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Research Article

Clinical Significance of Crescent Formation in IgA Nephropathy – a Multicenter Validation Study

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Key Words
IgA nephropathy • Renal prognosis • Crescent • End stage renal disease • Glomerulonephritis

Abstract
Background/Aims: Additional validation study was warranted to confirm the clinical significance of C score, which was recently added to the Oxford classification for immunoglobulin A nephropathy (IgAN). ***Methods:*** We performed a multicenter retrospective cohort study in four hospitals in Korea. Patients who had biopsied glomeruli less than eight or inadequate follow-up information were excluded. Clinicopathologic parameters, including the degree of cellular or fibrocellular crescents, were collected and included in multivariable models for Cox regression analysis. The main outcome was a composite renal outcome, defined as a merge of progression to end-stage renal disease (ESRD) and halving of estimated glomerular filtration rate (eGFR) from baseline. ***Results:*** Among included 3,380 biopsy-confirmed IgAN patients, there were 664 (19.6%) patients with C1 and 60 (1.8%) patients with C2 scores in the study population. Although C0 and C1 patients shared similar baseline characteristics, C2 patients frequently had more clinicopathologic risk factors for poor prognosis of IgAN.

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Both C1 [adjusted HR 1.33 (1.11-1.58), P=0.002] and C2 [adjusted HR 2.24 (1.46-3.43), P<0.001] scores were associated with an increased risk of the composite outcome. C2 was a strong predictive parameter associated with both progression to ESRD and halving of eGFR, whereas C1 was mainly associated with the increased risk of halving of eGFR. Notably, the proportion of crescent showed a linear association with the risk of adverse renal outcome. ***Conclusion:*** The C score in the Oxford classification is a valid predictive parameter for IgAN prognosis. Additional clinical attention is necessary for IgAN patients with identified cellular or fibrocellular crescents.

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Introduction

Immunoglobulin A nephropathy (IgAN) is one of the most common etiologies of primary glomerulonephritis [1-3]. Although IgAN is frequently diagnosed in young patients with a few comorbidities, it substantially contributes to the burden of end-stage renal disease (ESRD) worldwide [2, 4-6]. IgAN is also a very heterogeneous disease category, and its prognosis highly varies according to the patients' disease characteristics [4, 7, 8].

The Oxford classification, the pathologic scoring system for IgAN, has been widely used and its predictive value has been confirmed by other studies [9-13]. Recently, there was a major update in the Oxford classification system, and the presence of cellular or fibrocellular crescent was added to the graded parameters, consisting of the MEST-C scores [14]. This update was mainly based on a large-scale multicenter study, which expanded the patient group including patients with both reduced estimated glomerular filtration rate (eGFR) and rapid disease progression[15]. Recent reports partially supported their findings [16, 17], despite the fact that there were other studies, mostly with more restrictive criteria, did not observe the clinical significance of crescents [11, 12, 18]. Therefore, an additional large-scale validation study would further confirm the importance of crescent formation in IgAN and inspect the validity of the cutoff values.

Herein, we analyzed a large multicenter IgAN cohort in Korea, which is an Asian country with a high incidence and worse renal outcomes of IgAN [19-21]. We first tested whether the current C score is significantly associated with worse renal prognosis in our cohort. Additionally, we reviewed the cutoff values and further performed various subgroup analysis.

Materials and Methods

Study design and study population

This study was a multicenter retrospective cohort study including IgAN patients from the four government-designated tertiary hospitals in Korea, performed under a project by the Korean Glomerulo Nephritis Study Group (KoGNET). Patients with pathology-confirmed IgAN were included in the study. The exclusion criteria were as follows: 1) patients who were biopsied before the time when the electronic medical record (EMR) became available, as the study was conducted mainly via an EMR review; 2) with a previous history of maintenance renal replacement therapy; 3) with the number of biopsied glomeruli less than eight [14]; and 4) without follow-up information.

Diagnosis of IgAN and pathologic parameters

The diagnosis of IgAN was confirmed by the attending experienced pathologists in each study hospital when a typical immunofluorescent pattern is identified. The degree of cellular or fibrocellular crescents in the biopsied tissue was stratified according to the following C scores: C0 (none), C1 (> 0% and <25 %), and C2 (≥ 25%) [14]. The severity of tubular atrophy or interstitial fibrosis was graded as none (0%), mild (>0% and ≤25%), moderate (>25 and ≤50%), and severe (>50%).

