Supplemental Material Table of Contents

Supplemental Table 1. Demographic and clinical characteristics of four groups defined by quartiles of plasma galactose-deficient IgA1 levels.

Characteristics	Quartiles of galactose-deficient IgA1 (U/ml)			
	1	2	3	4
	268±22	308±8	335±8	388±49
Sex (male)	168(55)	160(53)	141(47)	145(48)
Age, yr	35±13	34±12	36±12	35±10
Hypertension (%)	136(45)	121(40)	126(42)	130(43)
Initial proteinuria, g/24 h	1.38(0.68,2.72)	1.28(0.72,2.47)	1.22(0.64,2.46)	1.35(0.71,2.62)
eGFR, ml/min/1.73 m^2	85±33	84±31	82±31	80±32
Oxford classification[a] (%)				
M1	115(39)	116(39)	106(36)	144(48)
E1	96(32)	92(31)	103(35)	100(33)
S1	187(63)	177(60)	185(63)	196(65)
T1	68(23)	81(28)	72(24)	79(26)
T2	23(8)	24(8)	35(12)	42(14)
C1	141(47)	138(47)	139(47)	143(48)
C2	31(10)	40(14)	33(11)	40(13)
Plasma IgA1, mg/ml	2.05(1.48,2.77)	2.45(1.73,3.08)	2.76(2.12,3.52)	2.76(2.26,3.79)
Serum C3, mg/dl	103±23	102±23	103±25	99±23
Treated with immunosuppressive agents or prednisone[c] (%)	139(46)	128(42)	141(47)	142(47)

Abbreviations: eGFR, estimated glomerular filtration rate; M, mesangial hypercellularity; E, the presence of endocapillary proliferation; S, segmental glomerulosclerosis/adhesion; T, severity of tubular atrophy/interstitial fibrosis; C, presence of crescent.
[a] The Oxford classification was developed by the Working Group of the International IgA Nephropathy Network and the Renal Pathology Society. Oxford scores of 23 patients were unavailable because each of them had fewer than eight glomeruli.
[b] The treatment regimens of eight patients were unavailable.

Supplemental Table 2. Demographic and clinical characteristics of four groups defined by quartiles of serum C3 levels.

Characteristics	Quartiles of C3 (mg/dl)			
	1	**2**	**3**	**4**
	75±9	93±4	106±4	133±7
Sex (male)	152(50)	163(54)	164(54)	136(45)
Age, yr	33.8±10.8	34.8±12.4	35.5±11.6	35.8±12.4
Hypertension (%)	118(39)	122(40)	125(41)	149(49)
Initial proteinuria, g/24h	1.2(0.61,2.46)	1.13(0.57,2.14)	1.34(0.74,2.58)	1.58(0.88,2.97)
eGFR, ml/min/ 1.73 m^2	80±33	84±34	82±31	85±30
Oxford classification[a] (%)				
M1	135(45)	124(42)	125(42)	97(32)
E1	99(33)	71(24)	116(39)	105(35)
S1	193(64)	188(64)	181(61)	184(61)
T1	79(26)	70(24)	82(28)	69(23)
T2	45(15)	38(13)	25(8)	16(5)
C1	140(47)	149(51)	150(51)	123(41)
C2	37(12)	33(11)	36(12)	38(13)
Plasma IgA1 (mg/ml)	2.50(1.74,3.36)	2.70(1.92,3.36)	2.54(1.75,3.35)	2.74(1.88,3.39)
Plasma Gd-IgA1 (U/ml)	327±51	327±61	324±48	321±44
Follow-up interval, mo	40(22,78)	44(24,70)	41(23,75)	46(26.3,80)
Treated with immunosuppressive agents or prednisone[b](%)	144(48)	129(43)	141(47)	136(45)

Abbreviations: eGFR, estimated glomerular filtration rate; M, mesangial hypercellularity; E, the presence of endocapillary proliferation; S, segmental glomerulosclerosis/adhesion; T, severity of tubular atrophy/interstitial fibrosis; C, presence of crescent.

