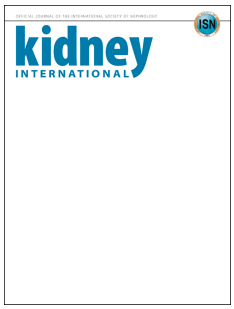

Improving treatment decisions using personalized risk assessment from the International IgA Nephropathy Prediction Tool

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Improving treatment decisions in IgA nephropathy using personalized risk assessment from the International IgA Nephropathy Prediction Tool

International IgAN cohort

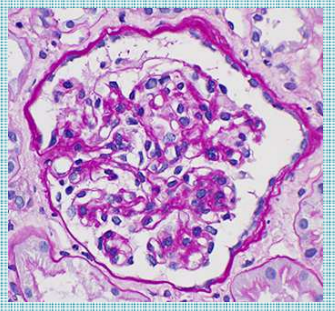
Simulated allocation of immunosuppression

Evaluated using net benefit

↑ net benefit = better treatment allocation

3,299 adults

Biopsy-proven IgAN

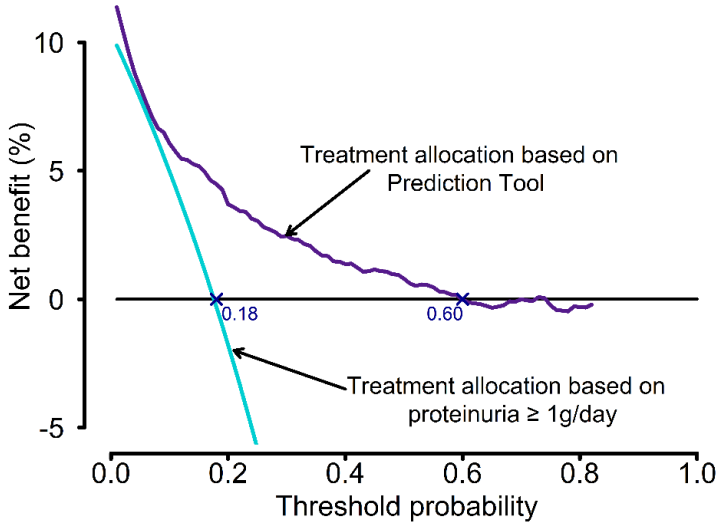


Treatment allocation based on

Predicted risk from IgAN Prediction Tool ≥ threshold probability

Proteinuria ≥1g/day

Repeated for all possible threshold probabilities between 0% and 100%



CONCLUSION:

The accuracy of any immunosuppression treatment allocation in IgAN can be substantially improved using the IgAN Prediction Tool instead of relying solely on proteinuria

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Improving treatment decisions using personalized risk assessment from the International IgA Nephropathy Prediction Tool

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Abstract

Immunosuppression in IgA nephropathy (IgAN) should be reserved for patients at high-risk of disease progression, which KDIGO guidelines determine based solely on proteinuria 1g or more/day. To investigate if treatment decisions can be more accurately accomplished using individualized risk from the International IgAN Prediction Tool, we simulated allocation of a hypothetical immunosuppression therapy in an international cohort of adults with IgAN. Two decision rules for treatment were applied based on proteinuria 1g or more/day or predicted risk from the Prediction Tool above a threshold probability. An appropriate decision was defined as immunosuppression allocated to patients experiencing the primary outcome (50% decline in eGFR or ESKD) and withheld otherwise. The net benefit and net reduction in treatment are the proportion of patients appropriately allocated to receive or withhold immunosuppression, adjusted for the harm from inappropriate decisions, calculated for all threshold probabilities from 0-100%. Of 3299 patients followed for 5.1 years, 522 (15.8%) experienced the primary outcome. Treatment allocation based solely on proteinuria oϕ 1g or more/day had a negative net benefit (was harmful) because immunosuppression was increasingly allocated to patients without progressive disease. Compared to using proteinuria, treatment allocation using the Prediction Tool had a larger net benefit up to 23.4% (95% confidence interval 21.5-25.2%) and a larger net reduction in treatment up to 35.1% (32.3-37.8%). Thus, allocation of immunosuppression to high-risk patients with IgAN can be substantially improved using the Prediction Tool compared to using proteinuria

Key words: IgA nephropathy, net benefit, decision curve, immunosuppression, renal progression, treatment allocation

Introduction

The treatment paradigm in IgA nephropathy (IgAN) is changing rapidly[1]. Based on an improved understanding of disease mechanisms, multiple novel immunosuppression therapies are currently being evaluated that target different pathways in the pathogenesis of IgAN including toll-like receptor inhibition with hydroxychloroquine, targeted-release budesonide, and inhibitors of the complement and APRIL-signaling pathways[2-6]. If found to be efficacious, clinicians will be faced with the difficult task of choosing the most appropriate therapy for each individual patient. An ideal precision-medicine approach to selecting an immunosuppression therapy would consider both the likelihood of treatment response and the risk of disease progression without treatment, weighed against the side effects of immunosuppression. Therefore, the decision to treat a patient with immunosuppression is inherently linked to the probability of experiencing disease progression to end-stage kidney disease (ESKD). A typical treatment algorithm based on the risk of disease progression is shown in Figure 1, in which there are four possible health states (A, B, C and D) that are intuitively considered by clinicians and patients each time an immunosuppression treatment decision is made[7]. Amongst patients with either extremely high or low risk disease, treatment decisions are clinically obvious and less controversial. In between these extremes, there is a point of true equipoise for each patient at which the expected benefit of immunosuppression is equal to the expected benefit of avoiding immunosuppression and around which treatment decisions have the greatest uncertainty. The challenge for clinicians and patients is to identify this point of equipoise and decide if the balance of risk versus benefit favors (or not) a decision to treat with immunosuppression.

