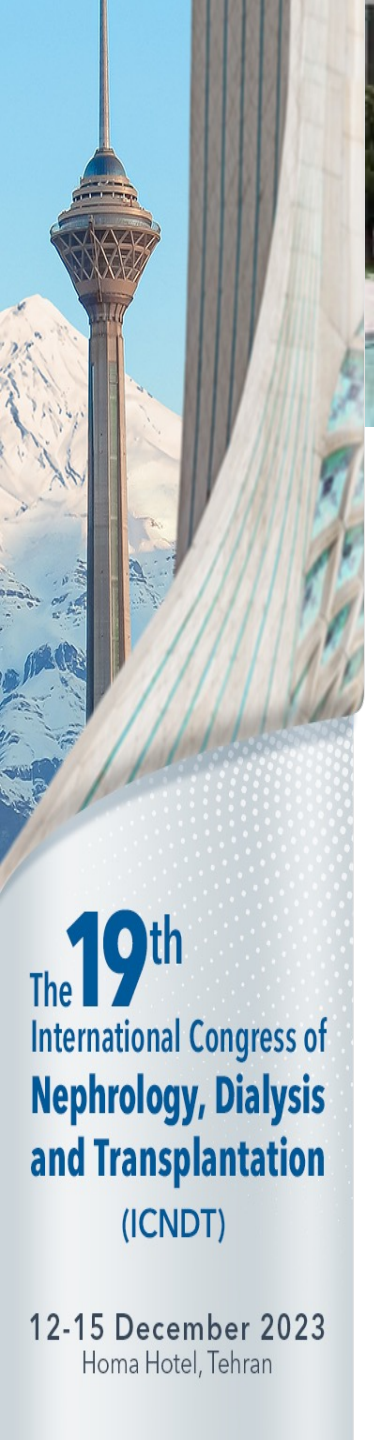

Predicting kidney function and recovery in ANCA-associated vasculitis

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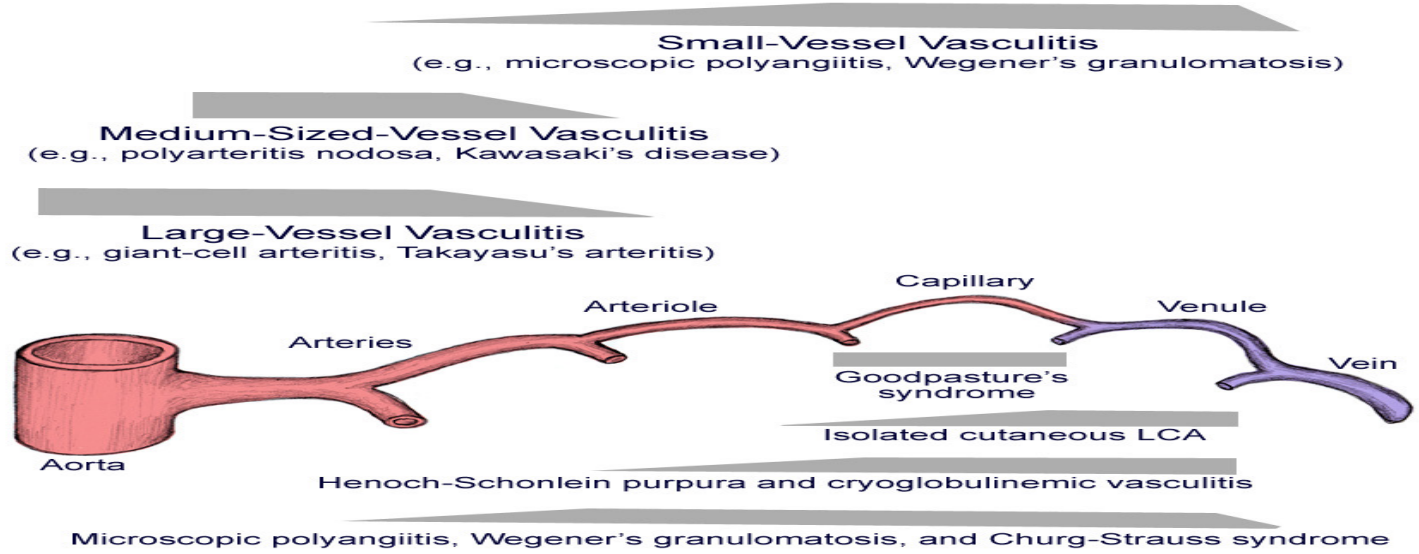
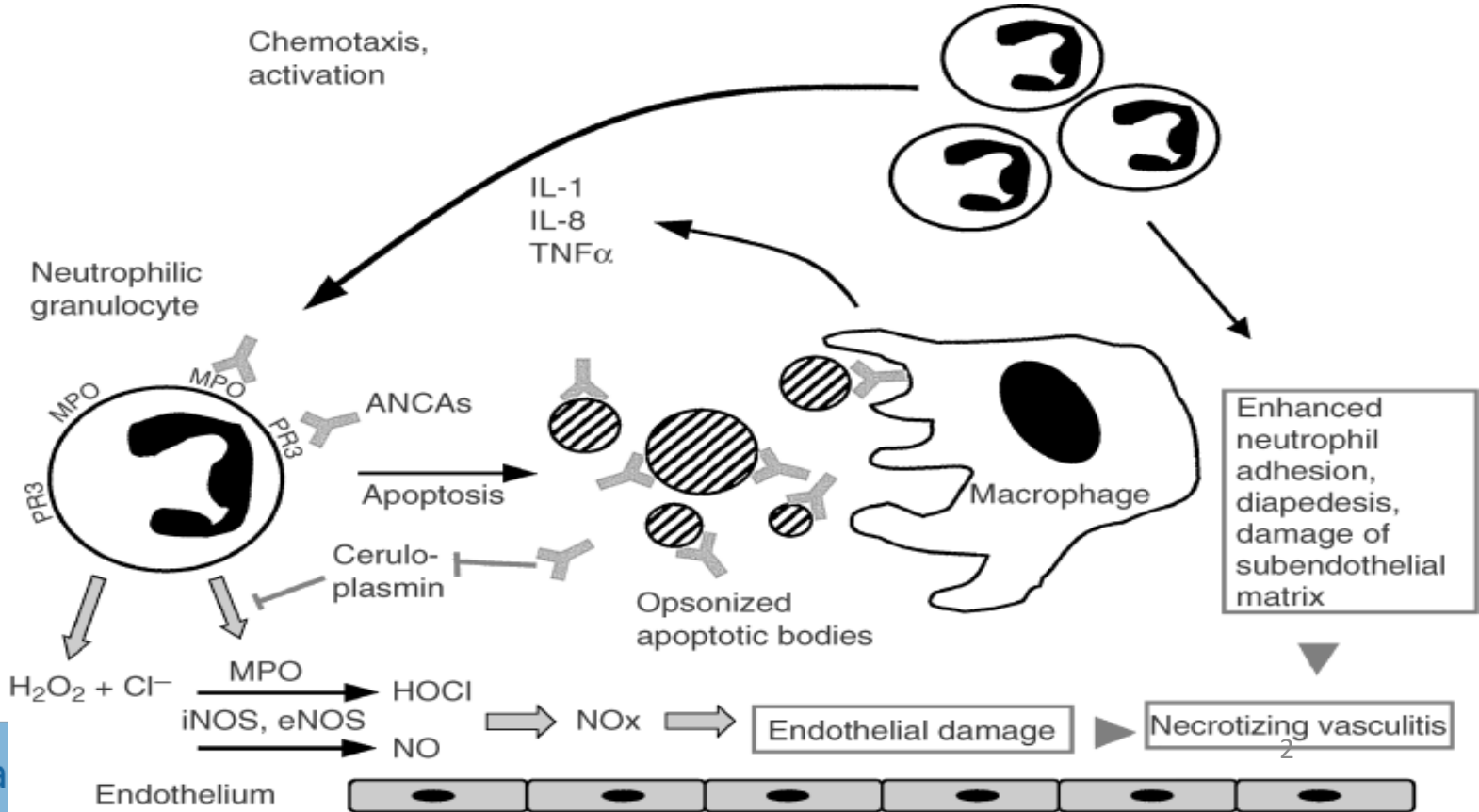
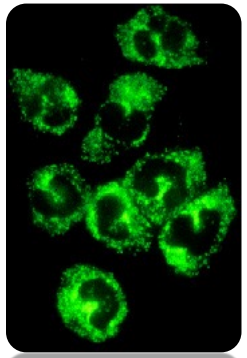
Introduction

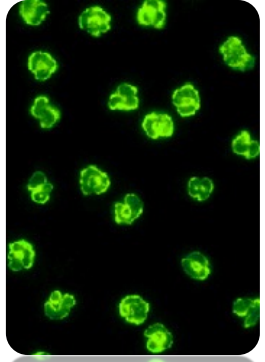
Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a rare systemic autoimmune disease affecting small to medium-sized vessels and is characterized by autoantibodies against the major target of the neutrophil proteins, leucocyte proteinase 3 (PR3) and myeloperoxidase (MPO)





Introduction





- AAV includes three clinically distinct groups:

-granulomatosis with polyangiitis (GPA),

-microscopic polyangiitis (MPA)

-and eosinophilic granulomatosis with polyangiitis (EGPA).

- There is a 2.7-fold increased all-cause mortality risk among AAV patients compared with the general population

Introduction….

- Although cardiovascular disease and infections are important contributors to premature death **, the initial presence and the severity of kidney dysfunction are the most important predictors of mortality** .
- Patients with systemic forms of MPA and GPA, characterized by multi-organ involvement, present with MPO- and PR3-ANCA and with kidney involvement in approximately 90–100% and 50–80%, respectively .
- In contrast, EGPA patients have a substantially lower rate of kidney involvement (≈25%).

Introduction

- Typically, AAV patients present with the clinical picture of rapidly progressive glomerulonephritis and face a rapid decline in kidney function, necessitating immediate therapy initiation to preserve kidney function.

- A subset of predominantly MPO-ANCA-positive patients may follow a slowly progressive course of kidney function deterioration, frequently associated with irreversible kidney lesions at their first presentation

- A tool to quantify renal response is crucial not only to assess therapeutic response, but also to provide guidance for future clinical trials.

How do we define renal response in AAV ?

