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Histologic classification of IgA Nephropathy : Its role in patient care

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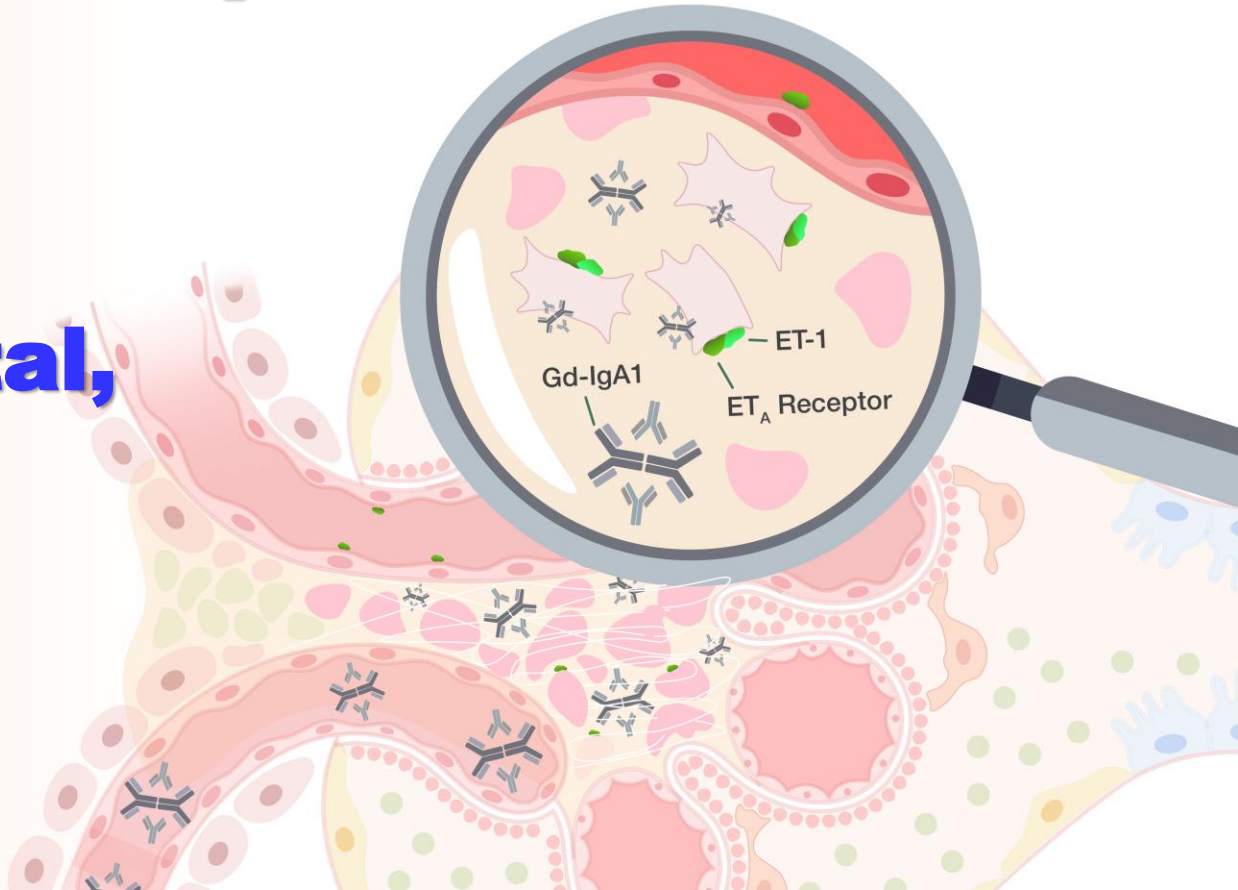
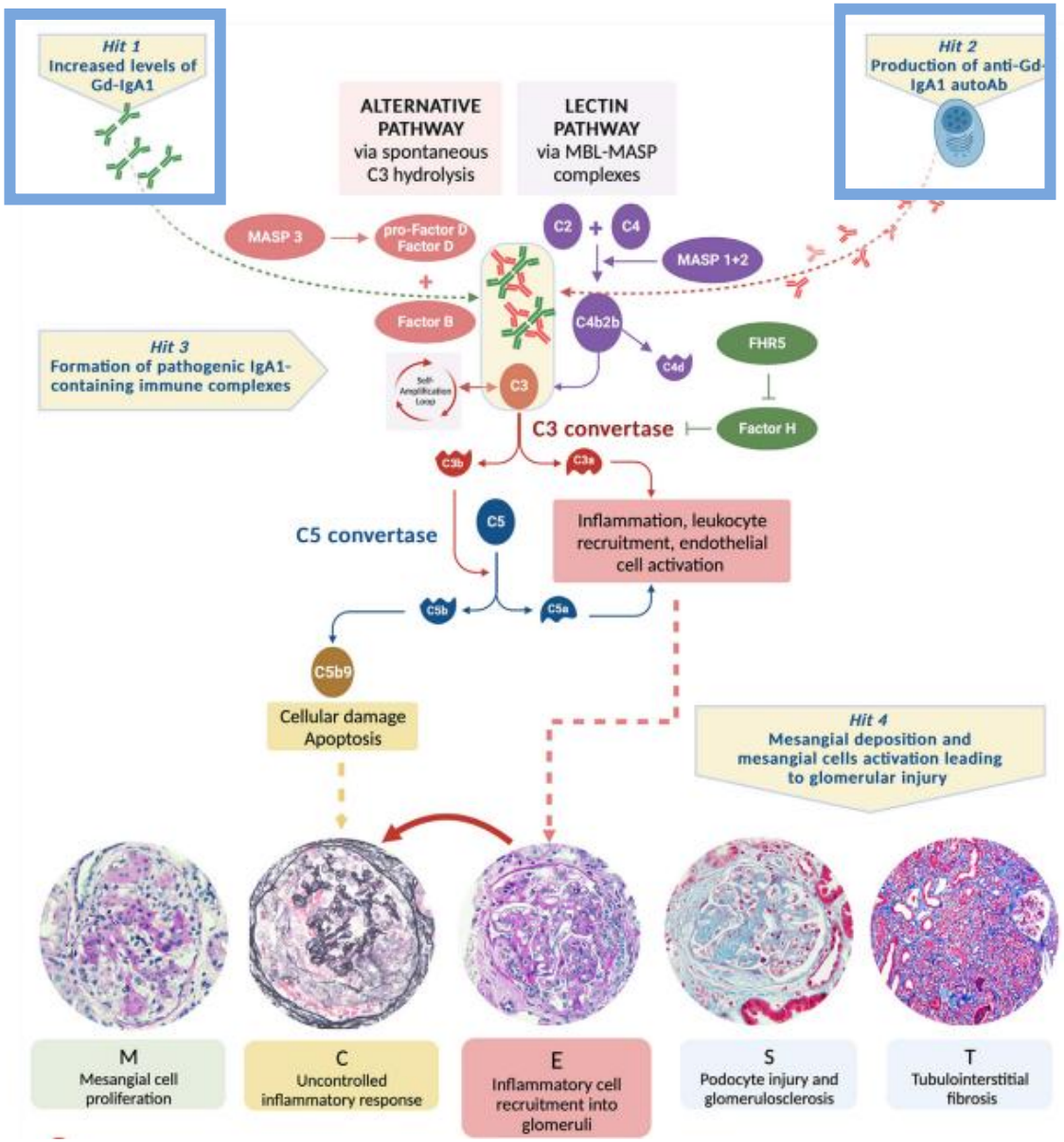


Outline

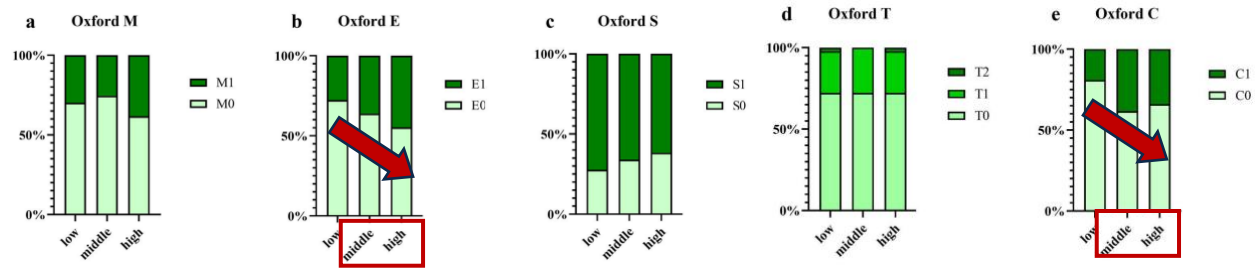
- From 4-Hit Theory to Histological Interpretation
- Histological Classification and Renal Outcome: Evidence from Asia-Pacific Research
- Beyond MEST-C: What Additional Features Might Refine Prognostication?
- From Histology to Therapy
- Conclusion and Take Home message

