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Risk Factors Associated with End-Stage Renal Disease (ESRD) in Patients With Atherosclerotic Renal Artery Stenosis

A Nationwide Population-Based Analysis

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Abstract: The aim of this study was to investigate the risk factors associated with end-stage renal disease (ESRD) in patients with atherosclerotic renal artery stenosis (ARAS).

Information about the study participants was extracted from the National Health Insurance Research Database of Taiwan for the years 1999 through 2011. We conducted this retrospective cohort study of patients with ARAS to identify the potential risk factors associated with long-term renal outcomes.

A total of 2184 patients with ARAS were enrolled, of whom 840 had ESRD and were classified as the study group, and 1344 patients who were without ESRD were included in the comparison cohort. After adjusting for related variables, univariable, and multivariable logistic regression analysis showed that ESRD was associated with higher Charlson-comorbidity index (CCI) score (adjusted odds ratio [OR] = 6.78, 95% CI = 4.59–10.0 for CCI = 2; adjusted OR = 20.0, 95% CI = 13.7–29.2 for CCI ≥3), diabetes (adjusted OR = 1.55, 95% CI = 1.24–1.93), hypertension (adjusted OR = 3.66, 95% CI = 2.36–5.66), and age 20 to 49-years old (adjusted OR = 2.14, 95% CI = 1.51–3.03). Moreover, our data showed that renal artery revascularization (RAR) was significantly associated with a lower risk of ESRD in ARAS patients (crude OR = 0.64, 95% CI = 0.50–0.84).

Our study is the first to disclose that CCI score was significantly associated with the risk of ESRD in ARAS patients, and comorbid diseases including diabetes mellitus and hypertension significantly affect renal outcomes in patients with ARAS. Of note, our data showed that renal artery revascularization was associated with a lower risk of ESRD in ARAS patients in long-term follow-up.

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Abbreviations: ARAS = atherosclerotic renal artery stenosis, CCI = Charlson comorbidity index, CHF = congestive heart failure, CI = confidence interval, ESRD = end-stage renal disease, ICD-9-CM = the International Classification of Diseases, Ninth Revision, Clinical Modification, RAR = renal artery revascularization.

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INTRODUCTION

Atherosclerosis is a common degenerative disorder, which is closely related to the aging process. Because of the aging of the general population, atherosclerotic renal artery stenosis (ARAS) is anticipated to become increasingly prevalent over the coming decades.

ARAS is a common cause of hypertension and chronic renal failure, particularly in middle-aged and elderly patients.[1,2] Ischemic nephropathy caused by ARAS has been reported to be a leading cause of end-stage renal disease (ESRD) in the elderly.[3] Revascularization of arterial critical stenosis through percutaneous trans-luminal renal angioplasty or stent placement can overcome renal vascular hypertension and halt the disease progression of ischemic nephropathy in patients with ARAS. This treatment is now extensively used in patients with ARAS and may be of benefit under some conditions; however, the renal disease may progresses in ARAS patients after revascularization.[4] Previous studies indicated that the severity of stenosis and renal outcome in patients with ARAS is not always parallel, and that improvements in renal function after revascularization may only develop in some conditions.[4] Instead, chronic renal parenchymal disease caused by

atherosclerotic factors or coexisting detrimental factors has been suggested to be more closely related to the condition of the kidney in patients with ARAS, and that the development of significant stenosis in renal arteries could be assumed to be a harbinger of the coexisting atherosclerotic renal parenchymal disease in ARAS.[5]

To date, the data to elucidate the impact of these coexisting risk factors in ARAS patients with or without renal arterial revascularization (RAR) are lacking.[6,7] This study aimed to investigate the effect of coexisting risk factors on long-term renal outcomes in patients with ARAS.

MATERIALS AND METHODS

Data Source

The Taiwan Bureau of National Health Insurance consolidated 13 insurance programs into a single-payer National Health Insurance program in March 1995, and this program now covers over 99% of the population of 23.74 million people in Taiwan. The claims database from all health providers and all medical registries is managed and maintained by the National Health Research Institutes (NHRI). The NHRI created a scrambled, anonymous identification number to insure privacy when combining each person's information, including sex, birth date, and registry of medical services. The details of this database have been previously published.[8] The disease diagnoses were based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). This study was approved by the Ethics Review Committee of the China Medical University and Hospital (CMU-REC-101–012).

