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Clinical decision support system for end-stage kidney disease risk estimation in IgA nephropathy patients

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ORIGINAL ARTICLE

ABSTRACT

Background. The progression of IgA nephropathy (IgAN) to end-stage kidney disease (ESKD) depends on several factors that are not quite clear and tangle the risk assessment. We aimed at developing a clinical decision support system (CDSS) for a quantitative risk assessment of ESKD and its timing using available clinical data at the time of renal biopsy.

Methods. We included a total of 1040 biopsy-proven IgAN patients with long-term follow-up from Italy ($N = 546$), Norway ($N = 441$) and Japan ($N = 53$). Of these, 241 patients reached ESKD: 104 Italian [median time to ESKD = 5 (3–9) years], 134 Norwegian [median time to ESKD = 6 (2–11) years] and 3 Japanese [median time to ESKD = 3 (2–12) years]. We independently trained and validated two cooperating artificial neural networks (ANNs) for predicting first the ESKD status and then the time to ESKD (defined as three categories: ≤3 years, between >3 and 8 years and over 8 years). As inputs we used gender, age, histological grading, serum creatinine, 24-h proteinuria and hypertension at the time of renal biopsy.

Results. The ANNs demonstrated high performance for both the prediction of ESKD (with an AUC of 89.9, 93.3 and 100% in the Italian, Norwegian and Japanese IgAN population, respectively) and its timing (f-measure of 90.7% in the cohort from Italy and 70.8% in the one from Norway). We embedded the two ANNs in a CDSS available online (www.igan.net). Entering the clinical parameters at the time of renal biopsy, the CDSS returns as output the estimated risk and timing of ESKD for the patient.

Conclusions. This CDSS provides useful additional information for identifying 'high-risk' IgAN patients and may help stratify them in the context of a personalized medicine approach.

Keywords: artificial neural networks, clinical decision support system, end-stage kidney disease, IgA nephropathy, risk stratification

INTRODUCTION

IgA nephropathy (IgAN) is the commonest form of glomerulonephritis worldwide [1]. The hallmark of this disease, initially described by Berger in 1968 [2], is the deposition of IgA in the glomerular mesangium. Episodes of macroscopic haematuria, concomitant with upper respiratory tract infections (synpharyngitic), are present at onset in 30–40% of cases. The same percentage of patients manifests asymptomatic microscopic haematuria. High degrees of proteinuria, renal impairment and hypertension at the onset might complicate the disease. The diagnosis relies on renal biopsy, as clinical features are not pathognomonic. The heterogeneity of clinical features, along with the wide range of possible histopathological lesions [3, 4], influences the accuracy of prognosis. Up to 40% of the patients develop end-stage kidney disease (ESKD) within 20 years of the biopsy-proven diagnosis with a calculated incidence rate of 1.5% per year from the first symptoms [5].

The importance of risk stratification in IgAN, to identify 'high-risk' patients, has been delineated by Barbour and Reich

[6]. A number of studies have evaluated the implication of clinical variables and histopathological features at onset for IgAN progression [7]. However, predictors like proteinuria, estimated glomerular filtration rate (eGFR) and histologic grading, which indicate the severity of the disease at presentation, are correlated, and their individual contribution on the overall risk is not easily weighted. Although a cumulative effect of these parameters combined in risk scores has also been tested in IgAN [8–14], an alternative effective strategy to tackle this issue can be the application of artificial neural network (ANN) as a non-linear statistical approach for pattern recognition in order to weight all the relationships between input and output variables.

The ANNs are inspired by biological neural networks. An artificial neurone is a processing unit, which receives signals from other neurones, performs a simple computation and provides an output. An ANN is a system of interconnected neurones used to estimate or approximate functions that can depend on a large number of inputs. Each connection between the neurones is characterized by a weight, which represents the influence that one neurone has on another one. An ANN can learn from a set of data by adjusting its own weight via proper training algorithms.