Because an essential element of the decision-making process is an assessment of the risk of disease progression, it will be increasingly important to accurately predict this risk at the individual level and understand how this is best integrated into the allocation of treatment. The traditional approach to risk-stratification for immunosuppression treatment decisions in IgAN is based solely on proteinuria because it is the best validated clinical risk factor for disease progression[8]. The 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines suggest that patients be identified for treatment with corticosteroids based on persistent proteinuria ≥1g/day despite maximum conservative therapy[9], however this approach is not sufficiently accurate. For example, 64-74% of patients in the control groups of corticosteroid clinical trials do not experience kidney function decline over 3-5 years despite having proteinuria ≥1g/day[10-12]. Observational data suggest that 33% of patients with high-risk histology features and proteinuria <1g/day eventually experience kidney function decline, yet these patients would not have been eligible for corticosteroids because of their low-level proteinuria[11-14]. Therefore, there is clearly a need for a more accurate risk-stratification tool that can inform immunosuppression treatment decisions in IgAN. The International IgAN Prediction Tool (IIgAN-PT) was recently derived and validated as a model to predict disease progression near the time of biopsy in multiple ethnic groups worldwide using a combination of readily available clinical risk factors and the MEST-C histology score, and is available for use on-line and in the mobile-app Calculate by QxMD (https://qxmd.com/calculate-by-qxmd) [15]. However, it remains unproven whether the prediction tool can be used to improve the accuracy of immunosuppression treatment decisions in IgAN.

We hypothesized that immunosuppression can be more accurately allocated to patients with progressive disease using treatment decisions based on personalized risk from the IIgAN-PT compared to decisions based on proteinuria alone. To test this, we simulated the allocation of a hypothetical immunosuppression treatment in a large cohort of adult patients with biopsy-proven IgAN using a net benefit analysis to account for the consequences of both appropriate and inappropriate treatment decisions

Results

There were 3,299 patients who satisfied the inclusion criteria (see Supplementary Figure S1). Characteristics of the analytic cohort are shown in Table 1. The median estimated glomerular filtration rate (eGFR) at biopsy was 87ml/min/.173m^2 (interquartile range (IQR) 62-110) with proteinuria 1.2g/day (IQR 0.7-2.2). Over a median duration of follow-up of 5.1 years (IQR 3.2-8.0), the majority (81.6%) were treated with medications that block the renin-angiotensin system (RASB), and 39.5% were treated with immunosuppression. The primary outcome (50% decline in eGFR or ESKD) occurred in 522 patients (15.8%), with a 5-year risk of 12.3% (95% confidence interval (CI) 11.0-13.6%, see Supplementary Figure S2). Using the IIgAN-PT, the distribution of predicted 5-year risk of the primary outcome is shown in Supplementary Figure S3.

Allocating treatment to high-risk patients

The net benefit is the proportion of patients appropriately allocated to receive immunosuppression (Figure 1: A) penalized for the consequences from inappropriate treatment allocation (Figure 1: B and C). Figure 2A describes the net benefit for two decision rules to allocate immunosuppression, the first based on 5-year risk from the IIgAN-PT model without race/ethnicity (*ie* predicted risk ≥ threshold probability (P_t)), and the second based on proteinuria at biopsy ≥1g/day. The net benefit depends on the threshold probability, and was therefore calculated for all possible P_t between 0 and 1 (0-100%). Across the majority of P_t, treatment allocation based on the Prediction Tool model had a larger net benefit compared to using proteinuria ≥1g/day. When P_t exceeded 60%, there were so few patients with predicted risk above the threshold that treatment allocation based on the Prediction Tool became similar to an approach of treating nobody. There was no range in P_t in which treatment allocation based on proteinuria ≥1g/day had a larger net benefit compared to using the Prediction Tool. For P_t above 18%, treatment allocation based on proteinuria had a negative net benefit and was therefore potentially harmful to patients. The differences in net benefit between decision rules are shown in Figure 3 with 95% confidence intervals. For P_t above 9%, there was a significant increase in the net benefit for immunosuppression allocation using the Prediction Tool model compared to using proteinuria ≥1g/day, as demonstrated by the lower bound of the 95% CI for the difference in net benefit exceeding zero (0.9%, 95% CI 0.2-1.6%). Results were similar for the alternative IIgAN-PT model which includes race/ethnicity (see Supplementary Figures S4A and S5).

Avoiding treatment in low-risk patients

The net reduction in treatment is the proportion of patients appropriately allocated to *not* receive immunosuppression (Figure 1: D) penalized for the consequences from inappropriate treatment allocation (Figure 1: B and C), and is shown in Figure 2B for the IIgAN-PT model without race/ethnicity. For P_t above 8% the curves start to diverge demonstrating that, in this range, treatment allocation using the Prediction Tool resulted in the appropriate avoidance of immunosuppression from more low-risk patients compared to using only proteinuria ≥1g/day. Results were similar for the IIgAN-PT model with race/ethnicity (see Supplementary Figure S4B).

