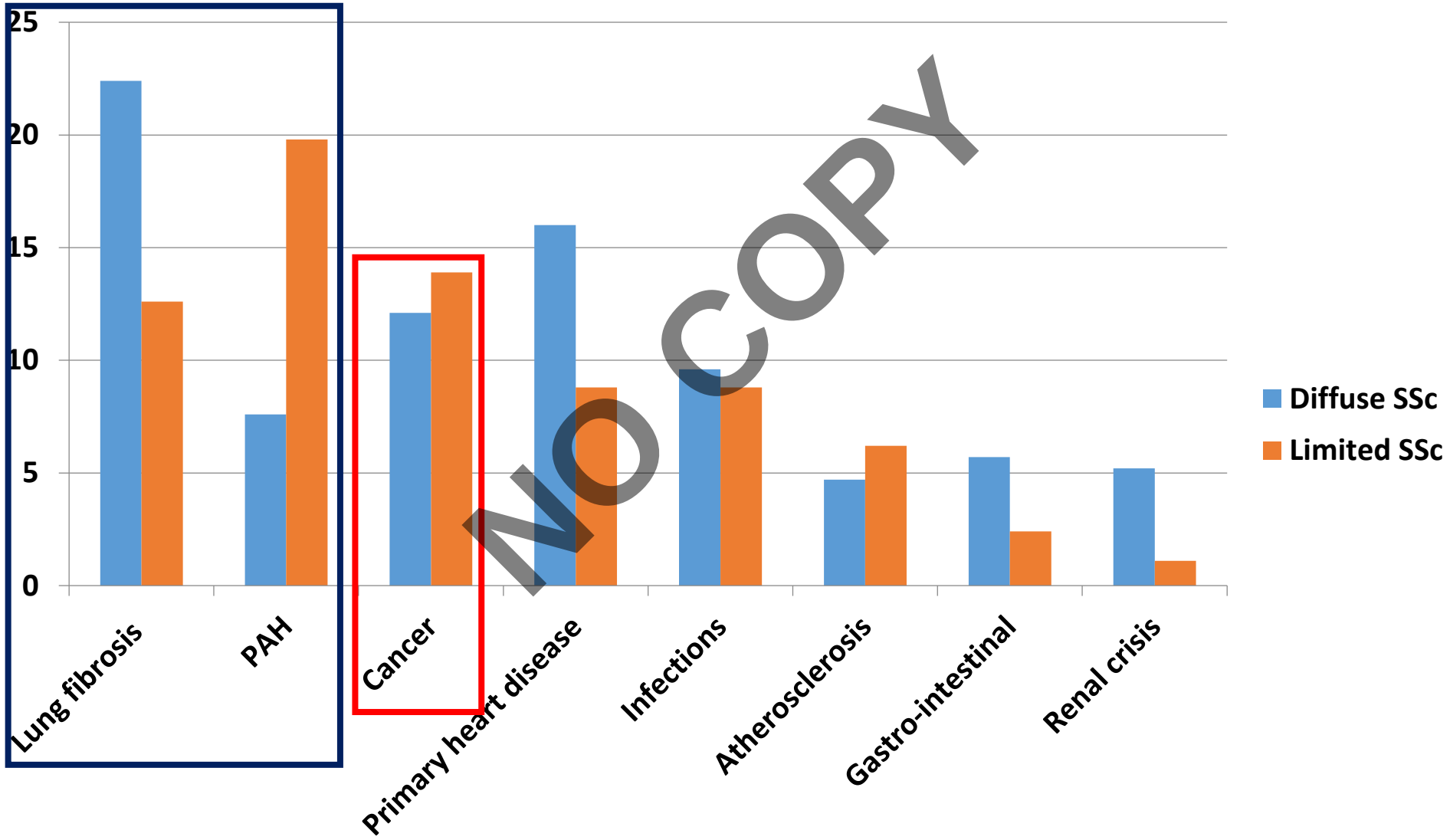
Mapping and predicting mortality from systemic sclerosis.