[a] The Oxford classification was developed by the Working Group of the International IgA Nephropathy Network and the Renal Pathology Society. Oxford scores of 23 patients were unavailable because each of them had fewer than eight glomeruli.

[b] The treatment regimens of eight patients were unavailable.

Supplemental Table 3. Associations of plasma galactose-deficient IgA1 with CKD progression.

	Galactose-deficient IgA1 levels(U/ml)	N at risk	Events (incidence rate[a])			Hazard ratio (95% confidence interval)			
			CKD progression event[b]	ESKD	50% eGFR decline	Unadjusted	Model 1[c]	Model 2[d]	Model 3[e]
CKD progression event per 1 s.d. galactose-deficient IgA1	325±51	1210	172(3.1)	114(2.0)	165(3.0)	1.23(1.08-1.40)	1.26(1.11-1.44)	1.19(1.04-1.37)	1.16(1.01-1.33)
Galactose-deficient IgA1 quartiles									
1	268±23	303	24(1.8)	13(0.9)	23(1.7)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
2	308±8	302	39(3.0)	27(2.0)	38(2.9)	1.66(1.00-2.76)	1.64(0.99-2.73)	1.84(1.10-3.07)	1.93(1.14-3.26)
3	335±8	302	50(3.5)	35(2.3)	46(3.2)	1.82(1.11-2.96)	1.88(1.15-3.07)	2.06(1.26-3.38)	2.40(1.45-3.97)
4	388±47	303	59(4.0)	39(2.6)	58(3.9)	2.04(1.26-3.29)	2.11(1.31-3.41)	1.72(1.06-2.79)	1.65(1.01-2.71)
P for trend[f]			<0.001	<0.001	<0.001	0.005	0.002	0.06	0.08

Abbreviations: ESKD, end-stage kidney disease; eGFR, estimated glomerular filtration rate.
[a]annual incidence rate of events per 100 patients.
[b]CKD pregression event was defined as a 50% decline in eGFR or ESKD. The events are not mutually exclusive.
[c]Model 1 was adjusted for sex and age. Sex was analyzed as dichotomous data.
[d]Model 2 was adjusted for covariates in model 1 plus eGFR, proteinuria, and hypertension (yes or no).
[e]Model 3 was adjusted for covariates in model 2 plus Oxford M (mesangial hypercellularity), E (the presence of endocapillary proliferation), S (segmental glomerulosclerosis/adhesion), T (severity of tubular atrophy/interstitial fibrosis), and C (presence of crescent) scores and steroids or other immunosuppressive agents (yes or no).
[f]Test for trend of CKD progression event, ESKD or 50% eGFR decline across quartiles of galactose-deficient IgA1/C3 levels based on Cochran-Armitage trend test. Test for trend based on variable containing median value for each quartile.

Supplemental Table 4. Associations of serum C3 with CKD progression.

	C3 levels (mg/dl)	N at risk	Events (incidence rate[a])			Hazard ratio (95% confidence interval)			
			CKD pregression event[b]	ESKD	50% eGFR decline	Unadjusted	Model 1[c]	Model 2[d]	Model 3[e]
CKD progression event per 1 s.d. C3	102±24	1210	172(3.1)	114(2.0)	165(3.0)	0.80(0.68-0.94)	0.81(0.69-0.95)	0.82(0.70-0.96)	0.85(0.71-1.00)
C3 quartiles									
1	75±9	303	53(3.9)	41(2.8)	52(3.8)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
2	93±4	302	48(3.5)	27(1.9)	46(3.3)	0.82(0.55-1.21)	0.81(0.54-1.19)	0.86(0.58-1.28)	0.76(0.50-1.14)
3	106±4	302	34(2.4)	21(1.5)	33(2.4)	0.58(0.38-0.89)	0.58(0.37-0.89)	0.57(0.37-0.87)	0.55(0.35-0.86)
4	133±17	303	37(2.6)	25(1.7)	34(2.4)	0.61(0.40-0.93)	0.65(0.42-0.99)	0.62(0.40-0.95)	0.65(0.42-1.02)
P for trend[f]			0.02	0.02	0.01	0.04	0.05	0.03	0.06

