Risk of hospitalization in patients with diabetes mellitus who have solid-organ malignancy

Background: To determine the relationship between diabetes mellitus (DM) and hospitalization risk in patients with solid-organ malignancies, hospitalized patients with a new solid-organ malignancy and DM were retrospectively analyzed. **Results:** The presence of DM conferred a 72% greater chance (odds ratio [OR]: 1.72, 95% CI: 1.46–2.04; $p < 0.01$) of requiring any hospitalization and increased the chances of having multiple admissions by 84% (OR: 1.84, 95% CI: 1.53–2.21; $p < 0.01$). Additionally, the presence of DM increased the duration of hospital stay by 0.57 days ($p < 0.01$). **Conclusion:** The presence of DM in patients with solid-organ malignancies increases the risk of any hospitalization, multiple hospitalizations and length of hospital stay.

Lay abstract: To determine the relationship between diabetes mellitus (DM) and hospitalization risk in patients with solid-organ malignancies, hospitalized patients with a new solid-organ malignancy and DM were retrospectively analyzed. The study found that the presence of DM conferred a 72% greater chance of requiring any hospitalization and increased the chances of having multiple admissions by 84%. Additionally, the presence of DM increased the duration of hospital stay by more than half a day. The study concluded that the presence of DM in patients with solid-organ malignancies increases the risk of any hospitalization, multiple hospitalizations and duration of hospital stay.

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Keywords: diabetes mellitus • hospital stay • hospitalization • risk • solid-organ malignancy

The presence of diabetes mellitus (DM) is associated with a greater risk of both onset and mortality in many types of solid-organ malignancies, including breast, colorectal, endometrial, pancreatic, liver and bladder cancers [1–7]. Hyperglycemia, even among patients without DM, has also been linked to increased cancer mortality and to more aggressive clinical behavior of the cancer [8–10]. Obesity, diet and hyperinsulinemia are some of the identified shared risk factors for DM and certain types of cancers [2,5,6].

For many types of solid-organ cancers, hospitalizations pose a considerable burden and contribute to the high costs of these diagno-

ses [11–15]. Similarly, hospitalizations account for 40% of all DM-related costs [16]. Additionally, DM is associated with greater odds of requiring a hospitalization, a higher risk of multiple hospitalizations and longer hospital stays than in the non-DM population [17–21]. However, the interactions among DM, patients with solid-organ malignancy and the risk of hospitalization have never been established, and data on the topic are lacking. These interrelationships should be explored as a prelude to future investigations focused on economic burden or modifiable factors that could be targeted to reduce hospital risk in patients with these dual diagnoses.

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The authors have analyzed institutional data to examine the interactions among DM, glycemic control and risk of mortality among patients with solid-organ malignancies [22,23]. A recent report assessed the status of glycemic control among hospitalized patients with coexisting cancer and DM [24]. However, no studies have described the hospital characteristics of patients with cancer who have DM or how DM affects the risk of hospitalizations among patients with solid-organ malignancies. Hence, a retrospective analysis of patients who had cancer with and without DM was conducted to determine the association between DM and risk of hospitalization, the need for multiple hospitalizations and duration of hospital stay.

Methods

Description of institutional cancer registry

The authors' institution is an academic facility located in southwestern USA. The cancer registry maintained by the authors' institution is an information system designed for the collection, management, analysis and dissemination of data on persons with the diagnosis of malignant or neoplastic disease seen at the facility. When a patient receives the diagnosis of cancer, information obtained from the medical record becomes part of the registry. Certified cancer registrars enter and abstract information and enter it into the database. The registry contains up to 350 items pertinent to each case, including demographics, diagnosis, year of diagnosis and recurrence data.

Case selection

The study was approved by the Mayo Clinic Institutional Review Board (protocol ID: 12-008284) and included patients from the authors' academic institution. Patients with a new solid-organ malignancy diagnosed from 1 January 2009, through 31 December 2011, were identified in the institutional cancer registry, as previously described [22–24]. Patients with more than one primary malignancy, hematologic malignancies or skin cancers were excluded. This data set was linked to electronic health records to determine which patients had a diagnosis of DM at the time of the cancer diagnosis. This file was then cross-referenced against hospital discharge data to determine who had evidence of hospitalizations within the authors' facility from 1 January 2010, through 31 December 2013 (the analytic period). The later dates were included to ensure capture of all hospitalizations within the authors' institution over a period of time for which data were available at the time of the analysis. Hemoglobin A_{1c} (HbA_{1c}) values obtained during the inpatient stay were extracted from the laboratory infor-

mation system. Measurement of HbA_{1c} for inpatients with DM is part of the facility's guidelines for management of these patients. For patients who were not hospitalized, HbA_{1c} values would not have been available because their outpatient DM care likely would have been obtained elsewhere.

