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Original Article

ORIGINAL ARTICLE

Long-term follow-up of IgA nephropathy: clinicopathological features and predictors of outcomes

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ABSTRACT

Background. The establishment of the Oxford classification and newly developed prediction models have improved the prognostic information for immunoglobulin A nephropathy (IgAN). Considering new treatment options, optimizing prognostic information and improving existing prediction models are favorable.

Methods. We used random forest survival analysis to select possible predictors of end-stage kidney disease among 37 candidate variables in a cohort of 232 patients with biopsy-proven IgAN retrieved from the Norwegian Kidney Biopsy Registry. The predictive value of variables with relative importance >5% was assessed using concordance statistics and the Akaike information criterion. Pearson's correlation coefficient was used to identify correlations between the selected variables.

Results. The median follow-up period was 13.7 years. An isolated analysis of histological variables identified six variables with relative importance >5%: T %, segmental glomerular sclerosis without characteristics associated with other subtypes (not otherwise specified, NOS), normal glomeruli, global sclerotic glomeruli, segmental adherence and perihilar glomerular sclerosis. When histopathological and clinical variables were combined, estimated glomerular filtration rate (eGFR), proteinuria and serum albumin were added to the list. T % showed a better prognostic value than tubular atrophy/interstitial fibrosis (T) lesions with C-indices at 0.74 and 0.67 and was highly correlated with eGFR. Analysis of the subtypes of segmental glomerulosclerosis (S) lesions revealed that NOS and perihilar glomerular sclerosis were associated with adverse outcomes.

Conclusions. Reporting T lesions as a continuous variable, normal glomeruli and subtypes of S lesions could provide clinicians with additional prognostic information and contribute to the improved performance of the Oxford classification and prognostic tools.

LAY SUMMARY

Immunoglobulin A nephropathy (IgAN) is the most prevalent glomerulonephritis and a leading cause of end-stage kidney disease (ESKD) in young adults. It has a heterogenous clinical picture, where some rapidly progress to ESKD while others experience a slight decrease in kidney functions over decades. A kidney biopsy is mandatory for the

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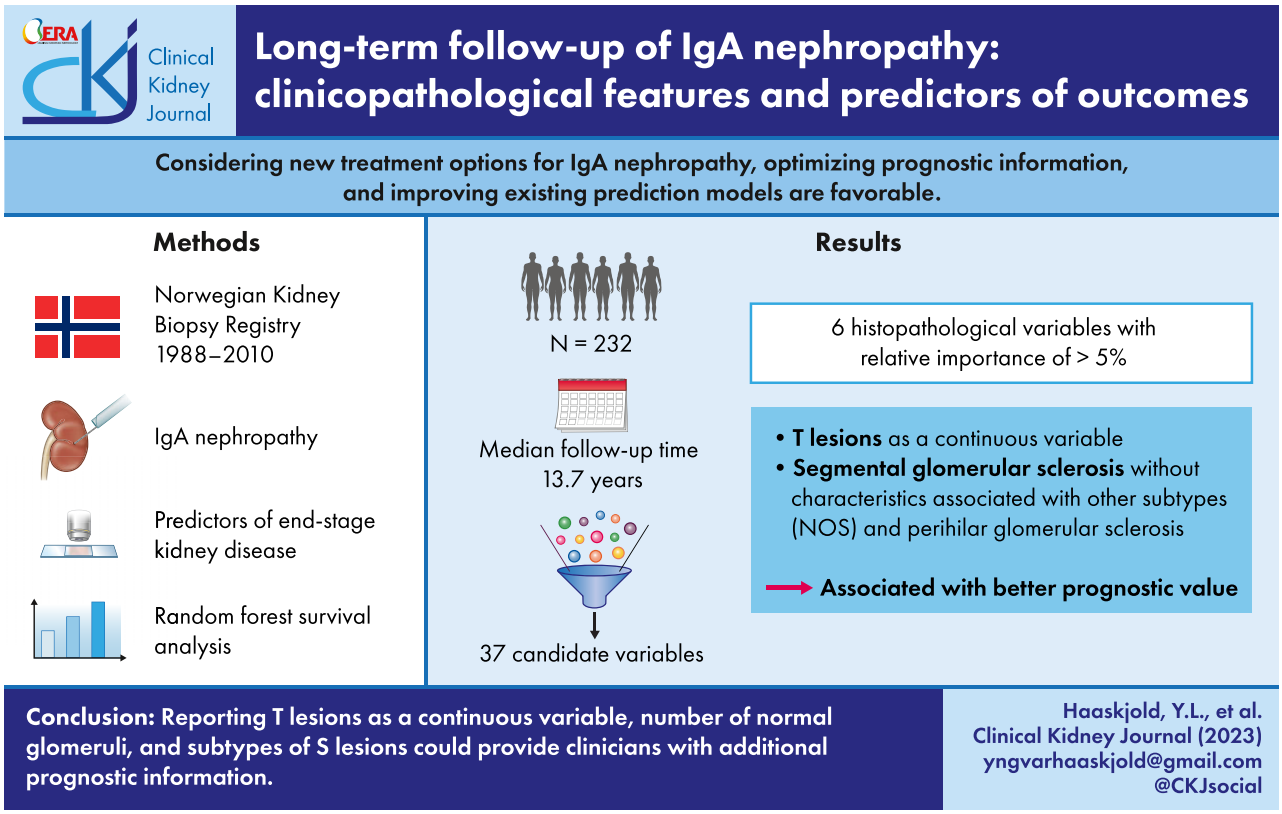
diagnosis, and several histopathological features have been associated with disease progression. Currently, limited treatment options are available, but several promising treatment studies are underway. Therefore, it is important to identify patients at risk of disease progression. We used random forest survival analysis to identify clinical and histopathological variables associated with adverse outcomes, using a cohort of 232 patients with IgAN with an assumed moderate risk. We found that reporting tubular atrophy and interstitial fibrosis as an exact continuous variable, reporting subtypes of segmental glomerular sclerosis, and the number of normal glomeruli could improve prognostic information in IgAN.