WHAT IS THE CURRENT DEFINITION OF RENAL RESPONSE IN AAV AND WHAT IMPORTANT POINTS ARE MISSED?

- Stabilization of serum creatinine level and resolution of renal hematuria are considered as markers of control of kidney inflammation.

- Improving Global Outcomes (KDIGO) 2021 Clinical Practice Guideline for the Management of Glomerular Diseases defines renal remission as stable or improved estimated glomerular filtration rate (eGFR), while the presence of hematuria and proteinuria may be considered as markers of active disease or chronic parenchymal damage .

Challenges of defining renal response in ANCA-associated vasculitis: call to action? *Clinical Kidney Journal*, 2023, vol. 16, no. 6, 965–975

Time points of outcome assessment

- A 3- to 6-month assessment of disease activity is typically used to investigate the efficacy of remission-inducing agents, and this should pick up differences in the speed of action of therapeutic agents, although earlier remission has been shown to reduce long-term ESKD and mortality risks .

Challenges of defining renal response in ANCA-associated vasculitis: call to action? *Clinical Kidney Journal*, 2023, vol. 16, no. 6, 965–975

Relevance of kidney function recovery

- Baseline kidney function is an important subject when discussing outcome.

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- Importantly, **age** plays a crucial role in the prediction of kidney function recovery in those with acute presentation and recovery is more pronounced in pediatric patients and young adults .

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Challenges of defining renal response in ANCA-associated vasculitis: call to action? *Clinical Kidney Journal*, 2023, vol. 16, no. 6, 965–975

WHICH KIDNEY SURROGATE MARKERS ARE USED TO ASSESS RENAL RESPONSE IN AAV AND WHAT ARE THE LIMITATIONS?

- **creatinine and GFR**
- Although a rapid rise in serum creatinine predicts chronic kidney damage in AAV , the use of serum creatinine has limitations.

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- The estimation of GFR is more accurate since it includes other variables and should be used rather than serum creatinine alone .

- **Challenges of defining renal response in ANCA-associated vasculitis: call to action?** *Clinical Kidney Journal*, 2023, vol. 16, no. 6, 965–975

Traditional urinary markers: hematuria

- **Hematuria** is a characteristic feature of kidney involvement in AAV.
- Some observational studies have reported an association between persistent hematuria and higher risk of renal relapses or worsening of kidney function , while other authors have found no relationship with kidney function at 1 year after remission induction therapy .
- Studies using repeated kidney biopsies in the case of persistent or worsening hematuria are essential to answer these questions.
- More important information might be related to changes in the severity of hematuria [i.e. percentage of dysmorphic red blood cells (RBCs)], and additional studies in which the quantity of hematuria as part of the renal response and its association with the renal outcome are analyzed are needed.
- As essential nephrological investigations, automated (blood cell counting or urine flow cytometry) or microscopic (light, including phase contrast microscopy) evaluations can be used for urinalysis**, whereas microscopic assessment (ideally performed by a nephrologist) is essential to identify dysmorphic RBCs or RBC casts.**

- *Clinical Kidney Journal*, 2023, vol. 16, no. 6, 965–975

Traditional urinary markers: proteinuria

- According to the KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases , **persistent proteinuria** is considered as a marker of chronic kidney damage in patients with AAV.
- In patients with CKD, the **severity of proteinuria** is associated with worse renal outcome, irrespective of baseline eGFR, and is a strong predictor of ESKD .
- In AAV, the degree of proteinuria might vary on a larger scale , but observational studies have found a positive correlation between **baseline proteinuria** and renal outcome .
- However, the tubular toxicity of proteinuria might directly contribute to interstitial fibrosis and tubular atrophy , and consequently to worse renal outcome.

- **Challenges of defining renal response in ANCA-associated vasculitis: call to action?** *Clinical Kidney Journal*, 2023, vol. 16, no. 6, 965–975

Birmingham Vasculitis Activity Score (BVAS)

- The BVAS is a validated tool for assessing disease activity of various systemic vasculitis and consists of scored items divided into nine organ systems .
- The renal items include the presence of hypertension, proteinuria (>1+ assessed by urine protein spot), hematuria (≥10 RBCs/high-power field), serum creatinine divided into three groups (1.41–2.82, 2.83–5.64 and ≥5.66 mg/dl) and an increase in serum creatinine by >30% or a decrease in creatinine clearance by >25%, all related to active vasculitis.
- Nevertheless, it does not provide reliable information on the activity of the inflammatory processes at the tissue level and its use in assessing renal response might be limited in various clinical scenarios (i.e. in the setting of acute kidney injury, in the presence of chronic tissue damage or if extrarenal hematuria is present) due to its semiquantitative analysis.
- **Challenges of defining renal response in ANCA-associated vasculitis: call to action?** *Clinical Kidney Journal*, 2023, vol. 16, no. 6, 965–975

CAN THE ANCA TITER AND NEWER BLOOD AND URINE BIOMARKERS REVEAL RENAL RESPONSE IN AAV PATIENTS?

