RESEARCH ARTICLE

Diabetes Management

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Hyperglycemia among hospitalized cancer patients with coexisting diabetes mellitus

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Practice points

- The purpose of this study was to examine glycemic care of hospitalized patients with diabetes mellitus (DM) and coexisting cancer.
- Variations in inpatient glycemic control among patients with solid organ malignancies are not due to the type of cancer.
- Increased hemoglobin A_{1c}, mean glucose values during the first 24 h after admission and increased insulin administration were all associated with hyperglycemia.
- Some standards of inpatient care were not met and provide opportunities for quality improvement projects.
- Considerable research still needs to be conducted to learn more about hospitalized patients with coexisting DM and cancer.
- It is not known whether DM increases the risk of requiring an inpatient stay for patients with solid organ malignancies.
- Further study is needed to determine whether a DM diagnosis is associated with increased length of hospital stay, greater adverse inpatient outcomes or readmission risk among patients with cancers.

Aims: The objective was to study the care of hospitalized patients with diabetes mellitus and coexisting cancer. **Patients & methods:** Hospitalized patients with a new solid organ malignancy and diabetes were retrospectively analyzed. Multivariable generalized estimating equation models evaluated associations between cancer type and hyperglycemia (glucose >180 mg/dl). **Results:** Among 443 patients with 914 hospitalizations, cancer types included prostatic, liver, lung, kidney, pancreatic, bladder, breast, colorectal and gynecologic. Increased hemoglobin A_{1c} ($\beta = 2.72$; $p < 0.01$), mean glucose within 24 h after admission ($\beta = 0.27$; $p < 0.01$) and insulin administration ($\beta = 10.16$; $p < 0.01$) were significantly associated with hyperglycemia. No association existed between cancer type and hyperglycemia frequency ($p = 0.79$). **Conclusion:** Inpatient hyperglycemia management is not associated with type of solid organ malignancy.

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The topic of coexisting diabetes mellitus (DM) and solid organ malignancies has been one of emerging interest. The presence of DM is associated with a greater risk of both onset and mortality in many types of cancers, including breast, colorectal, endometrial, pancreatic, liver and bladder cancers [1–7]. Hyperglycemia among patients without DM has also been linked to increased cancer mortality and to more aggressive clinical behavior of the cancer [8–10]. Shared risk factors for DM and certain types of cancers have been identified (e.g., obesity, diet and hyperinsulinemia) [1–3].

Previous analyses conducted by the authors have characterized the institutional prevalence of DM in cancer patients, the level of outpatient glycemic control and the effect that a coexisting diagnosis of DM had on survival for several classes of solid organ malignancies [11,12]. The medical literature has only a limited number of studies of how therapy is managed for hospitalized patients with coexisting DM and malignancies [13,14]. Effective management of hyperglycemia in inpatients with DM is standard of care. Clinical practice guidelines provide recommendations for optimal insulin regimens, glycemic targets and the need for glucose monitoring that should apply equally to hospitalized patients with cancer [15,16]. Moreover, given the heterogeneity of the population with solid organ malignancies, it is not known whether inpatient management of hyperglycemia needs to be modified according to the type of malignancy. To guide quality improvement initiatives, we conducted a retrospective analysis of hospitalized patients who had a spectrum of solid organ malignancies and a diagnosis of DM.

Patients & methods

• Case selection

After Institutional Review Board approval, patients with a new solid organ malignancy diagnosed from 1 January 2009 to 31 December 2011 were identified in the institutional cancer registry. Excluded were patients with more than one primary malignancy, hematologic malignancies or skin cancers. This data set was linked to electronic medical records to determine which of these patients had hospital discharge data with a diagnosis of DM from 1 January 2010 to 31 December 2013. Additional links to laboratory and pharmacy information systems were used to retrieve data on bedside point-of-care blood glucose (POC-BG) and insulin therapy as detailed in previous studies [17–20]. Besides demographic information, the final data set included cancer type, length of inpatient stay and whether glucocorticoids were administered during hospitalization.