GRAPHICAL ABSTRACT



Keywords: histology, IgA nephropathy, predictors, prognosis

INTRODUCTION

The diverse clinical course of immunoglobulin A nephropathy (IgAN) complicates patient information and clinical decision-making. Several classifications and prognostic models have been developed during the last few decades; however, none has been widely accepted or put to clinical use [1]. Considering the possibilities of future therapeutics, the need for reliable prognostic tools has become pressing [2–4]. In 2009, an international group of clinicians and pathologists developed the Oxford classification system to identify mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental glomerulosclerosis (S) and tubular atrophy/interstitial fibrosis (T) as risk factors for adverse outcomes in IgAN [1, 5]. Crescents (C) were added to the original classification in 2016 [6]. The primary purpose of the Oxford classification was to design a user-friendly and reproducible biopsy reporting system that could also predict renal disease progression, help clinicians provide patients with more accurate prognostic information, and identify patients suitable for inclusion in clinical trials and those who might benefit from immunosuppressive treatment [5]. However, this classification has not been fully developed and validated as a prognostic tool, and its clinical usefulness remains debatable. A recent study suggested that the Oxford classification could be used to assess prognosis [7]; however, these findings require further validation. Maillard and Mariat reported that the possible combined scores must be examined instead of using each of the individual values from the classification when predicting prognosis and that the prognostic value of subgroups should be assessed [8]. This has been done by Itami *et al.*, who recently concluded that this classification could be used to select patients for immunosuppressive treatment [9]. Several prognostic tools that combine the Oxford classification with the clinical risk factors for disease progression have been developed [10–12]. However, only the International

IgA Prediction Tool developed by Barbour *et al.* has been sufficiently validated. The 2021 KIDGO guidelines encourage clinicians to use the International IgA Nephropathy Prediction Tool (IIGAN-PT) for patient information but not as a tool to select patients requiring immunosuppressive treatment [13]. Recently, a simulation study showed that IIGAN-PT might help clinicians select patients for treatment [14]. Furthermore, Barbour suggests that, rather than developing new prediction tools, the IIGAN-PT should be improved by updating the current parameters and considering new predictors [15]. The Oxford classification has made the biopsy reporting of IgAN more standardized and reliable. However, there could still be possible prognostic information from a renal biopsy not covered by the Oxford classification [16, 17], which might improve the prognostic value of both the classification and IIGAN-PT.

In this study, we aimed to identify the clinical and histopathological risk factors for disease progression in IgAN using a Norwegian cohort of 232 patients with a moderate risk of end-stage kidney disease (ESKD) retrieved from the Norwegian Kidney Biopsy Register (NKBR).

MATERIALS AND METHODS

Ethics

This study was approved by the Western Norway Regional Committee for Medical and Health Research Ethics (reference no. 2013/553). Informed consent was obtained from all the study participants. The research was done according to the Declaration of Helsinki.

Data collection

Patient data and biopsy specimens were retrieved from the NKBR at Haukeland University Hospital, Bergen, Norway. Follow-up data were obtained from The Norwegian Renal Registry, Rikshospitalet, Oslo, Norway, and patient records.

Study cohort

The study cohort consisted of patients >18 years with biopsy-proven IgAN and estimated glomerular filtration rate (eGFR) >30 mL/min/1.73 m^2 with biopsy specimens available for reanalysis. In patients with eGFR >60 mL/min/1.73 m^2, only patients with proteinuria >1 g/day were included, whereas patients with eGFR of 30–60 mL/min/1.73 m^2 were included irrespective of the proteinuria level. All kidney biopsies were performed before 2010. The study period was defined as the time from diagnostic kidney biopsy to ESKD or the end of follow-up in April 2020.

Histopathological studies

The original light microscopy biopsy slides, including immunohistochemistry for IgA, IgG, IgM, C3, and C1q, were retrieved from the NKBR files. Biopsies were stained with hematoxylin and eosin, periodic acid–Schiff, periodic acid–silver methenamine (Jones) and Masson trichrome. All biopsies were reviewed by an experienced renal pathologist blinded to the clinical data, and biopsies including >8 glomeruli were scored according to the Oxford classification: M, E, S, T and C. The numbers of normal and global sclerotic glomeruli and global and segmental necrotic glomeruli were also recorded. The S lesions were subtyped into the perihilar, tip, collapsing and NOS (not otherwise specified; segmental sclerosis without characteristics associated with other subtypes) variants. These characteristics were recorded as continuous variables. The occurrences of adhesions, podocyte hypertrophy, resorption droplets, hyalinosis and endocapillary foam cells were recorded. Light microscopic normal glomeruli were defined as having fewer than four cells in a mesangial area combined with the absence of other pathological findings, as included in the Oxford classification.

Statistical analysis

To identify histopathological and clinical parameters of prognostic value, we used a random forest (RF) algorithm, a machine learning (ML) algorithm that creates prognostic models based on decision trees [18]. This algorithm can identify prognostic variables in high-dimensional datasets and rank them according to importance [19]. The RF algorithm has recently been used to create risk prediction models [20], whereas others have used decision trees for variable selection before developing traditional Cox models [21]. The RF algorithm has been suggested to be suitable for prognostic IgAN modeling [22]. The variables were listed according to their absolute and relative importance. Relative importance >5% was set as the cutoff for further assessment. Variable importance is the aggregated importance of a selected variable from all decision trees and shows the impact of the variable on predicting the outcome [23]. Imputation was used in cases of missing treatment data, as excluding patients with missing data could compromise generalizability [24]. Cox regression was used for survival analysis. Comparison of prognostic value between variables was performed using concordance statistics (C-statistics) and the Akaike information criterion (AIC). A comparison C-test was performed to determine significant differences between the C-indices [25]. Potential correlations between the variables were assessed using Pearson's correlation coefficients. Cox regression analysis was used to assess the survival rates.

