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New-Onset Diabetes After Renal Transplantation (NODAT): Is It a Risk Factor for Renal Cell Carcinoma or Renal Failure?

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Background: Diabetes mellitus (DM) is a risk factor for renal failure and possibly for renal cell carcinoma (RCC). Post-transplantation DM occurs frequently after solid organ transplantation. We investigated whether new-onset diabetes after renal transplantation (NODAT) is a risk factor for RCC or renal failure.


Material/Methods: Data of 96,699 discharged patients with and without NODAT were extracted from the 2005–2014 Nationwide Inpatient Sample (NIS) database, after excluding patients with DM diagnosed at least 1 year prior to renal transplantation. Main outcomes were RCC diagnosis less than 1-year post-transplantation, RCC stage, and renal failure. Univariate and multivariate regression analyses were performed to identify demographic and clinical factors associated with post-transplantation RCC or renal failure.

Results: Significant differences were found in age and race between patients with and without NODAT (both $P < 0.001$). The renal failure rate was 0.8% ($n=1$) in NODAT patients and 0.3% ($n=314$) in those without NODAT. Older age (OR, 1.030; 95% CI: 1.023 to 1.036), male (OR, 1.872; 95% CI: 1.409 to 2.486), Black (OR, 2.199; 95% CI: 1.574 to 3.071) and hospitalization in urban teaching hospitals were associated with increased risk of RCC.

Conclusions: Analysis of over 90,000 NIS hospitalizations with diagnosis-coded kidney transplantation suggested that NODAT may not be an independent risk factor for RCC and renal failure.

MeSH Keywords: **Kidney Neoplasms • Kidney Transplantation • Neurology**

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Background

Diabetes mellitus (DM) is a known risk factor for renal failure and a possible risk factor for renal cell carcinoma (RCC) [1]. Post-transplantation DM occurs frequently after solid organ transplantation and is associated with increased risk of opportunistic infection and higher mortality rates [2]. Risk of RCC in renal transplantation patients has also been reported to be 5- to 7-fold higher than in the general population [3]. However, the mechanism of new-onset diabetes after transplantation (NODAT) may not be the same as that for general DM due to differences in pathogenesis and patient clinical characteristics [2,4]. Even though the short-term and long-term manifestations of DM may be similar in NODAT, the rate at which they occur is remarkably accelerated [5]. While renal transplantation restores renal function and simultaneously reduces cardiovascular risk factors, it requires the use of immunosuppressants, such as corticosteroids or calcineurin inhibitors, that may in some patients introduce new cardiovascular risk factors such as impaired glucose tolerance, DM, hypertension, or dyslipidemia [1].

The International Consensus Guidelines for the Diagnosis and Management of NODAT defines post-transplantation DM according to the World Health Organization (WHO) criteria for pre-diabetic states of impaired fasting plasma glucose and impaired glucose tolerance [6]. NODAT incidence in the United States are estimated to be about 9.1% of patients at 3 months post-transplantation, 16% at 12 months post-transplantation, and 24% at 36 months post-transplantation [7]. The main non-modifiable risk factors include age, male gender, race, and family history/genetic background [1]. The main modifiable risk factors are obesity and metabolic syndrome [8], and immunosuppressants given to prevent allograft rejection [4]. The post-transplantation effects of immunotherapy may compound the association between acute rejection and NODAT and the clinical challenge of modifying immunotherapy to avoid these complications after transplantation.

NODAT is a significant contributor to cardiovascular risk, which must be considered for all renal transplantation patients along with the risk of allograft rejection [8]. Since DM is already a known risk factor for renal failure and a possible risk factor for RCC, and NODAT occurs frequently for up to 15 years after solid organ transplantation, we hypothesized that NODAT may also be a risk factor for RCC and renal failure. Therefore, the purpose of this study was to investigate whether new-onset diabetes after renal transplantation is a risk factor for RCC or renal failure, and to also identify risk factors associated with RCC and renal failure in transplantation patients with and without NODAT.