ANCA

- Although ANCA has an undisputed diagnostic value in AAV, its role as a response biomarker in the assessment of disease relapse risk is debated.
- A meta-analysis found that persistent positive or increasing ANCA levels are modestly associated with **future disease relapses** .
- Nevertheless, patients with PR3-ANCA positivity (either persistent or reappearance) treated with RTX had a higher risk of relapse while the absence of PR3-ANCA is highly associated with a relapse-free status .
- Interestingly, an increase in PR3-ANCA titer specifically predicted disease relapse in patients with baseline kidney involvement or alveolar hemorrhage .

- **Challenges of defining renal response in ANCA-associated vasculitis: call to action?** *Clinical Kidney Journal*, 2023, vol. 16, no. 6, 965–975

Novel markers: urinary sCD163 and monocyte chemoattractant protein-1 (MCP-1)

- Several promising markers, such as complement components and urinary proteins and chemokines, have been investigated in recent years .
- One of these marker molecules is urinary soluble CD163 (sCD163), a membrane protein localized on the surface of monocytes and macrophages, which was shown to be associated with the activity of renal vasculitis and also indicated renal relapse with an excellent discrimination .
- Moreover, the addition of the T cell activation marker sCD25, both in urine and serum, helped to identify patients with early renal damage, as some patients might remain undetected if urinary sCD163 is measured alone .
- Among others, monocyte chemoattractant protein-1 (MCP- 1), a potent chemotactic factor for monocytes, was shown to be a useful marker to identify kidney involvement and assess therapy response .
- . Nevertheless, these markers need further validation, especially in the setting of renal response, which first requires an understanding of their role in the development of kidney disease in AAV.

- **Challenges of defining renal response in ANCA-associated vasculitis: call to action?** *Clinical Kidney Journal*, 2023, vol. 16, no. 6, 965–975

The future of biomarker discovery in AAV

- Significant developments in biomarker discovery, such as omics- based strategies, are currently arising; nevertheless, data with a focus on AAV are yet limited.
- Proteomics approaches have identified distinct dysregulated pathways in AAV , and gene expression signatures using transcriptomics-predicted clinical outcomes are examples of the potential of 'omics' approaches , but data from well-defined clinical cohorts in AAV are currently missing.
- Cutting-edge omics-based technologies could enable a new era of biomarker discovery in AAV.

- **Challenges of defining renal response in ANCA-associated vasculitis: call to action?** *Clinical Kidney Journal*, 2023, vol. 16, no. 6, 965–975

CAN A KIDNEY TISSUE SPECIMEN PREDICT KIDNEY FUNCTION RECOVERY?

- Kidney biopsy results inform about the potential of kidney function recovery in most cases.
- Analysis of 55 patients with PR3-ANCA and 74 patients with MPO-ANCA vasculitis revealed that patients with **PR3-ANCA** vasculitis more frequently have acute lesions, i.e. a **focal** form of crescentic glomerulonephritis and glomerular necrosis, while patients with **MPO-ANCA** vasculitis present with more severe damage at the time of initial diagnosis, characterized by **diffuse** crescentic glomerulonephritis, glomerulosclerosis and interstitial fibrosis .

- **Challenges of defining renal response in ANCA-associated vasculitis: call to action?** *Clinical Kidney Journal*, 2023, vol. 16, no. 6, 965–975

CAN A KIDNEY TISSUE SPECIMEN PREDICT KIDNEY FUNCTION RECOVERY?.....

- Histopathologic prediction scores were established in recent years.
- **The Berden score** focuses on histology and incorporates the percent of normal glomeruli, the percent of crescents and the percent of glomerulosclerosis.
- Long-term prognosis is excellent in patients with a focal class, intermediate in those with either a crescentic or mixed class and worst in those with a sclerotic class.
- Notably, kidney function at baseline is similar in patients with a crescentic or sclerotic class, while marked differences are observed in terms of kidney function recovery . .
- Consequently, implementation of **protocol biopsies** might be a useful tool to determine therapy response. .
- **Brix score** and the **Mayo Clinic Chronicity Score (MCCS)** both found a value of IF/TA in prognostication.
- The Brix score incorporates the percent of normal glomeruli, percent of IF/TA and baseline eGFR and subdivides the groups into low, medium and high risk to develop kidney failure.
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- **Challenges of defining renal response in ANCA-associated vasculitis: call to action?** *Clinical Kidney Journal*, 2023, vol. 16, no. 6, 965–975

Table 2: Summary of different risk scores used to predict outcomes of patients with ANCA glomerulonephritis.