All statistical analyses were performed using R software (version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria) and the *randomForestSRC* package for RF statistics.

RESULTS

In total, 232 patients were included in this study; 181 (78%) were men and 62 (29.7%) developed ESKD during the study period. The median follow-up period was 13.7 years, and the median number of glomeruli in the biopsies was 11. The baseline characteristics of the patients are shown in Table 1.

A total of 37 candidate variables were assessed. All available variables are listed in Table 2. The RF analysis ranked the variables according to their importance, as shown in Fig. 1a and b. An isolated analysis of histological variables showed that six variables presented relative importance >5%: T %, S-NOS, normal glomeruli, global sclerotic glomeruli, segmental adherence and perihilar glomerular sclerosis. When histopathological and clinical variables were combined, eGFR, proteinuria and serum albumin were added to the list, whereas the importance of perihilar glomerular sclerosis was diminished. The variables are listed according to absolute and relative importance in Tables 3A and 3B, respectively.

The prognostic value of T % (0%–100%) and T lesions (T1 + T2) were demonstrated with a C-index at 0.74 [standard deviation (SD) = 0.03] and 0.67 (SD = 0.029), respectively ($P = .004$). Further, AIC was 640.5 for T %, compared with 651.9 for T lesions. This indicates that reporting the presence of T lesions could provide better prognostic information than reporting according to the Oxford classification. Furthermore, Pearson's test of

Table 1: Baseline characteristics of the study participants.

Characteristics	Cohort
Number of patients	232
Follow-up (years) all patients, median (IQR)	13.7 (6.4–17.9)
Follow-up (years) renal survival, median (IQR)	15.8 (11.1–19.6)
Age at biopsy (years), median (IQR)	37.0 (27.0–48.0)
Male sex (%)	181 (78.0)
Number of glomeruli, median (IQR)	11 (8–15)
MEST-C score[a]	
M = 1 (%)	87 (47.5)
E = 1 (%)	75 (40.9)
S = 1 (%)	149 (81.4)
T (T1 + T2)[b] = 1 (%)	27 (14.8)
Crescents	82 (44.8)
C = 1 (%)	73 (39.9)
C = 2 (%)	9 (4.9)
eGFR (mL/min/1.73 m^2), median (IQR)	66.9 (50.4–87.1)
Proteinuria (g/day), median (IQR)	2.13 (1.1–4.0)
Serum albumin (g/L), median (IQR)	39 (35–43)
Systolic blood pressure (mmHg), median (IQR)	135.0 (125.0–150.0)
Diastolic blood pressure (mmHg), median (IQR)	85 (80.0–94.2)
MAP (mmHg), median (IQR)	102,0 (93.0–112.0)
RAAS (%)	178 (76.7)
Immunosuppressants (%)[c]	45 (19.5)
Clinical outcome	
ESKD (%)	69 (29.7)

[a]A total of 183 of 232 (79%) patients with >8 glomeruli, and 49 (21%) had >5–8 glomeruli.
[b]T1 and T2 lesions merged for statistical simplicity (three patients had T2 lesions in total).
[c]Immunosuppressants at the time of biopsy or during follow-up.
IQR: interquartile range; M: mesangial hypercellularity; E: endocapillary hypercellularity; S: segmental glomerulosclerosis; T: tubular atrophy/interstitial fibrosis; MAP: mean arterial pressure; RAAS: renin–angiotensin–aldosterone system.

correlation between T % and eGFR revealed R = –0.53 [95% confidence interval (CI) −0.61 to −0.43, $P < .001$], indicating a strong correlation between the variables. This correlation is shown in a correlation plot (Fig. 2).

The analysis of S lesion subgroups revealed that S-NOS and perihilar glomerular sclerosis were associated with adverse outcomes and that reporting of perihilar glomerular sclerosis and S-NOS variants has a more substantial prognostic value than S1 lesions. This was illustrated by an assessment of the predictive value between a Cox model, which combined S-NOS and perihilar glomerular sclerosis with a Cox model based on S lesions (C-index: 0.68 vs 0.59, $P = .005$, and AIC: 676 vs 681). Correlation analysis revealed that S-NOS variants were highly associated with proteinuria [R = 0.26 (95% CI 0.14–0.38), $P < .001$]; however, no such correlation was observed in perihilar, tip, collapsing and segmental adherence variants.

Additionally, neither any other component of the Oxford classification (M, E and C lesions) nor other histopathological features (such as C3 deposits, vascular pathology and clinical features—hypertension, age and sex) proved to have a significant influence on outcome in our study.

DISCUSSION

In this study, we explored the clinical and histopathological data of a cohort with a very long follow-up period using an RF algorithm to identify several variables associated with ESKD in IgAN. We observed that the prognostic value of T lesions might improve if reported as a continuous variable rather than categorized as T0–T2 lesions and that S lesion subtypes, such as S-NOS and perihilar glomerular sclerosis, have increased prognostic value over other S lesions. Additionally, the reporting of normal glomeruli could provide valuable prognostic information. These findings support adjustments in biopsy reporting in patients with IgAN.

T lesions

The prognostic value of T lesions has been demonstrated in several studies [6] and was confirmed in this study. The original Oxford classification defines T lesions as the "percentage of the cortical area involved in tubular atrophy or interstitial fibrosis." It divides the lesions into three groups: T0 (0%–25%), T1 (26%–50%) and T2 (>50%), arguing that "this straightforward reproducible classification is widely used in clinical practice" [5]. The mean hazard ratio increased from 1.0 in T0 to 5.0 and 8.8 in the T1 and T2 groups, respectively. Furthermore, they observed that the outcomes in patients without T lesions and those with up to 25% T lesions were the same, and therefore chose to merge these two categories for statistical simplicity. We also observed that the percentage of T lesions present had a prognostic value, suggesting that the presence of T lesions <25% could be of prognostic value and that the percentage of T lesions could be used as a continuous variable in prognostic models rather than categorized as T0–T2. Notably, dichotomizing continuous variables should be avoided because they may compromise prognostic information [26]. However, whether a renal biopsy is fully representative is unclear, which supports a more general classification [27]. Furthermore, the reproducibility of T lesions among pathologists may be inaccurate if the reporting of T lesions is more detailed. Reproducibility can be improved through automated morphological analyses based on deep learning [28]. Moreover, as modern prognostic tools are available as mobile applications and online tools, clinicians can easily enter the exact percentage of T lesions if provided in the pathology report.