Statistical analysis

Descriptive statistics were used to describe the characteristics of the patients, categorized according to DM diagnosis. Patient-level characteristics were compared between groups by F test for continuous variables and χ^2 test for frequency data. Generalized estimating equations (GEEs) were used to account for the correlation between the repeated measurements within a patient. Therefore, multivariable GEE models were used to examine the association between hospitalization risk and DM while controlling for age, cancer type, race or ethnicity and sex. A logistic model was also used to examine the risk of having multiple admissions, and the relationship between DM and duration of hospital stay was assessed with a linear GEE model. A patient was considered to have multiple admissions if two or more hospitalizations occurred during the analytic period. Sequential models were tested in a backward elimination fashion for each outcome variable to determine the best fit, and those variables that were not significant were removed from the final model.

The relationships of the HbA_{1c} level with the risk of needing multiple hospitalizations and with duration of stay were evaluated. The authors' institution has recommended that HbA_{1c} values be determined when appropriate at admission. Because HbA_{1c} levels were available only for patients who were inpatients in this data set, the analysis was restricted to the subset of patients with DM who were hospitalized. All statistical analysis was conducted with SAS 9.3 (SAS Institute Inc). All tests were two-sided, and statistical significance was set at $p < 0.05$.

Results

Patient characteristics

Of the 4620 patients identified with solid-organ malignancies (Table 1), 732 (15.8%) had a coexisting DM diagnosis and 3888 (84.2%) did not. Among the 4620 patients, 2378 (51.5%) had at least one hospitalization, and 2242 (48.5%) did not have a hospitalization documented in the system. Of the 2378 patients requiring a hospitalization, 1406 (59.1%) had only one admission, and the remaining 972 (40.9%) of patients had more than one admission during the analytic period.

On examination of demographic differences, patients with DM were slightly but significantly older

Table 1. Characteristics of patients with solid-organ malignancies according to status of diabetes mellitus.				
Characteristic	Diabetes mellitus		Total (n = 4620)	p-value
	No (n = 3888)	Yes (n = 732)		
Age, mean (SD), years	65.6 (13.3)	68.4 (10.7)	66.0 (12.9)	<0.01
Time from cancer diagnosis, mean (SD), years [†]	1.65 (1.12)	1.57 (1.10)	1.64 (1.12)	0.06
Sex:				<0.01
– Female	1527 (39.3)	238 (32.5)	1765 (38.2)	
– Male	2361 (60.7)	494 (67.5)	2855 (61.8)	
Race:				0.26
– Nonwhite	263 (6.9)	56 (8.0)	319 (7.0)	
– White	3567 (93.1)	640 (92.0)	4207 (93.0)	
Missing	58	35	94	
Cancer type:				<0.01
– Bladder	138 (3.5)	34 (4.6)	172 (3.7)	
– Breast	423 (10.9)	47 (6.4)	470 (10.2)	
– Colorectal	252 (6.5)	42 (5.7)	294 (6.4)	
– Gynecologic	170 (4.4)	33 (4.5)	203 (4.4)	
– Kidney	207 (5.3)	65 (8.9)	272 (5.9)	
– Liver	89 (2.3)	59 (8.1)	148 (3.2)	
– Lung	442 (11.4)	76 (10.4)	518 (11.2)	
– Other	1062 (27.3)	201 (27.5)	1263 (27.3)	
– Pancreas		61 (8.3)	235 (5.1)	
– Prostate	174 (4.5)	114 (15.6)	1045 (22.6)	
Hospitalized:				
– No	1968 (50.6)	274 (37.4)	2242 (48.5)	
– Yes	1920 (49.4)	458 (62.6)	2378 (51.5)	
No. of hospitalizations:				<0.01
– 1	1,184 (61.7)	222 (48.5)	1,406 (59.1)	
– 2	382 (19.9)	114 (24.9)	496 (20.9)	
– 3	160 (8.3)	49 (10.7)	209 (8.8)	
– 4	194 (10.1)	73 (15.9)	267 (11.2)	
Duration of stay (hospitalized patients), mean (SD), days	5.6 (5.2)	6.1 (5.5)	5.7 (5.3)	0.003

Values are expressed as number of patients (%) unless otherwise indicated.
[†]Time from cancer diagnosis until last institutional hospital date.

than patients without DM, and more patients with DM were men (Table 1). No differences in race or ethnicity or in the duration of cancer diagnosis were detected. The distribution of solid-organ malignancies included in the analysis was different between the two groups. For instance, breast and prostate cancers were more common among patients without DM, whereas renal, hepatic and pancreatic malignancies occurred more frequently among patients with DM.