Clinical data collection

We collated clinical characteristics at the time of IgAN diagnosis. Mean arterial pressure (MAP) was calculated as 1/3 of the systolic blood pressure (BP) plus 2/3 of diastolic BP. Laboratory parameters were also collected, including the baseline serum creatinine level and eGFR, calculated by the CKD-EPI equation. The amount of baseline proteinuria was the result of a 24-hour urine collection or, when absent, the random urine protein/creatinine ratio. Whether a patient was treated with any immunosuppressive drugs (ISD) or renin-angiotensin-aldosterone aldosterone (RAAS) blockades, not considering the duration or the amount of the drug, was recorded [15]. ISD usage included mainly steroid treatments, and other agents, representatively cyclophosphamides or calcineurin inhibitors, were also included.

Clinical outcome assessment

Main clinical outcome was an adverse composite renal outcome, which was a merge of progression to ESRD and halving of eGFR from baseline [15]. Progression to ESRD was defined as the initiation of chronic renal replacement therapy. The ESRD outcome was identified by reviewing the EMR in each study hospital and the nationwide renal replacement therapy registry maintained by the Korean Society of Nephrology [22]. Halving of eGFR, as an earlier adverse outcome than ESRD, from baseline was additionally collected [15]. The eGFR values after the dialysis initiation were censored.

Statistical analysis

We presented categorical variables as frequencies (percentages) and analyzed them using the chi-squared test. We expressed the continuous variables as median values [interquartile ranges] and analyzed them using the Kruskal-Wallis test. We plotted the Kaplan Meier survival curves to show the renal prognosis of the studied patients. The Cox regression analysis was performed to investigate the patients' prognosis, and the following variables were adjusted for the multivariable model: age, sex, baseline MAP (continuous, mmHg), eGFR (continuous, mL/min/1.73m^2), and amount of proteinuria (continuous, g/day or g/g), proportion of global sclerosis (continuous, %), degree of interstitial fibrosis (categorical, none or mild, moderate, and severe), degree of tubular atrophy (categorical, none or mild, moderate, and severe), and presence of segmental sclerosis (categorical, S1 or S0). A panelized spline regression model was used, with the same adjustment variables mentioned above, to investigate the association between the proportion of crescents and the risk of composite renal outcome. Subgroup analysis results were adjusted for age and sex. We inspected the value of crescent formation as a predictive biomarker using the net reclassification improvement (NRI) [23]. Continuous NRI values, calculated with the R package "nricens" as we studied survival outcomes, were considered to be statistically significant when the calculated 95% CI was above zero. The 95% CI of the parameter was extracted from the results by bootstrapping for a thousand times [24].

The followings were the missing values in our multivariable models: baseline BP (n=176, 5.2%), proteinuria (n=404, 12.0%), creatinine and eGFR (n=30, 0.9%), degree of tubular atrophy (n=131, 3.9%), and interstitial fibrosis (n=168, 5.0%). Medication usage history was missing in 581 (17.2%) cases with a non-random manner, thus the variable was not included in the multivariable model. Non-imputed data was used to show the baseline characteristics and stratify the subgroups. For missing variables included in the multivariable models, nonlinear transformation and imputation of the variables were performed using the 'transcan' function of the R package "Hmisc."

All statistical analyses were performed using the R (version 3.4.3, The R foundation). A two-sided p-value of 0.05 was considered as statistically significant.

Results

Study population

We screened 4,623 biopsy-confirmed IgAN patients in the study hospitals. After excluding the patients with inadequate information for EMR review (n=640), with a previous history of maintenance renal replacement therapy (n=18), with biopsied glomeruli less than eight (n=498), and without follow-up information (n=87), the final study cohort consisted

of 3,380 biopsy-confirmed IgAN patients with a median follow-up duration of 8.74 [5.44-12.24] years. Among them, 724 (21.4 %) patients had at least one cellular or fibrocellular crescent in their biopsied kidney tissue.

Characteristics of the study population

When we graded patients with C scores, 664 and 60 patients had C1 and C2 scores, respectively. The distribution of crescent portions was relatively skewed left (Fig. 1). Regarding the baseline characteristics (Table 1), although the C1 and C0 IgAN patients mostly had similar baseline clinical characteristics, the C2 patients were older, had higher BP, and worse baseline renal function compared to the other two groups. The degrees of tubular atrophy and interstitial fibrosis were more severe in patients with higher C scores. The patients with C2 score more commonly received ISD and were less commonly treated with RAAS blockade, although this was insignificant.

