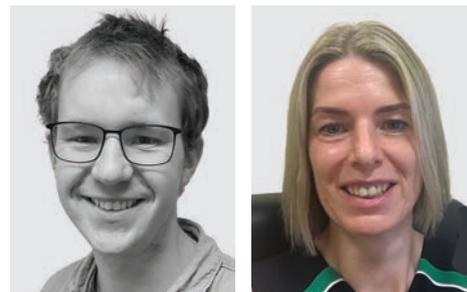


Editorial

From Prediction Tools to Precision Medicine in Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

Sebastian Bate¹  and Silke R. Brix² 



Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAVs) are multiorgan autoimmune disorders resulting in irreversible organ damage. Left untreated, AAVs are fatal, and aggressive immunosuppressive treatment has transformed them into chronic relapsing conditions. Outcomes in ANCA-associated glomerulonephritis (ANCA-GN) remain unsatisfactory, and kidney failure is too common for this rare condition. The presentation of ANCA kidney disease is heterogenous, yet a one-size-fits-all approach is still used for its treatment due to a missing disease stratification.

ANCA-GN confers significant morbidity and mortality. The severity of kidney disease has demonstrated its significance with the different stages of kidney function at presentation established as independent risk factors for mortality. Kidney failure, measured as an estimated glomerular filtration rate (eGFR) of less than 15 mL/min/1.73 m² at the time of diagnosis, confers a significantly higher risk of mortality.¹

Accurate and reliable prediction tools are needed both to inform patients and their families of prognosis and to be able to stratify patients for more efficient interventional trials in the future. Given the rarity of the condition, recruiting to these trials can be difficult and stratification by prognosis can reduce the required sample size.² Aggressive immunosuppression is the first-line treatment; however, it may not suit all patients, particularly those who are frail. A reliable risk stratification will allow

treatment to be personalized and yield better outcomes. This approach is already well established in oncology—where there are rigorous criteria for disease staging and patient fitness—and has seen vast improvements in survival over the past decades.

In this issue of *The Journal of Rheumatology*, Ni et al³ present a new nomogram model for clinical prediction in ANCA-GN. Three prediction models have already been proposed: the Berden classification⁴ based on glomerular pathology, the Mayo Clinic Chronicity Score (MCCS)⁵ based on 4 components of chronic scarring, and the ANCA Renal Risk Score (ARRS),⁶ which uses a combination of histopathologic parameters and biochemical indicators. The Berden classification used a consensus from pathologists, and the MCCS from pathologists and nephrologists, whereas the ARRS developed the scoring from a statistical analysis of a detailed clinicopathological investigation of a multi-center cohort.^{4–6} Berden and ARRS investigated European multi-center cohorts.^{4,6} The MCCS used a North American cohort and Ni et al now a Chinese single-center retrospective cohort.^{3,5}

The nomogram is similar to the ARRS as it uses the parameters percentage of normal glomeruli and creatinine (for kidney function, instead of eGFR). It incorporates interstitial fibrosis but not tubular atrophy. It adds glomerular sclerosis, hypertension, and proteinuria. Clinical variables such as ANCA antibody subtype and older age that have previously been proposed as predictive do not feature in the nomogram. Ni et al used a cohort of mainly myeloperoxidase (MPO)-positive patients and could therefore not investigate the effect of the antibody subtype.³ Histopathological studies have demonstrated the influence of the fresh fibrinoid necrosis and cellular crescents on the recovery of kidney function.^{7,8} In the current study,³ acute vasculitic lesions did not affect outcome prediction, but further lesions of chronicity were added to the tool.