Histologic Lesions and the Four-Hit Pathogenesis Model



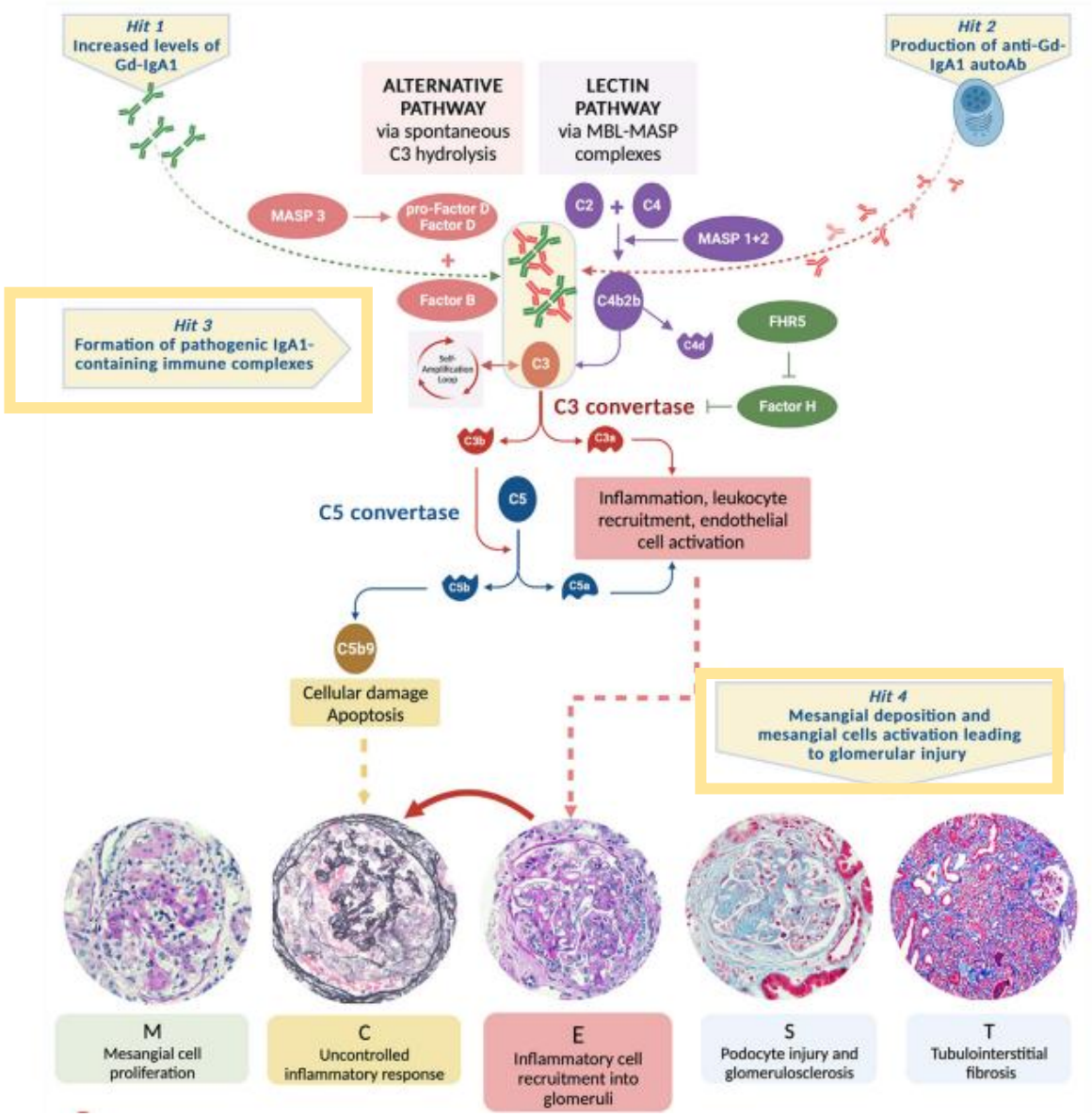
Hit 1 & Hit 2:

- Serum BAFF levels were significantly higher in patients with mesangial hypercellularity and segmental glomerulosclerosis and correlated with the severity of tubular atrophy/interstitial fibrosis.[1]
- The distribution of Gd-IgA1 at 3 months was found to differ significantly between different grades of S score.[2]
- The percentages of E1 and C1 in the Oxford classification increased in patients of the high Gd-IgA1 intensity group.[3]



1. Xin G, Shi W, Xu LX, Su Y, Yan LJ, Li KS. Serum BAFF is elevated in patients with IgA nephropathy and associated with clinical and histopathological features. J Nephrol. 2013;26(4):683-690. doi:10.5301/jn.5000218 2. Shukla M, Malhotra KP, Chandra A, Rao NS, Ahmad MK. Correlation of Serum Galactose-Deficient IgA1 and Oxford Class in Cases of IgA Nephropathy. Arch Pathol Lab Med. 2024;148(11):1244-1250. doi:10.5858/arpa.2023-0190-OA Ştefan G, Alamartine E, Mariat C, Maillard N. 3. Nakayama M, Suzuki H, Fukao Y, Lee M, Kano T, Suzuki Y. Clinical Significance of the Intensity of Glomerular Galactose-Deficient IgA1 Deposition in IgA Nephropathy. Kidney Int Rep. 2022;7(12):2726-2729. Published 2022 Sep 29. doi:10.1016/j.ekir.2022.09.022

Histologic Lesions and the Four-Hit Pathogenesis Model



Hit 3 & Hit 4:

- The involvement of alternative and lectin complement pathways across all MEST-C classes.[1]
- All examined complement factors were associated with the C1-2 class, emphasizing the critical role of complement activation, possibly at the endothelial surface.[1]

1. .Systematic Review of the Link Between Oxford MEST-C Classification and Complement Activation in IgA Nephropathy. *Kidney Int Rep*. 2023;9(2):356-369. Published 2023 Nov 14.

Correlation of Serum Galactose-Deficient IgA1 and Oxford Class in Cases of IgA Nephropathy

Table 4. Correlation of Oxford Classification and Immunofluorescence Findings With Galactose-Deficient Immunoglobulin A1 (Gd-IgA1) Levels at Baseline and 3 Months

Variable (Quantitative)	*P* Value for Correlation With Gd-IgA1 (at Baseline)	*P* Value for Correlation With Gd-IgA1 (at 3 Months)
C score	.82	.14
M score	.55	.77
E score	.36	.78
S score	.44	**.008**
T score	.27	.75
IgG	.99	>.99
IgM	.61	.52
IgA	.58	.31
C3	.81	.14
C1q	.74	.71

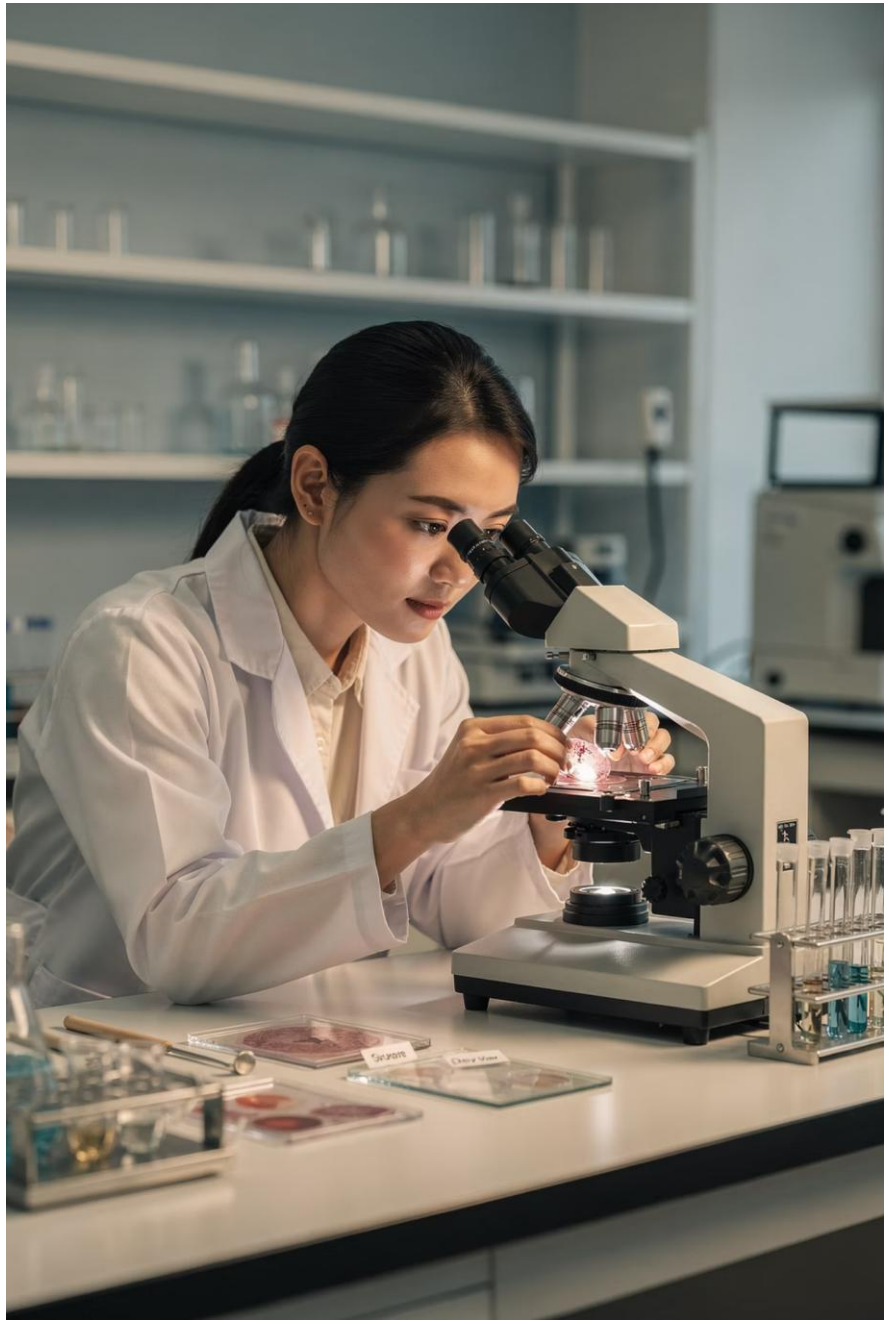
- There was no significant correlation between C-MEST score and serum Gd-IgA1 levels at baseline (P > .05)
- however, the distribution of Gd-IgA1 at 3 months was found to differ significantly between different grades of S score (P = .008).