Only one study, 15 years ago, described the potential of ANNs for IgAN risk prediction. Geddes *et al.,* using an early system, demonstrated a better performance of ANN compared with the predictions of six experienced nephrologists [15]. Some papers have shown a similar approach applied to idiopathic membranous nephropathy [16] and renal allograft function after transplantation [17, 18]. Here, we present an application of ANNs to stratify IgAN patients on the basis of their risk to reach ESKD and also to assess time to ESKD using basal clinical and histological grading data. Our aim was to develop an effective and advanced clinical decision support system (CDSS) [19] easily accessible by clinicians to provide additional quantitative information at the time of renal biopsy.

MATERIALS AND METHODS

Study cohorts

We evaluated data from 677 biopsy-proven IgAN patients enrolled in a single centre, the Renal, Dialysis and Transplant Unit at the University of Bari, Italy, between May 1972 and June 2010. Renal biopsy was performed on the basis of the following indications: asymptomatic urinary abnormalities such as persistent microscopic haematuria and/or mild-to-moderate proteinuria, recurrent episodes of macroscopic haematuria, nephrotic syndrome, acute renal failure or chronic kidney disease of unknown origin without ultrasound alterations. The diagnosis of IgAN was based on the findings of predominant mesangial deposits of IgA by immunofluorescence after exclusion of lupus nephritis, Henoch Schönlein purpura and liver cirrhosis.

We also included two cohorts from different populations, 441 Norwegian and 53 Japanese biopsy-proven IgAN patients. The Norwegian IgAN cohort was identified in the Norwegian Kidney Biopsy Registry. All primary IgAN patients diagnosed 1988–2004 were included. Cases with ESKD during follow-up through June 2013 were identified by record linkage of the study cohort with the Norwegian Renal Registry using the unique Norwegian 11-digit social security number. Identification and characteristics of the Norwegian cohort is described in greater detail in Knoop *et al.* [20]. A cohort of 53 IgAN patients was collected at Juntendo University hospital, Japan, from 1974 to 2013. This study was approved by the local medical ethics committees and conducted in accordance with the guidelines of the Declaration of Helsinki. Due to the retrospective nature of the study, written informed consent was waived from patients.

Investigated parameters

Demographic data, clinical and laboratory findings were obtained from patients' medical records at the time of renal biopsy and stored in an electronic database in Excel format, regularly updated during the follow-up on annual basis. Data used as input included gender, age, histological grading, serum creatinine (sCr), 24-h proteinuria, hypertension status defined as arterial blood pressure over 140/90 mmHg and/or use of antihypertensive agents. Histological lesions were coded according to the Schena's classification [21] described in Manno *et al.* [22] who reported three grades (G): G1 (mild) in patients with minor or minimal lesions, G2 (moderate) in subjects with focal-segmental or diffuse proliferative glomerulonephritis and G3 (severe) in individuals with sclerotic lesions and advanced chronic glomerulonephritis. ESKD was defined as the need for renal replacement therapy by dialysis treatment or kidney transplantation. The time from renal biopsy to the start of renal replacement therapy was calculated in years and then categorized into three variables: ≤3 years, between >3 and 8 years and over 8 years. Furthermore, using the criteria reported by Berthoux *et al* [12], which take into account hypertension, proteinuria of ≥1 g/24 h and severe pathologic lesions, we attributed an absolute renal risk (ARR) of dialysis to each patient. The estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula [23].

Statistical analyses

Continuous data were reported as mean and SD or as median and interquartile range for non-normal distributions. A P-value of <0.05 was considered statistically significant. Two separate ANNs, predicting the ESKD status and time to ESKD, were initially trained and then validated in each cohort separately. The final classifier consisted of the paired trained ANNs with the one predicting the timing subsequently invoked when the ESKD status was deemed positive (Online Methods). The performance of the final classifier was described in terms of true positives, false positives, true negatives and false negatives, accuracy, precision, recall and f-measure. In addition, the area under the ROC curve (AUC) was used as a measure of aggregated classification performance. The performance indicators for the classification performed by five experienced nephrologists were computed individually for each nephrologist and then averaged to summarize the category. Similarly, the ROC curve was obtained by interpolating the five individual ROC

curves. The final version of the classifier was then translated into Java code and incorporated in the CDSS (Online Methods) available at www.igan.net and http://dee020.poliba.it/migan/