So far, all models have been developed on small cohorts, both prospective and retrospective, and reflect the challenges of assembling large cohorts of patients in this rare condition. Ni et al³ used a single-center retrospective cohort of 201 patients and the prognostic ability depends on the quality of the datasets.^{9–11} The presented cohort has more women, a lower median age, and

¹S. Bate, MMath, Manchester Academic Health Science Centre, Research and Innovation, Manchester University NHS Foundation Trust, Manchester, and Centre for Biostatistics, Division of Population Health, Health Services Research, and Primary Care, University of Manchester; ²S.R. Brix, MD, Manchester Academic Health Science Centre, Research and Innovation, Manchester University NHS Foundation Trust, Manchester, Division of Cell Matrix Biology and Regenerative Medicine, School of Biological Sciences, University of Manchester, Manchester, and Renal, Transplantation and Urology Unit, Manchester University NHS Foundation Trust, Manchester, UK.

The authors declare no conflicts of interest relevant to this article.

Address correspondence Dr. S.R. Brix, Renal, Transplantation and Urology Unit, Manchester University NHS Foundation Trust, Manchester Royal Infirmary, Oxford Road, Manchester, M13 9WL, UK.
Email: silke.brix@manchester.ac.uk.

See AAV nomogram model, page xxx

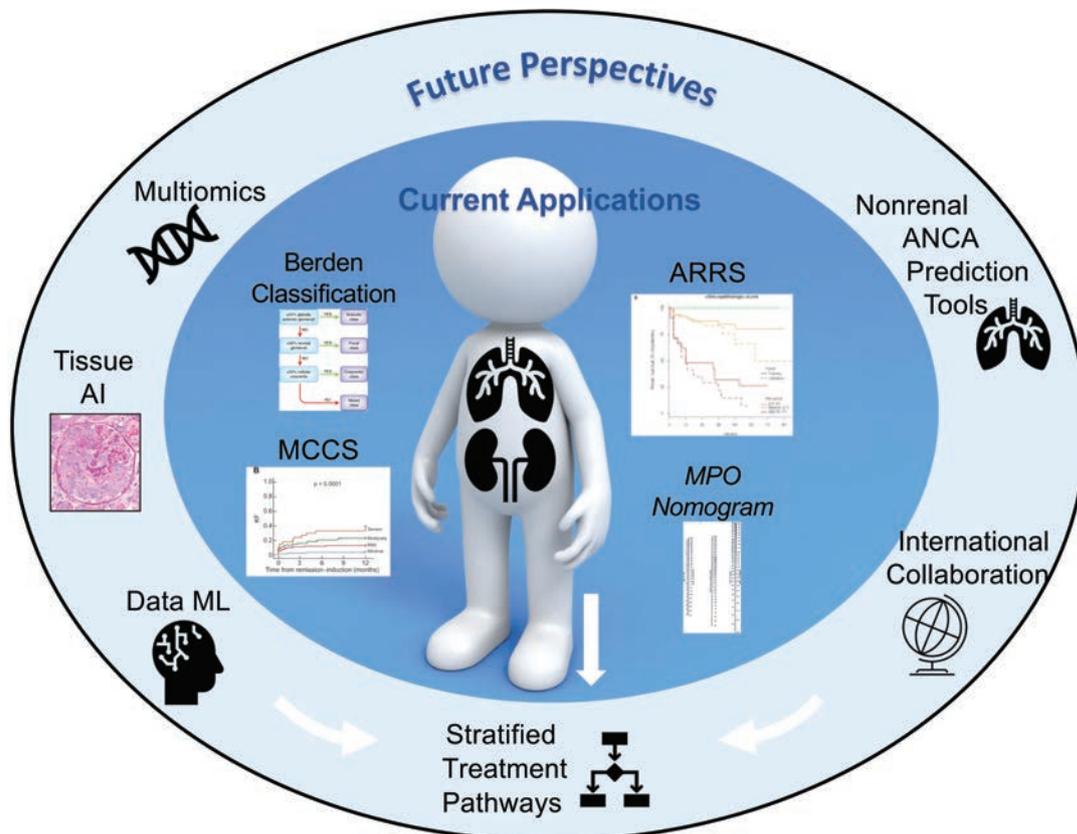


Figure. Current applications and future perspectives of precision medicine in ANCA vasculitis. Three models have been proposed to add outcome prediction in ANCA glomerulonephritis, the Berden classification, the Mayo Clinic Chronicity Score (MCCS) and the ANCA Renal Risk Score (ARRS). In this issue of *The Journal of Rheumatology*, Ni et al³ add a nomogram as a further proposal. Future perspectives lie in gathering larger validation cohorts of international collaborations to refine prediction tools. Results from multiomics analyses and artificial intelligence (AI) of tissue histology will provide in depth data beyond the current models. Prediction models of nonrenal ANCA disease will follow and ultimately integrated datasets using machine learning (ML) will allow personalized vasculitis care with stratified treatment approaches. ANCA: antineutrophil cytoplasmic antibody; MPO: myeloperoxidase.

considerably more MPO-positive patients than the ARRS development cohort, but it is comparable to 2 other Chinese cohorts that have been used in validation studies of the ARRS.^{12,13} It is yet unknown whether outcomes differ for Chinese patients after adjustment for histopathology and kidney function, the parameters used by the current models.

