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The Mildly Elevated Serum Bilirubin Level is Negatively Associated with the Incidence of End Stage Renal Disease in Patients with IgA Nephropathy

Oxidative stress plays various roles in the development and progression of IgA nephropathy, while bilirubin is known as a potent antioxidant. We therefore hypothesized that serum bilirubin would be associated with renal prognosis in IgA nephropathy. The study subjects comprised 1,458 adult patients with primary IgA nephropathy in Korea. We grouped patients according to the following quartile levels of bilirubin: <0.4 mg/dL (Q1), 0.4-0.5 mg/dL (Q2), 0.6-0.7 mg/dL (Q3), and >0.8 mg/dL (Q4). The outcome data were obtained from the Korean Registry of end-stage renal disease (ESRD). Eighty patients (5.5%) contracted ESRD during a mean follow-up period of 44.9 months. The ESRD incidences were 10.7% in Q1, 8.2% in Q2, 2.8% in Q3, and 2.8% in Q4 (p<0.001). The relative risk of ESRD compared to that in Q1 was 0.307 (95% confidence interval [CI], 0.126-0.751) in Q3 and 0.315 (95% CI, 0.130-0.765) in Q4. The differences of ESRD incidence were greater in subgroups of males and of patients aged 35 yr or more, with serum albumin 4.0 g/dL or more, with normotension, with eGFR 60 mL/min/1.73 m^2 or more, and with proteinuria less then 3+ by dipstick test. In conclusion, higher bilirubin level was negatively associated with ESRD incidence in IgA nephropathy.

Key Words : *Bilirubin; Glomerulonephritis, IGA; Kidney Failure, Chronic*

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INTRODUCTION

As the most common glomerulonephritis worldwide, IgA nephropathy has the potential for slowly progressive chronic renal impairment, leading to end-stage renal disease (ESRD) (1). Although many studies have identified the features related to poor prognosis, no single or combination of prognostic factors has been demonstrated to account for the overall risk for ESRD in IgA nephropathy (2). Until now, no treatment has been shown to modify the mesangial deposition of IgA and the available treatment options are directed at downstream immune reaction to lead on to renal scaring (2).

Although the glomerular injury in IgA nephropathy is usually provoked by IgA-induced mesangial cell activation and complement activation (2), increased oxidative stress was reported to play a role in the development and progression of IgA nephropathy (3-6). The oxidative stress detected in the reduced glutathione and hemoglobin oxidation on peripheral red blood cells (RBCs) and lipid peroxidation in RBCs and plasma was increased in patients with IgA nephropathy compared to normal controls (6), as was the immunohistochemistry for intrarenal 4-hidroxy-2-nonenal as the product of lipid peroxidation (4). The renal infiltration of polymorphonuclear leukocyte which has a high potential for the production of reactive oxygen species (ROS) increased in patients with IgA nephropathy (5). Advanced oxidation protein products increased in IgA nephropathy compared with that in stable IgA nephropathy and was an independent risk factor to the renal outcome of IgA nephropathy (3). Intrarenal immunoreactivity of heme oxygenase-1 (HO-1), which is the inducible HO isoform that metabolizes heme to carbon monoxide, iron, and bilirubin converted from biliverdin, also increased in IgA nephropathy compared to that in controls (4).

Bilirubin is not merely an end product of heme degradation but a potent antioxidant (7) which is usually mediated by inhibition of NADPH oxidase (8), a key source of oxidants in phagocytic and non-phagocytic cells, and of protein kinase C activity (9). Several studies have been published showing the relation between serum bilirubin and oxidative stress-mediated diseases, including coronary artery disease (10, 11), angiotensin II-mediated hypertension (12), and renal ischemia-reperfusion injury in vivo (13-15).

In the present study, we investigated the role of serum bilirubin on the progression to ESRD in IgA nephropathy. We also analyzed the data in subgroups stratified by well-known risk factors to renal progression in IgA nephropathy and by possible confounding factors affecting serum bilirubin levels, such as gender, age (16), and serum albumin, to which unconjugated bilirubin is bound (17).