Shukla M, Malhotra KP, Chandra A, Rao NS, Ahmad MK. Correlation of Serum Galactose-Deficient IgA1 and Oxford Class in Cases of IgA Nephropathy. *Arch Pathol Lab Med*. 2024;148(11):1244-1250. doi:10.5858/arpa.2023-0190-OA

Histological classification and Renal Outcome:

Evidence from Asia-Pacific Research

Validation studies from diverse Asia-Pacific populations have examined how MEST-C scores predict long-term kidney function decline and progression to end-stage renal disease.
These cohorts provide critical insights into regional variations in IgAN presentation and the reproducibility of the Oxford classification across different ethnic groups and healthcare settings.



MEST C Score and Treatment Response in IgA Nephropathy in a Tertiary Care Hospital: A Descriptive Cross-sectional Study

Nepal

Table 4. Treatment outcomes and MEST C scores (n= 52).

	Sub-group	CR †	PR*	ESRD§
M	0	6 (11.54)	13 (25)	3 (15.79)
	1	10 (19.23)	18 (34.62)	2 (6.90)
E	0.0	6 (11.54)	17 (32.69)	4 (7.69)
	1.0	10 (19.23)	14 (26.92)	1 (3.85)
S	0.0	5 (9.62)	1 (1.92)	-
	1.0	11 (21.15)	30 (57.69)	5 (9.62)
T	0.0	15 (28.85)	17 (32.69)	-
	1.0	1 (1.92)	13 (25)	4 (7.69)
	2.0	-	1 (1.92)	1 (1.92)
C	0.0	7 (13.46)	19 (36.54)	4 (7.69)
	1.0	9 (17.31)	9 (17.31)	0 (1.92)
	2.0	-	3 (5.77)	1 (1.92)

Table 5. Relationship between IFTA% and clinical outcomes.

IFTA% ‡	CR †	PR*	ESRD§
0-25% (n= 32)	15 (46.88)	17 (53.12)	0 (0.00)
25-50% (n= 18)	1 (5.56)	13 (72.22)	4 (22.22)
≥50% (n= 2)	-	1 (50)	1 (50)
Total	**16**	**31**	**5**

- The S1 and T1/2 components of the MEST-C score had higher rates of partial remission and progression to end-stage renal disease, while other indices showed mixed results.
- Interstitial fibrosis/tubular atrophy >25% significantly reduced complete remission rates.

Thapa S, Sigdel MR. JNMA J Nepal Med Assoc. 2024;62(276):536-541.

External validation of the Oxford classification of IgA nephropathy: A retrospective study of 70 patients from Saudi Arabia

Saudi Arabia

Table 3 The relationships between baseline proteinuria and Oxford histological classifications of kidney biopsies.

Classification	Baseline proteinuria	p[a]
M0	0.57 (0.28–1.28)	0.13
M1	1.44 (0.61–2.56)	
S0	0.79 (0.24–1.37)	0.09
S1	1.68 (0.57–2.73)	
E0	0.86 (0.35–1.94)	0.05
E1	1.86 (1.10–4.99)	
T0	0.62 (0.34–1.19)	0.009
T1	1.79 (1.42–3.69)	
T2	3.69 (1.25–5.73)	

Data are presented as median (IQR).
[a] Calculated with the use of Kruskal-Wallis test.

Table 5 Adjusted odds ratios in various Oxford classes for the outcomes of worsening renal function.[a]

Parameter	Odds ratio (95% confidence interval)	p
M	0.360 (0.074–1.757)	0.206
E	1.852 (0.349–9.832)	0.469
S	1.349 (0.261–6.967)	0.721
T	1.545 (0.228–10.485)	0.655

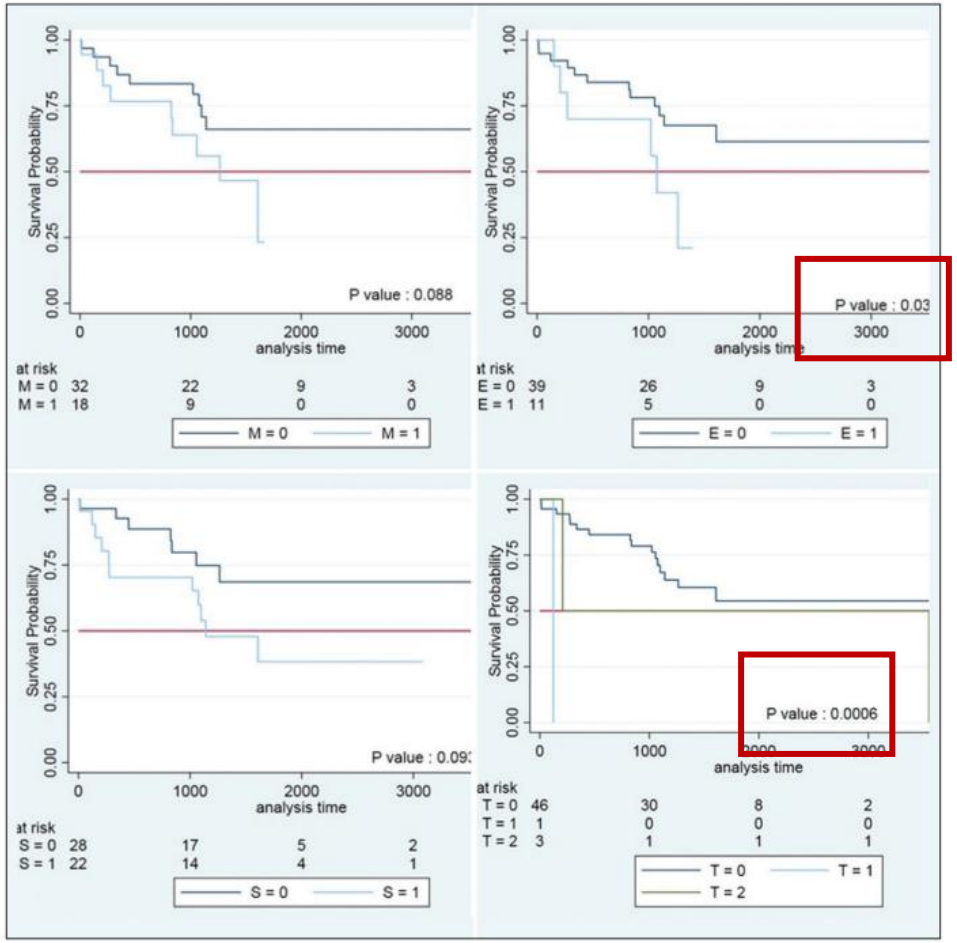
[a] The analysis was adjusted for baseline estimated glomerular filtration rate, blood pressure, age and sex.

- Higher mesangial scores, advanced segmental glomerulosclerosis, and endocapillary hypercellularity correlated with increased proteinuria and reduced GFR, though these associations did not achieve statistical significance.
- Tubular atrophy and interstitial fibrosis, however, were associated with significantlyr educed initial eGFR and higher initial proteinuria.
- However, logistic regression analysis revealed no individual histological parameter could independently predict long-term renal function decline after adjusting for baseline eGFR, hypertension, age, and sex.

Kfoury H, Alsuwaida A, Hussain S, AlOudah N, Alhejaili F, Alsaad K, Alghonaim M. Hong Kong J Nephrol. 2014;16(2):29-33

A retrospective study in an Indian cohort with clinicopathological correlations and outcome

India



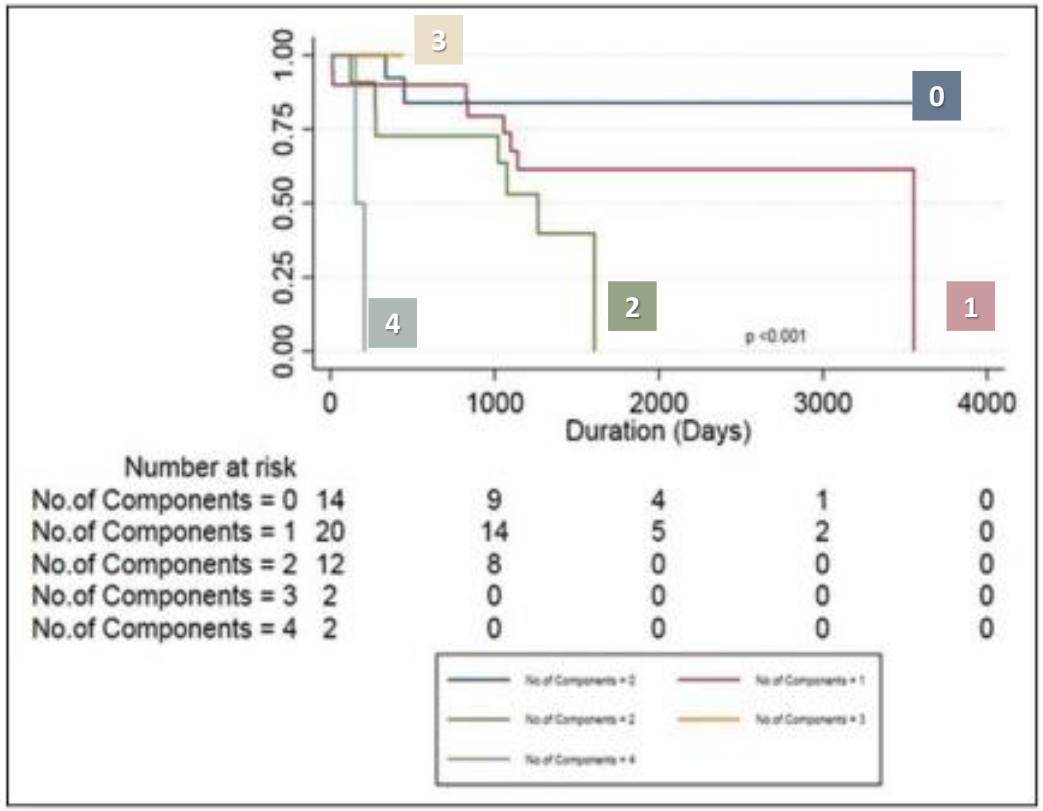


Figure 4: Kaplan-Meier survival analysis for patients with multiple lesions (M, E, S, and T)

- Kaplan-Meier survival analyses for individual parameters showed that patients with endocapillary hypercellularity and interstitial fibrosis/ tubular atrophy progressed significantly faster to stage 5 CKD which reached statistical significance.
- Patients with multiple parameters predominantly lesions like segmental sclerosis and interstitial fibrosis/tubular atrophy, progressed significantly faster to stage 5 CKD.

