New-Onset Diabetes After Acute Kidney Injury Requiring Dialysis

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OBJECTIVE

Acute kidney injury (AKI) is related to a high prevalence of insulin resistance. However, information is lacking on the sequelae of further metabolic change among AKI requiring dialysis in patients who could be weaned off dialysis (acute kidney disease [AKD]).

RESEARCH DESIGN AND METHODS

Using the National Health Insurance Research Database from 2000 to 2010, with the exclusion of those with diabetes at the start, we identified 3,307 subjects with AKD and 9,921 matched control subjects from 963,037 hospitalized patients for the comparison of the outcomes, including new-onset diabetes and all-cause mortality.

RESULTS

Within the median follow-up period of 5.99 years, AKD patients had a higher incidence of new-onset diabetes than the matched control patients (5.16% vs. 4.17% per person-year, $P = 0.001$). AKD patients were at higher risk of mortality than control patients (adjusted hazard ratio [aHR] 1.27 [95% CI 1.18–1.36], $P < 0.001$). With mortality as a competing risk, a Cox proportional hazards analysis showed that AKD patients had a higher risk of subsequent diabetes (subhazard ratio [sHR] 1.18 [95% CI 1.07–1.30], $P < 0.001$) compared with the matched control patients. Subgroup analysis showed that patients with baseline hypertension (aHR 1.15 [95% CI 1.04–1.28]), hyperlipidemia (aHR 1.23 [95% CI 1.02–1.48]), and gout (aHR 1.23 [95% CI 1.03–1.46]) had increased odds of developing new-onset diabetes during follow-up.

CONCLUSIONS

Patients who experienced AKI had a higher incidence of developing new-onset diabetes and mortality. This observation adds evidence regarding potential metabolic dysregulation after AKI.

Several studies have shown that acutely and critically ill patients may have a higher risk of subsequent diabetes than the general population (1). The incidence of acute kidney injury requiring dialysis (AKI-D) is increasing by 10% per year in the U.S. and is higher than that for end-stage renal disease (2). Patient survival from an episode of AKI has improved; therefore, an increasing number of hospitalized patients are being discharged alive after AKI-D (3). A high prevalence of insulin resistance in patients with AKI has been observed in several studies (4,5). However, it is unknown whether a temporal episode of AKI is related to the subsequent risk of diabetes.

Thus, we assessed whether the most severe form of AKI, even for only a temporary dialysis, would carry a subsequent risk of new-onset diabetes in the long run after discharge from a nationwide cohort.

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RESEARCH DESIGN AND METHODS

Data Sources

Patients in this population-based study were retrospectively collected from the National Health Insurance Research Database (NHIRD). The Taiwan National Health Insurance program is a nationwide insurance program that covers outpatient visits, hospital admissions, prescriptions, intervention procedures, and disease profiles for >99% of the population of Taiwan (23.12 million people in 2009) (6). The NHIRD is one of the largest and most comprehensive databases in the world, and the accuracy of the diagnoses have been previously validated (7–10).

Design and Study Participants

From the 2000–2010 claims data, we identified patients who underwent dialysis during hospitalization and patients who had no AKI and dialysis history before index hospitalization. In patients with dialysis during hospitalization, we excluded patients with previous vascular access, dialysis, or renal transplantation in the year before hospitalization, and those who died during the index hospitalization. We excluded patients with a medical history of diabetes (ICD-9 codes 250.x0 and 250.x2) or antidiabetic agent use before the index hospitalization. Patients who died or who commenced any renal replacement therapy within 30 days after the index discharge were also excluded. Finally, we identified AKI-D patients weaning from dialysis as acute kidney disease (AKD) enrollees because the term AKD has originally been proposed to define the course of disease after AKI among patients in whom the renal pathophysiologic processes are ongoing (11). We selected patients aged between 18 and 80 years and further excluded patients with diabetes, AKI, and dialysis history before the index hospitalization as control enrollees (Fig. 1).