MATERIALS AND METHODS

Study subjects

This study was approved by the Institutional Review Board in Seoul National University Bundang Hospital and other participated hospitals before the data were gathered. Informed written consent was obtained from all patients. The subjects were enrolled in the Progressive REnal disease and Medical Informatics and gEnomics Research (PREMIER) program sponsored by the Korean Society of Nephrology (KSN) since August 2003. Thirty-four hospitals and clinics in Korea participated in the PREMIER study and shared the clinical data of 1,469 adult patients aged 18 yr or more who were diagnosed as primary IgA glomerulonephritis by renal biopsy from April 1988 to May 2007. From this group, 1,458 patients whose serum bilirubin data were available were included in this study. We enrolled 30 (2.1%) patients diagnosed before 2000, 41 (2.8%) in 2000, 81 (5.6%) in 2001, 123 (8.4%) in 2002, 170 (11.7%) in 2003, 351 (24.1%) in 2004, 411 (28.2 %) in 2005, 209 (14.3%) in 2006, and 42 (2.9%) in 2007.

Clinical data

The participating researchers had selected the candidate patients and one qualified nurse, who visited every participated institution, input the clinical data into the formatted database on the website (http://www.gn.or.kr) at the time of renal biopsy and during follow-up visits. We gathered the data of age, gender, history of diabetes mellitus, and current hypertension, blood pressure, serum protein, serum albumin, serum cholesterol, serum bilirubin, alanine aminotransferase, aspartate aminotransferase, hemoglobin, serum creatinine, proteinuria by dipstick test, urine RBC measured by microscopic examination of urine at renal biopsy, and medication of angiotensin-converting enzyme inhibitors (ACEI), angiotensin II type I receptor blockers (ARB), any kind of steroid and HMG-CoA reductase inhibitor during the follow-up period. Hypertension was defined as a systolic blood pressure (SBP) of 140 mmHg or more, diastolic blood pressure (DBP) of 90 mmHg or more, or the taking of anti-hypertensive medication before renal biopsy. The estimated glomerular filtration rate (eGFR) was calculated by the modified modification of diet in renal disease (MDRD) equation as follow (18);

$$\text{eGFR (mL/min/1.73 m}^2) = 186.3 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \ (\times 0.742 \text{ for female})$$

We classified the following clinical parameters: age, with the criterion of 35 yr, which was the median value, serum albumin level with 4.0 g/dL, proteinuria by dipstick test with 3+, and hematuria with urine RBC 5 or more in microscopic examination of urine in the field of 400-fold magnification.

We grouped the patients according to the following quartile levels of serum bilirubin and compared the basal characteristics and ESRD incidence during the follow-up period:

<0.4 mg/dL (Q1), 0.4-0.5 mg/dL (Q2), 0.6-0.7 mg/dL (Q3), and >0.8 mg/dL (Q4).

Renal outcome

The end point was the time to the first treatment for ESRD. The ESRD data were obtained from the Korean ESRD registry, "Insan Memorial Dialysis Registry", of KSN (19). The registry contained the data of patients entering into renal replacement therapy (RRT), dialysis or transplantation, in Korea from 1985 to April 2008. The data was reported by providers of RRT on paper documents before 2001 and through an on-line registry program in the KSN website (http://www.ksn.or.kr) from 2001. The response rate to collect the data from providers in Korea was 65.1% in 2001 (19) and 66.8% in 2002 (20). We searched the data based on the unique personal identifier which all Koreans aged 18 yr or more have and identified the RRT status of patients with IgA nephropathy.

