

RESEARCH ARTICLE

Clinical impact of endocapillary proliferation with modified cutoff points in IgA nephropathy patients

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Abstract

Predictive values of mesangial proliferation (M), endocapillary proliferation (E), segmental glomerulosclerosis (S), and crescents (C) among 19 validation studies of the Oxford Classification of IgA nephropathy (IgAN) were discrepant, especially in Asian patients. These validation studies indicate that cutoffs of MESC score in the Oxford Classification may not be generalizable. Thus, we aimed to improve the clinical value of MESC scores by modifying the cutoff points. A total of 104 patients with IgAN were diagnosed from 2001 to 2012 via renal biopsy and retrospectively evaluated at Nagoya University Hospital. The cutoff point for modified (M'E'S'C') was determined using the receiver operating characteristic curve in association with renal outcome in the training cohort. Clinical values of the Oxford MESTC vs M'E'S'C' cutoff points were analyzed using Kaplan-Meier and Cox regression in association with poor renal outcome in the validation and the entire cohort. Of 104 patients, 12.5% reached poor renal outcome over a median of 6.25 [4.16–9.61] years of follow-up. The modified cutoffs were defined as $\geq 40\%$, $\geq 10\%$, $\geq 20\%$, and $\geq 5\%$ in the glomeruli for M'E'S', and C' respectively. In univariate analysis, E', S', and T were significantly associated with poor renal outcome, whereas Oxford MESC, M', and C' in the training and validation cohort were not associated with poor renal outcome. Using multivariate analysis in the presence of estimated glomerular filtration rate (eGFR), only E' was a significant predictive factor for poor renal outcome. The E' with modified cutoff point of 10% significantly improved predictive value for poor renal outcome in IgAN. Therefore, the clinical value of modified cutoff points for M'E'S'C' scores should be validated with various cohort studies in different regions.

Introduction

IgA nephropathy (IgAN) is one of the most common glomerulonephritis, with a higher incidence in the Pacific Rim and Mediterranean countries.[1,2] Renal biopsy confirms the

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diagnosis of IgAN, assesses disease severity, and guides therapeutic strategies in clinical practice.[3] Although several pathological classifications have been developed from expert opinion, each has its limitations and none has achieved widespread agreement. [3–6] Therefore, the International IgA Network and Pathology Society developed the Oxford Classification of IgAN in a cohort of 265 patients with IgAN comprising mainly Caucasians, as only 20 and 28 adults with IgAN from Japan and China, respectively, were included. [6,7]

The original Oxford Classification study has demonstrated prognostic values of mesangial hypercellularity (M), endocapillary proliferation (E), segmental glomerulosclerosis (S), tubular atrophy/ interstitial fibrosis (T). Nineteen validation analyses, including the Oxford Classification, have been reported, of which 17 showed predictive value of T score. However, the prognostic value of S, M, E, and C were confirmed only in 8, 6, 3, and 0 validation studies, respectively. [8] In Japan, Katafuchi et al. reported the predictive value of T and C scores in adult patients with IgAN, [9] and our former study showed that only T score was associated with renal outcome.[10] Most of the validation studies from Asian countries could not demonstrate the predictive values of MESC score in the Oxford Classification.[10–16]

Both Katafuchi et al.'s and our previous study revealed a considerably smaller positive number of M and T scores and a higher positive number of E and C scores. In Japan, patients with IgAN seem to be diagnosed at an earlier phase because Japanese people undergo annual health examinations, including urinalysis.[17] Therefore, cutoff points of MESC in the Oxford Classification may not be optimal for Japanese patients with IgAN. Thus, in this study, we aimed to improve the clinical value of MESC scores by modifying their cutoff points.

Materials and methods

Study design and participants

This retrospective cohort study was conducted at the Nagoya University Hospital. All patients with IgAN were enrolled between 2001 and 2012. Patients with the following criteria (age ≥ 18 years, primary IgAN, follow-up period > 1 year) and specimens with ≥ 8 glomeruli were included. Forty-six patients were excluded from this study (Fig 1), and the remaining 104 patients with IgAN were analyzed, including patients with < 0.5 g/day proteinuria ($n = 24$) and advanced stage of disease (eGFR < 30 ml/min per 1.73 m^2 , $n = 4$). The ethics committee of the Nagoya University Hospital approved this retrospective study design without written informed consents, but the informed consent was obtained from almost entire patients with IgAN at the time of renal biopsy (IRB no. 1135/2015-0386).