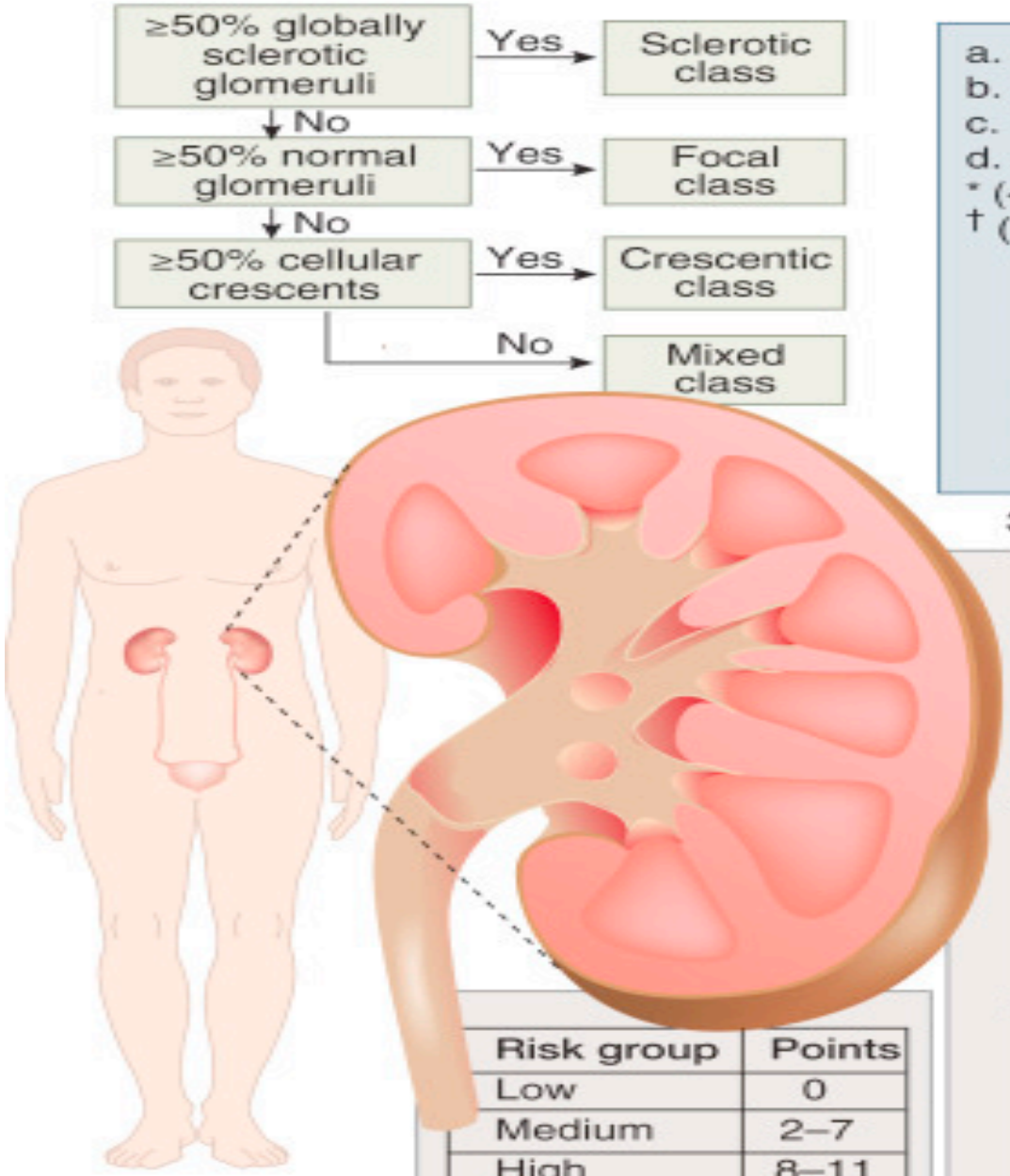
Risk groups	Score		
	Berden [73]	Brix[a] [74]	MCCS[b,c] [75]
	Focal (≥50% normal glomeruli) eGFR at presentation: 50 ± 29 ml/min/1.73 m^2 eGFR at 1 year: 61 ± 24 ml/min/1.73 m^2	Low risk (0), kidney survival at 3 years: 100%	Minimal (0–1) eGFR at baseline: 48.3 ml/min/1.73 m^2Renal recovery: 83.8%
	Crescentic (≥50% cellular crescents) eGFR at presentation: 18 ± 16 ml/min/1.73 m^2eGFR at 1 year: 37 ± 21 ml/min/1.73 m^2	Intermediate risk (2–7), kidney survival at 3 years: 96%	Mild (2–4) eGFR at baseline: 29.2 ml/min/1.73 m^2Renal recovery: 68.5%
	Mixed (<50% normal, cellular crescents, globally sclerotic, each) eGFR at presentation: 27 ± 19 ml/min/1.73 m^2eGFR at 1 year: 38 ± 21 ml/min/1.73 m^2	High risk (8–11), kidney survival at 3 years: 77%	Moderate (5–7) eGFR at baseline: 23.7 ml/min/1.73 m^2Renal recovery: 52.4%
	Sclerotic (≥50% globally sclerotic glomeruli) eGFR at presentation: 19 ± 12 ml/min/1.73 m^2eGFR at 1 year: 20 ± 16 ml/min/1.73 m^2		Severe (≥8) eGFR at baseline: 18.5 ml/min/1.73 m^2Renal recovery: 39.3%

[a]ANCA renal risk score comprises percentage of normal glomeruli [N0 (>25%, 0 points), N1 (10–25%, 4 points), N2 (<10%, 6 points)], tubular atrophy/interstitial fibrosis [T0 (≤25%, 0 points), T1 (>25%)] and kidney function at the time of diagnosis (eGFR) [G0 (>15 ml/min/1.73 m^2), G1 (≤15 ml/min/1.73 m^2)].

[b]MCCS: (a) global and segmental glomerulosclerosis; (b) tubular atrophy; (c) interstitial fibrosis (<10% = 0; 10–25% = 1; 26–50% = 2; ≥50% = 3; each category a–c), (d) arteriosclerosis (intimal thickening ≥ media thickness = 1).