Statistical analysis

The SPSS (SPSS version 12.0, Chicago, IL, U.S.A.) package was used for statistical analysis. Differences in proportions among groups were compared by chi-square test. Group differences for continuous variables were assessed by the Student t-test or One-way ANOVA test according to the number of groups. We compared the cumulative incidence of ESRD by Log-rank test. To determine whether the bilirubin level was independently related to the incidence of ESRD, we used the Cox's hazard proportional analysis adjusted for age, gender, and univariate risk factors to the incidence of ESRD. We repeated the analyses after stratification by gender, age and serum albumin, which are the important factors associated with the serum level of bilirubin, and by hypertension, urine protein level and eGFR, which are the well-known prognostic factors of IgA nephropathy. Two-sided *p* values were reported with 0.05 taken as the level of statistical significance. All data are shown as mean±standard deviation or frequency per observation.

RESULTS

The basal characteristics of patients according to bilirubin levels

The mean values of age, SBP, serum protein, serum albu-

Table 1. The characteristics of patients at renal biopsy

	Completeness of data (%)	Bilirubin groups				
		Q1 (n=224)	Q2 (n=391)	Q3 (n=386)	Q4 (n=457)	*p* value
Age (yr)	100.0	39.5/13.2[3]	37.8/14.3[2,3]	36.6/14.0[1,2]	35.3/12.6[1]	0.001
Gender (female %)	100.0	58.9	51.4	45.3*	30.0*	<0.001
Current smoking (%)	91.8	9.3	13.0	14.8	16.7	0.076
History of DM (%)	92.5	2.3	1.9	4.8	4.0	0.122
Hypertension (%)	90.4	44.8	48.0	44.2	42.5	0.505
SBP (mmHg)	94.3	128/20[3]	128/19[2,3]	125/17[1,2]	125/16[1]	0.018
DBP (mmHg)	94.3	81/13	80/13	79/12	79/11	0.264
Glucose (mg/dL)	90.4	104/21	102/23	101/28	100/27	0.239
Protein (g/dL)	99.1	6.2/1.0[1]	6.5/0.9[2]	6.7/0.8[3]	6.9/0.6[4]	<0.001
Albumin (g/dL)	99.4	3.4/0.7[1]	3.7/0.7[2]	3.9/0.6[3]	4.0/0.5[4]	<0.001
Bilirubin (mg/dL)	100.0	0.3/0.1[1]	0.5/0.1[2]	0.7/0.1[3]	1.1/0.6[4]	<0.001
AST (U/L)	97.6	20/9[1]	21/11[1,2]	21/10[1,2]	23/19[2]	0.052
ALT (U/L)	99.8	17/12[1]	19/17[1,2]	20/17[1,2]	23/57[2]	0.054
Cholesterol (mg/dL)	95.1	217/97[2]	195/58[1]	190/52[1]	188/119[1]	<0.001
Hemoglobin (g/dL)	99.1	11.8/2.2[1]	12.3/2.1[2]	13.0/1.9[3]	13.7/1.8[4]	<0.001
Creatinine (mg/dL)	99.9	1.5/1.5[2]	1.6/1.4[2]	1.3/1.0[1]	1.2/0.8[1]	0.001
eGFR (mL/min/1.73 m^2)	99.9	67/38[1]	71/32[1]	77/30[2]	82/30[2]	<0.001
Proteinuria ≥3+ (%)	95.2	31.6	22.6*	22.7*	15.2*	<0.001
Hematuria (%)	95.5	92.9	88.9	89.9	85.4*	0.029
Medication (%)						
ACEI or ARB	100.0	60.3	51.7*	53.1	54.7	0.207
Statin	100.0	21.4	13.8*	14.0*	9.6*	<0.001

*, Difference of frequency compared to Q1 bilirubin group, $p<0.05$, number/number: mean/standard deviation.
Number right upper side of data: Duncan post hoc analysis in One-Way ANOVA test.
DM, diabetes mellitus; AST, aspartate aminotransferase; ALT, alanine aminotransferase; proteinuria ≥3+, proteinuria 3+ or more by dipstick test; hematuria, urine RBC 5 or more by microscopic examination of urine in a filed of 400-fold magnification; ACEI or ARB, angiotensin converting enzyme inhibitor or angiotensin II type I receptor blocker; Statin, HMG-Co reductase inhibitor.