Definitions

The baseline was defined as the time of renal biopsy. The clinical variables measured at the time of renal biopsy were; age (yr), BMI (kg/m^2), serum cholesterol (mg/dl), proteinuria (g/day), eGFR ($\text{ml}/\text{min}/1.73\text{m}^2$). Hypertension was defined as systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP), ≥ 90 mmHg and/or on antihypertensive therapy; estimated glomerular filtration rate (eGFR) was estimated using the Japanese GFR equation [$= 194 \times \text{SCr}^{-1.094} \times \text{age}^{-0.287} \times 0.739$ (if female)] (SCr; serum creatinine).[18] The time interval between renal biopsy and the last outpatient visit, death, end-stage renal disease (ESRD) (eGFR < 15 ml/min/ 1.73 m^2) or initiation of hemodialysis during this time period was defined as follow-up period. RAS-blockade (ACE inhibitors and/or angiotensin receptor blockers) treatment described at any dose during follow-up and Immunosuppressive therapy was defined according to uniformed treatment regimens of Pozzi's et al.[19] After renal biopsy. Renal outcome was defined as a 50% increase in SCr and/or initiation of hemodialysis (HD)

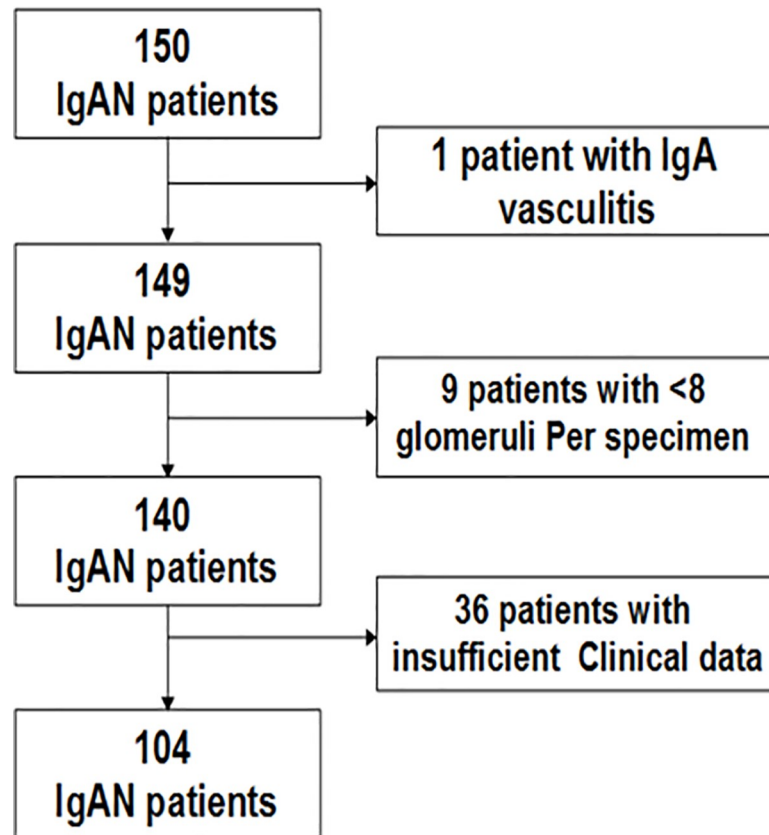


Fig 1. The flowchart shows the number of IgAN patients excluded from the cohort study.

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from baseline. [2,10,20–22] Proteinuria and eGFR at the end of follow-up were also measured, and followed until the end of 2016.

Renal biopsy review

All specimens were analyzed according to the Oxford Classifications [23]: mean M score was measured in all scorable glomeruli based on severity of cell proliferation per mesangial area (0–3), and the proportions of E1, S1, and cellular and fibro-cellular crescents (C1) in all obtained glomeruli were recorded in a scoring sheet. These histological characteristics blinded from the clinical data.

All specimens with a thickness of 2–3 μm were stained with periodic acid-Schiff, hematoxylin and eosin, periodic acid-methenamine silver, and Masson's trichrome was assessed by AB, K and a group of expert nephrologist (YY, TK, TI, TO, MH, KI).

