Association between Leptospirosis-associated AKI and Long-term Renal Outcome : A Nationwide Study in Taiwan

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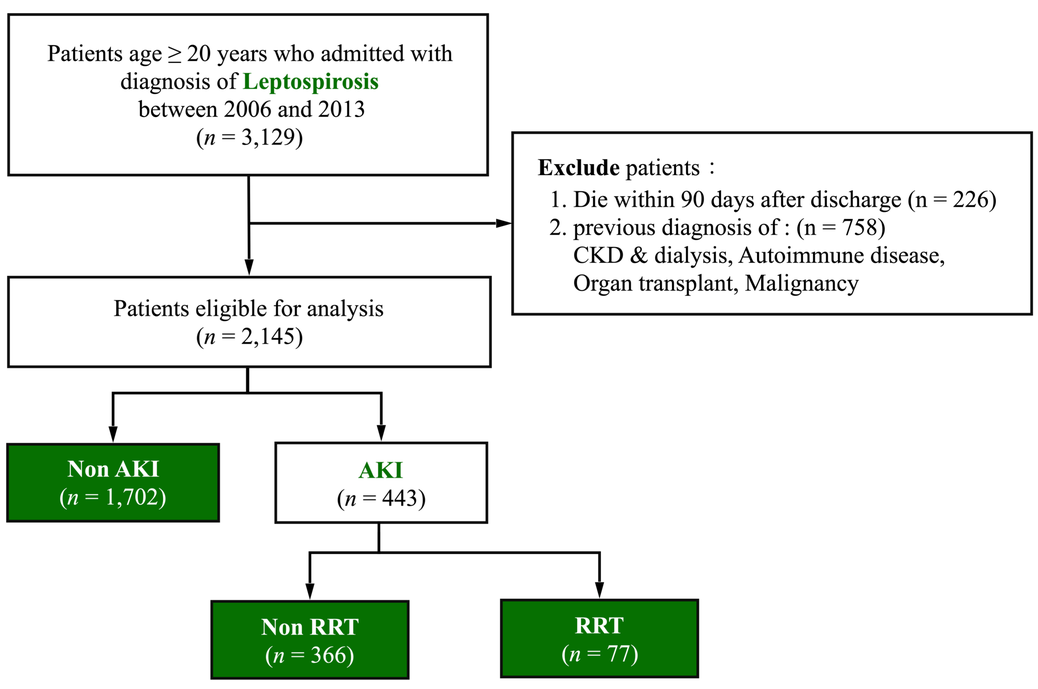
Purpose

Leptospirosis usually results in acute kidney injury (AKI) and even multiple organ failure requiring renal replacement therapy (RRT) but is associated with favorable short-term outcomes if timely treatment is initiated. Animal studies suggest chronic leptospirosis may develop if leptospira persists in the tubular lumen and interstitium as a continuum of AKI, leading to chronic interstitial fibrosis and progressive kidney failure. However, human information on long-term risk of adverse outcome such as chronic kidney disease (CKD) or end stage renal disease (ESRD) after leptospirosis associated AKI is limited.

Methods

Figure 1. Flow chart of the study population



We performed a nationwide study used claim data obtained from Taiwan National Health Insurance Research Database. Patients who had an admission for leptospirosis from 2006 to 2013 were identified (Figure1). We exclude patients who die within 90 days after discharge (n=226). To clarify the relationship between leptospirosis-associated AKI and long-term risk of kidney failure, patients with prior renal dysfunction, organ transplantation, malignancy, or autoimmune disease were excluded (n=758). Ultimately, a study population of 2145 patients with leptospirosis were eligible for analysis. Patients were divided into the non-AKI (n=1702, 79.3%), AKI (n=366, 17.1%), and AKI requiring RRT groups (n=77, 3.6%). The incidence of new-onset CKD or ESRD among the study groups was compared using Fine and Gray subdistribution hazards model, which considered mortality as a competing risk.