Applying these results to future immunosuppression therapies

To apply these results, one would need to first identify a threshold probability that is applicable to an immunosuppression treatment decision under consideration, and then proceed vertically from the x-axes in Figures 2A and 2B to determine the net benefit and net reduction in treatment that can be expected if that treatment decision was based on either proteinuria ≥1g/day or based on the Prediction Tool. A practical limitation of this approach is that for any specific type of immunosuppression being considered, the optimal P_t to use in a decision rule that allocates treatment may not be known, although it is mathematically related to all four health states outlined in Figure 1 (A, B, C and D). As discussed in the Supplementary Methods, this can be simplified to the utility ratio of harm to patients from not being treated when it could have been beneficial (*ie* health state C: consequences of preventable ESKD), to the harm caused by unnecessary treatment exposure (*ie* health state B: consequences of drug toxicity). For illustrative purposes using example threshold probabilities between 5% and 40%, Table 2 and Supplementary Table S2 demonstrate the utility ratios, their corresponding P_t, and the resulting difference in net benefit and net reduction in treatment between decision rules using the IIgAN-PT versus proteinuria ≥1g/day to allocate treatment. A higher P_t such as 40% would be appropriate for immunosuppression therapies with substantial toxicity in which the harm from disease progression to ESKD is only 1.5-fold the harm from drug exposure. Conversely, a lower P_t such as 5% would be appropriate for therapies with less side-effects in which the harm of disease progression is 19-fold higher than that from drug exposure. Figure 4 illustrates the application of our results using a threshold probability of 11% (which is the threshold probability where the lower bound of the 95% confidence interval exceeds zero in Supplementary Figure S5). All patients with proteinuria ≥1g/day would qualify for immunosuppression if treatment was allocated based on proteinuria alone, however 47% have low predicted risk below 11% and hence *would not* qualify for treatment if it was allocated using the IIgAN-PT. Conversely, patients with proteinuria <1g/day would not qualify for immunosuppression if treatment was allocated based only on proteinuria, of whom 17% have high-predicted risk (above the threshold of 11%) and therefore *would* qualify for treatment if it was allocated using the IIgAN-PT.

Sensitivity analyses

The net benefit analysis was repeated in subgroups based on immunosuppression exposure after biopsy within the analytic cohort (see Figure 5 and Supplementary Figure S6), with no change to the results. The analysis was also repeated in subgroups based on age and exposure to RASB at biopsy, again with no change to the results (see Supplementary Figure S6).

Discussion

By using a net benefit analysis to simulate the allocation of immunosuppression to a large multi-ethnic international cohort of adults with IgAN, our results demonstrate the potential improvement in immunosuppression treatment decisions that are anticipated to result from using personalized risk assessment from the IIgAN-PT instead of using proteinuria ≥1g/day. This was achieved by both increasing treatment allocation to patients at high-risk of disease progression and avoiding treatment in patients with non-progressive disease. As new therapies become available in IgAN, these findings illustrate the benefit of developing drug-specific, precision-medicine approaches to immunosuppression treatment decisions that are based on individualized risk assessment rather than continuing to rely exclusively on a proteinuria threshold.

Our results provide an important framework for the future development of personalized treatment approaches specific to each type of immunosuppression. With the recent acceptance by drug approval agencies of proteinuria as a surrogate outcome measure in IgAN[16], an increasing number of clinical trials are investigating novel therapeutic agents targeting different pathways in the intestinal and systemic immune systems[17]. As the repertoire of immunosuppression therapies increases in IgAN, clinicians and patients will benefit from precision-based methods of selecting the most appropriate treatment option. In order for this to be accomplished in the context of the decision algorithm in Figure 1, drug-specific threshold probabilities will need to be determined so that treatment decisions can be made at the individual-patient level. This will require comprehensive clinical trial data for each of the four identified health states (A, B, C and D), which include the efficacy of treatment, the risk of adverse events, and the impact on quality of life both while on immunosuppression and during the subsequent disease trajectory. This may also require understanding patient-level perspectives on quality of life in each of these health states, which may differ between individuals. Because the threshold at which these risks and benefits are balanced could vary among individual patients, we calculated the net benefit across the full spectrum of threshold probabilities. As shown in Table 2, as threshold probabilities increase from 5% to 40%, treatment allocation based on the IIgAN-PT compared to proteinuria results in a larger net reduction in treatment (up to 35%) than it does an improvement in net benefit (up to 23%). This suggests that for novel immunosuppression therapies with more side-effects that have higher threshold probabilities, the main impact on patient care from precision-based treatment decisions using the Prediction Tool will be better identification of lower-risk patients in whom treatment can be avoided. This may also be relevant to the current use of high-dose corticosteroids, which were associated with a substantial 15-35% absolute risk of serious adverse events in the TESTING and STOP-IgAN trials[13, 18]. Drug-specific health utility data from clinical trials will be needed to determine which type of therapies with significant side-effects are an acceptable

tradeoff for patients given that progression of IgAN results in ESKD, which is associated with a severely reduced quality of life[19].

Our analysis provides insight into the advantages of using the full complement of clinical and histologic predictor variables to inform therapeutic decisions in IgAN. Treatment allocation based on proteinuria at biopsy ≥1g/day had a negative net benefit and hence was potentially harmful to patients for threshold probabilities above 18%. This is because the 5-year risk of the primary outcome in our cohort amongst those with proteinuria at biopsy ≥1g/day was only 18% (95% CI 16-20%), indicating that most patients (82%) who would qualify for immunosuppression based on proteinuria alone did not experience disease progression and so would be considered inappropriately exposed to treatment. Compared to using proteinuria alone, the Prediction Tool provided a significant increase in net benefit and net reduction in treatment for threshold probabilities above 8-11%. This improvement in treatment allocation is due to the prediction benefit that results from considering other variables in the model in addition to proteinuria. These include eGFR, blood pressure, age, MEST histology scores, medication use and race/ethnicity, which are supported by multiple cohort studies that have demonstrated these risk factors are associated with disease progression independent of proteinuria[14, 20-23]. As the Prediction Tool is updated in the future to include novel predictor variables such as biomarkers or histology characteristics, the impact on the net benefit and treatment allocation will need to be re-evaluated. Importantly, there was no threshold probability at which proteinuria was superior to the IIgAN-PT. This suggests that the Prediction Tool models can be used to develop drug-specific precision-based treatment algorithms for future immunosuppression therapies that span the full spectrum of efficacy versus toxicity.