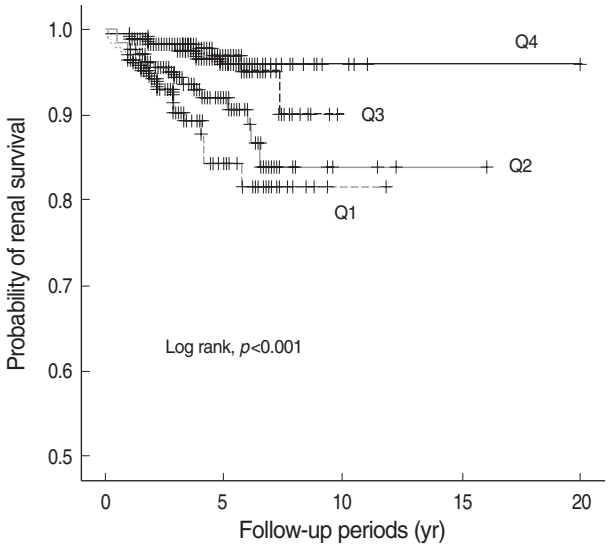

Fig. 1. The probability of renal survival according to serum bilirubin level at renal biopsy.
Q1, First quartile group; Q2, Second quartile group; Q3, Third quartile group; Q4, Forth quartile group.

Table 2. The difference of basal characteristics according to renal progression to end-stage renal disease (ESRD)

	No-ESRD (n=1,378)	ESRD (n=80)	*p* value
Age (yr)	36/14	40/14	0.022
Gender (female %)	44.8	35.0	0.087
Current smoking (%)	13.9	16.7	0.531
History of DM (%)	3.2	7.4	0.066
Hypertension (%)	43.3	72.7	<0.001
SBP (mmHg)	126/17	137/26	<0.001
DBP (mmHg)	79/12	85/16	<0.001
Glucose (mg/dL)	101/25	104/31	0.481
Protein (g/dL)	6.7/0.8	6.0/1.0	<0.001
Albumin (g/dL)	3.8/0.6	3.2/0.6	<0.001
Bilirubin (mg/dL)	0.7/0.5	0.5/0.4	0.002
AST (U/L)	21/13	21/17	0.848
ALT (U/L)	21/36	19/21	0.781
Cholesterol (mg/dL)	193/71	226/226	0.198
Hemoglobin (g/dL)	13.0/2.0	10.7/2.2	<0.001
Creatinine (mg/dL)	1.2/0.9	3.0/2.6	<0.001
eGFR (mL/min/1.73 m^2)	77.7/31.3	35.7/21.0	<0.001
Proteinuria ≥3+ (%)	21.0	33.8	0.010
Hematuria (%)	88.7	87.7	0.785
Medication (%)			
ACEI or ARB	54.8	46.3	0.136
Statin	13.6	16.3	0.498

Number/number, mean/standard deviation.
DM, diabetes mellitus; AST, aspartate aminotransferase; ALT, alanine aminotransferase; proteinuria ≥3+, proteinuria 3+ or more by dipstick test; hematuria, urine RBC 5 or more by microscopic examination of urine in a filed of 400-fold magnification; ACEI or ARB, angiotensin converting enzyme inhibitor or angiotensin II type I receptor blocker; Statin, HMG-Co reductase inhibitor.

min, serum cholesterol, serum creatinine, eGFR, and hemoglobin differed among the bilirubin groups (Table 1). The mean values of age, SBP, serum cholesterol and serum creatinine were lower, but those of serum protein, serum albumin, eGFR and hemoglobin were higher, in patients with higher bilirubin level. The frequencies of being female, having proteinuria 3+ or more, having hematuria, and using statin were higher in patients with lower serum bilirubin level.

