IgA Nephropathy: Morphologic Findings Associated with Disease Progression and Therapeutic Response

A Working Group Approach

Mark Haas
Department of Pathology & Lab Medicine
Cedars-Sinai Medical Center
Los Angeles, California USA

Statement of Disclosure

Mark Haas serves as a paid consultant on pathology adjudication committees for two industry-sponsored clinical trials:

Shire ViroPharma – Treatment of Acute ABMR

AstraZeneca – Treatment of Proliferative Lupus Nephritis

Neither represents a conflict of interest relevant to any of the material presented in this talk.

Brief Overview of Oxford (MEST) Classification of IgA Nephropathy

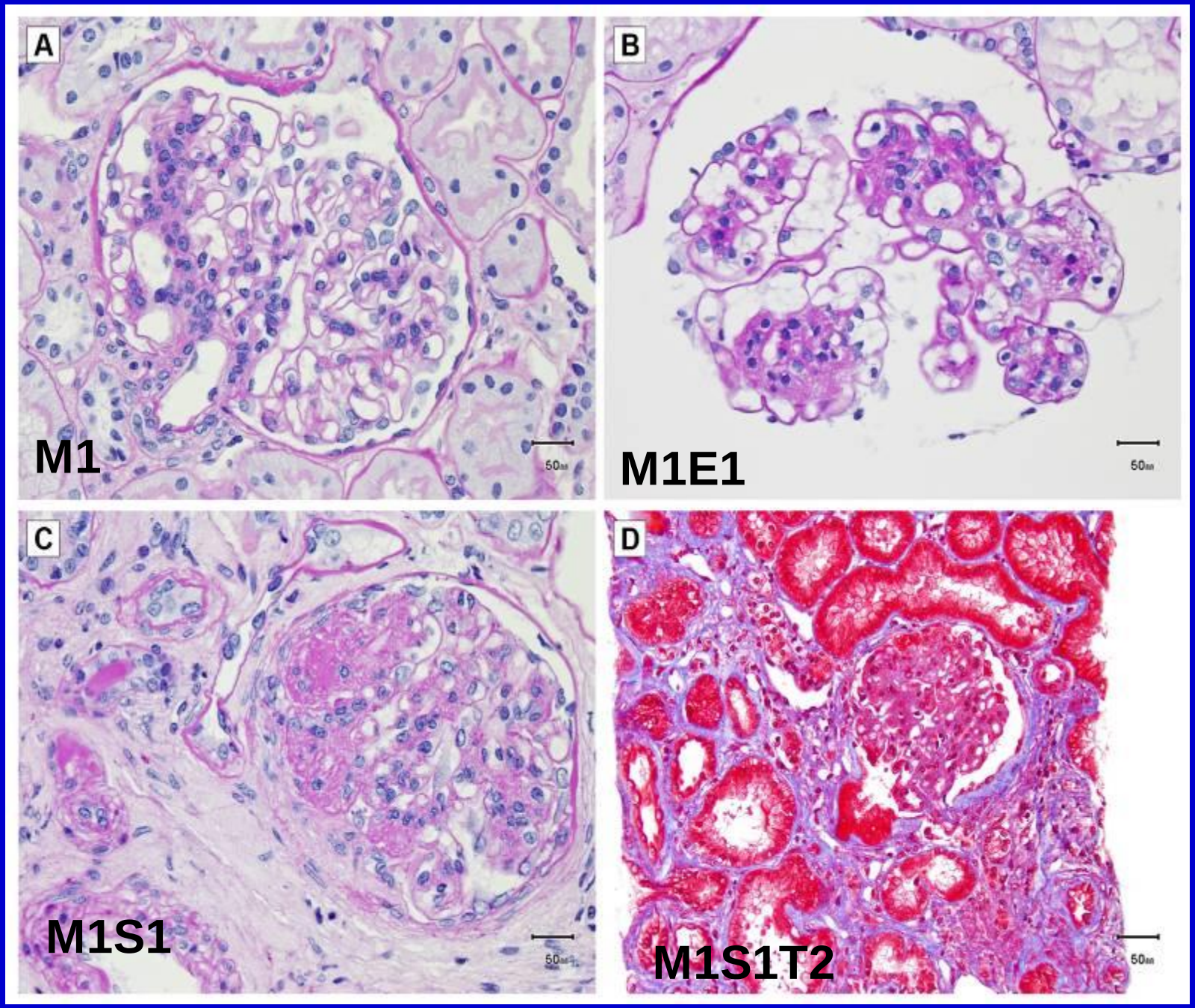
Crescents

Segmental Glomerulosclerosis

Mannose-Binding Lectin Pathway Activation/ Glomerular C4d Staining

Oxford Classification of IgA Nephropathy

Evidence-based derivation based on reproducibility between pathologists and correlation with clinical outcomes (slope of eGFR decline, composite endpoint of ESRD/$\geq$50% decline in eGFR) - Took 5 years to develop, and represents the current “gold standard” for glomerular disease classifications


A
M1
50μm
B
M1E1
50μm
C
M1S1
50μm
D
M1S1T2
50μm

Pathology and outcomes

Model A: multivariate - 3 pathological features + initial GFR, MAP, proteinuria.
Model B: multivariate - 3 pathological features + initial GFR + follow-up MAP, proteinuria

	Rate of renal function decline (Linear regression)			Survival from renal failure or a 50% drop in GFR (Cox regression)		
	Univariate slope	Multivariate Model A	Multivariate Model B	Univariate Hazard ratio	Multivariate Model A	Multivariate Model B
	(ml/min/1.73m2/y)	ß	ß	(95% CI)		
Mesangial hypercellularity score						
≤0.5	-0.5 ± 3.3	-2.2	-0.8	0.06 (0.01-0.45)	0.07 (0.01-0.53)	0.11 (0.01-0.80)
>0.5	-4.2 ± 9.0			1	1	1
	p<0.001	0.10	p>0.1	p=0.006	p=0.01	p=0.03
Segmental glomerulosclerosis						
absent	-0.5 ± 7.5			1	1	1
present	-4.4 ± 8.4	-3.6	-2.5	3.1 (1.4-7.3)	1.8 (0.6-5.3)	2.5 (0.9-7.3)
	p=0.001	p=0.005	p=0.03	p=0.009	p>0.1	p=0.09
Tubular atrophy/interstitial fibrosis						
0-25%	-2.5 ± 7.6			1	1	1
26-50%	-5.7 ± 8.8	-5.2	-3.7	3.5 (1.9-6.5)	6.0 (2.7-13.9)	5.0 (2.3-11.1)
>50%	-11.1 ± 12.6			15.5 (7.5-31.9)	17.3 (5.9-50.9)	8.8 (2.9-26.4)
	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001

D.C. Cattran et al, Kidney Int. 76: 534-545, 2009

Interaction of pathological features with immunosuppressive therapy

- Relationship between pathology variables and the rate of renal function decline was not influenced by immunosuppression except for endocapillary lesions.