Sampled Participants

We identified patients with a diagnosis of renal artery stenosis (RAS) (ICD-9 code 440.1) from claims data for inpatients from 1999 to 2011. Patients aged 18 years or older with newly diagnosed ESRD (ICD-9-OP code 585) were selected for the ESRD case group. ESRD was identified from the hospitalization records and Registry for Catastrophic Illness Patient Database in Taiwan. The registration of catastrophic illness for ESRD requires lifelong dialysis; these documents are formally reviewed by the Taiwan Bureau of National Health Insurance. The date of the first admission for ESRD was used as the index date. The control group consisted of subjects randomly selected from among the other RAS patients who were not ESRD. In the present study, patients with the diagnosis of RAS were according to the abdominal image examinations such as computed tomography angiography (CTA), magnetic resonance angiography (MRA), or aortic angiography and those who were subjected to revascularization should have had critical stenosis of more than 70% in the arterial lumen or an arterial pressure gap >15 mm Hg. The ESRD and control groups were selected with an approximately 1:2 ratio in order to enhance the power of any statistical tests. Risk factors associated with renal outcomes were retrospectively compared in the study cohort.

Variables of Interest

Information extracted from the claims data included sex and age, Charlson comorbidity index (CCI) and baseline comorbidities. We categorized CCI into 4 levels 0, 1, 2, and 3 or more. CCI was determined for each subject from claims data for outpatient visits or hospitalizations at baseline. The CCI is a scoring system that includes weighting factors on important concomitant diseases; it has been validated for the use with ICD-9-CM coded administrative database.[9] The pre-existing comorbidities and surgery included diabetes (ICD-9 code 250), hypertension (ICD-9 codes 401–405), hyperlipidemia (ICD-9 code 272), stroke (ICD-9 codes 430–438), congestive heart failure (CHF) (ICD-9 code 428), vascular disease(ICD-9 codes 410-414, 443.89, 444) RAR (ICD-9-OP code 39.50 or 39.90), and nonalcoholic fatty liver disease (ICD-9-CM 571.8).

Statistical Analysis

Distributions of categorical demographic factors and comorbidities, including sex, age, CCI, diabetes, hypertension, hyperlipidemia, stroke, CHF, vascular disease, and RAR, were compared between the ESRD and control groups. Differences were examined using the Chi-square test for categorical variables and the *t* test for continuous variables. The odds ratio (OR) and 95% confidence intervals (CIs) were determined by univariable and multivariable logistics regression models. The multivariable models were included age, sex, CCI, and comorbidities. The data analysis also evaluated the joint effect among diabetes, hypertension, CHF, and RAR. All data analyses were performed using the SAS statistical package (version 9.2; SAS Institute Inc., Cary, NC). A 2-tailed *P*-value <0.05 was considered statistically significant.

RESULTS

During the 13-year observational period, 840 patients with ESRD were enrolled in the case group, and 1344 patients without ESRD were included in the control group. Of the 840 ESRD patients, 51.7% were male, and 59.1% were aged more than 65 years. The mean age of the group with ESRD and the control group was 65.2 (SD = 13.4) and 66.7 (SD = 13.0) years, respectively. Patients in the ESRD group were more commonly associated with CCI. As compared with the control group, patients with ESRD were more likely to have comorbidities including diabetes (59.6% vs 33.3%, $P < 0.001$), hypertension (96.4% vs 84.5%, $P < 0.001$), and CHF (41.8% vs 19.7, $P < 0.001$) (Table 1).

Results of univariable and multivariable logistic regression analysis showed that ESRD was associated with higher CCI score (adjusted OR = 6.78, 95% CI = 4.59–10.0 for CCI = 2; adjusted OR = 20.0, 95% CI = 13.7–29.2 for CCI ≥3), diabetes (adjusted OR = 1.55, 95% CI = 1.24–1.93), hypertension (adjusted OR = 3.66, 95% CI = 2.36–5.66), and age 20 to 49-years old (adjusted OR = 2.14, 95% CI = 1.51–3.03). A significantly lower risk of ESRD was associated with RAR in ARAS patients, which reached a statistical difference (adjusted OR = 0.64, 95% CI = 0.50–0.84) (Table 2).

