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Three-Year Clinical Outcomes of the First South Asian Prospective Longitudinal Observational IgA Nephropathy Cohort

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Introduction: Glomerular Research And Clinical Experiments—IgA Nephropathy in Indians (GRACE-IgANI) is the first prospective South Asian IgA nephropathy (IgAN) cohort with prespecified objectives, protocolized longitudinal follow-up, and extensive biosample collection. The baseline risk scores predicted high risk of kidney disease progression.

Methods: A total of 195 of 201 patients (97%) completed 3-year follow-up in September 2020. All patients received optimized supportive care, and those at high risk of progression were offered systemic corticosteroids.

Results: A total of 76 patients (76 of 193, 39.4%) had rapid progression in 3 years (≥5 ml/min per 1.73 m^2 decline in estimated glomerular filtration rate [eGFR] per year). A total of 72 patients (72 of 195, 36.9%) experienced the composite outcome (CO), defined as ≥50% fall in eGFR, eGFR < 15 ml/min per 1.73 m^2, commenced kidney replacement therapy or death, in 3 years. At each scheduled follow-up, achievement of proteinuria level < 1 g/d significantly delayed the time to the CO. The receiver operating characteristic curve of average annual decline in eGFR ≥ 5 ml/min per 1.73 m^2 had 86% sensitivity and 89% specificity for CO in 3 years and had good discrimination from 1 year onwards (area under the curve 0.8, SE 0.04, 95% CI 0.7–0.9, $P < 0.0001$). The significant predictors of CO by Cox proportional-hazards model were as follows: baseline MEST-T2 score (hazard ratio [HR] 3.3, 95% CI 1.7–6.5, $P < 0.001$), along with 24-hour urine protein level ≥ 1 g/d (HR 2.1, 95% CI 1.1–3.9, $P = 0.02$), eGFR < 60 ml/min per 1.73 m^2 (HR 2.9, 95% CI 1.1–7.6, $P = 0.03$), and rate of eGFR decline ≥ 5 ml/min per 1.73 m^2/yr (HR 2.7, 95% CI 1.6–4.8, $P < 0.001$) all measured at 6 months. Mortality was 11 of 195 (5.6%).

Conclusion: We identified longitudinal clinical variables measured at 6 months and ≥5 ml/min per 1.73 m^2 annual fall in eGFR after kidney biopsy as important predictors for composite outcome in addition to baseline histology.

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IgAN exhibits a well-documented geographic variation in both incidence and likelihood of progression to end-stage kidney disease (ESKD). India is the most populous country in South Asia, and the Global Burden of Disease study 2015[1] ranks chronic kidney disease (CKD) as the eighth leading cause of death. Retrospective kidney biopsy studies from India report that IgAN is the most commonly diagnosed primary glomerulonephritis; however, there are currently no data from prospective studies describing the natural history of IgAN in the Indian population. The GRACE-IgANI prospective longitudinal cohort study was designed specifically to address this gap. The study protocol has been published[2] and is registered with the World Health Organization trial identification: ISRCTN36834159.[3]

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A total of 201 consenting adult patients with IgAN who satisfied the prespecified inclusion criteria (Supplementary Table S1) were consecutively recruited postkidney biopsy from March 2015 to September 2017.[2] The baseline characteristics and calculated progression risk for this incident cohort have previously been reported.[4] The median baseline total risk score by Tanaka *et al.*[5] was 19 (interquartile range [IQR] 13–24), which equated to a predicted 5-year absolute risk of ESKD of 19.8% (IQR 2.7–57.4). The predicted 5-year risk of a 50% decline in eGFR or ESKD using the International IgA Nephropathy Network risk prediction tool (Barbour *et al.*[6]) was 35.5% (IQR 13.7–56.2).[4] Both scores predicted a high-risk cohort based on baseline variables. Here, we report the actual 3-year longitudinal clinical outcomes of the GRACE-IgANI cohort.

METHODS

As described in the full study protocol, all patients were consecutively and prospectively recruited into the GRACE-IgANI study after written informed consent at the Christian Medical College, Vellore.[2] Consistent with the Kidney Disease: Improving Global Outcomes 2012 guidelines,[7] all patients were treated with a maximally tolerated dose of renin-angiotensin system blocker (RASB). All patients with a 24-hour urinary protein (24UP) level $>$ 1 g/d or an eGFR $<$ 60 ml/min per 1.73 m^2 with any proteinuria received oral prednisolone at 2 mg/kg for 3 months along with optimized supportive care, which was then tapered and stopped at 6 months. Mycophenolic acid was added as a second immunosuppressive drug, if the patient could afford the drug, with monitoring of area under the curve (target 30–50 mg $\times$ h/l).[2] In-center scheduled follow-up visits were at 6 months, 1 year, 2 years, and 3 years with additional visits dictated by the clinical needs of the patient. Patients were contacted at least once every 3 to 6 months to determine medication adherence and monitor for medication side effects, ensure optimization of blood pressure (BP) medications using self-reported/clinic BPs, and review of local blood test results. CKD-Epidemiology Collaboration equation[8] was used to calculate eGFR.

The primary end point was CO defined as $\geq$50% fall in eGFR (CKD-Epidemiology Collaboration) from baseline, eGFR (CKD-Epidemiology Collaboration) $<$ 15 ml/min per 1.73 m^2, commencement of kidney replacement therapy, or death. We defined rapid progressors (RPs) as patients who exhibited an average annual fall in eGFR $\geq$ 5 ml/min per 1.73 m^2 and non/slow progressors (N/SP) as patients with an average annual fall in eGFR $<$ 5 ml/min per 1.73 m^2. Complete remission (CR) in proteinuria was defined as a 24UP level $<$ 0.3 g/d maintained for at least 3 months and partial remission (PR) in proteinuria as a decrease in 24UP by $\geq$50% of baseline and $<$3 g/d if $\geq$3.5 g/d at baseline, or $<$1.5 g/d if $<$3.5 g/d at baseline, maintained for at least 3 months.

Statistical Analysis

Data were presented as mean $\pm$ SD or median (IQR) or frequency and percentage according to the types and distribution of variables. Likewise or case-deletion approach was used to handle missing data. Differences among groups of normally distributed variables were analyzed by *t* test or one-way analysis of variance. *Post hoc* comparisons were performed using *t* test with Bonferroni correction. Differences among groups of nonparametric variables were analyzed by Mann–Whitney *U* test or the Kruskal–Wallis test. Categorical variables were compared using Pearson's χ^2 test or Fisher exact test. Mixed effects analyses using the maximum likelihood method was performed to study linear trends in laboratory parameters performed in-center at baseline, 6 months, 1 year, 2 years, and 3 years. The mixed effects model treats the different participants as a random variable. Possible violations of the assumption are tested using the method of Geisser and Greenhouse, and effectiveness of matching with an F test. Survival analysis for time to kidney failure was by Kaplan and Meier using log-rank test for comparison between groups. A Cox proportional-hazards model was used to identify predictors of progression to kidney failure. Univariate variables of known biological importance with a $P < 0.05$ and satisfying the proportional-hazards assumption were considered for the multivariable model, and the step-wise method was performed. The missing data were at random and were minimal to affect outcomes. The goodness of fit was evaluated using the -2 log likelihood ratio. Statistical analyses were performed using Statistical Package for Social Sciences software for Windows, version 28.0 (SPSS Inc., Chicago, IL), and graphs were made using GraphPad Prism 9.0e (GraphPad Software Inc., San Diego, CA). A $P < 0.05$ was taken as significant.

RESULTS

A total of 195 patients (97%) completed the 3-year longitudinal follow-up in September 2020. A total of 6 patients (3%) were lost to follow-up. Two patients who reached CO and started dialysis in an outside center did not report their predialysis serum creatinine value to us and were excluded from calculation of rate of decline in eGFR for rapid progression (193 patients). The demographic and baseline clinical, laboratory, and kidney histopathologic characteristics of the 195 patients are summarized in Table 1.