- Patients with endocapillary proliferation:

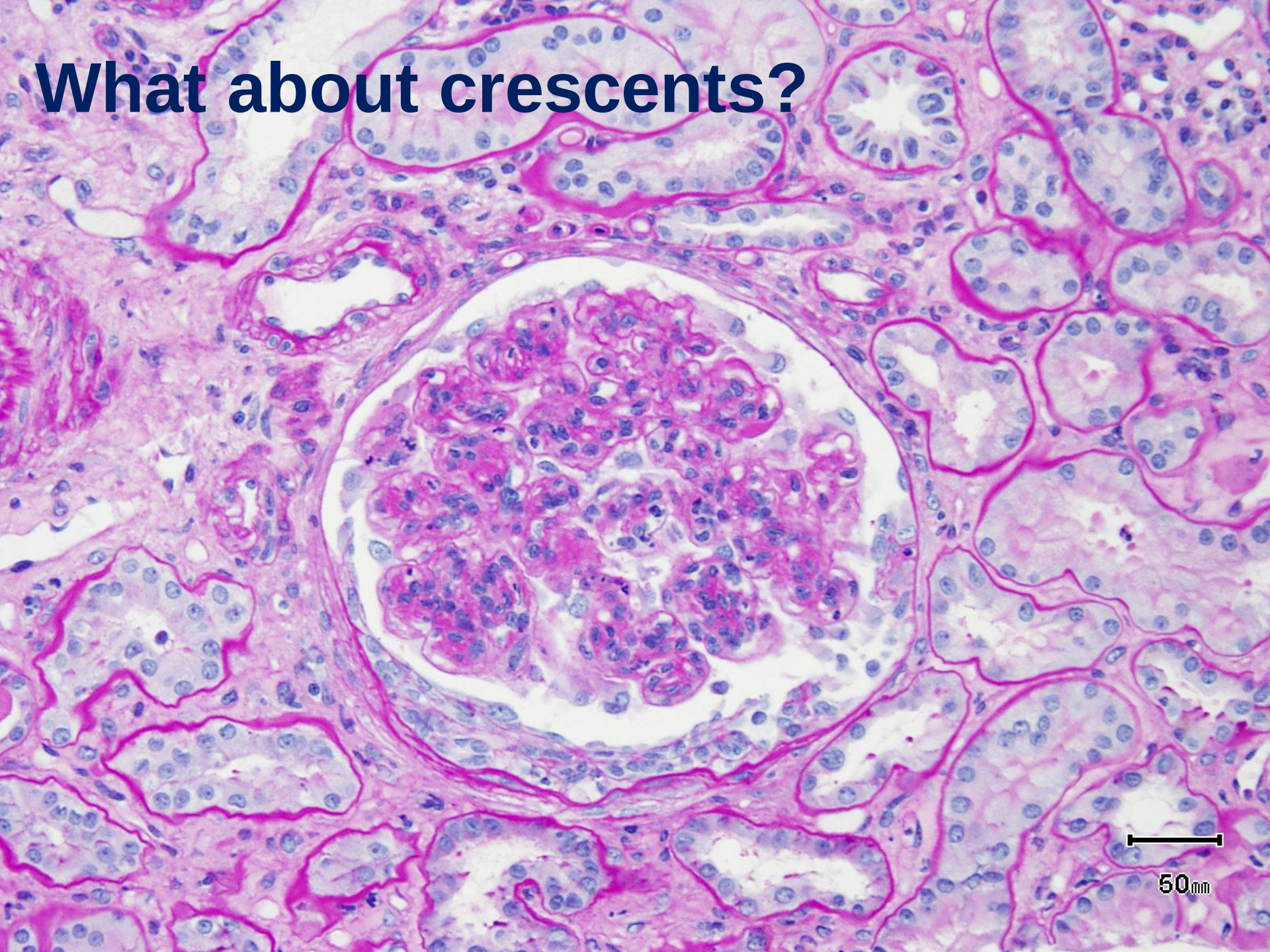
	Rate of renal function decline
+ immunosuppression	-1.5+/-8.3 ml/min/1.73m2 / /yr
no immunosuppression	-5.4+/-1.1 ml/min/1.73m2 / /yr

D.C. Cattran et al, Kidney Int. 76: 534-545, 2009

Multivariate Determinants of Survival from ESRD or ≥50% Decline in eGFR (2394 patients)

	All patients			No Immunosuppression			Any Immunosuppression		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
eGFR at biopsy	0.99	0.98-0.99	<0.001	0.98	0.97-0.99	<0.001	0.99	0.99-1.01	0.59
TA MAP (mmHg)	1.02	1.01-1.03	0.001	1.00	1.00-1.02	0.17	1.05	1.02-1.07	<0.001
TA Proteinuria (g/day)	1.60	1.51-1.68	<0.001	1.56	1.45-1.66	<0.001	1.71	1.57-1.87	<0.001
M (1 versus 0)	1.37	1.11-1.70	0.003	1.39	1.07-1.81	0.01	1.44	0.99-2.09	0.054
E (1 versus 0)	0.76	0.56-1.04	0.08	0.88	0.61-1.28	0.51	0.72	0.41-1.26	0.25
S (1 versus 0)	1.45	1.04-2.01	0.03	1.32	0.90-1.95	0.16	2.14	1.11-4.15	0.24
T (1-2 versus 0)	2.85	2.23-3.63	<0.001	2.43	1.80-3.27	<0.001	3.48	2.27-5.34	<0.001
Crescents (any versus none)	1.37	1.07-1.75	0.01	1.51	1.13-2.02	0.005	1.13	0.71-1.80	0.62

What about crescents?



The original Oxford study and several validation studies with similar exclusion criteria (including eGFR <30 ml/min and progression to ESRD within 12 months) did **NOT** find the presence of any cellular/fibrocellular crescents to be an independent predictor of the rate of eGFR decline or a combined outcome of ESRD or ≥50% reduction in eGFR.

