

# Impact of Malglycemia on Clinical Outcomes in Hospitalized Patients With Cancer: A Review of the Literature

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**M**alglycemia has been shown to affect critical- and noncritical-care patient populations. Malglycemia is defined as hypoglycemia (blood glucose less than 70 mg/dl), hyperglycemia (blood glucose of 126 mg/dl or greater), or glycemic variability (standard deviation of two or more blood glucose measurements of 29 mg/dl or greater) (Hammer et al., 2009). Among critically ill patients, researchers have found that malglycemia is associated with increased incidence of infection or sepsis (Benfield, Jensen, & Nordestgaard, 2007), longer inpatient lengths of stay (Krinsley, 2004), and increased morbidity and mortality (Kreutziger, Schlaepfer, Wenzel, & Constantinescu, 2009; Krinsley, 2004; Umpierrez et al., 2002; Van den Berghe et al., 2001). Noncritical-care patients with elevated glucose on hospital admission also have demonstrated poorer outcomes such as increased urinary tract infections, strokes, hemorrhaging, other infections, ileus, increased length of stay, venous thromboembolism (Carr, 2001; Mraovic et al., 2010), and mortality (Kent, Soukup, & Fabian, 2001; Marchant, Viens, Cook, Vail, & Bolognesi, 2009). In addition, patients with hyperglycemia during hospitalization are less likely to be discharged directly home (Umpierrez et al., 2002).

Malglycemia may be particularly important to patients with cancer. Hyperglycemia has been shown to facilitate a physiologic environment that promotes tumor cell proliferation (Barone et al., 2008). Researchers also have noted that hyperglycemia can increase reactive oxidative stress, resulting in structural changes to the endothelial cells and increasing the likelihood of metastasis (Barone et al., 2008), and that high levels of glucose may aid malignant cells in resistance to apoptosis (normal programmed cell death) (Zeng et al., 2010). In addition, the frequent use of steroids and total parenteral nutrition (TPN) as part of the treatment and symptom management plan potentially place the patient at a higher risk for malglycemia and subsequent

**Purpose/Objectives:** To examine empirical research regarding the role of malglycemia (hyperglycemia, hypoglycemia, or glycemic variability) on clinical outcomes among hospitalized patients with cancer.

**Data Sources:** Research articles were obtained from the Ovid, PubMed, and CINAHL® databases. Key words used in the search included *hyperglycemia* or *malglycemia* and *neoplasm* combined with *venous thromboembolism*, *infection*, or *mortality*.

**Data Synthesis:** Eleven research articles were examined reporting the impact of malglycemia on various outcomes, including infection, mortality or survival, length of hospital stay, and toxicity.

**Conclusions:** Findings suggest that malglycemia may have a negative impact on outcomes for hospitalized patients with cancer. Increased rates of infection, mortality, length of stay, and toxicities, as well as decreased survival, were reported.

**Implications for Nursing:** Oncology nurses play an important role in the identification of patients with malglycemia. Early assessment and intervention for those patients can improve outcomes and quality of life.

adverse outcomes. However, little is known about malglycemia in patients with cancer. Therefore, the purpose of this article is to examine the impact of malglycemia on clinical outcomes in patients with cancer. Findings from this review will be used to understand the relationships between malglycemia and outcomes in hospitalized patients with cancer to improve clinical outcomes and identify areas for future research.

## Data Sources

A review of the literature regarding malglycemia was conducted using the Ovid, PubMed, and CINAHL® databases. Key search terms included *hyperglycemia* or *malglycemia* and *neoplasm* combined with *venous thromboembolism*, *infection*, or *mortality*. The terms were used as key words and Medical Subject Heading terms to

obtain the maximum number of studies. In addition, reference lists were searched for relevant articles. Inclusion criteria were empirical research studies published in English from 2000–2011 that focused on hospitalized adult patients with cancer.