Table 1. Baseline characteristics of the GRACE-IgANI cohort

Baseline characteristics	Entire cohort (N = 195)	No composite outcome (n = 123)	Composite outcome (n = 72)	P value
Sex (male:female; ratio)	137:58 (2.4:1)	91:32 (2.8:1)	46:26 (1.8:1)	0.14
Age (yr, mean ± SD)	35.8 ± 9.9	35.9 ± 10.3	35.6 ± 9.3	0.81
BMI (kg/m^2, mean ± SD)	24.8 ± 4.1	25.2 ± 3.8	24.2 ± 4.5	0.09
Hypertension, *n*/*N* (%)	164/194 (84.5)	96/123 (78)	68/71 (95.8)	0.001[a]
Mean arterial pressure (mm Hg) (mean ± SD)	104.1 ± 14.5	102.9 ± 13.4	106.2 ± 16.1	0.13
Syngharyngitic presentation *n*/*N* (%)	8/194 (4.1)	8/123 (6.5)	0/71 (0)	0.7
Pedal edema at presentation *n*/*N* (%)	90/194 (46.4)	50/123 (40.7)	40/71 (56.3)	0.04[a]
Visible hematuria at presentation *n*/*N* (%)	20/194 (10.3)	17/123 (13.8)	3/71 (4.2)	0.03[a]
Renal dysfunction before biopsy *n*/*N* (%)	146/183 (79.8)	82/114 (71.9)	64/69 (92.8)	0.001[a]
Proteinuria before biopsy *n*/*N* (%)	153/156 (98.1)	95/96 (99)	58/60 (96.7)	0.56
Nonvisible hematuria before biopsy *n*/*N* (%)	87/121 (71.9)	57/77 (74)	30/44 (68.2)	0.49
Family history of CKD *n*/*N* (%)	11/194 (5.7)	6/123 (4.9)	5/71 (7)	0.53
On RASB before biopsy *n*/*N* (%)	71/194 (36.6)	50/123 (40.7)	21/71 (29.6)	0.12
Hemoglobin (g/dl, mean ± SD, *n*)	12.1 ± 2 (195)	12.6 ± 1.8 (123)	11.3 ± 2.2 (72)	<0.001[a]
Serum total protein (g/dl, mean ± SD, *n*)	6.8 ± 0.7 (192)	7 ± 0.7 (121)	6.5 ± 0.7 (71)	<0.001[a]
Serum albumin (g/dl, mean ± SD, *n*)	3.9 ± 0.6 (192)	4.1 ± 0.6 (121)	3.7 ± 0.5 (71)	<0.001[a]
24-hr urine protein (g/d), median (IQR)	2.1 (1–3.8)	1.5 (0.9–2.7)	3.4 (1.8–5)	<0.001[a]
Serum total cholesterol (mg/dl, mean ± SD, *n*)	177 ± 57.6 (192)	180.8 ± 62.9 (120)	170.7 ± 47.3 (72)	0.24
Serum creatinine (mg/dl, mean ± SD)	2.1 ± 1.1	1.7 ± 0.9	2.7 ± 1	0.2
eGFR CKD-EPI (ml/min per 1.73 m^2), median (IQR)	38.9 (25.7– 67.1)	53.1 (37.8–86.8)	26.8 (16.5–39.8)	<0.001[a]
≥60 ml/min per 1.73 m^2 *n*/*N* (%)	60/195 (30.8)	52/123 (42.3)	8/71 (11.1)	fx1 <0.001
30–59 ml/min per 1.73 m^2 *n*/*N* (%)	75/195 (38.5)	54/123 (43.9)	21/71 (29.2)	
15–30 ml/min per 1.73 m^2 *n*/*N* (%)	60/195 (30.8)	17/123 (13.8)	43/71 (59.7)	
MEST-C M1/M0 (M1%)	19/161 (10.6)	13/104 (11.1)	6/57 (9.5)	0.74
MEST-C E1/E0 (E1%)	77/103 (42.8)	46/71 (39.3)	31/32 (49.2)	0.2
MEST-C S1/S0 (S1%)	145/35 (80.6)	86/31 (73.5)	59/4 (93.7)	0.001[a]
MEST-C T2/T1/T0 (T2%/T1%)	76/66/38 (42.2/36.7)	29/55/33 (24.8/47)	47/11/5 (74.6/17.5)	<0.001[a]
MEST-C C2/C1/C0 (C2%/C1%)	4/11/165 (2.2 / 6.1)	3/7/107 (2.6/6)	1/4/58 (1.6/6.3)	0.91
(GS/total glomeruli) * 100, % median (IQR)	33.33 (12.5–45.5)	22.2 (7.1–41.3)	42.9 (33.3–60)	<0.001[a]
GS ≥ 30% *n* (%)	93/195 (47.7)	45/123 (36.6)	57/72 (79.2)	<0.001[a]
IF IgA, +++, *n* (%)	144 (73.8)	95 (77.2)	49 (68.1)	0.16
IF IgG, ++ and +++, *n* (%)	9 (4.6)	6 (4.9)	3 (4.2)	0.82
IF IgM, ++ and +++, *n* (%)	4 (2.1)	4 (3.3)	0	0.31
IF C3, ++ and +++, *n* (%)	69 (35.4)	43 (35)	26 (36.1)	0.87
Treatment with RASB, *n* (%)	131 (67.2)	82 (67.7)	49 (68.1)	0.84
Antihypertensives ≥2 drugs, *n* (%)	105 (53.8)	54 (43.9)	51 (70.8)	<0.001[a]
Immunosuppression treatment				
Steroid treatment postbiopsy, *n* (%)	146 (74.9)	90 (73.2)	56 (77.8)	0.35
Add on MPA treatment, *n* (%)	25 (12.8)	16 (13)	9/72 (12.5)	0.92

BMI, body mass index; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; GRACE-IgANI, Glomerular Research And Clinical Experiments—IgA Nephropathy in Indians; GS, glomerulosclerosis; IF, immunofluorescence; IQR, interquartile range; MPA, mycophenolic acid; RASB, renin-angiotensin receptor blocker.

Of 201 patients, 195 had follow-up status known at 3 years or earlier and 6 were lost to follow-up. Total number of glomeruli per biopsy (median [IQR]) = 10 (7–13). Of 195 patients, 180 had complete MEST-C score.[4]

[a]P value is significant at < 0.05.

Treatment Exposure and Treatment-Emergent Adverse Events

Table 1 and Figure 1 summarize the treatment allocations in GRACE-IgANI. The use of RASB at each scheduled follow-up visit (6 months, 1 year, 2 years, and 3 years) was between 66% and 75%. RASB use was similar in both sex (males: 88 of 137, 64.2%; females: 43 of 58, 75.1%, P = 0.18) and across age groups (≤35 years: 71 of 106, 67% vs. >35 years: 60 of 88, 68.2% P = 0.86). In addition, 55% of patients with IgAN received ≥2 antihypertensives at baseline and at each scheduled follow-up visit (6 months, 1 year, 2 years, and 3 years), and it was significantly different between the 2 outcome groups (Table 1). Most of the patients in GRACE-IgANI received oral steroids 74.9% (146 of 195) with 12.8% (25 of 195) of these also receiving second-line treatment with mycophenolic acid (subgroup 2). The remainder of the cohort were not treated with immunosuppression either because of advanced kidney failure (eGFR < 17 ml/min per 1.73 m^2, subgroup 3) or owing to low baseline proteinuria (24UP < 1 g/d and eGFR > 60 ml/min per 1.73 m^2, subgroup 1). Immunosuppression use was similar across both sex (males: 108 of 137, 78.8%; females: 38 of 57,

66.7%, $P = 0.07$) and age groups (≤35 years: 78 of 106, 73.6% vs. >35 years: 68 of 88, 77.3% $P = 0.55$).

There was nonadherence to medications in 17 of 195 of patients (8.7%) with equal sex distribution (Table 2). Of these, 13 of 17 patients (76.5%) stopped taking RASB and 14 of 17 (82.4%) discontinued immunosuppression. Documented reasons for treatment discontinuation were that one patient became pregnant, one developed steroid-induced hyperglycemia, and one developed mycophenolic acid-related diarrhea. Nonadherence was not associated with socioeconomic status or frequency of in-center visits. Nonadherence to medications was more common in patients who experienced the CO (no CO; 6 of 123, 4.9% vs. CO; 11 of 72, 15.3%, $P = 0.01$).

The frequency of immunosuppression emergent adverse events is summarized in Table 3. Hyperglycemia was the most common adverse event (19 of 141, 13.5%) and required rapid taper of steroids. All patients achieved euglycemia during follow-up. A total of 5% (7 of 141) of patients developed cataract affecting vision. Of the 25 patients who received second-line treatment with mycophenolic acid, sustained weight loss with gastrointestinal symptoms led to discontinuation of the drug in 6 patients (6 of 25, 24%). Infections were frequent at 50 of 146 (34.2%), and the common sites were skin and mucous membranes (14 of 146, 9.6%), respiratory (10 of 146, 6.8%), gastrointestinal (9 of 146, 6.2%), and undifferentiated febrile illnesses. There was 1 death owing to infection (Table 3).

Kidney Outcomes

eGFR-Based Outcomes

The median annual fall in eGFR for the entire GRACE-IgANI cohort was −3.3 (IQR −9.8 to 1.7) ml/min per 1.73 m^2 with a median percentage decrease in eGFR of −16.8 (IQR −51.4 to 10)% at 3 years (Table 4). A total of 76 patients (76 of 193, 39.4%) met the criteria for RP at 3 years (Table 2). The likelihood of developing RP was greatest for those in subgroup 3 and least in subgroup 1 (Figure 2a). Sex, age, and mean arterial pressure at baseline did not influence the rate of decline in eGFR, but as expected, RP was associated with higher proteinuria at baseline (<1 g/d; 12 of 44, 27.3% vs. 1–2.9 g/d; 28 of 83, 33.7% vs. ≥3 g/d; 36 of 66, 54.5%, $P = 0.006$) (Table 4). When baseline proteinuria was stratified by eGFR, higher baseline proteinuria for a given level of eGFR was also associated with RP (Supplementary Table S2 and Supplementary Figure S1). The likelihood of RP was also significantly increased with MEST S1 and T1/T2 scores (S1T0; 7 of 19, 36.8% vs. S1T1; 13 of 55, 23.6% vs. S1T2; 41 of 68, 60.3%, $P < 0.001$) (Supplementary Table S3). Interestingly, although the use of RASB was similar in the RP and N/SP groups at baseline (RP: 56 of 76, 73.7% vs. N/SP: 75 of 117, 64.1%, $P = 0.16$), at each