The risk factors to the incidence of ESRD in IgA nephropathy

Eighty of the 1,458 patients (5.5%) contracted ESRD during a mean follow-up period of 44.9 months (SD: 22.3 months). The overall renal survival rate was 98.6% at 1 yr, 93.2% at 5 yr, and 80.7% at 10 yr after renal biopsy. The incidences of ESRD were 10.7% in Q1, 8.2 % in Q2, 2.8% in Q3, and 2.8% in Q4 (p<0.001). The mean follow-up period was not different among the bilirubin groups (p>0.05). The numbers of patients followed at renal biopsy, at 1, 2, 3, 4, and 5 yr after renal biopsy were 224, 215, 179, 120, 53, and 36 in Q1, 391, 372, 324, 224, 113, and 79 in Q2, 386, 381, 328, 232, 146, and 92 in Q3, and 457, 450, 403, 283, 152, and 93 in Q4, respectively. The probability of ESRD was the highest in Q1 among the bilirubin groups, as shown in Fig. 1.

The age, SBP, DBP, serum protein, serum albumin, serum bilirubin, hemoglobin, serum creatinine and eGFR, and the frequencies of hypertension, proteinuria 3+ or more, and the usage of steroids were the univariate factors for the incidence of ESRD (Table 2). In Cox's hazard proportional model adjusted for gender and univariate risk factors, the bilirubin group was one of the independent risk factors for ESRD (Table 3). The relative risk (RR) of ESRD compared to that in Q1 was 0.307 (95% confidence interval [CI], 0.126-0.751) in Q3 and

Table 3. The independent risk factor to the incidence of end-stage renal disease in IgA nephropathy analyzed by Cox's hazard proportional model

Variables	B	Wald	*p* value	OR [95% C.I.]
Bilirubin Group*	–	9.956	**0.019**	–
Q2 (0.4-0.59 mg/dL)	-0.476	1.968	0.161	0.621 [0.319-1.208]
Q3 (0.6-0.79 mg/dL)	-1.180	6.689	**0.010**	0.307 [0.126-0.751]
Q4 (≥0.8 mg/dL)	-1.154	6.514	**0.011**	0.315 [0.130-0.765]
Hypertension	0.901	8.190	**0.004**	2.462 [1.328-4.563]
Serum creatinine (mg/dL)	0.373	84.240	**<0.001**	1.453 [1.341-1.573]
Serum albumin (g/dL)	-0.794	16.294	**<0.001**	0.452 [0.308-0.665]

Adjusted with age, gender, hypertension, systolic blood pressure, diastolic blood pressure, serum albumin, serum creatinine, urine protein 3+ or more by dipstick test, and bilirubin groups.
*Compared to bilirubin group, first quartile group with bilirubin less than 0.4 mg/dL.
OR, odds ratio; C.I., confidence interval.

0.315 (95% CI, 0.130-0.765) in Q4. The other risk factors for ESRD were the presence of hypertension, higher serum creatinine level, and lower serum albumin level at renal biopsy.

The RR for ESRD among bilirubin groups in subgroups

We analyzed the RR for ESRD in the bilirubin groups by Cox's hazard proportional model adjusted with univariate risk factors in each subgroup stratified by possible confounding factors to serum bilirubin level and the renal prognosis in IgA nephropathy. In males, the bilirubin group was a risk factor for ESRD and the RR was decreased in Q3 and Q4 compared to that in Q1. Similarly, in patients aged 35 yr or more, with normotension, with serum albumin 4.0 g/dL or more, with eGFR 60 mL/min/1.73 m^2 or more, or with proteinuria less then 3+ by dipstick test, the RR for ESRD in Q3 and Q4 was lower than that in Q1 (Table 4).