Elhai M, et al Ann Rheum Dis. 2017;76:1897-1905

Causes of death- 1072 out of 11193 SSc patients

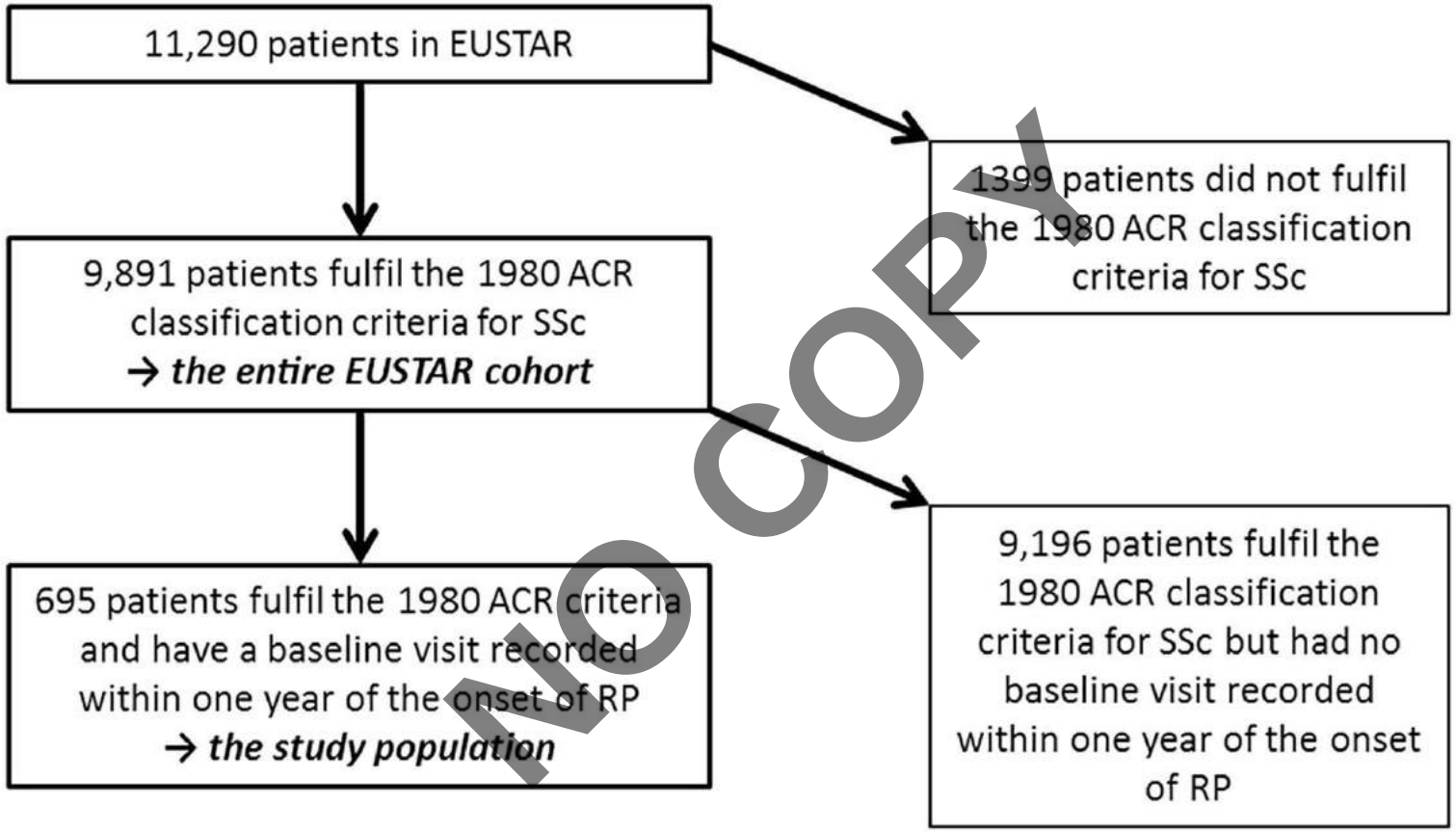


Causes of death according to SSc-cutaneous subset



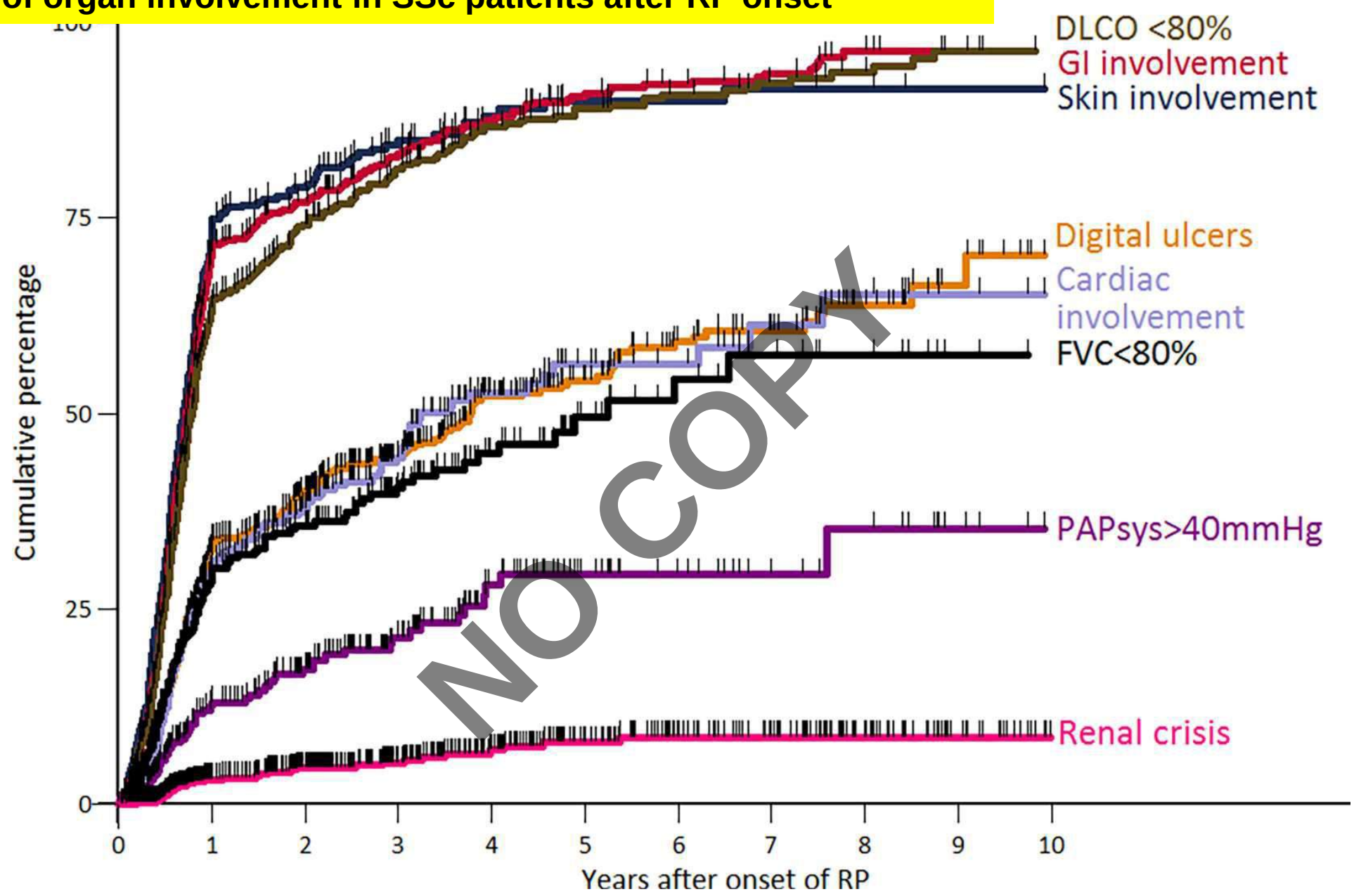
Incidences and Risk Factors of Organ Manifestations in the Early Course of Systemic Sclerosis: A Longitudinal EUSTAR Study

Jaeger VK et al PLOS ONE October 5, 2016



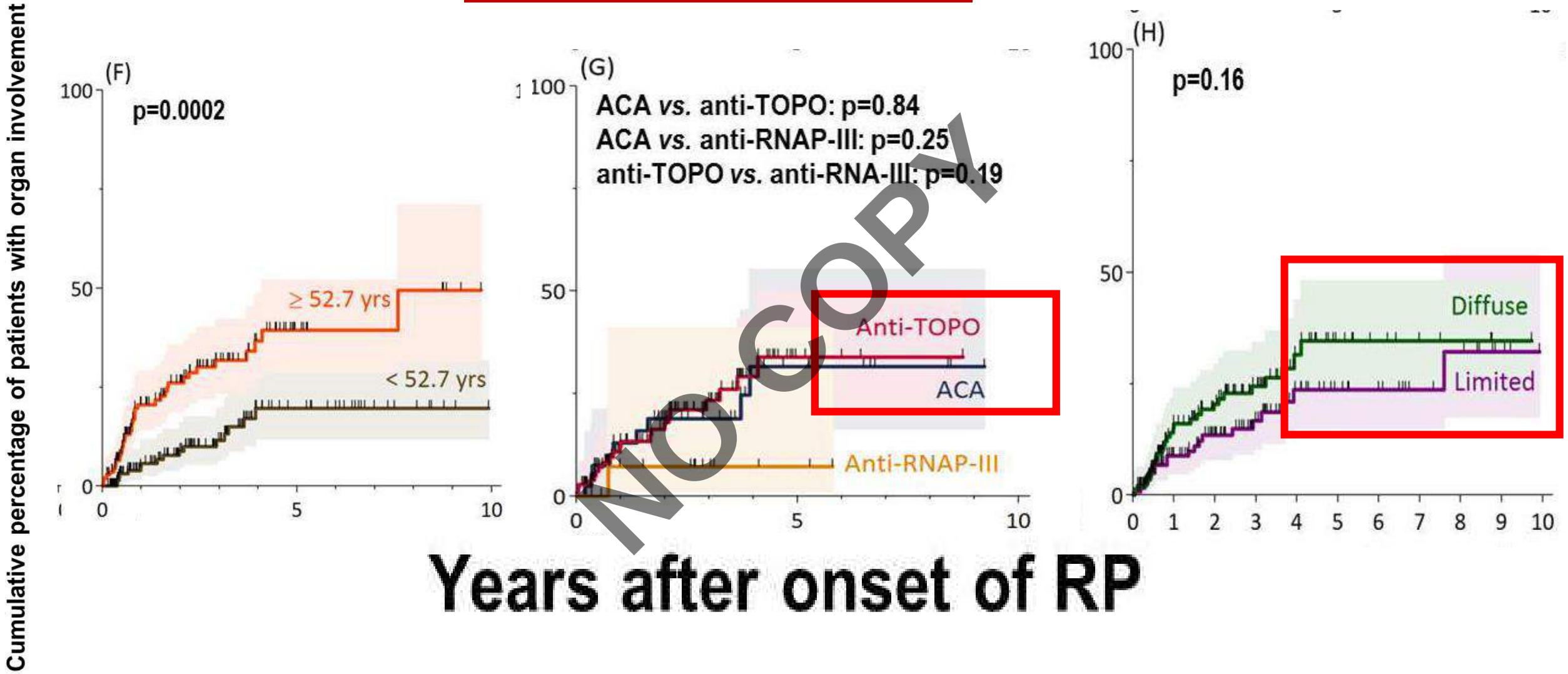
early SSc were identified as those who had a visit within the first year after RP onset. Incident SSc organ manifestations and their risk factors were assessed using Kaplan-Meier methods and Cox regression analysis