Renal prognosis according to C scores

All studied outcomes, including the composite outcome (P<0.001), ESRD (P<0.001), and eGFR halving (P<0.001), differed significantly according to C scores (Fig. 2). Overall, proportion of crescent formation showed a relatively linear association with the increased risk of composite renal outcome, both in the univariable and multivariable models (Fig. 3). Both C1 [adjusted HR 1.37 (95% CI 1.15-1.63), P<0.001] and C2 [adjusted HR 2.67 (95% CI 1.76-4.06), P<0.001] were associated with the increased risk of adverse composite renal outcome in a score-dependent manner (Table 2). This was similar with the halving of eGFR outcome, but only the C2 score was significantly associated with the progression to ESRD [adjusted HR 2.04 (95% CI 1.26-3.30), P=0.004]. The other variables included in the multivariable model also showed certain associations with the studied outcomes (Table 3). We further analyzed with patients who had a follow-up duration, or time to outcome, of 1 year or more (n=3, 075) to assess long-term predictability of C scores (Table 4). We again identified that both C1 and C2 were associated with increased risks of long-term

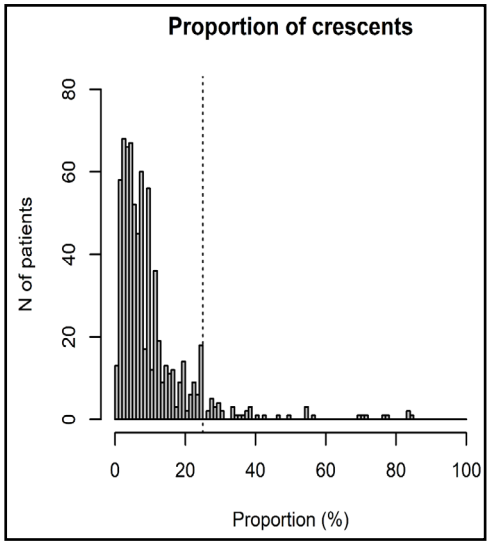

Fig. 1. Distribution of proportion of crescents in the study patients with crescents. The x-axis indicates the proportion of crescents, and the y-axis indicated the number of patients. The vertical dotted line is the 25% cutoff value for C1/2 score in the Oxford classification.

Table 1. Baseline characteristics according to the C scores

Parameter	C0 (N=2,656)	C1 (N=664)	C2 (N=60)	P
Age	36[24-47]	34[22-47]	41[23-60]	0.02
Male sex	1,332(50.2%)	333(50.2%)	34(56.7%)	0.61
BP (mmHg)				
Systolic	121[112-134]	122[112-136]	133[119-140]	0.002
Diastolic	79[70-86]	79[70-88]	80[70-87]	0.20
MAP	93[83-101]	93[84-103]	99[89-105]	0.02
Laboratory findings				
Serum creatinine (mg/dL)	1.0[0.8-1.3]	1.0[0.8-1.4]	1.5[1.0-2.5]	<0.001
CKD-EPI eGFR (mL/min/1.73 m^2)	83.1[58.5-108.4]	81.7[53.6-113.0]	53.5[30.9-79.1]	<0.001
≥60	1,941(73.7%)	452(68.6%)	23(39.0%)	
≥30 and <60	509(19.3%)	144(21.9%)	21(35.6%)	
<30	182(6.9%)	63(9.6%)	15(25.4%)	
Proteinuria (g/day or g/g)	1.06[0.49-2.10]	1.41[0.73-2.69]	2.32[1.24-4.46]	<0.001
Pathological findings				
Global sclerosis (%)	11.8[1.2-29.4]	11.1[2.6-27.3]	12.5[4.1-26.6]	0.60
Segmental sclerosis (%)	2.7[0.0-10.6]	6.3[0.0-14.0]	0.0[0.0-9.7]	<0.001
S1	1,435 (54.0)	432 (65.2)	25 (41.7)	< 0.001
Tubular atrophy				0.009
None	516(20.3%)	93(14.3%)	7(11.9%)	
Mild	1,395(54.9%)	364(56.1%)	34(57.6%)	
Moderate	439(17.3%)	138(21.3%)	12(20.3%)	
Severe	192(7.6%)	53(8.2%)	6(10.2%)	
Interstitial fibrosis				0.006
None	417(16.6%)	73(11.4%)	5(8.5%)	
Mild	1,776(70.6%)	484(75.7%)	40(67.8%)	
Moderate	228(9.1%)	58(9.1%)	10(16.9%)	
Severe	93(3.7%)	24(3.8%)	4(6.8%)	
Medication usage				
ISD	614(28.1%)	189(32.9%)	25(59.5%)	<0.001
RAAS blockade	1,723(78.9%)	457(79.8%)	29(69.1%)	0.26

