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Type 2 Diabetes Mellitus and Adverse In-Hospital Outcomes after Nephroureterectomy

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Keywords
National inpatient sample · Upper tract urothelial cancer · Insulin dependence · Perioperative risk · Complications · Propensity score matching

Abstract

Introduction: The effect of insulin dependence in type 2 diabetes mellitus (T2DM) on adverse in-hospital outcomes after nephroureterectomy (NU) for upper tract urothelial carcinoma (UTUC) is unknown. ***Methods:*** Descriptive statistics, propensity score matching (PSM), and multivariable regression models were applied to the National Inpatient Sample (2004–2019) UTUC patients treated with NU. T2DM was stratified between insulin-dependent (ID) and non-insulin-dependent (NID) subtypes. ***Results:*** In 10,761 NU patients, rates of ID-T2DM, and NID-T2DM were 2.7% and 19.1%, respectively. During the study period, ID-T2DM rates increased from 0.1 to 4.2% (estimated annual percentage change [EAPC]: +11.8%, $p < 0.001$), whereas NID-T2DM rates increased from 13.6 to 18.0% (EAPC: +1.1%, $p = 0.045$). After PSM, ID-T2DM patients (294 vs. 588 nondiabetic controls) exhibited higher rates of blood transfusions (+4.9%) and genitourinary complications (+7.8%), as well as higher total hospital charges (THCs; +9.3%). After multivariable adjustment, these increases translated into higher odds of blood transfusions (odds ratio [OR]: 1.88, $p = 0.008$) and genitourinary complications (OR: 1.40, $p = 0.027$), as well as higher

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THCs (incidence rate ratio [IRR]: 1.08, $p < 0.001$). NID-T2DM patients (2,051 vs. 4,102 nondiabetic controls) exhibited smaller increases in blood transfusions (+2.5%) and THC (+5.3%), corresponding to OR 1.28 ($p = 0.002$) and IRR 1.05 ($p < 0.001$), respectively. ***Conclusion:*** Although ID-T2DM represents a relatively small subgroup, its rates increased over time. ID-T2DM was associated with higher rates of blood transfusions, genitourinary complications, and increased THC after NU. These findings suggest that ID-T2DM patients undergoing NU may represent a potential target population for perioperative optimization to reduce surgical morbidity and resource utilization.

Introduction

Rates of type 2 diabetes mellitus (T2DM) in North America are rising, and a substantial proportion of patients undergoing major urologic cancer surgery may harbor T2DM [1–3]. Previous studies in diabetology have identified insulin-dependent (ID) T2DM as a risk factor for worse long-term outcomes compared to non-insulin-dependent (NID) T2DM, including significantly higher all-cause and cardiovascular mortality [4, 5]. Furthermore, emerging evidence from several surgical disciplines indicates that insulin dependence may represent an important modifier of perioperative risk [6–9]. In the context of urologic oncology, recent work in kidney cancer patients undergoing partial or radical nephrectomy demonstrated that T2DM, particularly ID-T2DM, was associated with increased rates of adverse in-hospital outcomes [3]. However, whether T2DM and insulin dependence are associated with adverse in-hospital outcomes after nephroureterectomy (NU) for upper tract urothelial carcinoma (UTUC) remains unknown [10]. Patients undergoing NU differ substantially from kidney cancer patients undergoing nephrectomy with respect to age, comorbidity burden, smoking exposure, baseline renal function, and procedure-specific perioperative risks [11–15]. Moreover, NU combines extirpative surgery of both the kidney and upper urinary tract and is associated with distinct postoperative complications and patterns of resource utilization [11–15]. Consequently, the perioperative impact of T2DM and insulin dependence observed in nephrectomy patients cannot be assumed to apply to the UTUC population undergoing NU.

We therefore investigated the perioperative implications of T2DM, stratified according to insulin-dependent status, in patients undergoing NU for UTUC using a large contemporary cohort derived from the National Inpatient Sample (NIS) database. Given the structure and purpose of the NIS database, which captures events during the index hospitalization, the present analysis focuses on adverse in-hospital outcomes as clinically relevant, short-term endpoints [16]. We hypothesized that patients with T2DM may experience higher rates of adverse in-hospital outcomes after NU for UTUC. Additionally, we hypothesized that the magnitude of perioperative risk may differ according to insulin-dependent status.