Paul SP, Roy S, Gopinath V, Yusuf S. Indian J Pathol Microbiol. 2025;68(3):547-554.

Characterisation of IgA Nephropathy in an Australian Cohort

Australia

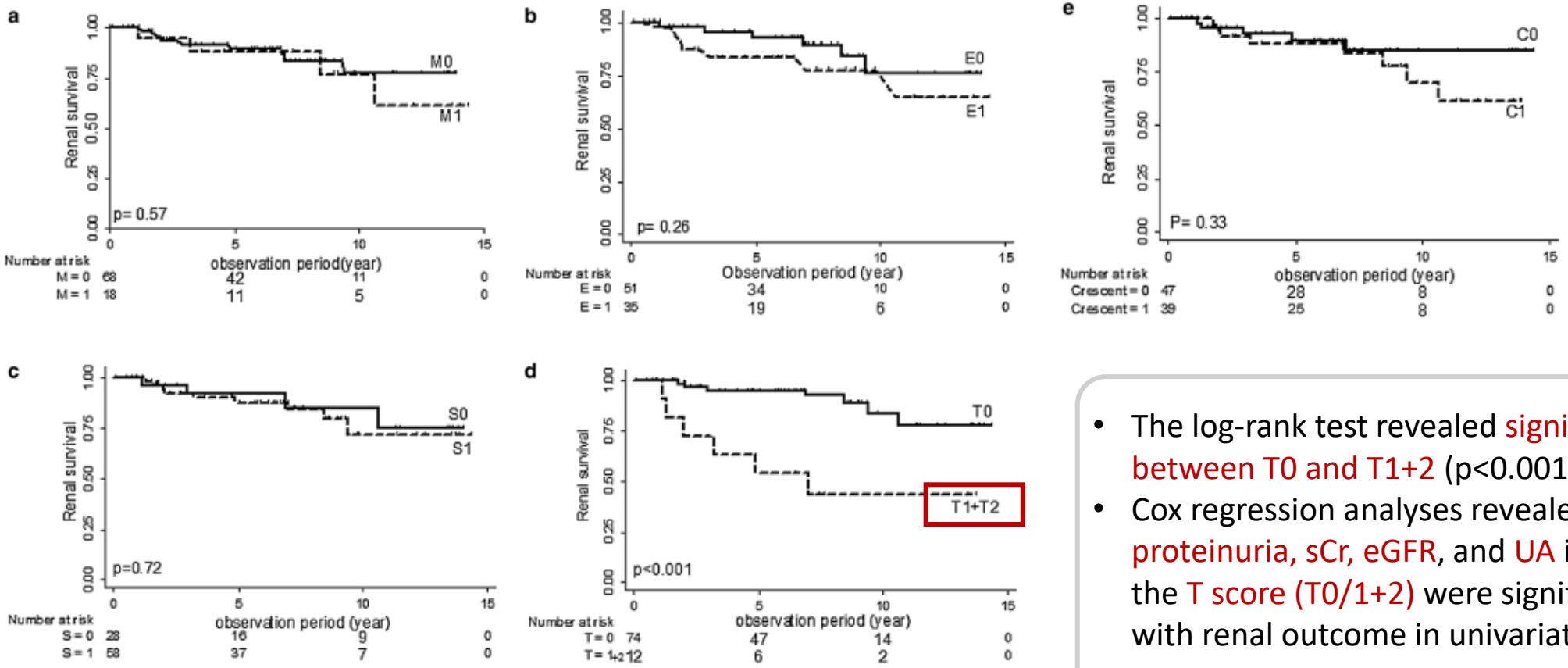
	Risk factors for progression to kidney failure by multivariate (cox regression) analysis				95.0% CI	
	Regression coefficient (B)	Standard error	*p* value	Hazard ratio	Lower	Upper
Mesangial cellularity > 50% glomeruli (M1)	1.00	0.61	0.095	2.63	0.85	8.15
Interstitial fibrosis/tubular atrophy 25%–50% (T1)	−0.20	0.48	0.674	0.82	0.32	2.09
Interstitial fibrosis/tubular atrophy > 50% (T2)	1.95	0.56	0.001*	7.00	2.32	21.05
Additional renal pathology on biopsy	1.36	0.44	0.002*	3.90	1.63	9.29
Baseline proteinuria	0.14	0.06	0.024*	1.15	1.02	1.29

- T2 (HR 7.00, 95% CI 2.32–21.05), baseline proteinuria (HR 1.15, 95% CI 1.02–1.29) and the presence of an additional renal pathology on biopsy (HR 3.90, 95% CI 1.63–9.29) were all statistically significant risk factors for the progression to kidney failure by the multivariate (Cox regression) analysis.
- Specifically, a classification of T2 showed the greatest risk for the progression, with a HR of 7.00.

Swaminathan S, Neelakantan N, Bryant H, Rattanamastip P, Sandhu G, Chacko B. Characterisation of IgA Nephropathy in an Australian Cohort. *Int J Nephrol*. 2025;2025:9976879. Published 2025 Mar 27

T-score in the Oxford Classification system could predict renal outcome in Japanese IgA nephropathy patients

Japan



- The log-rank test revealed significant differences between T0 and T1+2 ($p<0.001$).
- Cox regression analyses revealed that the amount of proteinuria, sCr, eGFR, and UA in clinical variables, the T score (T0/1+2) were significantly associated with renal outcome in univariate analyses.

Kaihan, A.B., Yasuda, Y., Katsuno, T. *et al.* The Japanese Histologic Classification and T-score in the Oxford Classification system could predict renal outcome in Japanese IgA nephropathy patients. *Clin Exp Nephrol* **21**, 986–994 (2017).

Validation of the Oxford Classification of IgA Nephropathy: A Single-Center Study in Korean Adults

Korea

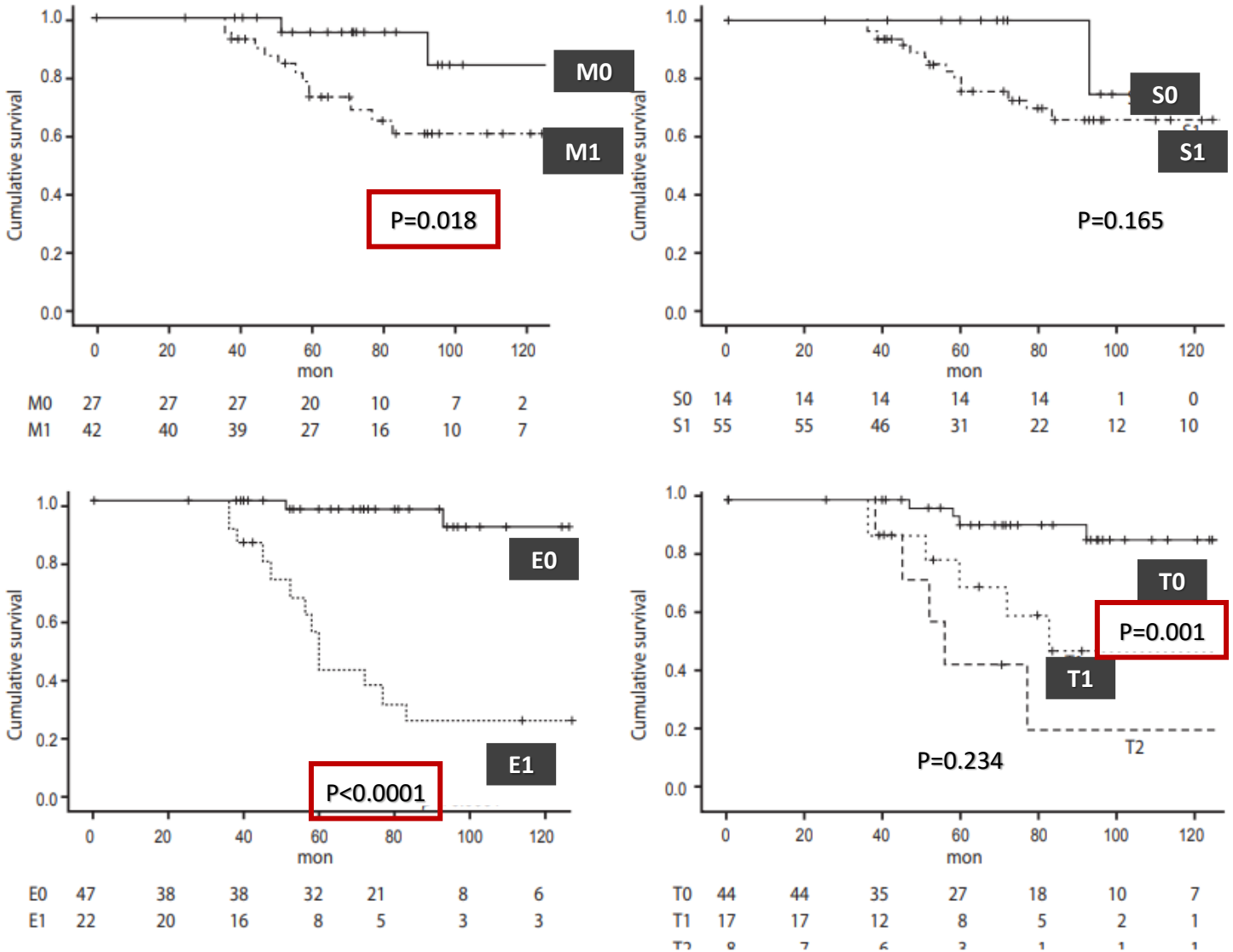


Figure 2. Kaplan Meier plot of renal survival according to pathological features of the Oxford classification.