outcomes; however, C2 was associated only with the increased risk of ESRD.

Subgroup analysis

The clinical significance of crescents varied among the subgroups (Fig. 4). In terms of eGFR, C1 was associated with the composite renal outcome of IgAN patients with preserved eGFR (≥ 60 mL/min/1.73m^2); in contrast, only C2 showed a significant association with the outcome in those with impaired baseline renal function. When the subgroups were categorized according to the amount of proteinuria and MAP, both C scores were significant predictors for renal prognosis in those with milder clinical characteristics; meanwhile, only C2 but not C1 was associated with the worse renal prognosis irrespective of proteinuria amount or MAP. Regarding subgroups according to chronic pathologic changes, the presence of both C1 and C2 was a significant risk factor in patients with a relatively mild degree of tubular atrophy or interstitial fibrosis. However, no significant association between the C scores and the risk of worse renal outcome was identified in those with advanced pathologic findings. Lastly, regardless of the usage of RAAS blockade, the predictive value of C1 and C2 remained significant. Both C1 and C2 scores showed a predictive value for the composite renal outcome in those who were treated with ISD; however, only the C1 showed marginal (P=0.07) association with the risk of composite outcome in those who did not receive any ISD after their diagnosis.

Cutoff values for C scores

Further, we investigated the lower cutoff value (Table 5), as low-grade crescent formation, which was identified in a large portion of patients, might not bear clinical significance. The tested mild degrees of crescents were still associated with worse composite renal outcome, although this did not reach statistical significance level with the ESRD outcome. Even the patients with cellular or fibrocellular crescents in less