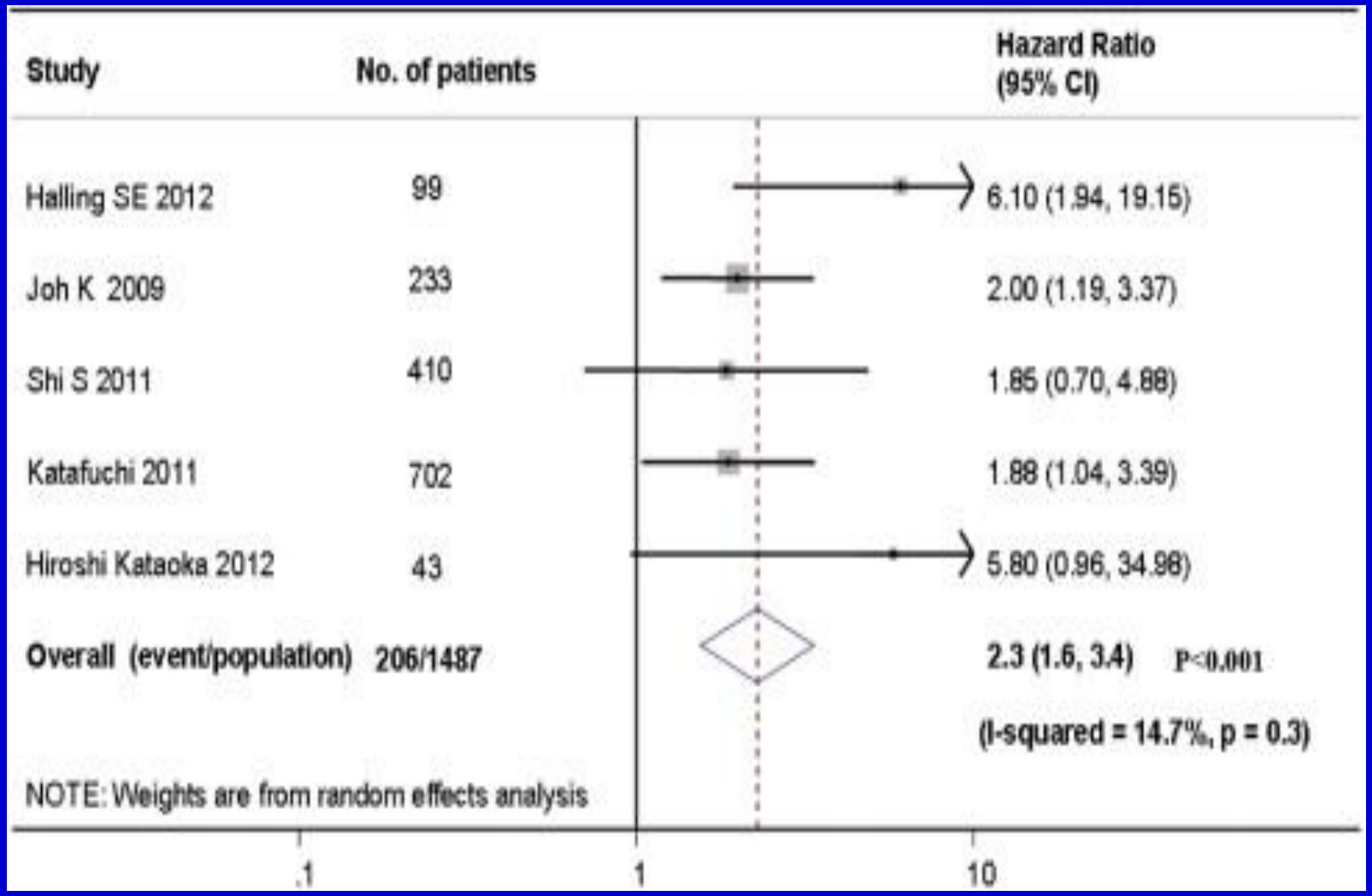
Katafuchi et al (Fukoka, Japan)
CJASN 6: 2806-2813, 2011

Study of 702 adults and children with IgA nephropathy:
416 meeting Oxford entry criteria (eGFR >30, Upr/Ucr >0.5)
286 not meeting these criteria (eGFR >30 but Upr/Ucr <0.5 [97% with M0] OR eGFR <30 (88% with T2, 78% with crescents; **median percentage of crescents only 10%**)

For all patients, only T and crescents were predictive of ESRD by multivariate analysis including clinical parameters, MEST, and crescents. M and S had p values of 0.09 and 0.06, respectively.

Crescents were a significant predictor of ESRD in the 286 patients **not** meeting Oxford entry criteria, but were not in the 416 patients that did meet these criteria.

Lv et al (Beijing), AJKD 62: 891-9, 2013 Meta-analysis of studies of IgAN analyzed by Oxford Classification



Shen et al (Nanjing), J Nephrol 28: 441-9, 2015 - 60 IgAN patients biopsies before and after immunosuppressive therapy

	First biopsy	Second biopsy	p
Clinical features			
MAP (mmHg)	95 ± 11	92 ± 12	0.276
Proteinuria (g/24 h)	1.98 (1.36–3.06)	0.80 (0.34–1.63)	<0.001
Hematuria (10^4 cells/ml)	195 (83–689)	23 (4–105)	<0.001
SCr (μmol/l)	90.17 (72.49–127.30)	82.21 (67.18–114.26)	0.067
eGFR (ml/min 1.73 m^2)	75.7 ± 29.3	88.9 ± 44.3	0.122
Total cholesterol (mmol/l)	5.75 ± 2.43	5.67 ± 2.53	0.794
Triglyceride (mmol/l)	2.08 ± 1.28	1.87 ± 0.97	0.539
Pathological features			
M, n (%)	15 (25.0)	16 (26.7)	1.000
S, n (%)	52 (86.7)	54 (90.0)	0.727
E, n (%)	22 (36.7)	5 (8.3)	<0.001
C, n (%)	51 (85.0)	15 (25.0)	<0.001
T, n (%)	14 (23.3)	30 (50.0)	<0.001

Thus, even the “gold standard” of histologic classifications has limitations and requires periodic re-evaluation and possible revision

Study of IgAN Crescents Working Group

1. Combined database of 3096 patients with data from the original Oxford and VALIGA studies and from the validation studies of Katafuchi et al (CJASN 6: 2806-2813, 2011) and of Zeng et al (AJKD 60: 812-820, 2012).

2. Data analyzed combining cellular and fibrocellular crescents of all sizes and excluding fibrous crescents ($\geq$90% matrix)

Study of IgAN Crescents Working Group

Key Issues:

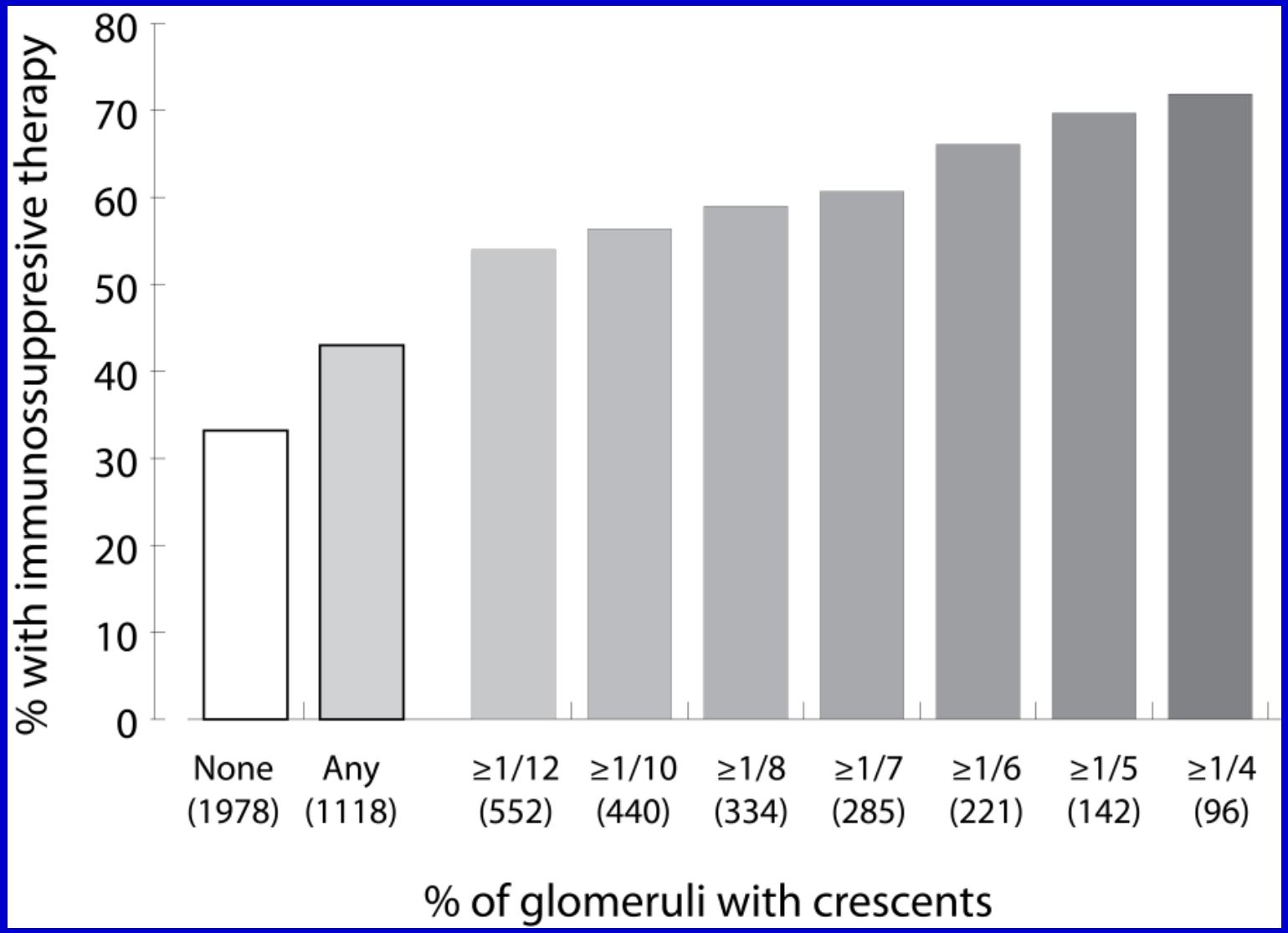
Predictive value of crescents on outcomes?

Rate of eGFR decline

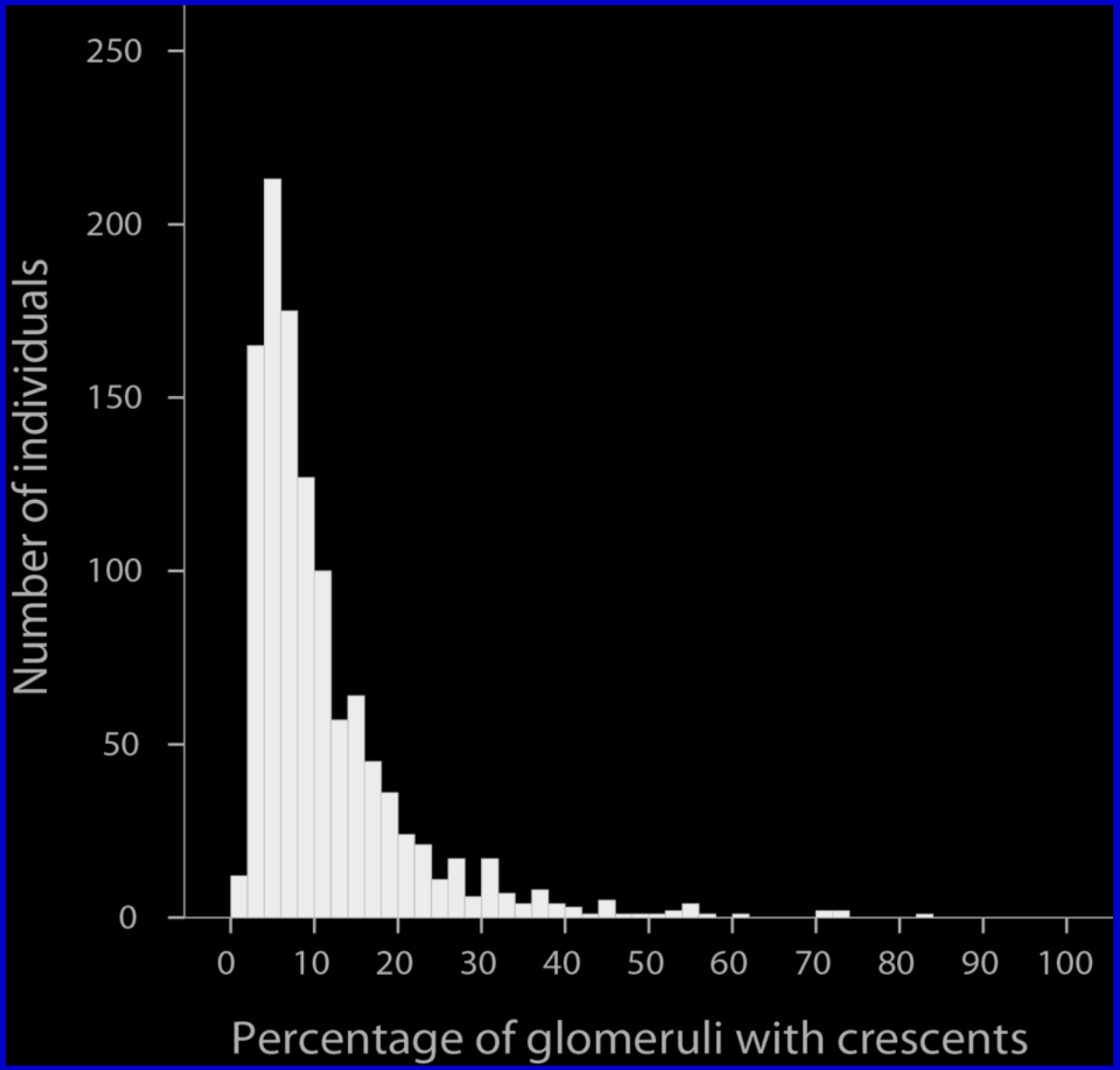
≥50% eGFR decline or ESRD (combined endpoint)

Interaction of crescents & immunosuppressive therapy?