The association between T lesions and reduced kidney function has been described in numerous previous studies [29, 30]. We identified a strong correlation between the percentage of T lesions and eGFR, with a steady decrease in eGFR coinciding with an increase in T lesions.

S lesions

S lesions have been associated with adverse outcomes in numerous studies [6]. The Oxford classification recommends that S lesions should be scored as S0 when S lesions are absent and S1 if present. Reportedly, S lesions are associated with proteinuria, reduced eGFR and higher mean arterial pressure [5]. In our study, we observed that S lesion subtypes such as S-NOS, global sclerotic glomeruli, segmental adherence and perihilar glomerular sclerosis are associated with adverse outcomes, and that S-NOS and perihilar glomerular sclerosis have a more substantial prognostic impact than other subtypes and S lesions as a whole.

S-NOS levels are strongly correlated with proteinuria. Bellur *et al.* showed that S lesions are associated with proteinuria. In addition, podocyte hypertrophy and tip lesions were associated with an even higher level of proteinuria, suggesting that pathological podocyte findings should be reported alongside visible S lesions in an updated version of the Oxford classification [31]. However, our results do not fully support their conclusion. Neither tip lesions nor podocyte hypertrophy turned out to be valuable prognostic predictors. El Karoui *et al.* discovered that IgAN presents with findings similar to those of primary focal

Table 2: All variables available.

	Number	Variables	Variable type
Clinical variables			
	1	Age	Categorical
	2	Sex	Categorical
	3	eGFR	Continuous
	4	Proteinuria	Continuous
	5	Serum albumin	Continuous
	6	Systolic blood pressure	Continuous
	7	Diastolic blood pressure	Continuous
Glomeruli (L)			
	8	Normal glomeruli	Continuous
	9	Segmental/global necrotic glomeruli	Continuous
	10	Global necrotic glomeruli	Continuous
	11	Global sclerotic glomeruli	Continuous
Oxford classification (L)			
	12	Mesangial hypercellularity (M)	Categorical
	13	Endocapillary hypercellularity (E)	Categorical
	14	Segmental glomerulosclerosis (S)	Categorical
	15	Segmental adherence	Continuous
	16	Peripheral unspecific segmental glomerular sclerosis (NOS)[a]	Continuous
	17	Tip lesion	Continuous
	18	Perihilar	Continuous
	19	Collapsing glomeruli	Continuous
	20	Podocyte hypertrophy	Continuous
	21	Resorption droplets within podocytes	Categorical
	22	Hyalinosis	Categorical
	23	Endocapillary foam cells	Categorical
	24	Tubular atrophy/interstitial fibrosis (T)[b]	Categorical
	25	T percent (%)	Continuous
	26	Crescents (C)[c]	Categorical
Vascular damages (L)			
	27	Arteriole present	Categorical
	28	Interlobar artery present	Categorical
	29	Interlobar artery intima thickening	Categorical
	30	Arcuate artery present	Categorical
	31	Arcuate artery intima thickening	Categorical
	32	Arterial hyalinosis	Continuous
Deposits (I)			
	33	IgA deposits	Categorical
	34	IgG deposits	Categorical
	35	IgM deposits	Categorical
	36	C3 positivity	Categorical
	37	C1 positivity	Categorical

[a]Segmental sclerosis without characteristics associated with other subtypes.
[b]T lesions include T1 and T2 lesions.
[c]Crescents include C1 and C2 lesions.
L: assessed using light microscopy; I: assessed using immunohistochemistry; Ig: immunoglobulin.

segmental glomerulosclerosis (FSGS) and suggested that the Columbia classification used for primary FSGS could supplement the Oxford classification [32]. However, the prognostic value of this combination remains unclear. Yu *et al.* came to another conclusion, suggesting that S lesions be subclassified into S0, S1 and S2 because patients with <25% and >25% of S lesions have different prognoses [33].

The number of light microscopic normal glomeruli

We observed that the number of normal glomeruli had a prognostic value. This variable was considered for the 2009 Oxford classification but was omitted because of poor reproducibility [1]. However, the number of normal glomeruli has been shown to have prognostic value in the Renal Risk Score for ANCA-associated vasculitis [34], and later for anti-glomerular basement membrane disease [35] where the percentage of normal glomeruli was the only independent risk factor for ESKD in multivariate analysis [35]. Despite their prognostic value, care should be taken when including histopathological findings with low reproducibility in prediction models [36]. Nevertheless, reproducibility may improve with future diagnostic aids, such as ML.

Other histopathological findings

In our cohort, some patients exhibited a combination of mesangial and capillary IgA deposits; however, we identified no association between IgA or IgG deposits and adverse outcomes. These findings are consistent with those of a previous study by