Comorbidities were ascertained using the ICD-9, Clinical Modification (ICD-9-CM code) of the discharge diagnoses. We used a 1-year period before the index hospitalization to identify preadmission comorbidities to avoid selection bias. To determine preexisting comorbidities, we used a strict criterion, at least one inpatient admission or three outpatient visits to treat a certain disease during the year before the index hospitalization, which was well validated with good predictive power (10). Patients with a history of prior congestive heart failure (CHF) were categorized with mild (treated in an outpatient setting or who had a length of hospital stay ≤7 days) or severe (length of hospital stay >7 days) because the mean duration of stay in Taiwan for CHF was 6–9 days from 1999 to 2008. The Charlson comorbidity index was used to quantify patient comorbidity profiles. According to Taiwan National Health Insurance reimbursement policy, erythropoiesis-stimulating agents may only be prescribed for predialysis chronic kidney disease (CKD) patients with anemia who have a hematocrit ≤28% and a serum creatinine >6 mg/dL (equivalent to an estimated glomerular filtration rate of <15 mL/min/1.73 m^2, CKD stage 5). To address confounding by observed covariates, we applied a propensity score (PS) for the likelihood of diabetes by logistic regression analysis contingent on the baseline covariates listed in Supplementary Table 1. After that, the AKD patients were matched to control counterparts in a 1:3 ratio based on the PS.

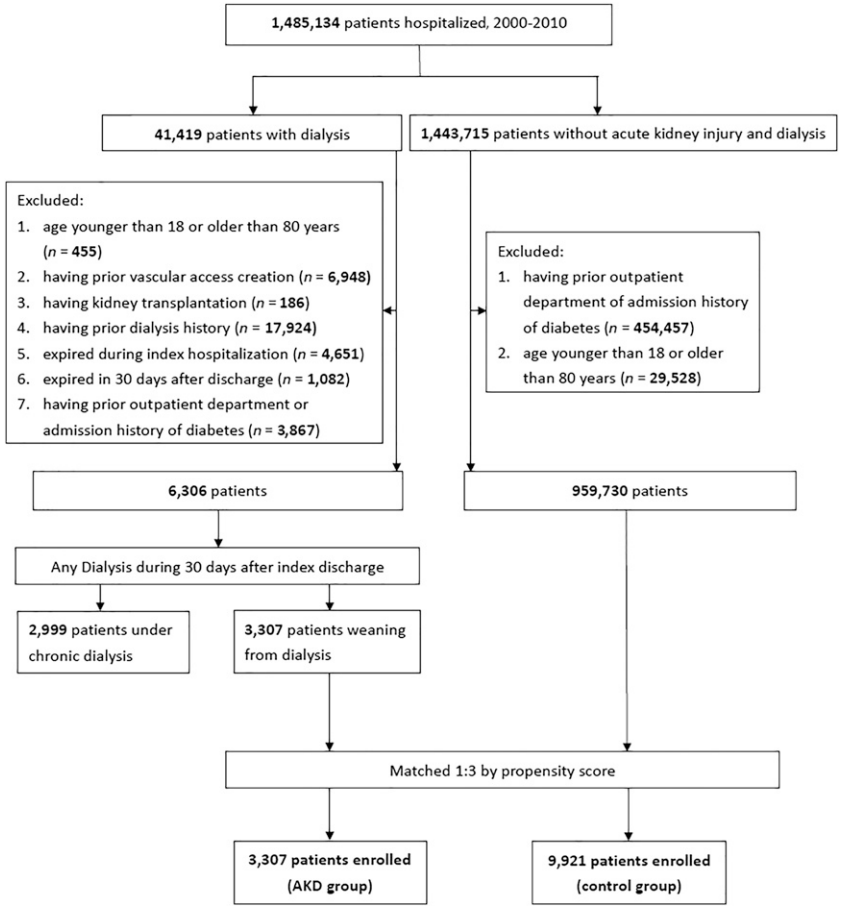

Figure 1—The flow diagram of the enrollee.