## Results

A total of 11 articles met the inclusion criteria. Table 1 presents the study design, sample population, outcomes measured, findings, limitations, and level of evidence for each empirical study. Articles were assessed using the Rating System for Hierarchy of Evidence, and levels of evidence ranged from I (highest) to VII (lowest) (Melynck, 2004). Among the studies reviewed, various parameters were used to classify blood glucose, yielding multiple definitions of hyperglycemia. Multiple definitions and some overlap of terms also were noted among the descriptions of outcomes.

## Description of Studies

Most of the studies ( $n = 9$ ) reviewed were retrospective, whereas two were prospective in design. Ten of the 11 studies were descriptive and one was an intervention study. Using the Rating System for the Hierarchy of Evidence for each study, all of the studies were rated at a level IV because they were well-designed case control or cohort studies. The populations of patients with cancer varied among the studies; most ( $n = 6$ ) included patients undergoing bone marrow transplantation (BMT) (Derr, Hsiao, & Saudek, 2008; Fugi et al., 2007, 2009; Garg, Bhutani, Alyea, & Pendergrass, 2007; Hammer et al., 2009; Sheean, Freels, Helton, & Braunschweig, 2006). Similarly, two studies focused on patients with hematologic diagnoses of acute myeloid leukemia (AML) and acute lymphocytic leukemia (ALL) (Ali et al., 2007; Weiser et al., 2004). One study examined the relationship among hyperglycemia and toxicities in two distinct cancer populations (non-Hodgkin lymphoma and prostate cancer) (Brunello, Kapoor, & Extermann, 2010). The remaining two studies focused on the impact of hyperglycemia in patients with brain tumors (Derr et al., 2009; Hardy, Nowacki, Bertin, & Weil, 2010).

A variety of outcomes were examined in the studies reviewed. The outcomes included infection, mortality, survival, length of hospital stay, and toxicities. The impact of malglycemia for each of these main outcomes has been presented in the data synthesis.

## Outcomes

### Infection

Infection among patients with malglycemia was examined more than any other outcome variable (10 of 11 studies). Infection was defined in those studies as docu-

mented evidence of infection or sepsis anytime during inpatient hospitalization (Ali et al., 2007; Derr et al., 2008, 2009; Fugi et al., 2007; Garg et al., 2006; Hardy et al., 2010; Sheean et al., 2006; Weiser et al., 2004) or post-transplantation (Fugi et al., 2009; Hammer et al., 2009).

Six of the 10 studies examining the relationships among malglycemia and infection and/or sepsis noted a significant increase of infection or sepsis in patients with cancer who had hyperglycemia (Ali et al., 2007; Derr et al., 2008; Fugi et al., 2009; Hammer et al., 2009; Sheean et al., 2006; Weiser et al., 2004). Ali et al. (2007) found that hyperglycemia increased the odds of developing sepsis (odds ratio [OR] = 1.15,  $p < 0.005$ ), severe sepsis (OR = 1.24,  $p < 0.001$ ), or severe sepsis with respiratory failure (OR = 2.04,  $p < 0.001$ ) in 283 patients with AML. Similarly, Weiser et al. (2004) found in a study of 278 adult patients that those with ALL who experienced hyperglycemia were more likely to develop an infection (72% versus 56%,  $p = 0.009$ ) and were more prone to develop sepsis (17% versus 8%,  $p = 0.03$ ) or a complicated infection (sepsis, pneumonia, or fungal) (39% versus 25%,  $p = 0.016$ ) compared to those who did not experience hyperglycemia. In patients who underwent BMT, hyperglycemia prior to ablative therapy (preneutropenic period) was associated with a higher risk for infection after ablative therapy (neutropenic period) (Derr et al., 2008). The researchers noted that an increase in blood glucose of only 10 mg/dl prior to ablative therapy was associated with a subsequent risk of blood stream infections (OR = 1.15,  $p = 0.01$ ) after ablative therapy. Importantly, that relationship was noted even after adjusting for known confounding variables including age, gender, race, diagnosis, type of transplantation, and total glucocorticosteroid dose prior to neutropenia (Derr et al., 2008). In addition, Fugi et al. (2009) conducted an intervention trial that examined the infection rates of 64 patients who underwent BMT, comparing those who received an intense glucose control intervention ( $n = 22$ ) to those who received usual care ( $n = 42$ ). A significantly lower number of infections ( $p = 0.004$ ) and bacteremia ( $p = 0.002$ ) were found among patients who underwent BMT in the intense glucose control group (Fugi et al., 2009). Hammer et al. (2009) examined malglycemia and its association with infection and found a positive relationship among each component of malglycemia and infection. The researchers noted that the risk of infection was two-fold higher ( $p < 0.001$ ) among those with the most variability in blood glucose (Hammer et al., 2009).