Treatment decisions in IgAN are often challenging. Similar to many other conditions, there is currently insufficient data in IgAN to accurately capture the different health states depicted in Figure 1. The net benefit construct was developed by Vickers in 2006 to specifically address this problem[7]. By starting with the concept and properties of a threshold probability, and repeating the analysis over all possible threshold probabilities, the net benefit analysis accounts for all combinations of risk versus benefit that may be applicable to any particular treatment decision, and thus does not require explicit quality of life data for each potential health state[7]. The interpretation of the results in IgAN can be considered in the context of a shared decision-making process to allocate a future hypothetical immunosuppression therapy. The physician and patient would collectively discuss the risks and benefits of the treatment under consideration and the impact on quality of life, identify an appropriate threshold probability, and proceed vertically from the x-axis in Figure 2 to identify the improvement in net benefit that can be expected if the treatment was allocated using the IIgAN-PT instead of proteinuria ≥1g/day[24]. Less effective treatments may have a higher threshold probability so that only the highest-risk patients are allocated to receive a potentially less beneficial therapy. This process is potentially cumbersome and prone to inaccuracies in the quantification of patient-perceived quality of life in different clinical scenarios. As such, our results are better interpreted as a demonstration of the *potential* benefits that can be achieved from personalized risk-based treatment decisions using the Prediction Tool as compared to continuing to rely solely on proteinuria ≥1g/day, as is currently standard of care. In this way, the net

benefit analysis is fundamentally a statistical tool to evaluate the performance characteristics of a prediction model, similar to a C-statistic, Akaike Information Criterion, or calibration curve[24]. However, it is unique in that the interpretation of the results can be considered in the context of a treatment decision. It is important to note that this decision is based on the allocation of a hypothetical immunosuppression therapy external to the analytic cohort, and does not relate to the actual exposure to any treatment that may have occurred to patients within the dataset. In our analysis, immunosuppression during follow-up was used in 39.5% of patients. This is common in prediction modeling studies, including many that have used a net benefit analysis to assess prediction models in cohorts exposed to some type of treatment during follow-up that itself can alter the risk of the primary outcome[25-31]. To investigate the implications of treatment used within the analytic dataset on the accuracy of the Prediction Tool, and therefore on the net benefit results, the analysis was repeated in subgroups based on immunosuppression exposure (Figure 5). Because the decision curves were very similar in the two subgroups, any exposure to treatment within the analytic dataset did not impact the primary conclusion that allocation of a new hypothetical immunosuppression therapy can be improved using personalized risk from the Prediction Tool as compared to relying solely on proteinuria.

There are several limitations to our study. Because the IIgAN-PT was designed to predict risk at the time of biopsy, the current results have a similar time constraint. This is not an unreasonable assumption given the median time from biopsy to immunosuppression treatment in the analytic cohort was only 1.3 months (IQR 0-4.9), suggesting that treatment decisions near the time of biopsy are common in patients with IgAN. In addition, the ability to make treatment decisions earlier in the disease course without longer periods of observation offers the opportunity to intervene before the onset of irreversible tissue damage. The IIgAN-PT was developed in a mostly Caucasian, Japanese and Chinese cohort to predict the risk of disease progression between 5 and 7 years after biopsy. As such, treatment allocation based on the Prediction Tool may not account for disease progression over a longer time horizon or in patients from other ethnic groups without further validation. The development of any future personalized treatment approach in IgAN that incorporates the IIgAN-PT should not replace clinical decision making and should instead complement a shared decision between physicians and patients. Immunosuppression treatment decisions should be ideally based on proteinuria ≥1g/day after a period of optimized conservative care that includes RASB[9]. In our analysis proteinuria was assessed at the time of biopsy, at which point RASB was used in only 31.9% of patients and drug dosing and duration was not known. As such we were not able to assess if conservative care had been optimized. However, we repeated our analysis in the subgroup of patients on RASB at biopsy with no change in the results.

In conclusion, we have shown that the accuracy of allocating immunosuppression treatment can be substantially improved by using the IIgAN-PT compared to the traditional approach based on proteinuria alone. This improvement is achieved by increasing the identification of both high-risk patients that can be considered for treatment and low-risk patients in whom immunosuppression can be avoided. With the increasing repertoire of immunosuppression therapies being studied in IgAN, these results demonstrate the clear need to develop precision-

medicine treatment approaches that are drug-specific, incorporate individual risk of disease progression, and no longer rely exclusively on proteinuria.

Methods

Study population

The study population comprised the international multi-ethnic cohort from the IIgAN-PT analysis (N=3927)[15], which included patients with biopsy-proven idiopathic IgAN, available MEST-C scores, age ≥18 years, who did not have ESKD at the time of biopsy, and who had available eGFR data during longitudinal follow-up after biopsy. Further details are provided in the Supplementary Methods. We additionally excluded patients with missing predictor variable data, and those with eGFR at biopsy <30ml/min/1.73m^2 because this latter group is considered ineligible for immunosuppression according to the 2012 KDIGO GN guidelines[9]. This project was approved by the University of British Columbia research ethics board, with waived patient consent.

Definitions

Definitions were the same as those used in the IIgAN-PT analysis, including for mean arterial blood pressure (MAP), eGFR, and proteinuria at biopsy; prior use of immunosuppression or RASB; self-reported race/ethnicity; the MEST-C score; and the presence of cellular or fibrocellular crescents (see Supplementary Methods for further details). The primary outcome was a composite of the first occurrence of either ESKD or a persistent reduction in eGFR to below 50% of the value at biopsy.

Statistical Analysis

The IIgAN-PT comprises two Cox proportional hazards models of time from biopsy to the primary outcome, with or without race/ethnicity as a predictor variable, censored at death or the end of follow-up[15]. These were used to calculate the predicted 5-year risk of the primary outcome for each patient using the following predictor variables: age; race/ethnicity; eGFR, MAP and proteinuria at biopsy; prior use of RASB and immunosuppression; and the MEST histology scores. A *decision rule* was created based on Figure 1 to simulate the allocation of a hypothetical immunosuppression treatment. Risk assessment in Step 1 was based on the IIgAN-PT, in which treatment was allocated to patients with predicted 5-year risk greater than or equal to a threshold probability (P_t). Disease progression in Step 2 was defined as experiencing the primary outcome in the analytic cohort. The threshold probability (P_t) reflects the risk of disease progression at which there is true equipoise as outlined in Figure 1, and the benefits of treatment are exactly equal to the benefits of not being treated. For any hypothetical type of immunosuppression, the exact threshold probability is not known, however it is assumed to exist. As such, the analysis was repeated for all possible P_t between 0 and 1. The *net benefit* was calculated as the proportion of