DISCUSSION

In this study, we observed the incidence of ESRD and the important role of bilirubin level on renal prognosis in a large number of patients with IgA nephropathy in Korea. The overall 10-yr survival rate in IgA nephropathy was reported as about 80% (21, 22), which was comparable to the rate in this study, although the study population and follow-up duration differed among the various studies. In a U.S.A. paper by Radford et al., the renal survival rate was below the average survival rate because the clinical presentation at renal biopsy was more advanced than in the other studies (23).

We collected the data of renal outcome through the Korean ESRD registry. In the database, it was estimated that 65% of the total ESRD patients from institutions undergoing RRT in Korea were registered. Although this registry did not contain 100% of RRT data, we could estimate the effects of bilirubin group on renal survival because the renal survival rate was in agreement with that from other reports and the period of renal biopsy was relatively recent in this study, even though the necessary duration to progress to ESRD in IgA nephropathy is known to be relatively long. In IgA nephropathy, the calculated incidence of ESRD from initial presentation has been reported to be approximately 1.5% per year and about 25 to 30% of published cohorts required RRT within 20 to 25 yr of presentation (2). In the present study, the frequencies of ESRD according to the diagnosed period were 14.1% before 2001, 12.3% in 2001, 4.1% in 2002, 5.9% in 2003, 6.8% in 2004, 3.4% in 2005, and 2.8% after 2005. These data indicated that the possible error due to incomplete data in estimating renal survival would be less

Table 4. The relative risk to ESRD in patients with IgA nephropathy after stratification with clinical parameters analyzed by Cox's hazard proportional model

Stratified subgroups	Relative risk to the incidence of ESRD in bilirubin groups*				
	Q1	Q2	Q3	Q4	*p* value
Gender subgroups					
Male†	Ref.	0.708 [0.303-1.655]	**0.242 [0.075-0.779]**	**0.310 [0.111-0.869]**	**0.035**
Female	Ref.	–	–	–	0.289
Age subgroups (yr)					
Age <35	Ref.	–	–	–	0.073
Age ≥35‡	Ref.	**0.369 [0.160-0.852]**	**0.316 [0.126-0.795]**	**0.189 [0.067-0.534]**	**0.004**
Hypertension subgroups					
Normotension§	Ref.	0.573 [0.173-1.893]	**0.067 [0.007-0.629]**	**0.097 [0.012-0.807]**	**0.023**
Hypertension	Ref.	–	–	–	0.095
eGFR subgroups (mL/min/1.73 m^2)					
eGFR ≥60‖	Ref.	0.577 [0.169-1.970]	**0.237 [0.055-1.029]**	**0.053 [0.006-0.454]**	**0.028**
eGFR <60	Ref.	–	–	–	0.118
Albumin subgroups (g/dL)					
Albumin ≥4.0¶	Ref.	0.995 [0.552-1.791]	**0.388 [0.180-0.836]**	**0.380 [0.176-0.824]**	**0.006**
Albumin <4.0	Ref.	–	–	–	0.417
Proteinuria subgroups (by dipstick test)					
Proteinuria <3+**	Ref.	0.322 [0.132-0.785]	**0.169 [0.057-0.499]**	**0.120 [0.038-0.379]**	**<0.001**
Proteinuria ≥3+	Ref.	–	–	–	0.074

*: Compared to bilirubin group, first quartile group with bilirubin less than 0.4 mg/dL, ref.: reference group; †: Model adjusted with age, hypertension, SBP, serum albumin, serum creatinine, proteinuria 3+ or more, and bilirubin groups which were univariate factors to ESRD in this subgroup; ‡: Model adjusted with gender, hypertension, SBP, DBP, serum albumin, serum creatinine, and bilirubin groups which were univariate factors to ESRD in this subgroup; §: Model adjusted with age, serum albumin, serum creatinine, proteinuria 3+ or more, and bilirubin groups which were univariate factors to ESRD in this subgroup; ‖: Model adjusted with serum albumin, serum creatinine, and bilirubin groups which were univariate factors to ESRD in this subgroup; ¶: Model adjusted with gender, age, and bilirubin groups which were univariate factors to ESRD in this subgroup, **: Model adjusted with diabetes mellitus, hypertension, SBP, DBP, serum albumin, serum creatinine, and bilirubin groups which were univariate factors to ESRD in this subgroup.

