The Added Value of Crescents on Oxford Classification Score in Risk Stratification of End-stage Kidney Disease in Patients with IgA Nephropathy

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Introduction. Crescents (C) have been recently added to the Oxford classification of IgA nephropathy (IgAN) consisting of mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental sclerosis (S) and tubular atrophy/ interstitial fibrosis (T) (MEST). The aim of the study was to assess the added impact of crescents, on development of end-stage kidney disease (ESKD) in IgAN patients

Methods. On-hundred fifteen IgAN patients (76% male, mean age: 37 ± 13 years, mean serum creatinine: 4.0 ± 4.3 mg/dL, mean proteinuria: 3.4 ± 2.5 g/d) were followed for 43 ± 29 months. MEST score was defined according to Oxford classification (M0/M1, E0/E1, S0/S1). To increase the power, T was defined as T0 ≤ 25% and T1 > 25%. Crescents were defined as C0, "absence" and C1 "at least one" crescent. In sensitivity analysis, the risk of ESKD was estimated at different cut-off levels of at least 10, 20, and 30% crescents.

Results. Forty patients (35%) developed ESKD. Among those 14% with at least one crescent, 21 patients (46%) developed ESKD. In 11 patients with C ≥ 30%, 66% and among 57 patients with T1, 60% and in 27 patients with T1 + C1 74% developed ESKD. In adjusted model, only C ≥ 30% (HR = 3.15, 95% CI: 1.15 to 11.00; *P* = 0.027) and the presence of T1+ C1 (HR = 7.18, 95% CI: 1.90 to 27.10, *P* = 0.004) were associated with increased risk of ESKD. The median kidney survival was 78.0 months (95% CI: 70.5 to 85.6 months), in patients with T0 + C0 and 32.3 months (95% CI: 19.3 to 45.3 months) in patients with T1 + C1.

Conclusion. In this study T ≥ 25%, and the presence of crescents ≥ 30%, were independently associated with increased risk of ESKD. This risk was strongly increased in the combined presence of at least one crescent and T1 ≥ 25%, that predicted a high ESKD rate.

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INTRODUCTION

IgA nephropathy (IgAN) is the leading cause of the primary glomerulonephritis (GN) globally.[1] It is primarily identified by dominant mesangial deposition of IgA in immunofluorescence microscopy.[2,3] Various degrees of glomerular damage may be observed by light microscope.[4,5]

The clinical manifestations of IgAN are very

diverse, ranging from asymptomatic microscopic hematuria to rapidly progressive end-stage kidney disease (ESKD).

The Oxford classification of IgAN was published in 2009 with the purpose of prediction of renal outcome at the time of biopsy and during the follow-up, based on MEST histologic classification.[6,7] This classification consists of four key pathologic features including mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental glomerulosclerosis (S), and tubular atrophy and interstitial fibrosis (T). In biopsy specimens with a minimum of 8 glomeruli, M, S, and T lesions predicted clinical outcome and patients with E lesions had an improved outcome if treated with corticosteroids.[7]

The Oxford classification was later evaluated by the Validation of the Oxford Classification of IgA Nephropathy (VALIGA) study, which included patients with proteinuria less than 0.5 g/d (< 0.5 g/d), estimated GFR (eGFR) less than 30 mL/min (< 30 mL/min) / 1.73 m^2 at renal biopsy, and more than or equal to 1 (≥ 1) year of follow-up, who had not been addressed in the original Oxford classification.[8] M, S, and T lesions independently predicted the loss of GFR and lower renal survival. In individuals with eGFR less than 30 mL/min/ 1.73 m^2 (< 30 mL/min/ 1.73 m^2), the M and T lesions independently predicted poor survival.[8] More recently the presence of cellular and/or fibrocellular crescents have been added to MEST score, but the additive effect of crescents on prediction of renal outcome in IgAN still remains to be studied.[9,10]

The aim of study is to evaluate the impact of the presence of crescents alone or in combination with other pathological features of Oxford classification on the risk of ESKD in patients with IgA Nephropathy.

MATERIALS AND METHODS

In this retrospective cohort study, we included 115 patients with diagnose of IgAN from native kidney biopsy. The patients were followed up for a mean period of 43 ± 29 months. Diagnosis of IgAN was confirmed by the presence of dominant IgA deposition in mesangium by immunofluorescence. The patients with secondary etiologies such as Henoch-Schönlein purpura were excluded. Four patients were younger than 18 years old at the time of kidney biopsy (between 13 to 16 years old). Laboratory analyses were performed at local laboratories. Demographic, clinical, laboratory and histological data were extracted from our GN database in the hospital. Kidney function was expressed as the eGFR (mL/min/ 1.73 m^2) calculated using the Modification of Diet in Renal Disease study equation (MDRD).