Modified cutoff points

All 104 patients were divided into three equal sets: two-third of samples accounted for the training cohort and one-third of samples accounted for the validation cohort. A random selection was conducted according to the date of renal biopsy. The cutoff point for modified (M'E'S'C') was determined using receiver operating characteristic curve (ROC) analysis. Youden Index[24] was used to obtain optimal cutoffs according to mean M score and the proportions of positive ESC scores in association with poor renal outcome in the training cohort. The

clinical value of traditional MESTC vs M'E'S'C' cutoff points were analyzed using Kaplan-Meier and Cox regression in association with poor renal outcome in the validation cohort.

Statistical analysis

The clinical values of the Oxford MESTC cutoffs vs. modified M'E'S'C' cutoff points were analyzed using Kaplan-Meier analysis and the significant difference in renal survival curve between the two groups was assessed using the log-rank test. The Cox proportional hazards model was used in the univariate and multivariate analyses in association with poor renal outcome in the training cohort, validation cohort, and in the entire cohort. Significant variables determined using univariate Cox-regression analysis and the clinical relevant factor (eGFR) was selected in multivariate Cox-regression models in all 104 patients. Results were expressed as hazard ratios (HR) with 95% confidence intervals (CI). The correlation between histological features and clinical variables was analyzed using the Spearman test.

Parametric and nonparametric variables were represented as the median and interquartile range [IQR]. The student's test was used to analyze the difference in parametric variables. Categorical variables were depicted in percentages and compared using the chi-squared test. The proportional hazards assumption for covariates was tested using Schoenfeld residuals. $P < 0.05$ was considered statistically significant. All statistical analyses were conducted using STATA/SE 14.2. (Stata Corp.2015, College Station, Texas, USA).

Results

Clinical characteristics

The patient's baseline characteristics are shown in [Table 1](#). Between the training and validation cohorts, significant differences were shown only in baseline eGFR and the total number of patients treated with RAS-blockade, but differences were not observed in other clinical variables.

Of 104 patients, 12.5% reached poor renal outcome in over 6.25 [4.16–9.61] years of follow-up. The baseline proteinuria, SCr, and proportion of hypertension in this study vs. original Oxford Classification were (0.96 vs 1.7) g/day, SCr (0.8 vs 1.2) mg/dl, and (35 vs 65) %, respectively.

Modified threshold

ROC analysis determined a mean M score of $\geq 38\%$ as the optimal cutoff point for M', and the proportions of $\geq 8\%$, $\geq 17\%$, $\geq 4\%$ as optimal cutoffs for E', S', and C' respectively, in the training cohort. For the ease of clinical use, modified cutoff points of 40%, 10%, 20%, and 5% for M', E', S', and C' were defined, respectively. The chi-squared test demonstrated significant differences between proportions of M1 vs. M'1, E1 vs. E'1, S1 vs. S'1, and C1 vs. C'1 and the results are shown in [Table 2](#).

Univariate analysis

Kaplan-Meier analysis. Renal survival free from renal outcome was significantly lower in E' ($p = 0.01$) and S' ($p < 0.01$) in the log-rank test in both training and validation cohorts (Figs 2 and 3).

Cox regression analysis. The risk of progression to poor renal outcome was significantly higher in E' (HR = 7.98, $p = 0.01$) and S' (HR = 13.67, $p = 0.003$); whereas, the Oxford MESTC, M', and C' had no significant association with poor renal outcome in the training cohort ([Table 3](#)). Similarly, in the validation study, E' (HR = 11.27, $p = 0.03$) and S' (HR = 10.60,

Table 1. Baseline and follow-up clinical characteristics in the training and validation cohorts.