Materials and Methods

Data Source and Study Population

Relying on discharge data from the NIS 2004 to 2019, we assessed perioperative complications, length of stay, and in-hospital mortality of UTUC patients treated with NU within the USA. NIS is a set of longitudinal hospital inpatient databases included in the Healthcare Cost and Utilization Project (HCUP) [16].

All diagnoses and procedures were coded using the International Classification of Disease (ICD), 9th revision (ICD-9), Clinical Modification, ICD 10th revision (ICD-10), Clinical Modification, or ICD-10 Procedure Coding System. In accordance with previously reported methodology, we identified patients aged ≥18 years with a primary diagnosis of nonmetastatic UTUC and who were treated with NU [11, 12]. Patients were stratified according to the diagnosis of T2DM and insulin-dependent status [3, 7, 17]. Patients with other or unknown forms of diabetes were excluded.

Outcomes of Interest

The primary objective of the study was to evaluate the association between T2DM status and adverse in-hospital outcomes after NU. Evaluated outcomes included overall complications, intraoperative complications, postoperative complications, critical care therapies, blood transfusions, cardiovascular complications, pulmonary complications, genitourinary complications, gastrointestinal complications, infectious complications and neurologic complications, identified by ICD-9 and ICD-10 codes following previously established methodology [13, 17–19]. In addition, in-hospital mortality, prolonged length of stay (exceeding the third quartile for the cohort; >6 days), and total hospital charges (THCs) were assessed [13]. THC were obtained directly from the NIS and were based on accounting reports in accordance with the NIS methodological guidelines [16]. THC values are reported in inflation-adjusted 2016 US dollars (USD)

using the Consumer Price Index from the US Bureau of Labor Statistics [20]. We relied on the coding algorithms by Quan et al. [21] to define comorbidities using ICD-9 and ICD-10 codes. The Deyo adaption of the Charlson Comorbidity Index (CCI) was applied, excluding T2DM from the calculation [22]. The covariables included age (in years), sex (male vs. female), race/ethnicity (Caucasian vs. non-Caucasian), CCI (0–1 vs. ≥2), obesity (yes vs. no), year of surgery, minimally invasive surgery (yes vs. no), and hospital size (large vs. medium vs. small; defined by bed count specific to region, urban or rural location, and teaching-hospital status) [16]. According to the World Health Organization, obesity was defined as a body mass index exceeding 30 kg/m^2 [23].

Statistical Analyses

For continuously coded variables, medians and interquartile ranges were calculated. For categorically coded variables, absolute frequencies and proportions were determined. Wilcoxon rank-sum and Pearson chi-squared tests assessed differences between ID-T2DM and NID-T2DM patients compared to nondiabetic patients. The estimated annual percentage changes (EAPCs) of ID-T2DM and NID-T2DM rates were calculated using least-squares linear regression. To minimize bias and confounding, we applied propensity score matching (PSM) in 2 separate analytical steps. First, PSM was applied between ID-T2DM patients and nondiabetic controls. Second, it was reapplied between NID-T2DM patients and nondiabetic controls. PSM relied on patient age, sex, race/ethnicity, CCI, obesity status, year of surgery, and minimally invasive procedure as matching covariates and was performed using nearest neighbor PSM in a 1:2 ratio without replacement and without caliper restriction. Covariate balance after matching was assessed using standardized mean differences, with values <0.1 considered indicative of adequate balance. Multivariable logistic and Poisson regression models predicting adverse in-hospital outcomes and adjusting for patient age, sex, race/ethnicity, CCI, obesity status, year of surgery, minimally invasive procedure, and hospital size were fitted [24]. The analysis followed the NIS reporting guidelines. Therefore, absolute counts for samples <11 could not be reported [16]. R software was used for statistical computing and graphics (R version 4.4.1, The R Foundation for Statistical Computing, Vienna, Austria). All tests were two-sided, with statistical significance set at $p < 0.05$. Given the exploratory nature of the study and the evaluation of multiple clinically relevant outcomes, emphasis was placed on effect estimates and corresponding 95% confidence intervals (CIs) rather than statistical significance alone [25].

Results

Descriptive Characteristics of the Study Population

Within the NIS (2004–2019), we identified 10,761 UTUC patients treated with NU (Table 1). Of them, 294 (2.7%) had ID-T2DM and 2,051 (19.1%) had NID-T2DM. From 2004 to 2019, the rates of ID-T2DM increased 42-fold from 0.1 to 4.2% (EAPC: +11.8%, $p < 0.001$), whereas the rates of NID-T2DM increased 1.3-fold from 13.6 to 18.0% (EAPC: +1.1%, $p = 0.045$, Fig. 1).