Abbreviations: ESKD, end-stage kidney disease; eGFR, estimated glomerular filtration rate.
[a]annual incidence rate of events per 100 patients.
[b]CKD progression event was defined as a 50% decline in eGFR or ESKD. The events are not mutually exclusive.
[c]Model 1 was adjusted for sex and age. Sex was analyzed as dichotomous data.
[d]Model 2 was adjusted for covariates in model 1 plus eGFR, proteinuria, and hypertension (yes or no).
[e]Model 3 was adjusted for covariates in model 2 plus Oxford M (mesangial hypercellularity), E (the presence of endocapillary proliferation), S (segmental glomerulosclerosis/adhesion), T (severity of tubular atrophy/interstitial fibrosis), and C (presence of crescent) scores and steroids or other immunosuppressive agents (yes or no).
[f]Test for trend of CKD progression event, ESKD or 50% eGFR decline across quartiles of Galactose-deficient IgA1/C3 levels based on Cochran-Armitage trend test. Test for trend based on variable containing median value for each quartile.

Supplemental Table 5. Unadjusted and multivariable-adjusted Cox regression models testing associations of plasma galactose-IgA1/ C3 ratio with CKD progression.

Characteristics	Univariate		Multivariate	
	HR (95%CI)	P	HR (95%CI)	P
Age, yr	1.00(0.98-1.01)	0.71	0.98(0.97-1.00)	0.04
Gender	0.70(0.52-0.95)	0.02	1.15(0.82-1.62)	0.42
Hypertension	2.75(2.01-3.77)	<0.001	1.81(1.26-2.62)	<0.001
Initial proteinuria, g/24 h	1.76(1.50-2.07)	<0.001	1.32(1.07-1.62)	0.001
eGFR, ml/min /1.73 m^2	0.98(0.97-0.98)	<0.001	0.99(0.98-1.00)	<0.001
Oxford classification[a]				
M1	2.36(1.74-3.22)	<0.001	1.22(0.87-1.71)	0.26
E1	1.39(1.01-1.90)	0.04	1.45(1.05-2.01)	0.02
S1	2.18(1.52-3.13)	<0.001	1.60(1.08-2.37)	0.02
T1	3.64(2.51-5.28)	<0.001	1.89(1.24-2.89)	<0.001
T2	8.86(5.92-13.25)	<0.001	3.40(2.05-5.63)	<0.001
C	1.81(1.44-2.28)	<0.001	1.14(0.90-1.45)	0.28
Immunosuppression[b]	2.48(1.80-3.41)	<0.001	1.10(0.75-1.62)	0.62
Galactose-deficient IgA1/C3				
Quartile 1	Reference		Reference	
Quartile 2	1.60(0.97-2.66)	0.07	1.71(1.01-2.89)	0.05
Quartile 3	1.83(1.12-3.01)	0.02	1.55(0.91-2.63)	0.10
Quartile 4	2.55(1.59-4.1)	<0.001	2.17(1.33-3.56)	<0.001

Abbreviations: HR, Hazard ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; M, mesangial hypercellularity; E, the presence of endocapillary proliferation; S, segmental glomerulosclerosis/adhesion; T, severity of tubular atrophy/interstitial fibrosis; C, presence of crescent.
[a] The Oxford classification was developed by the Working Group of the International IgA Nephropathy Network and the Renal Pathology Society. Oxford scores of 23 patients were unavailable because each of them had fewer than eight glomeruli.
[b] The treatment regimens of eight patients were unavailable.

Supplemental Table 6. Associations of plasma galactose-deficient IgA1/C3 ratio with end-stage kidney disease.