Differences were found in the hospital data (Table 1). Hospitalizations were significantly more frequent among patients with DM than those without DM. Patients with DM also experienced more multiple hospitalizations than those without DM. Also, patients with DM remained in the hospital on average a half day longer than patients without coexisting DM. Total amount of follow-up time from cancer diagnosis date until last contact date or death was similar between patients

with DM (15.5 months) and those without DM (16.7 months; $p = .29$).

DM & hospitalization risk among patients with cancer

After adjustment for other variables, GEE models predicting hospitalization risk showed that DM conferred a 72% greater chance of requiring a hospitalization (Table 2). In contrast, for every 5-year increase in age, the odds of requiring a hospitalization decreased by 5%. When compared with patients who had prostate cancer, patients with some solid-organ malignancies (e.g., bladder, colorectal, kidney) had greater odds of requiring a hospitalization. Coexisting DM also increased the chances of having multiple admissions by 84% (Table 3). White race or ethnicity also increased the odds, and all cancer types evaluated were associated with higher odds of multiple hospitalizations than prostate cancer.

DM & hospital duration of stay

Linear GEE models were used to assess the association between duration of hospital stay and DM (Table 4). After adjustment for cancer type and sex, the presence of DM significantly increased the duration of stay by 0.57 day. All cancer types included in the analysis were associated with longer durations of stay when compared with prostate cancer. Also, men were in the hospital nearly a half day longer than women.

HbA_{1c} level, multiple hospitalizations & duration of stay

Among the subset of DM patients who were hospitalized ($n = 458$), the mean (SD) HbA_{1c} value was 6.8

(1.3)%. After adjustment for cancer type, age, sex and race or ethnicity, there was no correlation between HbA_{1c} level and the need for multiple admissions (odds ratio [OR]: 0.95; 95% CI: 0.77–1.17; $p = 0.63$). In addition, there was no relationship between HbA_{1c} level and duration of stay (β estimate = -0.21; 95% CI: -0.75–0.32; $p = 0.45$).

Discussion

DM is associated with a greater chance of a patient being hospitalized [17–20]. DM and cancer are high-profile topics that individually garner much attention in the literature. DM and solid-organ malignancies place a high burden on the health care system, and hospitalizations compose a substantial part of this burden for both categories of patients. However, the interactions among DM, cancer and risk of hospitalization have not been specifically examined.

Analysis of this institutional dataset indicates that patients with solid-organ malignancies who had DM had a substantially increased risk of being hospitalized. Moreover, patients who had cancer with coexisting DM had more hospitalizations and remained in the hospital for slightly longer than their non-DM counterparts. The reasons for this greater risk cannot be ascertained from this dataset. Possible factors are the number and severity of DM complications and the presence of other comorbidities commonly found with DM (e.g., cardiovascular disease, hypertension). Additional study is required to determine what specific characteristics of patients with DM may predispose them to needing a hospital admission compared with the non-DM population with solid-organ malignancies.

Table 2. Generalized estimating equation models predicting hospitalization risk.			
Factor	Odds ratio	95% CI	p-value
Diabetes: yes vs no	1.72	1.46–2.04	<0.01
Age (per 5-year increase)	0.95	0.93–0.98	<0.01
Cancer type [†]			
Bladder	2.29	1.63–3.22	<0.01
Breast	0.97	0.78–1.21	0.79
Colorectal	1.74	1.33–2.27	<0.01
Gynecologic	1.18	0.87–1.60	0.30
Kidney	1.39	1.06–1.82	0.02
Liver	1.32	1.07–1.88	0.12
Lung	1.16	0.94–1.44	0.16
Other	1.23	1.04–1.45	0.02
Pancreas	1.11	0.83–1.47	0.48
Sex and race did not contribute and were removed from the final model.			
[†] Referent: prostate cancer.			

Table 3. Generalized estimating equation models predicting risk of multiple hospitalizations.

Factor	Odds ratio	95% CI	p-value
Diabetes: yes vs no	1.84	1.53–2.21	<0.01
White vs nonwhite	1.55	1.12–2.13	<0.01
Cancer type [†]			
Bladder	4.67	3.18–6.86	<0.01
Breast	2.80	2.06–3.80	<0.01
Colorectal	4.74	3.42–6.59	<0.01
Gynecologic	3.40	2.31–5.00	<0.01
Kidney	2.45	1.70–3.54	<0.01
Liver	4.44	2.93–6.72	<0.01
Lung	2.42	1.79–3.28	<0.01
Other	2.91	2.27–3.74	<0.01
Pancreas	3.03	2.09–4.37	<0.01

Age and sex did not contribute and were removed from the final model.
[†]Referent: prostate cancer.