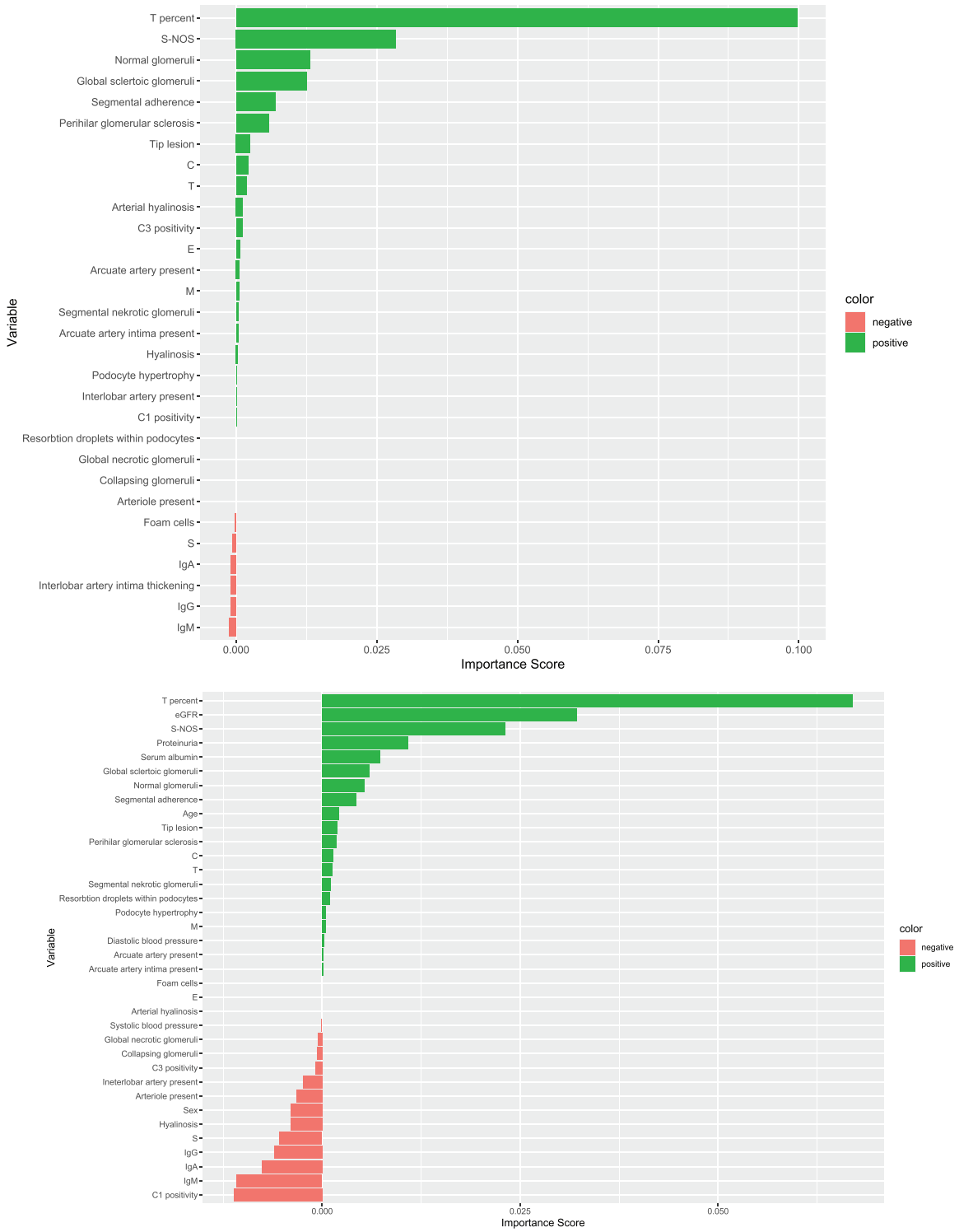


Figure 1: (**a**) All histological variables ranged after importance. (**b**) Clinical and histological variables ranged after importance.

Bellur *et al*. However, they recommended that IgA and IgG deposits should be included in the biopsy report [37]. Also in line with our findings, Turgutalp *et al*., in a recent study, discovered that neither glomerular IgG negativity nor positivity, as assessed by immunofluorescence, had prognostic value in IgAN [38]. Interestingly, we did not find C lesions to have any prognostic significance. This is consistent with the current understanding of C lesions [39]; they may be strongly influenced by immunosuppressive therapy [39]. Despite having high levels of proteinuria, relatively few patients in our study received immunosuppressive treatment. However, the course of the disease could be modified by treatment in some cases. Park *et al*. concluded that C3 deposits have an additional prognostic value in patients that presented with M, S or T lesions, suggesting that complement

Table 3A: Histological variables listed according to importance[a,b].

Variable	Absolute importance	Relative importance
T percent	**0.114**	**1.000**
Peripheral unspecific segmental glomerular lesion (NOS)	**0.026**	**0.226**
Normal glomeruli	**0.013**	**0.117**
Global sclerotic glomeruli	**0.011**	**0.097**
Segmental adherence	**0.009**	**0.079**
Perihilar glomerular sclerosis	**0.008**	**0.071**
Tip lesion	0.004	0.038
C lesion[c]	0.004	0.031
T lesions[d]	0.002	0.017
Hyalinosis	0.001	0.008

[a]Only the 10 highest-ranked variables are listed.
[b]Variables with relative variable importance >5% are marked in bold.
[c]Crescents include C1 and C2 lesions.
[d]T lesions include T1 and T2 lesions
C: crescents; T: tubular atrophy/interstitial fibrosis.

Table 3B: Clinical and histological variables listed according to importance[a,b].

Variable	Absolute importance	Relative importance
T percent	**0.077**	**1.000**
eGFR	**0.029**	**0.376**
Peripheral unspecific segmental glomerular lesion (NOS)	**0.020**	**0.254**
Proteinuria	**0.015**	**0.198**
Serum albumin	**0.012**	**0.158**
Global sclerotic glomeruli	**0.009**	**0.112**
Normal glomeruli	**0.007**	**0.093**
Segmental adherence	**0.005**	**0.068**
Age	0.003	0.040
Tip lesion	0.003	0.037

[a]Only the 10 highest-ranked variables are listed.
[b]Variables with relative variable importance >5% are marked in bold.

deposition should be included in the Oxford classification [40]. Our findings do not support their conclusion, as C3 deposits had no prognostic value in our cohort. In the original Oxford classification study, the Artery score showed good reproducibility and was initially considered for inclusion in the classification [1]. It was associated with hypertension and a decline in eGFR but not proteinuria. Furthermore, the severity of arterial lesions was not associated with decreased renal survival [5]. Wu *et al.* discovered that intrarenal arterial lesions were a common finding related to several risk factors for disease progression but did not examine the impact on renal survival [41]. In our study, vascular pathology was not identified as a risk factor for ESKD.