Before PSM, male sex was more frequent among patients with ID-T2DM (68.4%) and NID-T2DM (64.7%) compared with nondiabetic patients (60.1%). A lower proportion of Caucasian patients was observed among patients with ID-T2DM (77.9%) and NID-T2DM (80.6%) compared with nondiabetic patients (86.7%). CCI ≥2 was recorded in 57.8% of ID-T2DM patients and 44.9% of NID-T2DM patients compared with 33.6% among nondiabetic patients. Similarly, obesity occurred in 30.6% of ID-T2DM patients and 18.0% of NID-T2DM patients compared with 7.3% among nondiabetic patients. Minimally invasive procedures were more frequently performed in patients with ID-T2DM compared with nondiabetic patients (49.3% vs. 39.0%), whereas rates in NID-T2DM patients (36.7%) did not differ significantly from nondiabetic patients. No relevant differences were observed in hospital size distribution or patient age.

Propensity Score Matching

We applied PSM in 2 separate analytical steps. First, 294 of 294 patients with ID-T2DM (100%) were matched in 1:2 fashion with 588 of 8,416 nondiabetic controls (7.0%). Second, 2,051 of 2,051 patients with NID-T2DM (100%) were matched in 1:2 fashion with 4,102 of 8,416 nondiabetic controls (48.7%). After PSM, all covariates were well balanced, with post-matching standardized mean differences <0.1 for all matching variables (Table 2).

ID-T2DM vs. Adverse In-Hospital Outcomes

Patients with ID-T2DM exhibited significantly higher rates in 3 of 13 examined categories compared with their nondiabetic counterparts (Table 3), namely blood transfusions (+4.9%), genitourinary complications (+7.8%), and higher THC (+9.3%, +6,004 USD, all $p < 0.05$). After multivariable adjustment, these absolute increases translated into higher odds of blood transfusions (odds ratio [OR]: 1.88, 95% CI: 1.18–3.01, $p = 0.008$) and genitourinary complications (OR: 1.40, 95% CI: 1.04–1.89, $p = 0.027$), as well as higher THC (incidence rate ratio [IRR]: 1.08, 95% CI: 1.07–1.08, $p < 0.001$).

Table 1. Descriptive characteristics of UTUC patients undergoing NU, stratified according to T2DM and insulin dependence, before PSM

Characteristic	Overall, n = 10,761	ID-T2DM patients, n = 294 (2.7%)	p value[1]	NID-T2DM patients, n = 2,051 (19.1%)	p value[1]	Nondiabetic patients, n = 8,416 (78.2%)
Age, median (IQR), years	72 (65, 79)	71 (65, 77)	0.3	73 (67, 79)	<**0.001**	72 (64, 79)
Male sex, n (%)	6,589 (61.2)	201 (68.4)	**0.005**	1,327 (64.7)	<**0.001**	5,061 (60.1)
Caucasian race/ethnicity, n (%)	9,177 (85.3)	229 (77.9)	<**0.001**	1,653 (80.6)	<**0.001**	7,295 (86.7)
Charlson Comorbidity Index[2], n (%)			<**0.001**		<**0.001**	
0–1	6,847 (63.6)	124 (42.2)		1,131 (55.1)		5,592 (66.4)
≥2	3,914 (36.4)	170 (57.8)		920 (44.9)		2,824 (33.6)
Obesity[3], n (%)	1,074 (10.0)	90 (30.6)	<**0.001**	369 (18.0)	<**0.001**	615 (7.3)
Year of surgery, median (IQR)	2013 (2008, 2016)	2016 (2012, 2017)	<**0.001**	2013 (2009, 2016)	**0.010**	2012 (2008, 2016)
Minimally invasive procedure, n (%)	4,180 (38.8)	145 (49.3)	<**0.001**	753 (36.7)	0.1	3,282 (39.0)
Hospital size[4], n (%)			0.3		0.5	
Large	6,800 (63.2)	180 (61.2)		1,271 (62.0)		5,349 (63.6)
Medium	2,611 (24.3)	69 (23.5)		507 (24.7)		2,035 (24.2)
Small	1,350 (12.5)	45 (15.3)		273 (13.3)		1,032 (12.3)

ID, insulin-dependent; IQR, interquartile range; NID, non-insulin-dependent; T2DM, type 2 diabetes mellitus. [1]Wilcoxon rank-sum test, Pearson's chi-squared test, Reference: nondiabetic patients, statistically significant values are shown in bold ($p < 0.05$). [2]The point contribution of CCI due to T2DM and metastatic disease was subtracted. [3]Body mass index >30 kg/m^2. [4]Defined by bed count; specific to region, urban or rural location, and teaching-hospital status.

