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Correlation between MEST-C score in kidney biopsy of IgA nephropathy patients with prognosis

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ABSTRACT

Introduction: IgA nephropathy (IgAN) is the most common type of primary glomerulonephritis, and is the most common type of glomerulopathy which leading to end-stage renal disease (ESRD). Prompt diagnosis of high-risk patients is important to initiate specific treatment early and prevent progression to ESRD. Oxford pathological classification, known as MEST-C score, attempts to predict prognosis based on pathological factors.

Objectives: In this study, we evaluated the value of pathological and clinical variables in estimating the prognosis of IgAN in Iranian patients.

Patients and Methods: In this retrospective cohort study, 165 specimens were reviewed by a nephropathologist, who reported the MEST-C score after the definitive diagnosis of IgAN. Patient records were reviewed to gather clinical data, including serum creatinine, 24-hour urine protein levels, diagnosis of hypertension and/or diabetes, and any treatment received. The pre-specified endpoints were determined as progression to ESRD, a reduction in estimated glomerular filtration rate (eGFR) to less than 50% of its baseline, performance of renal transplant, or death. The variables were compared in patients who had reached the pre-specified endpoints and those who had not, to estimate their prognostic value.

Results: Findings showed that the urinary protein level and T-score on biopsy were significant prognostic factors. Other pathological factors such as C, S, and M scores lost their significance on multivariate analysis. Further research is needed to validate the efficacy of the MEST- C score in different racial populations.

Conclusion: In our study, urinary protein level at diagnosis and T-score on biopsy were validated as prognostic factors, while M, E, S and C scores were not deemed significant. Further research is necessary to validate the MEST-C scoring system in different populations before its use in routine clinical practice.

Implication for health policy/practice/research/medical education:
IgA nephropathy (IgAN) is the most common type of primary glomerulonephritis. The Oxford pathological classification, known as MEST-C score, is designed to predict prognosis of IgAN based on pathological factors. This study pointed out that only urinary protein level at diagnosis and T-score on biopsy could predict IgAN prognosis.

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Introduction

IgA nephropathy (IgAN) is the most common primary glomerulonephritis (1). The prevalence of IgAN varies in different regions, with the highest incidence being among the Asian population (2). It is more common in males and young adults (3,4). The disease has variable renal manifestations, from asymptomatic hematuria with preserved renal function to progression toward end-stage

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renal disease (ESRD) (4). While previously considered benign, IgAN is now recognized as the most common type of glomerulopathy leading to ESRD (5), with a 20-year risk of ESRD approaching 30% (3). Since most affected individuals are young, the resulting morbidity causes long-term socioeconomic damage, making this disease a significant global challenge (4).

Despite the high prevalence of IgAN, developing clear treatment guidelines has been challenging and, aside from supportive measures, no medical treatment has been approved (6,7). Researchers have evaluated different methods to estimate prognosis in order to initiate early, curative treatment in high-risk patients (8). While clinical manifestations can be used as a guide, renal biopsy pathology has proven to be a reliable independent measure for determining prognosis (9).

The Oxford pathological classification, developed in 2009 and revised in 2016, is now used in clinical practice as the MEST-C score (10,11). It includes criteria such as mesangial hypercellularity (M-M0/1), endocapillary hypercellularity (E-E0/E1), segmental glomerulosclerosis (S-S0/1), tubular atrophy and interstitial tissue fibrosis (T-T0/T1/T2), and the presence of cellular or fibro-cellular crescents (C-C0/1/2) (12). Despite extensive research to validate the prognostic value of this system, the results are contradictory, making the identification of high-risk patients challenging (2,4,5,9,13-20).

Given the impact of race on the incidence of IgAN (21), the limited investigation of the MEST-C scoring system in the Iranian population, and the conflicting data on the usefulness of this scoring system.

Objectives

Our aim was to investigate the prognostic value of each of the pathological factors included in the Oxford pathological classification in Iranian patients.

Patients and Methods

Study design

We collected renal biopsy specimens diagnosed with IgAN from April 2014 to the end of May 2023 from a referral laboratory in Mashhad, Iran. The specimens were re-analyzed, and follow-up data was collected until September 2023. Patients were contacted to elicit any missing information.

This was a retrospective cohort study, that followed up on patients until they reached any of the pre-specified endpoints or the end of the study period. Tissues were collected through percutaneous needle biopsies, and two slides were prepared: one for light microscopy and another for immunofluorescence examination. All samples were evaluated by a nephropathologist who reported the MEST-C score after the definitive diagnosis of IgAN.