Specificity Analysis

To compare new-onset diabetes and all-cause mortality in AKD patients and AKI-D patients who could not be weaned off dialysis, we further identified the 2,999 AKI-D patients who could not be weaned off dialysis with the matched AKD patients by PS in a 1:1 manner.

Study Outcome and Follow-Up

New-onset diabetes was defined as one of the following conditions in those who had no history of diabetes at baseline: records of greater than three consecutive outpatient visits with the codes of prescriptions of oral antidiabetic drugs or insulin (12). Patients were monitored from the index date until death, diabetes diagnosis, 5-year follow-up period, or 31 December 2011, whichever occurred first.

Ethical Considerations

Informed consent was originally documented in the National Health Research Institutes (NHRI), and because the patients

were not identifiable in the current study, informed consent was not required. Additionally, because the identification numbers of all individuals in the NHRI databases are encrypted to protect privacy, this study was exempt from full ethical review by the National Taiwan University Hospital Review Board (201212021RINC).

Statistical Analysis

Demographic characteristics and the baseline comorbidities were compared using the χ^2 test for categorical variables and independent Student *t* test for continuous variables. After discharge, the status of diabetes was integrated as time-varying risks to avoid immortal time bias (13,14). Time-varying multivariate Cox proportional hazards models were used to determine the effect of AKI on the risk of new-onset diabetes by using hazard ratios (HRs) with 95% CIs. The PS matching method was adopted to compare the risk of diabetes and mortality between the AKD and control patients by the factors in the multivariate model (Supplementary Table 1). We calculated adjusted HR (aHR) values after adjusting for age, sex, Charlson comorbidity index, and propensity covariates. Death before the occurrence of diabetes was considered a competing risk event in the Fine and Gray model (12,15). To assess the difference in the diabetes-free probability curve and survival curve between the two patient groups, we analyzed competing regression plots. We conducted subgroup analyses for the comparison of aHR values of new-onset diabetes risk among baseline comorbidities stratified by the status of AKD. Interactions between AKD, hypertension, hyperlipidemia, gout, and CHF were formally tested by including interaction terms within a Cox regression model. The PS matching method was adopted to compare the risk of diabetes and mortality between the AKD patients and AKI-D patients who could not wean off dialysis. All analyses were performed using R software, version 2.8.1 (Free Software Foundation, Inc., Boston, MA); competing-risk analysis was performed with Stata MP version 14 (Stata Corporation, College Station, TX). A two-sided *P* value <0.05 was considered statistically significant.

RESULTS

Study Patients

Of the individuals with AKI-D who survived at least 30 days after hospital discharge, 6,306 were eligible for the study. Of them, 3,307 (52.4%) patients were weaned from dialysis and were designated as AKD patients. The mean age of the AKD patients was 56.8 ± 19.1 years, and the proportion of men was 62.5%, whereas the proportion of women was 37.5%. The mean age of the control patients was 60.97 ± 17.24 years, and the proportion of men was 54.6% (women, 45.4%) (Table 1). All patients were monitored for a median period of 5.99 years. Before matching, AKD patients were younger, predominantly male, and more likely to have comorbidities including myocardial infarction, CHF, cancer, and hyperuricemia, whereas control patients were older and more likely to have comorbidities including dementia, chronic obstructive pulmonary disease, rheumatic disease, peptic ulcer disease, hemiplegia or paraplegia, and hyperlipidemia. After matching, the distributions of the two patient groups were similar for baseline characteristics (Table 1).