Baseline variables	Training cohort (n = 70)		Validation cohort (n = 34)		p value
	Median, no	IQR, (%)	Median, no	IQR, (%)	
Gender (F)	37	(53)	21	(62)	0.39
Age (year)	33	[24–45]	37	[28–46]	0.84
BMI (kg/m ²)	21	[20–24]	22	[21–24]	0.701
HT + (-)	23/47	(33)/(67)	9/25	(27)/(73)	0.51
SBP (mm-Hg)	120	[107–129]	120	[108–130]	0.831
DBP (mm-Hg)	70	[63–80]	71	[64–82]	0.83
TCH (mg/dl)	205	[180–228]	198	[176–222]	0.181
Serum IgA (mg/dl)	300	[237–360]	326	[259–375]	0.89
Proteinuria (g/day)	0.96	[0.57–1.68]	0.83	0.49–1.43]	0.36
SCr (mg/dl)	0.8	[0.7–1.0]	0.9	[0.7–1.1]	0.911
eGFR (ml/min/1.73m ²)	79	[59–95]	66	[55–83]	0.02*
Follow-up					
Follow-up period (year)	6.5	[4.2–9.8]	6.4	[4.2–9.6]	-
Prednisone + (-)	50/20	(71)/(29)	21/13	(62)/(38)	0.32
RAS-blockade (ACEi/ARB) + (-)	58/12	(83)/(17)	22/12	(65)/(35)	0.04*
Underwent to tonsillectomy + (-)	26/44	(37)/(63)	27-Jul	(21)/(79)	0.09
SBP (mm-Hg)	114	[106–129]	117	[102–124]	0.586
DBP (mm-Hg)	70	[60–80]	67	[60–72]	0.164
Proteinuria (g/g Cr)	0.34	[0.18–1.28]	0.31	[0.13–0.98]	0.798
eGFR (ml/min-1.73m ²)	68.2	[44.1–85.7]	64.3	[45.4–81.8]	0.386

IQR interquartile range, *f* female, *BMI* body mass index, *SBP/DBP* systolic/ diastolic blood pressure, *TCH* total serum cholesterol, *IgA* Immunoglobulin A, *SCr* serum creatinine, *eGFR* estimated glomerular filtration rate.

*P<0.05: statistically significant

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p = 0.003) demonstrated a significant risk of progression to poor renal outcome, but neither the Oxford MESC nor M' and C' cutoffs were associated with poor renal outcome (Table 3). Among the clinical variables, eGFR was significantly associated with poor renal outcome but not proteinuria.

In the multivariate model-I analysis, E', S', C', and T scores were significantly associated with poor renal outcome. The significant pathological factors in univariate analysis, namely E', S', T, and eGFR were selected in the multivariate model-II analysis, which demonstrated

Table 2. Numbers and proportions of positive MESTC scores according to Oxford and modified cutoff points in the entire cohort.

Pathologic features	Original Oxford MESTC	Modified M' E' S' C'	P value
M1 no (%)	22 (21)	38 (37)	<0.001*
E1 no (%)	37 (36)	18 (17)	<0.001*
S1 no (%)	78 (75)	24 (23)	0.001*
C1 no (%)	53 (52)	38 (37)	<0.001*
^a T1+2 no (%)	17 (16)	-	-

M' modified mesangial hypercellularity, E' modified endocapillary proliferation, S' modified segmental glomerulosclerosis, C' modified crescents.

^a Cutoff for tubular atrophy and interstitial fibrosis in modified classification is the same as Oxford classification.