patients appropriately allocated to receive immunosuppression (Figure 1: A) penalized by the relative harm to patients from inappropriate treatment decisions (Figure 1: B and C)[7, 32]. The *net reduction in treatment* was calculated as the proportion of patients appropriately allocated to not receive immunosuppression (Figure 1: D) similarly penalized for inappropriate decisions[7, 32]. This analytic approach is designed for application in observational data and is not dependent on the type or efficacy of the hypothetical immunosuppression treatment being considered. The consequences of appropriate and inappropriate treatment decisions are accounted for using the *relative* ratio of the utility in the different health states in Figure 1, and therefore do not require the explicit measurement of quality of life or drug-related adverse events. The decision rule using the IIgAN-PT was compared to the traditional alternative where risk assessment in Step 1 was based solely on proteinuria at biopsy ≥1g/day because this reflects the 2012 KDIGO GN guideline suggestions for corticosteroid treatment[9]. An increase in net benefit or net reduction in treatment between decision rules suggests a better treatment decision that will benefit patients[7]. Further details regarding the analysis are provided in the Supplementary Methods.

Author contributions

SJB, MC, DI, LE, HNR and DCC designed the study and analytic plan. All analyses were performed by DI and LE. Data was contributed by RC, HZ, ZHL, YS, KM, RK, HNR and DCC. All authors reviewed the results, drafted and revised the paper, and approved the final manuscript. Each author accepts personal accountability for the author's own contributions, and agrees to ensure that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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Financial Disclosures

There are no conflicts of interest for any of the authors.

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Table 1: Description of the analytic cohort.

Data presented as median (IQR) or count (frequency). The primary outcome was the first occurrence of either a permanent 50% decline in eGFR from that at biopsy or ESRD. Mean arterial blood pressure (MAP), estimated glomerular filtration rate (eGFR), use of medications that block the renin-angiotensin system (RASB), end-stage kidney disease (ESKD).

	Analytic Cohort
Number of patients	3299
Follow up (years)	5.1 [3.2, 8.0]
Death	18 (2.7%)
Year of biopsy	2005 [1999, 2007]
Age (years)	35.0 [27.6, 44.8]
Male sex	1795 (54.4%)
Race/ethnicity	
Caucasian	1072 (32.5%)
Japanese	935 (28.3%)
Chinese	1239 (37.6%)
Other	53 (1.6%)
Creatinine at biopsy (µmol/L)	88 [69, 115]
eGFR at biopsy (ml/min/1.73m^2)	87 [62, 110]
30-60	755 (22.9%)
60-90	1025 (31.1%)
>90	1519 (46%)
MAP at biopsy (mmHg)	95.0 [86.7, 103.7]
Proteinuria at biopsy (g/day)	1.2 [0.7, 2.2]
<0.5	480 (14.5%)
0.5 - 1	872 (26.4%)
1 - 2	1016 (30.8%)
2 - 3	426 (12.9%)
>3	505 (15.3%)
Pathology:	
M1	1274 (38.6%)
E1	803 (24.3%)
S1	2561 (77.6%)
T1	670 (20.3%)
T2	165 (5%)
Crescents	1357 (41.1%)
RASB use at biopsy	1054 (31.9%)
RASB use during follow-up	2645 (81.6%)
Immunosuppression use prior to biopsy	297 (9%)
Immunosuppression use after biopsy	1303 (39.5%)
Primary outcome:	
50% decline in eGFR	428 (13%)
ESKD	94 (2.8%)
Primary outcome	522 (15.8%)

Table 2: The differences (Δ) in net benefit and net reduction in treatment between decision rules using the International IgAN Prediction Tool model without race/ethnicity compared to using proteinuria at biopsy ≥1g/day at various example threshold probabilities from 5% to 40%.

A 95% CI that does not include 0 is considered statistically significant. Results are provided for each 5% increase in threshold probability between 5% and 40%. The net benefit represents the proportion of patients appropriately allocated to receive treatment penalized for the relative impact of inappropriate decisions on quality of life. Similarly, the net reduction in treatment represents the proportion of patients appropriately allocated to not receive treatment penalized for inappropriate decisions. The utility ratio provided is based on the threshold probability, and is the harm to patients from preventable ESKD divided by the harm from unnecessary drug toxicity. End-stage kidney disease (ESKD).

Threshold Probability	**Utility ratio of ESKD vs drug toxicity**	**Model without race/ethnicity versus proteinuria ≥1g/day**	
		Δ Net benefit (95% CI)	**Δ Net reduction in treatment (95% CI)**
5%	19	0.4% (-0.1, 0.9)	7.8% (-1.9, 18.0)
10%	9	1.1% (0.4, 1.8)	9.7% (3.5, 15.9)
15%	5.7	3.4% (2.5, 4.2)	19.1% (14.2, 23.8)
20%	4	5.5% (4.4, 6.5)	21.9% (17.6, 25.9)
25%	3	8.9% (7.6, 10.1)	26.6% (22.9, 30.2)
30%	2.3	12.9% (11.5, 14.2)	30.1% (26.8, 33.2)
35%	1.9	17.7% (16.0, 19.2)	32.8% (29.7, 35.7)
40%	1.5	23.4% (21.5, 25.2)	35.1% (32.3, 37.8)

Figure Titles and Captions

Figure 1: A decision algorithm for immunosuppression treatment allocation in IgAN based on the risk of disease progression.