RESULTS

Characteristics of the study population

A total of 546 Italian IgAN patients, out of 677 biopsy-proven IgAN, were available for analysis because 131 patients were excluded as they had one or more missing parameters. Nineteen per cent ($N = 104$) of them reached ESKD within a median time of 5 years. The patients were receiving no medication at the time of renal biopsy. After diagnosis, 36 patients received corticosteroids plus angiotensin-converting enzyme (ACE) inhibitors, 160 received ACE inhibitors alone and 3 received cyclophosphamide.

We also studied additional cohorts of 441 biopsy-proven IgAN patients from Norway and 53 from Japan. In the Norwegian population, 134 patients reached ESKD (30%) within a median time of 6 years whereas among the Japanese IgAN patients, 3 patients (5%) did (median time to ESKD of 3 years). Altogether 241 (23%) patients reached ESKD. Table 1 shows the demographic and clinical features of each cohort at time of renal biopsy.

The male/female ratio was 2.1 in the Italian cohort; it was higher in the Norwegian (2.6) whereas in the Japanese, there was approximately the same proportion of male and female. The mean age at renal biopsy was higher in the Norwegian (38.2 years) and comparable in the Italian and Japanese (32.5 and 32.7, respectively) group. A higher proportion of patients with moderate histological lesions was observed in the Norwegian (65%) and Japanese group (41%), whereas patients with mild lesions were prominent in the Italian group (44%).

Most patients were categorized as KDOQI stage I: 48% in the Italian and Norwegian (who also had a comparable mean eGFR of 86 mL/min) and 70% in the Japanese (mean eGFR = 101 mL/min) group. The mean sCr was higher in the Norwegian cohort (1.5 ± 1.2 mg/dL) compared with that in patients from Italy (1.2 ± 0.7) and Japan (0.9 ± 0.3 mg/dL). Proteinuria was not heavy but was higher in the Norwegian (1.3, 0.5–3.3 g/24 h) than in the Italian (0.7, 0.3–1.4 g/24 h) and Japanese (0.4, 0.2–0.7 g/24 h) cohort. Hypertension was observed in 50% of Norwegian, 39% of Italian and 2% of Japanese patients, respectively.

Using hypertension status, proteinuria of ≥1 g/24 h and severe degree of renal lesions (G3) as risk factors, we attributed an ARR of dialysis to each patient. The score ranges from 0 to 3 based on the presence of any one or two of these factors [12]. We observed, in terms of prevalence, that 232 (42%) and 36 (68%) patients in the Italian and Japanese data sets, respectively, were scored as ARR = 0 having none of the risk factors whereas 176 (40%) patients were scored with intermediate risk (ARR = 1) in the Norwegian data set.

ESKD predictors as input for the ANNs

In order to identify significant predictors of ESKD to be used as input for the ANN, we first assessed their importance by logistic regression. Univariate analysis, illustrated in Table 2, showed that gender (male, OR 1.59; 95% CI 1.15–2.23; P = 0.005), age (OR 1.02; 95% CI 1.01–1.03; P < 0.001), histological grade, serum creatinine (OR 4.50; 95% CI 3.31–7.53; P < 0.001), proteinuria (OR 2.21; 95% CI 1.80–2.73; P < 0.001) and hypertension (OR 5.25; 95% CI 3.30–8.33; P < 0.001), evaluated at the time of renal biopsy, had a significant impact on ESKD in our data sets. The largest effect was observed in patients with severe histological grade (OR 26.45; 95% CI 15.39–47.77; P < 0.001). We used these independent parameters resulted significant at the univariate analysis as inputs for the ANNs.