- Kaplan-Meier analyses demonstrated M1, E1, and T1 lesions were significantly associated with either ESRD or 50% reduction in initial eGFR.
- No significant difference in outcomes was observed between T2 and T1 lesions.

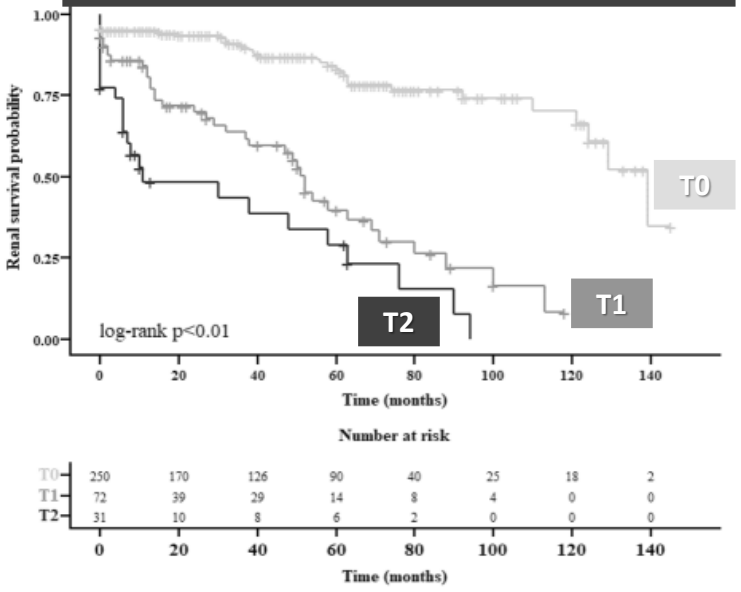
Lee H, et al. Korean J Intern Med. 2012;27(3):293-300.

The association of Oxford classification and renal function deterioration among Taiwanese IgAN individuals

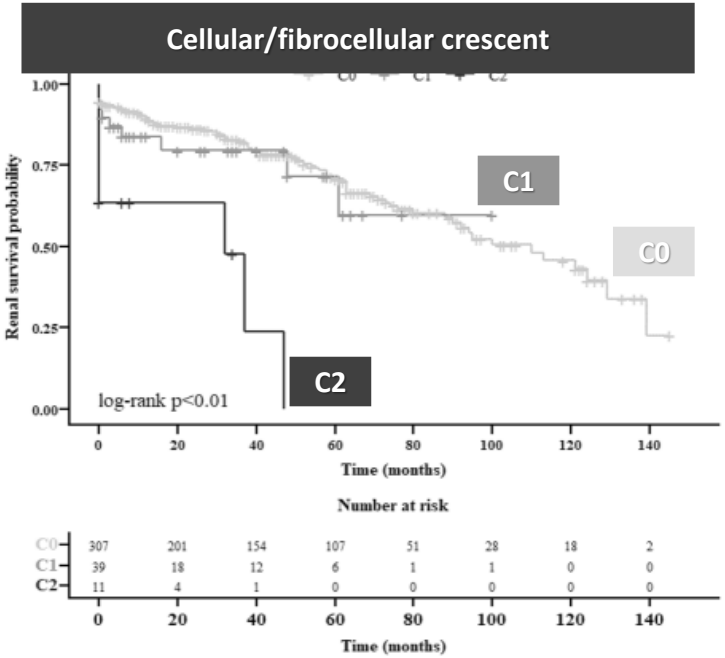
Taiwan

10-Year Follow-Up Results

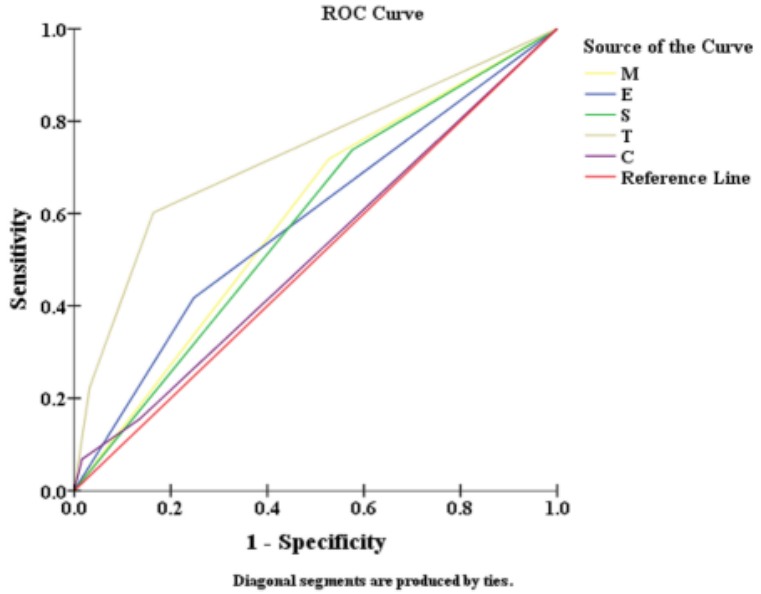
Tubular atrophy/Interstitial inflammation



Cellular/fibrocellular crescent



ROCs for individual M,E,S,T and C variables



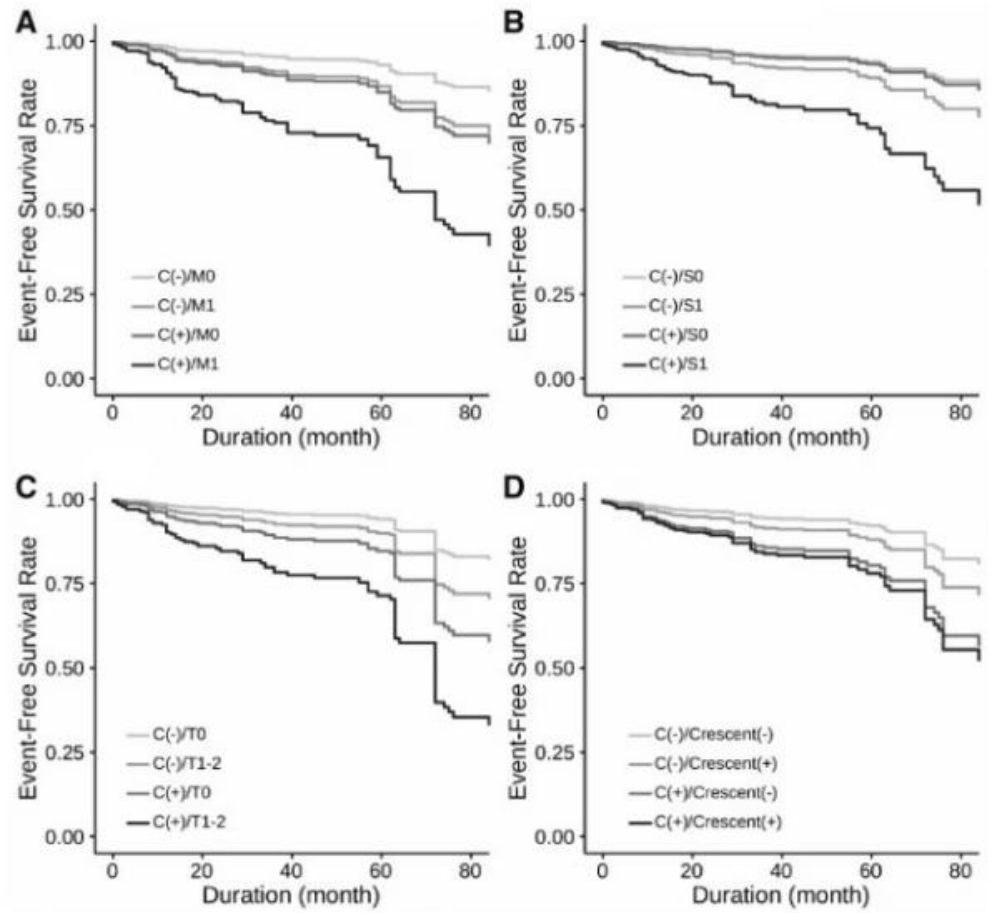
- Over a 10-year follow-up, median survival of entire cohort was 89.4 months . Among all, T1 and T2 had poorest survival (54.7 and 34.4 months), followed by C1 and C2 (71.8 and 27.7 months).
- T score exhibited the highest predictive power for composite renal outcomes with AUC 0.73, sensitivity 60.2%, and specificity 83.6%. This significantly outperformed all other MEST-C components, which showed AUCs below 0.6.