significant in patients with a short duration of disease. Furthermore, if we defined renal progression as a doubling or more of serum creatinine level at follow-up compared to that at renal biopsy, then the RR to renal progression compared to that in Q1 was 0.419 (95% CI, 0.189-0.930) in Q3 and 0.205 (95% CI, 0.075-0.562) in Q4 and the bilirubin group was an independent prognostic factor to renal progression (p=0.013 by Cox's hazard progression model adjusted with univariate factors to a doubling or more of serum creatinine) among the 1,031 patients who had repeated serum creatinine values in this study.

The generally accepted renal prognostic factors in clinical characteristics are age, severity of proteinuria, hypertension, and impaired renal function (reviewed in 2). However, as these factors do not completely account for the risk for ESRD in IgA nephropathy (2), it is important to define new markers for estimating renal prognosis and for developing a new therapeutic modality in IgA nephropathy. There were few reports on the role of serum bilirubin in chronic renal disease, including glomerulonephritis. In addition to the traditional prognostic factors to renal progression, we revealed that the serum bilirubin level at renal biopsy was an important prognostic factor for ESRD. A serum bilirubin level of 0.6 mg/dL or more (i.e., the bilirubin level in Q3 and Q4) was associated with a lower incidence of ESRD, which is similar to the serum bilirubin level of 10 μM/L used as a cut-off point for the discrimination of cardiovascular risk in other studies (10).

Increased oxidative stress was reported to affect the development and progression of IgA nephropathy (3-6), although glomerular injury in IgA nephropathy is usually provoked by IgA-induced mesangial cell activation and complement activation (2). Several laboratory investigations have provided a biological background to explain the anti-oxidant and anti-inflammatory effects of bilirubin. Although bilirubin was known to scavenge peroxyl radicals in an in vitro study (7), the antioxidant effect of bilirubin is usually mediated by inhibition of NADPH oxidase (8) and protein kinase C activity (9). Increased endothelial NADPH oxidase activity is a key mediator of atherosclerosis, including glomerulosclerosis (24, 25), and activation of NADPH oxidase appears to play a key role in TGF-beta signaling and in the responsiveness of collagen synthesis (26, 27), which is a common pathway to glomerulosclerosis in various types of glomerulonephritis. The other possibilities to explain the effect of bilirubin on the prognosis of IgA nephropathy are the inverse relationship of bilirubin to insulin resistance, metaolic syndrome (28) and the atherosclerosis (10, 11). It is well known that the chronic kidney disease including IgA nephropathy is related to insulin resistance and atherosclerosis. The beneficial effect of bilirubin on the prognosis might not be related to the pathogenetic process of IgA nephropathy per se but related to atherosclerosis or insulin resistance which is manifested in IgA nephropathy. But, considering bilirubin was reported to inhibit antigen-specific and polyclonal T cell responses at multiple steps in recent report (29), bilirubin might also have some roles on the immune regulation in the IgA nephropathy which remains to be verified.

Although the reason that the relation between bilirubin and renal prognosis in IgA nephropathy was only evident in the male group was not elucidated, the gender effect on the heme oxygenase inducibility to stress, which is the rate-limiting enzyme to produce bilirubin, would be considerable. Trauma and hemorrhage doubled the hepatic HO-1 expression in female rats compared with male rats (30). The bilirubin effect on renal progression may have been overwhelmed by further severe risk factors such as hypertension, massive proteinuria, or renal impairment, which was in agreement with the finding that the bilirubin group was only a prognostic factor among patients with normotension, with serum albumin 4.0 g/dL or more, with proteinuria less then 3+ by dipstick test, or with eGFR 60 mL/min/1.73 m^2 or more.