• Assessment of inpatient glycemic control

POC-BG measurement data were used to evaluate inpatient glycemic control with standardized instrumentation (Accu-Chek Inform; Roche Diagnostics). The mean of bedside POC-BG values during the first 24 h after admission ($F24BedGluc_{avg}$) and the mean of bedside POC-BG values during the 24 h before discharge ($L24BedGluc_{avg}$) were calculated as previously described [17,18]. The frequency of hyperglycemic events per patient was calculated by dividing the number of measurements that were greater than 180 mg/dl by the total number of measurements for that patient. The cutoff POC-BG of 180 mg/dl was chosen to correspond with current inpatient hyperglycemia recommendations to maintain glucose levels below this value [15–16,21]. Any available hemoglobin A_{1c} (HbA_{1c}) data were also extracted. Detailed reviews of medical records were conducted when no documented POC-BG data were available, and those patients were removed from the data set if DM could not be confirmed.

• Definitions of inpatient insulin regimen

Current guidelines for management of hyperglycemia promote the use of a basal-bolus insulin regimen, defined as use of a long- or immediate-acting insulin combined with a rapid- or short-acting insulin with meals, when the patient is eating, along with additional amounts to correct for high glucose values [15–16,21–24]. Only insulin doses administered to the patient were included. As previously described, long-acting insulin therapy (insulin glargine or NPH insulin in the authors' hospital) was classified as 'basal,' and rapid- or short-acting insulin (regular insulin or insulin aspart) was classified as 'short-acting' if it was provided as a prandial dose or as a correction dose (or as both). Patterns of insulin administration were then designated as 'none', 'basal only', 'short-acting only', or 'basal plus short-acting'. Premixed insulin was classified in the 'basal plus short-acting' category [17,19,25].

• Data analysis

It is not clear whether there is value in assessing glucose control or in escalating insulin therapy for patients with short lengths of hospital stay; hence, assessment of glycemic control and

changes in insulin therapy were conducted for patients whose length of hospital stay was 3 or more days [17,19,25]. Additionally, $F24BedGluc_{avg}$ and $L24BedGluc_{avg}$ were compared. Since inpatient practitioners caring for patients with DM typically make decisions regarding therapy for hyperglycemia by assessing daily POC-BG values, changes in insulin regimen were evaluated according to the percentage of POC-BG values greater than 180 mg/dl. More frequent hyperglycemia should prompt increased use of basal-bolus insulin therapy. Therefore, POC-BG values greater than 180 mg/dl were categorized into three groups according to tertile cutoffs within the data, and changes in insulin therapy were assessed by comparing changes in treatment across these tertiles of glucose control [17,19,25].

A patient may have had more than one hospitalization. Therefore, to determine whether cancer type was associated with the frequency of hyperglycemia, multivariable regression analyses were conducted with generalized estimating equations [25]. The percentage of POC-BG measurements greater than 180 mg/dl was used as the outcome measure. The analyses were adjusted for age at cancer diagnosis, sex, race, HbA_{1c}, length of stay, insulin use and glucocorticoid use. A similar analysis was conducted to determine whether cancer type was associated with the level of glycemic control at discharge, with $L24BedGluc_{avg}$ as the outcome measure. Data are expressed as mean (SD) for continuous variables and as number and percentage for categorical variables.

Results

• Patient characteristics

A total of 443 patients had newly diagnosed solid organ malignancies identified from 2009 to 2011. These 443 patients had a total of 914 hospitalizations from 2010 to 2013. At cancer diagnosis, the mean (SD) age was 67 (11) years; at hospitalization, the mean (SD) age was 68 (11) years **(Table 1)**. Most patients were men and of the white race. **Table 1** also lists the categories of solid organ malignancies considered in the analysis and their frequency of occurrence within the data. Included among the 'Other' category were rarer malignancies related to the CNS, thyroid, and head and neck. Outpatient metabolic control was assessed with the mean (SD) HbA_{1c} level, which was 6.8% (1.3%). Most patients required a hospital stay of 3 days or more, about three-quarters received insulin, and only about a third received glucocorticoids while hospitalized.