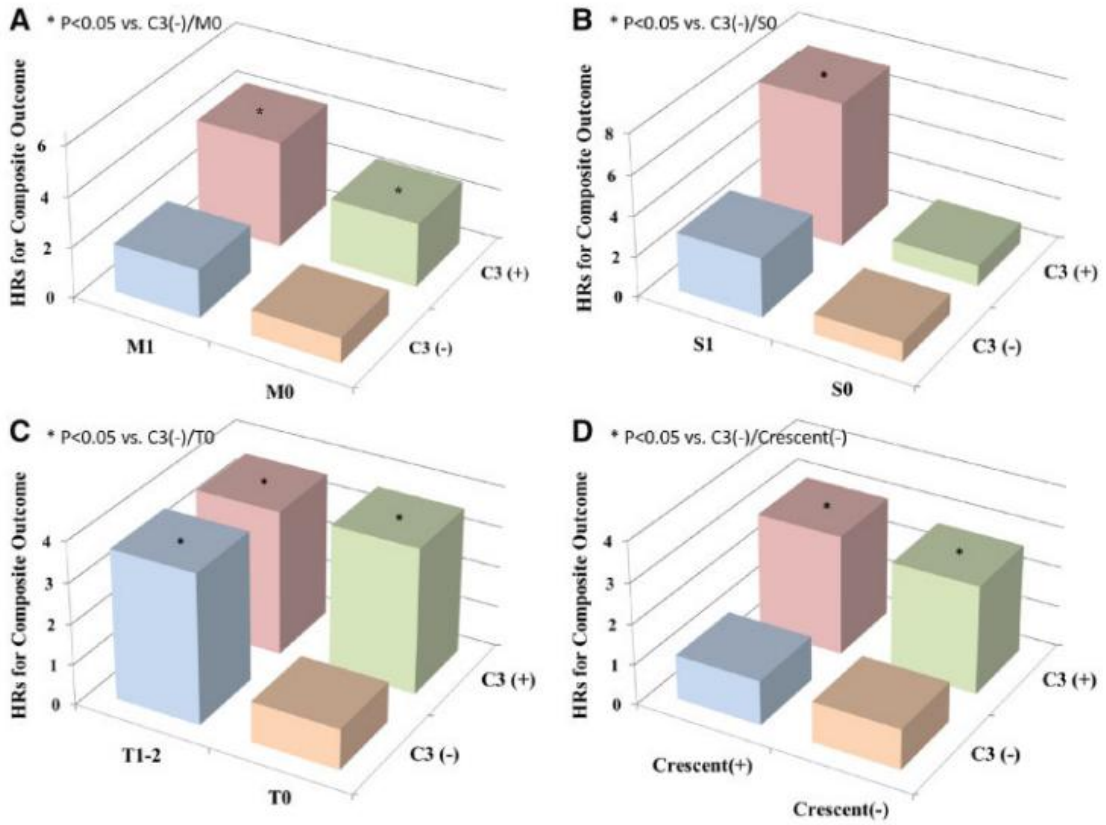
Beyond MEST-C

What Additional Features Might Refine Prognostication?

While the Oxford MEST-C classification provides a standardized framework, emerging evidence suggests additional histologic and immunohistologic features may enhance prognostic accuracy. Complement deposition patterns, glomerular injury morphology, and serial biopsy assessments offer promising avenues for risk stratification beyond the traditional scoring system.

Complement Deposition Enhances Oxford Classification





Complement deposition can strengthen the significance of the Oxford classification, and the presence of both components portends a poorer prognosis in IgA nephropathy.

Risk of adverse renal outcomes was significantly the highest in these double-positive lesions.

Park S, et al. Nephrol Dial Transplant. 2020;35(12):2103-2137.

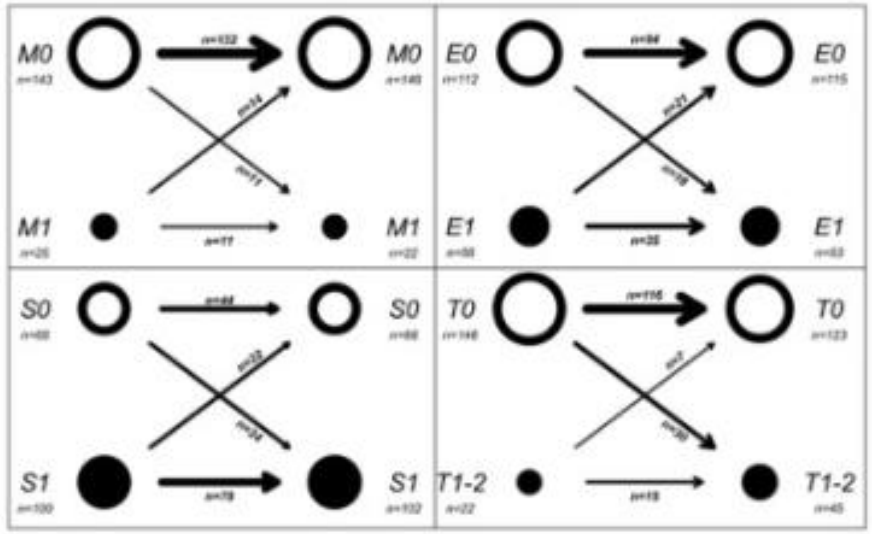
Serial Biopsies Improve ESRD Prediction

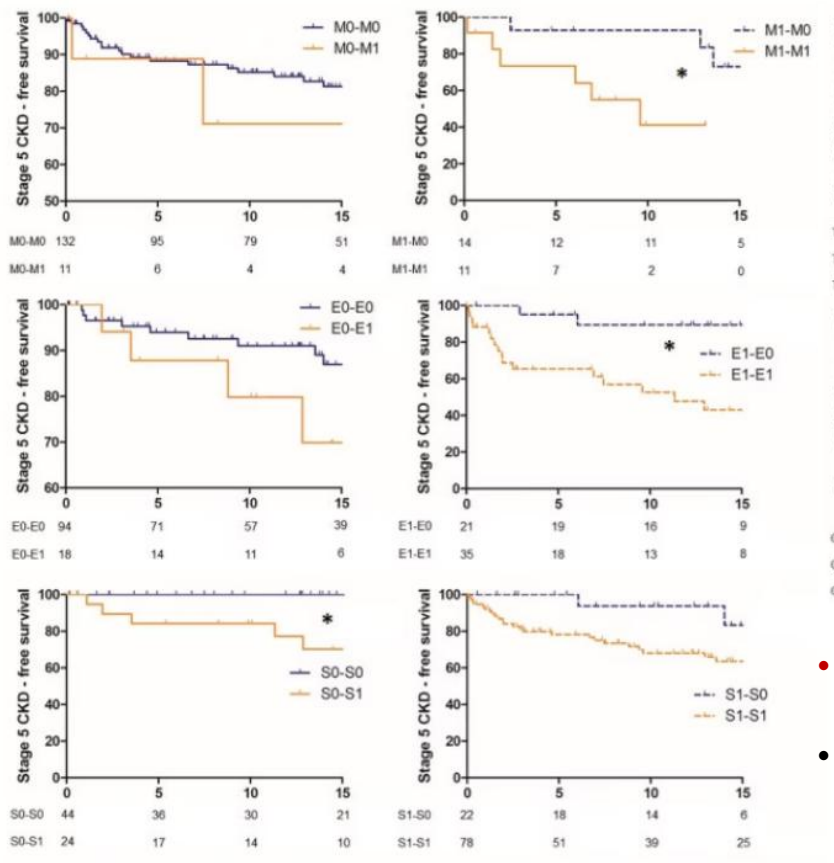
Initial Biopsy
Baseline MEST-C scoring establishes prognostic framework

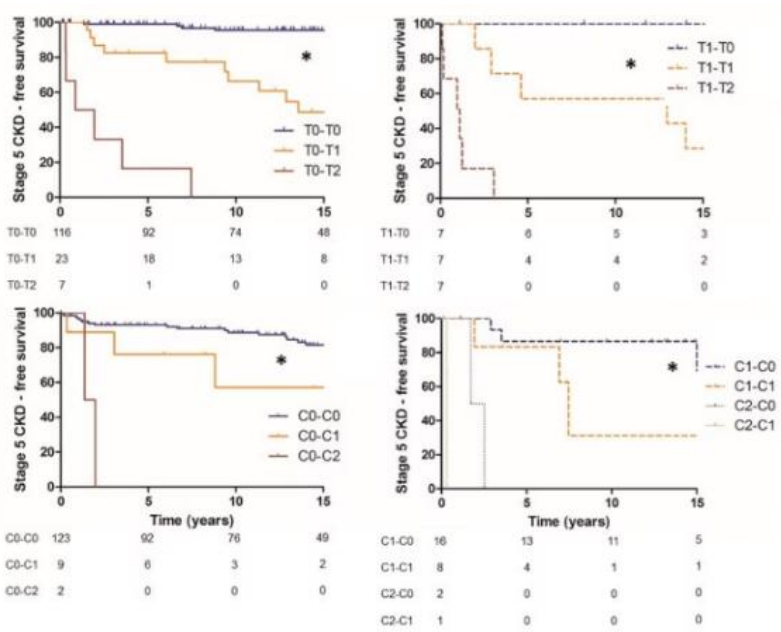
Repeat Assessment
Dynamic changes in lesion scores refine outcome prediction

Enhanced Prognosis
Serial evaluation improves accuracy of ESRD risk stratification

Item	Value/Description
Study population	168 adult patients
Median follow-up duration	18 years (range: 11–24 years)
Reason for second biopsy	Systematic (n = 112) or for-cause (n = 56)
Median time to second biopsy	5.4 years