Table 1. Demographic and clinical data of the study population at the time of renal biopsy

Country	Italy	Norway	Japan
No. of IgAN patients	546	441	53
Gender (male/female)	372/174	320/121	27/26
Age at the time of renal biopsy (years)	32.5 ± 11.2	38.2 ± 15.3	32.7 ± 10.9
Histological grade			
Mild	239 (43.8%)	107 (24.3%)	17 (32.1%)
Moderate	197 (36.1%)	289 (65.5%)	22 (41.5%)
Severe	110 (20.1%)	45 (10.2%)	14 (26.4%)
Serum creatinine (mg/dL)	1.2 ± 0.7	1.5 ± 1.2	0.9 ± 0.3
eGFR (mL/min/1.73 m^2)	86 ± 29	86 ± 25	101 ± 26
KDOQI stage			
I	265 (48.5%)	215 (48.4%)	37 (69.8%)
II	183 (33.5%)	160 (36.3%)	13 (24.5%)
III	62 (11.4%)	54 (12.2%)	2 (3.6%)
IV	31 (5.7%)	7 (1.6%)	1 (1.9%)
V	5 (0.9%)	5 (1.1%)	0
24-h proteinuria (g/24 h)	0.7 (0.3–1.4)	1.3 (0.5–3.3)	0.4 (0.2–0.7)
Hypertension (yes/no)	215/331	219/222	1/52
ESKD (yes, %)	104 (19.0%)	134 (30.4%)	3 (5.7%)
Time to ESKD (years)	5 (3–9)	6 (2–11)	3 (2–12)
ARR			
0	232 (42.5%)	106 (24.0%)	36 (67.9%)
1	151 (27.6%)	176 (39.9%)	12 (22.6%)
2	107 (19.6%)	125 (28.4%)	4 (7.6%)
3	56 (10.3%)	34 (7.7%)	1 (1.9%)

Data are presented as absolute value and percentage: *N* (%); continuous measures are reported as median and interquartile range or mean ± SD as appropriate.
RB, renal biopsy; ESKD, end-stage kidney disease; eGFR, estimated glomerular filtration rate; ARR, absolute renal risk.

Table 2. Univariate logistic regression for ESKD status

Predictor	OR (95% CI)	P-value
Gender		
Female	Referent	
Male	1.59 (1.15–2.23)	0.005
Age	1.02 (1.01–1.03)	<0.001
Histological Grade		
Mild	Referent	
Moderate	6.25 (3.83–10.80)	<0.001
Severe	26.45 (15.39–47.77)	<0.001
Serum creatinine (mg/dL)	4.50 (3.31–7.53)	<0.001
24-h Proteinuria	2.21 (1.80–2.73)	<0.001
Hypertension		
No	Referent	
Yes	5.25 (3.30–8.33)	<0.001

OR, odds-ratio; CI confidence interval.

Performance of the ANNs

We trained and validated two independent ANNs: the first one for the ESKD status prediction and a second one for the prediction of time to ESKD categorized as follows: (i) within 3 years, (ii) between >3 years and 8 years and (iii) after 8 years. Thereafter, with the aim to provide a complete CDSS, we concatenated the two ANNs, so if the first ANN classified the patients as ESKD then the second ANN performed the prediction of the time to ESKD (Figure 1).

ESKD status prediction. The total data set, including 1040 patients, was split into two groups: 830 patients for the training and 210 for the validation study (110 Italian, 89 Norwegian and 11 Japanese IgAN patients) of the ANNs predicting the ESKD status (Supplementary Tables S1–S3). In the first place, the validation group was used to assess the performance of our ANN in predicting the ESKD and to compare it with an established scoring system such as the ARR. Although the ARR was reliable, showing an AUC of 76.9% in the Italian, 77.0% in the Norwegian and 100% in the Japanese cohort, it was outperformed by our ANN in the two largest data sets (89.9% for the Italian and 93.3% for the Norwegian) whereas it was identical in the Japanese (AUC = 100%) (Figure 2).

In addition, we presented the validation data set to five experienced nephrologists asking the question: '*Given these parameters, do you feel this patient will reach ESKD in the next decade?*' We then evaluated the performance of their prediction with the same metrics applied to the ANN and ARR.

As shown in Table 3, the ANN performed better than the experienced nephrologists in all the cohorts (Figure 2).