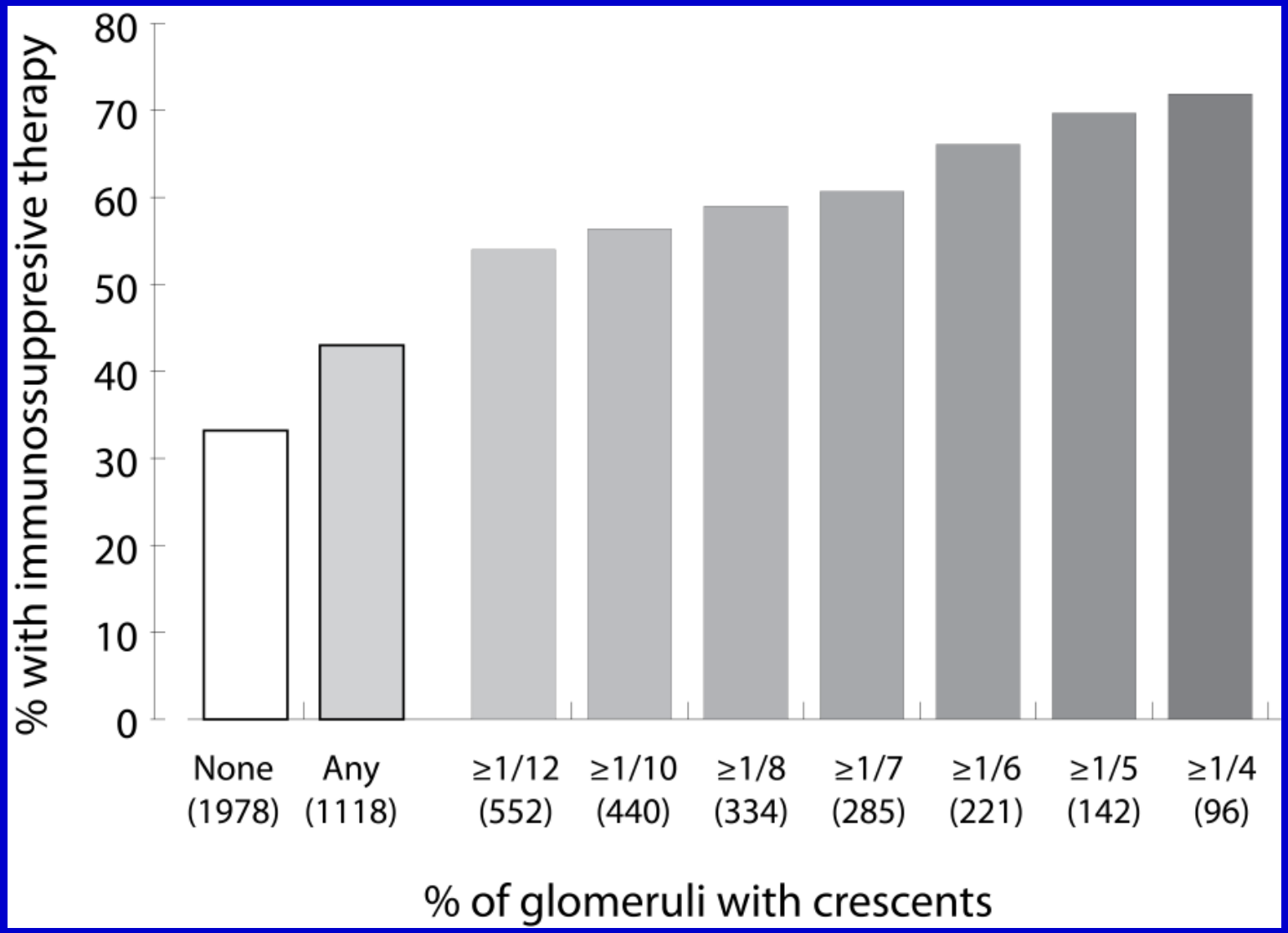
Optimal cutoff(s) for percent of glomeruli with crescents