[c]Definition of renal recovery: independence of kidney replacement therapy (for those in whom this therapy was initiated, as improvement of eGFR to values >30 ml/min/1.73 m^2 (if severe renal disease at diagnosis), improvement of renal function (if non-severe renal disease at diagnosis) or sustained eGFR

1. Berden classification



Risk group	Points
Low	0
Medium	2–7
High	8–11

2. Mayo Clinic/Renal Pathology Society Chronicity Score (CS)

a. Global and segmental glomerulosclerosis*
b. Tubular atrophy*
c. Interstitial fibrosis*
d. Arteriosclerosis†

* (<10% = 0, 10%–25% = 1, 26%–50% = 2, ≥50% = 3)
† (intimal thickening ≥ media thickness = 1)

Score	Points
Minimal	0–1
Mild	2–4
Moderate	5–7
Severe	≥8

3. ANCA renal risk score (ARRS)

Percentage of normal glomeruli	Points
N_0 (>25%)	0
N_1 (10%–25%)	4
N_2 (<10%)	6
Tubular atrophy and interstitial fibrosis	
T_0 (≤25%)	0
T_1 (>25%)	2
Renal function at the time of diagnosis (GFR)	
G_0 (>15 ml/min per 1.73 m^2)	0
G_1 (≤15 ml/min per 1.73 m^2)	3

- **Methods**
- Forty kidney biopsy-proved myeloperoxidase (MPO)-ANCA associated AAV patients who required dialysis at disease onset were enrolled. Relationships between laboratory and pathological characteristics and prognoses were analyzed.
- **Results**
- Twenty-five patients obtained dialysis independence within 3 months, while the other 15 patients remained dialysis dependent. No sclerotic class was identified among the 40 patients. Only two biopsies exhibited focal class diagnoses and both these patients recovered their renal function. The renal recovery rate of the 20 patients with mixed class was significantly lower than that of the 18 patients with crescentic class (40.0% vs. 83.3%, $p = 0.006$). Receiver operating characteristics (ROC) curves showed fibrous crescent+global glomerulosclerosis greater than 32.6% was a strong predictor of dialysis dependence with a sensitivity of 93.3% and specificity of 88.0%. When the percentage of fibrous crescent+global glomerulosclerosis exceeded 47.9%, dialysis independence was not possible. Correlation analysis indicated that platelet counts were negatively correlated with the percentage of fibrous crescent+global glomerulosclerosis ($R = -0.448$, $p = 0.004$). Most patients with increased platelets (84.62%) obtained renal recovery. Compared with methylprednisolone pulse therapy, plasma exchange accelerated renal recovery (29.4 ± 15.6 vs. 41.4 ± 11.7 days, $p = 0.039$).

Pathological severity determines the renal recovery for anti-myeloperoxidase antibody-associated vasculitis requiring dialysis at disease onset: a retrospective study *BMC Nephrology* **volume 20,** Article number: 287 (2019)

Conclusions

- The renal outcome of mixed class patients was worse than that of crescentic class.
- **A high proportion of fibrous crescent+global glomerulosclerosis is a predictor of dialysis dependence**.
- **Increased platelet count is associated with active and reversible renal lesions.**
- In the current study, **pathological severity** was the most important factor affecting renal outcome.

- **Pathological severity determines the renal recovery for anti-myeloperoxidase antibody-associated vasculitis requiring dialysis at disease onset: a retrospective study** *BMC Nephrology* **volume 20**, Article number: 287 (2019)

Platelet count and disease activity

- In clinical work, not all patients are able to undergo kidney biopsy, so an alternative biomarker is of great importance .
- In our study, platelet count was the only laboratory parameter which exhibited a significant difference between patients who obtained renal recovery and those who remained dialysis dependent.
- **Most importantly, platelets could activate the alternative complement pathway, which is crucial in the pathogenesis of AAV .**

- **Pathological severity determines the renal recovery for anti-myeloperoxidase antibody-associated vasculitis requiring dialysis at disease onset: a retrospective study** *BMC Nephrology* **volume 20**, Article number: 287 (2019)

Platelet count and disease activity

- The peripheral levels of platelet-derived microparticles (PMPs) were significantly associated with disease activity and the proportion of crescents in the renal specimen .
- We found platelet counts correlated with the percentages of fibrous crescent+global glomerulosclerosis.
- However, there was not a suitable cut-off value for platelet counts to predict kidney outcome.
- In addition, the diagnosis of thrombocytosis was influenced by the definition of upper normal limit of platelets.
- In our hospital, thrombocytosis was diagnosed when platelet counts were greater than 300×10^9/L.
- . **Pathological severity determines the renal recovery for anti-myeloperoxidase antibody-associated vasculitis requiring dialysis at disease onset: a retrospective study** *BMC Nephrology* **volume 20**, Article number: 287 (2019)

CRP

- CRP is a classical acute-phase protein.
- Interestingly, although there was a correlation between platelets and CRP , there was no significant difference in CRP among patients with different renal outcomes.
- One possible explanation is that CRP is more easily affected by other factors (such as potential infection) than platelets

- **Pathological severity determines the renal recovery for anti-myeloperoxidase antibody-associated vasculitis requiring dialysis at disease onset: a retrospective study** *BMC Nephrology* **volume 20**, Article number: 287 (2019)

What is the practical value of better predictors of renal response and what are the target endpoints?