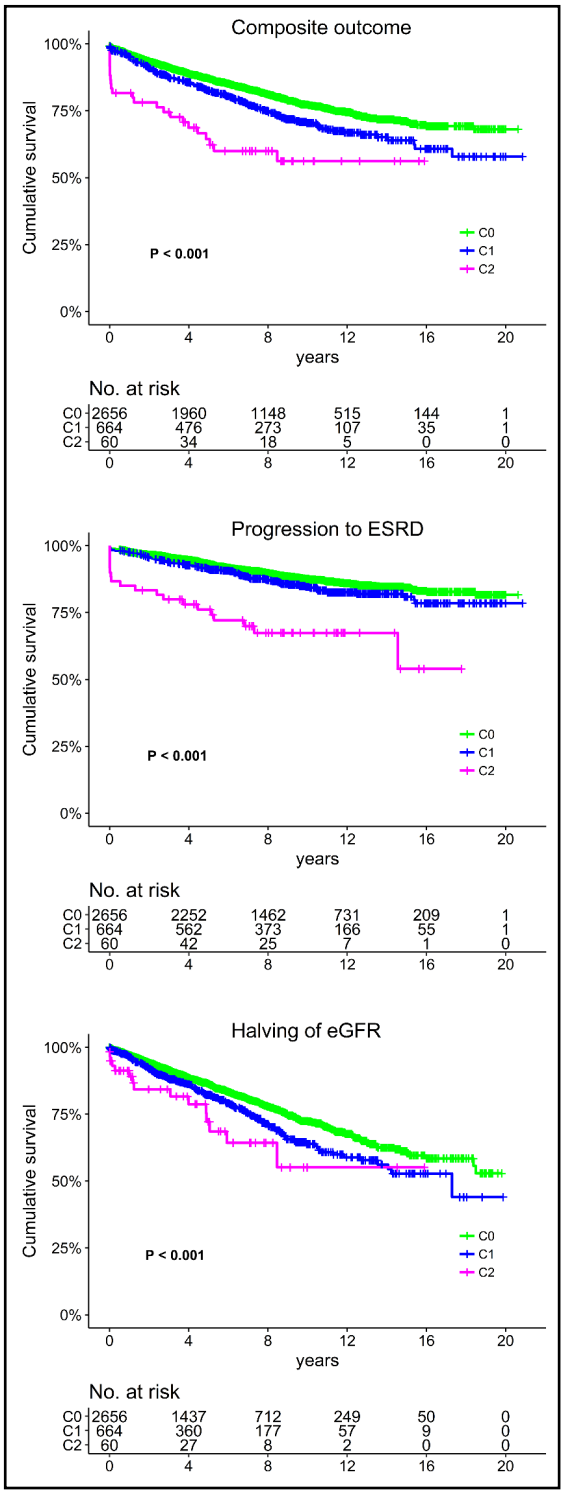

Fig. 2. Kaplan Meier survival curve of the study patients according to C scores. The x-axis indicates the time from initial biopsy (years), and the y-axis indicates the cumulative survival. Each line indicates the survival curve of the patients with C2, C1, and C0 score, respectively. Tables containing the number at risk are shown in below of the survival graphs.

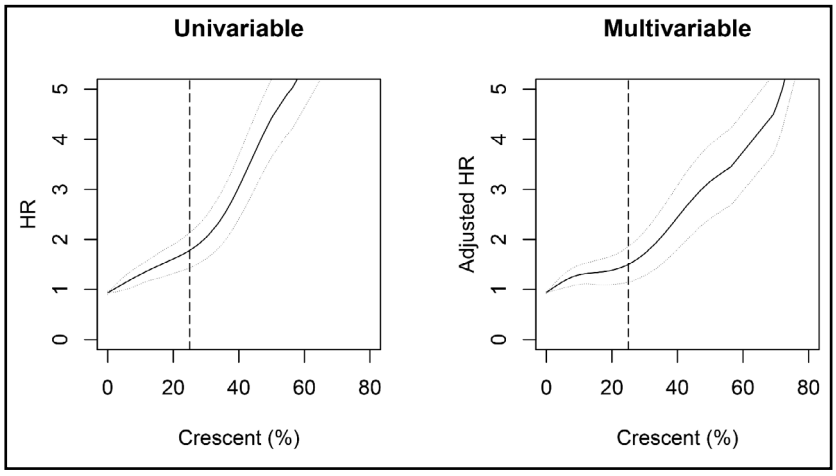

Fig. 3. Association between proportion of cellular or fibrocellular crescents and risk of adverse composite outcome. The x-axis indicates the proportion of crescents among biopsied glomeruli (%), and the y-axis indicates the hazard ratio. The vertical broken line indicates the 25% cutoff value for C1/C2 score. The left graph is the result from an univariable analysis, and right graft is the result from a multivariable analysis, adjusted for age, sex, baseline mean arterial pressure (continuous, mmHg), eGFR (continuous, mL/min/1.73m^2), and amount of proteinuria (continuous, g/day or g/g), proportion of global sclerosis (continuous, %), degree of interstitial fibrosis (categorical, none or mild, moderate, and severe), degree of tubular atrophy (categorical, none or mild, moderate, severe), presence of segmental sclerosis (categorical, S1 or S0).

than 1/10 of biopsied glomeruli showed worse composite renal outcome [adjusted HR 1.38 (95% CI 1.13-1.69), P=0.002] than those without crescents.

Table 2. Multivariable analysis showing the association between C scores and renal prognosis

Outcomes	N(%) of outcome	Univariable		Multivariable[a]	
		HR (95% CI)	P	Adjusted HR (95% CI)	P
Composite outcome					
C0	509 (19.2)	Reference	-	Reference	-
C1	168 (25.3)	1.37 (1.15-1.63)	< 0.001	1.33 (1.11-1.58)	0.002
C2	23 (38.3)	2.67 (1.76-4.06)	< 0.001	2.24 (1.46-3.43)	< 0.001
Progression to ESRD					
C0	302 (11.4)	Reference	-	Reference	-
C1	96 (14.5)	1.26 (1.01-1.59)	0.05	1.22 (0.96-1.54)	0.10
C2	19 (31.7)	3.43 (2.16-5.45)	< 0.001	2.04 (1.26-3.30)	0.004
Halving of eGFR					
C0	453 (17.1)	Reference	-	Reference	-
C1	150 (22.6)	1.34 (1.11-1.61)	0.002	1.31 (1.09-1.58)	0.004
C2	15 (25.0)	2.06 (1.23-3.44)	0.006	1.777 (1.05-3.00)	0.03

Next, we tested the value of adding the C scores into the multivariable models changing the cut-off value for the C2 score and compared their discrimination performance (Table 6). A significant net classification improvement was identified with all tested cutoff proportions of crescent formation, and the current cutoff values showed valid performance.