• Glycemic control

Figure 1 depicts the state of outpatient glycemic control documented at admission for each cancer type. Overall, the mean (SD) HbA_{1c} level was 6.8% (1.3%) for patients who had an available value, but it varied by cancer type **(Figure 1A)**. The overall mean (SD) $F24BedGluc_{avg}$ was 167 (55) mg/dl, and $F24BedGluc_{avg}$ varied according to cancer type: Glycemic control during the first 24 hours following admission was worst for hospitalized patients who had lung, prostate or kidney cancer and best for patients who had colorectal cancer **(Figure 1B)**.

POC-BG data were available for 807 (88%) of the 914 hospitalizations. For hospitalizations lasting 3 days or more, the mean (SD) daily number of measurements was 3 (1). **Figure 2** shows the frequency of hyperglycemia during hospitalization and the state of metabolic control at discharge, both of which varied by cancer type. The overall

Table 1. Characteristics of 443 patients who had solid organ malignancies and diabetes mellitus with 914 hospitalizations from 2010 to 2013.

Characteristic	Value†
Patients	
Age at cancer diagnosis (years)	67 (11)
Age at admission (years)	68 (11)
Men	316 (71.3)
White race	380 (85.8)
Hospitalizations	
Cancer type:	
– Bladder	68 (7.4)
– Breast	49 (5.4)
– Colorectal	41 (4.5)
– Gynecologic	36 (3.9)
– Kidney	87 (9.5)
– Liver	106 (11.6)
– Lung	97 (10.6)
– Pancreatic	84 (9.2)
– Prostatic	110 (12.0)
– Other	236 (25.8)
Hemoglobin A_{1c} (%)‡	6.8 (1.3)
Length of stay ≥3 days	532 (58.2)
Administered insulin	704 (77.0)
Administered glucocorticoids	337 (36.9)

†Continuous data are presented as mean (SD); categorical data as number and percentage of sample.
‡Available for 586 (64%) of the 914 hospitalizations.