A common measure of model performance is the C-index, also referred to as the area under the receiver-operating characteristic curve (AUC) based on a scale 0.5 to 1 (coincidence to perfection).¹⁴ The measure used for these models is an extension, Harrell C, which is used for time-to-event studies. Ni et al³ found that, in their cohort, the ARRS retained strong discriminative ability at $C = 0.783$, and the nomogram's performance was $C = 0.822$. The nomogram uses 5 more parameters, and as the number of parameters increases, so does the risk of overfitting.

The aim is to implement the proposed tools into clinical practice, and barriers to the adoption into practice need to be considered. Van Royen et al set out the leaky pipeline that suggests reasons why a clinical prediction model may not be adopted into wider practice.¹⁵ Software is commonly developed alongside these models to aid implementation. The current nomogram would require printing to calculate the predicted kidney

survival rate. The use of readily available parameters and a certain simplicity assist in clinical implementation. Clinical prediction models ideally undergo regular updates. Critical care uses scoring systems for a multitude of conditions, and one commonly used is the Acute Physiology and Chronic Health Evaluation (APACHE) score, which itself has undergone multiple revisions.¹⁶⁻¹⁹ The revision process has ensured that the score remains clinically relevant. Further, studies are required to confirm that the model performs as expected even after widespread adoption. The ARRS has undergone multiple validations²⁰ and so has the Berden classification.²¹

The paucity of large studies has hampered efforts for more effective prognostication in ANCA-GN. Intra- and international collaborations gathering larger cohorts will improve the existing tools and derive reliable and useful tools for routine practice, ultimately improving patient outcomes. Transparency in the model formulations will allow future studies to accurately make and test predictions and not leave any room for ambiguity. The Enhancing the Quality and Transparency of Health Research (EQUATOR) network has made huge efforts to improve reporting, including the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis

or Diagnosis (TRIPOD) statement.^{22,23} TRIPOD is now a common part of any submission process for a prediction model; however, there are still improvements to be made.

The future perspective is the development of a reliable risk stratification tool in clinical practice to enable personalized vasculitis care. Ultimately, we aim to combine histopathological prediction tools with integrated patient datasets, with improved imaging and additional information using artificial intelligence analyzing histopathology. Multiomics will combine genomic data with transcriptomics, epigenetics, and proteomics, and provide an integrated perspective into the cellular and molecular signatures of the tissue inflammation in AAV. Our next immediate steps are, however, to gather large cohorts to validate the proposed tools and to use them prospectively.