- Outcome prediction can eventually lead to refinement of induction therapy.
- In patients with the potential for kidney function recovery (high percentage of cellular crescents, younger age, non-oliguric/anuric kidney function, PR3-ANCA positive) , greater immunosuppression might be initiated.
- Demographic and laboratory parameters and histology need to be assessed in a large sample with discovery and replication cohorts to estimate the value to predict eGFR in the short and long term.
- In those with a critical impairment of kidney function, the avoidance of a further decline in eGFR needs to be the target of continuous follow-up.
- Long-term maintenance strategies and eventually the addition of nephroprotective substances such as ***sodium–glucose cotransporter 2 inhibitors*** after successful induction therapy need to be considered in such cases.


CONCLUSION

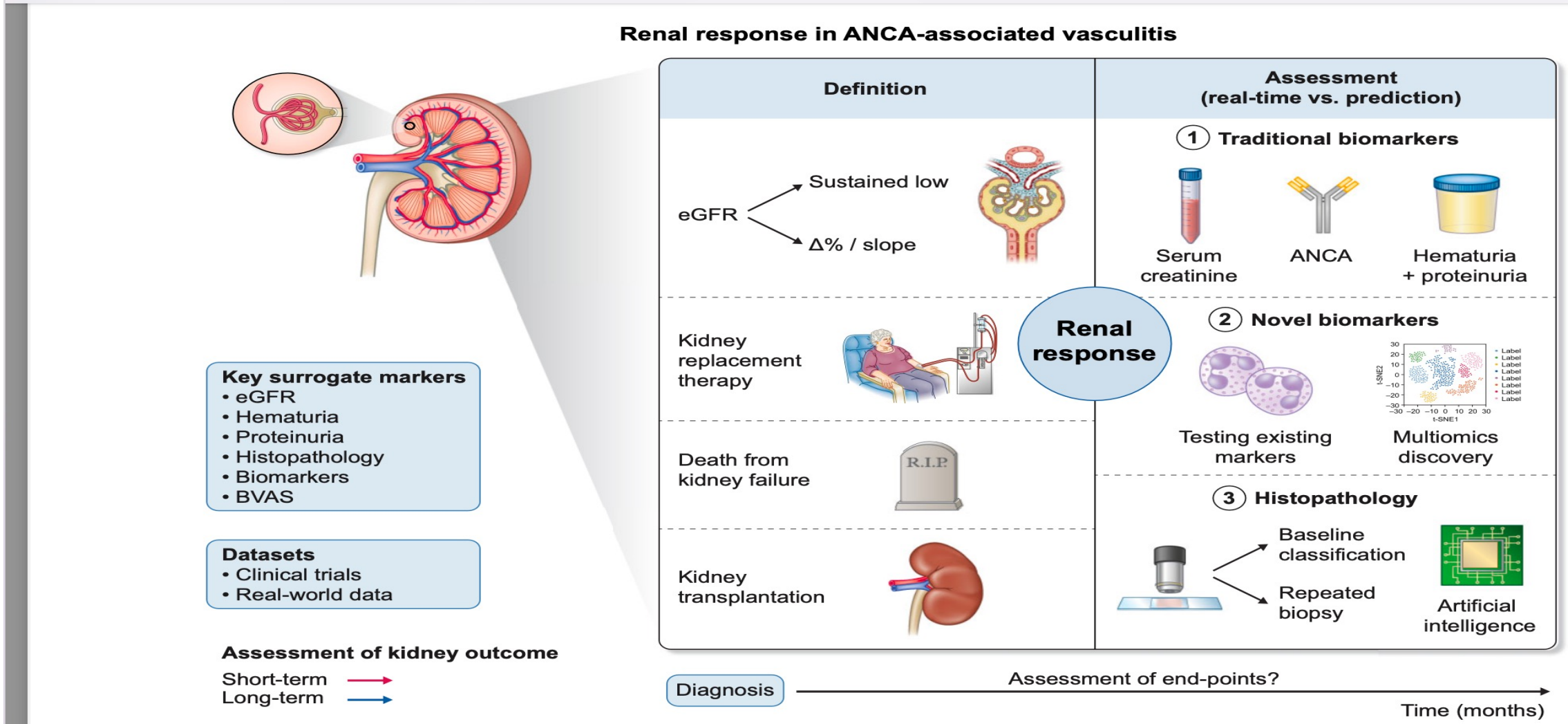


Figure 1: Definition and assessment of renal response in AAV. A schematic overview of surrogate markers of renal injury and potential renal recovery prediction, including differences in the definition ('hard' endpoints such as kidney replacement therapy or death from kidney failure) and assessment with novel and established methods).

Clinical Kidney Journal, 2023, vol. 16, no. 6, 965–975

https:/doi.org/10.1093/ckj/sfad009
Advance Access Publication Date: 11 January 2023
CKJ Review

CKJ REVIEW

Challenges of defining renal response in ANCA-associated vasculitis: call to action?