Definitions

ESKD or death due to kidney disease, as the kidney outcome: Patient on maintenance dialysis or kidney transplant.

Arterial hypertension: Systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg.

Pathological Findings Definitions

We basically defined the pathologic findings according to the four key pathologic features of MEST Oxford classification. The absence/presence of 50% of glomeruli showing mesangial hypercellularity is denoted as M0/M1, respectively; E1 indicates any endocapillary hypercellularity; S1 represents any segmental glomerulosclerosis. In original Oxford classification tubular atrophy/interstitial fibrosis was defined as T0, T1, and T2 reflecting involvement of 1 to 25%, 26 to 50% or > 50% of the cortical area. But to increase the power of the study, we defined T0 as tubular atrophy/interstitial fibrosis between 1 to 25% and T1 as > 25%. Crescents, as added later to Oxford score, was defined as C0: no cellular or fibrocellular crescents; C1: cellular/fibrocellular crescents in < 25% of glomeruli and C2: crescents in ≥ 25% of glomeruli. To further evaluate the cutoff point of percentage of crescents as predictors of ESKD, we defined 4 different models in sub-analysis:

1. Model 1; C0 = No crescents vs. C1 > 0 = at least one cellular/fibrocellular crescents
2. Model 2; C0 = 0 to 9% vs. C1 ≥ 10% cellular/fibrocellular crescents
3. Model 3; C0 = 0 to 19% vs. C1 ≥ 20% cellular/fibrocellular crescents
4. Model 4; C0 = 0 to 29% vs. C1 ≥ 30% cellular/fibrocellular crescents

Patients were further classified according to combinations of C and T scores into three groups:

Low risk (C0 + T0)
Medium risk (C1 + T0 or C0 + T1)
High risk (C1 + T1)

Statistical Analyses

Continuous data were presented as mean ± standard deviation (SD) or median and interquartile range. Categorical data were expressed as integers, frequencies, and percentages. Data comparison was performed using Chi-square or Fisher's exact test and one-way Analysis of Variance (ANOVA).

In univariate analyses the hazard ratio (HR) with 95% confidence interval (95% CI) was calculated by using Cox proportional hazards model for each clinical, laboratory and pathological independent risk factor to estimate the risk of ESKD.

In sub- analysis, we performed a sensitivity analysis to evaluate the impact of presence of at least one crescent on the development of ESKD and at the next level we ran a subanalysis at the presence of crescents in ≥ 10%, ≥ 20% or ≥ 30% of the glomeruli. Cox proportional hazards and Kaplan- Meier with the log-rank test were used to estimate renal survival in each model.

Analysis of interaction between Oxford classification findings did not show any interaction.

In prognostic model, discrimination was evaluated by using the C-statistic, i.e., the area under the receiver operating characteristic (ROC) curve.

RESULTS

Baseline Characteristics

Baseline characteristics of 115 patients and details of pathologic findings according to Oxford classification are shown in Table 1.

Clinical and Laboratory Findings at Baseline

The mean age was 37 ± 13 years old and 76% of patients were male. The mean serum creatinine (SCr) at presentation was 4.0 ± 4.3 (mg/dL) and eGFR according MDRD was 37.5 ± 27 mL/min/ 1.73 m^2 which indicated diversity of kidney function among the study population at the time of kidney biopsy. The mean 24-hour urine protein was 3.4 ± 2.5 g/24h and in 69 % of patients proteinuria was in nephrotic range. About 50% of patients had hypertension.

Clinical and Laboratory Findings in Each Pathological Feature of Oxford Classification

The clinical and laboratory findings in each pathological component of Oxford classification are shown in Table 1. The frequency of M1, E1, S1, and T1 were 20, 19, 56, and 50%; respectively.

Overall 40% of patients had at least one crescent and the mean percentage of crescents in total glomerular number was 22 ± 14%. In classification for subgroup analysis, 24 patients (21%) had C ≥ 10%, 12 patients (10.4%) had C ≥ 20% and 11 patients (9.5%) had C ≥ 30% crescents in kidney biopsy.