Material and Methods

Data for this study were extracted from the Nationwide Inpatient Sample (NIS) database, which was developed in the United States by the Healthcare Cost and Utilization Project (HCUP) [9]. The database is maintained by the Agency for Healthcare Research and Quality (AHRQ). The NIS represents a 20% sample of inpatient admissions from 45 states that participate in HCUP. Data drawn from 1,051 participating hospitals contain a core set of clinical and nonclinical information on all discharged patients, including principal and secondary diagnoses, principal and secondary procedures, admission and discharge status, patient demographics, and hospital length of stay.

Study design and ethical considerations

A cross-sectional, retrospective study was conducted to analyze hospital discharge information from the HCUP-NIS administrative database for a 10-year period from 2005 to 2014. This study obtained the certificate number, HCUP-29M60HZT5, and conforms to the data-use agreement for the NIS from the HCUP Project [8]. Because the NIS originally received permission from all patients to participate in data collection, and patient data in the NIS database were deidentified, signed informed consent of patients was waived for the present study.

Study population

The data of patients from the NIS database 2005–2014 with ICD-9 diagnostic code indicating renal transplantation status more than 1 year earlier (DXn=V420 & CHRONn=1) were included. Patients with the diagnosis of DM for more than 1 year prior to renal transplantation (DXn=250 & CHRONn=1) were excluded.

Main outcomes and variables

The NIS data of 96,699 patients with and without NODAT, defined as patients with DM (DXn=250 & CHRONn=0) within 1 year after renal transplantation, were analyzed to identify factors associated with post-transplantation renal cancer (ICD-9-CM=189.0) or renal failure (ICD-9-CM=5856, 5859, and 586).

The primary outcomes of this study were the diagnosis of renal cancer less than 1 year after transplantation, the stage of renal cancer, and occurrence of renal failure. The main independent variable was DM diagnosis within 1 year of renal transplantation or not. Other independent variables were patient demographic and clinical characteristics, including age, gender, race/ethnicity (grouped by NIS as White, Black, Hispanic, and others) and severity of illness and comorbidities (hypertension, metastases, obesity). Elixhauser comorbidity measures were assigned using AHRQ comorbidity software. Independent

hospital-provider variables included hospital bed count (small, medium, large), hospital census region (Northeast, Midwest, South, West) and hospital location/teaching status (rural hospital, urban teaching hospital, urban nonteaching hospital).

Statistical analysis

Differences in categorical variables between NIS patients discharged with and without NODAT were determined using the Rao-Scott chi-square test, and differences in a single continuous variable (age) was examined using the Complex Samples General Linear Model (CSGLM). Demographic data and outcome measurements are expressed as mean \pm standard error for continuous variables, and unweighted counts (weighted%) for categorical variables. Univariate and multivariate logistic regression models were used to determine the factors associated with renal cancer or renal failure in NIS discharges without NODAT. Statistically significant variables (P value <0.05) in univariate analysis were entered into multivariate logistic regression analysis. Since the NIS database is a 20% sample of United States yearly inpatient admissions, weighted samples (DISCWT), stratum (NIS_STRATUM), and cluster (HOSPID) were used to produce national estimates for all analyses. All statistical assessments were 2-sided and evaluated at the 0.05 level of significance. Statistical analyses were performed using the statistical software package SPSS complex sample module version 22.0 (IBM Corp, Armonk, NY, USA).

Results

Study population

The data of 184,218 hospitalized patients in the United States during 2005–2014 who had undergone renal transplantation more than 1 year earlier were identified in the NIS and were eligible for inclusion in this study. After excluding 87,549 patients with a discharge diagnosis of DM more than 1 year prior to renal transplantation, the data of 96,669 patients were included in the analysis. Using discharge weights, the analytic sample size ($n=96,669$) was equivalent to a population-based sample size of 479,753 patients (Figure 1).