Although most studies showed a significant relationship among hyperglycemia and infection, others did not. Fugi et al. (2007) reported that rates of documented infections among three groups (normal, mild, and moderate-to-severe hyperglycemia) of patients who underwent BMT did not significantly differ. Similarly, no difference was noted in infections among 126 patients

**Table 1. Summary of Studies of Hyperglycemia or Malglycemia in Hospitalized Patients With Cancer**

Study	Design and Sample	Measurement	Outcome	Findings
Ali et al., 2007	A retrospective study of 28 patients with acute myeloid leukemia (AML)	<b>Variable:</b> hyperglycemia <b>Source:</b> all serum glucose <b>Parameters:</b> > 110 mg/dl > 150 mg/dl > 200 mg/dl	Infection and mortality	Sepsis and mortality were statistically significant.
Brunello et al., 2010	A retrospective study (N= 349) of 162 patients with non-Hodgkin lymphoma and 187 patients with prostate cancer	<b>Variable:</b> hyperglycemia <b>Source:</b> all serum glucose <b>Parameters:</b> ≥ 100 (fasting) ≥ 140 (post-prandial)	Survival and toxicity	Toxicities were statistically significant; survival was not statistically significant.
Derr et al., 2008	A retrospective study of 382 patients undergoing blood and marrow transplantation (BMT)	<b>Variable:</b> hyperglycemia <b>Source:</b> all serum glucose; point of care <b>Parameters:</b> interquartile range (25th–75th percentile)	Infection and mortality	Infection was statistically significant; mortality and length of stay were not statistically significant.
Derr et al., 2009	A retrospective study of 191 patients with glioblastoma	<b>Variable:</b> hyperglycemia <b>Source:</b> all serum glucose <b>Parameters:</b> mean glucose divided into quartiles: Q1 is < 94 mg/dl Q2 is 94–109 mg/dl Q3 is 110–137 mg/dl Q4 is > 137 mg/dl	Infection and survival	A nonsignificant trend toward infection was noted. Decrease in survival was statistically significant.
Fuji et al., 2007	A retrospective design of 91 patients undergoing BMT, with 28 in the normoglycemia group, 49 in the mild hyperglycemia group, and 14 in the moderate-to-severe hyperglycemia group	<b>Variable:</b> hyperglycemia <b>Source:</b> fasting blood glucose <b>Parameters:</b> categorized by mean glucose Normoglycemia < 110 mg/dl Mild hyperglycemia 110–150 mg/dl Moderate-to-severe hyperglycemia > 150 mg/dl	Infection, mortality, survival, and toxicity	Mortality, toxicities, and survival were statistically significant; infection was not statistically significant.
Fugi et al., 2009	A case control prospective/retrospective study of 64 patients undergoing BMT, with 22 in the intense glucose control group and 42 in the standard glucose matched control group	<b>Variable:</b> malglycemia <b>Source:</b> all serum blood glucose <b>Parameters:</b> mean glucose categorized 80–110 mg/dl 111–140 mg/dl 141–179 mg/dl ≥ 180 mg/dl and glycemic variability Glycemic variability was measured as the standard deviation of mean glucose	Infection, mortality, and toxicity	Infection, bacteremia, and toxicity (C-reactive protein) were statistically significant; mortality was not statistically significant.
Garg et al., 2007	A retrospective study of 126 patients undergoing BMT	<b>Variable:</b> hyperglycemia <b>Source:</b> all serum blood glucose <b>Parameters:</b> mean glucose divided into quintiles < 91 mg/dl 91–100 mg/dl 101–110 mg/dl 111–120 mg/dl > 120 mg/dl	Infection and length of stay	Length of stay was statistically significant; infection was not statistically significant.