To determine the effect of multiple cardiovascular risk factors on renal outcomes in ARAS, we calculated the joint effects of these risk factors in multivariable analysis. When compared with those without diabetes, hypertension, and CHF, patients with diabetes, hypertension, and CHF exhibited an adjusted OR of 5.33 (95% CI = 2.92–9.74), followed by simultaneous diabetes and hypertension that exhibited an adjusted OR of 3.62 (95% CI = 2.01–6.52), and only hypertension exhibited an adjusted OR of 3.07 (95% CI = 1.73–5.45) (Table 3).

To evaluate the effect of RAR on renal outcomes in ARAS patients with hypertension and diabetes, the risk of renal failure in hypertension and diabetes ARAS patients with or without RAR were calculated. When compared with those without diabetes, hypertension, and revascularization, a significantly increased the risk of ESRD (adjusted OR = 6.02, 95%

TABLE 1. Demographic Characteristics and Comorbidities in Renal Artery Stenosis Patients With and Without ESRD

	ESRD		
	No	Yes	
Variable	**N = 1344**	**N = 840**	***P*-value**
Sex	N (%)	N (%)	0.02
Female	580 (43.2)	406 (48.3)	
Male	764 (56.9)	434 (51.7)	
Age, years			0.09
≦64	491 (36.5)	343 (40.8)	
65–79	676 (50.3)	401 (47.7)	
80+	177 (13.2)	96 (11.4)	
Median (IQR)*	69.1 (17.4)	67.7 (17.9)	0.01
CCI score			<0.001
0	444 (33.0)	45 (5.36)	
1	342 (25.5)	44 (5.24)	
2	235 (17.5)	139 (16.6)	
3 or more	323 (24.0)	612 (72.9)	
Comorbidity			
Diabetes	447(33.3)	501 (59.6)	<0.001
Hypertension	1136 (84.5)	810 (96.4)	<0.001
Hyperlipidemia	430 (32.0)	290 (34.5)	0.22
Stroke	417 (31.0)	291 (34.6)	0.08
CHF	265 (19.7)	351 (41.8)	<0.001
Vascular disease	905 (67.3)	536 (63.8)	0.09
RAR	292 (21.7)	154 (18.3)	0.06
NAFLD	54 (4.02)	37 (4.40)	0.66

Chi-square test. CCI score = Charlson comorbidity index score, CHF = Ccongestive heart failure, NAFLD = Nonalcoholic fatty liver disease, RAR = renal artery revascularization.

* Wilcoxon signed-rank test.

TABLE 2. Odds Ratios and 95% Confidence Intervals of Renal Failure Associated With Comorbidities

	Crude	Adjusted†
Variable	**OR (95%CI)**	**OR (95%CI)**
RAR	0.81 (0.66, 1.01)	0.64 (0.50, 0.84)**
Sex (male vs female)	1.22 (1.04, 1.47)*	1.22 (0.98, 1.51)
Age, year		
20–49	1.29 (0.97, 1.71)	2.14 (1.51, 3.03)***
50–64	1.09 (0.83, 1.44)	0.98 (0.71, 1.36)
65+	1.00	1.00
CCI score		
0	1.00	1.00
1	1.27 (0.82, 1.97)	1.40 (0.90, 2.20)
2	5.84 (4.03, 8.46)***	6.78 (4.59, 10.0)***
3 or more	18.7 (13.4, 26.1)***	20.0 (13.7, 29.2)***
Comorbidity		
Diabetes	2.97 (2.48, 3.55)***	1.55 (1.24, 1.93)***
Hypertension	4.94 (3.33, 7.32)***	3.66 (2.36, 5.66)***
Hyperlipidemia	1.12 (0.93, 1.35)	–
Stroke	1.18 (0.98, 1.42)	–
CHF	2.92 (2.41, 3.54)***	1.03 (0.81, 1.31)
Vascular disease	0.86 (0.71, 1.03)	–
NAFLD	1.10 (0.72, 1.69)	–

CCI score = Charlson comorbidity index score, CHF = congestive heart failure, NAFLD = nonalcoholic fatty liver disease, RAR = renal artery revascularization. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

† Adjusted for sex, age, CCI score, and comorbidities of diabetes, hypertension, stroke, and CHF.