*p<0.05: Statistically significant by chi-squared test

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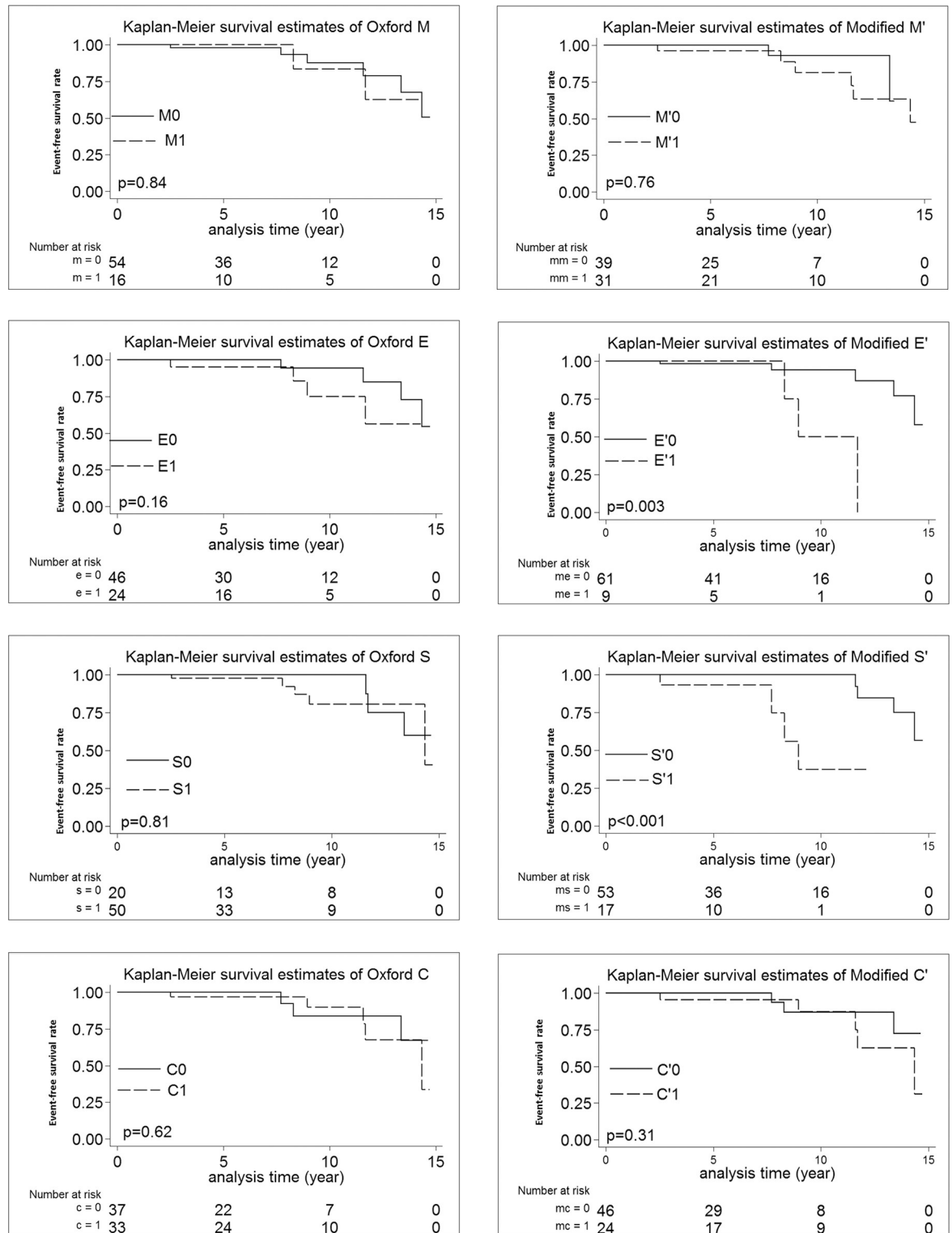


Fig 2. Kaplan-Meier analysis according to the original Oxford MESC vs. modified M'E'S'C' cutoffs in the training cohort.