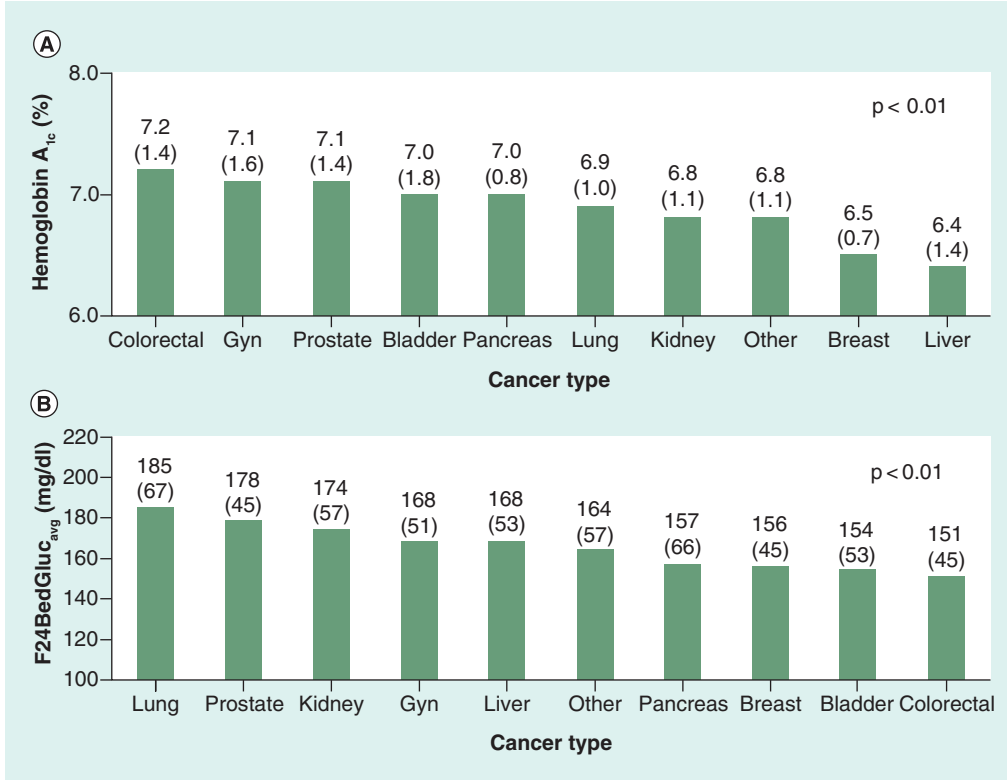

Figure 1. State of glycemic control at admission for each cancer type. (A) Mean (SD) hemoglobin A_{1c} values by cancer type. **(B)** Mean (SD) bedside point-of-care blood glucose levels during the first 24 h after admission (F24BedGluc$_{avg}$) by cancer type. Gyn indicates gynecologic malignancies.

frequency of POC-BG measurements greater than 180 mg/dl was 31% **(Figure 2A)**. Patients with cancer of the prostate, kidney or lung had the highest frequency of hyperglycemia while hospitalized (>40% of the measurements were >180 mg/dl), and patients with colorectal cancer had the lowest. The overall mean (SD) L24BedGluc$_{avg}$ was 159 (47) mg/dl **(Figure 2B)**. Patients with prostatic or pancreatic malignancies had the highest values for L24BedGluc$_{avg}$, and patients with gynecologic cancer had the lowest.

• Variables associated with glycemic control

In adjusted analyses, longer length of hospital stay was associated with a lower frequency of glucose measurements greater than 180 mg/dl **(Table 2)**, and increased HbA_{1c}, F24BedGluc$_{avg}$ and use of insulin were all positively and significantly associated with an increased frequency of hyperglycemia. The use of corticosteroids during hospitalization was not significantly related to hyperglycemia frequency. The percentage of POC-BG values greater than 180 mg/dl was not statistically associated with cancer type after adjusting for length of stay, HbA_{1c} result, F24BedGluc$_{avg}$, sex, corticosteroid use and insulin use.

An analysis that used glycemic control 24 h before discharge (L24BedGluc$_{avg}$) as the outcome variable showed similar results **(Table 3)**. In this analysis, length of hospital stay was not significantly associated with glycemic control during the 24 h before discharge, and increased HbA_{1c}, F24BedGluc$_{avg}$ and insulin use were all positively associated with higher L24BedGluc$_{avg}$ levels. In the analyses **(Tables 2 & 3)**, the overall cancer type was not significant. Therefore, the individual cancer-type comparisons are not presented because of the insignificant results.

• Changes in insulin therapy

The positive association of insulin use with glycemic control suggested that practitioners were responding to the occurrence of hyperglycemia with appropriate pharmacotherapy. To further examine whether the recommended regimen of basal-bolus insulin therapy also increased in accordance with the frequency of hyperglycemia, POC-BG measurements greater than 180 mg/dl were stratified into tertiles and the corresponding

insulin regimens were examined (Figure 3). As the frequency of hyperglycemia increased, a significant change occurred in the type of insulin regimen used to treat inpatients with cancer and DM. The use of basal-bolus insulin therapy progressively increased. However, 42% of patients continued to receive only rapid-acting insulin to treat hyperglycemia, and a small proportion (3%) received no insulin at all.

Discussion

The subject of coexisting DM and solid organ malignancies has emerged as a topic of great interest. This retrospective analysis focused on a previously unreported aspect of cancer care by examining how patients with coexisting DM and solid organ malignancies were being managed in the hospital. The study should be seen within the context of the authors' broader efforts at understanding how inpatient DM care is delivered to the general inpatient population [17,25–26] as well as to more specific subpopulations of inpatients, such as those undergoing surgery, postoperative patients and patients who have undergone renal transplant [18–20,27–29].