*(Continued on the next page)*

Note. Level of evidence was rated from I (highest) to VII (lowest). All studies had a level of evidence of IV, except Weiser et al. (2004), which had a level of VI.

**Table 1. Summary of Studies of Hyperglycemia or Malglycemia in Hospitalized Patients With Cancer (Continued)**

Study	Design and Sample	Measurement	Outcome	Findings
Hammer et al., 2009	A retrospective study of 1,175 patients undergoing BMT	<b>Variable:</b> malglycemia <b>Source:</b> all serum blood glucose <b>Parameters:</b> Hypoglycemia < 70 mg/dl Hyperglycemia ≥ 126 mg/dl Malglycemia is measured as a standard deviation of two or more measurements of 29 mg/dl or greater.	Infection and mortality	Infection and mortality were statistically significant.
Hardy et al., 2010	A retrospective study of 114 patients undergoing craniotomy, with 57 in the surgical-site infection group and 57 in a control group (no surgical-site infection)	<b>Variable:</b> hyperglycemia <b>Source:</b> all serum blood glucose <b>Parameters:</b> ≥ 130 mg/dl ≥ 150 mg/dl	Infection	A nonsignificant trend toward infection was noted.
Sheean et al., 2006	A retrospective study of 357 patients, with 107 in the allogeneic group and 250 in the autologous group	<b>Variable:</b> hyperglycemia <b>Source:</b> fasting serum blood glucose <b>Parameters:</b> ≥ 110 mg/dl ≥ 200 mg/dl	Infection and toxicity	Infection, use of blood products, and delay in white blood cell and platelet engraftment was statistically significant.
Weiser et al., 2004	A prospective design study of 278 patients with acute lymphocytic leukemia	<b>Variable:</b> hyperglycemia <b>Source:</b> all serum blood glucose <b>Parameters:</b> ≥ 2 glucose ≥ 200 mg/dl	Infection, survival, and toxicity	Infection, sepsis, and survival were statistically significant; mucositis peripheral neuropathy and delay in neutrophil recovery were not statistically significant.

Note. Level of evidence was rated from I (highest) to VII (lowest). All studies had a level of evidence of IV, except Weiser et al. (2004), which had a level of VI.

with and without hyperglycemia who had undergone BMT (Garg et al., 2007). Two studies of patients with brain cancer noted a nonsignificant trend in the relationship between hyperglycemia and infection. In 191 patients with glioblastoma, Derr et al. (2009) found a positive trend toward an association among hyperglycemia and infection ( $p = 0.09$ ). Hardy et al. (2010) studied patients with brain tumors to determine if an association existed among postoperative glucose levels and development of a surgical site infection. Although not statistically significant, patients who developed surgical site infections after craniotomy had higher blood glucose levels than those who maintained normoglycemia (Hardy et al., 2010).

### Supportive Cancer Treatment and Infection

Two studies examined the effects of supportive cancer treatment (glucocorticosteroids and TPN) (Derr et al., 2009; Sheean et al., 2006) and their impact on development of hyperglycemia and subsequent infection. Patients who underwent BMT receiving gluco-

corticosteroids during the neutropenic period were more likely to develop hyperglycemia and, in turn, any infection (OR = 1.21,  $p < 0.000$ ), subsequent infection, or blood stream infection (OR = 1.24,  $p < 0.000$ ) (Derr et al., 2008). Sheean et al. (2006) examined the impact of hyperglycemia among patients who underwent BMT and received TPN ( $n = 202$ ) versus no TPN ( $n = 155$ ). Patients who received TPN experienced more days of hyperglycemia than those who did not receive TPN (88% versus 8%,  $p < 0.001$ ). Among patients with TPN-induced hyperglycemia, the likelihood of developing an infection doubled (OR = 2.2, 95% confidence interval [1.4–3.5]) after adjusting for donor type, diagnosis, age, gender, ethnicity, institution, mucositis, and obesity (Sheean et al., 2006).