ESKD timing prediction. For the second ANN, predicting ESKD timing in three categories, 241 patients were available for analyses: 195 of them were used for the training study and 46 (20 Italian and 26 Norwegian IgAN patients) for the validation study. Given the low number of patients reaching ESKD in the Japanese cohort (3 of 53), we did not use this data set for the analysis. Again here, the set of indicators showed a good performance of the ANN, with an f-measure of 90.7 and 70.8% in the Italian and Norwegian cohort, respectively.

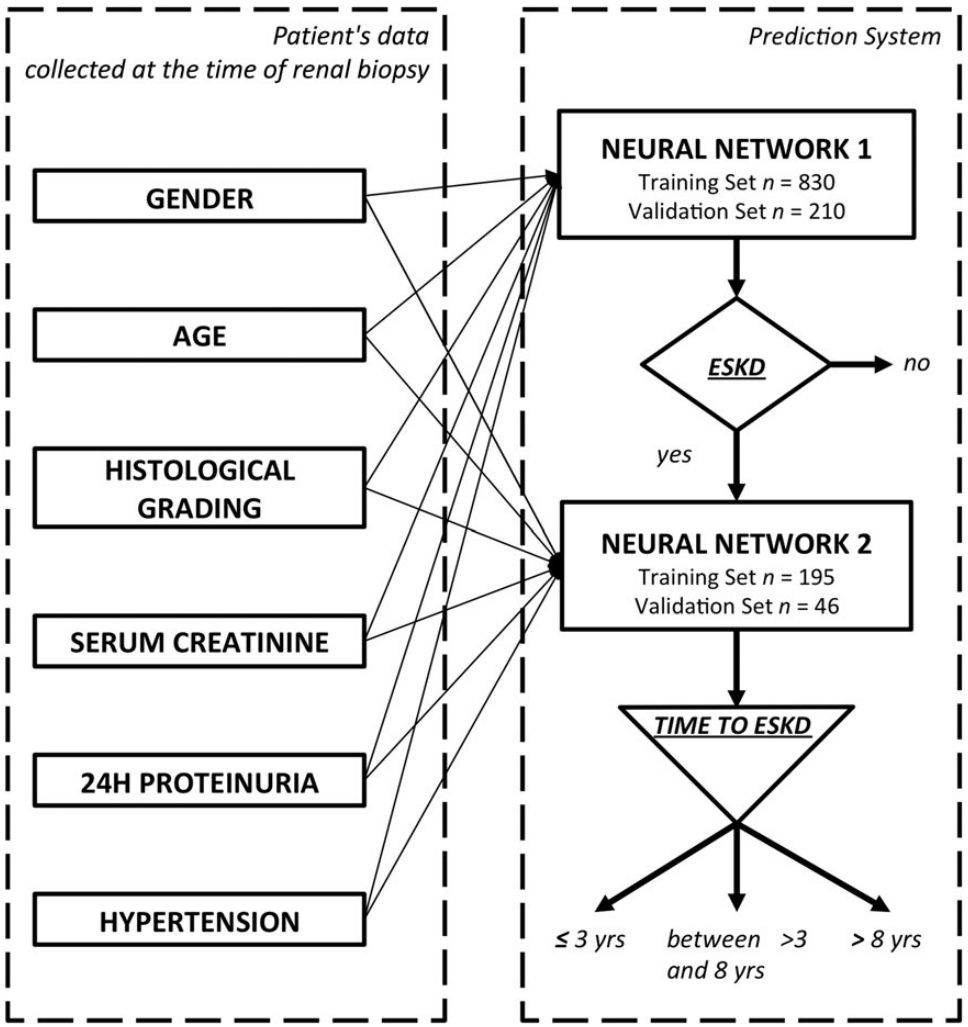

FIGURE 1: Structure of the CDSS. The CDSS consisted of two cooperating ANNs independently trained to predict the ESKD status (yes or no) and the time to ESKD (≤3 years, between >3 and 8 years and over 8 years), respectively. As inputs we used gender, age, histological grading, serum creatinine, 24-h proteinuria and hypertension status at the time of renal biopsy (RB).