	Galactose-deficient IgA1/C3 levels(U/mg)	N at risk	ESKD	Hazard ratio (95% confidence interval) and P-value			
				Unadjusted	Model 1[a]	Model 2[b]	Model 3[c]
ESKD per ln (Galactose-deficient IgA1/C3)	123.2-982.3	1210	114(2.0)	3.39(1.91-6.02)	3.5(1.96-6.25)	2.41(1.40-4.15)	2.09(1.19-3.68)
Galactose-deficient IgA1/C3 quartiles							
1	123.2-268.4	303	18(1.3)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
2	268.7-322.3	302	22(1.5)	1.15(0.62-2.15)	1.09(0.58-2.05)	1.15(0.61-2.16)	1.4(0.72-2.69)
3	322.4-386.9	302	28(2.0)	1.50(0.83-2.72)	1.38(0.76-2.51)	1.44(0.79-2.63)	1.32(0.70-2.50)
4	387.2-982.3	303	46(3.1)	2.40(1.38-4.15)	2.37(1.37-4.11)	1.95(1.12-3.40)	1.96(1.09-3.50)
P for trend[d]			<0.001	<0.001	<0.001	0.01	0.02

Abbreviations: ESKD, end-stage kidney disease.
[a] Model 1 was adjusted for sex and age. Sex was analyzed as dichotomous data.
[b] Model 2 was adjusted for covariates in model 1 plus eGFR, proteinuria, and hypertension (yes or no).
[c] Model 3 was adjusted for covariates in model 2 plus Oxford M (mesangial hypercellularity), E (the presence of endocapillary proliferation), S (segmental glomerulosclerosis/adhesion), T (severity of tubular atrophy/interstitial fibrosis), and C (presence of crescent) scores and steroids or other immunosuppressive agents (yes or no).
[d] Test for trend of ESKD across quartiles of Galactose-deficient IgA1/C3 levels based on Cochran-Armitage trend test. Test for trend based on variable containing median value for each quartile.

Supplemental Table 7. Associations of plasma galactose-deficient IgA1/C3 ratio with end-stage kidney disease stratified by use of immunosuppression.

	Treated with immunosuppressive agents or prednisone	Hazard ratio (95% confidence interval) and P-value			
		Unadjusted	Model 1[a]	Model 2[b]	Model 3[c]
CKD progression event[d] per ln(galactose deficient-IgA1/C3)	Yes	2.67(1.52-4.71)	2.73(1.55-4.79)	2.34(1.33-4.11)	2.21(1.20-4.08)
	No	2.59(1.10-6.09)	2.98(1.25-7.14)	2.23(1.04-4.81)	1.71(0.75-3.94)
Galactose-IgA1/C3 quartiles					
1		1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
2	Yes	1.74(0.90-3.36)	1.63(0.84-3.17)	1.89(0.97-3.68)	2.08(1.03-4.18)
	No	1.10(0.47-2.54)	1.18(0.51-2.75)	1.23(0.52-2.92)	1.32(0.55-3.16)
3	Yes	2.26(1.18-4.34)	2.15(1.12-4.16)	2.20(1.13-4.29)	2.07(1.03-4.19)
	No	1.26(0.57-2.79)	1.34(0.60-2.98)	1.64(0.73-3.67)	1.05(0.44-2.48)
4	Yes	2.54(1.35-4.77)	2.60(1.38-4.89)	2.42(1.27-4.59)	2.43(1.24-4.77)
	No	2.26(1.09-4.67)	2.41(1.16-5.01)	2.47(1.17-5.19)	2.07(0.97-4.40)
P for trend[e]	Yes	0.003	0.002	0.01	0.03
	No	0.01	0.01	0.01	0.05

[a]Model 1 was adjusted for sex and age. Sex was analyzed as dichotomous data.
[b]Model 2 was adjusted for covariates in model 1 plus eGFR, proteinuria, and hypertension (yes or no).
[c]Model 3 was adjusted for covariates in model 2 plus Oxford M (mesangial hypercellularity), E (the presence of endocapillary proliferation), S (segmental glomerulosclerosis/adhesion), T (severity of tubular atrophy/interstitial fibrosis), and C (presence of crescent) scores.
[d] CKD progression event was defined as a 50% decline in eGFR or ESKD.
[e]Test for trend based on variable containing median value for each quartile.