Discussion

In this study, we confirmed the clinical significance of cellular or fibrocellular crescents in IgAN patients. The current C score was a valid predictive marker for renal prognosis, independent from many clinical and pathologic characteristics. The predictability even remained significant for a risk of adverse outcome after more than a year from biopsy. Overall, the proportion of crescent formation showed a positive linear association with the risk of adverse renal outcome.

Recent updates in the Oxford classification suggested the MEST-C scoring system [14, 15]. The clinical significance of crescents was also shown in several reports [25-27], with a smaller sample size than the study by Haas M et al. [15]. Still, additional large-scale validation study was further warranted, as controversial results could also be found in the literature [12, 18, 28-30]. In this study, we analyzed over 3,000 IgAN patients and again

Table 3. Association of other variables and the risk of adverse renal outcome. [a]All variables in the table were simultaneously included in the multivariable model

Parameter	Composite outcome		Progression to ESRD		Halving of eGFR	
	[a]Adjusted HR	P	[a]Adjusted HR	P	[a]Adjusted HR	P
Age (continuous)	0.99 (0.98-0.99)	< 0.001	0.98 (0.98-0.99)	< 0.001	1.00 (0.99-1.01)	0.85
Male sex	1.32 (1.13-1.54)	< 0.001	1.50 (1.23-1.83)	< 0.001	1.25 (1.06-1.47)	0.007
MAP (mmHg, continuous)	1.00 (1.00-1.01)	0.33	1.01 (1.00-1.01)	0.02	1.00 (1.00-1.01)	0.67
eGFR (mL/min/1.73 m^2, continuous)	0.98 (0.98-0.98)	< 0.001	0.96 (0.96-0.97)	< 0.001	0.99 (0.99-0.99)	< 0.001
Proteinuria (g/day or g/g, continuous)	1.03 (1.02-1.04)	< 0.001	1.03 (1.02-1.04)	< 0.001	1.04 (1.03-1.05)	< 0.001
Global sclerosis (%, continuous)	1.02 (1.02-1.02)	< 0.001	1.02 (1.02-1.03)	< 0.001	1.02 (1.01-1.05)	< 0.001
Segmental sclerosis, S1 (.vs S0)	1.21 (1.02-1.42)	0.03	1.08 (0.87-1.33)	0.51	1.23 (1.03-1.47)	0.02
Interstitial fibrosis (categorical)						
None or mild	Reference		Reference		Reference	
Moderate	1.20 (0.95-1.52)	0.12	1.25 (0.95-1.66)	0.12	1.72 (1.33-2.21)	< 0.001
Severe	1.42 (1.06-1.91)	0.02	1.54 (1.09-2.17)	0.01	1.95 (1.41-2.71)	< 0.001
Tubular atrophy (categorical)						
None or mild	Reference		Reference		Reference	
Moderate	1.12 (0.91-1.38)	0.27	1.04 (0.80-1.35)	0.79	1.19 (0.96-1.47)	0.11
Severe	1.25 (0.97-1.61)	0.08	0.90 (0.67-1.22)	0.50	1.47 (1.13-1.90)	0.004

confirmed the clinical significance and validity of the suggested C scores. As we included a comparable number of patients to the previous multicenter study and assessed the prognosis of patients with C1 and C2 scores, our study may serve as a validation study for the predictive value of cellular or fibrocellular crescents. In addition, long-term predictability of C score for renal prognosis was shown herein. This clear demonstration for association of C score and worse renal prognosis may have been derived from the high incidence and worse prognosis of IgAN in Korea [19-21].