incidence of organ involvement in SSc patients after RP onset

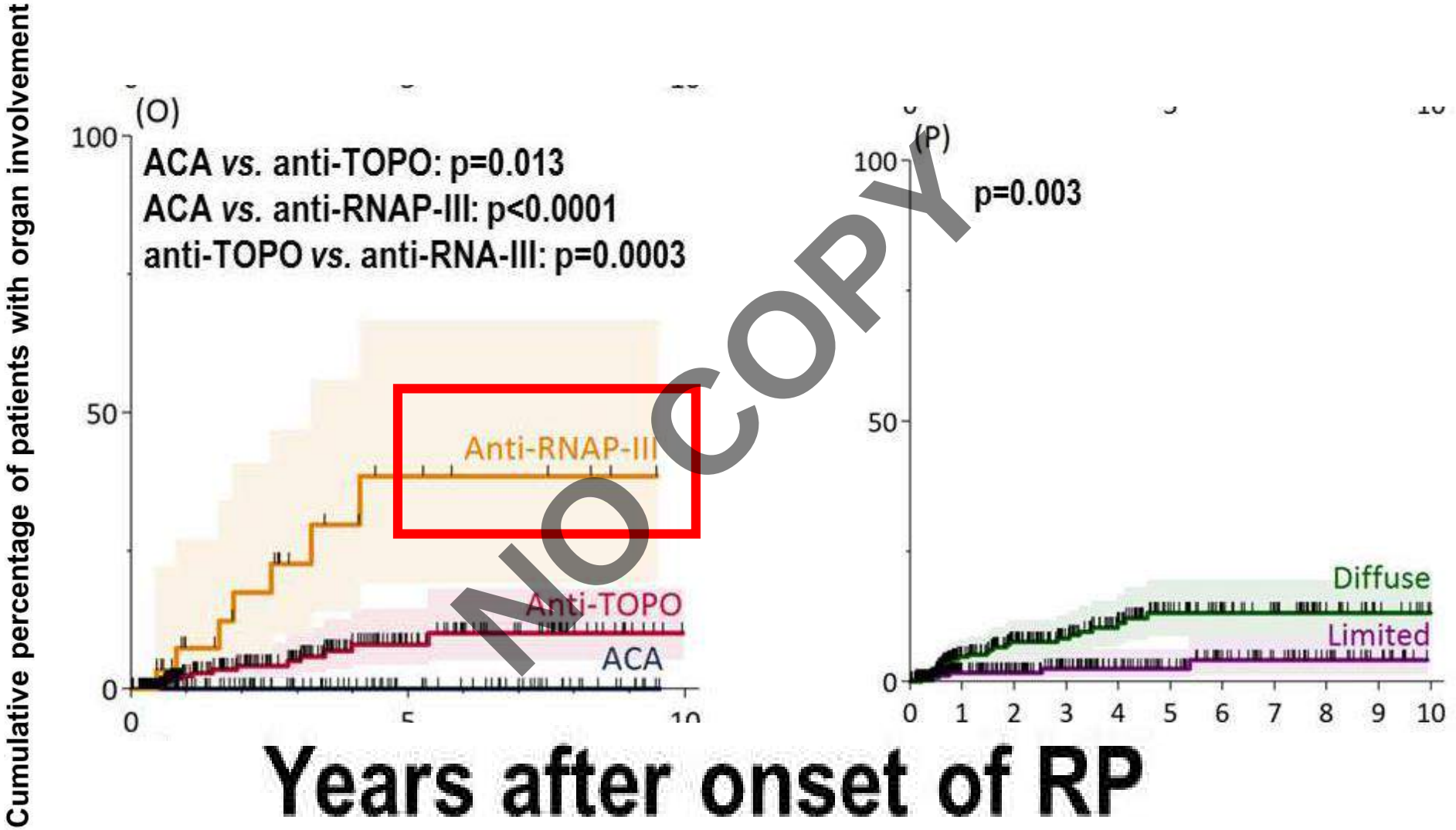


Kaplan-Meier curves

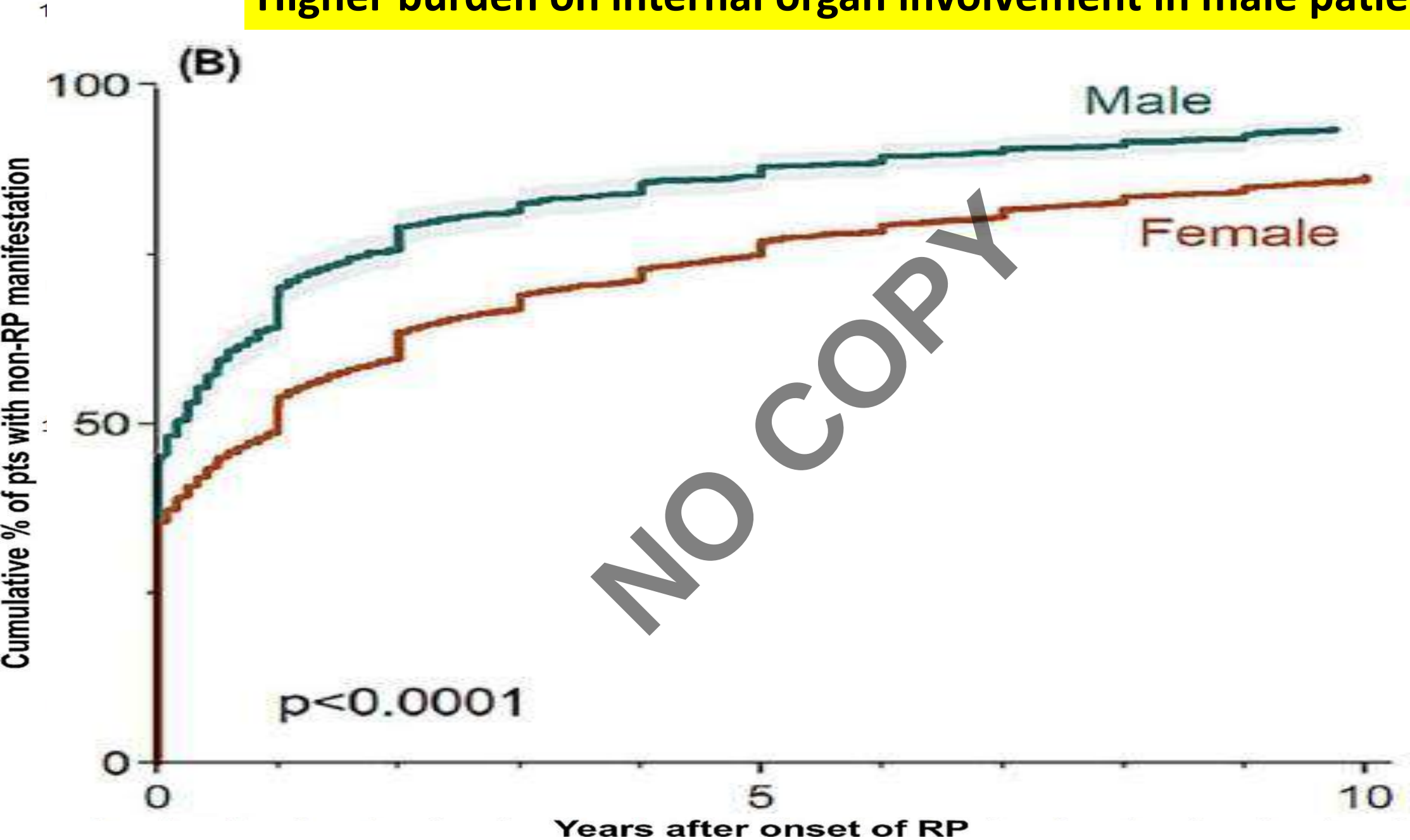
Heart Involvement



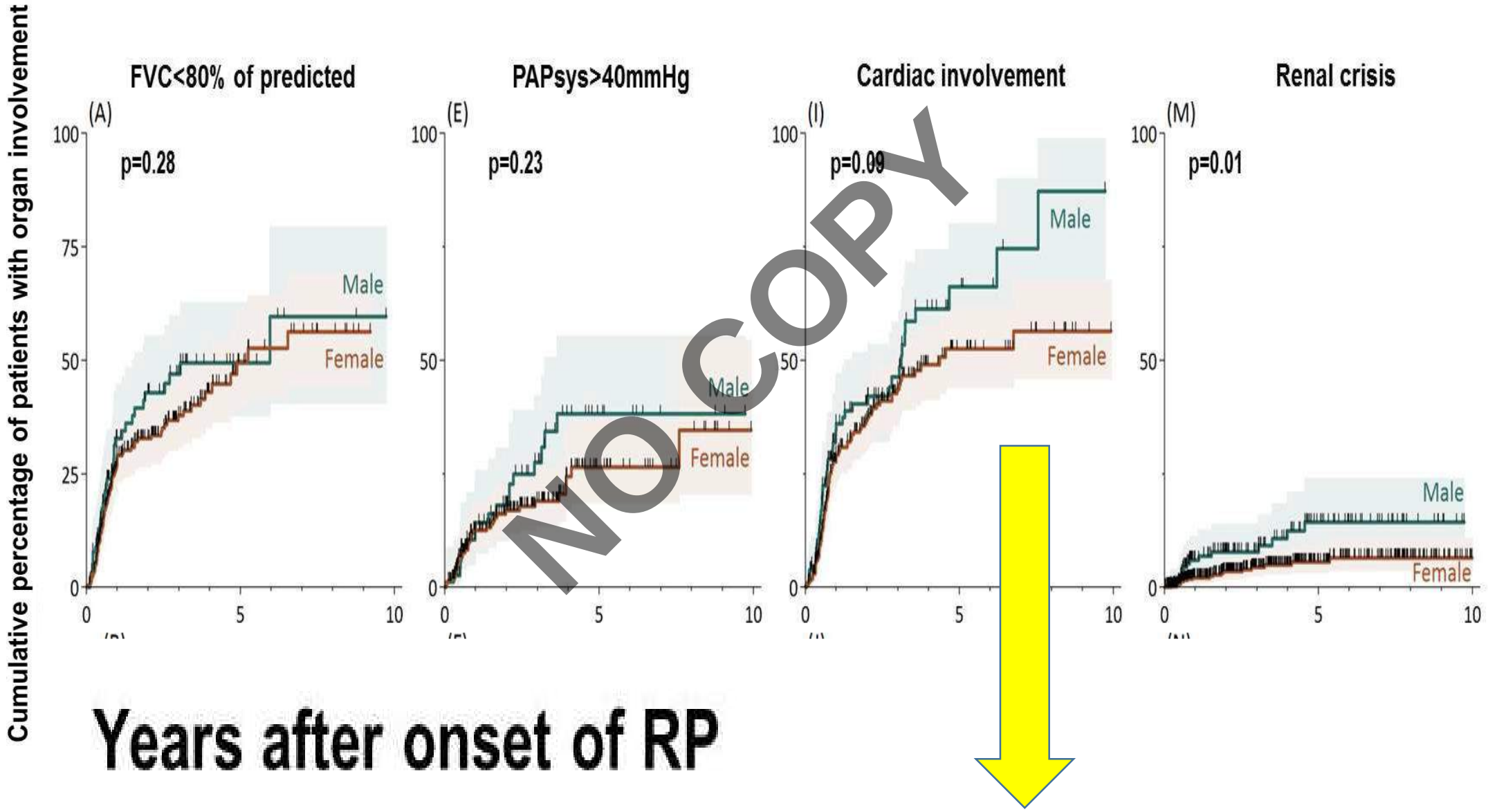
Scleroderma renal crisis



Higher burden on internal organ involvement in male patients



The gender enigma !!!



A gender gap in primary and secondary heart dysfunctions in systemic sclerosis: a EUSTAR prospective study.

Elhai M et al Ann Rheum Dis.2016 ;75(1):163-9.

9182 patients with SSc were available (1321 men) for the baseline analyses.

In multivariate analysis, male sex was independently associated with

- ✓ a higher risk of diffuse cutaneous subtype (OR: 1.68, (1.45 to 1.94); p<0.001),
- ✓ a higher frequency of digital ulcers (OR: 1.28 (1.11 to 1.47); p<0.001)
- ✓ pulmonary hypertension (OR: 3.01 (1.47 to 6.20); p<0.003).
- In the longitudinal analysis (n=4499), after a mean follow-up of 4.9 (±2.7) years,

male sex was predictive of new onset of pulmonary hypertension (HR: 2.66 (1.32 to 5.36); p=0.006) and heart failure (HR: 2.22 (1.06 to 4.63); p=0.035).

- 908 deaths were recorded,

male sex predicted deaths of all origins (HR: 1.48 (1.19 to 1.84); p<0.001),
but did not significantly account for SSc-related deaths.

SSc appears as strikingly more severe in men.
Our results obtained through the largest worldwide database demonstrate a higher risk of severe cardiovascular involvement in men.
These results raise the point of including sex in the management and the decision-making process.