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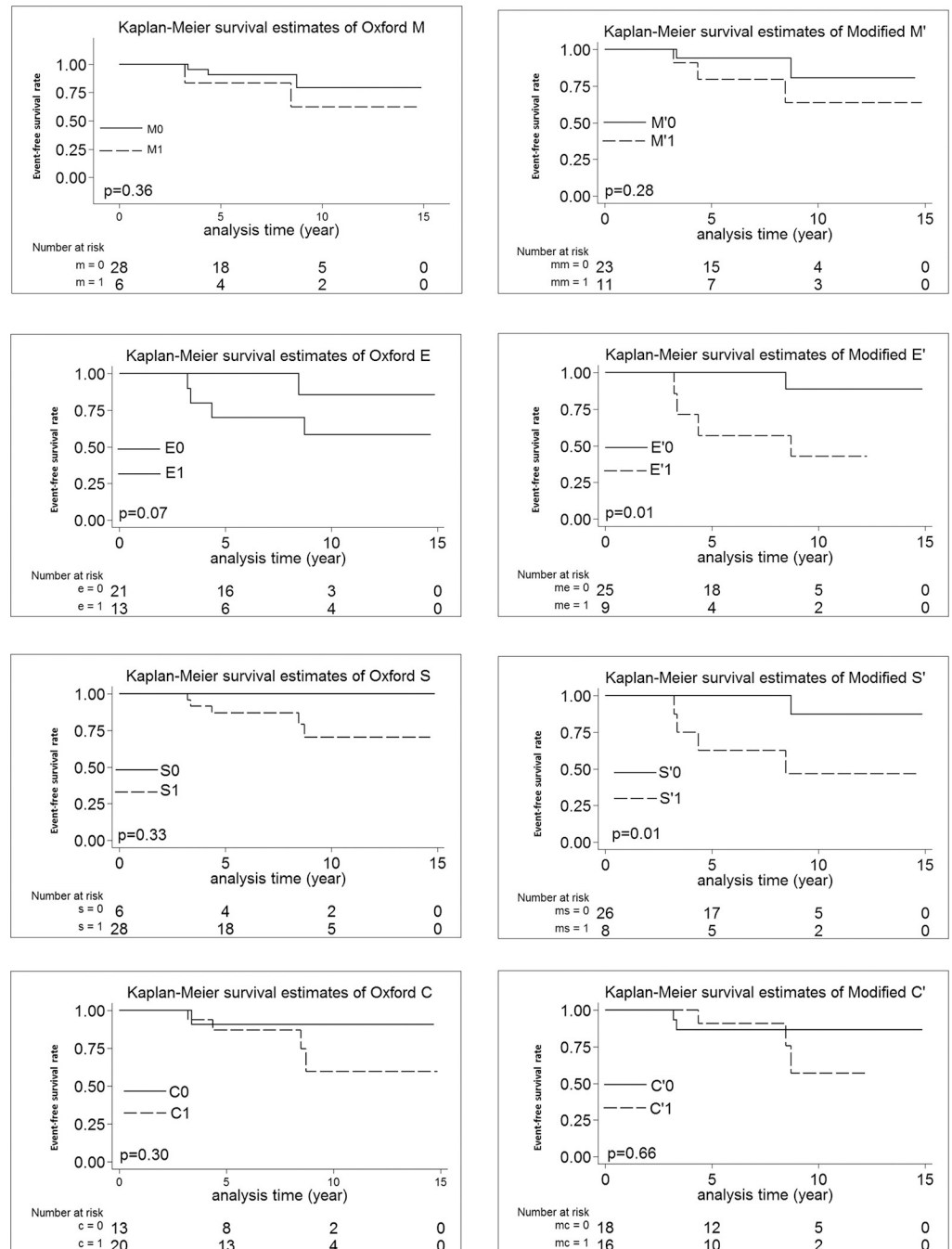


Fig 3. Kaplan-Meier analysis according to the original Oxford MESC vs. modified M'E'S'C' cutoffs in the validation cohort.

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that E' (HR = 8.25, p = 0.004) and eGFR (HR = 0.96, p = 0.029) were significant factors for poor renal outcome (Table 4).

Among clinical and pathological features, T score was significantly correlated with eGFR, proteinuria, and S' score (Table 5).

Table 3. The hazard ratio of the Oxford MESTC and modified M'E'S'C' scores for renal outcome in the training and validations cohorts.

Training cohort			
Original Oxford cutoffs	Univariate HR (95% CI)	Modified M'E'S'C' cutoffs	Univariate HR (95% CI)
M0 <50%	Reference	M'0 <40%	Reference
M1 ≥50%	1.19 (0.23–6.16)	M'1 ≥40%	1.27 (0.27–5.87)
p	0.840	p	0.761
E0 (absent)	Reference	E'0 <10%	Reference
E1 (present)	2.85 (0.63–12.87)	E'1 ≥10%	7.98 (1.58–40.45)
p	0.171	p	0.010*
S0 (absent)	Reference	S'0 <20%	Reference
S1 (present)	1.32 (0.31–5.72)	E'1 ≥20%	13.67 (2.39–78.25)
p	0.710	p	0.003*
C0 (absent)	Reference	C'0 <5%	Reference
C1 (present)	1.44 (0.34–6.09)	C'1 ≥5%	2.09 (0.49–8.86)
p	0.620	p	0.320
T0 (<25%)	Reference	-	-
T1+2 (≥25%)	14.14 (3.07–65.04)	-	-
p	0.001*	-	-
Validation cohort			
M0 <50%	Reference	M'0 <40%	Reference
M1 ≥50%	2.28 (0.37–13.89)	M'1 ≥40%	2.57 (0.43–15.4)
p	0.371	p	301
E0 (absent)	Reference	E'0 <10%	Reference
E1 (present)	6.12 (0.67–55.74)	E'1 ≥10%	11.27 (1.24–102.21)
p	0.110	p	0.030*
S0 (absent)	Reference	S'0 <20%	Reference
S1 (present)	1.52 (0.29–7.98)	E'1 ≥20%	10.60 (1.18–94.99)
p	0.800	p	0.003*
C0 (absent)	Reference	C'0 <5%	Reference
C1 (present)	3.00 (0.33–27.02)	C'1 ≥5%	1.49 (0.25–8.93)
p	0.331	p	0.660
T0 (<25%)	Reference	-	-
T1+2 (≥25%)	6.87 (1.14–41.28)	-	-
p	0.034*	-	-