Patient demographic and clinical characteristics

The mean age was 50.1 ± 0.24 years and the majority of patients were male (53.5%) and White (60.9%). During the 10-year period from 2005–2014, there were 131 patients (weighted $n=637$) with NODAT diagnosis and 96 538 patients (weighted $n=479,116$) without NODAT diagnosis. Differences in patient demographics and baseline characteristics between patients with and without NODAT are shown in Table 1. Significant differences were found in age and race between patients with and

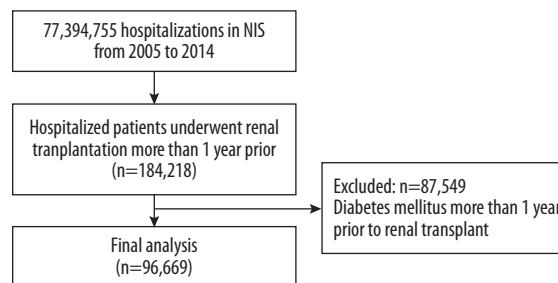


Figure 1. Flowchart of the study population.

without NODAT (both $P < 0.001$). All 131 patients with NODAT had been hospitalized in west coast hospitals (Table 1).

Table 2 shows the rates of renal cancer and renal failure between NIS patients with and without NODAT. No significant differences were found in rates of renal cancer and renal failure between the 2 groups (0% in NODAT patients, 0.3% in those without NODAT, $n=255$). The rate of renal failure was 0.8% ($n=1$) in patients with NODAT and 0.3% ($n=314$) in those without NODAT (Table 2).

Table 3 shows factors associated with renal cancer or renal failure in NIS patients without NODAT. Univariate analysis revealed that age, gender, race, severity, hypertension, and location were significantly associated with renal cancer. The results of multivariate regression analysis of renal cancer revealed that older age (OR, 1.030; 95% CI: 1.023 to 1.036), male (OR, 1.872; 95% CI: 1.409 to 2.486), Black (OR, 2.199; 95% CI: 1.574 to 3.071) and urban teaching hospitals were associated with increased risk of RCC. However, extreme loss of function (OR, 0.462; 95% CI: 0.260 to 0.822) and having hypertension (OR, 0.295; 95% CI: 0.225 to 0.388) were significantly associated with lower risk of renal cancer in discharges without NODAT (Table 3).

Univariate logistic regression analysis showed that age, severity, hypertension, hospital size (by bed count), and region of the United States were significantly associated with renal failure. Multivariable analysis indicated that older age (OR, 0.980; 95% CI: 0.975 to 0.985) and having hypertension (OR, 0.077; 95% CI: 0.053 to 0.112) were associated with lower risk of renal failure. Patients from hospitals with large and medium bed counts were associated with higher risk of renal failure among discharges without NODAT (OR, 1.391; 95% CI: 1.057 to 1.830) (Table 4).

Table 1. Baseline demographic and clinical characteristics between NIS discharges with and without new-onset diabetes mellitus after kidney transplantation (Unweighted n=96,669, Weighted N=479,753)^a.

Variables	Without NODAT (n=96,538)	With NODAT (n=131)	P-value
Age (years)	50.1± 0.2	57.0± 1.0	<0.001*
Gender, n (%)			
Male	51597 (53.5%)	77 (58.9%)	0.128
Female	44882 (46.5%)	54 (41.1%)	
Race, n (%)			
White	49611 (61.0%)	48 (36.7%)	<0.001*
Black	16226 (19.9%)	14 (10.7%)	
Hispanic	10134 (12.4%)	54 (42.2%)	
Others	5453 (6.7%)	14 (10.3%)	
Severity, n (%)			
Non-extreme	86633 (89.8%)	116 (89.0%)	0.681
Extreme	9849 (10.2%)	15 (11.0%)	
Comorbidity, n (%)			
Hypertension	62881 (65.1%)	97 (73.3%)	0.051
Metastatic cancer	1181 (1.2%)	1 (0.8%)	0.603
Solid tumor without metastasis	1142 (1.2%)	1 (0.8%)	0.624
Obesity	5014 (5.2%)	11 (8.6%)	0.257
Hospital size by bed count, n (%)			
Small	8548 (8.6%)	12 (9.8%)	0.119
Medium	19212 (20.1%)	51 (39.8%)	
Large	68225 (71.3%)	68 (50.5%)	
Hospital census region n (%)			
Northeast	18722 (20.0%)	0	0.096
Midwest	23981 (25.1%)	0	
South	34170 (34.9%)	0	
West	19665 (20.0%)	131 (100%)	
Hospital location, n (%)			
Rural	6345 (6.6%)	3 (2.1%)	0.125
Urban, non-teaching	26359 (27.2%)	59 (43.0%)	
Urban, teaching	63281 (66.3%)	69 (54.9%)	

^a Data are weighted according to the National Inpatient Sample protocol. Values are unweighted counts (weighted%). * Significant difference between groups, P<0.05. NODAT – new-onset diabetes mellitus after kidney transplantation.