Overall mean SCr was 4.0 ± 4.3 and eGFR was 37 ± 27 mL/min/1.73 m^2. Expect for the patients with M1, who had a mean SCr of 4.8 ± 5.9 mg/dL, in other patients the amount of SCr at baseline was

Table 1. Baseline Characteristics in All Patients and Histological Finding According to Oxford Classification and Development of ESKD

	Total	M1	E1	S1	T1	C1	*P*
N, %	115	23 (20)	22 (19)	65 (56)	57 (50)	46 (40)	-
Age at Biopsy, y	37 ± 13	34 ± 8	35 ± 9	37 ± 12	36 ± 13	39 ± 14	> .05
Sex (male%)	76	77	77	75	78	78	> .05
Weight, kg	71 ± 11	70 ± 8	72 ± 10	72 ± 11	72 ± 9	69 ± 9	.001
Serum Creatinine, mg/dL	4.0 ± 4.3	4.8 ± 5.9	5.7 ± 5.3	5.5 ± 4.5	5.6 ± 5.0	5.1 ± 5.0	.001
eGFR, mL/min/ 1.73 m^2	37 ± 27	38 ± 28	32 ± 29	34 ± 24	26 ± 22	32 ± 28	.001
Urine Proteing/24h	3.4 ± 2.5	3.5 ± 2.4	3.8 ± 2.1	3.6 ± 2.1	4.7 ± 4.7	3.4 ± 2.9	
Hypertension, %b	51	40	59	51	67	54	> .05
M1, %	20	-	32	28	23	26	> .05
E1, %	19	30	-	26	25	39	.001
S1, %	56	78	77	-	64	74	> .05
T1, %	50	57	64	56	-	60	.001
C1, %	40	52	81	52	47	-	.001
ESKD, %	35	26	45	42	60	46	-

Data are means ± SD or frequencies (%).
Notes: M1, mesangial hypercellularity ≥ 50%; E1, any endocapillary hypercellularity; S1, any segmental glomerulosclerosis; T1, tubular atrophy and interstitial fibrosis > 25%; C1, at least one cellular or fibrocellular crescents; eGFR, according to MDRD; Hypertension, systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg (ESKD, end stage renal disease).

more than 5 mg/dL. Presence of T1 was associated with the lowest eGFR (26 ± 22 mL/min/ 1.73 m²) compared to other Oxford classification components, whereas in C1 the baseline SCr was 5.1 ± 5.0 mg/dL and eGFR was 32 ± 28 (mL/min/ 1.73 m²). Existence of crescents ≥ 30% correlated with significantly higher serum creatinine (5.6 ± 3.2) and lower eGFR (23 ± 32 mL/min/ 1.73 m²) at baseline. The largest amount of 24-hour urine protein was observed in patients with T1 (4.7 ± 4.7 g/24h).

Development of ESKD

During a mean follow- up period of 43 ± 29 months, 40 patients developed ESKD (35%). T1 was associated with a high frequency of ESKD i.e., in 34 out of 57 patients (60%). Twenty one (46%) of patients with at least one crescents (C1) developed ESKD. The risk of ESKD in patients with C ≥ 10% and C ≥ 20% or C ≥ 30crescents, was 50, 58, and 64%, respectively.

Risk Factors Associated with ESKD

Association between continuous and categorical independent variables and the risk of development of ESKD are shown in Table 2.

In univariate analyses with continuous variables, higher SCr at baseline was associated with higher risk of ESKD. Among categorical variables hypertension at baseline, T1 and the presence of any crescents were associated with increased risk of ESKD. However in multivariate analysis, only serum creatinine at baseline, T1 and C ≥ 30% were significantly associated with development of ESKD.

Additive Effect of Crescents of Other Oxford Classification Components on the Risk of ESKD

The additive effect of crescents on other Oxford classification components is shown in Table 3. The

Table 2. Univariate and Multivariate Analyses of Baseline Clinical and Laboratory Predictors of ESKD