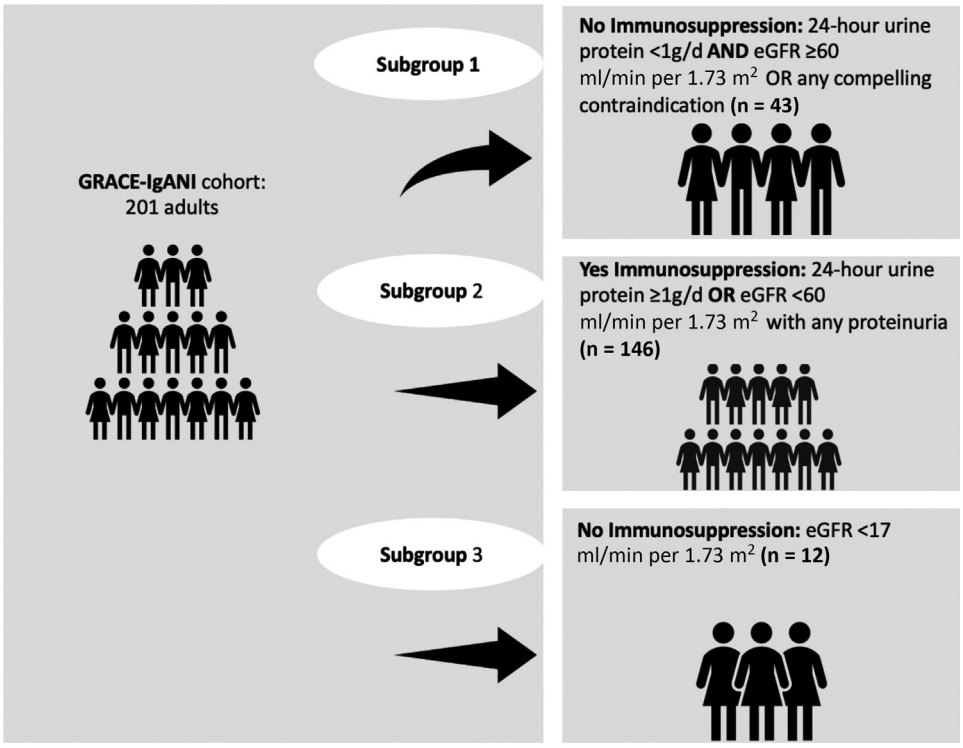


Figure 1. Treatment subgroups. All patients with ≥1 g/d of proteinuria and/or renal impairment were treated with short course of oral steroids (subgroup 2) except for patients with chronic sclerosing IgAN or with compelling contraindications. eGFR, estimated glomerular filtration rate; GRACE-IgANI, Glomerular Research And Clinical Experiments—IgA Nephropathy in Indians; IgAN, IgA nephropathy.

Table 2. Three-year longitudinal clinical outcomes of the GRACE-IgANI cohort

Outcomes	(*N* = 195)
Proteinuria status at	
6 mo:	
Partial remission, *n*/*N* (%)	95/159 (59.7)
Complete remission, *n*/*N* (%)	26/159 (16.4)
1 yr:	
Partial remission, *n*/*N* (%)	77/145 (53.1)
Complete remission, *n*/*N* (%)	46/145 (31.7)
2 yrs:	
Partial remission, *n*/*N* (%)	65/128 (50.8)
Complete remission, *n*/*N* (%)	41/128 (32)
3 yrs:	
Partial remission, *n*/*N* (%)	41/85 (48.2)
Complete remission, *n*/*N* (%)	27/85 (31.8)
Cumulative at 3 yrs or at last follow-up:	
Partial remission, *n*/*N* (%)	85/182 (46.7)
Complete remission, *n*/*N* (%)	51/182 (28)
eGFR progression at 3 yrs	
Percentage decrease in eGFR from baseline (ml/min per 1.73 m^2), median (IQR)	−16.8 (−51.4 to 10)
Median annual rate of decrease in eGFR (ml/min per 1.73 m^2/yr), median (IQR)	−3.3 (−9.8 to 1.7)
Rapid progression (≥ 5 ml/min per 1.73 m^2/yr), *n*/*N* (%)	76/193 (39.4)
Composite outcome, *n*/*N* (%)	72/195 (36.9)
Death, *n*/*N* (%)	11/195 (5.6)
Nonadherence to medications, *n*/*N* (%)	17/195 (8.7)

eGFR, estimated glomerular filtration rate; GRACE-IgANI, Glomerular Research And Clinical Experiments—IgA Nephropathy in Indians; IQR, interquartile range.

Table 3. Immunosuppression-related adverse events in the GRACE-IgANI cohort

Immunosuppression-related adverse events	Entire cohort *N* = 144
Steroid-related toxicities	
Dysglycemia, *n* (%)	19 (13.2)
Cushing features, *n* (%)	10 (6.9)
Acne, *n* (%)	8 (5.5)
Vision	
Cataract, *n* (%)	7 (4.9)
Myopia, *n* (%)	1 (0.7)
Mycophenolate-related toxicities	
Weight loss with/without GI symptoms, *n* (%)	6/25 (24)
Immunosuppression-related infections	50 (34.7)
Skin and mucosa	
Herpes zoster, *n* (%)	6 (4.2)
Dermatophyte infection, *n* (%)	8 (5.5)
Varicella, *n* (%)	1 (0.7)
Erythrasma, *n* (%)	2 (1.4)
Folliculitis, *n* (%)	2 (1.4)
Scabies, *n* (%)	1 (0.7)
Genital candidiasis, *n* (%)	1 (0.7)
Urinary tract infection, *n* (%)	3 (2.1)
Respiratory tract infections	
Upper, *n* (%)	6 (4.2)
Lower, *n* (%)	4 (2.8)
Gastrointestinal	
Infectious diarrhea, *n* (%)	8 (5.5)
Helicobacter pylori gastritis, *n* (%)	1 (0.7)
Central nervous system infection, *n* (%)	1 (0.7)
Undifferentiated acute febrile illness, *n* (%)	6 (4.2)
Death related to infection, *n* (%)	1 (0.7)

Italics font indicates organ systems.
GI, gastrointestinal; GRACE-IgANI, Glomerular Research And Clinical Experiments—IgA Nephropathy in Indians.

scheduled follow-up, the use of RASB was significantly less in the RP compared with the N/SP group (Figure 2b). In addition, those patients who subsequently developed RP were taking more antihypertensives at baseline (N/SP: 53 of 117, 45.3% vs. RP: 50 of 76, 65.8%, $P = 0.005$) and at each scheduled follow-up visit.

A total of 72 patients (72 of 195, 36.9%) reached the CO at 3 years. The mean time to the CO for the entire cohort was 32 (95% CI 30.2–33.7) months (Figure 2c). The mean time to the CO was significantly different between the treatment subgroups 1 and 2 (log-rank $P = 0.003$) and between subgroups 2 and 3 (log-rank $P < 0.0001$) (Figure 2c).

The baseline variables for those patients with and without a CO are summarized in Table 1. The presence of hypertension (no CO: 96 of 123, 78% vs. CO: 68 of 71 95.8%, $P = 0.001$), higher median proteinuria (no CO: 1.5 [IQR 0.9–2.7] vs. CO: 3.4 [IQR 1.8–5] g/d, $P < 0.001$), and lower median eGFR (no CO: 53.1 [IQR 37.8–86.8] vs. CO: 26.8 [IQR 16.5–39.8] ml/min per 1.73 m^2, $P < 0.001$) at baseline was significantly associated with the CO (Tables 1 and 4 and Supplementary Table S3). Age, sex, body mass index, and socioeconomic status were not associated with the CO, whereas patients with visible hematuria were at a significantly lower risk of developing the CO. The association between CO and baseline eGFR and proteinuria is pictorially illustrated in Supplementary Figure S1. Those patients who experienced the CO had significantly greater segmental sclerosis (MEST-S1: 73.5% vs. 93.7%, $P = 0.001$), tubulointerstitial scarring (MEST-T2/T1: 24.8/47% vs. 74.6/17.5%, $P < 0.001$), and global glomerulosclerosis (≥33%: 36.6% vs. 79.2%, <0.001). The relationship between the MEST-C scores, baseline eGFR, 24UP, and the risk of a CO is found in Supplementary Tables S3 and S4 and Supplementary Figure S2A and B.