Table 2. Outcomes between NIS discharges with and without new-onset diabetes mellitus after kidney transplantation (Unweighted n=96,669, Weighted N=479,753)^a.

Variables	Without NODAT (n=96,538)	With NODAT (n=131)	P-value
Renal cancer, n (%)			
No	96,283 (99.7%)	131 (100.0%)	0.732
Yes	255 (0.3%)	0	
Renal failure, n (%)			0.459
No	96,224 (99.7%)	130 (99.2%)	
Yes	314 (0.3%)	1 (0.8%)	

^a Data were weighted according to the National Inpatient Sample protocol. Values were unweighted counts (weighted%).
NODAT – new-onset diabetes mellitus after kidney transplantation.

Discussion

In the present study, analysis of inpatient data of post-transplantation patients in the NIS database from 2005 to 2014 showed that 131 inpatients were diagnosed with NODAT among over 90 thousand inpatients in participating hospitals in the United States. Most NODAT patients were male and White, and all had been hospitalized in the western region of the United States. Significant differences were found in age and race between patients with and without NODAT. However, no significant differences were found in rates of RCC and renal failure between the 2 groups; the rate of renal failure was only 0.8% (0 out of 131) in patients with NODAT and 0.3% (1 out of 96 538) in those without NODAT. Risk factors associated with renal cancer in NIS patients without NODAT were older age, male gender, Black, and hospitalized in urban teaching hospitals. Age, severity, hypertension, hospital size (by bed count), and region of the United States were significantly associated with renal failure in those without NODAT. Risk factors for NODAT were not apparent given the exceptionally low case numbers.

Underlying our hypothesis that a relationship may exist between NODAT and RCC and/or renal failure, is the knowledge that DM is a risk factor for RCC and renal failure [2–4]. One study of hospitalized DM patients reported increased risk for several cancers, including RCC, but the increased risk of kidney cancer was confounded by obesity [10]. Lindblad et al. [11] reported a 50% increased risk of RCC in males and females with diagnosed DM without regard to differences in age, DM duration, or the presence of other risk factors such as obesity and hypertension; those authors concluded that DM was indeed a risk factor for RCC but may be part of the causal pathway in conjunction with other risk factors rather than being an independent risk factor. In the present study of renal transplantation patients, the renal failure rate was 0.8% in NODAT patients (n=1) versus 0.3% in those without NODAT (n=314),

with no significant differences found in rates of RCC between the groups. Even without considering the possible influence of NODAT, risk of RCC in renal transplantation patients is already 5- to 7-fold higher than in the general population and is associated with significantly increased post-transplantation morbidity and mortality [3]. Patients with end-stage renal disease (ESRD) undergoing renal transplantation are at a 2-fold increased risk of malignancy compared to the general population [12]. RCC incidence in allograft kidneys is fairly low (0.19–0.5%) but when compared to the general population, the risk of developing this solid malignancy is 10-fold [12]. Therefore, considering that kidney damage and dysfunction in patients with DM may progress to ESRD and renal failure, and RCC risk is increased in kidney transplant recipients, results of the present study suggest that NODAT is more likely related to the overall morbidity and mortality of kidney transplant recipients rather than being an independent risk factor for RCC and renal failure.