	Univariate Analyses (HR 95% CI)	*P*	Multivariate Analyses (HR 95% CI)	*P*
Age, y	0.99 (0.97 to 1.01)	> .05	0.99 (0.96 to 1.03)	> .05
Sex (male)	0.63 (0.29 to 1.37)	> .05	0.78 (0.36 to 1.78)	> .05
Weight, kg	0.99 (0.96 to 1.02)	> .05	0.98 (0.94 to 1.03)	> .05
Baseline Serum Creatinine, mg/dL	1.20 (1.14 to 1.26)	< .0001	1.22 (1.12 to 1.29)	< .0001
Urine Protein, g/24h	1.00 (1.00 to 1.00)	> .05	1.00 (1.00 to 1.00)	.057
Hypertension	2.71 (1.37 to 5.33)	.004	1.69 (0.94 to 3.06)	> .05
M1	0.58 (0.24 to 1.39)	> .05	2.26 (0.91 to 5.64)	> .05
E1	1.65 (0.80 to 3.38)	> .05	0.68 (0.26 to 1.81)	> .05
S1	1.71 (0.88 to 3.32)	> .05	0.69 (0.33 to 1.45)	> .05
T1	7.20 (3.01 to 17.18)	< .0001	6.95 (2.20 to 22.02)	.01
C1	2.13 (1.14 to 3.97)	.017	1.02 (0.39 to 2.63)	> .05
C1 (10%)	1.94 (0.99 to 3.82)	.055	0.631 (0.25 to 1.58)	> .05
C1 (20%)	2.77 (1.21 to 6.29)	.015	1.41 (0.51 to 3.90)	> .05
C1 (30%)	3.37 (1.48 to7.68)	.004	3.56 (1.15 to 11.00)	.027

All variables are at baseline.
In multivariate analysis the main variable was adjusted for all other variables.
Notes: HR, hazard ratio with 95% confidence interval (CI); M1, mesangial hypercellularity ≥ 50%; E1, any endocapillary hypercellularity; S1, any segmental glomerulosclerosis; T1, tubular atrophy and interstitial fibrosis > 25%; C1, at least one cellular or fibrocellular crescents; C1 (10%) ≥ 10% cellular or fibrocellular crescents; C1 (20%) ≥ 20% cellular or fibrocellular crescents; C1 (30%) ≥ 30% cellular or fibrocellular crescents.

Table 3. Development of ESKD in Univariate and Multivariate Analyses with Combination of C1 with Other Oxford Classification

	ESKD (%)	Univariate Analyses (HR 95% CI)	*P*	Multivariate Analyses (HR 95% CI)	*P*
C1 + M1	25	0.93 (0.27 to 3.20)	> .05	0.63 (0.23 to 1.14)	> .05
C1 + E1	30	1.36 (0.53 to 3.48)	> .05	0.68 (0.26 to 1.81)	> .05
C1 + S1	44	2.22 (1.00 to 4.95)	> .05	1.30 (0.49 to 3.45)	> .05
C1 + T1	74	9.20 (3.43 to 24.63)	< .0001	6.54 (1.75 to 24.34)	.004
C1 (≥ 30%) + T1	75	12.54 (3.80 to 41.30)	< .0001	7.95 (2.05 to 30.75)	.003

Notes: HR, hazard ratio with 95% confidence interval (CI); Definitions of M1, E1, S1, T1, and C1 according Tables 1 and 2.
In each combined independent variable, C0 + M0, C0 + E0, C0 + S0, and C0 + T0 were used as the reference group.
In multivariate analysis the main variable was adjusted for all other variables the same as Table 2.

highest incidence of ESKD was seen in patients with C1 + T1, of whom 20 out of 27 patients (74%) developed ESKD. In both, univariate and multivariate analyses, only presence of C1 with T1 were associated with higher risk of ESKD. In sub-analysis in patients with crescents ≥ 30% and T1, 75% developed ESKD and in multivariate model the risk increased considerably (HR = 7.95, 95% CI: 2.05 to 30.75).

Proportion of Crescents and Renal Survival

Kaplan- Meier survival curves of crescent subgroups are shown in Figure 1. The mean renal survival was 50.64 months (95% CI: 39.3 to 61.9) in C1 (at least one crescent), 47.2 months (95% CI: 32.2 to 62.3) in C ≥ 10%, 35.0 months (95% CI: 12.7 to 57.3) in C ≥ 20% and 29.3 months (95% CI: 7.2 to 51.4) in C ≥ 30%. The renal survival curves in different C and T combinations are shown in