Table 4. Prognosis according to C scores within patients who had follow-up duration (or time to outcome) of 1 years or more (n=3,075)

Outcomes	Univariable		Multivariable	
	Adjusted HR (95% CI)	P	Adjusted HR (95% CI)	P
Composite outcome				
C0	Reference	-	Reference	-
C1	1.40 (1.15-1.70)	< 0.001	1.40 (1.15-1.70)	< 0.001
C2	1.82 (1.02-3.23)	0.04	1.71 (0.95-3.06)	0.07
Progression to ESRD				
C0	Reference			
C1	1.35 (1.04-1.75)	0.02	1.33 (1.11-1.73)	0.04
C2	2.65 (1.41-5.00)	0.003	2.14 (1.12-4.12)	0.02
Halving of eGFR				
C0	Reference			
C1	1.39 (1.14-1.70)	0.001	1.35 (1.10-1.66)	0.004
C2	1.59 (0.82-3.08)	0.17	1.29 (0.66-2.54)	0.46

Our study further showed some notable findings, firstly the characteristics of the patients with C2 score. Although the clinicopathologic findings of C0 and C1 patients did not differ largely, the patients with C2 score had significantly worse baseline clinical and pathological parameters. Moreover, risk of the both studied outcomes, eGFR and halving and progression to ESRD, was elevated and ISD was more commonly tried in C2 patients. We did include C2 patients who were biopsied at the impending state of dialysis initiation, in hope to search for any reversible condition, as they started renal replacement therapy within a short period from diagnosis. The abovementioned findings may explain that the clinical significance of crescents was less prominent in the previous version of the Oxford classification, which excluded patients with reduced eGFR and rapid kidney function deterioration [9, 10]. In addition, IgAN patients with C2 score, whose prognosis was obviously worse than the others, was relatively rare (1.8%). Therefore, a sufficient number of study patients, which were not well-secured in the previous studies with debating results [12, 28-30], could also be the reason for the positive results of ours and the previous study [15].

On the other hand, C1 score was a parameter that predicted mainly halving of eGFR and long-term ESRD, which may indicate C1 is an early marker of progressive kidney dysfunction. In addition, C1 score and its' association with the renal outcome was different according to the investigated subgroups. In general, the predictive value of C1 score was less prominent in patients with preexisting clinical risk factor, including reduced eGFR, significant proteinuria, and high BP [7, 8]. As cellular or fibrocellular crescents may represent an ongoing immunologic process, it may be more an important biomarker in those with development state of active glomerulonephritis, rather than in those with established kidney dysfunction

[31, 32]. Furthermore, the result that both C1 and C2 scores were not associated with the renal outcome in patients with advanced pathologic changes, such as tubular atrophy and interstitial fibrosis, also supports this hypothesis. Therefore, clinicians may particularly pay attention to the finding of C1 when other clinicopathologic risk factors are absent.

Regarding the medication usage, usage of RAAS blockade was not a factor that affected the predictive significance of crescent formation. On the other hand, the association of crescents and renal outcome in the patients who received ISD was not identical with the previous report [15]. In the current study, the association was better observed in the patients who received ISD, rather than in patients without ISD treatment. Again, the patients in the current study who were biopsied at the impending state of renal failure, those who were more likely to receive ISD, might have affected this result. As the clinical practice and patients' condition could not have been the same between the two study cohorts, the difference in this subgroup analysis result could hardly be explained robustly.

Finally, when the cutoff values were considered, we showed that even formation of crescent in less than a 1/10 of biopsied glomeruli was significantly associated with worse renal prognosis. This result further encourages clinicians to pay attention to the possible renal dysfunction progression in IgAN patients with even a single cellular or fibrocellular crescent formation in biopsied glomeruli. In addition, C scores with various cutoff values for C1/C2 all improved the prediction power of the tested multivariable models, and the current C score cutoff was proven to be a valid threshold. However, as the proportion of crescents showed a positive linear association with the risk of adverse renal outcomes, clinicians may not be obsessed with the strict cutoff values but interpret the results according to the patients' coexisting risk factors.

Several limitations should be considered when interpreting our study. First, we did not have the information of other components of MEST-C scores, except for the presence of segmental sclerosis that was included in our multivariable model. Instead of the other scoring components, we included chronic pathologic parameters, such