Risk Factors for Incident Diabetes

Supplementary Table 2 shows the clinical predictors of incident diabetes by applying the multivariate Cox proportional

Table 1—Basic demographic characteristics and comorbidities before and after PS matching

	Before PS match (*n* = 963,037)				After PS match (*n* = 13,228)			
Variables	Control (*n* = 959,730)	AKD (*n* = 3,307)	*P* value	SMD	Control (*n* = 9,921)	AKD (*n* = 3,307)	*P* value	SMD
Age (years)	60.97 ± 17.24	56.77 ± 19.08	<0.001	−0.231	57.29 ± 18.37	56.77 ± 19.08	0.171	−0.028
Male sex	524,443 (54.64)	2,068 (62.53)	<0.001	0.161	6,166 (62.15)	2,068 (62.53)	0.694	0.008
Baseline comorbidities								
Charlson score	1.82 ± 1.47	1.50 ± 1.40	<0.001	−0.225	1.56 ± 1.42	1.50 ± 1.40	0.051	−0.039
CHF	97,632 (10.17)	527 (15.94)	<0.001	0.172	1,565 (15.77)	527 (15.94)	0.826	0.004
Chronic obstructive pulmonary disease	362,273 (37.75)	903 (27.31)	<0.001	−0.224	2,831 (28.54)	903 (27.31)	0.174	−0.027
Dementia	44,604 (4.65)	110 (3.33)	<0.001	−0.068	352 (3.55)	110 (3.33)	0.548	−0.012
Gout	184,133 (19.19)	674 (20.38)	0.082	0.030	2,025 (20.41)	674 (20.38)	0.970	−0.001
Hemiplegia or paraplegia	35,282 (3.68)	54 (1.63)	<0.001	−0.127	182 (1.83)	54 (1.63)	0.448	−0.015
Hypertension	528,719 (55.09)	1,792 (54.19)	0.298	−0.018	5,467 (55.11)	1,792 (54.19)	0.359	−0.018
Hyperlipidemia	232,117 (24.19)	607 (18.36)	<0.001	−0.143	1,836 (18.51)	607 (18.36)	0.846	−0.004
Hyperuricemia	39,614 (4.13)	162 (4.90)	0.026	0.037	512 (5.16)	162 (4.90)	0.553	−0.012
Moderate or severe liver disease	193,990 (20.21)	634 (19.17)	0.137	−0.026	1,866 (18.81)	634 (19.17)	0.644	0.009
Myocardial infarction	30,161 (3.14)	161 (4.87)	<0.001	0.088	462 (4.66)	161 (4.87)	0.619	0.010
Peptic ulcer disease	370,249 (38.58)	1,060 (32.05)	<0.001	−0.137	3,337 (33.64)	1,060 (32.05)	0.094	−0.034
Peripheral vascular disease	28,116 (2.93)	110 (3.33)	0.177	0.023	319 (3.22)	110 (3.33)	0.755	0.006
Rheumatologic disease	52,778 (5.50)	148 (4.48)	0.010	−0.047	437 (4.40)	148 (4.48)	0.864	0.003
Tumor	52,717 (5.49)	269 (8.13)	<0.001	0.105	862 (8.69)	269 (8.13)	0.324	−0.020
Obesity	1,138 (0.12)	2 (0.06)	0.332	−0.019	7 (0.07)	2 (0.06)	0.847	−0.004
Steroid use in AKD	104,486 (10.89)	374 (11.31)	0.436	0.013	979 (9.87)	374 (11.31)	0.018	0.047

Data are *n* (%) and mean ± SD. SMD, standardized mean difference.

hazards models after the PS matching. AKD (HR 1.23 [95% CI 1.12–1.35]), hypertension (HR 1.38 [95% CI 1.24–1.53]), gout (HR 1.15 [95% CI 1.04–1.28]), CHF (HR 1.34 [95% CI 1.21–1.49]), and steroid use in AKD (HR 1.17 [95% CI 1.03–1.33]) were risk factors of incident diabetes.

Outcome Analyses

Before PS matching, the median follow-up periods (interquartile range) for the patients with diabetes in the AKD and control patients were 4.49 years (4.35) and 5.99 years (1.99), respectively. The overall incident diabetes was higher in the AKD patients than in the control subjects (5.16% vs. 3.80% per person-year). After adjusting for the PS, the risk of new-onset diabetes was significantly higher in the AKD patients (21%) than in the control patients (aHR 1.21 [95% CI 1.10–1.32]). Moreover, the risk of mortality was 1.27-fold greater in the AKD patients compared with the control patients (aHR 1.27 [95% CI 1.18–1.36]). After adjustment for the relevant confounding factors and taking mortality as the competing risk, AKD patients were at higher risk for new-onset diabetes than the control patients (subhazard ratio [sHR] 1.18, $P < 0.001$) (Table 2). The cumulative proportion of new-onset diabetes and all-cause mortality was significantly higher in the AKD patients than in the control patients (Fig. 2*A* and *B*).