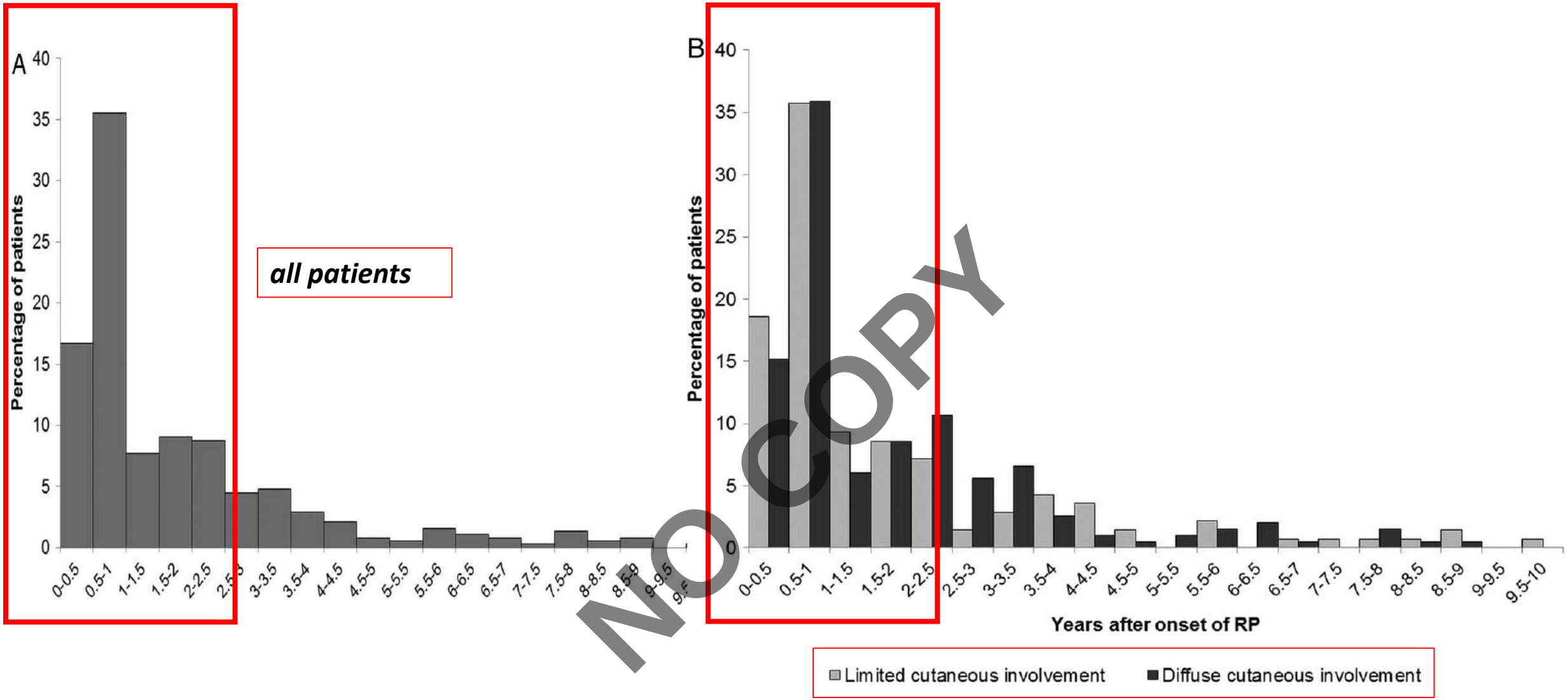
Incidence and predictors of cutaneous manifestations during the early course of systemic sclerosis: a 10-year longitudinal study from the EUSTAR database

Elina G Wirz et al ARD 2016;75:1285–1292

to analyse the incidence of skin sclerosis and DUs in patients who developed SSc within 1 year after the onset of Raynaud's phenomenon

- The median **modified Rodnan skin score (mRSS) peaked 1 year after RP** onset, and was 15 points.
- The 1-year probability to develop a mRSS ≥2 in at least one area of the arms and legs was 69% and 25%, respectively.
- **25%** of patients developed dSSc in the ***first year*** after RP onset. This probability increased to **36%** during the subsequent ***2 years***. Only 6% of patients developed dSSc thereafter.
- The probability to develop **DUs increased to a maximum of 70% at the end of the 10-year observation.**
- The main factors associated with dSSc were the presence of RNApolIII, followed by TopoI and male sex.
- The main factor associated with incident DUs was the presence of Topo I autoantibodies.

Early after RP onset, cutaneous manifestations exhibit rapid kinetics in SSc.



Time to peak mRSS. The histogram plots the percentage of patients as a function of the time to reach their maximal mRSS from RP onset; The median peak mRSS was

- 15 points (IQR 7–24) overall, 9.5 points (IQR 6–14) in patients with lSSc involvement
- 23 points (IQR 16–29.5) in patients with dSSc.
-

Prediction of improvement in skin fibrosis in diffuse cutaneous systemic sclerosis: an EUSTAR analysis

AIM: to identify predictors for improvement of skin fibrosis in patients with dcSSc

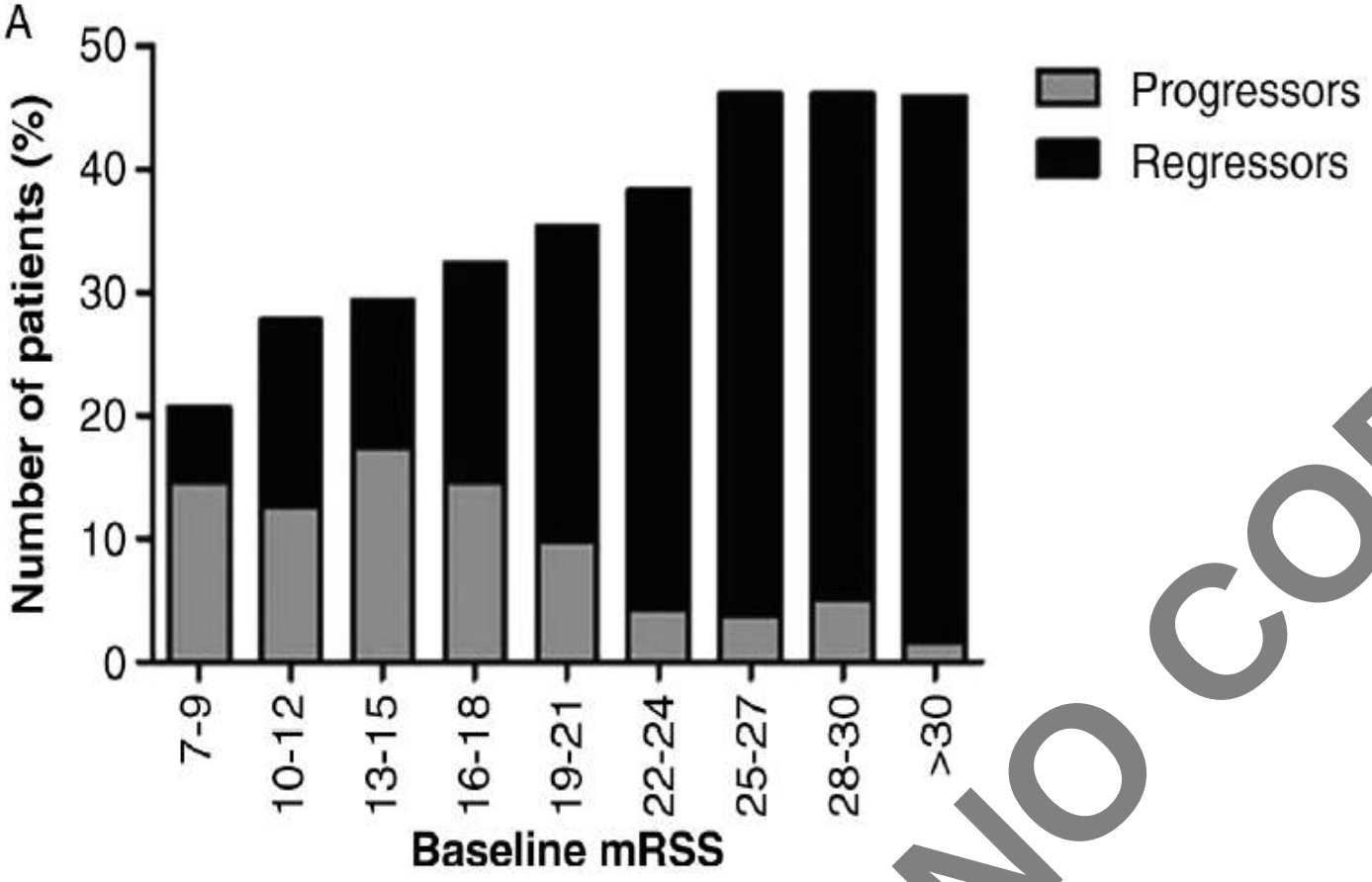
From the 919 patients included, 218 (24%) improved and 95 (10%) progressed. Eleven candidate predictors for skin improvement were analysed. The final model identified high **baseline mRSS** and **absence of tendon friction** rubs as independent predictors of skin improvement.