In Step 1, treatment is allocated using an assessment of individual patient risk of disease progression. This step could be based on proteinuria alone (*ie* ≥1g/day) or based on individual risk from the International IgAN Risk Prediction Tool. In Step 2, it is determined whether, in the absence of treatment, a patient would have experienced disease progression or not. This is used to identify appropriate versus inappropriate treatment allocation. This algorithm considers appropriate treatment allocation as providing immunosuppression to patients who would otherwise experience disease progression or avoiding immunosuppression from patients with non-progressive disease. It is assumed that disease progression, no matter how it is defined, would ultimately result in ESKD thereby resulting in the health utility states listed in A and C. The point of treatment equipoise occurs for each patient when the health utility from treatment (*ie* A + B) is exactly equal to the health utility from not being treated (*ie* C + D). QOL = quality of life. End-stage kidney disease (ESKD). IgA nephropathy (IgAN).

Figure 2: The net benefit (panel A) and net reduction in treatment (panel B) for immunosuppression treatment allocation based on the International IgAN Prediction Tool model without race/ethnicity, based on proteinuria at biopsy ≥1g/day, treating everybody, or treating nobody.

At each threshold probability from 0 to 1 (*ie* 0% to 100%), treatment was allocated based on the Prediction Tool if the predicted 5-year risk was greater than or equal to the threshold probability. The net benefit represents the proportion of patients appropriately allocated to receive treatment penalized for the relative impact of inappropriate decisions on quality of life. Similarly, the net reduction in treatment represents the proportion of patients appropriately allocated to not receive treatment penalized for inappropriate decisions. The X marks in (A) are the threshold probabilities where the net benefit curves are zero, and in (B) is the threshold probability where the net reduction in treatment for the prediction model diverges from the net reduction in treatment for proteinuria ≥1g/day.

Figure 3: The difference between the net benefit from immunosuppression treatment allocation based on the International IgAN Prediction Tool model without race/ethnicity and the net benefit from treatment allocation based on proteinuria at biopsy ≥1g/day.

The 95% confidence intervals are indicated by the shaded lines. The X mark is the threshold probability where the lower bound of the 95% confidence interval exceeds zero, and corresponds to a difference in net benefit of 0.9% (95% CI 0.2-1.6%).

Figure 4: The distribution of predicted 5-year risk of the primary outcome from the time of biopsy using the International IgAN Prediction Tool model, in subgroups with proteinuria ≥1g/day and <1g/day.

An example threshold probability is provided for 11% (based on the results from Supplementary Figure S5) and using the prediction model with race/ethnicity to allocated immunosuppression treatment. All patients with predicted 5-year risk above 11% would be allocated to receive treatment and patients with predicted 5-year risk below 11% would be allocated to not receive treatment. The shaded regions demonstrate the percentage of patients with discordant treatment allocation based on proteinuria ≥1g/day compared to allocation based on individual risk from the prediction model.

Figure 5: The net benefit for immunosuppression treatment decisions based on the International IgAN Prediction Tool model without race/ethnicity, based on proteinuria at biopsy ≥1g/day, treating everybody, or treating nobody, analyzed separately in subgroups based on immunosuppression exposure after biopsy within the analytic dataset.

Interpretation of net benefit is related to the allocation of a hypothetical immunosuppression treatment that is external and unrelated to the analytic dataset. Conversely, subgroups in this figure were identified based on actual immunosuppression exposure that did (panel A) or did not (panel B) occur within the analytic dataset.

Supplementary Material

Supplementary Methods

Supplementary Table S1: Description of the analytic cohort compared to the overall cohort prior to exclusion criteria based on missing predictor variables.

Supplementary Table S2: The differences (Δ) in net benefit and net reduction in treatment between decision rules using the International IgAN Prediction Tool model with race/ethnicity compared to using proteinuria at biopsy ≥1g/day at various example threshold probabilities from 5% to 40%.

Supplementary Figure S1: Derivation of the analytic cohort.

Supplementary Figure S2: The cumulative incidence of the primary outcome (50% decline in eGFR or ESRD) in the analytic cohort with 95% confidence intervals.

Supplementary Figure S3: The distribution of predicted 5-year risk of the primary outcome using the International IgAN Prediction Tool.

Supplementary Figure S4: The net benefit (panel A) and net reduction in treatment (panel B) for immunosuppression treatment allocation based on the International IgAN Prediction Tool models with or without race/ethnicity, based on proteinuria at biopsy ≥1g/day, treating everybody, or treating nobody.

Supplementary Figure S5: The difference between the net benefit from immunosuppression treatment allocation based on the International IgAN Prediction Tool model with race/ethnicity and the net benefit from treatment allocation based on proteinuria at biopsy ≥1g/day.

Supplementary Figure S6: The net benefit for immunosuppression treatment decisions based on the International IgAN Prediction Tool models with or without race/ethnicity, based on proteinuria at biopsy ≥1g/day, treating everybody, or treating nobody, analyzed in subgroups based on median age at biopsy (panel A), immunosuppression exposure after biopsy (panel B), membership in the IgAN Prediction Tool derivation versus validation cohorts (panel C), and RASB use at biopsy (D).

Supplementary information is available at Kidney International's website.