Supplemental Figure 1. Galactose-deficient IgA1 levels were higher in 1210 patients with IgA nephropathy than 208 healthy controls (P<0.001).
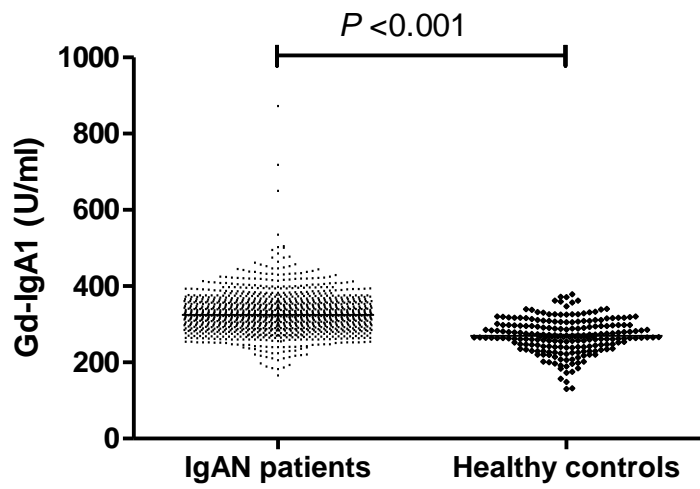
Supplemental Figure 2. Associations of serum C3 concentration with CKD progression. Models were performed using restricted cubic splines with knots at the 25th, 50th, and 75th percentiles. The solid line represents the estimated hazard ratio, the shaded area represents the 95% confidence bands, and the histogram represents the distribution of galactose-deficient IgA1/C3 ratio in patients with IgA nephropathy. Models were adjusted for age; sex; eGFR; proteinuria; hypertension; Oxford M (mesangial hypercellularity score), E (the presence of endocapillary proliferation), S (segmental glomerulosclerosis/adhesion), T (severity of tubular atrophy/interstitial fibrosis), and C (presence of crescent) scores; and corticosteroids/ immunosuppressive therapy.
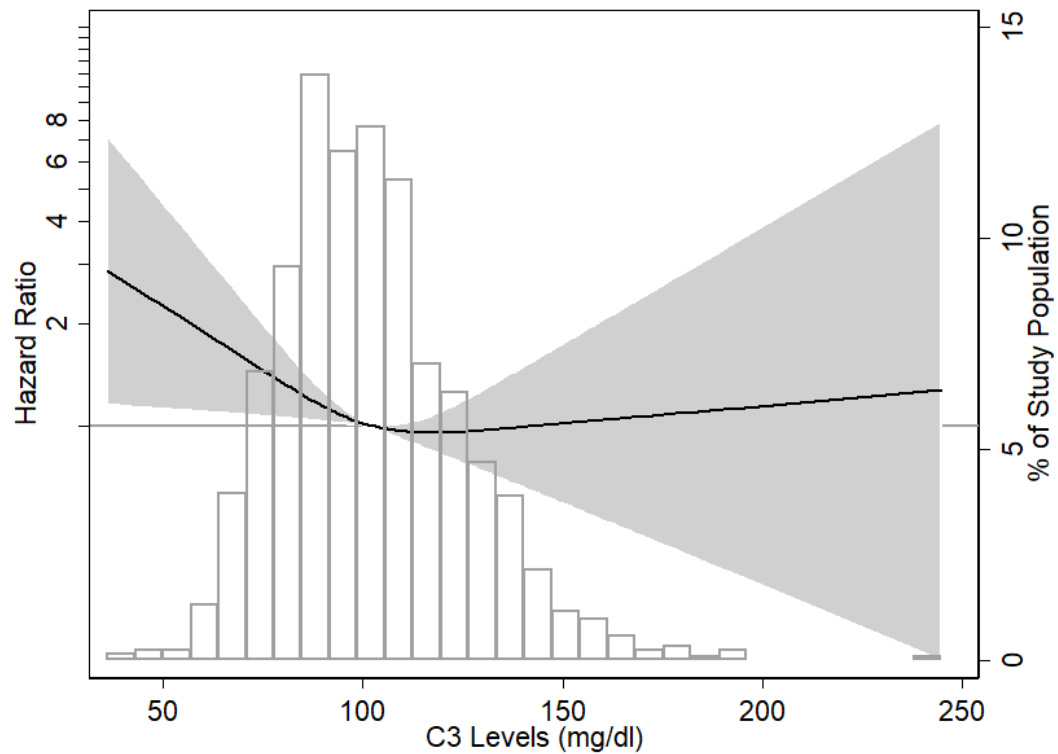