The baseline mRSS was the strongest predictor of skin improvement, independent of disease duration. An upper **threshold between 18 and 25 performed best in enriching for progressors over regressors**.

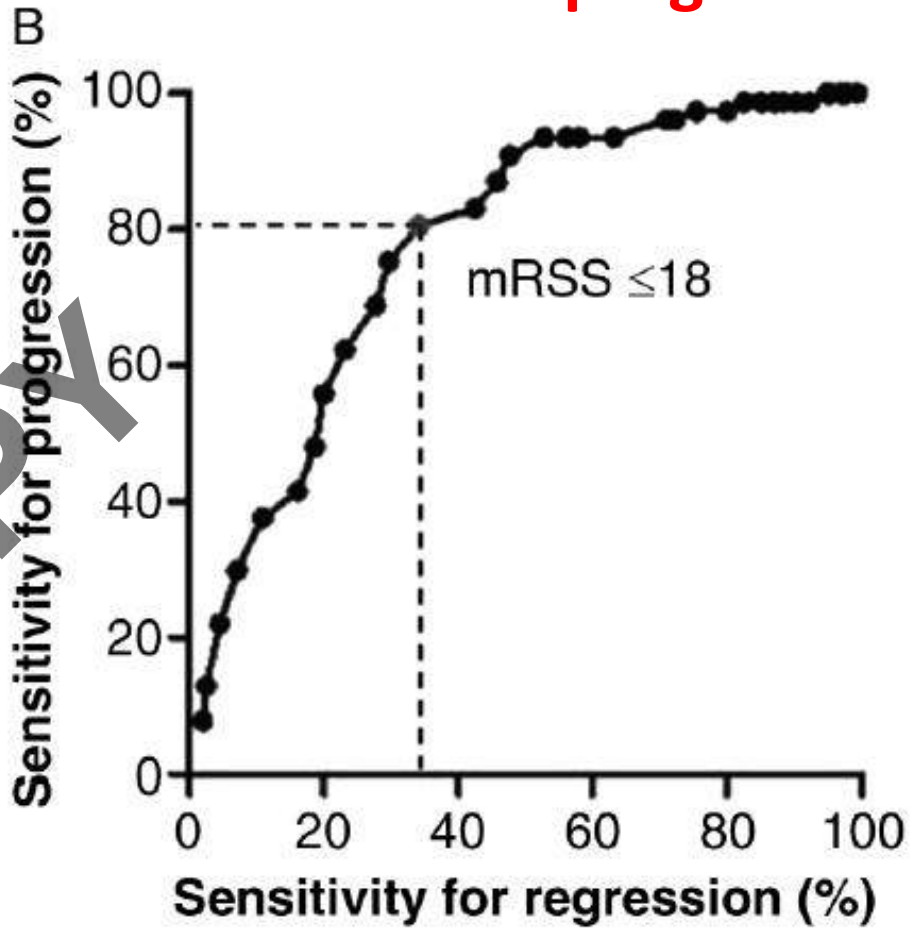
Patients with advanced skin fibrosis at baseline and absence of tendon friction rubs are more likely to regress in the next year than patients with milder skin fibrosis.

Dobrota R et al ARD 2016;75:1743–1748

Lower mRSS at inclusion enriches for patients with skin fibrosis progression



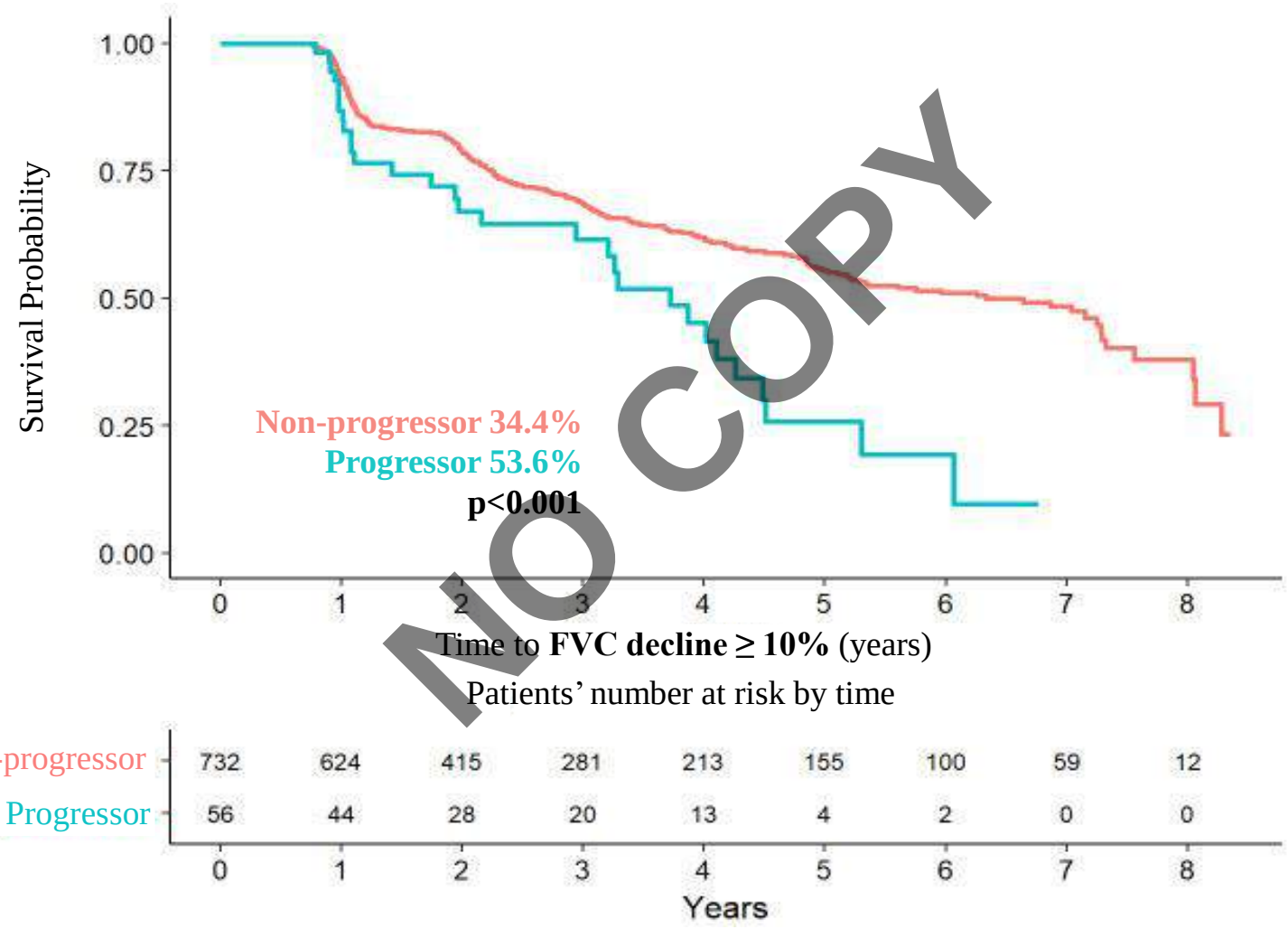
(A) Percentage of progressors and regressors per baseline mRSS range. Patients with lower skin score are more likely to progress, whereas those with higher skin scores are much more likely to regress.