Apart from pathological data, other collected data included serum creatinine and 24-hour urine protein levels at the beginning and end of the follow-up period, comorbidities such as hypertension and diabetes, and the treatment received during the course of the disease, such as renin-angiotensin system (RAS) inhibitors and immunosuppressive drugs. The estimated glomerular filtration rate (eGFR) was calculated using the chronic kidney disease epidemiology collaboration equations (EPI) at the beginning and end of the follow-up.

Exclusion criteria included specimens from transplanted kidneys, specimens with fewer than six glomeruli, patients under 18 years of age, immunosuppressive treatment prior to biopsy, missing serum creatinine level at the beginning or within three months of the termination of follow-up, dialysis on presentation, and less than six months of follow-up. Finally, based on all the above criteria, 165 patients were successfully followed up out of a total of 314 biopsy samples. The endpoints of the study included progression to ESRD, a reduction in eGFR to less than 50% of its baseline, performance of renal transplant, or death due to renal disease.

Statistical analysis

Quantitative variables were reported as mean ± standard deviation (SD), and qualitative variables were reported as frequency (percentage). An independent samples *t* test was conducted to evaluate the effect of quantitative variables, such as age, urinary protein level, and eGFR, on renal prognosis in patients who had reached the pre-specified endpoints and those who had not.

The chi-square and Fisher-exact tests were conducted to evaluate the effect of qualitative variables, such as gender, diabetes, hypertension, pathologic findings on MEST-C score, and the treatment received, in the two mentioned groups. The logistic regression test evaluated the odds ratio (OR), both in univariate format for crude OR and multivariate format for adjusted OR. Due to the infrequent occurrence of three endpoints, i.e., >50% reduction in eGFR (2 patients), performance of renal transplantation (3 patients), and death (5 patients), they were combined with patients that had progressed to ESRD, forming an unfavorable outcome group, to increase the statistical power of the study. Patients who reached ESRD were also evaluated independently. The limited number of T2 (one patient) and C2 (seven patients) lesions on the MEST-C score led to the reporting as T (T1 and T2) lesions and C (C1 and C2) lesions. A P value < 0.05 was considered statistically significant. The analysis was conducted using statistical package for the social sciences version 22.

Results

This study included 165 biopsy proven IgAN patients. Table 1 presents the baseline characteristics of the patients. 65.5% were male, and 34.5% were female. Hypertension was present in 52.1% of the patients, while 6.1% had diabetes.

During the follow-up period, 30 patients (18.3%)

Table 1. Baseline clinical and histologic characteristics

	All patients (N=165)
Male, n (%)	108 (65.5)
Female, n (%)	57 (34.5)
Follow up duration (months)	39.60±26.29
Age(years) at biopsy	38.71±12.20
eGFR at biopsy	57.19±31.72
Proteinuria (g) at biopsy	2.76±1.82
Diabetes mellitus, n (%)	10 (6.1)
Hypertension, n (%)	78 (52.1)
ESRD, n (%)	30 (18.3)
Poor outcome, n (%)	40 (24.2)
RAS blocker, n (%)	120 (74.1)
Any immunosuppression during follow up, n (%)	155 (95.7)
M0, n (%)	62 (37.6)
M1, n (%)	103 (62.4)
E0, n (%)	35 (21.2)
E1, n (%)	130 (78.8)
S0, n (%)	45 (27.3)
S1, n (%)	120 (72.7)
T0, n (%)	134 (81.2)
T1, n (%)	30 (18.2)
T2, n (%)	1 (0.6)
C0, n (%)	107 (64.8)
C1, n (%)	51 (30.9)
C2, n (%)	7 (4.2)

GFR: Glomerular filtration rate, ESRD: End-stage renal disease, M: Mesangial hypercellularity, E: Endocapillary hypercellularity, S: Segmental sclerosis, T: Interstitial fibrosis/tubular atrophy, C: Crescent.

progressed to ESRD, while 40 patients (24.2%) experienced unfavorable outcomes. RAS inhibitors were given to 74.1% of the patients, and 95.7% were treated with immunosuppressive drugs (none of them have received immunosuppressive treatment before a definite diagnosis). The maximum follow-up period was 100 months (39.60 ± 26.29) (Table 2).

In our study, the logistic regression analysis was conducted. In the univariate analysis, variables significantly associated with ESRD included clinical variables of age ($P=0.049$), hypertension ($P\leq0.001$), and urinary protein level at diagnosis ($P<0.0001$), and also pathological factors including S1 ($P=0.021$), T lesion ($P<0.0001$), and finally C lesion ($P<0.0001$). In the multivariate analysis, urinary protein level at diagnosis ($P=0.010$), hypertension ($P=0.018$), and T lesion ($P=0.004$) remained significant (Table 3). Hypertension had an OR of 5 for ESRD, while T lesion had an OR of 6 (Table 3).