The population of patients with solid organ malignancies is quite broad, though cancer treatment protocols may differ depending on the diagnosis. However, standards of care for management of inpatient hyperglycemia and DM do not make distinctions according to cause of hyperglycemia, type of DM or type of comorbid condition; instead, they apply equally to all patients, including those with cancer [15,16]. This cross-sectional, retrospective analysis of a heterogeneous population of inpatients with coexisting solid organ malignancies and DM was undertaken to characterize this population, identify areas of care possibly in need of improvement and determine whether cancer type was associated with glycemic control.

One easily identified aspect of care that needs to be reinforced is the need for POC-BG monitoring. In this data set, most patients did receive POC-BG monitoring, but 12% did not have any POC-BG data even though they were hospitalized for 3 or more days. Even if a patient is hospitalized for only a short period, steps should still be taken to monitor POC-BG levels as a safety measure to ensure detection and treatment of extremes

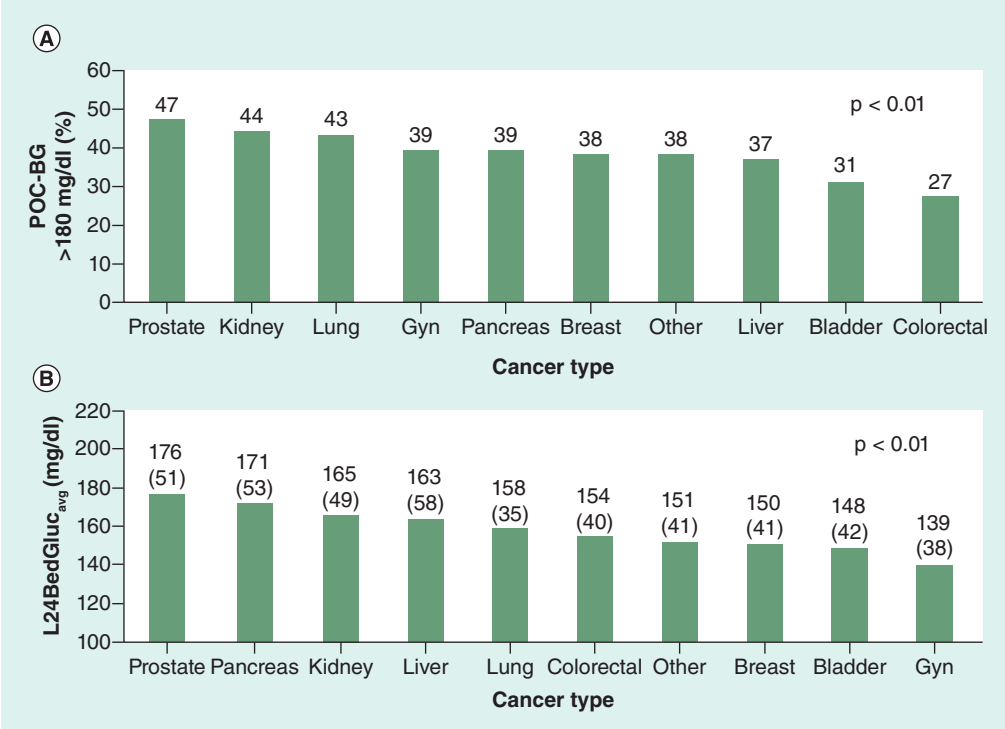

Figure 2. Frequency of hyperglycemia during hospitalization and the state of metabolic control at discharge. (A) Percentage of bedside point-of-care blood glucose (POC-BG) levels greater than 180 mg/dl by cancer type. **(B)** Mean (SD) POC-BG levels during the 24 h before discharge (L24BedGluc$_{avg}$) by cancer type. Gyn indicates gynecologic malignancies.