(B) Sensitivity for progression and regression depending on different cut-off values for baseline mRSS

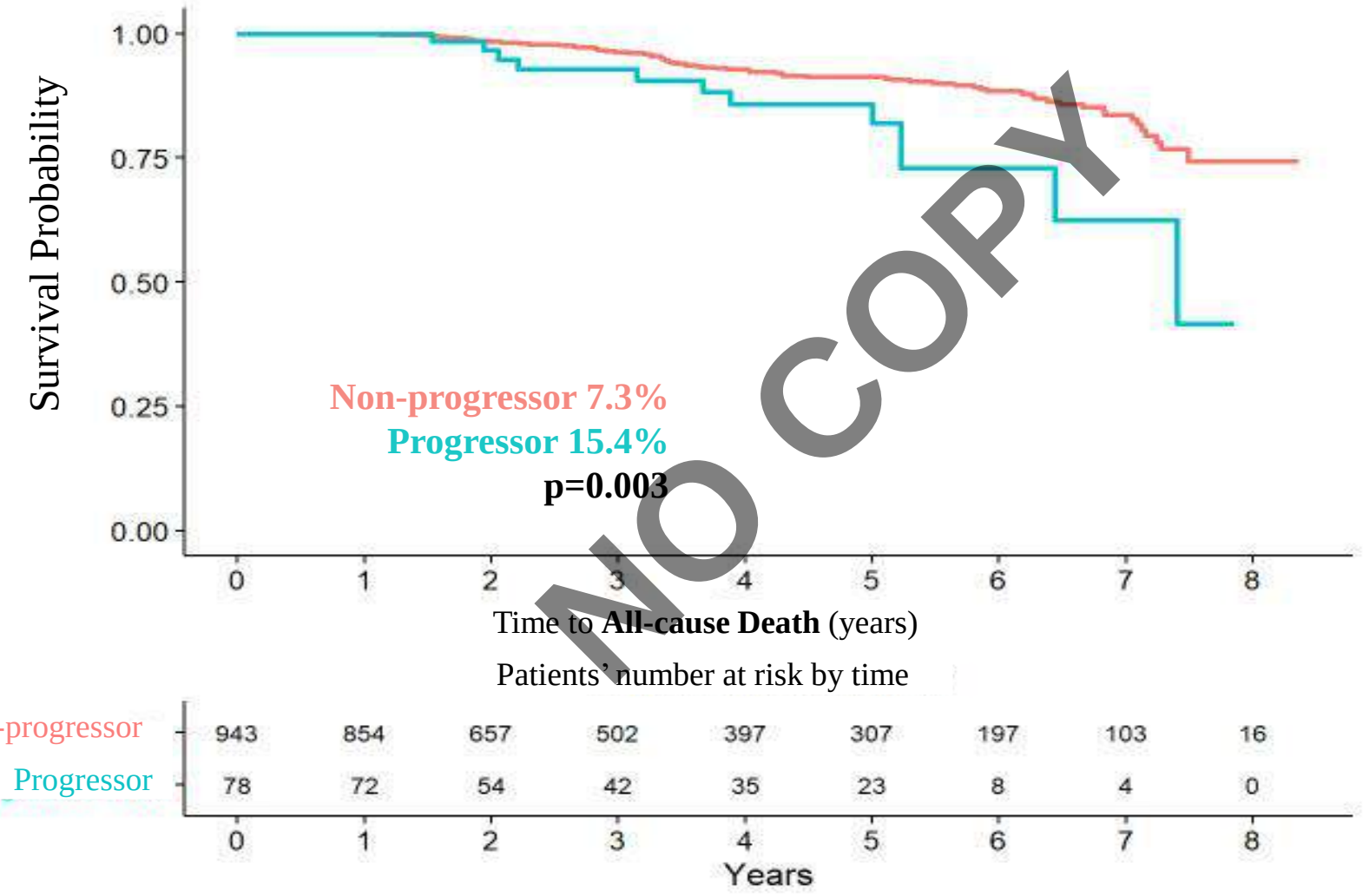
Dobrota R et al ARD 2016;75:1743–1748

Progression of skin fibrosis is associated with FVC decline at follow up



Wu et al, oral presentation WSC 2018

Progression of skin fibrosis is associated with all-cause death at follow up



Reliability and Validity of the Tender and Swollen Joint Counts and the Modified Rodnan Skin Score in Early Diffuse Cutaneous Systemic Sclerosis—Analysis from the Prospective Registry of Early Systemic Sclerosis Cohort Gordon JK et al J Rheumatol. 2017; 44: 791–794

Determine inter/intra-observer reliability of tender and swollen joint counts (TJC,SJC) and Modified Rodnan Skin Score (MRSS) in diffuse systemic sclerosis (dcSSc) and assess content validity of TJC/SJC

- ✓ **Ten rheumatologists completed SJC, TJC, and MRSS on 7 patients. Musculoskeletal ultrasound (MSUS) was performed**
- **Inter-observer and intra-observer reliability for TJC was 0.97 and 0.99, for SJC was 0.24 and 0.71, and for MRSS was 0.81 and 0.94, respectively. *MSUS abnormalities did not correspond with SJC/TJC***

excellent inter and intra-observer reliability for MRSS and TJC in dcSSc.
However, SJC and TJC did not correspond to MSUS