NID-T2DM vs. Adverse In-Hospital Outcomes

Patients with NID-T2DM exhibited significantly higher rates in 2 of 13 examined categories compared with their nondiabetic counterparts (Table 4), namely, blood transfusions (+2.5%) and higher THC (+5.3%, +3,026 USD, all $p < 0.05$). After multivariable adjustment, these absolute increases translated into relative differences for blood transfusions (OR: 1.28, 95% CI: 1.09–1.49, $p = 0.002$) and THC (IRR: 1.05, 95% CI: 1.05–1.06, $p < 0.001$).

Discussion

No previous study evaluated T2DM as a risk factor for adverse in-hospital outcomes after NU for UTUC. We addressed this knowledge gap using the NIS database and made several noteworthy observations.

First, our investigation included 10,761 nonmetastatic UTUC patients who underwent NU. Among them, diagnosis of NID-T2DM was relatively frequent (19.1%), whereas the rate of ID-T2DM was substantially lower (2.7%). These observations are consistent with epidemiological data reporting a prevalence of 29.2% for T2DM regardless of insulin-dependent status among US citizens older than 65 years [2]. They also agree with a NIS-based analysis of kidney cancer patients undergoing partial or radical nephrectomy, where NID-T2DM was observed in approximately one fifth (20.0% and 20.9%) of patients and ID-T2DM represented a substantially smaller subgroup (3.5% and 3.4%, respectively) [3]. In that investigation of kidney cancer patients treated with nephrectomy, stratification according to insulin-dependent status allowed a granular assessment of the association between T2DM and adverse in-hospital outcomes and demonstrated that this distinction is important when examining the effect of T2DM. The present study relies on the same stratification and therefore is expected to provide robust observations addressing T2DM as a surgical risk factor in patients undergoing NU for UTUC.

Second, to the best of our knowledge, we provide the first report of temporal trends in rates of either ID-T2DM