The reported association between glycemic control and risk of multiple hospitalizations among patients with DM is inconsistent [21]. In one study, the HbA_{1c} level was significantly correlated with risk of readmissions between 30 and 90 days among patients with congestive heart failure [25]. In our analysis, the HbA_{1c} level was not found to be significantly associated with more frequent hospitalizations among patients with DM who were hospitalized at least once. If future studies confirm this finding, then intensified outpatient treatment of hyperglycemia may not be of benefit in terms of decreasing the risk of multiple admissions among patients with cancer, and a search for other modifiable risk factors would have to be undertaken.

However, this finding by no means negates the need to optimize glycemic control in patients with cancer as it would with patients with other comorbidities. For instance, patients with newly diagnosed solid-organ malignancies may require surgery as first-line treatment, and optimizing glycemic control before and after the episode of surgical care can improve outcomes [26].

The increased risk of hospitalization, multiple hospitalizations and longer duration of stay imposed by DM on patients with cancer has potentially significant economic implications. When considered separately, hospitalizations represent a large part of the costs to the healthcare system for patients with DM

Table 4. Generalized estimating equation models predicting duration of hospital stay.

Factor	β estimate	95% CI	p-value
Diabetes: yes vs no	0.57	0.16–0.97	<0.01
Male vs female	0.50	0.07–0.93	0.02
Cancer type [†]			
Bladder	3.63	2.84–4.42	<0.01
Breast	1.35	0.75–1.94	<0.01
Colorectal	3.15	2.41–3.90	<0.01
Gynecologic	2.37	1.54–3.19	<0.01
Kidney	1.16	0.66–1.65	<0.01
Liver	2.36	1.31–3.40	<0.01
Lung	2.63	2.07–3.18	<0.01
Other	2.77	2.33–3.22	<0.01
Pancreas	3.38	2.57–4.18	<0.01

Age and race did not contribute and were removed from the final model.
[†]Referent: prostate cancer.

and cancer [11–16]. When the two diseases coexist, the economic impact is likely to be magnified above that of either alone, and because no data exist, the topic requires further discussion and analysis.

This analysis has some limitations. It is from a single institution and results cannot be generalized to patients in other facilities. The use of the institutional cancer registry as the primary data source did not allow for inclusion of some patient-level variables, such as presence of DM-related complications or the duration of DM, which are not part of the registry but could be important predictors of hospitalization risk. Additionally, electronic data do not accurately collect the cause of DM (e.g., Type 1 vs Type 2). Although there is no reason to suspect that the cause of DM changes hospitalization risk, this variable should be considered in future analyses. Chart review on a smaller sample size to collect more characteristics, as was recently done for patients who had breast cancer and DM [23], would allow a more in-depth case-control analysis to be performed. Moreover, no information is available on whether patients may have been hospitalized outside the institution. Also, the lack of HbA_{1c} values in patients with DM who were not hospitalized did not permit an analysis of correlation between HbA_{1c} levels and risk of any inpatient stay.

Conclusion

Limitations aside, to the authors' knowledge this is the first analysis that has specifically examined the association between DM and the risk of any hospitalization, multiple hospitalizations and duration of hospital stay among patients with cancer. DM coexisting with solid-organ malignancies was significantly associated with all three measures. The economic implications of both diagnoses together must be studied, and a better understanding of why patients with DM and cancer have these higher risks should be explored so that mitigating strategies can be developed. Further

study of the DM–cancer–hospitalization connection is needed.

Future perspective

Currently, there is a dearth of research in the literature about patients with cancer and DM who are hospitalized. In this study, we found that patients with DM who have solid-organ malignancies have an increased risk of hospitalization and duration of hospital stay. Determination of DM-related factors contributing to increased risk of hospitalization in these patients is an ideal next step for future research. This knowledge will help to implement appropriate preventive measures to decrease risk of hospitalization and duration of hospital stay in patients with DM who have solid-organ malignancies.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Ethical disclosure

For studies involving data relating to human or animal experimental investigations, appropriate institutional review board approval has been obtained and is described within the article (for those investigators who do not have formal ethics review committees, the principles outlined in the Declaration of Helsinki have been followed).

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Executive summary

- Diabetes mellitus (DM) coexisting with solid-organ malignancies is associated with risk of hospitalization and multiple hospitalizations.
- DM coexisting with solid-organ malignancies is associated with longer duration of hospital stay.
- Hemoglobin A1c level was not associated multiple hospitalizations or length of stay.
- The economic implications of both diagnoses together must be studied.
- A better understanding of why patients with DM and cancer have these higher risks should be explored so that mitigating strategies can be developed.
- Possible factors for the findings are the number and severity of DM complications and the presence of other comorbidities that are commonly found with DM (e.g., cardiovascular disease, hypertension).
- The findings have potentially significant economic implications: hospitalizations, considered separately, represent a large part of the costs to the health care system for patients with DM and cancer.
- When DM and cancer coexist, the economic impact is likely to be magnified above that of either alone.

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