The use of RASB at baseline was similar in those patients who did and did not experience the CO (82 of 123, 66.7% vs. 49 of 72, 68.1%, $P = 0.84$) (Table 1 and Figure 2d). Nevertheless, patients who experienced the CO were significantly less likely to be maintained on RASB at each scheduled follow-up (Figure 2d). Treatment with antihypertensive medication at baseline and at each scheduled follow-up was significantly greater in those patients who had the CO (54 of 123, 43.9% vs. 51 of 72, 70.8%, $P < 0.001$) (Supplementary Figure S3). Immunosuppression exposure was similar in those who

Table 4. The association of baseline variables with kidney function outcome

Categories: *N*	CKD-EPI eGFR ml/min per 1.73 m^2 median (IQR) Baseline	CKD-EPI eGFR ml/min per 1.73 m^2 median (IQR) At 3 yrs/at CO	Percentage decrease in eGFR median (IQR)	Rate of fall in eGFR ml/min per 1.73 m^2/yr median (IQR)	Rapid progression *n* (%)
Male: 136	38.4 (26.6–63.9)	34.2 (12.9–68.4)	−13.8 (−53.1 to 14.6)	−2.7 (−9.7 to 1.9)	50 (36.8)
Female: 57	39.3 (23.3–85.7)	32.3 (10.6–96.2)	−25.2 (−49.9 to 3.2)	−3.7 (−10.7 to 0.8)	26 (45.6)
Age ≤ 35 yrs: 105	43.9 (27.7–85.2)[a]	37.4 (11.3–90.8)[b]	−16.6 (−52.9 to 10)	-3.6 (−9.9 to 2.4)	43 (41)
>35 yrs: 88	35.7 (23.5–49.3)[a]	27.1 (12.3–47.5)[b]	−18.2 (−50.2 to 11.6)	-2.6 (−8.8 to 1.4)	33 (37.5)
MAP < 104 mm Hg: 105	43.8 (28.4–81.3)[c]	36.8 (14.1–89.9)[d]	−13.1 (−48.7 to 11.4)	−2.6 (−8.5 to 2.3)	37 (35.2)
≥104 mm Hg: 88	35.7 (24.4–50.4)[c]	26.7 (10.4–53.4)[d]	−24.4 (−54.9 to 6.7)	−3.4 (−11.4 to 1.1)	39 (44.3)
24-hr UP < 1 g/d: 44	64.8 (35–111.7)	64.4 (33.5–110.1)	−3.1 (−26.7 to 12.8)	−0.9 (−5 to 3.3)	12 (27.3)[e]
1–2.9 g/d: 83	43.4 (28.1–64)	30.9 (20.6–65.3)	−13.1 (−40.9 to 14.4)	-2 (−6.6 to 2.3)	28 (33.7)[e]
≥3 g/d: 66	30.7 (23.3–42)	13.4 (8.9–37.8)	−44 (−64.9 to −6.3)	-5.9 (−15.2 to −1.4)	36 (54.5)[e]
All categories 193	38.9 (25.7–67.1)	33.5 (12.1–72.6)	−16.8 (−51.4 to 10)	−3.3 (−9.8 to 1.7)	193 (39.4)

Categories: *N*	≥50% decrease AND eGFR <15 ml/min per 1.73 m^2 *n* (%)	eGFR <15 ml/min per 1.73 m^2 *n* (%)	Dialysis *n* (%), Transplant *n* (%)	Death *n* (%)	Composite outcome *n* (%)
Male: 137	46 (33.6)	41 (29.9)	20 (14.6), 7 (5.1)	1 (0.7)	46 (33.6)
Female: 58	24 (41.4)	21 (36.2)	12 (20.7), 3 (5.2)	0	26 (44.8)
Age ≤ 35 yrs: 106	39 (36.8)	35 (33)	17 (16), 9 (8.5)[d]	0	40 (37.7)
>35 yrs: 89	31 (34.8)	27 (30.3)	15 (16.9), 1 (1.1)[d]	1 (1.1)	32 (36)
MAP < 104 mm Hg: 106	36 (34)	30 (28.3)	16 (15.1), 3 (2.8)	1 (0.9)	37 (34.9)
≥104 mm Hg: 89	34 (38.2)	32 (35.9)	16 (18), 7 (7.9)	0	35 (39.3)
24-hr UP < 1 g/d: 44	8 (18.2)[e]	6(13.6)[e]	3 (6.8)[c], 0[a]	0	8 (18.2)[e]
1–2.9 g/d: 83	22 (26.5)[e]	18 (21.7)[e]	10 (12)[c], 2 (2.4)[a]	0	23 (27.7)[e]
≥3 g/d: 68	40 (58.8)[e]	38 (55.9)[e]	19 (27.9)[c], 8 (11.8)[a]	1 (1.5)	41 (60.3)[e]
All categories 195	70 (35.9)	62 (31.8)	32 (16.4), 10 (5.1)	1 (0.5)	195 (36.9)

24-hr UP, 24-hour urine protein; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CO, composite outcome; eGFR, estimated glomerular filtration rate; IQR, interquartile range; MAP, mean arterial pressure.
[a]$P = 0.002$ between the groups.
[b]$P = 0.001$ between the groups.
[c]$P = 0.005$ between the groups.
[d]$P = 0.015$ between the groups.
[e]$P = 0.006$ between the groups.
Of 201 patients, 195 had CO status known at 3 years or earlier and 6 were lost to follow-up. Two patients who reached CO and started dialysis in an outside center did not report their predialysis serum creatinine value to us and were excluded from calculation of rate of decline in eGFR for rapid progression (193 patients).

did and did not experience the CO (90 of 123, 73.2% vs. 56 of 72, 77.8%, $P = 0.35$). The receiver operating characteristic curve for CO at 3 years by rate of eGFR change in the first year of follow-up (Figure 2e) revealed that >5 ml/min per 1.73 m^2 annual fall in eGFR after kidney biopsy had 86% sensitivity and 89% specificity for predicting the CO in a 3-year period and revealed good discrimination from 1 year onwards (area under the curve 0.81, SE 0.04, 95% CI 0.7–0.9, $P < 0.0001$) (Figure 2f).

Complete and PR of Proteinuria

A total of 51 patients (51 of 182, 28%) had a CR in proteinuria in 3 years (subgroup 1: 19 of 37, 51.3%; subgroup 2: 31 of 135, 22.9%; subgroup 3: 1 of 10, 0.1%).

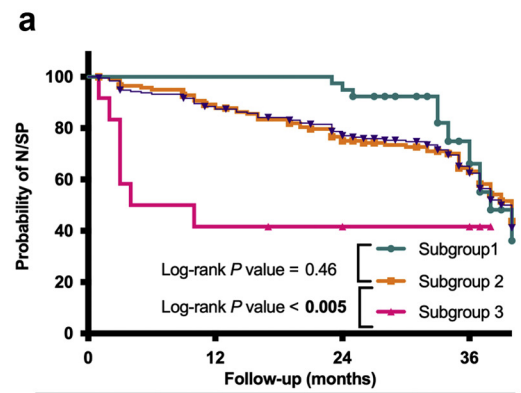
The mean time to CR for the entire cohort was 30 (95% CI 27.5–32.6) months (Figure 3a). The time to CR was not different between the treatment subgroups 1 and 2 (log-rank $P = 0.3$) and between subgroups 2 and 3 (log-rank $P = 0.3$) (Figure 3a).

A total of 85 patients (85 of 182, 46.7%) had a PR in proteinuria in 3 years (subgroup 1: 13 of 37, 35.1%; subgroup 2: 68 of 135, 50.4%; subgroup 3: 4 of 10, 0.4%).

The mean time to PR for the entire cohort was 10.2 (95% CI 7.8–12.6) months (Figure 3b). The time to PR was not different between the treatment subgroups 1 and 2 (log-rank $P = 0.4$) and between subgroups 2 and 3 (log-rank $P = 0.8$) (Figure 3b).

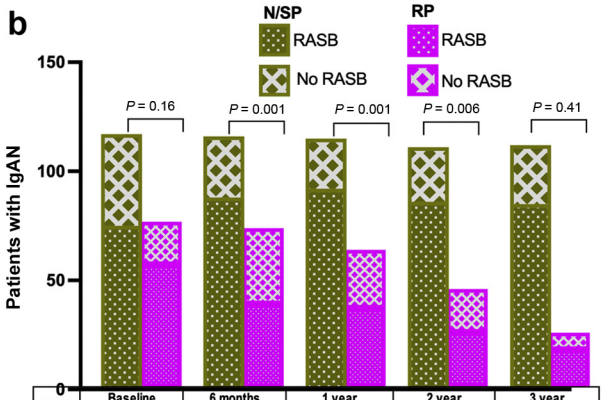
Proportion of RP and N/SP patients who had PR of proteinuria was 36 of 54 (66.7%) and 52 of 57 (91.2%), respectively. Likewise, proportion of RP and N/SP patients who had CR of proteinuria was 12 of 73 (16.4%) and 51 of 108 (47.2%), respectively. The time to PR of proteinuria was significantly longer in those with RP compared with those with N/SP (log-rank $P = 0.01$), and the same was true for the mean time to CR of proteinuria (log-rank $P = 0.002$) (Figure 3c).

Proportion of CO and no CO patients who had PR of proteinuria was 35 of 55 (63.6%) and 53 of 57 (93%),

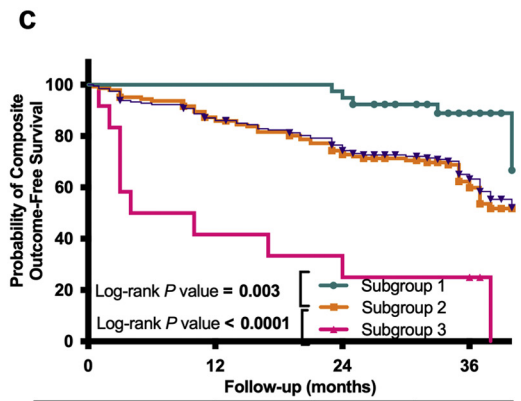


	Subgroup 1	Subgroup 2	Subgroup 3
# censored subjects	25	87	5
# deaths/events	14	55	7

GRACE-IgANI cohort: KM curve for the entire cohort is superimposed and refletcs the KM curve of Subgroup 2 almost accurately.