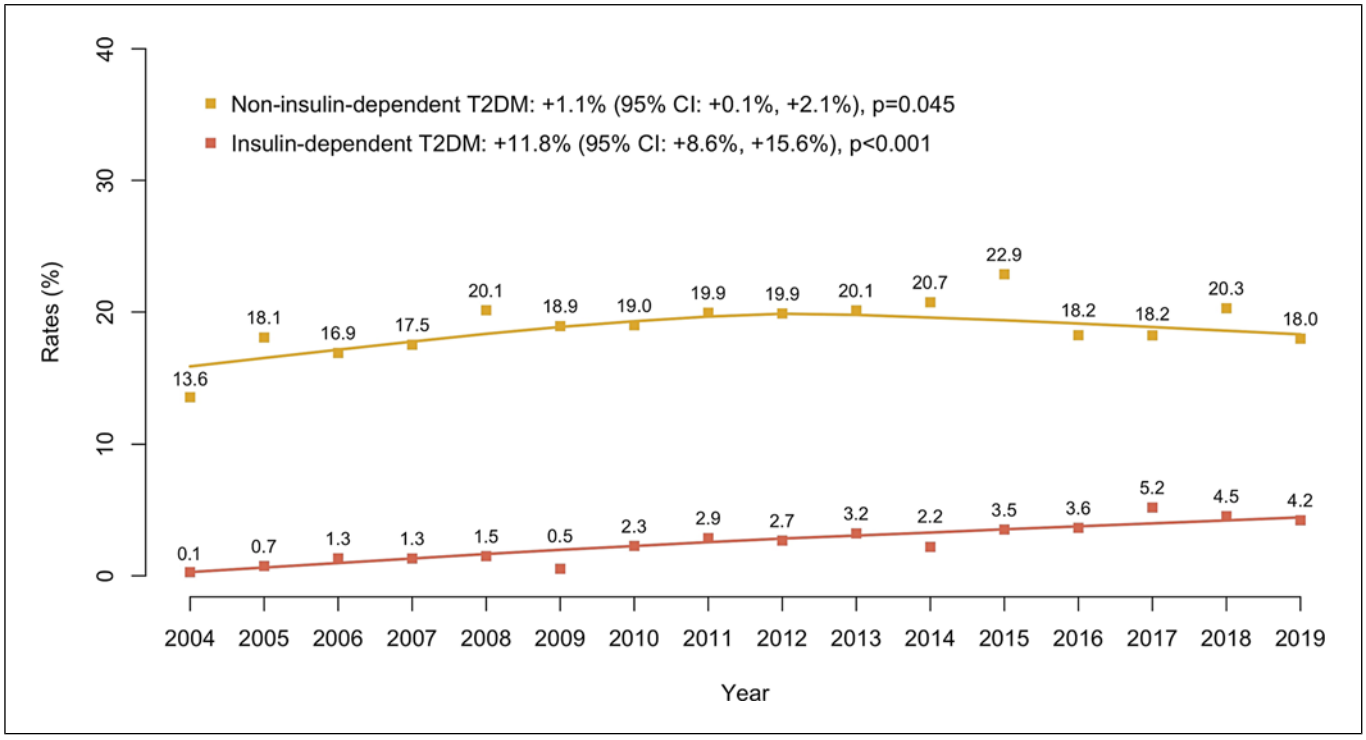

Fig. 1. Estimated annual percentage change of type 2 diabetes mellitus (T2DM) stratified according to insulin dependence in upper tract urothelial cancer patients undergoing nephroureterectomy within the National Inpatient Sample (NIS) from 2004 to 2019.

or NID-T2DM in NU patients. The rates increased significantly over time, with a steep slope for ID-T2DM (from 0.1 to 4.2%). Conversely, the increase of NID-T2DM was moderate (from 16.3 to 18.0%). These differences further support the relevance of stratification between ID-T2DM and NID-T2DM, as was done in the current study. The temporal trend observations regarding rates of ID-T2DM and NID-T2DM cannot be directly compared with previous studies addressing T2DM in NU patients. However, they can be interpreted in the context of findings in kidney cancer patients undergoing radical nephrectomy, where both ID-T2DM (0.3–6.3%) and NID-T2DM (17.4–21.6%) showed similar increases over time (2004–2019). In addition, ID-T2DM rates recorded in the current study are consistent with general US population data, where an increase in ID-T2DM rates from 0.7% in 2009 to 18.4% in 2018 (26-fold) was reported [26]. This trend may be attributed to the well-described increase of metabolic syndrome in the USA that, according to experts, is mainly driven by increased consumption of ultra-processed foods, sugary drinks, larger portion sizes, and physical inactivity [26, 27].

Third, we identified important differences that distinguished diabetic from nondiabetic patients. Diabetic patients were more frequently non-Caucasian, more frequently obese, and more frequently exhibited a CCI ≥2. Differences were more pronounced in ID-T2DM than in NID-T2DM patients. These findings are consistent with the current literature, as well as with epidemiological data from the USA [2, 28, 29]. Given these baseline imbalances, PSM was applied according to T2DM subtype (ID vs. NID) in 2 separate analytical steps, matching each group to nondiabetic controls. All covariates were well balanced after PSM.

Fourth, after PSM, multivariable logistic regression models were fitted to first test the effect of ID-T2DM vs. no T2DM. Subsequently, the same models were refitted to test the effect of NID-T2DM vs. no T2DM. The analyses demonstrated that ID-T2DM was associated with higher rates of selected adverse in-hospital outcomes after NU. Specifically, patients with ID-T2DM exhibited higher rates of blood transfusions (+4.9%) and genitourinary complications (+7.8%), which translated into increased odds of these events after multivariable adjustment (OR: 1.88 and 1.40). Notably, the categories

Table 2. Descriptive characteristics of upper tract urothelial cancer patients undergoing NU, stratified according to T2DM and insulin dependence, after 1:2 PSM