### Mortality

Five studies addressed mortality, which was defined as hospital death (Ali et al., 2007; Derr et al., 2008) or time to non-relapse mortality, defined as death in a certain time parameter post-transplantation (Fugi

et al., 2007, 2009; Hammer et al., 2009). A significant relationship of malglycemia to mortality was noted in three (Ali et al., 2007; Fugi et al., 2007; Hammer et al., 2009) of the four studies examining this relationship. Fugi et al. (2007) found in 91 patients undergoing BMT that non-relapse mortality was significantly related to the degree of hyperglycemia. They noted an increase in non-relapse mortality of 5%, 17%, and 35% for three levels of glycemia, including normal, mild, and moderate to severe, respectively ( $p = 0.014$ ). Similar findings were reported in patients with AML; hyperglycemia during patients' hospitalization was associated with an increase in hospital mortality ( $p < 0.001$ ) (Ali et al., 2007). A clear association among even mild levels of hyperglycemia (110–150 mg/dl) and mortality was noted and remained after adjusting for disease-specific and clinical variables (Ali et al., 2007). In contrast, Derr et al. (2008) did not find a relationship among hyperglycemia and hospital mortality in a study of 382 patients who underwent BMT.

The role of malglycemia among 1,175 patients who underwent BMT was examined in a study by Hammer et al. (2009). All three types of malglycemia (hypoglycemia, hyperglycemia, and glycemic variability) were associated with an increased rate of non-relapse mortality ( $p < 0.001$ ) even after adjusting for age and clinical factors (severity of disease, type of donor, year of transplantation, and presence of grades 2–4 graft-versus-host disease [GVHD]). Hazard ratios for death were 1.93 ( $p = 0.000$ ) and 2.78 ( $p = 0.000$ ) for blood glucose greater than 200 mg/dl and 300 mg/dl, respectively. The hazard ratio for death related to hypoglycemia was reported at 2.17 ( $p = 0.00$ ) for blood glucose less than 89 mg/dl. In addition, the upper quartile of glycemic variability was associated with a 15-fold increase in risk of non-relapse mortality (Hammer et al., 2009), suggesting that malglycemia may be a predictor of mortality in this group of hospitalized patients with cancer. Those results indicate that variations in blood glucose levels are as equally meaningful as mean blood glucose levels and warrant consideration.

## Survival

Four studies focused on the relationship between hyperglycemia and survival. Survival was defined in a variety of ways, including (a) progression-free survival (first day of chemotherapy to progression of disease to any site, second primary tumor, or death from any cause) (Fugi et al., 2007), (b) overall survival (first day of chemotherapy to death for any cause) (Brunello et al., 2010), (c) time from histologic diagnosis of cancer to death (Derr et al., 2009), and (d) the duration of complete remission achievement until evidence of recurrence (Weiser et al., 2004). Three of the four studies found a significant relationship among hyperglycemia

and survival. Researchers noted that those who did not develop hyperglycemia had relatively longer survival periods. Derr et al. (2009) examined the impact of hyperglycemia on survival in 191 patients diagnosed and treated for glioblastoma, an important group to monitor because they are at higher risk for hyperglycemia because of the inclusion of high-dose steroids in their treatment regimen. Patients who experienced hyperglycemia (greater than 137 mg/dl) had shorter median survival time than those with normoglycemia (less than 94 mg/dl) (9.1 months versus 14.5 months), and hazard ratios (HR) for every 10 mg/dl increase in mean glucose were noted (HR = 1.05,  $p < 0.0001$ ) (Derr et al., 2009). The relationship persisted after adjusting for glucocorticosteroid dosage, age, and performance status (Derr et al., 2009). Similarly, in 91 patients undergoing BMT, hyperglycemia was associated with lower overall survival time ( $p = 0.008$ ) (Fugi et al., 2007). This relationship also was found for 278 patients with ALL. Patients with ALL who experienced hyperglycemia had shorter median complete remission duration (24 months versus 52 months,  $p < 0.001$ ) and shorter median survival (29 months versus 88 months,  $p < 0.001$ ) compared to those without hyperglycemia (Weiser et al., 2004). In contrast, Brunello et al. (2010) did not find a correlation among hyperglycemia and poorer survival in patients with non-Hodgkin lymphoma and prostate cancer; however, this was not the primary aim of the study and the authors acknowledged that the sample may not have been adequately powered to detect this relationship.