Conclusions

- Prevention of skin and organ damage in dcSSc - a new clinical trial concept
- Progression of skin fibrosis can be modeled – short disease duration, lower mRSS, arthritis
- Progression of skin fibrosis is associated with ILD worsening and worse survival at follow up

Conclusions

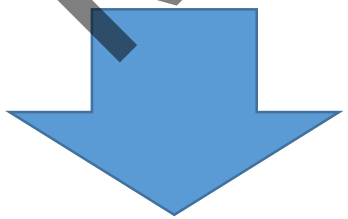
1. The presence of **Malignancy** is today an issue which needs to be carefullya ddrssed by the physician
2.In the first 2 years of the disease the skin and GI and DLCo as well are the most affected
3.The most severely affected gender is **male**
4. Overall, the main clinical issues are the **Cardiopulmonary involvement, Cancer and Infections.**
5. **Progression of skin fibrosis can be modeled** identifying a short disease duration and a lower mRSS
6.skin progression is associated with ILD worsening and worse survival at follow up

prevention of skin and organ damage in dcSSc is a new clinical trial concept

Registries are very useful to understand the disease and show us their particular realities

Registries from different continents can show different aspects of the disease

However, sometimes they do not show the same results



Speculate about Why

There may be several answers to the *Why*…

1. Selection bias depending on the centers
2. Cultural differences
3. Time when patients are entered
4. Enviromental differences
5. Genetic differences

Because of the differences we can design better our RCT

Education opportunities on SSc and its complications

- Online courses
- Books
- Courses
- Hands on courses
- Masterclasses

Eular online courses

The EULAR On-line Course on Systemic Sclerosis consists of **10 modules** which deal with physiopathology, clinical aspects and management of this complex disease.

MODULE 1: Introduction Module

MODULE 2: Pathogenesis

MODULE 3: Clinical manifestations : skin, peripheral vascular

MODULE 4: Heart involvement

MODULE 5: Pulmonary interstitial/vascular involvement

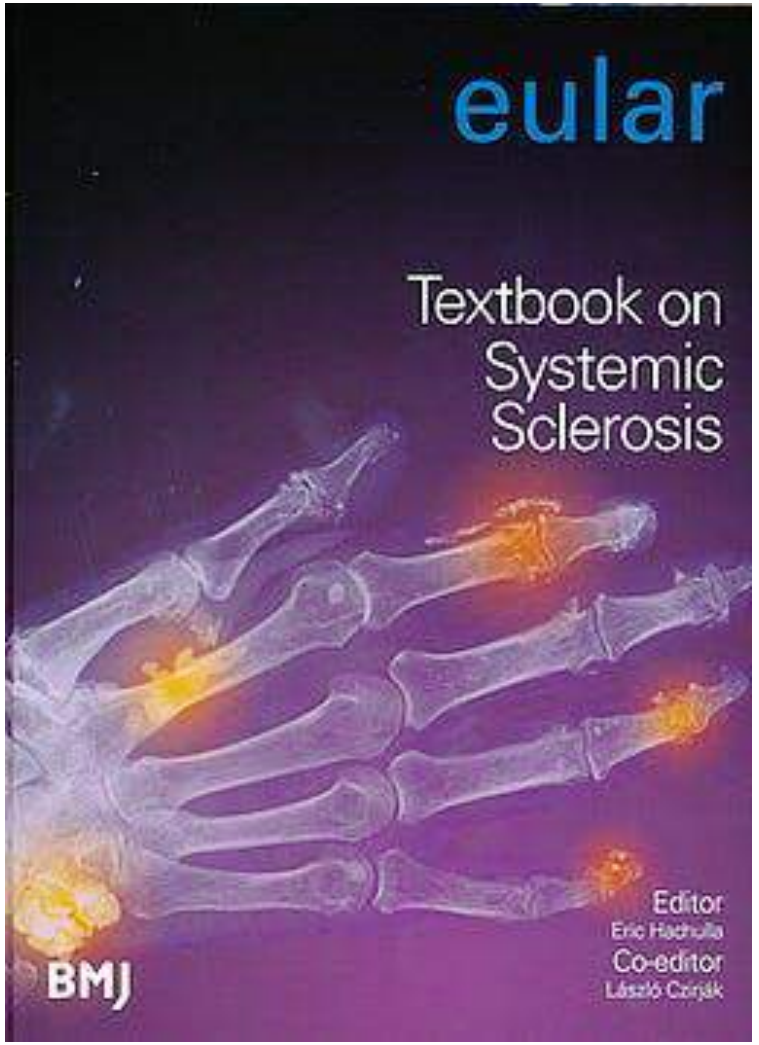
MODULE 6: Clinical manifestations: GI

MODULE 7: Clinical manifestations: Kidney

MODULE 8: Clinical manifestations: Musculoskeletal, disability

MODULE 9: Management

MODULE 10. Special conditions



WSF Courses & Masterclasses

- **PAH** Firenze 2011
- **Ulcers** 2015-2016

✓Bucharest

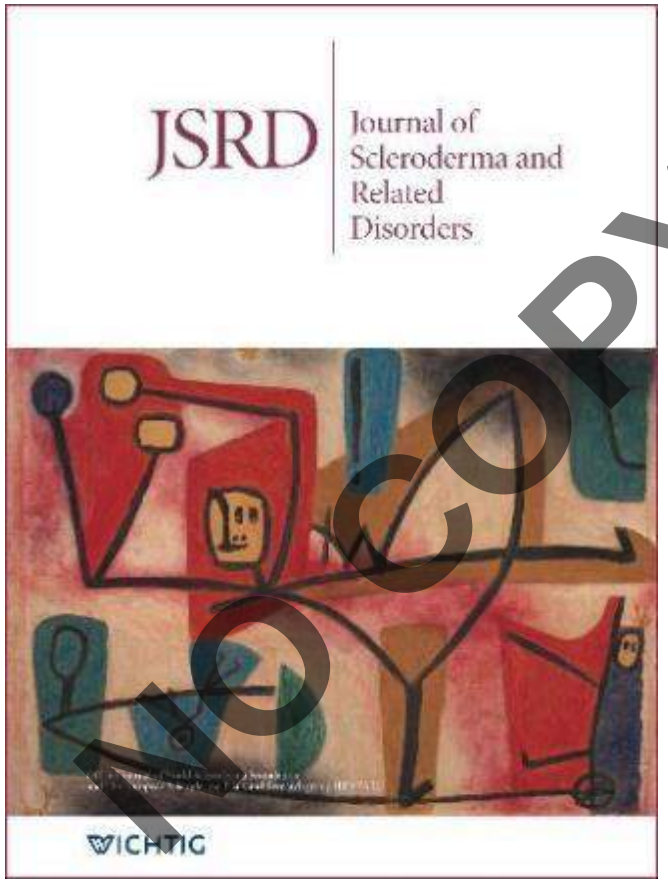
✓Split

✓Tel aviv

World Scleroderma Foundation

Eustar Courses

- Budapest 2005
- Bad Nauheim 2007
- Paris 2009
- Belgrade 2011
- Cluj Napoca 2013
- Katowice 2015
- Split 2017
- *Nijmegen 2019*



www.sclerodermajournal.com