Characteristic	ID-T2DM patients, *n* = 294 (100% after PSM)[1]	Nondiabetic patients, *n* = 588 (7.0% after PSM)[1]	*p* value[2]	NID-T2DM patients, *n* = 2,051 (100% after PSM)[1]	Nondiabetic patients, *n* = 4,102 (48.7% after PSM)[1]	*p* value[2]
Age, median (IQR), years	71 (65, 77)	71 (65, 77)	>0.9	73 (67, 79)	73 (67, 80)	0.2
Male sex, *n* (%)	201 (68.4)	409 (69.6)	0.7	1,327 (64.7)	2,714 (66.2)	0.3
Caucasian race/ethnicity, *n* (%)	229 (77.9)	467 (79.4)	0.6	1,653 (80.6)	3,313 (80.8)	0.9
Charlson Comorbidity Index[3], *n* (%)			0.9			0.8
0–1	124 (42.2)	251 (42.7)		1,131 (55.1)	2,275 (55.5)	
≥2	170 (57.8)	337 (57.3)		920 (44.9)	1,827 (44.5)	
Obesity[4], *n* (%)	90 (30.6)	181 (30.8)	>0.9	369 (18.0)	677 (16.5)	0.3
Year of surgery, median (IQR)	2016 (2012, 2017)	2016 (2011, 2017)	0.2	2013 (2009, 2016)	2013 (2009, 2016)	0.1
Minimally invasive procedure, *n* (%)	145 (49.3)	303 (51.5)	0.5	753 (36.7)	1,490 (36.3)	0.8
Hospital size[5], *n* (%)			0.7			0.2
Large	180 (61.2)	369 (62.8)		1,271 (62.0)	2,621 (63.9)	
Medium	69 (23.5)	142 (24.1)		507 (24.7)	1,001 (24.4)	
Small	45 (15.3)	77 (13.1)		273 (13.3)	480 (11.7)	

ID, insulin-dependent; IQR, interquartile range; NID, non-insulin-dependent; PSM, propensity score matching; T2DM, type 2 diabetes mellitus. [1]PSM relied on patient age, sex, race/ethnicity, Charlson Comorbidity Index, obesity status, year of surgery, and minimally invasive procedure. [2]Wilcoxon rank-sum test, Pearson's chi-squared test, reference: nondiabetic patients, after PSM all covariates were well balanced with standardized mean differences <0.1. [3]The point contribution of CCI due to T2DM and metastatic disease was subtracted. [4]Body mass index >30 kg/m^2. [5]Defined by bed count; specific to region, urban or rural location, and teaching-hospital status.

affected in the current analysis correspond to those previously observed in kidney cancer patients undergoing partial or radical nephrectomy, where blood transfusions and genitourinary complications also represented the most consistently affected outcomes [3]. Although patients undergoing NU differ substantially from nephrectomy patients with respect to baseline characteristics and surgical context, the observed pattern of complications was similar. This observation suggests that the association between insulin dependence and perioperative morbidity may extend beyond a single urologic procedure and may reflect more general biological mechanisms related to diabetes severity. Patients with diabetes are known to exhibit altered microvascular perfusion, impaired wound healing, and a higher prevalence of anemia and chronic kidney disease, which may increase susceptibility to bleeding events, acute kidney injury, and urinary tract infections [8, 29–32]. These pathophysiological factors may partially explain the observed increase in transfusion rates and genitourinary complications in diabetic patients undergoing major renal surgery, since the genitourinary complication category primarily comprised acute kidney injury, urinary tract infections, and urinary retention. However, alternative or complementary explanations should be acknowledged, including unmeasured tumor-related factors, such as tumor stage or overall disease burden that are not captured in the NIS.

Fifth, the observed increase in adverse outcomes translated into higher THC, indicating that the clinical impact of T2DM is also reflected in increased resource utilization. This observation highlights that the influence of T2DM extends beyond perioperative morbidity and may also represent a relevant economic factor in the perioperative management of patients undergoing NU.

Table 3. Adverse in-hospital outcomes after NU, stratified according to presence of insulin-dependent type 2 diabetes mellitus or absence of any diabetes mellitus, after 1:2 PSM

Characteristic	ID-T2DM patients $n = 294$	Nondiabetic patients $n = 588$	Difference (Δ)[1]	Multivariable LRM OR/IRR (95% CI)[2]
Overall complications, *n* (%)	164 (55.8)	324 (55.1)	+0.7	1.00 (0.74–1.34)
Intraoperative complications, *n* (%)	15 (5.1)	41 (7.0)	−1.9	0.89 (0.58–1.13)
Postoperative complications, *n* (%)	163 (55.4)	316 (53.7)	+1.7	1.04 (0.78–1.40)
Blood transfusion, *n* (%)	40 (13.6)	51 (8.7)	**+4.9***	**1.88 (1.18–3.01)****
Cardiovascular complications, *n* (%)	34 (11.6)	66 (11.2)	+0.4	0.85 (0.53–1.36)
Pulmonary complications, *n* (%)	33 (11.2)	63 (10.7)	+0.5	1.15 (0.72–1.82)
Genitourinary complications, *n* (%)	120 (40.8)	194 (33.0)	**+7.8***	**1.40 (1.04–1.89)***
Gastrointestinal complications, *n* (%)	35 (11.9)	86 (14.6)	−2.7	0.83 (0.54–1.27)
Infectious complications, *n* (%)	<11 (<3.7)	14 (2.4)	<+1.3	1.06 (0.41–2.57)
Critical care therapies, *n* (%)	13 (4.4)	26 (4.4)	0.0	0.95 (0.46–1.89)
In-hospital mortality, *n* (%)	<11 (<3.7)	<11 (<1.9)	NA	NA
Length of stay >6 days[3], *n* (%)	62 (21.1)	117 (19.9)	+1.2	1.10 (0.76–1.58)
THCs (USD), median (IQR)	70,337 (46,262, 103,983)	64,333 (42,024, 94,601)	**+9.3% (+6,004)***	**1.08 (1.07–1.08)*****