## Length of Stay

Length of hospital stay, the number of days a patient was hospitalized, was addressed as an outcome in two studies, with mixed results (Derr et al., 2008; Garg et al., 2007). Garg et al. (2007) found a significant correlation between mean blood glucose and length of stay ( $p < 0.001$ ), as well as a relationship among highest blood glucose value during hospitalization for BMT and length of stay ( $p < 0.001$ ). Patients in the normoglycemic group had an average length of stay of 3.9 days less than the hyperglycemic group ( $\bar{X} = 15.9$ ,  $SD = 5.7$  days versus  $\bar{X} = 19.8$ ,  $SD = 9$  days;  $p < 0.01$ ), and this relationship remained after controlling for glucocorticosteroid therapy (Garg et al., 2007). However, an association among mean glycemia and length of stay was not found among 382 patients undergoing BMT (Derr et al., 2008). The authors noted that the patients in this study were more acutely ill prior to and after BMT, which may have confounded length of stay.

## Toxicity

Five studies examined the association among hyperglycemia and toxicities in hospitalized patients with

cancer (Brunello et al., 2010; Fugi et al., 2007, 2009; Sheean et al., 2006; Weiser et al., 2004). Although the definition of toxicity varied depending on the study, the main toxicities examined across studies were organ dysfunction, including renal (creatinine clearance) and hepatic (bilirubin) function, increased inflammatory markers (C-reactive protein), other symptoms (peripheral neuropathy, GVHD in patients undergoing BMT, diarrhea, and mucositis), and indicators of recovery (white blood cell recovery and transfusion requirements). Fugi et al. (2007) found that patients in the moderate-to-severe hyperglycemia group had significantly higher incidence of hypercreatininemia (OR = 10.8,  $p = 0.018$ ), hyperbilirubinemia (OR = 6.3,  $p = 0.017$ ), and increased inflammatory markers (OR = 10.8,  $p < 0.001$ ). In addition, higher levels of hyperglycemia were associated with a higher incidence of grade II–IV acute GVHD ( $p = 0.002$ ) (Fugi et al., 2007). In another study, Fugi et al. (2009) found a statistically significant increase in the level of the pro-inflammatory C-reactive protein among the standard care group compared to the intense glucose control group ( $p < 0.05$ ), suggesting that glucose control may decrease the production of pro-inflammatory cytokines and, in turn, may result in reduced incidence of GVHD and mortality (Fugi et al., 2009). Hyperglycemia as a result of TPN was associated with an increased need for blood product support ( $p = 0.001$ ) and delayed white blood cell and platelet engraftment (autologous,  $p = 0.01$ ; allogeneic,  $p = 0.02$ ) (Sheean et al., 2006). In contrast, Fugi et al. (2009) found no difference in incidence of GVHD among the standard care group and the intense glucose control group. However, the lack of power to detect a decrease in GVHD is cited as a limitation of the study (Fugi et al., 2009). The incidence of treatment-related toxicities was not found to be significant for mucositis and peripheral neuropathy (Sheean et al., 2006; Weiser et al., 2004) or neutrophil recovery among patients with ALL (Weiser et al., 2004).