M. Haas et al, J Am Soc Nephrol 28: 691-701, 2017



M. Haas et al, J Am Soc Nephrol 28: 691-701, 2017

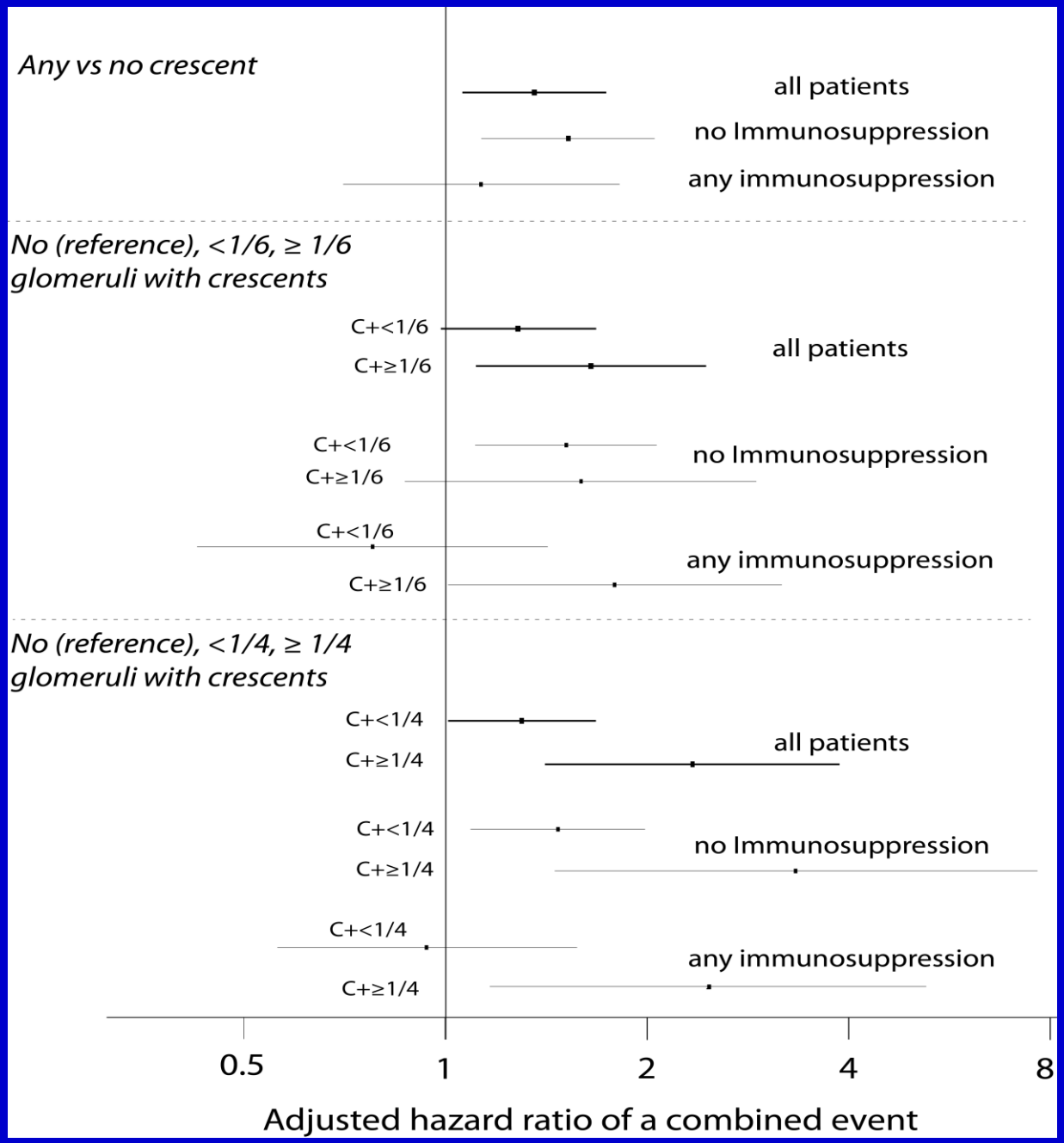


M. Haas et al, J Am Soc Nephrol 28: 691-701, 2017

Multivariate Determinants of Survival from ESRD or ≥50% Decline in eGFR

	All patients			No Immunosuppression			Any Immunosuppression		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
eGFR at biopsy	0.99	0.98-0.99	<0.001	0.98	0.97-0.99	<0.001	0.99	0.99-1.01	0.59
TA MAP (mmHg)	1.02	1.01-1.03	0.001	1.00	1.00-1.02	0.17	1.05	1.02-1.07	<0.001
TA Proteinuria (g/day)	1.60	1.51-1.68	<0.001	1.56	1.45-1.66	<0.001	1.71	1.57-1.87	<0.001
M (1 versus 0)	1.37	1.11-1.70	0.003	1.39	1.07-1.81	0.01	1.44	0.99-2.09	0.054
E (1 versus 0)	0.76	0.56-1.04	0.08	0.88	0.61-1.28	0.51	0.72	0.41-1.26	0.25
S (1 versus 0)	1.45	1.04-2.01	0.03	1.32	0.90-1.95	0.16	2.14	1.11-4.15	0.24
T (1-2 versus 0)	2.85	2.23-3.63	<0.001	2.43	1.80-3.27	<0.001	3.48	2.27-5.34	<0.001
Crescents (any versus none)	1.37	1.07-1.75	0.01	1.51	1.13-2.02	0.005	1.13	0.71-1.80	0.62

M. Haas et al, J Am Soc Nephrol 28: 691-701, 2017



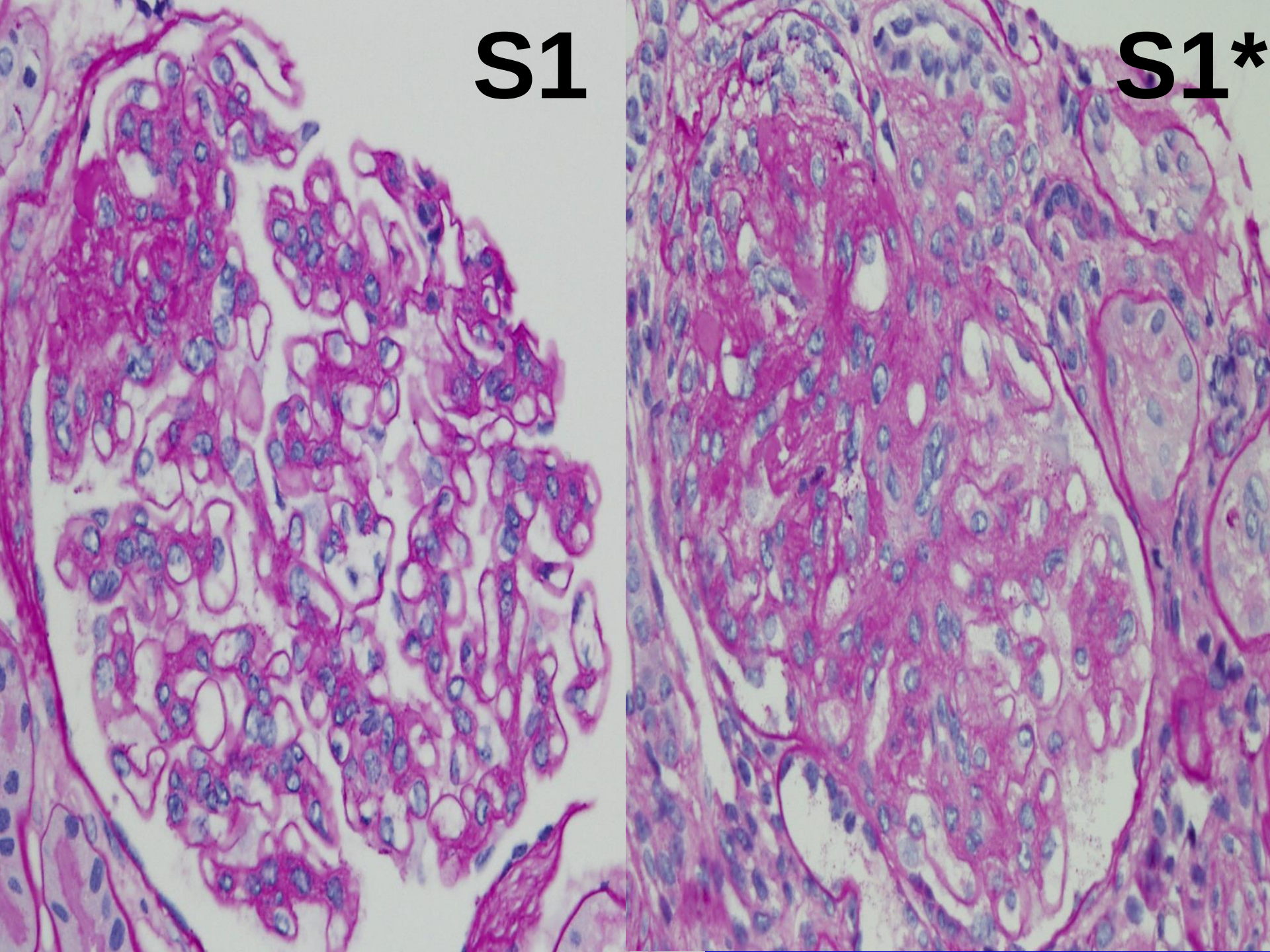
M. Haas et al, J Am Soc Nephrol 28: 691-701, 2017

We thus recommend addition of crescent (C) score to the Oxford MEST score:

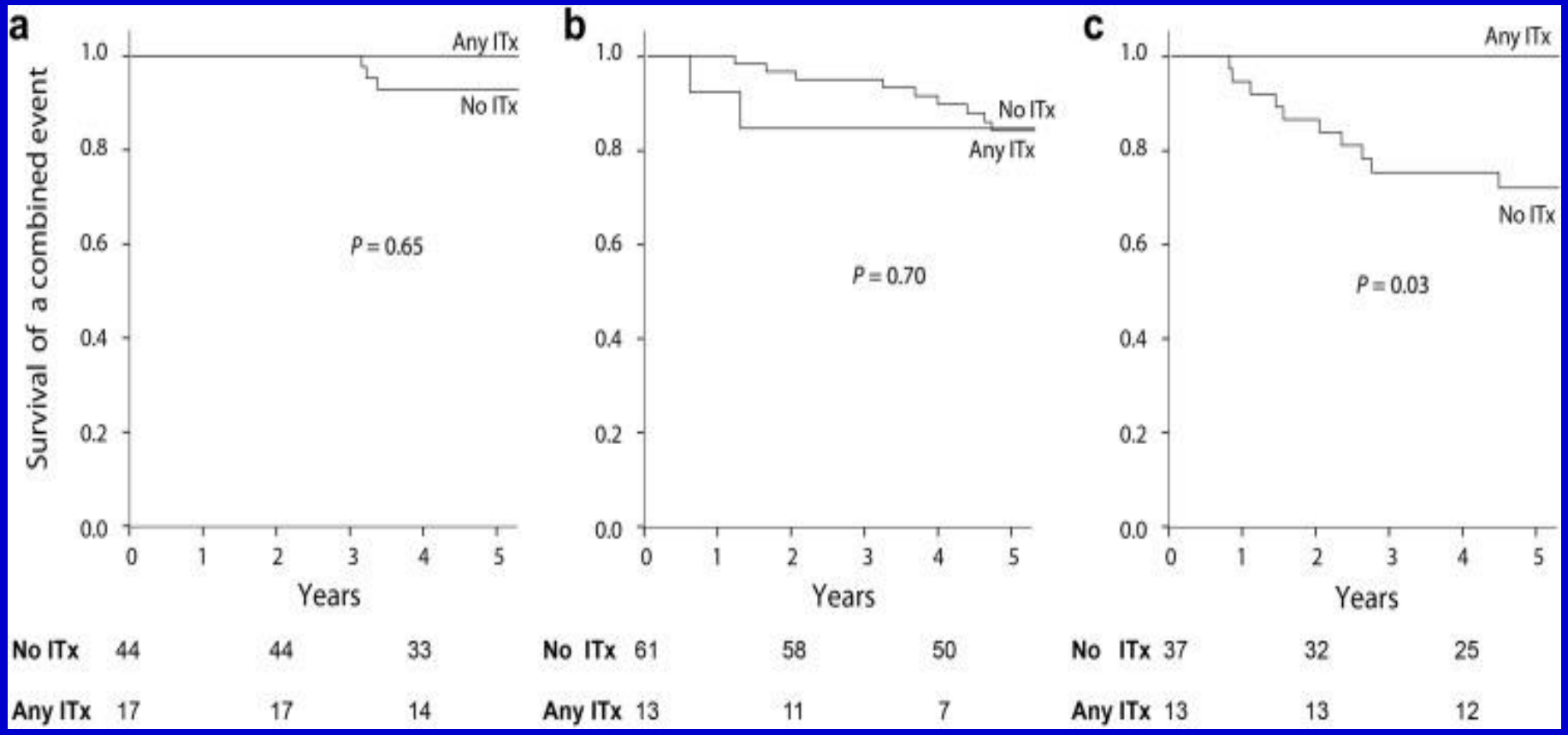
C0 – no crescents (cellular or fibrocellular)

C1 – crescents in <25% of glomeruli
identifies patients at risk of poor outcome if not given immunosuppressive therapy

C2 – crescents in ≥25% of glomeruli
identifies patients at risk of poor outcome even if given immunosuppressive therapy


S1
S1*

S0 S1, no tip/pod hyperpl S1 w/ tip or pod hyperpl



S.S. Bellur et al (Oxford), Kidney Int 91: 235-243, 2017

Combined event = ESRD or ≥50% decline in eGFR; iTx = immunosuppression

Glomerular Deposits of Immunoglobulins, Complement Components, MBL, and MASP-1 in Various Glomerular Diseases

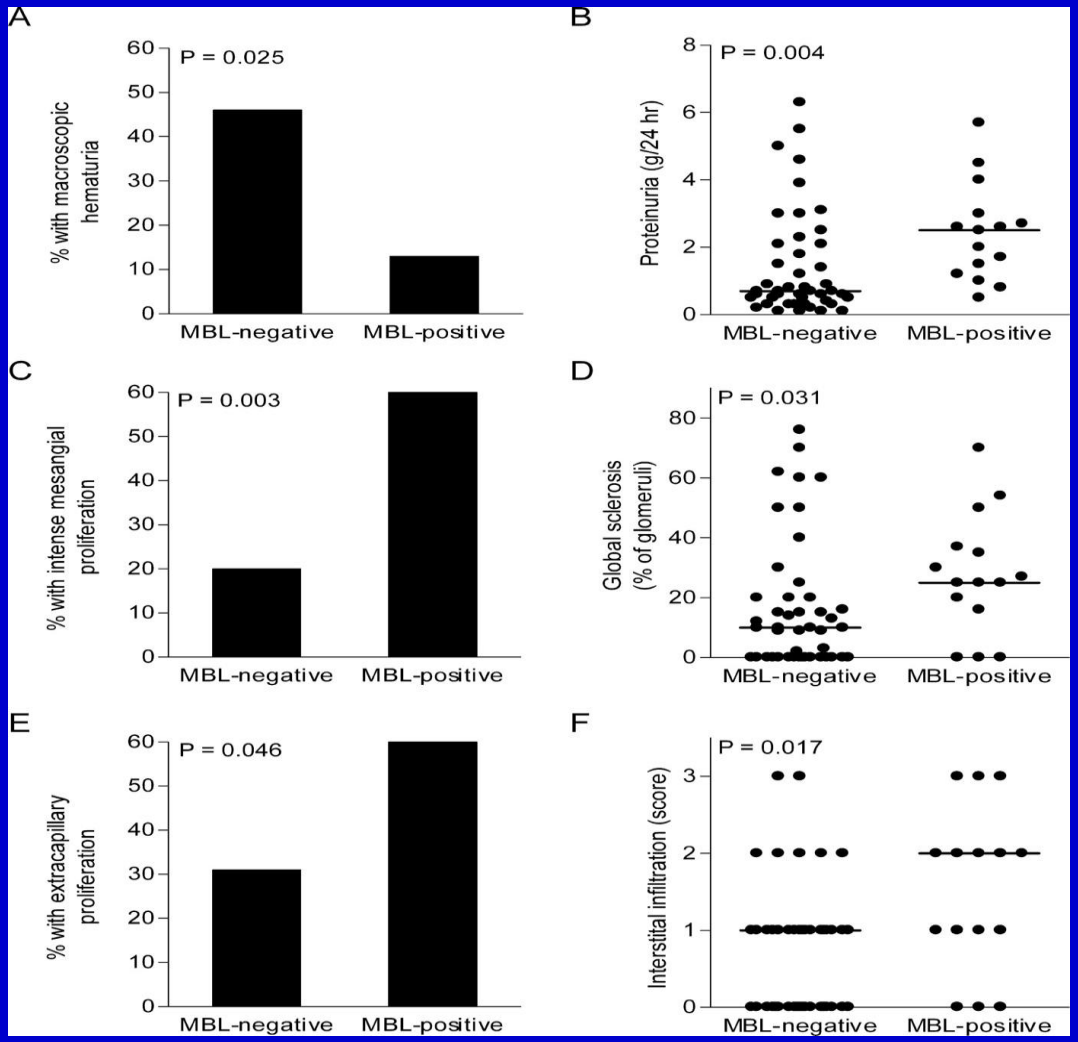
	No. of Cases	IgG	IgA	IgA1	IgA2	IgM	C1q	C4	C3c	MBL	MASP-1
IgA GN	36	11	36	36	19	10	0	19	31	19	19
Lupus nephritis	10	10	10	10	0	6	10	10	10	3	3
Minimal change nephrotic syndrome	5	0	0	0	0	0	0	0	0	0	0
Membranous GN	6	6	0	0	0	0	0	0	4	0	0
Thin basement membrane disease	5	0	0	0	0	0	0	0	0	0	0