Balazs Odler[1,2], Annette Bruchfeld[3,4], Jennifer Scott[5], Duvuru Geetha[6], Mark A. Little[5], David R.W. Jayne[2] and Andreas Kronbichler[2]

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Pathological severity determines the renal recovery for anti-myeloperoxidase antibody-associated vasculitis requiring dialysis at disease onset: a retrospective study

30 July 2019

Abstract

Background

Many patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) need dialysis at disease onset due to severe kidney injury. Determining whether they can become dialysis independent is an important clinical assessment.

Methods

Forty kidney biopsy-proved myeloperoxidase (MPO)-ANCA associated AAV patients who required dialysis at disease onset were enrolled. Relationships between laboratory and pathological characteristics and prognoses were analyzed.

Results

Twenty-five patients obtained dialysis independence within 3 months, while the other 15 patients

frontiers in Medicine

BRIEF RESEARCH REPORT
published: 09 February 2021
doi: 10.3389/fmed.2020.622028

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Histopathological Findings Predict Renal Recovery in Severe ANCA-Associated Vasculitis Requiring Intensive Care Treatment

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Edited by:
Hui Y. Lan,
The Chinese University of Hong Kong, China

Reviewed by:

Renal involvement is a common and severe complication of AAV as it can cause ESRD. Histopathological subgrouping and ARRS are helpful to predict long-term ESRD in patients with AAV. Because a subgroup of critically ill patients with severe AAV present with deterioration of kidney function requiring RRT at admission, we here aimed to evaluate histopathological findings and predictive value of Berden's histopathological

Predictors of renal survival in ANCA-associated vasculitis. Validation of a histopathological classification schema and review of the literature

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ABSTRACT

Objective. *In 2010 a histopathological classification of ANCA-associated glomerulonephritis was proposed to predict the outcomes at diagnosis. Our aim was to validate the proposed classification in our cohort of patients and to compare the studies already published.*

Methods. *The data of 93 patients who underwent kidney biopsy in a single Italian centre within 15 years were retrospectively collected.*

Results. *The 10-year renal and patients' survival were 60% and 81%, respectively. Biopsies were classified as*

Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis are heterogeneous autoimmune disorders characterised by inflammatory and necrotising alterations of the vascular wall, resulting in ischaemia of the tissue (1, 2). Renal involvement is particularly frequent in these patients and is characterised clinically, by a rapidly progressive renal failure and, at renal histology, by extracapillary necrotising glomerulonephritis with few or no immune deposits (pauci-immune) on immunofluorescence and electron microscopy. ANCA-associated

The Journal of Rheumatology 2023;xx:xxxx
doi:10.3899/jrheum.220818
First Release February 1 2023

The Journal of Rheumatology

Validation of the Antineutrophil Cytoplasmic Antibody Renal Risk Score and Modification of the Score in a Chinese Cohort With a Majority of Myeloperoxidase-Positive Patients

Anqi Ni[1], Liangliang Chen[1], Lan Lan[1], Yaomin Wang[1], Pingping Ren[1], Yilin Zhu[1], Ying Xu[1], Xiaoqi Shen[1], Qin Zhou[1], Xiaohan Huang[1], Huiping Wang[1], Jianghua Chen[1], and Fei Han[1]

ABSTRACT. ***Objective.*** We aimed to validate and modify the renal risk score for antineutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis (AAGN) in a Chinese cohort with a majority of myeloperoxidase (MPO)-positive patients.

Methods. A total of 285 patients with biopsy-proven AAGN in our center were retrospectively included. Patients were randomly assigned to the development set (n = 201) and the validation set (n = 84). We calculated the renal risk score and analyzed the clinicopathological characteristics and follow-up data. The nomogram was constructed based on the independent prognostic factors identified by the multivariable Cox regression and then compared with the renal risk score.

Results. Over a median follow-up period of 41.3 (range 20.0-63.8) months, 84 (29.5%) patients reached end-stage kidney disease (ESKD). In the development set, hypertension (hazard ratio [HR] 2.16, 95% CI 1.08-4.32, $P = 0.03$), high serum creatinine (HR 1.002, 95% CI 1.001-1.003, $P < 0.001$), high daily urine protein (HR 1.34, 95% CI 1.15-1.57, $P < 0.001$), high glomerular sclerosis (HR 13.98, 95% CI 3.50-55.92, $P < 0.001$), and interstitial fibrosis > 50% (HR 4.18, 95% CI 1.90-9.19, $P < 0.001$) were independent risk factors for ESKD, and these indicators were included in the nomogram. The C-indices of the nomogram model in the development set, validation set, and all-data set were 0.838 (range 0.785-0.891), 0.794 (range 0.774-0.814), and 0.822 (range 0.775-0.869), respectively, which were higher than those of the renal risk score model, 0.801 (range 0.748-0.854), 0.746 (range 0.654-0.838) and 0.783 (range 0.736-0.830), respectively. The net reclassification improvement and the integrated discrimination improvement further

Hindawi

Clinical Study

Prognostic Factors for Survival and Relapse in ANCA-Associated Vasculitis with Renal Involvement: A Clinical Long-Term Follow-Up Study

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Received 12 July 2018; Revised 23 September 2018; Accepted 1 October 2018; Published 16 October 2018

Academic Editor: Anil K. Agarwal

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Thanks for attention

Activate Windows
Go to PC settings to activate Windows