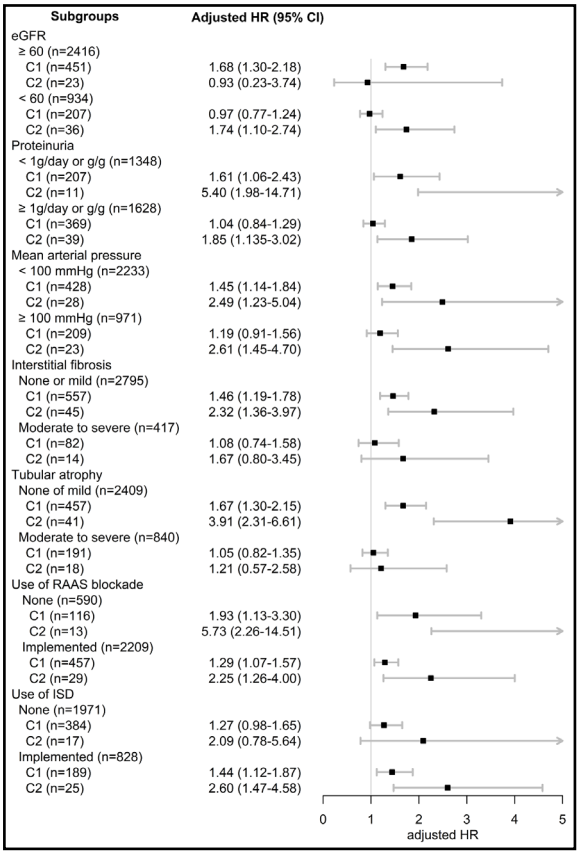

Fig. 4. Subgroup analysis result. Forest plot showing the association between C1, C2 and adverse composite renal outcome in various subgroups. Hazard ratios were adjusted for age and sex.

Table 5. Association of mild degree of crescent formation and renal prognosis

Proportion of crescents	Composite outcome		Progression to ESRD		Halving of eGFR	
	[a]Adjusted HR (95% CI)	P	[a]Adjusted HR (95% CI)	P	[a]Adjusted HR (95% CI)	P
None	Reference		Reference		Reference	
>0% and < 1/7 (n=579)	1.33 (1.10-1.61)	0.003	1.18 (0.91-1.52)	0.22	1.37 (1.13-1.68)	0.002
>0% and < 1/8 (n=551)	1.31 (1.08-1.59)	0.006	1.14 (0.87-1.48)	0.35	1.38 (1.13-1.69)	0.002
>0% and < 1/9 (n=514)	1.36 (1.120-1.66)	0.002	1.24 (0.95-1.62)	0.12	1.38 (1.13-1.70)	0.002
> 0% and < 1/10 (n=482)	1.38 (1.13-1.69)	0.002	1.24 (0.94-1.63)	0.13	1.41 (1.14-1.73)	0.001

Table 6. The discrimination performance of models predicting the survival from a composite outcome at 10 years from biopsy confirmation of IgAN

Patient group and model	N of C1/C2	cNRI (95% CI)	C-index
The Reference multivariable model without C scores[a]	-	-	0.783
Addition of C score with the following cut-off value for C1/C2			
Model 1: 1/3 of biopsied glomeruli	697/27	0.168 (0.084-0.269)	0.788
Model 2: 1/4 of biopsied glomeruli (current C score)	664/60	0.154 (0.074-0.234)	0.788
Model 3: 1/5 of biopsied glomeruli	629/95	0.157 (0.091-0.257)	0.787
Model 4: 1/6 of biopsied glomeruli	604/120	0.149 (-0.048-0.229)	0.788

as tubular atrophy, which may partially substitute the T scores, and interstitial fibrosis. Therefore, our study could not have investigated the exact updated Oxford classification, but only validated the clinical importance of crescents in IgAN kidney biopsy. Second, being a retrospective study, treatment strategies were not identical between the centers. Usage of RAAS blockades might have been initiated in different manner according to clinicians' preference. To overcome this limitation, an international guideline based on close collaboration and further investigation for evidence for ISD usage in IgAN is warranted. Third, time-averaged proteinuria or MAP was not recorded in our study group. However, the clinical significance of crescent formation in IgAN may certainly exist, as it was evident even after multiple adjustments with known clinical risk factors. Lastly, an inter-observer agreement for the studied pathologic parameters were not validated herein. Although all study hospitals were located close in a single nation, this might have also influenced our study results.

Conclusion

The suggested C score of the Oxford classification is a valid categorization to predict renal prognosis. The C2 and C1 scores were associated with rapid and progressive renal dysfunction, respectively. A small proportion of crescents should also be carefully identified as it bared clinical significance, particularly in those without other clinical risk factors. Considering that IgAN with crescents contributes to a large portion of consequent renal dysfunction, an appropriate treatment strategy for the condition may help in improving the prognosis of IgAN.

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Disclosure Statement

The authors of this manuscript state that they have no competing interests.

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