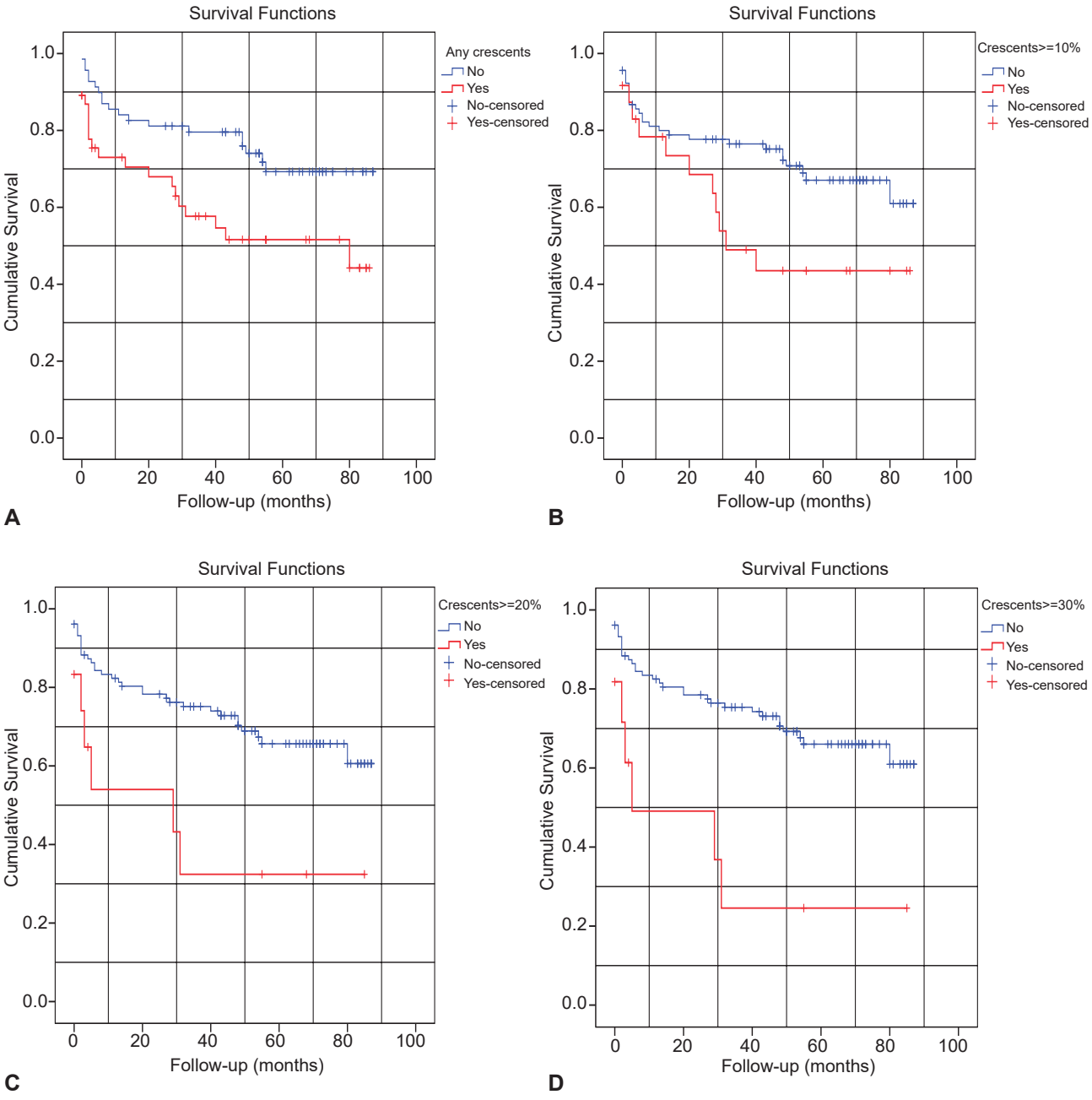


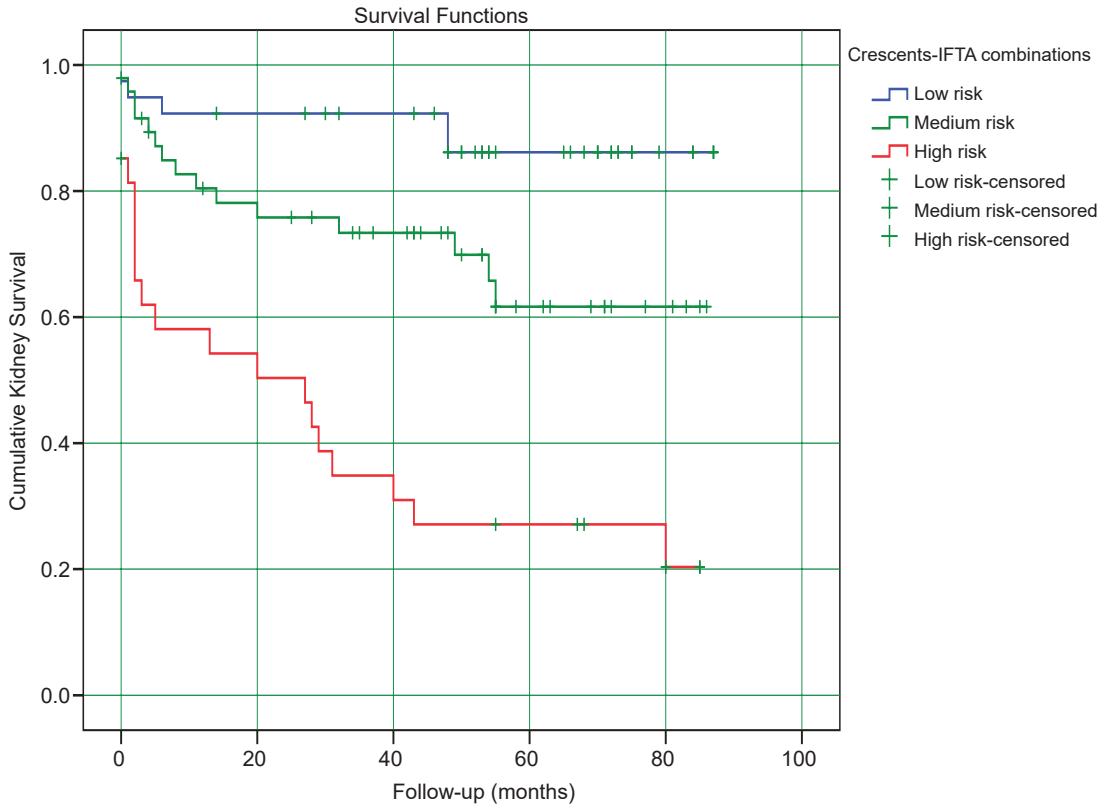
Figure 1. Kaplan–Meier plots for progression of ESKD according to percentage of crescents during the follow-up. A) at least one crescents (Log rank = 6.02, *P* = .014), B) Crescents ≥ 10% (Log Rank = 3.89, *P* = .048), C) Crescents ≥ 20% (Log rank = 6.59, *P* = .01), and D) Crescents ≥ 30% (Log rank = 9.62, *P* = .002).

Figure 2. The overall mean survival rate was 60.9 months (95% CI: 54.2 to 67.5) in all patients, 78.1 months (95% CI: 70.5 to 85.6) in low risk group (C0 + T), 61.6 months (95% CI: 51.4 to 71.8) in medium risk group (C1 + T0 or C0 + T1), and 32.3 months (95% CI: 19.2 to 45.3) in high risk group (C1 + T1).

The prediction risk of ESKD by the presence of C1 + T1 is given in Figure 3. The prediction of risk by receiver-operating characteristic curve (ROC-curve) showed a C-Statistic of 0.76 (95% CI: 0.67 to 0.85).

DISCUSSION

In the present study we assessed the impact of crescents alone or combination with other pathological features of Oxford classification on the risk of ESKD in patients with IgA nephropathy. Previously in patients with IgAN various risk factors for poor kidney prognosis were defined as decreased GFR at baseline (eGFR), proteinuria, age, gender and hypertension.[11-15] Pathologic severity has also been indicated as an important risk factor in many studies.[11,16,17] Since the introduction of Oxford classification by an international working group in 2009, renal outcome in IgAN has been mainly assessed by using pathological features as an independent risk factor.[7] Accordingly, evidence based histologic classification showed four histologic components (M1, E1, S1, T1-T2), which were associated with progression to ESKD or 50% decrease of eGFR. In multivariate analysis, after adjustment for initial eGFR, proteinuria and mean arterial pressure, M1, S1, and T1-T2 still independently predicted renal survival. E1 was



	Mean Survival Time (mo) (95% CI)
Low Risk	78.08 (70.50 to 85.66)
Medium Risk	61.64 (51.48 to 71-81)
High Risk	32.30 (19.29 to 45.31)
Overall	60.63 (53.93 to 67.32)

Figure 2. Impact of presence or absence of combination of C and T in progression of ESKD with Kaplan–Meier plots (Low Risk: C0 + T0. Medium Risk: C1 + T0 or C0 + T1, High Risk: C1 + T1) (Log Rank = 31.16, *P* < .001). Notes: C1, at least one cellular or fibrocellular crescents; T1, tubular atrophy and interstitial fibrosis > 25%.