Regarding unfavorable outcomes, the univariate analysis significant variables were hypertension ($P=0.008$), urinary protein level at diagnosis ($P=0.004$), M1 ($P=0.008$), S1 ($P=0.045$), T lesion ($P<0.0001$), and C lesion ($P=0.003$). The multivariate analysis showed that proteinuria level ($P=0.012$) and T score ($P=0.014$) remained significant (Table 4). The outcome was not significantly affected by treatment with immunosuppressants or renin–angiotensin–aldosterone system inhibitors.

Discussion

IgA nephropathy is the most prevalent type of glomerulonephritis (1). Clinicians determine early treatment strategies to reduce the risk of ESRD based on their assessment of the disease prognosis at the time of diagnosis (6). This retrospective cohort study analyzed 165 IgAN patients to evaluate the prognostic and predictive value of clinical factors, pathological factors, as assessed by the MEST-C score, as well as treatment, on the outcome.

In this study, we found that M1, S1, T1+T2, and C1+C2 lesions were statistically significant factors in the univariate analysis. However, only the T score remained significant in the multivariate analysis. We also found that T score is consistently reported as the most significant predictor of progression to ESRD (2,14,16,19), while the other pathological factors have shown inconsistent results. The E lesion has been associated with ESRD in some studies (4,16), and reported as unrelated in others (15,18,20). The M lesion identified as a prognostic factor for ESRD in the VALIGA study (9) while in another studies, it was significantly related to unfavorable outcomes along with T and S lesions (15) or T lesions alone (17); however, its association with reduced eGFR was refuted in other studies (18-20). Moreover. S and C lesions have also yielded mixed results (7,15,18,20). The inconsistent prognostic value of these pathological findings may be attributed to variations in inclusion and exclusion criteria among studies. Some excluded patients who progressed to ESRD within one to two years (9,14), while in our study, we only excluded patients with ESRD at the time of presentation. Differences in studied endpoints, sample size, duration of follow-up, and patient populations may also contribute to the inconsistencies, as the genetic makeup is proven to be prognostic factor (6).

Clinical findings are significant, as demonstrated by the VALIGA study, which showed that incorporating baseline eGFR, hypertension, and urinary protein level along with pathological findings improved the prediction of progression to ESRD (9). Several studies have identified mean arterial blood pressure (MAP), baseline eGFR, proteinuria, and age at the time of biopsy as independent risk factors for progression to ESRD (2,4,16,17,22). Previously, Martín-Penagos et al compared the prognostic value of pathological findings (Oxford

Table 2. Comparison of variables between subgroups of study endpoints

Variables	ESRD		*P* value	Outcome		*P* value
	Yes (n=30)	No (n=135)		Poor (n=40)	Favorable (n=125)	
Gender (male), No. (%)	21 (70)	86 (63.70)	0.545	28 (70)	80 (64)	0.488
Age (y)	34.70±8.99	39.63±12.70	0.049	36.57±11.01	39.39±12.52	0.205
Proteinuria (g) (mean ±SD)	4.09±2.28	2.49±1.61	<0.0001	3.68±2.18	2.48±1.61	0.004
eGFR (mean ±SD)	21.64±15.50	65.30±28.88	<0.0001	27.84±23.31	66.58±28.17	<0.0001
Hypertension, No. (%)	24 (80)	61 (45.9)	<0.001	27 (71.1)	58 (46.4)	0.008
Diabetes mellitus, No. (%)	1 (3.3)	9 (6.8)	0.690	1 (2.6)	9 (7.2)	0.455
Immunosuppressive, No. (%)	27 (93.1)	128 (96.2)	0.452	34 (91.9)	121 (96.8)	0.196
RAAS blocker, No. (%)	22 (75.9)	98 (73.7)	0.808	25 (67.6)	95 (76)	0.304
M1, No. (%)	23 (76.7)	79 (58.5)	0.071	32 (80)	71 (56.8)	0.008
E1, No. (%)	27 (90)	102 (75.5)	0.093	35 (87.5)	95 (76)	0.121
S1, No. (%)	27 (90)	93 (68.90)	0.021	34 (85)	86 (68.8)	0.045
T1+T2, No. (%)	14 (46.7)	17 (12.6)	<0.0001	16 (40)	15 (12)	<0.0001
C1+C2, No. (%)	19 (63.3)	38 (28.4)	<0.0001	22 (55)	36 (28.8)	0.003

ESRD: End-stage renal disease; GFR: Glomerular filtration rate, ESRD: End-stage renal disease, RAAS: Renin–angiotensin–aldosterone system, M: Mesangial hypercellularity, E: Endocapillary hypercellularity, S: Segmental sclerosis, T: Interstitial fibrosis/tubular atrophy, C: Crescent

Table 3. Univariate and multivariate analysis of risk factor associated with end stage renal disease