REFERENCES

1. Little MA, Nightingale P, Verburgh CA, et al; European Vasculitis Study (EUVAS) Group. Early mortality in systemic vasculitis: relative contribution of adverse events and active vasculitis. *Ann Rheum Dis* 2010;69:1036-43.
2. Kernan WN, Viscoli CM, Makuch RW, Brass LM, Horwitz RI. Stratified randomization for clinical trials. *J Clin Epidemiol* 1999;52:19-26.
3. Ni A, Chen L, Lan L, et al. 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. *J Rheumatol* xxxxxxxx.
4. Berden AE, Ferrario F, Bruijn JA, et al. Histopathologic Classification of ANCA-Associated Glomerulonephritis. *J Am Soc Nephrol* 2010;21:1628-36.
5. Sethi S, D'Agati VD, Nast CC, et al. A proposal for standardized grading of chronic changes in native kidney biopsy specimens. *Kidney Int* 2017;91:787-9.
6. Brix SR, Noriega M, Tennstedt P, et al. Development and validation of a renal risk score in ANCA-associated glomerulonephritis. *Kidney Int* 2018;94:1177-88.
7. Hauer HA, Bajema IM, Van Houwelingen HC, et al; European Vasculitis Study Group (EUVAS). Determinants of outcome in ANCA-associated glomerulonephritis: a prospective clinico-histopathological analysis of 96 patients. *Kidney Int* 2002; 62:1732-42.
8. Neumann I, Kain R, Regele H, Soleiman A, Kandutsch S, Meisl FT. Histological and clinical predictors of early and late renal outcome in ANCA-associated vasculitis. *Nephrol Dial Transplant* 2005;20:96-104.
9. Riley RD, Ensor J, Snell KIE, et al. Calculating the sample size required for developing a clinical prediction model. *BMJ* 2020 Mar 18;368:m441.
10. Riley RD, Collins GS, Ensor J, et al. Minimum sample size calculations for external validation of a clinical prediction model with a time-to-event outcome. *Stat Med* 2022;41:1280-95.
11. van Smeden M, de Groot JAH, Moons KGM, et al. No rationale for 1 variable per 10 events criterion for binary logistic regression analysis. *BMC Med Res Methodol* 2016;16:163.
12. An X-N, Wei Z-N, Yao X-Y, et al. Evaluating renal outcome of ANCA-associated renal vasculitis: comparative study of two histopathological scoring systems. *Clin Exp Rheumatol* 2021;39 Suppl 129:39-45.
13. You X, Zhang J, Ding X, Zhang J, Zhou Q, Lu G. Predictors of renal outcomes in crescentic and mixed class of ANCA-associated glomerulonephritis. *Clin Nephrol* 2021;95:81-6.
14. Harrell FE Jr. Regression modeling strategies: with applications to linear models, logistic and ordinal regression, and survival analysis. Second ed. Switzerland: Springer Cham; 2015.
15. van Royen FS, Moons KGM, Geersing G-J, van Smeden M. Developing, validating, updating and judging the impact of prognostic models for respiratory diseases. *Eur Respir J* 2022;60:2200250.
16. Knaus WA, Zimmerman JE, Wagner DP, Draper EA, Lawrence DE. APACHE—acute physiology and chronic health evaluation: a physiologically based classification system. *Crit Care Med* 1981;9:591-7.
17. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: A severity of disease classification system. *Crit Care Med* 1985;13:818-29.
18. Knaus WA, Wagner DP, Draper EA, et al. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. *Chest* 1991;100:1619-36.
19. Zimmerman JE, Kramer AA, McNair DS, Malila FM. Acute Physiology and Chronic Health Evaluation (APACHE) IV: hospital mortality assessment for today's critically ill patients. *Crit Care Med* 2006;34:1297-310.
20. Xia M, Yu R, Zheng Z, et al. Meta-analytical accuracy of ANCA renal risk score for prediction of renal outcome in patients with ANCA-associated glomerulonephritis. *Front Med* 2021;8:736754.
21. Chen Y-X, Xu J, Pan X-X, et al. Histopathological classification and renal outcome in patients with antineutrophil cytoplasmic antibodies-associated renal vasculitis: a study of 186 patients and metaanalysis. *J Rheumatol* 2017;44:304-13.
22. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. *BMJ* 2015;350:g7594.
23. Moons KG, Altman DG, Reitsma JB, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. *Ann Intern Med* 2015;162:W1-73.