HR hazard ratio, M' modified mesangial hypercellularity, E' modified endocapillary proliferations, S' modified segmental glomerulosclerosis, C' crescents.

*p<0.05: Statistically significant.

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Discussions

In this study, we proposed to improve the prognostic value of MESC scores in the Oxford Classification in association with poor renal outcome defined as a 50% increase in SCr and/or HD initiation from baseline. Our results showed that E' (≥10% of glomeruli with E lesion), S' (≥20% of glomeruli with S lesion) and T in both training and validation cohort were significantly associated with poor renal outcome. However, neither the Oxford MESC nor M' and C' scores demonstrated an association with poor renal outcome in both training and validation cohorts. Moreover, in multivariate analysis in the presence of E', S', T, and baseline eGFR among all 104 participants, only E' was an independent and significant histological factor for poor renal outcome. To best of our knowledge, this is the first study that analyzed modified thresholds of MESC score and validated them in an external cohort.

Table 4. Hazard ratio of covariates for renal outcome by Cox regression analysis in all 104 patients.

Variables	Univariate		Multivariate model-I		Multivariate model-II	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
M'0/1	1.78 (0.56–5.68)	0.330	2.04 (0.53–7.90)	0.300	-	
E'0/1	9.26 (2.69–31.95)	<0.001*	7.63 (1.93–30.19)	0.004*	8.25 (1.95–34.84)	0.004*
S'0/1	5.70 (1.88–17.33)	0.002*	8.79 (1.92–40.29)	0.005*	3.12 (0.80–12.08)	0.100
T0/T1+2	7.59 (2.46–23.41)	< 0.001*	9.82 (2.26–42.60)	0.002*	2.60 (0.68–9.99)	0.163
C'0/1	2.06 (0.67–6.32)	0.209	8.70 (1.40–53.86)	0.020*	-	
Age	1.01 (0.97–1.05)	0.530	-	-	-	
Gender	0.45 (0.15–1.38)	0.161	-	-	-	
BMI	1.04 (0.89–1.23)	0.610	-	-	-	
HT	2.27 (0.74–6.94)	0.150	-	-	-	
eGFR	0.95 (0.92–0.98)	0.002*	-	-	0.96 (0.93–0.99)	0.029*
UPE	1.33 (0.74–2.40)	0.334	-	-	-	

HR hazard ratio, M' modified mesangial hypercellularity, E' modified endocapillary proliferation, S' modified segmental glomerulosclerosis, and C' modified crescents, T tubular atrophy /interstitial fibrosis, HT hypertension, UPE urine protein excretion.

*p<0.05: Statistically significant

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In the literature to date, only one study by Shi et al. has analyzed the threshold of E25 (25% of glomeruli with E1) but failed to reveal a significant association of E25 with ESRD.[25] The major differences between our study and that of Shi et al.'s were in definition of renal outcome and methods to set cutoff points. We defined renal outcome as 50% SCr increase and/or HD initiation, whereas Shi et al. only analyzed ESRD for renal outcome. The reason they set the threshold of E25 was not documented. Moreover, patients with mild stage of disease were excluded in Shi et al.'s study; therefore, the patients in Shi et al.'s study had more proteinuria (1.7 g/day vs. 0.9 g/day) than our cohort.