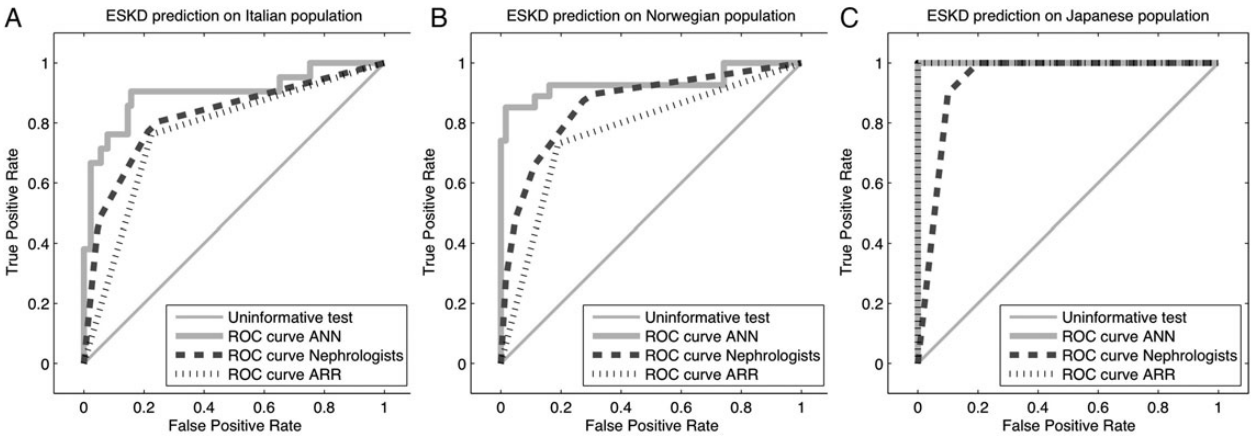

FIGURE 2: Performance of the ANN predicting the ESKD status The ANN trained to predict the ESKD status was validated in three different cohorts using the AUC. It performed better in the Italian (Panel **A**, $N = 110$, AUC = 89.9 versus 76.9%) and Norwegian population (Panel **B**, $N = 89$ AUC = 93.3 versus 77.0%), whereas it was identical in the Japanese (Panel **C**, $N = 11$, AUC = 100%) when compared with the absolute renal risk (ARR). It outperformed the prediction of five experienced nephrologists in all the cohorts.

Table 3. Performance comparison for the prediction on ESKD status

Country	Italy			Norway			Japan		
	ANN	EXP	ARR	ANN	EXP	ARR	ANN	EXP	ARR
Accuracy	91.8	85.6	77.3	92.1	85.6	78.7	90.9	90.9	100.0
Precision	90.0	79.7	68.8	91.1	84.5	74.6	75.0	78.3	100.0
Recall	82.2	82.0	76.9	90.2	86.1	77.0	95.0	95.0	100.0
F-measure	85.4	79.2	70.4	90.6	84.3	75.5	80.7	82.3	100.0
AUC	89.9	82.0	76.9	93.3	86.1	77.0	100.0	95.0	100.0

ANN, artificial neural networks; ARR, absolute renal risk; EXP, experienced nephrologists.

Table 4. Performance for the prediction on the timing of ESKD

Country	Italy		Norway	
	ANN	EXP	ANN	EXP
Accuracy	90.0	69.0	69.2	54.6
Precision	93.3	74.5	75.0	56.4
Recall	90.5	72.0	70.0	55.8
F-measure	90.7	69.6	70.8	53.6

ANN, artificial neural networks; EXP, experienced nephrologists.

We also found a considerable better performance of our ANN compared with the prediction of five experienced nephrologists (Table 4). We presented the validation data set with the 46 patients asking them, '*This patient had these parameters at the time of renal biopsy and reached ESKD in a decade. Do you think this happened within 3 years, between 3 and 8 years or after 8 years from diagnosis?*'

A detailed report, with specific results of the prediction of the ANNs for each cohort, is available in Supplementary Tables S1–S5.