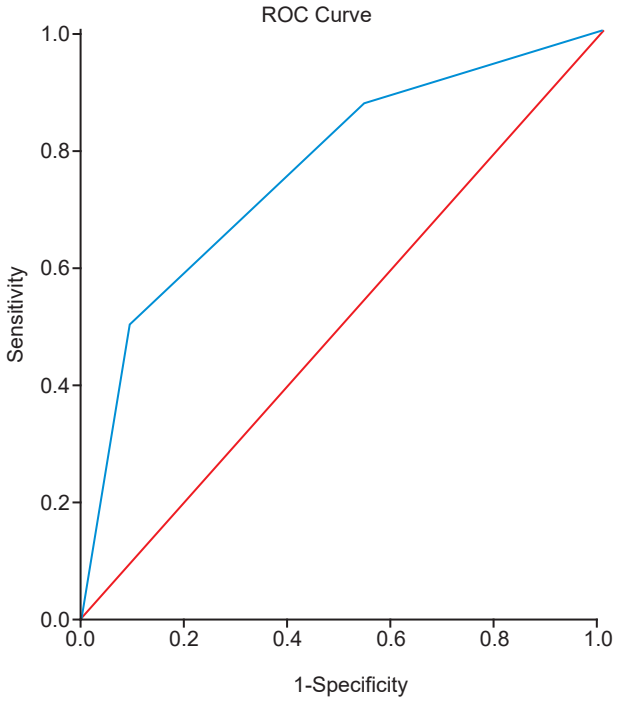


Figure 3. Receiver-operating characteristic curves (estimated for evaluating the capacity of discrimination of the risk to predict ESKD with presence of C1 + T1 in model (C-Statistic of 0.76 , 95% CI: 0.67 to 0.85).

independently associated with renal outcome only in patients who did not receive steroid or immunosuppressive therapy.[7] In the original study, the patients with proteinuria < 0.5 g/d, eGFR < 30 mL/min and patients who had been followed for less than 1 year were excluded.[7] The result of additional studies indicated T score as the strongest predictor of renal outcome.[18-20] Validation of the Oxford Classification of IgA Nephropathy (VALIGA) study included 1,147 IgAN patients from 13 European countries.[8] Patients with proteinuria < 0.5 g/d and eGFR < 30 mL/min were also included in this study. In VALIGA study presence of M1 and/or S1 were associated with high level of proteinuria. Decline of renal function related to more frequent M1,S1 and T1-2 lesions and renal survival was approximately 50% at 5 years.[8] However in other studies M and S score were not associated with an increased risk of ESKD in multivariate analysis.[18,19,21] It is suggested that probably this finding has been related to small sample size and low power of the study.[22] The effects of M and S on renal prognosis have been inconsistent among several studies.[18,19,23] In most of the studies E score was not significantly linked to risk of ESKD.[18,23,24] However it is shown that E1 lesions are more likely to be treated with steroids and the patients who did not receive steroid had higher risk of progression to CKD or ESKD.[18,25]

In our study the M, E and S scores were not significantly associated with the risk of ESKD and only T score increased the risk of ESKD in both univariate and multivariate analyses.

Presence of tubular atrophy and interstitial fibrosis in kidney biopsy has been well known as a strong risk factor of CKD and ESKD development, regardless of the type of the glomerular disease.[26-28] In the original Oxford Classification score, T was defined as fibrosis of T0 = 1 to 25%, T1 = 26 to 50%, and T2 > 50%.[7] As in our cohort 60% of the patients who had tubular atrophy and interstitial fibrosis ≥ 25% developed ESKD and in multivariate analyses, T ≥ 25% increased the risk of ESKD by almost 7 times compared to T < 25%, we defined T score as T0 < 25% and T1 ≥ 25%. So we suggest to consider T ≥ 25% as an important prognostic factor.

The difference between our cohort with most of the other studies is a considerably higher mean baseline serum creatinine (4 ± 4.3 mg/dL) and worse kidney function, which is most probabley due to late reffereal to our tertiary kidney center. Our findings suggests that with progression of CKD, T score, which indicates chronicity, becomes a more important risk factor. The other pathological features with Oxford classification are probably related to development of renal impairment in patients presenting with normal or near normal kidney function.