CI, confidence interval; LRM, logistic regression model; IRR, incidence rate ratio; ID, insulin-dependent; OR, odds ratio; T2DM, type 2 diabetes mellitus. [1]Wilcoxon rank-sum test, Pearson's chi-square test. [2]Reference: matched nondiabetic patients; adjusted for patient age, sex, race/ethnicity, Charlson Comorbidity Index, obesity status, year of surgery, minimally invasive procedure and hospital size. [3]Exceeding the third quartile for the cohort. *$p < 0.05$. **$p < 0.01$. ***$p < 0.001$, statistically significant values are shown in bold ($p < 0.05$).

Finally, no significant association was observed between either ID-T2DM or NID-T2DM on use of critical care therapies or in-hospital mortality. This finding suggests that while T2DM contributes to postoperative morbidity, it does not appear to translate into escalated therapeutic intensity or short-term mortality.

Taken together, these observations suggest that ID-T2DM represents a marker associated with higher adverse in-hospital outcomes after NU for UTUC. Notably, the most affected outcome categories in the current study, namely, blood transfusions and genitourinary complications, are the same as previously observed in kidney cancer patients undergoing partial or radical nephrectomy. This consistency suggests that ID-T2DM may exert comparable perioperative effects across different types of major renal surgery, including the distinct uro-oncological population of UTUC patients treated with NU. In contemporary clinical practice, radical NU remains the standard treatment for patients with localized high-risk UTUC, and current guidelines emphasize the importance of structured perioperative management [14, 15]. Against this background, identification of patient subgroups at increased risk of adverse in-hospital outcomes may contribute to a more individualized approach to structured perioperative management. Accordingly, patients with ID-T2DM undergoing NU may represent a potential target population for perioperative optimization to reduce the observed detrimental effects. Tailored prehabilitation, minimized fasting periods, and enhanced perioperative monitoring have been suggested as feasible and effective approaches [33–35]. Given that ID-T2DM patients represent a relatively small subgroup in patients undergoing NU, only a

Table 4. Adverse in-hospital outcomes after NU, stratified according to presence of NID-T2DM or absence of any diabetes mellitus, after 1:2 PSM

Characteristic	NID-T2DM patients, *n* = 2,051	Nondiabetic patients, *n* = 4,102	Difference (Δ)[1]	Multivariable LRM OR/IRR (95% CI)[2]
Overall complications, *n* (%)	1,110 (54.1)	2,224 (54.2)	−0.1	1.00 (0.90–1.12)
Intraoperative complications, *n* (%)	194 (9.5)	442 (10.8)	−1.3	0.88 (0.73–1.05)
Postoperative complications, *n* (%)	1,090 (53.1)	2,185 (53.3)	−0.2	1.00 (0.90–1.11)
Blood transfusion, *n* (%)	314 (15.3)	526 (12.8)	**+2.5**	**1.28 (1.09–1.49)****
Cardiovascular complications, *n* (%)	195 (9.5)	387 (9.4)	+0.1	0.96 (0.79–1.16)
Pulmonary complications, *n* (%)	237 (11.6)	459 (11.2)	−0.4	1.03 (0.87–1.22)
Genitourinary complications, *n* (%)	682 (33.3)	1,353 (33.0)	+0.3	1.02 (0.91–1.14)
Gastrointestinal complications, *n* (%)	295 (14.4)	619 (15.1)	−0.7	0.96 (0.82–1.11)
Infectious complications, *n* (%)	36 (1.8)	75 (1.8)	0.0	0.94 (0.62–1.40)
Critical care therapies, *n* (%)	107 (5.2)	180 (4.4)	+0.8	1.19 (0.93–1.53)
In-hospital mortality, *n* (%)	18 (0.9)	60 (1.5)	−0.6	0.65 (0.37–1.08)
Length of stay >6 days[3], *n* (%)	519 (25.3)	1,029 (25.1)	+0.4	1.04 (0.91–1.18)
THCs (USD), median (IQR)	60,530 (41,080, 95,536)	57,504 (39,584, 90,615)	**+5.3% (+3,026)****	**1.05 (1.05–1.06)*****