Online clinical decision support system

We embedded this classifier in a CDSS available online (www.igan.net) which, when a user enters the set of input variables listed above (Figure 3A), returns a quantitative measure of the estimated risk of ESKD and its timing. The complete output consists of the outcome prediction and a summary of the input parameters (plus the eGFR automatically calculated using the CKD-EPI formula). For example, a 20-year-old female patient with mild histological lesions (G1), sCr of 1.7 mg/dL, proteinuria of 1.5 g/24 h and hypertension is considered at risk of ESKD (confidence: 83%) after 8 years of time (Figure 3B). On the other hand, for a 40-year-old male patient with moderate histological lesions (G2), a proteinuria of 6.8 g/24 h and hypertension, but with sCr of 1.7 mg/dL, the prediction is to reach ESKD (confidence: 80%) between 3 and 8 years (Supplementary Figure S1). Additional examples, with a patient at no risk and one at high risk, are provided as Supplementary Figures S2 and S3.

DISCUSSION

In this study, we present a CDSS based on ANNs to predict the risk and time to ESKD for IgAN patients using clinical data collected at the time of renal biopsy. To date a single study [15] explored the advantage of ANNs for this purpose. However, the study included only 54 patients taking into account a surrogate end point, as the definition of the patient outcome was 'stable' or 'non-stable' based on the serum creatinine value after 7 years from the time of renal biopsy.

We previously published an experimental approach [24] used to determine the best possible ANN architecture to analyse our data set. In this study, we further refined the architecture of the ANN and implemented the final CDSS in the setting of a large clinical study with long-term follow-up in three different populations. The main advantage is that such a system is based on non-parametric machine-learning algorithms, which allow us to evaluate and weight the nonlinearities of the significant clinical variables at the time of renal biopsy ultimately returning a quantitative risk assessment of ESKD.

The CDSS showed an excellent performance in two European cohorts and also in Asian IgAN patients. In these cohorts, we confirmed the efficacy of the ARR score proposed by