The influence of crescents on renal outcome in IgA nephropathy has been evaluated in several studies. The results of the study by Roberts *et al* showed that crescents were associated with worse kidney function in univariate analysis but this effect was less important in multivariate analysis.[29] In other studies, presence of crescents predicted rapid decline of renal function.[30,31]

In 2014 the Oxford Conference on IgA Nephropathy assessed the association between the presence of crescents and renal outcome. They included 3096 patients from four studies, i.e., the original Oxford cohort, the VALIGA study cohort and two large Asian cohorts. Of these 1118 patients (36%) had cellular or fibrocellular crescents. The results showed that patients with

crescents portended a higher likelihood of receiving immunosuppression. They concluded that the presence of any number of crescents was associated with a worse renal outcome, only in those patients who had received immunosuppression. However crescents more than 25% of glomeruli related with poor renal outcome regardless of treatment.[9] This finding led to adding the crescent score to the original oxford classification. [10] In the study by Zang *et al.*, increasing of the number of crescents by 5% predicted nearly 50% risk of doubling of baseline serum creatinine or ESKD.[32] In our study 40% of patients had at least one crescent and the mean number of crescents was 22% of glomeruli which was higher compared to other studies. This maybe another reason for low baseline renal function in our study population. In our cohort the presence of any number of crescents was associated with higher risk of ESKD only in univariate analysis and the risk was not significant in multivariate analysis. In multivariate analysis only crescents ≥ 30% were associated with increased risk of ESKD and 64% of the patients developed ESKD. This finding is almost similar to Oxford classification that indicated that crescents > 25%, irrespective of treatment, increased the risk of renal outcome.

We analyzed the additive effects of crescents on M, E, S, and T score. As a result only the combination of C1 + T1 was highly associated with risk of ESKD and 74% of those patients developed ESKD. In multivariate analysis, even when adjusted for baseline serum creatinine and proteinuria, the patients with composite of any number of crescents and T ≥ 25% were at more than 5 times higher risk of ESKD compared to C0 + T0. The result of this finding suggests that any number of crescents predicted the risk of ESKD only in the presence of T1. In sub- group of patients with C1 ≥ 30% and T1, 75% developed ESKD and in multivariate analyses they had 8 times higher risk for ESKD, compared to C0 + T0.

It is important to remember that IgAN studies based on Oxford classification, are mostly observational and retrospective and uncontrolled for treatment.

In our study with by using clinical characteristics and laboratory data as independent variables, in multivariate analysis only serum creatinine at baseline was significantly associated with risk of ESKD. In other studies also lower kidney function at baseline was identified as a strong risk factor for progression of CKD/ESKD.[11,3,14]

In our study baseline albuminuria was not associated with increased risk of ESKD, which is contrary to the results of a number of other studies.[11,33] However in the study by Xie *et al* on patients with IgAN, four baseline variables including eGFR, serum albumin, hemoglobin and systolic blood pressure independently predicted the risk of ESKD, whereas proteinuria at baseline was not detected as a risk factor.[21] Our findings suggest that probably proteinuria is associated with increased risk of CKD/ESKD, in patients with normal or near normal kidney function, and is not counted as an independent risk factor in patients with low GFR at presentation.

It has to be mentioned that only approximately 30% of renal outcome may be predicted by Oxford classification score and clinical and laboratory data and additional biomarkers are needed to improve risk prediction in these patients.[34]

In the study by Fabiano *et al.*, in children with IgAN, positivity for C4d immunostaining in the mesangial area was an independent predictor of renal function deterioration.[35]

In the study by Ni *et al.*, which included 878 patients with IgAN, patients with time-averaged serum creatinine value > 120 mmol/L and time averaged serum albumin level < 38 g/L were less likely to recover from renal progression.[36]

Our study has several limitations. This is an observational study and the cause-effect relationship cannot be thoroughly determined. In this study the risk of ESKD was not adjusted for potential confounders such as treatment protocols and comorbidities. Diversity between time of the clinical manifestation and the renal biopsy in patients can also lead to time bias. This is a single center study with mostly low kidney function at the time of referral and our result cannot be generalized to all IgAN population.

The major strengths of this study is the good number of events (ESKD). We also analyzed a new and novel index, i.e., the additive impact of crescents on other Oxford classification score components.

CONCLUSION

In conclusion in our study on patients with IgAN, by using Oxford classification components as risk factors, tubular atrophy and interstitial

fibrosis ≥ 25% and crescents ≥ 30% were associated with higher risk of ESKD. Composite presence of any number of crescents with tubular atrophy and interstitial fibrosis ≥ 25% was highly related to increased risk of ESKD.

DISCLOSURES

None.

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