In the present study, patients with hypertension appeared to have a lower risk of renal failure (OR, 0.077; 95% CI: 0.053 to 0.112; see Table 4). An explanation for this trend may be found in previous review studies [13,14]. Patients with both diabetes and hypertension are well recognized as having an increased risk of cardiovascular and renal events if the underlying conditions are not controlled effectively [13]. Tighter blood pressure control can reduce progression of renal disease by 30% to 50% [14]. Measures to prevent the onset of kidney dysfunction include reducing hypertension through appropriate therapies as a means to slow the progression of renal parenchymal injury [13]; initial stages of effective blood pressure control may produce hypoperfusion of the kidneys and elevate creatinine levels, but this was not apparent in results of the present study. Therefore, we must assume that hypertensive patients in the NIS database used in the present study were already being treated prior to transplantation unrelated to developing NODAT.

Table 3. Odds ratios for probability of renal cancer in discharges without NODAT (n=96,538, weighted n=479,116).

	Crude OR (95%CI)	Adjusted OR (95%CI)
Age	1.020 (1.014, 1.026)	1.030 (1.023, 1.036)
Gender		
Male vs. Female	2.079 (1.590, 2.718)	1.872 (1.409, 2.486)
Race		
Black vs. White	1.896 (1.372, 2.622)	2.199 (1.574, 3.071)
Hispanic vs. White	1.113 (0.692, 1.793)	1.434 (0.887, 2.319)
Others vs. White	1.434 (0.813, 2.528)	1.608 (0.911, 2.839)
Severity		
Extreme vs. non-extreme	0.500 (0.288, 0.869)	0.462 (0.260, 0.822)
Hypertension		
Yes vs. no	0.382 (0.296, 0.493)	0.295 (0.225, 0.388)
Metastatic cancer		
Yes vs. no	0.998 (0.331, 3.003)	
Solid tumor without metastasis		
Yes vs. no	–	
Obesity		
Yes vs. no	1.128 (0.673, 1.891)	
Hospital size by bed count		
Medium vs. small	0.827 (0.426, 1.607)	
Large vs. small	1.240 (0.705, 2.179)	
Hospital census region		
Midwest vs. Northeast	0.974 (0.618, 1.533)	
South vs. Northeast	0.933 (0.608, 1.433)	
West vs. Northeast	0.900 (0.568, 1.429)	
Hospital location		
Urban non-teaching vs. rural	1.592 (0.533, 4.761)	1.153 (0.381, 3.493)
Urban teaching vs. rural	4.344 (1.514, 12.465)	3.581 (1.239, 10.348)

Significant values in bold (P<0.05). ‘–’ – cannot be detected; NODAT – new-onset diabetes mellitus after kidney transplantation.

Besides the main purpose for this study, we also aimed to identify risk factors associated with RCC and renal failure in transplantation patients with and without NODAT. Our results for associations between age, race, and gender and the diagnosis of NODAT were compatible with the results of previous studies. First, significant differences were found in age and race between patients with and without NODAT, agreeing with the results of other investigators. In the general United States population, risk factors for RCC include male gender, African American heritage, obesity, smoking tobacco, and hypertension, among others; in renal transplant patients, risk factors also include age and chronic kidney disease or obstruction, but not smoking [15].

RCC in patients who have undergone kidney transplantation occurs more often in the native kidney than in the renal allograft, although the reasons for this are not fully understood; risk factors that have been suggested including the type of immunosuppressant and the duration of immunosuppressive treatment, chronic native kidney disease, recipient’s age, and pre-transplantation dialysis duration [16]. While the etiology of increased risk of RCC remains elusive, and data are lacking on epidemiology and management of this solid renal mass in both native and allograft kidneys [12], the chronic immunosuppressed state of transplantation patients has been suggested to be an associated factor [17].

Table 4. Odds ratios for probability of renal failure in discharges without NODAT (n=96,538, weighted n=479,116).