CI = 3.45–10.5) was noted in diabetes and hypertension patients without RAR, followed by patients with diabetes, hypertension, and RAR (adjusted OR = 4.17, 95% CI = 2.27–7.66). The risk of ESRD (adjusted OR = 3.84, 95% CI = 2.22–6.67) was noted in hypertensive patients without RAR, and a lower risk of ESRD (adjusted OR = 2.50, 95% CI = 1.32–4.73) was noted in hypertension with RAR (Table 4).

DISCUSSION

In the present study with a large number of cases and a longer observational period, our findings disclose that CCI score was significantly associated with chronic renal failure in ARAS patients, and that renal outcomes in patients with ARAS were significantly affected by hypertension and diabetes mellitus. This finding highlights the influence of these comorbid factors in contributing to ESRD in ARAS which has been easily neglected.

Atherosclerosis is a systemic disease related to the aging process, and several risk factors such as hypertension, hyperlipidemia, and diabetes are known to involve ARAS.[4] Patients with ARAS are frequently coexisted with the other atherosclerotic diseases such as coronary artery diseases, CHF, and stroke, and this has been reported to be associated with advanced atherosclerotic changes throughout the body.[10,11]

Systolic hypertension is a classic risk factor contributing to atherosclerosis, and it is thought to be both a consequence of and a risk factor for aggravating ARAS. Goldblatt et al[12] reported that arterial hypertension from unilateral RAS would lead to damage of bilateral kidneys. It already has been well known that intensive control of blood pressure is vital to break through the vicious cycle of systemic hypertension resulting from ARAS and alleviate the progression of renal failure.[13] Our results showed that hypertension was associated with a 3.66-fold increased risk of ESRD in the patients with ARAS in multivariate analysis, which is consistent with previous findings.

Diabetes has been reported to be another important factor that could accelerate atherosclerotic changes in microvascular and macrovascular diseases; however, the impact of diabetes in patients with ARAS has not yet been determined. Increasing evidence suggests that RAS is associated with type 2 diabetes.[5,14] In an autopsy study including 5194 consecutive cases, ARAS was found in 10% of the cases with diabetes and suggested that diabetes increased the risk of developing ARAS.[15] In addition, a previous study aimed to identify the potential risk factors for the changes of arterial stenosis in ARAS in 220 subjects through renal duplex scanning, and their results showed that diabetes was associated with the risk of luminal stenosis in renal arteries.[13] In our study regarding the risk of ESRD in ARAS patients, multivariate analysis disclosed that diabetes was associated with a 1.55-fold increased risk of ESRD in the patients with ARAS over a long observation period, and it is the first to identify the importance of diabetes in contributing to renal failure in patients with ARAS.

Moreover, we investigated the effect of underlying comorbidity on renal outcomes in ARAS patients by CCI score and showed that a significant correlation with regards to CCI score

TABLE 3. Joint Effect of Renal Failure Among Comorbidities of Diabetes, Hypertension, and CHF

Diabetes	Hypertension	CHF	Case No./Control No.	Crude OR† (95% CI)	Adjusted OR† (95% CI)
No	No	No	17/143	1 (Reference)	1 (Reference)
No	No	Yes	2/20	0.84 (0.18, 3.92)	0.29 (0.06, 1.38)
Yes	No	Yes	4/10	3.37 (0.95, 11.9)	0.90 (0.24, 3.43)
Yes	No	No	7/35	1.68 (0.65, 4.37)	1.52 (0.52, 4.41)
No	Yes	Yes	87/114	6.42 (3.61, 11.4)***	2.14 (1.14, 4.02)*
No	Yes	No	233/620	3.16 (1.87, 5.34)***	3.07 (1.73, 5.45)***
Yes	Yes	No	232/281	6.95 (4.08, 11.8)***	3.62 (2.01, 6.52)***
Yes	Yes	Yes	258/121	17.9 (10.4, 31.0)***	5.33 (2.92, 9.74)***

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.
†Adjusted for sex, age, and CCI score.

and renal outcome was noted in ARAS, and an approximately 20.0-fold increased risk of renal failure was found if the CCI score was greater than 3. These novel findings highlight the importance of underlying comorbidity in contributing renal failure and suggest that CCI score should be taken into consideration in ARAS patients while encountering such patients in practice.