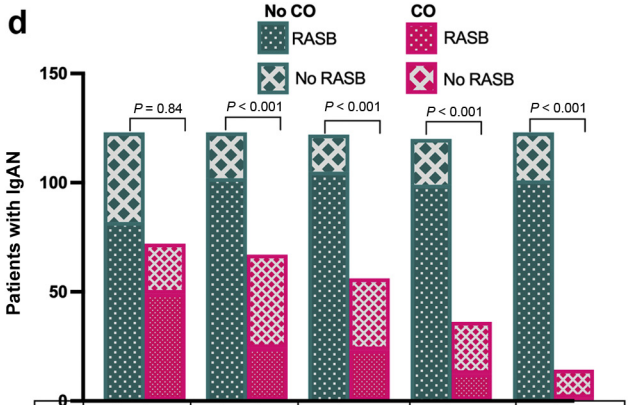


RASBs	Baseline		6 months		1 year		2 year		3 year	
	N/SP	RP	N/SP	RP	N/SP	RP	N/SP	RP	N/SP	RP
No	42 (35.9)	20 (26.3)	28 (24.1)	35 (47.9)	23 (20)	27 (42.9)	25 (22.5)	20 (44.4)	27 (24.1)	8 (32)
Yes	75 (64.1)	56 (73.7)	88 (75.9)	38 (52.1)	92 (80)	36 (57.1)	86 (77.5)	25 (55.6)	85 (75.9)	17 (68)
Total	117	76	116	73	115	63	111	45	112	25

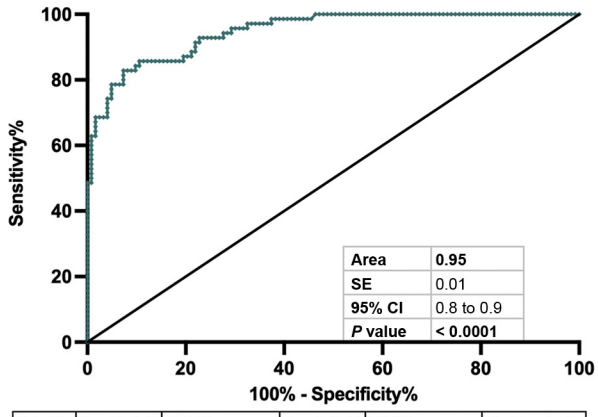


	Subgroup 1	Subgroup 2	Subgroup 3
# censored subjects	34	87	2
# deaths/events	5	57	10

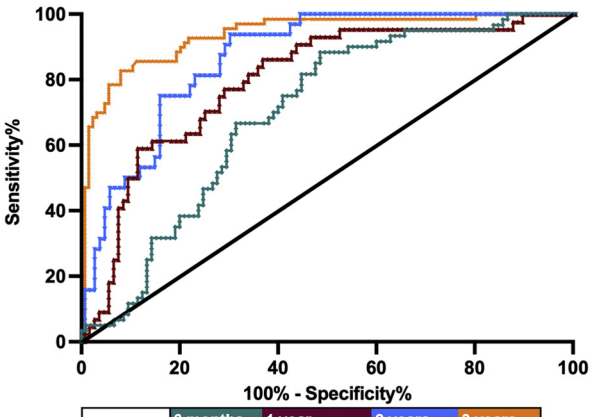
GRACE-IgANI cohort: KM curve for the entire cohort is superimposed and refletcs the KM curve of Subgroup 2 almost accurately.



RASBs	Baseline		6 months		1 year		2 year		3 year	
	No CO	CO	No CO	CO	No CO	CO	No CO	CO	No CO	CO
No	41 (33.3)	23 (31.9)	21 (17.1)	43 (64.2)	17 (13.9)	33 (58.9)	21 (17.5)	24 (66.7)	22 (17.9)	13 (92.9)
Yes	82 (66.7)	49 (68.1)	102 (82.9)	24 (35.8)	105 (86.1)	23 (41.1)	99 (82.5)	12 (33.3)	101 (82.1	1 (7.1)
Total	123	72	123	67	122	56	120	36	123	14



Cut-off	Sensitivity%	95% CI	Specificity%	95% CI	Likelihood ratio
< -6	81	71 to 89	93	87 to 96	11
< -5	86	76 to 92	89	83 to 94	8
< -4	86	76 to 92	81	73 to 87	4



	6 months	1 year	2 years	3 years
Area	0.7	0.8	0.87	0.94
SE	0.04	0.04	0.03	0.02
95% CI	0.6 to 0.8	0.7 to 0.9	0.8 to 0.9	0.9 to 1
P value	< 0.0001	< 0.0001	< 0.0001	< 0.0001

Figure 2. (a) KM curves of kidney survival (defined here as having N/SP) for the entire cohort and the treatment subgroups. (b) Trends in RASB use in patients with RP and N/SP. (c) KM curves of kidney survival (defined as composite outcome-free survival) for the entire cohort and treatment subgroups. (d) Trends in RASB use in the patients who did and did not experience the composite outcome. (e) ROC curve of average annual rate of eGFR change and the composite outcome at 3 years. (f) ROC curve for annualized fall in eGFR at each time period (continued)

respectively. Likewise, proportion of CO and no CO patients who had CR of proteinuria was 12 of 73 (16.4%) and 51 of 108 (47.2%), respectively. The time to both PR of proteinuria (log-rank $P = 0.07$) and CR of proteinuria (log-rank $P < 0.0001$) was longer in the CO group (Figure 3d). The proportion of patients in PR and CR at each follow-up period was significantly different between the outcome groups (Figure 3e). A total of 154 of 181 patients (85%) maintained remission at 3 years or at last follow-up.

When time to kidney survival (defined as no CO) was stratified by proteinuria in 6 months of follow-up, achieving <1 g/d significantly increased kidney survival (<0.3 g/d vs. 0.3–1 g/d vs. 1.1–3 g/d vs. >3 g/d, log-rank $P < 0.0001$) (Figure 4a). This relationship was found in subgroup 2 (Figure 4b and c).

When stratified for MEST S and T scores, time to PR of proteinuria was similar (Supplementary Figure S2C–D), but time to CR of proteinuria was significantly longer in higher MEST S and T scores (S0T0 vs. S0T1vs. S0T2, log-rank $P = 0.03$) (S1T0 vs. S1T1 vs. S1T2, log-rank $P = 0.007$) (Supplementary Figure S2E–F).

Patient Survival

Mortality at 3 years in GRACE-IgANI was 5.6% (11 of 195). A total of 9 patients died after reaching ESKD. Of these, 6 patients were on hemodialysis and 1 had a kidney transplant. One patient died of an unrelated cause (eGFR = 23 ml/min per 1.73 m^2) and 1 from encephalitis within a month of starting oral steroids (age = 50 years, baseline eGFR = 33 ml/min per 1.73 m^2, and eGFR at the time of death = 10 ml/min per 1.73 m^2). Sex, age, mean arterial pressure, and proteinuria were not associated with risk of death (Table 4).

Trends in Clinical and Laboratory Parameters During Scheduled Follow-Up Visits

Mean arterial pressure was consistently higher at each scheduled follow-up in those who experienced a CO (Figure 4d). Mixed effects analysis revealed a significant linear decrease in mean arterial pressure and proteinuria at each scheduled follow-up in the no CO group and a significant linear decrease of eGFR at each scheduled follow-up in the CO group (Figure 4d–f). The change in eGFR was greatest within 6 months of starting therapy (Figure 4f).

Although the mean systolic BP was significantly higher in the CO group (136.2 ± 19.5 vs. 142.8 ± 21.9, $P = 0.03$) at baseline, it was similar at follow-up visits (Supplementary Figure S4A). The mean diastolic BP was similar, both at baseline (86.2 ± 11.5 vs. 87.8 ± 14.6, $P = 0.39$) and follow-up (Supplementary Figure S4B). Notably, among other clinical variables, hemoglobin, serum total protein, and serum albumin were significantly lower in the CO compared with no CO group at each scheduled visit (Table 1) (Supplementary Figure S4C–L). Mixed effects analysis revealed significant linear increases over time for body mass index, hemoglobin, serum total protein, and serum albumin in the no CO group and for serum total protein and serum albumin in the CO group. Hemoglobin significantly decreased in a linear pattern in the CO group over time (Supplementary Figure S4C–L). The linear trends of other laboratory parameters in patients who did and did not experience a CO are summarized in Supplementary Figure S5A–H.