Subgroup Analyses

To investigate the consistency in risks of new-onset diabetes, we performed a subgroup analysis with respect to baseline comorbidity. We found that AKD was associated with higher new-onset diabetes risk across patients who had baseline comorbidity of hypertension (aHR 1.15 [95% CI 1.04–1.28]), hyperlipidemia (aHR 1.23 [95% CI 1.02–1.48]), and gout (aHR 1.23 [95% CI 1.03–1.46]) (Fig. 2*C*). In the evaluation of the interaction between AKD and the baseline comorbidities of hypertension, hyperlipidemia, gout, and CHF, regarding the incident diabetes, the interactions between AKD and hyperlipidemia (interaction $P = 0.895$), gout (interaction $P = 0.637$), and CHF (interaction $P = 0.177$) were not significant (Supplementary Table 3), which explained that AKD was independent of baseline hyperlipidemia, gout, and CHF and was related to new-onset diabetes. However, hypertension could augment the AKI-D effect, and both were associated with the incident diabetes (interaction $P = 0.035$) (Supplementary Table 3).

Specificity Analysis

To investigate the separate effect of dialysis on risks of incident diabetes and mortality, we further compared the risks in AKI patients between AKD patients and AKI-D patients who could not wean off dialysis. We found that the risk of mortality was higher in the AKI-D patients who could not wean off dialysis compared with the AKD patients (sHR 1.27 [95% CI 1.17–1.38], $P < 0.0001$) after taking mortality as the competing risk (Supplementary Table 4).

CONCLUSIONS

We found increased long-term incident risk of diabetes and mortality after AKI, particularly in patients with underlying comorbidities of hypertension, hyperlipidemia, and gout, the major components of metabolic syndrome. Our results imply that AKI-D, the most severe form of AKI, has a sequela of long-term systemic metabolic dysregulation, and this indicates that both patients and clinicians should notice the possibility of metabolic sequelae after AKI even after hospital discharge. It also highlights that the background of metabolic syndromes gives the predilection of diabetes while the inflammation from AKI makes it worse. Our findings support a call for closer follow-up of patients after an AKI episode so that appropriate management can be implemented in a timely manner (11). Regularly monitoring the serum sugar is mandatory after AKI with kidney function recovery.

The kidney plays a major role in glucose homeostasis (16,17). Stress-induced hypermetabolism and inflammation-related AKI may directly contribute to an increased risk of insulin resistance independent of the impact on CKD progression. We found augmentation of new-onset diabetes, with 5.16% of AKD patients developing new-onset diabetes after temporary dialysis. This result is remarkably higher than the general incidence of 1.16% found in the Taiwanese adult population during a similar period (18). Previous studies have proposed that the stress of acute and critical illness causes critical illness–induced "dysglycemia" to

Table 2—Comparison of new-onset diabetes and all-cause mortality before and after PS matching

	Control			AKD			Crude			Adjusted*			Competing risks		
	Events	Person-years	Incidence, %	Events	Person-years	Incidence, %	HR	95% CI	*P* value	HR	95% CI	*P* value	sHR	95% CI	*P* value
Before PS match															
Diabetes	162,199	4,268,923.21	3.80	587	11,386.44	5.16	1.31	1.21–1.42	<0.001	1.17	1.08–1.27	<0.001	1.21	1.12–1.32	<0.001
All-cause mortality	178,174	4,665,653.50	3.82	1,051	12,662.56	8.30	2.09	1.97–2.22	<0.001	1.12	1.05–1.19	<0.001			
After PS match															
Diabetes	1,649	39,516.21	4.17	587	11,386.44	5.16	1.17	1.07–1.29	0.001	1.21	1.10–1.32	<0.001	1.18	1.07–1.30	<0.001
All-cause mortality	2,661	43,419.66	6.13	1,051	12,662.56	8.30	1.25	1.17–1.35	<0.001	1.27	1.18–1.36	<0.001			

Incidence is the incidence rate, per person-year. *Adjusted for age, sex, Charlson comorbidity index, and propensity covariates.