Meanwhile, the effect of RAR on renal outcomes in ARAS was examined as well. After adjusting for confounders including age, gender, hypertension, hyperlipidemia, diabetes, CHF, and stroke, multiple variable analysis showed that the effect of revascularization on renal outcomes in the ARAS patients was significant and that was a 36% risk reduction in ESRD (adjusted OR = 0.64; 95% CI = 0.50–0.84) in long-term follow-up.

The optimal management in treating ARAS remains controversial.

A previous study using simple isotopic techniques that could quantify individual kidney function (single-kidney glomerular filtration rate) showed a negligible change before and after RAR. This suggests that renal parenchymal injury is the major determinant factor for renal dysfunction in patients with ARAS, rather than revascularization of RAS.[16] Accumulating evidence has shown that the benefit of RAR was equivocal in ARAS as compared with medication only.[17,18] However, in the present study, after adjusting for confounders, the multivariable analysis showed that RAR was significantly associated with a lower risk of ESRD in patients with ARAS. In addition, we calculated the competing risk of diabetes mellitus, hypertension, and renal artery revascularization on renal failure in ARAS patients. Our results showed a lower risk of ESRD in ARAS patients with hypertension and diabetes undergoing revascularization (adjusted OR: 4.17 vs 6.02 without RAR). Similarly, a trend was noted in hypertensive ARAS patients with and without RAR. Compared to ARAS patients without RAR, a lower risk of ESRD was noted in hypertensive patients receiving RAR (adjusted OR: 2.50 vs 3.50 without RAR) which was statistically significant. To a certain degree, our findings suggest a long-term beneficial effect of RAR in preventing progression to ESRD in patients with ARAS.

On the basis of our results, we suggest that aggressive control of these comorbid risk factors, and in particular hypertension and diabetes, is crucial to prevent the progression of kidney failure in patients with ARAS in addition to the RAR.

In conclusion, our study is the first to disclose the effect of underlying comorbidity on renal outcomes in patients with ARAS and shows that CCI score is significantly associated with it. In daily practice, taking their underlying comorbidity into consideration in treating ARAS patients is as important as renal artery intervention while encountering such patients with ARAS.

There are some limitations regarding this study that should be considered. First, details regarding arterial lumen stenosis could not be obtained. In the present study, patients with the diagnosis of RAS were according to the positive findings of abdominal image examinations such as CTA, MRA, or aortic angiography. Although not all ARAS patients were diagnosed with invasive angiography in this study, over 70% of the patients were diagnosed by invasive abdominal angiography. In addition, those who were subjected to RAR should have had critical stenosis of more than 70% in the arterial lumen or an

TABLE 4. Joint Effect of Renal Failure Among Comorbidities of Diabetes, Hypertension, and RAR

Diabetes	Hypertension	RAR	Case No./Control No.	Crude OR† (95% CI)	Adjusted OR† (95% CI)
No	No	No	18/152	1 (Reference)	1 (Reference)
No	No	Yes	1/11	0.77 (0.09, 6.30)	1.47 (0.16, 13.3)
Yes	No	No	9/39	1.95 (0.81, 4.67)	1.50 (0.57, 3.94)
Yes	No	Yes	2/6	2.82 (0.53, 15.0)	2.10 (0.32, 13.9)
No	Yes	Yes	48/166	2.44 (1.36, 4.38)**	2.50 (1.32, 4.73)**
No	Yes	No	272/568	4.04 (2.43, 6.73)***	3.84 (2.22, 6.67)***
Yes	Yes	Yes	103/109	7.98 (4.57, 13.9)***	4.17 (2.27, 7.66)***
Yes	Yes	No	387/293	11.2 (6.69, 18.6)***	6.02 (3.45, 10.5)***

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.
†Adjusted for sex, age, and CCI score.

arterial pressure gap >15 mm Hg. Second, serial renal changes could not be analyzed in this study; however, we selected a solid end-point of renal outcomes in the present study. Third, details on blood pressure, smoking, body mass index (BMI), and medication regimens could not be determined.