Predictors of the CO

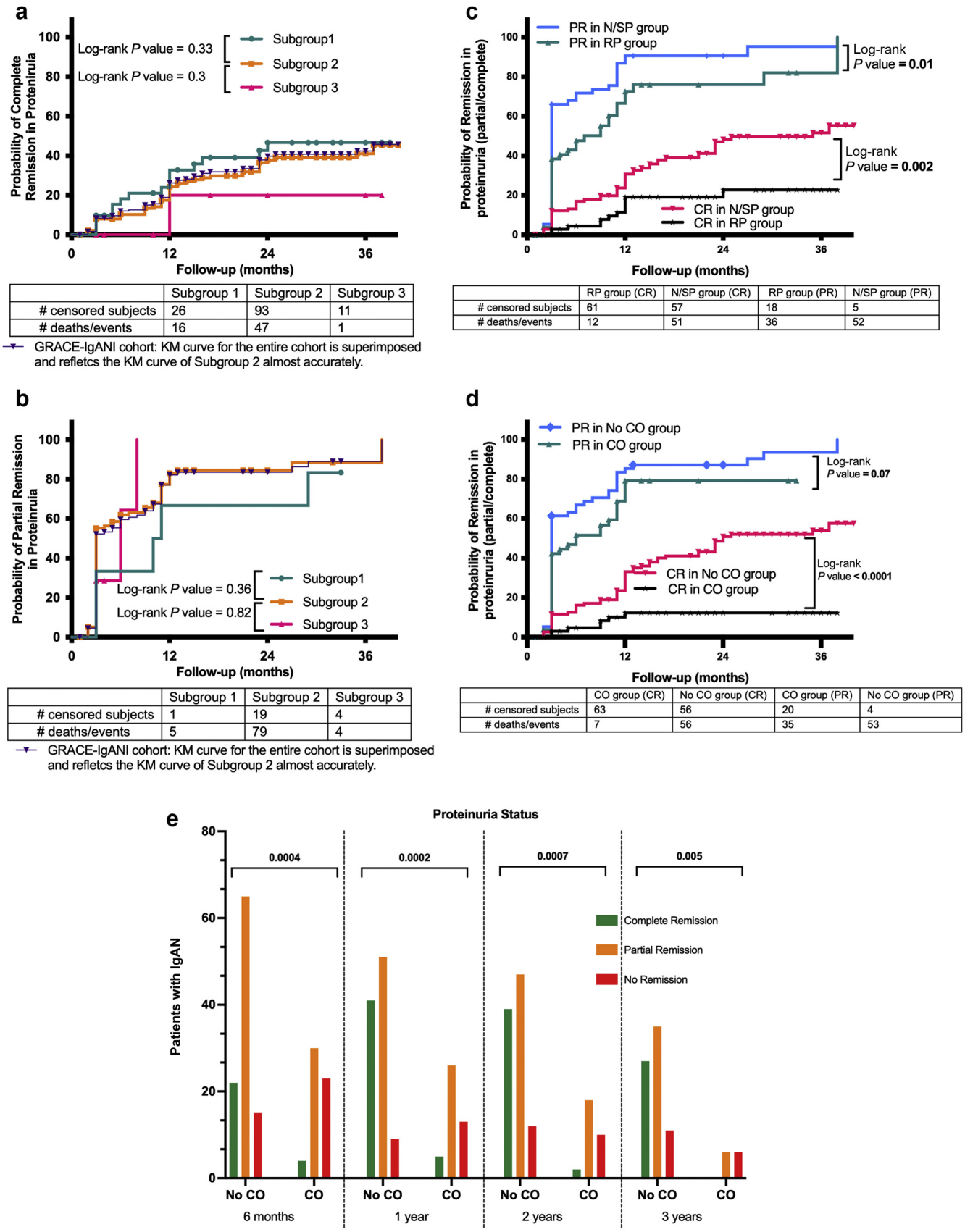
Two Cox proportional-hazards models were constructed to identify significant predictors for time to the CO (Table 5), one using baseline clinical variables and the other using longitudinal clinical variables at 6 months. In the baseline model, MEST-T2 score at baseline (HR 3.6, 95% CI 1.9–6.7, $P < 0.001$), combined 24-hour urine protein level < 2.5 g/d and serum albumin level > 4 g/dl (HR 0.3, 95% CI 0.2–0.6, $P = 0.001$) and eGFR level < 60 ml/min per 1.73 m^2 (HR 2.4, 95% CI 1–5.5, $P = 0.04$) were significant predictors for CO at 3 years. In the longitudinal model, MEST-T2 score at baseline (HR 3.3, 95% CI 1.7–6.5, $P < 0.001$), 24-hour urine protein at 6 months ≥1 g/d (HR 2.1, 95% CI 1.1–3.9, $P = 0.02$), and eGFR < 60 ml/min per 1.73 m^2 at 6 months (HR 2.9, 95% CI 1.1–7.6, $P = 0.03$) and rate of eGFR decline measured at 6 months of ≥5 ml/min per 1.73 m^2 per year (HR 2.7, 95% CI 1.6–4.8, $P < 0.001$) were significant predictors for CO at 3 years.

We also compared the predicted 3-year risk of a 50% decline in eGFR or ESKD using the International IgA Nephropathy Network risk prediction tool[6] (median 18.1; IQR 7.4%–31.2%) with the actual patient outcomes in 3 years (Supplementary Figure S6A). The area under the receiver operating characteristic curve for predicting the CO was 0.81 (95% CI 0.75–0.88) (Supplementary Figure S6B).

DISCUSSION

This is first South Asian IgAN cohort with prespecified and protocolized prospective longitudinal follow-up. In

Figure 2. (continued) and the composite outcome at 3 years. #, number; CO, composite outcome; eGFR, estimated glomerular filtration rate; GRACE-IgANI, Glomerular Research And Clinical Experiments—IgA Nephropathy in Indians; IgAN, IgA nephropathy; KM, Kaplan–Meier; N/SP, no/slow progression; RASB, renin-angiotensin system blocker; ROC, receiver operating characteristic; RP, rapid progression.



	Subgroup 1	Subgroup 2	Subgroup 3
# censored subjects	26	93	11
# deaths/events	16	47	1

GRACE-IgANI cohort: KM curve for the entire cohort is superimposed and refletcs the KM curve of Subgroup 2 almost accurately.

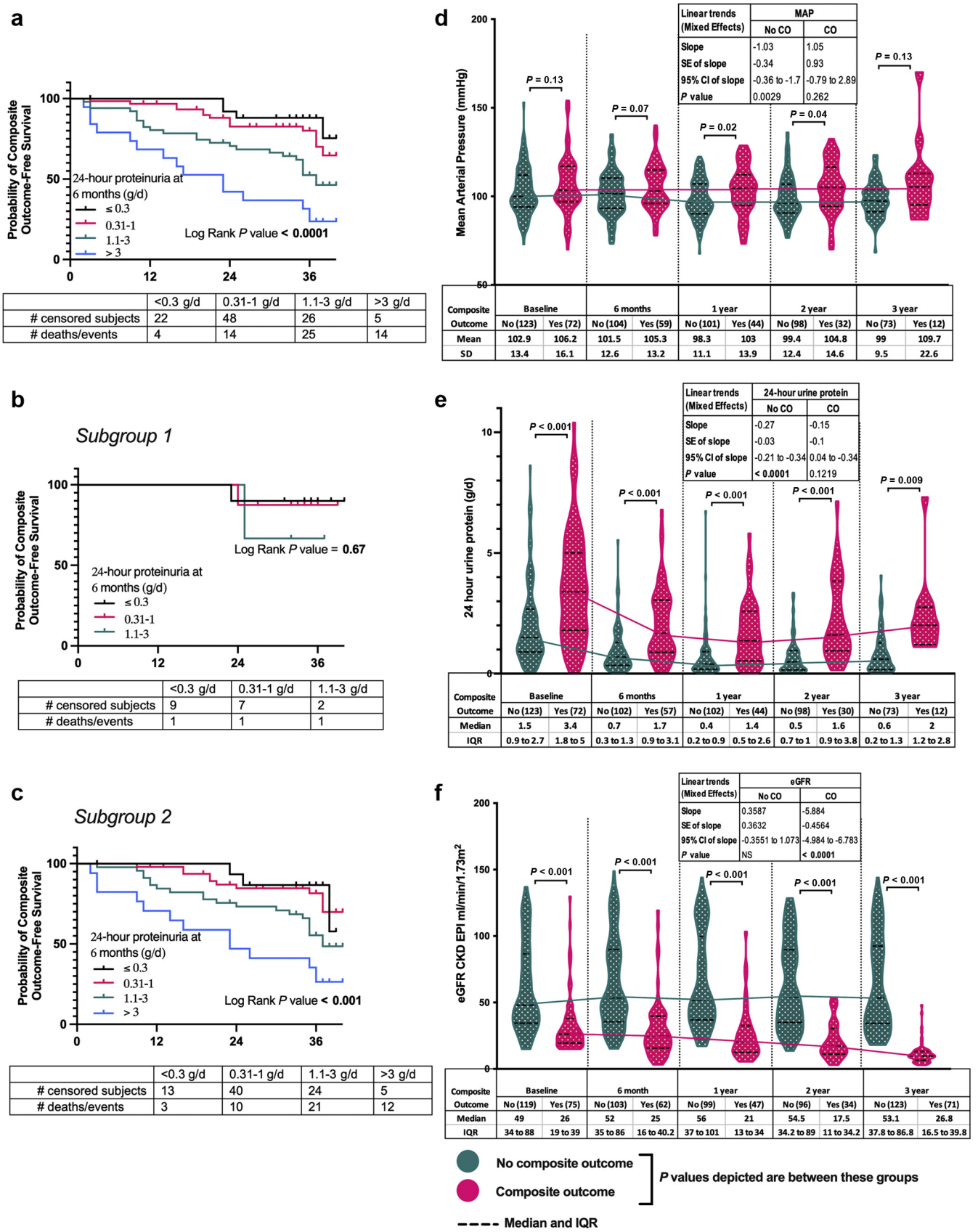
	RP group (CR)	N/SP group (CR)	RP group (PR)	N/SP group (PR)
# censored subjects	61	57	18	5
# deaths/events	12	51	36	52

	Subgroup 1	Subgroup 2	Subgroup 3
# censored subjects	1	19	4
# deaths/events	5	79	4

GRACE-IgANI cohort: KM curve for the entire cohort is superimposed and refletcs the KM curve of Subgroup 2 almost accurately.