Clinical risk factors

We identified several clinical risk factors in our cohort, including high proteinuria and reduced eGFR. This has been demonstrated in several previous studies. Decreased serum albumin levels, which are strongly associated with proteinuria, were also associated with adverse outcomes in this cohort. Further, eGFR and proteinuria were included in the IIGAN-PT parameters. Sex did not have prognostic value and was not included as a variable

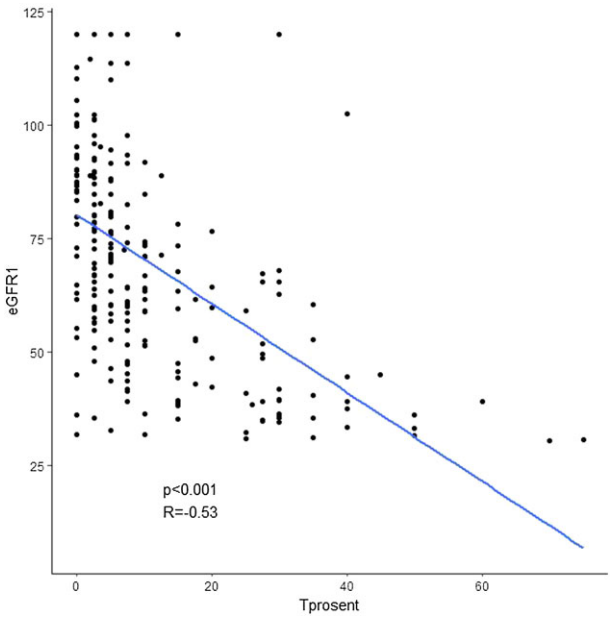


Figure 2: Correlation plot illustrating the correlation between eGFR and T %.

in IIGAN-PT [10]. However, Schena *et al.* recently developed another risk prediction tool for IgAN, the IgA Nephropathy Clinical Decision Support System, and included sex in their model [11]. The prognostic value of sex is still disputed, with some studies reporting male sex as a risk factor [42–44], while others report no differences between genders [45]. However, since sex is a factor in eGFR calculation, the prognostic value of sex in kidney disease may be difficult to assess.

Use of ML in predicting prognosis

Traditionally, the potential risk factors for disease progression have been identified using univariate and multivariate Cox regression analyses. However, these analyses may be insufficient for exploring datasets with many variables [46]. ML has become more prevalent in data exploration and the derivation of prognostic tools [47]. Chen *et al.* used a gradient tree boosting method to identify 10 of 36 candidate variables when developing a prognostic model for IgAN [21]. Conversely, Liu *et al.* used the RF technique to explore data and create a prognostic tool [48], and verified the selected prognostic values using traditional regression analyses.

The inclusion criteria were based on previous studies where we observed that in patients with assumed benign IgAN (proteinuria <1 g/day and eGFR >60 mL/min/1.73 m^2), the Oxford classification was not able to identify progressors [49], whereas in patients with more severe kidney failure (eGFR <30 mL/min/1.73 m^2), histopathological data also had limited prognostic value [50]. We, therefore, choose to include patients where risk prediction is most difficult.

This study has several limitations. First, it is a retrospective study with a relatively small cohort, although the total number of patients is similar to the original Oxford classification study. Second, this was an all-Norwegian cohort, and the findings may not be representative of other ethnic groups. Third, the biopsies were evaluated by a single highly experienced nephropathologist. Further detection of glomerular immune deposits was based on immunohistochemistry, and potential

information available from immunofluorescence was missing. Finally, more detailed treatment data would have been preferable. Nonetheless, the strengths of this study include long-term follow-up and robust endpoints.

In conclusion, we observed that reporting T lesions as a continuous variable, normal glomeruli and subtypes of S lesions could provide clinicians with valuable prognostic information and might contribute to improved performance of the Oxford classification and newly developed prognostic tools. Future research should focus on further improving the Oxford classification and prediction models for IgAN. However, it is worth noting that the importance of reproducibility and the addition of new variables could compromise user-friendliness.

CONFLICT OF INTEREST STATEMENT

T.K. is the national coordinating investigator for the Novartis LNP023X2203/APPLAUSE-IgAN trial in Norway. He has received consultancy and speaker honoraria from AstraZeneca and Vifor Pharma. Y.L.H. is the principal investigator for the Novartis LNP023X2203/APPLAUSE-IgAN trial at the Haukeland University Hospital. The other authors declare no conflicts of interest.

FUNDING

No funding was obtained for this study.

AUTHORS' CONTRIBUTIONS

Y.L.H. identified the study plot, collected clinical data, performed the statistical analysis, and drafted and approved the manuscript. N.G.L. identified the study plot, performed the statistical analysis, and drafted and approved the manuscript. R.B. identified the study plot and was responsible for the application to the ethics committee and statistical analysis, and drafted and approved the manuscript. L.S.B. drafted an application to the ethics committee, organized the database, and reviewed and approved the manuscript. T.K. was responsible for clinical data collection and statistical analysis, and drafted and approved the manuscript. L.B. identified and reclassified the biopsies, and drafted and approved the manuscript.

DATA AVAILABILITY STATEMENT

The data supporting this article cannot be shared publicly due to Norwegian regulations and the privacy of the study participants but may be shared upon reasonable request from the corresponding author if the request is accepted by the Regional Committee for Medical and Health Research Ethics and the Local Data Protection Official.