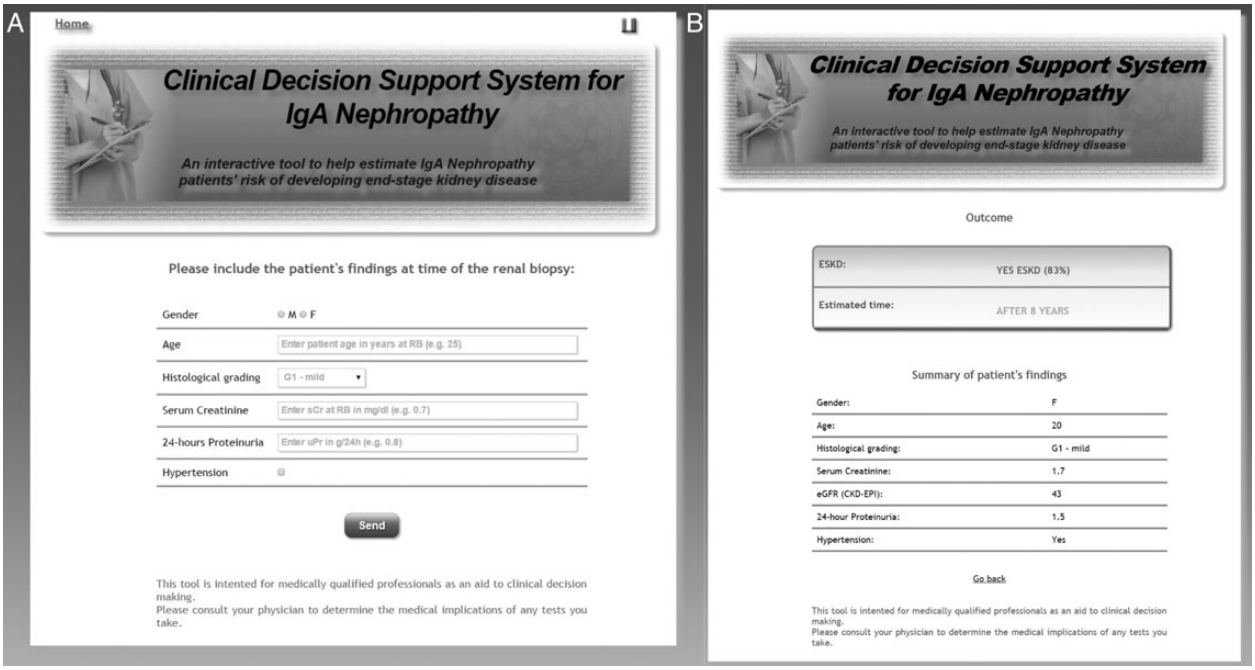

FIGURE 3: Web interface for the CDSS. On the left side (Panel **A**) is the entry form with the clinical parameters of the patient at the time of renal biopsy. The response screenshot is on the right (Panel **B**), where the box on the top shows the outcome prediction followed by a summary of the patient's characteristics entered by the user.

Berthoux *et al.* [12] but we demonstrated a better performance of our ANN for the prediction of ESKD. Given the methodology we applied, this may be due to the use of the complete set of clinical variables without categorization, yet we kept the input simple and effective.

After having verified this basic characteristic, we sought to give an additional layer of information for patients at risk, predicting three intervals for the timing of ESKD after renal biopsy: within 3 years, between >3 and 8 years and after 8 years. Hence, we trained and validated a second ANN for this purpose and embedded the two ANNs in the complete CDSS. The CDSS outperformed the prediction of five experienced nephrologists and interestingly revealed its clinical importance in identifying patients at 'high-risk'. The better accuracy in predicting the time intervals close to the time of renal biopsy can make the difference for patients reaching ESKD. In fact, the early years after diagnosis are those more likely to be effective in preventing irreversible damage with therapeutic interventions.

A potential technical shortcoming might be due to the error propagation from the first ANN to the second one, which is going to estimate the time to ESKD for a patient who in fact did not reach ESKD. The complete confusion matrixes (Supplementary Table S4 and S5) showed that such issue was entirely negligible. Indeed, the prediction of timing was accurate for both European cohorts we used for this analysis.

In this case, although the median time to ESKD limited the definition of our intervals (with thresholds at 3 and 8 years in order to achieve the highest predictive performance), our CDDS offers a range of risk categories fitting the course of IgAN, which can be an aid to clinical management.

It is noteworthy that in this study we adopted a simple histological classification based on a grading (lumped) system that classifies the tissue pathology according to the overall severity of the lesions found in each tissue compartment. The introduction of the Oxford Classification [3, 4, 25, 26], which is based on the scoring of four lesions (mesangial hypercellularity, segmental glomerulosclerosis, endocapillary hypercellularity and tubular atrophy/interstitial fibrosis), might convey additional information only on the progression of the renal damage. We reasoned that a multivariate prediction system like ours would benefit from incorporating a common yet simple denominator to summarize the histopathology as one of the input variables. The three-grade system (mild, moderate and severe) fits for this purpose, as it is readily interpretable, capturing the general overview of the biopsy, and easily coded with some adaptation from different scores as suggested by Berthoux *et al.* [12] in a similar setting. This strategy in fact has been proven effective in this retrospective study allowing us to analyse 1040 biopsies with different pathologic classifications.

A limitation is that the Japanese cohort is smaller than the Norwegian and Italian one; hence, generalizability to an Asian population might need further validation in a larger data set. However, the confident performance proved the usefulness of the tool in this population as well.

It is likely that our CDSS would benefit from incorporating, in the future, novel disease-specific genomic and serologic biomarkers. In fact, the predictive role of key pathogenetic players, such as serum levels of galactose-deficient IgA1, which is inherited in IgAN [27, 28], and micro-RNA [29, 30] still has to be unravelled [31].

In conclusion, this CDSS is an easy and valuable tool for clinical practice to estimate the risk of ESKD and its timing in IgAN patients. Moreover, in the context of stratified medicine,

it might provide additional information for optimal design and interpretation of clinical trials.

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SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

CONFLICT OF INTEREST STATEMENT

The results presented in this paper have not been published previously in whole or part, except in abstract format.

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