	Crude OR (95%CI)	Adjusted OR (95%CI)
Age	0.967 (0.962, 0.972)	0.980 (0.975, 0.985)
Gender		
Male vs. Female	1.210 (0.962, 1.522)	
Race		
Black vs. White	1.196 (0.877, 1.631)	
Hispanic vs. White	1.434 (1.006, 2.045)	
Others vs. White	0.958 (0.535, 1.716)	
Severity		
Extreme vs. non-extreme	0.606 (0.384, 0.956)	0.701 (0.434, 1.132)
Hypertension		
Yes vs. no	0.068 (0.048, 0.097)	0.077 (0.053, 0.112)
Metastatic cancer		
Yes vs. no	0.538 (0.132, 2.187)	
Solid tumor without metastasis		
Yes vs. no	0.220 (0.031, 1.569)	
Obesity		
Yes vs. no	0.767 (0.448, 1.312)	
Hospital size by bed count		
Medium vs. small	1.253 (0.836, 1.879)	1.203 (0.810, 1.785)
Large vs. small	1.447 (1.088, 1.926)	1.391 (1.057, 1.830)
Hospital census region		
Midwest vs. Northeast	1.216 (0.832, 1.776)	1.154 (0.802, 1.662)
South vs. Northeast	1.125 (0.785, 1.613)	1.107 (0.779, 1.574)
West vs. Northeast	1.517 (1.035, 2.224)	1.341 (0.919, 1.958)
Hospital location		
Urban non-teaching vs. rural	0.746 (0.450, 1.235)	
Urban teaching vs. rural	0.902 (0.563, 1.445)	

Significant values in bold (P<0.05). NODAT – new-onset diabetes mellitus after kidney transplantation.

The Consensus on Managing Modifiable Risk in Transplantation (COMMIT) committee recognized that NODAT was associated with patient survival and graft rejection as well as a cause of infection, listing it in a screening checklist for transplantation candidates [18]. Although much remains to be learned about risk of RCC and renal failure after transplantation, results of our present study and those of other authors have emphasized that screening for possible risk factors for NODAT, RCC, and renal failure in renal transplantation candidates is essential to achieve the best long-term outcomes.

Strengths and limitations

The present study was strengthened by using the NIS database, which is the largest all-payer inpatient care database available publicly in the United States. It contains data from about 8 million hospital stays in more than 1,000 hospitals in 45 states participating in HCUP. The NIS database includes all patient discharges from sampled hospitals within a defined time period, comprising a 20% stratified sample of community hospitals in the United States. Nevertheless, this study had certain limitations, including the use of a secondary database and retrospective analysis, which may limit the interpretation

and reliability of data. For example, in a study that used ICD-9 codes from the NIS to determine the final pathologic diagnosis of myasthenia gravis patients who underwent thymectomy, estimates of associations between preoperative risk factors and the use of mechanical ventilation were derived from a 20% sample, and these study results may still be under- or over-represented [19]. The present study also relied on ICD-9 diagnosis codes. In such studies, the reliability of the NIS data is dependent on the accuracy of hospital coders who review the pathology report and assign the appropriate diagnosis code. Regardless of this possible drawback, the NIS database has been used extensively to examine national health care trends, and NIS-related reports have shown that errors in ICD-9 coding are limited [20]. As an additional limitation, many variables known to increase risk of developing RCC (e.g., pre-transplantation dialysis vintage, acquired cystic disease in native kidneys) were not available in the NIS data and may have influenced our results. Also, certain unmeasured confounders could not be accounted for in the present study, including lifestyle and behavior factors (e.g., smoking status), environmental exposure, family history, and clinical laboratory data, none of which were included in the NIS database. Additionally, the database only includes the data of hospitalized patients and the absence of outpatient data or data of deceased patients may affect final results. In the present study, NODAT was reported in only 131 of 96,669 study participants, which is lower than reported in the literature and may reflect under-reporting in the database. Because the NIS database provides only inpatient outcomes

included in discharge data, findings from the present study cannot address long-term health status and the need for additional hospitalizations or procedures in the future. Further long-term prospective study is needed to confirm results of the present study and to provide additional information on the associations between NODAT, RCC, and renal failure in renal transplant recipients who had not previously been diagnosed with DM.

Conclusions

Analysis of over 90,000 NIS hospitalizations with diagnosis-coded kidney transplantation suggested that NODAT may not be an independent risk factor for RCC and renal failure. Further study is still warranted to examine the possible role of NODAT in the multifactorial development of RCC and renal failure in renal transplantation patients.

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Conflicts of interest

None.

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