REFERENCES

1. Roberts IS, Cook HT, Troyanov S *et al*. The Oxford classification of IgA nephropathy: pathology definitions, correlations, and reproducibility. *Kidney Int* 2009;**76**:546–56. https://doi.org/10.1038/ki.2009.168
2. Selvaskandan H, Cheung CK, Muto M *et al*. New strategies and perspectives on managing IgA nephropathy. *Clin Exp Nephrol* 2019;**23**:577–88. https://doi.org/10.1007/s10157-019-01700-1
3. Floege J, Rauen T, Tang SCW. Current treatment of IgA nephropathy. *Semin Immunopathol* 2021;**43**:717–28. https://doi.org/10.1007/s00281-021-00888-3
4. Cheung CK, Rajasekaran A, Barratt J *et al*. An update on the current state of management and clinical trials for IgA nephropathy. *J Clin Med* 2021;**10**:2493. https://doi.org/10.3390/jcm10112493
5. Cattran DC, Coppo R, Cook HT *et al*. The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification. *Kidney Int* 2009;**76**:534–45. https://doi.org/10.1038/ki.2009.243
6. Trimarchi H, Barratt J, Cattran DC *et al*. Oxford Classification of IgA nephropathy 2016: an update from the IgA Nephropathy Classification Working Group. *Kidney Int* 2017;**91**:1014–21. https://doi.org/10.1016/j.kint.2017.02.003
7. Haaskjold YL, Bjørneklett R, Bostad L *et al*. Utilizing the MEST score for prognostic staging in IgA nephropathy. *BMC Nephrol* 2022;**23**:26. https://doi.org/10.1186/s12882-021-02653-y
8. Maillard N, Mariat C. The Oxford Classification for immunoglobulin A nephropathy: a common language blurred by dissonant voices. *Nephrol Dial Transplant* 2019;**34**:1617–8. https://doi.org/10.1093/ndt/gfz009
9. Itami S, Moriyama T, Miyabe Y *et al*. A novel scoring system based on Oxford classification indicating steroid therapy use for IgA nephropathy. *Kidney Int Rep* 2022;**7**:99–107. https://doi.org/10.1016/j.ekir.2021.10.007
10. Barbour SJ, Coppo R, Zhang H *et al*. Evaluating a new international risk-prediction tool in IgA nephropathy. *JAMA Intern Med* 2019;**179**:942–52. https://doi.org/10.1001/jamainternmed.2019.0600
11. Schena FP, Anelli VW, Trotta J *et al*.; Members of the VALIGA study. Development and testing of an artificial intelligence tool for predicting end-stage kidney disease in patients with immunoglobulin A nephropathy. *Kidney Int* 2021;**99**:1179–88. https://doi.org/10.1016/j.kint.2020.07.046
12. Tanaka S, Ninomiya T, Katafuchi R *et al*. Development and validation of a prediction rule using the Oxford classification in IgA nephropathy. *Clin J Am Soc Nephrol* 2013;**8**:2082–90. https://doi.org/10.2215/CJN.03480413
13. Rovin BH, Adler SG, Barratt J *et al*. Executive summary of the KDIGO 2021 Guideline for the Management of Glomerular Diseases. *Kidney Int* 2021;**100**:753–79. https://doi.org/10.1016/j.kint.2021.05.015
14. Barbour SJ, Canney M, Coppo R *et al*. Improving treatment decisions using personalized risk assessment from the International IgA Nephropathy Prediction Tool. *Kidney Int* 2020;**98**:1009–19. https://doi.org/10.1016/j.kint.2020.04.042
15. Barbour SJ, Feehally J. Predicting the future in immunoglobulin A nephropathy: a new international risk prediction tool. *Nephrol Dial Transplant* 2020;**35**:379–82. https://doi.org/10.1093/ndt/gfz181
16. Soares MFS, Roberts ISD. Histologic classification of IgA nephropathy: past, present, and future. *Semin Nephrol* 2018;**38**:477–84. https://doi.org/10.1016/j.semnephrol.2018.05.017
17. Soares MF, Roberts IS. IgA nephropathy: an update. *Curr Opin Nephrol Hypertens* 2017;**26**:165–71. https://doi.org/10.1097/MNH.0000000000000312
18. Breiman L. Random forests. *Mach Learn* 2001;**45**:5–32. https://doi.org/10.1023/A:1010933404324
19. Biau G, Scornet E. A random forest guided tour. *Test* 2016;**25**:197–227. https://doi.org/10.1007/s11749-016-0481-7
20. Scheffner I, Gietzelt M, Abeling T *et al*. Patient survival after kidney transplantation: important role of graft-sustaining