Table 2. Generalized estimating equation estimates of blood glucose measurements greater than 180 mg/dl†.

Parameter	Adjusted β-estimate	SE	p-value
Length of stay (days)	-0.56	0.17	<0.01
Hemoglobin A_{1c} (%)	2.72	0.78	<0.01
$F24BedGluc_{avg}$ (mg/dl)	0.27	0.03	<0.01
Insulin use (yes vs no)	10.16	2.68	<0.01
Male vs female	3.48	2.93	0.24
Corticosteroid use (yes vs no)	2.42	2.15	0.26
Cancer type	NA	NA	0.79

†The following parameters were not statistically associated with frequency of hyperglycemia and were not included in the final model: race and age at cancer diagnosis.
$F24BedGluc_{avg}$: Mean of bedside point-of-care blood glucose values during the first 24 h after admission; NA: Not applicable.

of glucose levels. Hyperglycemia was common among these patients, sometimes exceeding 40% of the POC-BG measurements. This frequency of hyperglycemia is greater than what has been reported at the US national level overall [30]. While the severity of hyperglycemia during the 24 h before discharge and the frequency of hyperglycemic measurements during the entire hospitalization varied according to cancer type in univariate analyses, adjusted analyses detected no association between cancer type and hyperglycemia. The type of solid organ malignancy alone is not a cause of the variations in glycemic control observed in this study, which are likely due to other factors that were not included here, such as the acuity of illness or perhaps differences in doses of glucocorticoids.

In adjusted analysis, increased HbA_{1c} values and higher mean POC-BG values during the first 24 h after admission were significantly associated with the frequency of hyperglycemia and metabolic control at discharge. Therefore, these parameters could assist inpatient practitioners in identifying types of patients who might benefit from more aggressive therapy earlier in the hospital stay. Recent data indicate that an HbA_{1c} measurement soon after admission can assist with intensifying hyperglycemia therapy and with making decisions about discharge therapy [31,32].

Table 3. Generalized estimating equation estimates of $L24BedGluc_{avg}$†.

Parameter	Adjusted β-estimate	SE	p-value
Length of stay (days)	-0.49	0.44	0.26
Hemoglobin A_{1c} (%)	6.05	1.88	<0.01
$F24BedGluc_{avg}$ (mg/dl)	0.14	0.05	<0.01
Insulin use (yes vs no)	23.33	9.08	0.01
Age at cancer diagnosis	0.38	0.30	0.21
Cancer type	NA	NA	0.19

†The following parameters were not statistically associated with the GEE model predicting $L24BedGluc_{avg}$ and were not included in the final model: race, corticosteroid use and sex.
$F24BedGluc_{avg}$: Mean of bedside point-of-care blood glucose values during the first 24 h after admission; $L24BedGluc_{avg}$: Mean of bedside point-of-care blood glucose values during the 24 h before hospital discharge; NA: Not applicable.

Additionally, in adjusted analysis, increased insulin use was associated with more hyperglycemia and higher glucose levels at discharge. This suggests that practitioners were attempting to respond to hyperglycemia with increased use of insulin. Examination of the type of insulin regimen showed a significantly greater use of the recommended basal-bolus insulin therapy with higher frequencies of hyperglycemia. Nonetheless, a substantial portion of patients continued to receive only short- or rapid-acting insulin despite high glucose levels – a regimen that has been clearly identified as substandard to basal-bolus therapy and is not recommended for management in the hospital as the only pharmacologic means for managing hyperglycemia [15–16,21–24]. Evidence for this type of clinical inertia in the treatment of inpatient hyperglycemia has been previously described by the authors and by others [17,20,33–34]. Approaches to improving care may include alternative strategies to assist with management, such as the use of an advanced-level practitioner trained in hyperglycemia management to assist providers with care [19,25].