	CO group (CR)	No CO group (CR)	CO group (PR)	No CO group (PR)
# censored subjects	63	56	20	4
# deaths/events	7	56	35	53

Figure 3. (a) KM curves of CR of proteinuria for the entire cohort and the treatment subgroups. (b) KM curves of PR of proteinuria for the entire cohort and the treatment subgroups. (c) KM curves of proteinuria remission stratified by rate of progression. (d) KM curves of proteinuria remission stratified by composite outcome status. (e) Proteinuria status at each time period in the outcome groups. #, number; CO, composite outcome; CR, complete remission; GRACE-IgANI, Glomerular Research And Clinical Experiments—IgA Nephropathy in Indians; IgAN, IgA nephropathy; KM, Kaplan–Meier; N/SP, no/slow progression; PR, partial remission; RP, rapid progression.



	<0.3 g/d	0.31-1 g/d	1.1-3 g/d	>3 g/d
# censored subjects	22	48	26	5
# deaths/events	4	14	25	14

	<0.3 g/d	0.31-1 g/d	1.1-3 g/d
# censored subjects	9	7	2
# deaths/events	1	1	1

	<0.3 g/d	0.31-1 g/d	1.1-3 g/d	>3 g/d
# censored subjects	13	40	24	5
# deaths/events	3	10	21	12

Linear trends (Mixed Effects)	MAP	
	No CO	CO
Slope	-1.03	1.05
SE of slope	-0.34	0.93
95% CI of slope	-0.36 to -1.7	-0.79 to 2.89
P value	0.0029	0.262

Composite	Baseline		6 months		1 year		2 year		3 year	
Outcome	No (123)	Yes (72)	No (104)	Yes (59)	No (101)	Yes (44)	No (98)	Yes (32)	No (73)	Yes (12)
Mean	102.9	106.2	101.5	105.3	98.3	103	99.4	104.8	99	109.7
SD	13.4	16.1	12.6	13.2	11.1	13.9	12.4	14.6	9.5	22.6

Linear trends (Mixed Effects)	24-hour urine protein	
	No CO	CO
Slope	-0.27	-0.15
SE of slope	-0.03	-0.1
95% CI of slope	-0.21 to -0.34	0.04 to -0.34
P value	< 0.0001	0.1219

Composite	Baseline		6 months		1 year		2 year		3 year	
Outcome	No (123)	Yes (72)	No (102)	Yes (57)	No (102)	Yes (44)	No (98)	Yes (30)	No (73)	Yes (12)
Median	1.5	3.4	0.7	1.7	0.4	1.4	0.5	1.6	0.6	2
IQR	0.9 to 2.7	1.8 to 5	0.3 to 1.3	0.9 to 3.1	0.2 to 0.9	0.5 to 2.6	0.7 to 1	0.9 to 3.8	0.2 to 1.3	1.2 to 2.8

Linear trends (Mixed Effects)	eGFR	
	No CO	CO
Slope	0.3587	-5.884
SE of slope	0.3632	-0.4564
95% CI of slope	-0.3551 to 1.073	-4.984 to -6.783
P value	NS	< 0.0001

Composite	Baseline		6 month		1 year		2 year		3 year	
Outcome	No (119)	Yes (75)	No (103)	Yes (62)	No (99)	Yes (47)	No (96)	Yes (34)	No (123)	Yes (71)
Median	49	26	52	25	56	21	54.5	17.5	53.1	26.8
IQR	34 to 88	19 to 39	35 to 86	16 to 40.2	37 to 101	13 to 34	34.2 to 89	11 to 34.2	37.8 to 86.8	16.5 to 39.8

Figure 4. (a) Kaplan–Meier curves of kidney survival (defined as composite outcome-free survival) stratified by the achieved proteinuria at 6 months follow-up for the entire cohort. (b) Kaplan–Meier curves of kidney survival (defined as composite outcome-free survival) stratified by the achieved proteinuria at 6 months follow-up for treatment subgroup 1. (c) Kaplan–Meier curves of kidney survival (defined as composite outcome-free survival) stratified by the achieved proteinuria at 6 months follow-up for treatment subgroup 2. Linear trends in (d) mean arterial pressure, (e) proteinuria, and (f) eGFR over time and in relation to the development of the composite outcome. #, number; CO, composite outcome; eGFR, estimated glomerular filtration rate; IQR, interquartile range.

Table 5. Cox proportional-hazards models for predictors of composite outcome

Baseline demography, histology and clinical predictors	Total number of patients, *N*	Composite outcomes, *n* (%)	Unadjusted hazard ratio (95% CI); *P* value	Cox proportional-hazards model	
				Adjusted hazard ratio (95% CI)	*P* value
Model 1: −2 log likelihood = 538.4, $\chi^2 = 57.5$ (df = 3), $P < 0.001$					
Age: ≤ 35 yrs	106	40 (37.7)			
> 35 yrs	89	32 (35.9)	0.9 (0.5–1.4); 0.6		
Sex: Female	58	26 (44.8)			
Male	137	46 (33.6)	0.7 (0.4–1.1); 0.1		
MEST-C: S0	35	4 (11.4)			
S1	145	59 (40.7)	4 (1.5–11.1); 0.007[a]		
MEST-C: T0/T1	104	16 (15.4)			
T2	76	47 (61.8)	5.4 (3.1–9.6); <0.001[a]	3.6 (1.9–6.7)	<0.001[a]
Hypertension: No	30	3 (10)			
Yes	164	68 (41.5)	4.6 (1.4–14.6); 0.01[a]		
Hemoglobin: > 12 g/dl	94	23 (24.5)			
≤ 12 g/dl	102	49 (48)	2.5 (1.5–4.1); <0.001[a]		
S. albumin AND 24-hr urine protein:					
>4 g/dl AND <2.5 g/d	74	11 (14.9)			
vs. others	118	60 (50.8)	0.2 (0.1–0.4); <0.001[a]	0.3 (0.2–0.6)	0.001[a]
eGFR CKD-EPI: ≥60 ml/min per 1.73 m^2	60	8 (13.3)			
<60 ml/min per 1.73 m^2	135	64 (47.4)	4.5 (2.1–9.4); <0.001[a]	2.4 (1–5.5)	0.04[a]
Baseline demography, histology and longitudinal clinical predictors at 6 mo	**Total number of patients, *N***	**Composite outcomes, *n* (%)**	**Unadjusted hazard ratio (95% CI); *P* value**	**Cox proportional-hazards model**	***P* value**
				Adjusted hazard ratio (95% CI)	
Model 2: −2 log likelihood = 421, $\chi^2 = 53.7$ (df = 4), $P < 0.001$					
Age: ≤ 35 yrs	106	40 (37.7)			
> 35 yrs	89	32 (35.9)	0.9 (0.5–1.4); 0.6		
Sex: Female	58	26 (44.8)			
Male	137	46 (33.6)	0.7 (0.4–1.1); 0.1		
MEST-C: S0	35	4 (11.4)			
S1	145	59 (40.7)	4 (1.5–11.1); 0.007[a]		
MEST-C: T0/T1	104	16 (15.4)			
T2	76	47 (61.8)	5.4 (3.1–9.6); <0.001[a]	3.3 (1.7–6.5)	<0.001[a]
MAP at 6 mo: <102 mm Hg	80	28 (35)			
≥ 102 mm Hg	83	31 (37.3)	0.9 (0.6–1.6); 0.8		
Hemoglobin at 6 mo: >12 g/dl	93	26 (27.9)			
≤12 g/dl	70	34 (48.6)	2.2 (1.3–3.7); 0.002[a]		
Serum albumin at 6 mo: >4 g/dl	92	27 (29.3)			
≤4 g/dl	70	32 (45.7)	1.8 (1.1–3); 0.03[a]		
24-hr urine protein at 6 mo: <1 g/d	88	18 (20.4)			
≥1 g/d	71	39 (54.9)	3.1 (1.8–5.4); <0.001[a]	2.1 (1.1–3.9)	0.02[a]
eGFR CKD-EPI at 6 mo: ≥ 60 ml/min per 1.73 m^2	50	5 (10)			
<60 ml/min per 1.73 m^2	115	55 (47.8)	5.9 (2.3–14.6); <0.001[a]	2.9 (1.1–7.6)	0.03[a]
Rate of eGFR decline at 6 mo: <5 ml/min per 1.73 m^2/yr	107	31 (30)			
≥5 ml/min per 1.73 m^2/yr	58	29 (50)	2.2 (1.3–3.6); 0.003[a]	2.7 (1.6–4.8)	<0.001[a]

[a] *P* value is significant at < 0.05.

this cohort, 68 of 201 (34%) had proteinuria level ≥ 3.0 g/d and 32 of 68 (47%) of those had an eGFR level < 30 ml/min per 1.73 m^2 at baseline. As reported previously, this is a cohort at high risk of progressive CKD.[4] Consistent with Kidney Disease: Improving Global Outcomes guidelines, all patients were offered optimized supportive care and optimal BP control, and uptitration of RASB was achieved in 70% to 80% of the cohort in the 3 years of follow-up. In accordance with the prespecified protocol, all patients regarded as at high risk of progression were offered immunosuppression, and 146 of 194 patients (75.3%) received systemic corticosteroids.