factors as determined by predictive modeling using random survival forest analysis. *Transplantation* 2020;**104**:1095–107. https://doi.org/10.1097/TP.0000000000002922
21. Chen T, Li X, Li Y *et al*. Prediction and risk stratification of kidney outcomes in IgA nephropathy. *Am J Kidney Dis* 2019;**74**:300–9. https://doi.org/10.1053/j.ajkd.2019.02.016
22. Konieczny A, Stojanowski J, Krajewska M *et al*. Machine learning in prediction of IgA nephropathy outcome: a comparative approach. *J Pers Med* 2021;**11**:312. https://doi.org/10.3390/jpm11040312
23. Zhu R, Zeng D, Kosorok MR. Reinforcement learning trees. *J Am Stat Assoc* 2015;**110**:1770–84. https://doi.org/10.1080/01621459.2015.1036994
24. van Rijn MHC, van de Luijtgaarden M, van Zuilen AD *et al*. Prognostic models for chronic kidney disease: a systematic review and external validation. *Nephrol Dial Transplant* 2021;**36**:1837–50. https://doi.org/10.1093/ndt/gfaa155
25. Kang L, Chen W, Petrick NA *et al*. Comparing two correlated C indices with right-censored survival outcome: a one-shot nonparametric approach. *Stat Med* 2015;**34**:685–703. https://doi.org/10.1002/sim.6370
26. Royston P, Altman DG, Sauerbrei W. Dichotomizing continuous predictors in multiple regression: a bad idea. *Stat Med* 2006;**25**:127–41. https://doi.org/10.1002/sim.2331
27. Corwin HL, Schwartz MM, Lewis EJ. The importance of sample size in the interpretation of the renal biopsy. *Am J Nephrol* 1988;**8**:85–9. https://doi.org/10.1159/000167563
28. Testa F, Fontana F, Pollastri F *et al*. Automated prediction of kidney failure in IgA nephropathy with deep learning from biopsy images. *Clin J Am Soc Nephrol* 2022;**17**:1316–24. https://doi.org/10.2215/CJN.01760222
29. Schelling JR. Tubular atrophy in the pathogenesis of chronic kidney disease progression. *Pediatr Nephrol* 2016;**31**:693–706. https://doi.org/10.1007/s00467-015-3169-4
30. Bunnag S, Einecke G, Reeve J *et al*. Molecular correlates of renal function in kidney transplant biopsies. *J Am Soc Nephrol* 2009;**20**:1149–60. https://doi.org/10.1681/ASN.2008080863
31. Bellur SS, Lepeytre F, Vorobyeva O *et al*. Evidence from the Oxford classification cohort supports the clinical value of subclassification of focal segmental glomerulosclerosis in IgA nephropathy. *Kidney Int* 2017;**91**:235–43. https://doi.org/10.1016/j.kint.2016.09.029
32. El Karoui K, Hill GS, Karras A *et al*. Focal segmental glomerulosclerosis plays a major role in the progression of IgA nephropathy. II. Light microscopic and clinical studies. *Kidney Int* 2011;**79**:643–54. https://doi.org/10.1038/ki.2010.460
33. Yu F, Zhu X, Yuan S *et al*. Predictive value of sub classification of focal segmental glomerular sclerosis in Oxford classification of IgA nephropathy. *Ann Med* 2021;**53**:587–95. https://doi.org/10.1080/07853890.2021.1897664
34. 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. https://doi.org/10.1016/j.kint.2018.07.020
35. Floyd L, Bate S, Kafagi A *et al*. Risk stratification to predict renal survival in anti-glomerular basement membrane disease. *J Am Soc Nephrol* 2023;**34**:505–14. https://doi.org/10.1681/ASN.2022050581
36. Bellur SS, Roberts ISD, Troyanov S *et al*. Reproducibility of the Oxford classification of immunoglobulin A nephropathy, impact of biopsy scoring on treatment allocation and clinical relevance of disagreements: evidence from the validation of IGA study cohort. *Nephrol Dial Transplant* 2019;**34**:1681–90. https://doi.org/10.1093/ndt/gfy337
37. Bellur SS, Troyanov S, Cook HT *et al*. Immunostaining findings in IgA nephropathy: correlation with histology and clinical outcome in the Oxford classification patient cohort. *Nephrol Dial Transplant* 2011;**26**:2533–6. https://doi.org/10.1093/ndt/gfq812
38. Turgutalp K, Cebeci E, Turkmen A *et al*. The relationship between glomerular IgG staining and poor prognostic findings in patients with IgA nephropathy: the data from TSN-GOLD working group. *BMC Nephrol* 2021;**22**:352. https://doi.org/10.1186/s12882-021-02560-2
39. Trimarchi H, Haas M, Coppo R. Crescents and IgA nephropathy: a delicate marriage. *J Clin Med* 2022;**11**:3569. https://doi.org/10.3390/jcm11133569
40. Park S, Kim HW, Park JT *et al*. Relationship between complement deposition and the Oxford classification score and their combined effects on renal outcome in immunoglobulin A nephropathy. *Nephrol Dial Transplant* 2020;**35**:2103–37. https://doi.org/10.1093/ndt/gfz161
41. Wu J, Chen X, Xie Y *et al*. Characteristics and risk factors of intrarenal arterial lesions in patients with IgA nephropathy. *Nephrol Dial Transplant* 2005;**20**:719–27. https://doi.org/10.1093/ndt/gfh716
42. Wen D, Tang Y, Tan L *et al*. Sex disparities in IgA nephropathy: a retrospective study in Chinese patients. *Int Urol Nephrol* 2021;**53**:315–23. https://doi.org/10.1007/s11255-020-02631-7
43. Neugarten J, Acharya A, Silbiger SR. Effect of gender on the progression of nondiabetic renal disease: a meta-analysis. *J Am Soc Nephrol* 2000;**11**:319–29. https://doi.org/10.1681/ASN.V112319
44. Goto M, Wakai K, Kawamura T *et al*. A scoring system to predict renal outcome in IgA nephropathy: a nationwide 10-year prospective cohort study. *Nephrol Dial Transplant* 2009;**24**:3068–74. https://doi.org/10.1093/ndt/gfp273
45. Cattran DC, Reich HN, Beanlands HJ *et al*. The impact of sex in primary glomerulonephritis. *Nephrol Dial Transplant* 2008;**23**:2247–53. https://doi.org/10.1093/ndt/gfm919
46. Heinze G, Wallisch C, Dunkler D. Variable selection - A review and recommendations for the practicing statistician. *Biom J* 2018;**60**:431–49. https://doi.org/10.1002/bimj.201700067
47. Bülow RD, Dimitrov D, Boor P *et al*. How will artificial intelligence and bioinformatics change our understanding of IgA nephropathy in the next decade. *Semin Immunopathol* 2021;**43**:739–52. https://doi.org/10.1007/s00281-021-00847-y
48. Liu Y, Zhang Y, Liu D *et al*. Prediction of ESRD in IgA nephropathy patients from an Asian cohort: a random forest model. *Kidney Blood Press Res* 2018;**43**:1852–64. https://doi.org/10.1159/000495818
49. Knoop T, Vikse BE, Mwakimonga A *et al*. Long-term outcome in 145 patients with assumed benign immunoglobulin A nephropathy. *Nephrol Dial Transplant* 2017;**32**:1841–50. https://doi.org/10.1093/ndt/gfx242
50. Knoop T, Vågane AM, Vikse BE *et al*. Addition of eGFR and age improves the prognostic absolute renal risk-model in 1,134 Norwegian patients with IgA nephropathy. *Am J Nephrol* 2015;**41**:210–9. https://doi.org/10.1159/000381403

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