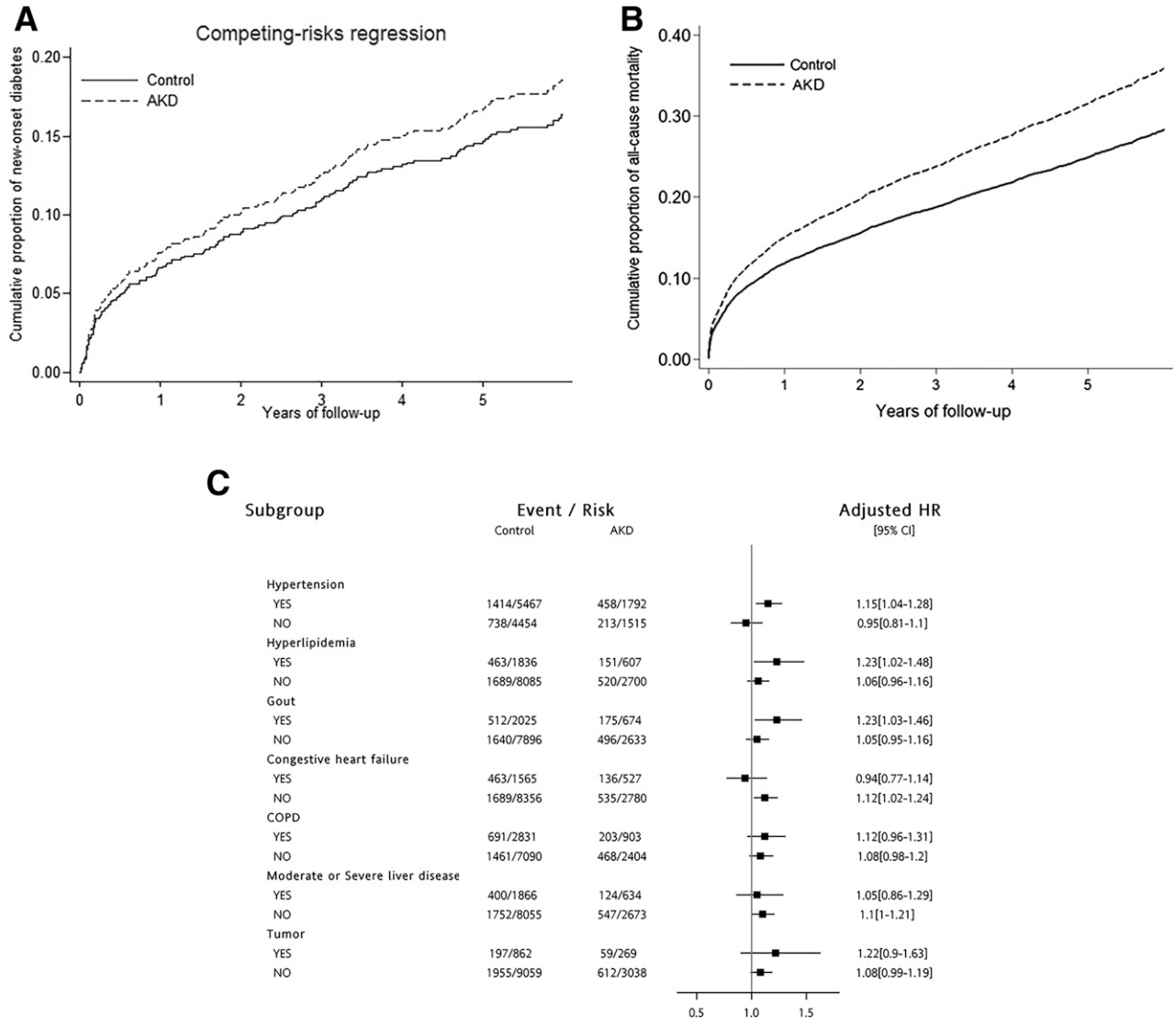

Figure 2—*A*: Cox proportional hazards model of cumulative new-onset diabetes, taking mortality as a competing risk ($P < 0.001$). *B*: Cox regression plot of the mortality between matched AKD and control cohorts ($P < 0.001$). *C*: Risk of new-onset diabetes associated with AKD by participant characteristics. aHRs for long-term risk of new-onset diabetes based on a comparison between matched AKD and control patients and subgroup analysis with respect to baseline comorbidity that further adjusted for age, sex, and Charlson score. COPD, chronic obstructive pulmonary disease.

susceptible patients, which results in overt diabetes later in life (19). A systematic review of patients with new-onset diabetes after acute and critical illness found that the prevalence of new-onset diabetes after hospital discharge was 8% for prospective patient studies (20). Surprisingly, the prevalence of new-onset diabetes in our study was 17.75% at 5 years after the initial episode of AKI, which is much higher than in other acute and critical illnesses that have been reported (20). Thus, there is a high prevalence of new-onset diabetes after AKI. Additionally, it has been reported that adipocytes from partially nephrectomized uremic rats have a decreased number of GLUTs (21). These changes in AKI could increase a patient's susceptibility to diabetes later in life. Recently, AKI and CKD have been seen as an integrated syndrome due to their bidirectional intertwined nature (22). Thus, we need to raise awareness of the long-term outcomes of AKI survivors, taking diabetes as a component of metabolism in the integrated AKI syndrome, which has a significant impact on public health.

Our results are pathophysiologically plausible given the evidence that stress-related insulin resistance in AKI and other acute and critical illnesses carries on even after hospital discharge (23). Several cytokines, of which some have been noted as AKI biomarkers, have been proposed to be involved in causing diabetes (24). All of these findings, together with our study results, reveal a paradigm for how AKI and metabolism are closely linked, providing a framework for understanding how AKI involving subsequent metabolic disturbances arises.