This study suffered several limitations on the generalizability of the results. We had no information on hormonal replacement and the menopausal status, although the mean age of women in this study was younger than the average age of menopause in Korean women, 47 yr, or on fasting status, which affected the level of serum bilirubin. As mentioned above, we could not guarantee 100% of participation rate of RRT providers in gathering information about ESRD and could not estimate the rate of RRT abandonment in newly diagnosed ESRD patients. The data in this study were from many institutions and might have inter-institutional variation according to the devices to measure biological parameters, such as, bilirubin. This limitation may act as a confounding factor to the relation between bilirubin group and renal prognosis.

Nevertheless, our results have revealed that serum bilirubin level is an important new prognostic factor for renal prognosis in a large cohort of IgA nephropathy. This finding suggests the importance of oxidative stress in renal progression and strengthens the possible therapeutic role of antioxidants in IgA nephropathy.

APPENDIX

Members are listed in Appendix.

Cheju National University Hospital (Eun Hee Jang), Chonbuk National University Medical School (Won Kim), Chonnam National University Medical School (Nam Ho Kim, Woo Kyun Bae), Chungbuk National University College of Medicine (Hye Young Kim), Chungnam National University College of Medicine (Young-Tai Shin, Kang Wook Lee, Ki-Ryang Na), Daegu Catholic University Medical Center (Ki Sung Ahn), Dankook University Hospital (Jong Tae Cho, Eun Kyeong Lee), Dong-A University College of Medicine (Ki Hyun Kim, WonSuk An, Seong Eun Kim),

Ewha Womans University School of Medicine (Choi Gyu Bog, Seung-Jung Kim), Gachon University of Medicine and Science (Woo Kyung Chung, Hyun Hee Lee, Jaeseok Yang, Sejoong Kim), Gyeongsang National University Hospital (Se-Ho Chang), Hallym University College of Medicine (Jung Woo Noh, Young Ki Lee, Seong Gyun Kim, Jieun Oh, Young Rim Song), Inha University College of Medicine (Moon Jae Kim, Seoung Woo Lee), Inje University College of Medicine (Yeong Hoon Kim, Won Do Park), Keimyung University School of Medicine (Hyun Chul Kim, Sung Bae Park), Konkuk University School of Medicine (Kyo-Soon Kim), Korea University Anam Hospital (Won Yong Cho, Hyoung Kyu Kim, Sang-Kyung Jo), Korea University Ansan Hospital (Cha Dae Ryong, Kang Young Sun), Korea University College of Medicine Guro Hospital (Young-Joo Kwon), Kyungpook National University School of Medicine (Yong-Lim Kim, Sun-Hee Park, Chan-Duck Kim), Pochon CHA University College of Medicine (Dong Ho Yang), Pusan National University School of Medicine (Ihm Soo Kwak,, Soo Bong Lee, Dong Won Lee, Sang Heon Song, Eun Young Seoung), Seoul Medical Center (Su-Jin Yoon), Seoul National University Bundang Hospital (Dong-Wan Chae, Ki Young Na, Ho Jun Chin), Seoul National University College of Medicine Boramae Medical Center (Chun Soo Lim, Yoon Kyu Oh), Seoul National University Hospital (Kook Hwan Oh, Kwon Wook Joo, Yon-Su Kim, Curie Ahn, Jin Suk Han, Suhnggwon Kim), Seoul National University Hosptial Clinical Institute (Hyung Jin Yoon), Sungkyunkwan University School of Medicine (Kyu-Beck Lee), Sungkyunkwan University School of Medicine Samsung Medical Center (Yoon Goo Kim, Jung Eun Lee), Ulsan University College of Medicine, Asan Medical Center (Sang Koo Lee), Yeungnam University College of Medicine (Jun-Young Do, Jong-Won Park, Kyung-Woo Yoon), ordered by alphabet.

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