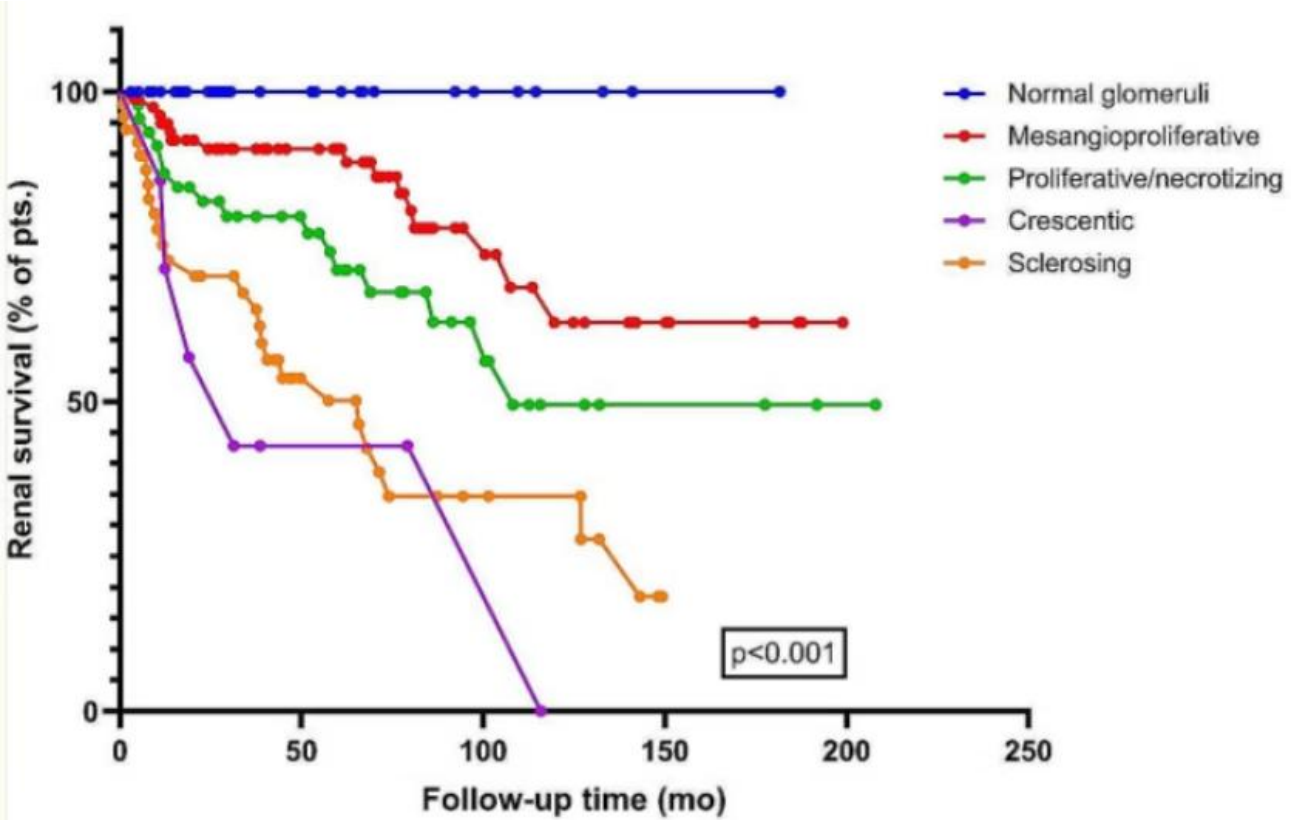


- Deterioration of the T lesions had the most pronounced impact on renal survival.
- This effect—albeit to a lesser extent—was also seen for the S and C lesions, while deterioration of M and E lesions did not significantly alter renal survival. Reversal of preexisting M, E and T lesions was associated with a better prognosis.

Jullien P, et al. Nephrol Dial Transplant. 2020;35(7):1179-1186.

Glomerular Injury Patterns and C3 Intensity Refine Risk Stratification

Oxford Classification Limitation: Reliance on T score (IFTA) does not capture severity of glomerular lesion patterns, which may better reflect disease activity and treatment responsiveness. Review the LM pattern of glomerular injury might stratify more accurately the renal outcome in patients with IgAN.



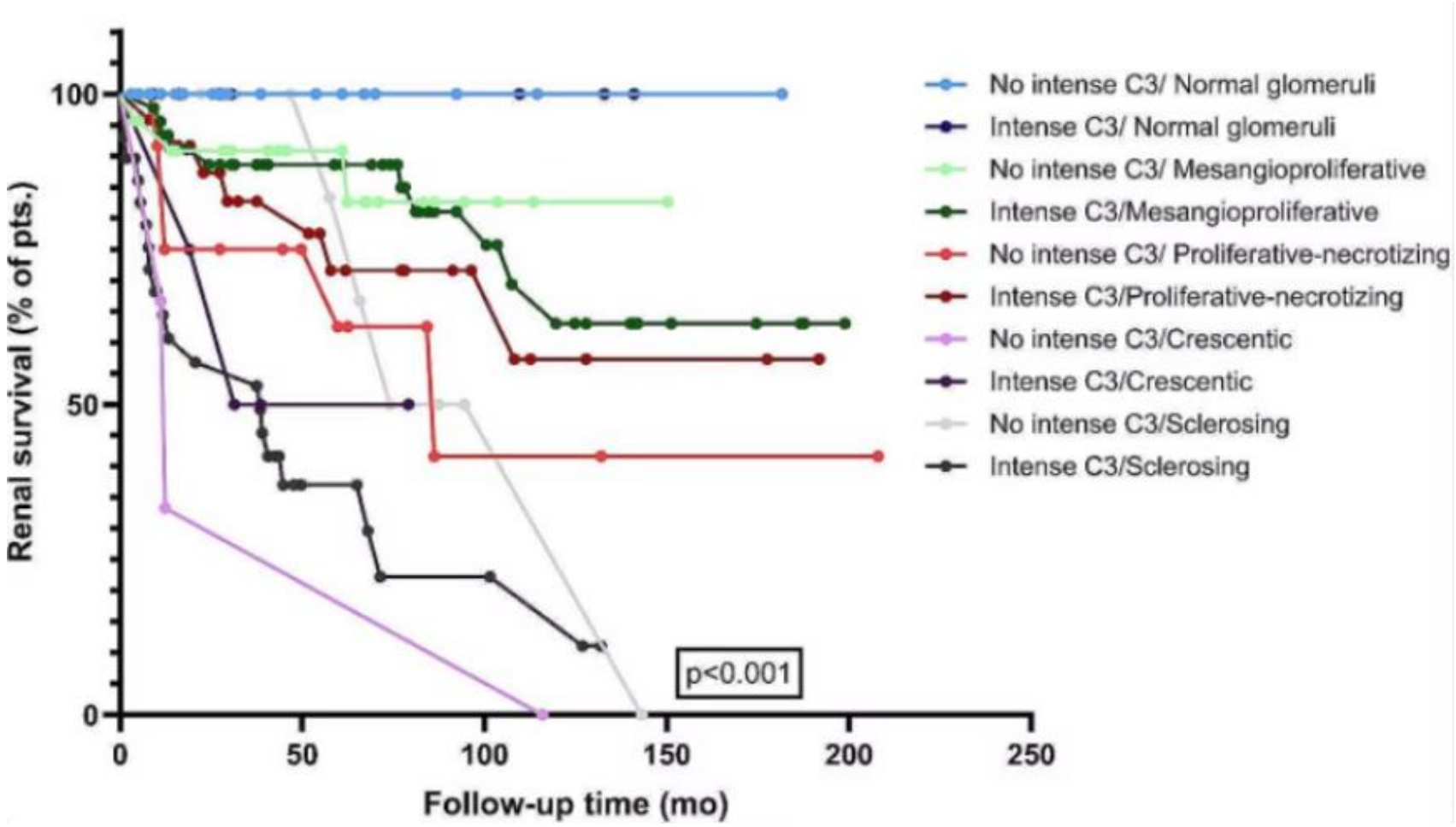
Mesangioproliferative Pattern
Resembles lupus nephritis Class II with best prognosis: 5-year renal survival >90%, eGFR decline -0.29 ml/min/year. May benefit from targeted mucosal therapy (e.g., TRF-budesonide).

Proliferative/Necrotizing Pattern
Intermediate outcomes: 5-year survival 71%, eGFR decline -0.45 ml/min/year. Steroids widely used; benefit of additional immunosuppressants remains controversial.

Crescentic Pattern
Worst prognosis: 5-year survival 43%, eGFR decline -2.32 ml/min/year. Treated similarly to ANCA-associated vasculitis but response remains poor.

Obrișcă B, et al. BMC Nephrol. 2024;25(1):145.

Glomerular Injury Patterns and C3 Intensity Refine Risk Stratification



Complement Activation Impact

Intense C3 staining associates with chronic lesions and adverse outcomes.