Strengths and Limitations

Our study had several limitations. First, we had no data regarding plasma glucose concentrations or glycated hemoglobin levels or the causes of mortality. Second, the NHIRD contains no information on lifestyle or BMI, adiposity, alcohol consumption, smoking status, or family history of diabetes, which all can raise the risk of diabetes. Third, we focused only on the patients with AKI-D, which is the most severe form of AKI; the relationship

of incident diabetes and the severity of AKI cannot be analyzed in the NHIRD national database. Finally, retrospective patient studies are subject to various biases because of the lack of adjustments or unknown confounding factors. However, with the use of PS matching, multivariate adjustments, and evaluation of model discrimination in the validation data sets, we have attempted to increase the internal validity of the competing risk models (25,26). Further prospective studies are warranted to delineate whether AKI is a causative factor for the development of new-onset diabetes.

Conclusion

In conclusion, the findings of this large population-based study indicate that patients with AKI are significantly associated with subsequent new-onset diabetes risk and mortality in the long run after hospital discharge. This study is the first to examine this potentially important connection between metabolic dysregulation, AKI, and diabetes. AKI may uncover latent metabolic disturbances, especially in those who did not wean from AKI-D, and plasma glucose should be periodically checked in order to decrease the possible complication in the long-term.

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Author Contributions. Y.-F.L. and V.-C.W. designed the study, planned analyses, conducted the data collection and statistical analysis, and drafted the manuscript. S.-L.L., T.-S.C., and K.-D.W. contributed to the quality control of the study. T.-M.H., S.-Y.Y., T.-S.L., and L.C. contributed to data collection and interpretation. All authors reviewed and approved the drafts of the manuscript. Y.-F.L. and V.-C.W. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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