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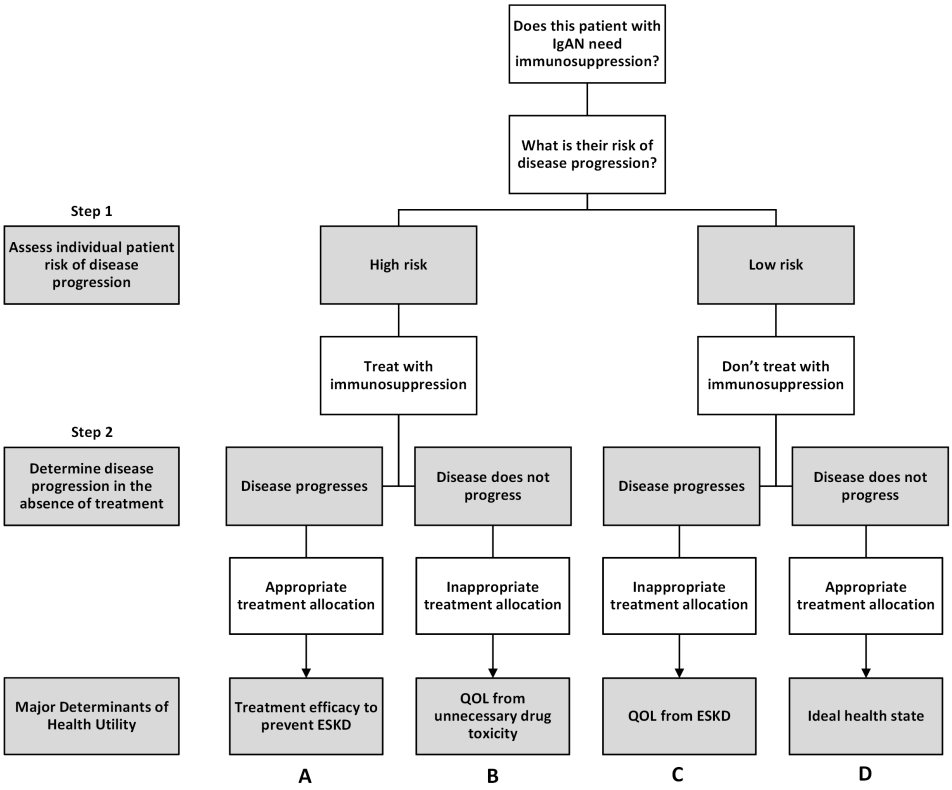
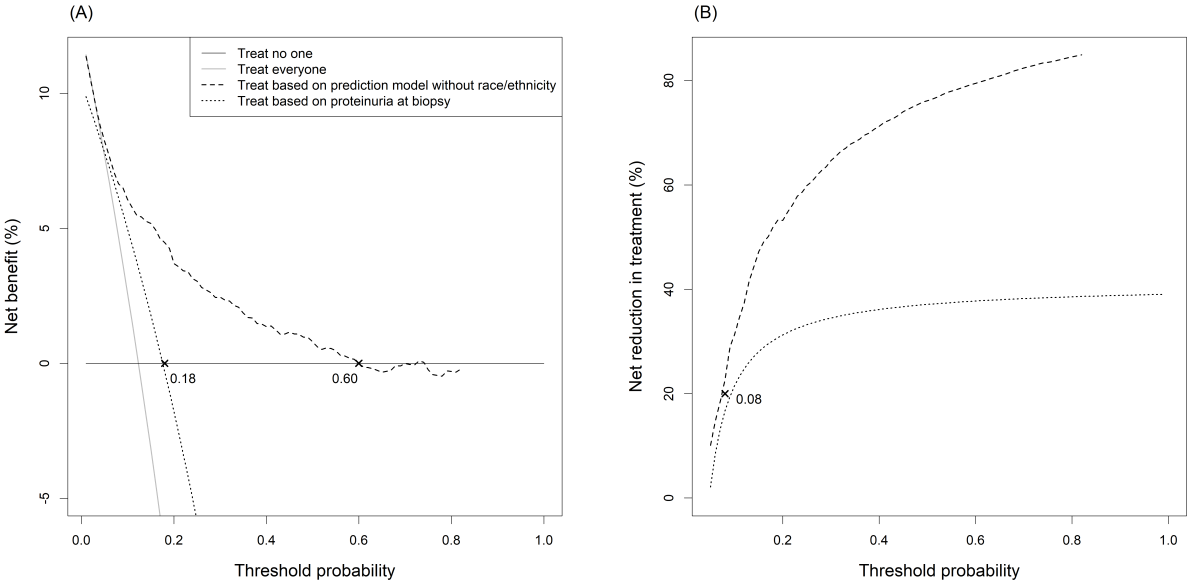
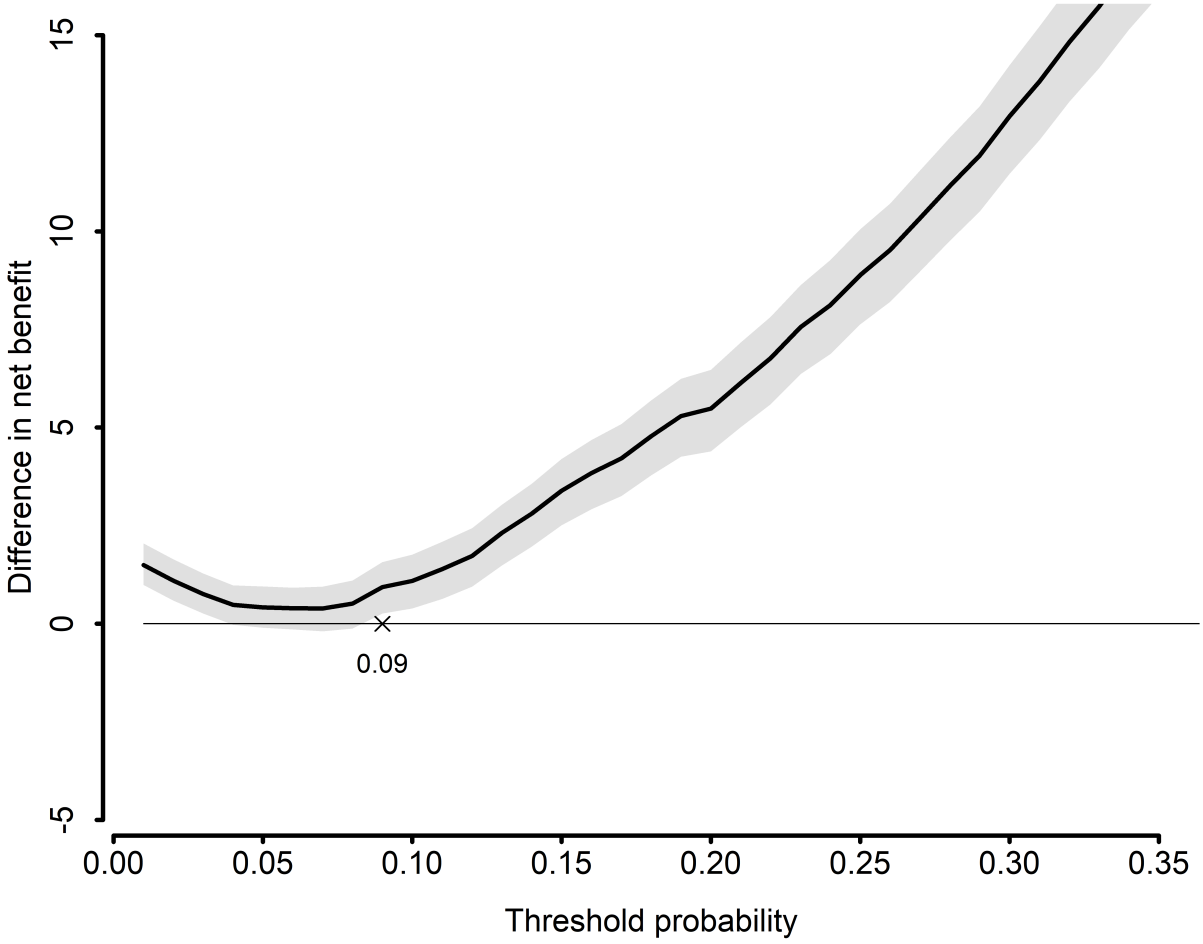
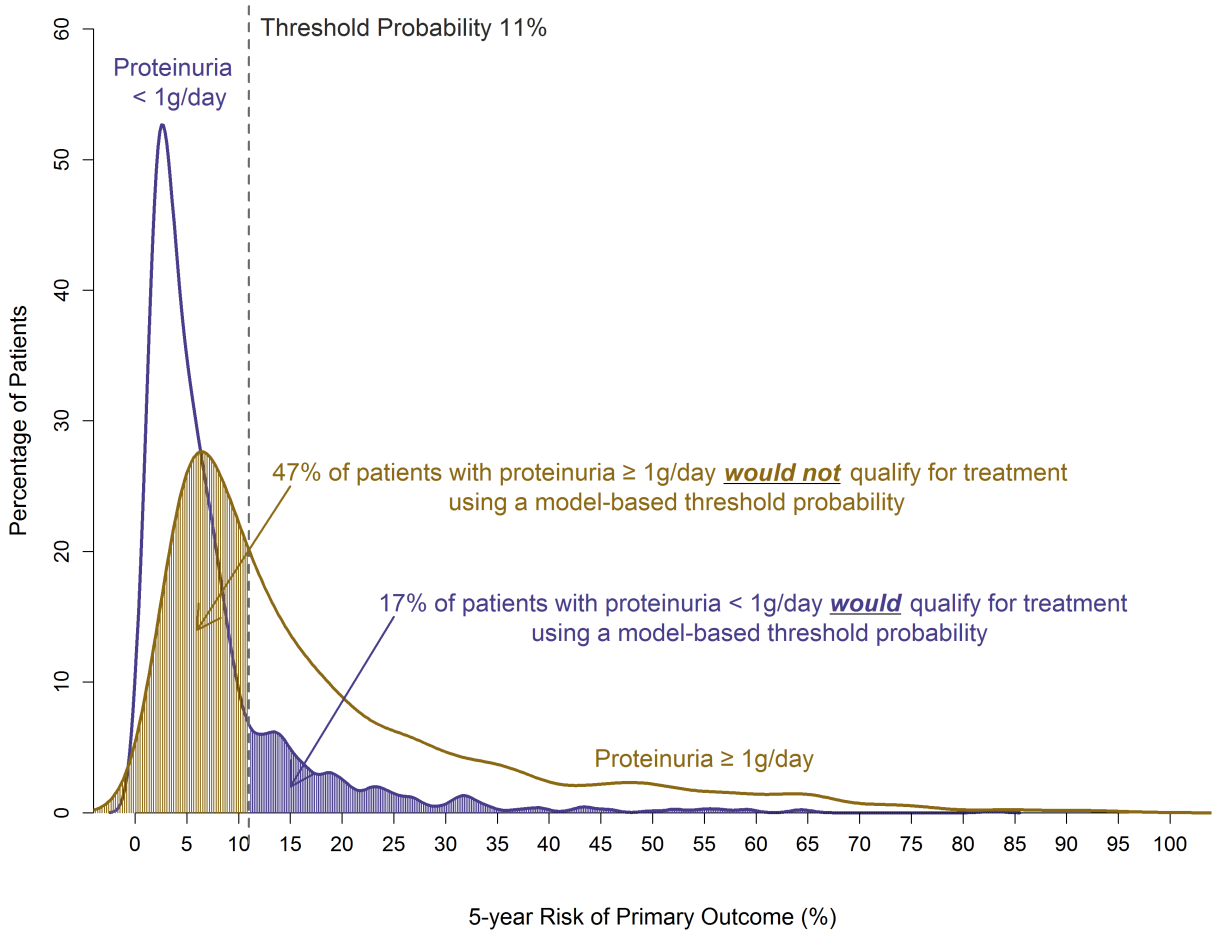


Point of equipoise is when the benefit of treatment is equal to the benefit of not being treated, *ie*. when A + B = C + D




Difference in net benefit
15
10
5
0
-5
0.09
0.00
0.05
0.10
0.15
0.20
0.25
0.30
0.35
Threshold probability


Threshold Probability 11%
Proteinuria
< 1g/day
47% of patients with proteinuria ≥ 1g/day would not qualify for treatment
using a model-based threshold probability
17% of patients with proteinuria < 1g/day would qualify for treatment
using a model-based threshold probability
Proteinuria ≥ 1g/day
Percentage of Patients
0
10
20
30
40
50
60
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
5-year Risk of Primary Outcome (%)