CI, confidence interval; LRM, logistic regression model; IRR, incidence rate ratio; NID, non-insulin-dependent; OR, odds ratio; T2DM, type 2 diabetes mellitus. [1]Wilcoxon rank-sum test, Pearson's chi-square test. [2]Reference: matched nondiabetic patients; adjusted for patient age, sex, race/ethnicity, Charlson Comorbidity Index, obesity status, year of surgery, minimally invasive procedure and hospital size. [3]Exceeding the third quartile for the cohort. *$p < 0.05$. **$p < 0.01$. ***$p < 0.001$, statistically significant values are shown in bold ($p < 0.05$).

limited number of individuals need to be identified and managed to potentially prevent a meaningful number of complications, which renders such optimization efforts clinically and economically feasible. In contrast, in patients with NID-T2DM undergoing NU, the efficient implementation of population-level health interventions may be limited given the higher prevalence of NID-T2DM and its weaker association with adverse in-hospital outcomes.

Several limitations require acknowledgment. First, our study shares the limitations of all similar studies that were based on the NIS database and relied on a retrospective data analysis [16, 36, 37]. The reliance on administrative coding may introduce potential biases, including misclassification of diagnoses and procedures. Second, the lack of data on tumor size, stage, and grade, as well as operative details such as surgeon or institutional volume, limits our ability to adjust for tumor-related and operative factors that may influence perioperative risk and introduces the potential for residual confounding. Third, detailed T2DM metrics, including HbA1c levels, are not available. A continuously coded HbA1c variable would have enabled a more granular assessment. However, the NIS provides T2DM classification in categorical form only, limiting such analysis. Fourth, insulin dependence should be interpreted as a surrogate marker of disease severity rather than a direct causal factor. In addition to reflecting greater disease severity or metabolic instability, insulin use may also capture disease duration, renal dysfunction, socioeconomic factors, or evolving treatment practices. As such, the observed associations

reflect risk stratification within the constraints of an observational study design and cannot establish causality. Moreover, the pronounced temporal increase in insulin-dependent T2DM observed in this study may in part reflect changes in coding practices and documentation over time, including the transition from ICD-9 to ICD-10, rather than true epidemiologic shifts alone. Finally, the present study was exploratory in nature and evaluated multiple clinically relevant perioperative outcomes. Therefore, the findings should be interpreted as hypothesis-generating and warrant validation in future datasets.

Statement of Ethics

This study is based on the NIS database, which includes only de-identified patient information. According to institutional policy, analyses of de-identified data do not require Institutional Review Board approval or informed consent. Therefore, ethical approval and the requirement for informed consent were waived by the Institutional Research Ethics Committee (Comité d'éthique de la recherche du Centre hospitalier de l'Université de Montréal).

Conflict of Interest Statement

M.F. was supported by a personal fellowship from the Giersch Foundation enabling research at the University of Montreal Health Center. The remaining authors have no relevant financial or nonfinancial conflicts of interest to disclose.

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Author Contributions

Conceptualization: M.F., L.Q., M.P., F.O., J.A.G., A.B., L.C., S.M., S.F.S., M.K., M.I.T., C.H., F.S., F.K.H.C., and P.I.K. Data curation: M.F., L.Q., M.P., and F.O. Formal analysis, project administration, visualization, software, writing – original draft, and investigation: M.F. Methodology: M.F. and P.I.K. Supervision: F.K.H.C. and P.I.K. Writing – review and editing: L.Q., M.P., F.O., J.A.G., A.B., L.C., S.M., S.F.S., M.K., M.I.T., C.H., F.S., F.K.H.C., and P.I.K.

Data Availability Statement

The data are available from HCUP following completion of the required data user training, acceptance of the data use agreement, and purchase of the NIS database. The authors had authorized access to these data. Researchers wishing to access the data must obtain them directly from HCUP through the same application process. Further inquiries can be directed to the corresponding author.

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