Results:

The mean follow-up time was 6.2 years. Long-term mortality was higher in the AKI-RRT group than in the AKI group and non-AKI group. Similarly, the incidence rate of CKD was highest in the AKI-RRT group (48.1%) followed by the AKI (38.3%) and non-AKI group (10.3%) (Table 1). Only five patients developed ESRD and all of them were AKI-RRT group. Multivariate Cox analysis revealed that **the hazard ratios for the development of CKD in patients with leptospirosis were 4.73 and 5.96 for patients with AKI and AKI-RRT compared with those with non-AKI** after adjusting for potential risk factors for CKD (Table 2).

Table 1. Baseline patient characteristics

Variable	Total (*n* = 2,145)	Non-AKI (*n* = 1702)	AKI without RRT (*n* = 366)	AKI with RRT (*n* = 77)	*p*
Age (years)	49.0±15.2	48.1±15.1	51.6±15.3	55.4±14.9	<0.001
Gender					<0.001
Male	1497 (69.8)	1145 (67.3)	297 (81.1)	55 (71.4)	
Female	648 (30.2)	557 (32.7)	69 (18.9)	22 (28.6)	
Comorbid conditions					
Diabetes mellitus	364 (17.0)	281 (16.5)	64 (17.5)	19 (24.7)	0.461
Hypertension	683 (31.8)	518 (30.4)	128 (35.0)	37 (48.1)	0.030
Heart failure	114 (5.3)	84 (4.9)	23 (6.3)	7 (9.0)	0.205
Coronary artery disease	325 (15.2)	253 (14.9)	52 (14.2)	20 (26.0)	0.910
Cerebrovascular disease	181 (8.4)	137 (8.0)	34 (9.3)	10 (13.0)	0.254
Chronic hepatitis (HBV or HCV)	209 (9.7)	171 (10.0)	28 (7.7)	10 (13.0)	0.219
Gout	405 (18.9)	304 (17.9)	82 (22.4)	19 (24.7)	0.027
Medication					0
ACEI/ARB	276 (12.9)	200 (11.8)	60 (16.4)	16 (20.8)	<0.01
OHA	175 (8.2)	134 (7.9)	29 (7.9)	12 (15.6)	0.7
Insulin	94 (4.4)	66 (3.9)	20 (5.5)	8 (10.4)	0.08
NSAID	322 (15.0)	264 (15.5)	51 (13.9)	7 (9.1)	0.3
Follow-up outcome					
All-cause mortality	182 (8.5)	119 (7.0)	46 (12.6)	17 (22.1)	<0.001
Chronic kidney disease	353 (16.5)	176 (10.3)	140 (38.3)	37 (48.1)	<0.001
ESRD/Dialysis	5 (0.2)	0 (0.0)	0 (0.0)	5 (6.5)	0.07

Categorical variables are expressed as number (percentage) and continuous variables as mean±SD; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; OHA, oral hypoglycemic agent; NSAID, non-steroidal anti-inflammatory drug

Table 2 comparison of follow-up outcomes according to the study groups.

Outcomes	AKI without RRT vs. Non-AKI		AKI with RRT vs. Non-AKI	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Chronic kidney disease §				
Unadjusted	5.14 (4.11-6.42)	<0.001	7.54 (5.27-10.79)	<0.001
Adjusted	4.73 (3.75-5.95)	<0.001	5.96 (4.10-8.65)	<0.001
All-cause mortality				
Unadjusted	1.99 (1.41-2.79)	<0.001	3.67 (2.21-6.11)	<0.001
Adjusted	1.20 (0.84-1.72)	0.329	2.13 (1.24-3.67)	0.006

HR, hazard ratio; CI, confidence interval; RRT, renal replacement therapy; outcomes were adjusted for baseline age, gender, comorbid conditions, medications listed in Table 1 and study year;
§ estimated using subdistribution hazard model which death was considered as a competing risk

Conclusion

Leptospirosis-associated AKI may play a critical role in the development of CKD. Additional investigations are warranted to explore the possible mechanisms in human beings.

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