Despite optimized supportive care and use of systemic corticosteroids, at 3 years, 40% of the GRACE-IgANI cohort displayed rapid CKD progression and 37% experienced the CO. By contrast, most studies from Europe, Asia, and Australia report far less severe outcomes, with actuarial 10-year kidney survivals in IgAN of between 81% and 87%.[9–12] Mortality

associated with IgAN has not been extensively reported. In a Chinese study, 71 deaths (5.3%) were reported in 13,916 person-years of follow-up and patient survival rates at 10, 20, and 30 years were 96.3%, 91.8%, and 82.7%, respectively.[13] Similar survival rates have been reported in smaller Korean and Swedish IgAN cohorts.[14,15] Nevertheless, in this Indian cohort, 11 of 195 patients had died within 3 years of diagnosis (5.6% mortality in 463 person-years). Most deaths occurred after reaching ESKD (9 of 11, 81.8%) and may be explained by the limited access to free ESKD care in this region.[16] This rapidity of progression to ESKD and increased mortality, combined with lack of access to renal replacement therapy in South Asia, highlight the large unmet need in IgAN, both in terms of early diagnosis and availability of safe and effective treatments to prevent CKD progression.

In line with previous studies, we reveal in the GRACE-IgANI cohort by multivariable analysis that baseline serum creatinine and proteinuria levels are independent predictors of poor renal outcome.[17,18] In addition, we identified that a $\geq$5 ml/min per 1.73 m^2 fall in eGFR in the first year after kidney biopsy had 86% sensitivity and 89% specificity for predicting the CO in a 3-year period and that this measure could in the future be used to better inform patients, plan for renal replacement therapy, and select patients for clinical trials or direct more intensive immunosuppression.

We reported previously that although younger ($\leq$35 years) patients presented with milder clinical disease, reflected by less hypertension, higher eGFR level, and lower proteinuria level, there was no difference in the frequency of chronic lesions on renal histology in terms of S1 and T1/T2 scores.[4] Perhaps reflecting the underlying extent of kidney scarring in these younger patients, we did not observe a greater likelihood of proteinuria remission or lower incidence of the CO in younger patients. This contrasts with other studies reporting a better prognosis in the young.[19–21] The International IgA Nephropathy Network risk prediction tool includes age at diagnosis and has been validated in a multiethnic population; however, there was no South Asian representation in the discovery or validation data sets.[6] Although men presented with a significantly more severe clinical phenotype and more extensive chronicity on kidney biopsy, sex did not influence longitudinal outcomes in our cohort.[4] This is again in contrast to the published literature which reports a worse renal outcome for males with IgAN.[22,23] Contrary to our expectations, residing in peripheral rural locations, distance to the center, and socioeconomic status did not affect renal outcomes in our cohort. The impact of these factors may in some parts have been mitigated by frequent teleconsultations and remote review of test reports, highlighting the important emerging role of telemedicine in promoting improved clinical care, disease surveillance, and clinical research.

As expected, persistent hypertension was associated with worse outcome and remission of proteinuria with improved outcome. Those patients who had a sustained reduction in proteinuria within 6 months of diagnosis to $<$1.5 g/d and to $<$1 g/d at 12 months were significantly less likely to experience the CO. Similarly, the time taken to achieve proteinuria remission (partial or complete) was significantly associated with rate of eGFR decline and likelihood of the CO. Consistent with a recent study by Canney *et al.*,[24] sustained reduction in proteinuria to 0.3 to 1 g/d was associated with long-term renal survival in our cohort. It is notable that in those patients who experienced the CO, proteinuria did fall over the 6 months from kidney biopsy; however, there was significant residual proteinuria between 1.5 and 3 g/d, and this likely reflects the extent of chronic glomerular and tubulointerstitial scarring present at the time of diagnosis. Indeed, the presence of T2 lesions significantly shortened the median time to the CO, especially when accompanied by S1 lesions. The time to CR of proteinuria was also significantly prolonged among those patients with T1 and T2 lesions. Consistent with registry data, residual proteinuria between 1.5 and 3 g/d, despite optimized supportive care and systemic corticosteroids, is strongly associated with a worse clinical outcome.[25–28] These observations, along with the widely recognized adverse effects of systemic corticosteroids, many of which were reported in our cohort, necessitate a re-evaluation of the risk-to-benefit ratio for systemic corticosteroids in our IgAN population.

Accurate risk stratification in IgAN is fundamental to inform clinical decision-making, enrollment in clinical trials, and patient education. The International IgA Nephropathy Network risk prediction tool is now the standard method used to risk stratify patients with IgAN at the time of diagnostic kidney biopsy.[6] In the initial derivation of the tool, no patients from South Asia, and in particular India, were included. Although this study was not designed to formally validate the risk prediction tool in an Indian population, our initial assessment of the performance of the tool in GRACE-IgANI has revealed that the tool underestimates the actual risk of the CO in an Indian population. A formal validation study in an Indian IgAN population is now required.

Using the data collected during follow-up, we identified that longitudinal clinical parameters measured at 6 months and rate of eGFR decline at 1 year along with MEST-C T2 score were independent risk factors for development of the CO at 3 years and performed better than baseline clinical parameters. We intend to validate these observations as we follow

patients out to 5 years and completion of the GRACE-IgANI study. In parallel with these clinical observations, extensive serum and urine biomarker phenotyping is currently being performed with the expectation that these data will be combined with the clinical datasets to determine both the added value of novel biomarkers in risk stratification and prognostication and facilitate the identification of important pathogenic pathways in Indian patients with IgAN.

CONCLUSIONS

GRACE-IgANI is the first extensively characterized South Asian IgAN cohort with protocolized, prospective, longitudinal follow-up and outcome assessments. The reported 3-year outcome data highlight the severity of IgAN in Indian patients, with 40% of cases displaying rapid CKD progression, 37% of cases having the CO, and a mortality rate of 5.6% at 3 years, despite optimized supportive care and use of systemic corticosteroids. The unprecedented severe disease course in the South Asian population is likely explained by the severe clinical phenotype at presentation, lack of effective disease-modifying therapies for IgAN, and a likely underlying propensity for progressive disease in this region.

DISCLOSURE

All the authors declared no competing interests.

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DATA SHARING

All data underlying the results are available as part of the article, and no additional source data are required.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Inclusion and exclusion criteria for the GRACE-IgANI cohort.

Table S2. The association of baseline proteinuria and eGFR with changes in eGFR in 3 years.

Table S3. The association of MEST-C S and T scores with changes in eGFR in 3 years.

Table S4. The association between MEST-C scores and the composite outcome when stratified by baseline proteinuria and eGFR.

Figure S1. Percentage dot plots of the rate of progression and achievement of the composite outcome in the GRACE-IgANI cohort. Each circle represents 1% of the selected population.

Figure S2. (a) Kaplan–Meier curves of kidney survival (defined as composite outcome-free survival) stratified by MEST T scores in MEST S0 group. (b) Kaplan–Meier curves of kidney survival (defined as composite outcome-free survival) stratified by MEST T scores in MEST S1 group. (c) Kaplan–Meier curves of partial proteinuria remission stratified by MEST T scores in MEST S0 group. (d) Kaplan–Meier curves of partial proteinuria remission stratified by MEST T scores in MEST S1 group. (e) Kaplan–Meier curves of complete proteinuria remission stratified by MEST T scores in MEST S0 group. (f) Kaplan–Meier curves of complete proteinuria remission stratified by MEST T scores in MEST S1 group.

Figure S3. Trends in antihypertensive use in the patients who did and did not experience the composite outcome.

Figure S4. Linear trends in clinical and laboratory parameters over time and in relation to the development of the composite outcome. (a) Systolic blood pressure. (b) Diastolic blood pressure. (c, d) Body mass index. (e, f). Hemoglobin. (g) Serum cholesterol. (h) Serum uric acid. (i, j) Serum total protein. (k, l). Serum albumin.

Figure S5. Linear trends in clinical and laboratory parameters over time and in relation to the development of the composite outcome. (a) Blood urea. (b) Serum sodium. (c) Serum potassium. (d) Serum bicarbonate. (e) Serum calcium. (f) Serum phosphorous. (g) Serum total bilirubin. (h) Serum alkaline phosphatase.

Figure S6. (a) The actual 3-year outcome for each patient in GRACE-IgANI compared with their predicted risk using the International IgAN Network Risk Prediction Tool. (b) The ROC curve for the 3-year risk prediction using the International IgAN Network Risk Prediction Tool compared with the actual outcome in GRACE-IgANI.

STROBE Statement (PDF).

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