Among the pathological variables, E', S', C', and T scores were significantly associated with poor renal outcome. However, in the presence of baseline eGFR with significant pathological variables in univariate analysis, only the E' score was significantly associated with poor

Table 5. Correlations between modified M'E'S'C' cutoffs, the Oxford T score, and clinical parameters.

variables		E'	S'	T	C'	proteinuria	eGFR
M'	rho	-0.03	0.01	0.01	0.70	0.41	0.97
	p	0.76	0.91	0.98	0.50	0.08	0.01*
E'	rho	-	0.05	0.24	0.04	0.29	0.16
	p	-	0.61	0.01*	0.70	0.003**	0.71
S'	rho	-	-	0.21	-0.03	0.19	-0.10
	p	-	-	0.03*	0.75	0.06	0.31
T	rho	-	-	-	-0.19	0.26	-0.30
	p	-	-	-	0.06	0.01**	<0.001**
C'	rho	-	-	-	-	0.18	0.05
	p	-	-	-	-	0.07	0.60

M' modified mesangial hypercellularity, E' modified endocapillary proliferation, S' modified segmental glomerulosclerosis, and C' modified crescents, T tubular atrophy /interstitial fibrosis, rho Spearman's correlation coefficient

**p< 0.05. Correlation is significant at the 0.01 level (2-tail)

*P <0.05. Correlation is significant at the 0.05 level (1-tail)*p <0.05. Correlation is significant at the 0.05 level (1-tail)

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renal outcome. Furthermore, a significant correlation between T score and baseline eGFR was also demonstrated. Therefore, the association between T score and renal outcome was attenuated by adding eGFR, implying that the effect of baseline eGFR on the renal outcome was mediated by the interstitial changes. This result is in line with that from Alamartin et al.'s study.[26] In addition, T1+T2 was less frequent in our cohort study than in former studies, which might be because Japanese patients with IgAN were diagnosed in an earlier phase of the disease in our study. Stefan et al [27] reported that tubular atrophy/interstitial fibrosis and segmental sclerosis indicates an advanced stage of IgAN renal damage and their predictive power for renal survival is not surprising. Additionally, tubular atrophy and interstitial fibrosis are not the characteristic lesions of IgAN, and they are universal predictors of renal outcome among most chronic kidney disease patients.

The prognostic value of C' in this study, could not be improved, which might be due to small sample size and only four patients having a baseline eGFR of $< 30\text{ml}/\text{min}/1.73\text{m}^2$. We were unable to analyze C2 ($\geq 25\%$ of glomeruli with crescents) in association with renal outcome because only two patients had $>25\%$ of crescents in our cohort.

Even though 68.3% of IgAN patients in our cohort were treated with corticosteroids, the significant association of E' with renal outcome was consistent. In the Oxford Classification study patients with positive E score were more likely to have been treated with immunosuppressive treatments including additional immunosuppressive agents in the follow-up, whereas no patients received cytotoxic agents in our study. Ballardie et al. reported the clinical effect of early combination therapy of corticosteroid with low dose cytotoxic immunosuppressive agents in a clinical trial study among IgAN patients.[28] Therefore, the treatment strategy for Japanese patients with IgAN should be reconsidered in the future.

This study has some limitations. First, it was a retrospective study design with a small number of participants. However, significant results were obtained in this study. Second, we determined the optimal cutoff points in a cohort of Japanese patients with IgAN, but these cutoff points may not be generalized to different regions and the cutoffs might change based on disease severity. However, we believe that the modified cutoff points for M'E'S'C' would be better prognostic predictors the original Oxford Classification MESC cutoff points that were considered only in the presence and absence for ES and C and need to be validated in different regions with larger sample size. Third, we defined renal outcome as 50% increase in SCr from baseline, although doubling of SCr was analyzed as renal outcome in clinical trials. Several previous studies among patients with IgAN demonstrated the clinical significance of 50% increase in SCr level as a renal endpoint [2, 20–22].

In conclusion, the E' with modified cutoff point of 10% significantly improved the predictive value for poor renal outcome in IgAN. The clinical value of the modified cutoff points for M'E'S'C' scores should be validated with various cohort studies in different regions.

Supporting information

S1 File. This supporting file shows ROC-Tables and ROC Figures for modified M'E'S'C'. (XLSX)

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