Supplemental Figure 3. Associations of plasma galactose-deficient IgA1/C3 ratio with end-stage kidney disease. Models were performed using restricted cubic splines with knots at the 25th, 50th, and 75th percentiles. The solid line represents the estimated hazard ratio, the shaded area represents the 95% confidence bands, and the histogram represents the distribution of galactose-deficient IgA1/C3 ratio in patients with IgA nephropathy. Models were adjusted for age; sex; eGFR; proteinuria; hypertension; Oxford M (mesangial hypercellularity score), E (the presence of endocapillary proliferation), S (segmental glomerulosclerosis/adhesion), T (severity of tubular atrophy/interstitial fibrosis), and C (presence of crescent) scores; and corticosteroids/ immunosuppressive therapy.
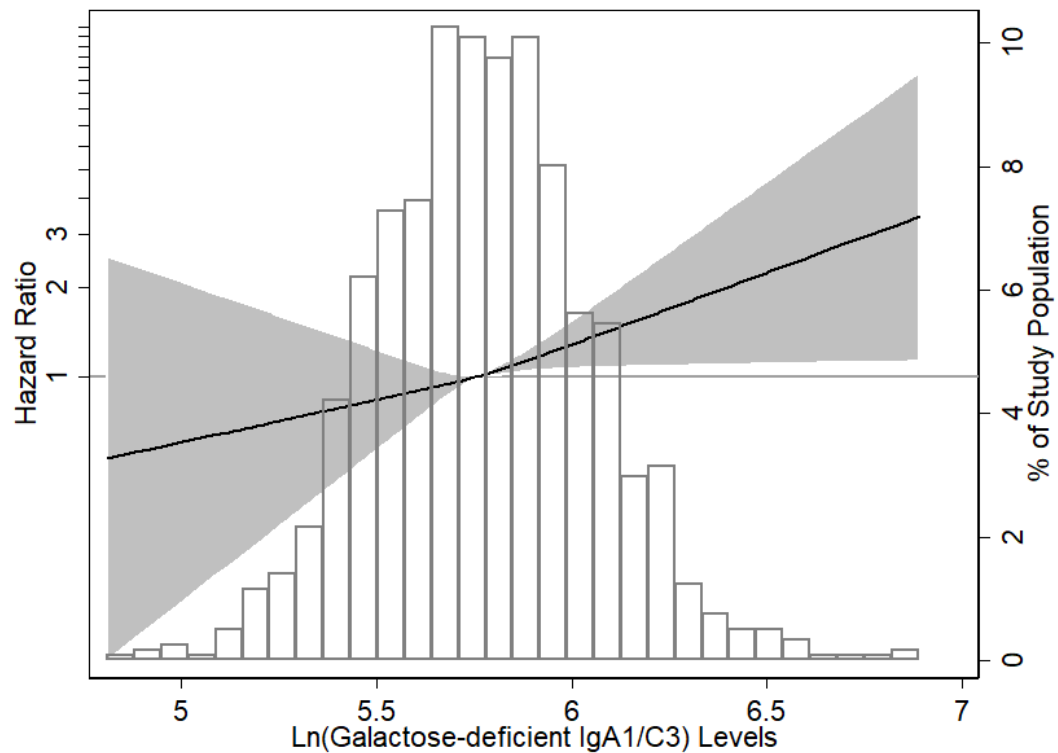
Supplemental Figure 4. Spaghetti plots of serial plasma Galactose-deficient IgA1 levels. The blue lines represent individual galactose-deficient IgA1 levels. The black line represents mean value of galactose-deficient IgA1 in IgA nephropathy patients.