Variables	ESRD			
	Crude OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Gender	1.302 (0.553-3.068)	0.545	1.376 (0.429-4.418)	0.592
Age (y)	0.962 (0.926-1.000)	0.049	0.986 (0.936-1.038)	0.587
Proteinuria (g)	1.000 (1.000-1.001)	<0.0001	1.000 (1.000-1.001)	0.010
Hypertension (%)	4.723 (1.811-12.301)	<0.001	4.337 (1.291-14.571)	0.018
S1 (%)	3.968 (1.139-13.823)	0.021	2.298 (0.530-9.966)	0.266
T1+T2 (%)	6.022 (2.499-14.509)	<0.0001	6.197 (1.802-21.313)	0.004
C1+C2 (%)	4.362 (1.901-10.020)	<0.0001	1.553 (0.509-4.736)	0.439

ESRD: End-stage renal disease; M: Mesangial hypercellularity, E: Endocapillary hypercellularity, S: Segmental sclerosis, T: Interstitial fibrosis/tubular atrophy, C: Crescent.

Table 4. Univariate and multivariate analysis of risk factor associated with unfavorable outcomes

Variables	Unfavorable outcomes			
	Crude OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Gender	1.312 (0.619-2.831)	0.488	1.517 (0.567-4.059)	0.407
Age (y)	0.980 (0.950-1.011)	0.205	1.006 (0.968-1.046)	0.745
Proteinuria (g)	0.998 (0.997-0.999)	0.004	1.000 (1.000-1.001)	0.012
Hypertension (%)	2.835 (1.294-6.212)	0.008	2.128 (0.842-5.376)	0.110
M1 (%)	3.042 (1.298-7.130)	0.008	1.640 (0.588-4.574)	0.334
S1 (%)	2.570 (1.000-6.623)	0.045	1.988 (0.625-6.328)	0.245
T1+T2 (%)	4.889 (2.129-11.227)	<0.0001	3.815 (1.317-11.048)	0.014
C1+C2 (%)	3.022 (1.451-6.292)	0.003	1.293 (0.504-3.314)	0.593

M: Mesangial hypercellularity, E: Endocapillary hypercellularity, S: Segmental sclerosis, T: Interstitial fibrosis/tubular atrophy, C: Crescent.

classification) and clinical findings assessed by the IgAN progression calculator (IgANPC) (5,23). IgANPC proved to be a non-invasive method that accurately identifies high-risk patients independently (5). These clinical factors more consistently demonstrated prognostic significance, similar to our findings, which showed the prognostic value of hypertension and proteinuria level at diagnosis.

Since several factors like the differences in follow up intervals and changes in treatment guidelines over time and also difference in population studies who receive immunosuppressive before definite diagnosis or not, seems are effective factors (19), therefore the possibility of a precise comparison between studies is not possible. The

STOP-IgAN and VALIGA studies found that treatment with RAAS inhibitors or immunosuppressants did not affect renal prognosis (9,13), which is consistent with our results. Another study with Japanese patients found that treatment with steroids independently improved renal prognosis and outcome (14).

In most studies, clinical factors such as baseline eGFR, proteinuria, hypertension or MAP, and age have been shown to be important prognostic factors. However, the prognostic value of pathologic factors (except T score) and medical treatment has been inconsistent. This study is limited by its retrospective nature and short duration of follow-up. On the other hand, the advantage of this study is the sample size and the evaluation of the scoring system in the Iranian population.

Conclusion

Our study has identified the urinary protein level at diagnosis and T-score on renal biopsy were the prognostic factors for predicting unfavorable outcomes. Additionally, C, S, and M scores lost their significance after multivariate analysis. Furthermore, E lesion in both univariate and multivariate analysis does not show any statistical significance. Therefore, further research is necessary to validate the MEST-C scoring system before it can be conducted in routine clinical practice, especially for different racial populations with varying genetic makeup.

Limitations of the study

One of the limitations of the present study was being a single center study. It is suggested that future studies be conducted on larger populations and in different centers and regions in order to reach a better consensus on the effectiveness of MEST-C scoring system in the prognosis of IgAN.

Authors' contribution

Conceptualization: Maryam Miri.
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Validation: Maryam Miri, Elahe Sanei.
Visualization: Elahe Sanei.
Writing–original draft: Elahe Sanei.
Writing–review & editing: Maryam Miri, Soude Arastouei, Indira Giri

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research conducted in this study adhered to the principles outlined in the Declaration of Helsinki and was approved by the Ethics Committee of the Mashhad University of Medical Science (Ethical code#IR.MUMS.MEDICAL.REC.1402.162). Prior to the study, all participants provided written informed consent. The study was extracted from Elahe Sanei's Nephrology thesis in the Department of Internal Medicine, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran (Thesis #U-4020129). Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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