The present analysis does have limitations. The retrospective nature of the data does not permit an assessment of the decision-making behavior of clinicians, such as why insulin therapy was not intensified. Additionally, depending on the cancer diagnosis, a patient's care may be managed by clinicians within different specialties. For instance, care of patients with urologic malignancies may be overseen by urologists, care of patients with breast cancer by oncologists and care of patients with gynecologic cancers by gynecologists, all with potentially different levels of awareness or expertise for treating inpatient hyperglycemia. Our analysis did not adjust for the primary service caring for the patient. Finally, the clinical consequence of differences in glycemic control in this population, such as the impact on length of stay or mortality, needs to be investigated. Future analyses are warranted to better define the impact of inpatient hyperglycemia on the cancer patients and the differences in metabolic control observed here.

Conclusion

Despite its limitations, the analysis did provide insight into management of therapy for a complex inpatient population that had coexisting solid organ malignancies and DM. The severity

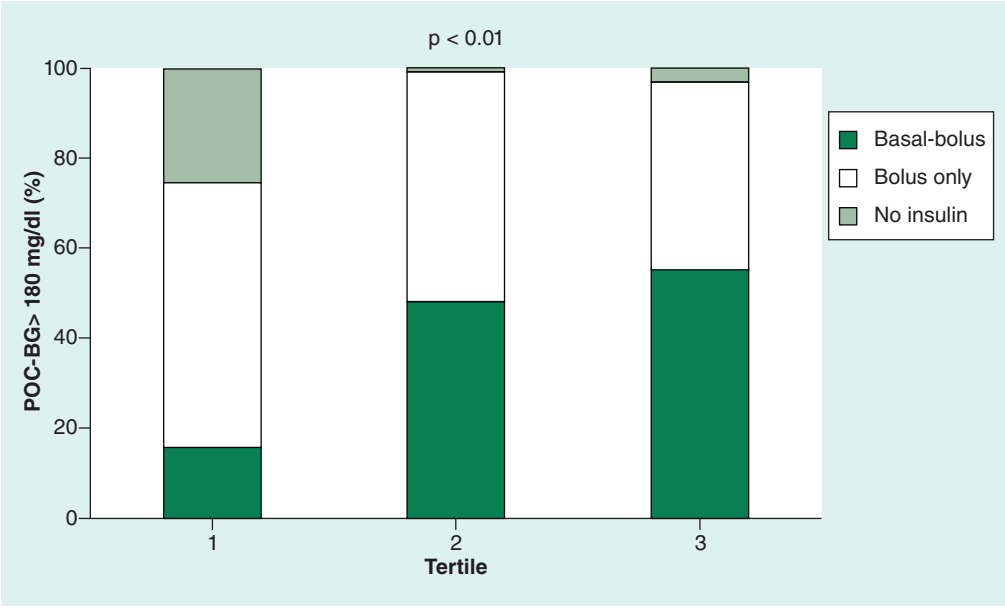

Figure 3. Insulin regimen according to tertile of the percentage of bedside point-of-care blood glucose levels greater than 180 mg/dl. Tertile 1 represents frequencies from 0 to 12% of measurements; tertile 2, frequencies from 12.1 to 37%; and tertile 3, frequencies greater than 37%.

of hyperglycemia does vary by cancer type, but the cancer type is not a cause of this variation. Areas identified as needing to be addressed in future quality improvement initiatives include ensuring that all patients receive POC-BG monitoring and training personnel on how to provide recommended insulin therapy for hyperglycemia. Educational programs should be implemented, so that the same standards of inpatient DM care are applied to all patients regardless of type of solid organ malignancy.

Future perspective

Considerable research still needs to be conducted to learn more about hospitalized cancer patients with coexisting DM. For instance, it is not known whether DM increases the risk of requiring an inpatient stay. Additionally, study is needed to determine whether a DM diagnosis is associated with an increased length of hospital stay, greater adverse inpatient outcomes such as higher rates of infections, or risk of readmission.

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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 conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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