Patients with strong C3 staining combined with sclerosing pattern or T2 score exhibited lowest survival rates (34.5% and 23.6%)

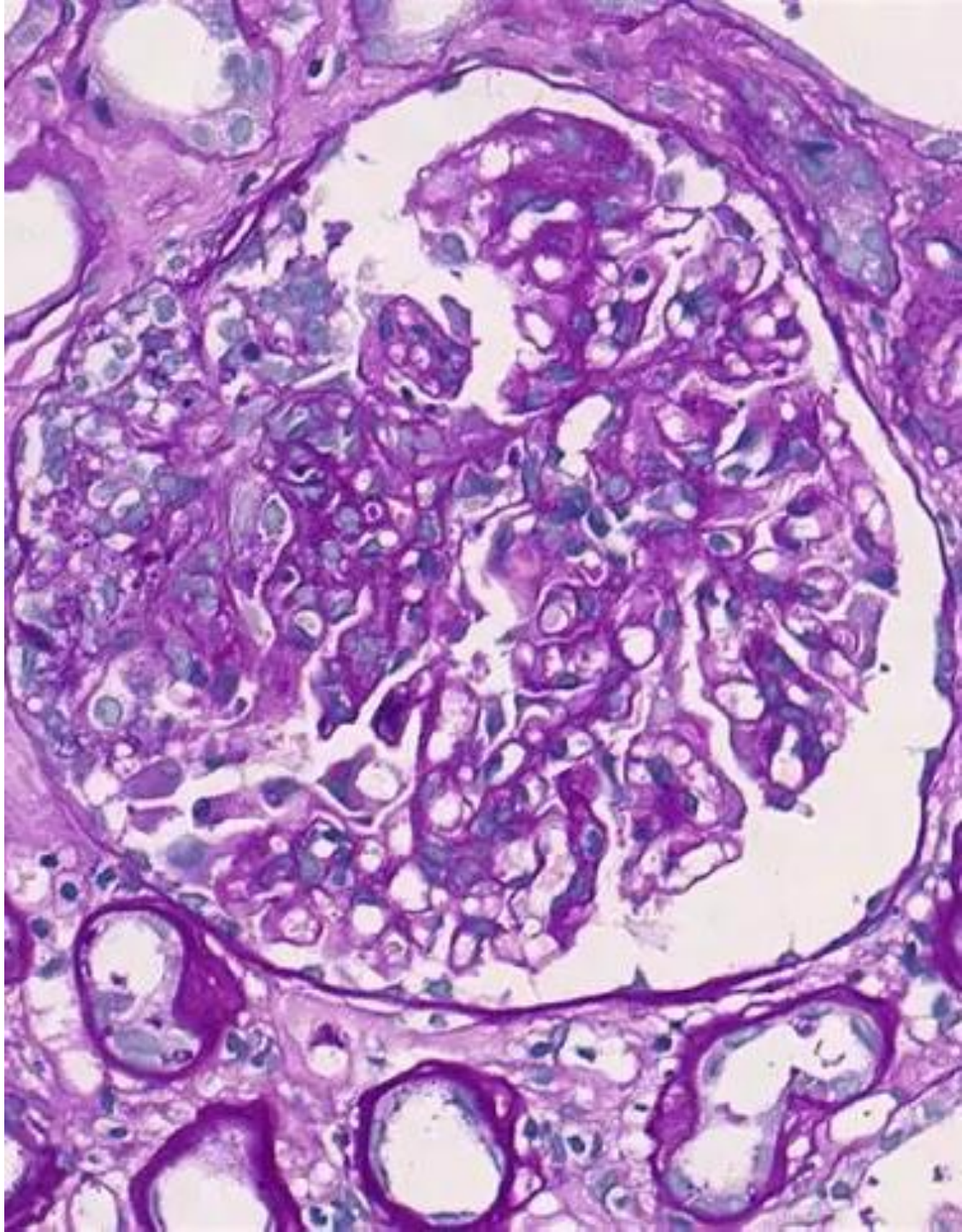
Obrișcă B, et al. BMC Nephrol. 2024;25(1):145.

From Histology to Therapy

Future Directions in IgAN Management

> Integrating detailed histopathologic assessment with immunohistologic profiling will enable precision medicine approaches, tailoring therapy to individual disease mechanisms rather than applying uniform treatment protocols.

The convergence of advanced histologic classification, complement pathway analysis, and targeted therapeutic development promises to transform IgAN management from empiric immunosuppression to mechanism-based interventions.



Potential Therapeutic Strategies Guided by Histopathology

All Patients: Foundational Care

Optimal supportive care per KDIGO guidelines including RAS blockade, blood pressure control, and lifestyle modifications.

Patients With Active Lesions: Immunosuppression

Target gd-IgA1 production or autoantibodies using corticosteroids (systemic or enteric-release budesonide) or B-cell inhibitors (APRIL, BAFF antagonists).
Address intraglomerular inflammation via complement inhibition.

Patients Without Active Lesions

Consider endothelin A antagonist to reduce proteinuria and fibrosis progression in patients with predominantly chronic changes.

Haas M. Semin Nephrol. 2024;44(5):151568.

Potential Therapeutic Strategies Guided by Histopathology

Complement-Based Stratification

Modest C3 Staining, No Lectin Path

Corticosteroid or APRIL/BAFF inhibitor monotherapy

Intense C3 Staining

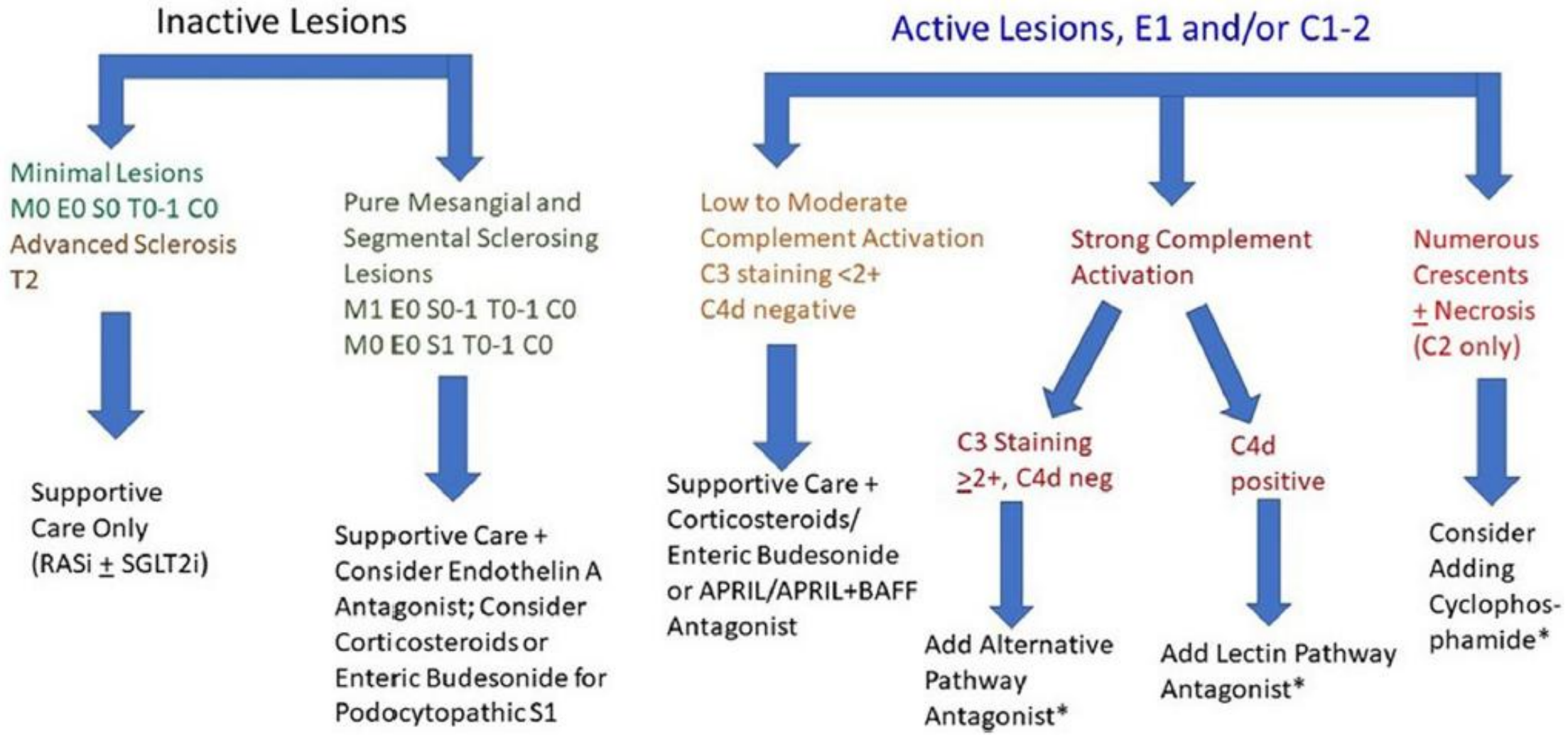
Add alternative pathway inhibitor (e.g., factor B or factor D inhibitor)

Lectin Pathway Activation

Consider lectin pathway-specific inhibitor. Complement inhibitor selection guided by IF (C3) and IHC (C4d) findings

Haas M. Semin Nephrol. 2024;44(5):151568.

Proposed Biopsy-Based Treatment Algorithm for IgA Nephropathy



Haas M. Semin Nephrol. 2024;44(5):151568.

Key Take Home Messages

1 **Pathogenetic Foundation**

Histopathologic findings link directly to IgAN pathogenesis and remain the gold standard for assessing glomerular injury severity at diagnosis. The MEST-C system provides standardized, reproducible assessment across institutions.

2 **International Validation**

Studies across diverse populations demonstrate correlation between MEST-C scores and clinical outcomes, though results show regional variation. The T score consistently emerges as the strongest predictor of progression across cohorts.

3 **Current Guideline Position**

KDIGO guidelines do not recommend using MEST-C for treatment decisions, reserving it for prognostic evaluation. Clinical parameters—particularly proteinuria—remain primary determinants of therapeutic intervention.

4 **Future Directions**

Studies incorporating detailed histopathologic assessments (complement deposition, glomerular injury patterns) or repeat biopsy protocols will clarify relationships between pathology and treatment response, enabling personalized therapeutic strategies in IgAN.


Thank You
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三軍總醫院關心您
Chia-Chao Wu M.D. Ph.D