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REFERENCES

1. Piccoli G, Salomone M, Quarello F, et al. Regional registry of dialysis and transplantation of Piedmont, Italy (RPDT). Thirteen years of experience. Regional Registry of Dialysis and Transplantation. *Nephrol Dial Transplant.* 1995;10:444–447.
2. Textor SC. Atherosclerotic renovascular disease as a cause of end-stage renal disease: cost considerations. *Blood Purif.* 1996;14:305–314.
3. Mailloux LU, Napolitano B, Bellucci AG, et al. Renal vascular disease causing end-stage renal disease, incidence, clinical correlates, and outcomes: a 20-year clinical experience. *Am J Kidney Dis.* 1994;24:622–629.
4. Conlon PJ, O'Riordan E, Kalra PA. New insights into the epidemiologic and clinical manifestations of atherosclerotic renovascular disease. *Am J Kidney Dis.* 2000;35:573–587.
5. Myers DI, Poole LJ, Imam K, et al. Renal artery stenosis by three-dimensional magnetic resonance angiography in type 2 diabetics with uncontrolled hypertension and chronic renal insufficiency: prevalence and effect on renal function. *Am J Kidney Dis.* 2003;41:351–359.
6. Nicholls AJ. The impact of atherosclerotic renovascular disease on diabetic renal failure. *Diabet Med.* 2002;19:889–894.
7. Zierler RE, Bergelin RO, Isaacson JA, et al. Natural history of atherosclerotic renal artery stenosis: a prospective study with duplex ultrasonography. *J Vasc Surg.* 1994;19:250–257.
8. Yu TM, Lin CL, Chang SN, et al. Osteoporosis and fractures after solid organ transplantation: a Nationwide Population-Based Cohort Study. *Mayo Clin Proc.* 2014;89:888–895.
9. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol.* 1992;45:613–619.
10. Chabova V, Schirger A, Stanson AW, et al. Outcomes of atherosclerotic renal artery stenosis managed without revascularization. *Mayo Clin Proc.* 2000;75:437–444.
11. Wright JR, Shurrab AE, Cheung C, et al. A prospective study of the determinants of renal functional outcome and mortality in atherosclerotic renovascular disease. *Am J Kidney Dis.* 2002;39:1153–1161.
12. Goldblatt H, Lynch J, Hanzal RF, et al. Studies on experimental hypertension: I. the production of persistent elevation of systolic blood pressure by means of renal ischemia. *J Exp Med.* 1934;59:347–379.
13. Caps MT, Perissinotto C, Zierler RE, et al. Prospective study of atherosclerotic disease progression in the renal artery. *Circulation.* 1998;98:2866–2872.
14. Valabhji J, Robinson S, Poulter C, et al. Prevalence of renal artery stenosis in subjects with type 2 diabetes and coexistent hypertension. *Diabetes Care.* 2000;23:539–543.
15. Sawicki PT, Kaiser S, Heinemann L, et al. Prevalence of renal artery stenosis in diabetes mellitus – an autopsy study. *J Intern Med.* 1991;229:489–492.
16. Scoble JE, Mikhail A, Reidy J, et al. Individual kidney function in atherosclerotic renal-artery disease. *Nephrol Dial Transplant.* 1998;13:1048–1049.
17. Wheatley K, Ives N, Gray R, et al. Revascularization versus medical therapy for renal-artery stenosis. *N Engl J Med.* 2009;361:1953–1962.
18. Bohlke M, Barcellos FC. From the 1990s to CORAL (cardiovascular outcomes in renal atherosclerotic lesions) trial results and beyond: does stenting have a role in ischemic nephropathy? *Am J Kidney Dis.* 2015;65:611–622.