Hisano et al,, Am J Kidney Dis 38: 1082-8 2001

MBL Staining	L-Ficolin	MASP-1/3	C4d	C4-Binding Protein	C1q	C3	IgA1	IgA2
Negative (%; *n* = 45)	0	0	0	0	0	82	100	0
Positive (%; *n* = 15)	100	100	100	100	0	60	100	0

A. Roos et al, JASN 17: 1724-34, 2006

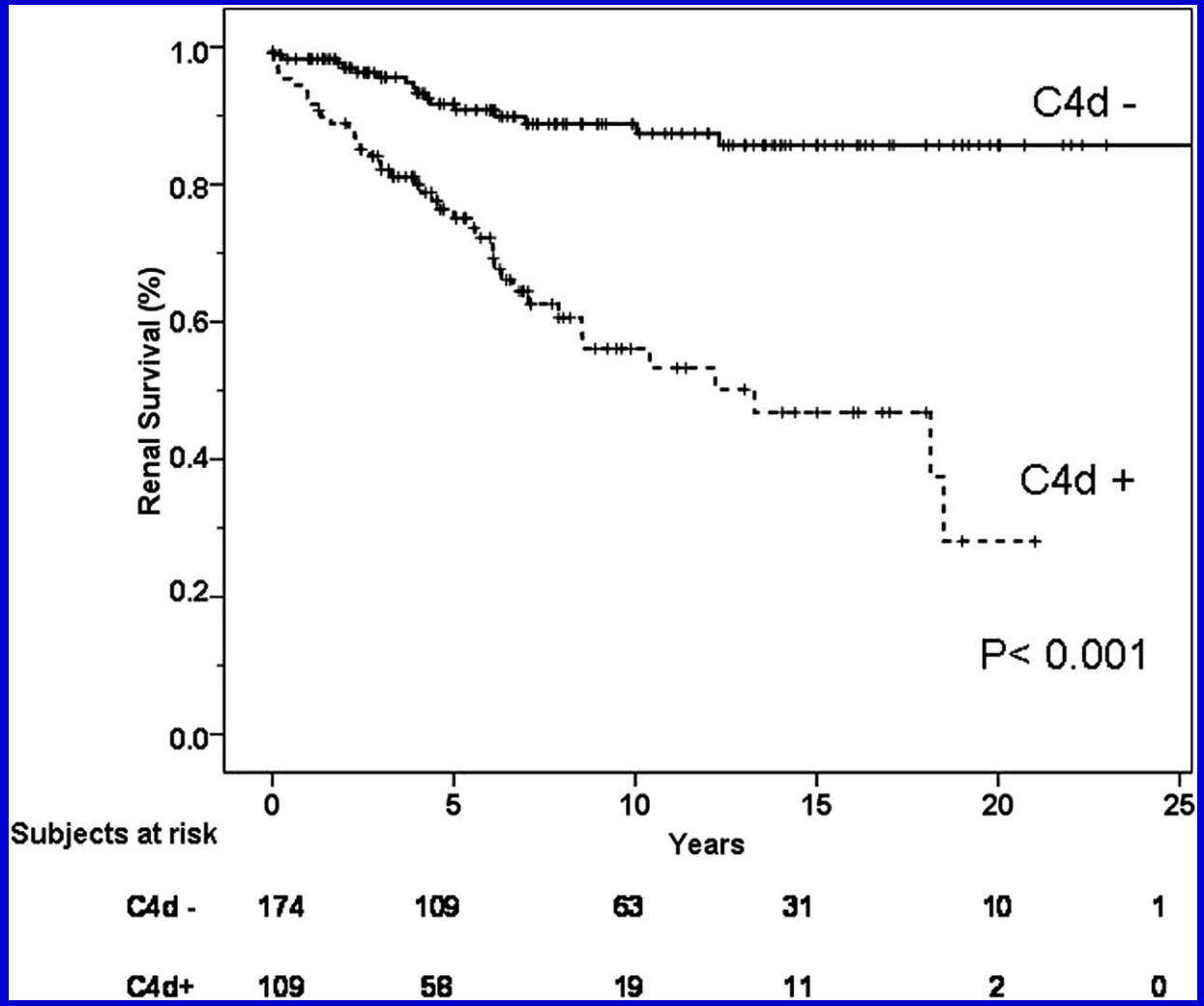
MBL positivity is associated with markers of renal damage



Anja Roos et al. JASN 2006;17:1724-1734

JASN

Renal survival according to C4d staining (univariate).



Espinosa et al. CJASN 2014;9:897-904

CJASN

M. Espinosa et al (Cordoba, Spain) CJASN 9: 897-904, 2014

Univariate and multivariate Cox regression analyses with ESRD as the endpoint in 283 patients with IgA nephropathy

Analysis	*β*	*P* Value	Hazard Ratio (95% Confidence Interval)
Univariate			
Age (yr)	0.02	0.001	1.02 (1.01 to 1.04)
Positive C4d staining	1.53	<0.001	4.65 (2.63 to 8.22)
Hypertension	1.84	<0.001	6.30 (2.98 to 13.31)
Proteinuria (g/d)	0.25	<0.001	1.28 (1.16 to 1.43)
eGFR (ml/min per 1.73 m^2)	−0.04	<0.001	0.95 (0.94 to 0.96)
Oxford classification			
S1	1.10	<0.001	3.02 (1.76 to 5.16)
T0			1 (reference)
T1	1.93	<0.001	6.89 (2.31 to 20.5)
T2	3.27	<0.001	26.23 (9.23 to 75.43)
Multivariate			
Positive C4d staining	0.89	0.01	2.45 (1.30 to 4.64)
Proteinuria (g/d)	0.15	0.01	1.16 (1.03 to 1.31)
eGFR (ml/min per 1.73 m^2)	−0.04	<0.001	0.96 (0.94 to 0.97)
Oxford classification			
T0			1 (reference)
T2	1.48	0.01	4.42 (1.40 to 13.88)

IgA Nephropathy Crescents Working Group

Ritsuko Katafuchi
National Fukuoka Higashi Medical Center, Fukuoka, Japan
Stéphan Troyanov
Hopital du Sacre-Coeur de Montreal, Montreal, Canada
Jacobien C. Verhave
Radboud Univ. Medical Center, Nijmegen, The Netherlands

Zhi-Hong Liu (China)
Charles Alpers (USA)
Jan Becker (Germany)
Jonathan Barratt (UK)
Daniel Cattran (Canada)
Terry Cook (UK)
Rosanna Coppo (Italy)
John Feehally (UK)
Antonello Pani (Italy)
Agnieszka Perkowska-Ptasinska (Pol)
Ian Roberts (UK)
Maria Fernanda Soares (Brazil)
Hernan Trimarchi (Argentina)
Suxia Wang (China)
Yukio Yuzawa (Japan)
Hong Zhang (China)

IGA®

ASSURED QUALITY SINCE 1926