Using the National Cancer Institute's (2006) *Common Toxicity Criteria for Adverse Events*, version 3.0, Brunello et al. (2010) studied older adult patients with a diagnosis of non-Hodgkin lymphoma or prostate cancer treated with chemotherapy. Non-hematologic toxicities (neuropathy, non-neutropenic fever, and fatigue) were noted to increase in severity to grade 3 (severe adverse event) and grade 4 (life-threatening or disabling) when hyperglycemia was present at baseline ( $p = 0.038$ ) or during chemotherapy ( $p = 0.004$ ) in patients with non-Hodgkin lymphoma (Brunello et al., 2010). Patients with prostate cancer experienced increased severity (grade 4) in hematologic toxicities (neutropenia, neutropenic fever, thrombocytopenia, and anemia) when hyperglycemia was present at

baseline ( $p = 0.024$ ) (Brunello et al., 2010). Those findings suggest that hyperglycemia at baseline or during treatment may exacerbate toxicity, particularly in older adults.

## Discussion

The purpose of this literature review was to explore and critically appraise empirical research addressing the role of malglycemia on clinical outcomes among hospitalized patients with cancer. Eleven studies matched the inclusion criteria and were summarized in this review. Five major outcomes (infection, mortality, survival, hospital length of stay, and toxicities) have been studied in relationship to malglycemia in a variety of patients with cancer. The majority of studies reviewed established an association among malglycemia and at least one of the identified outcomes.

Infection was the most common outcome studied, with six studies noting an increased risk of infection or sepsis among those with hyperglycemia and glycemic variability. That significant relationship was noted primarily in patients undergoing BMT and patients with leukemia. Those findings are clinically significant because the patients are immunocompromised and susceptible to life-threatening infections. Therefore, interventions to effectively manage malglycemia may reduce the risk of infection and ultimately mitigate negative outcomes and decrease mortality in this vulnerable population. In addition, supportive cancer treatments known to induce hyperglycemia (e.g., TPN and glucocorticoids) increased risk for infection (Derr et al., 2009; Sheean et al., 2006). That finding supports the need for an effective surveillance and blood glucose management program to promote optimal outcomes for patients with cancer.

Fugi et al. (2009) conducted the only published intervention study that compared outcomes for patients with cancer who were in an intense glucose control group to usual care. The authors noted a significant decrease in infection and bacteremia in the patients assigned to the intervention control group compared to usual care. The findings also supported the need for the implementation of glucose control programs for patients with hyperglycemia. In addition, based on the work of Hammer et al. (2009), patients who experienced variability in blood glucose were at an even greater risk of infection and mortality than those who experienced hyperglycemia only. Intervention programs need to focus not only on curtailing hyperglycemia, but also on reducing large variations in blood glucose levels. That finding is similar to studies that indicate variations of glucose during hospitalization are equally as concerning as acute or chronic hyperglycemia (Ali et al., 2008; Dossett et al., 2008;

Egi, Bellomo, Stachowski, French, & Hart, 2006; Hermanides et al., 2010).

The studies in this review also found significant relationships among hyperglycemia and mortality. Those findings are consistent with studies in other clinical populations (Kreutziger et al., 2009; Krinsley, 2004; Umpierrez et al., 2002; Van den Berghe et al., 2001). In addition, the studies in this review found that, in most cases, patients with cancer who had hyperglycemia also had shorter median survival and remission times. The one study that did not find this relationship was limited by a small sample size and, therefore, inadequately powered to detect this relationship (Brunello et al., 2010).

The relationship among malglycemia and length of hospital stay was examined in only two studies (Derr et al., 2008; Garg et al., 2007), and the results were mixed. Additional work is needed to understand the relationship because increased length of stay affects both direct (hospital costs) and indirect opportunity costs (days missed from work) for patients with cancer.

Malglycemia was shown to have a significant impact on the severity of toxicity reported in patients with cancer for most of studies reviewed. Organ dysfunction, pro-inflammatory cytokine release, GVHD, and hematologic or non-hematologic toxicities, as well as increased need for blood products and slower neutrophil recovery, were shown to be more profound in patients with malglycemia. Toxicities in patients with cancer may be debilitating and negatively affect quality of life. For example, research has shown that pro-inflammatory cytokines are associated with sickness behaviors (e.g., depression, fatigue) and lower quality of life in patients with cancer (Von Ah, Kang, & Carpenter, 2008). Additional research is needed to fully understand the impact of malglycemia on toxicities and quality of life in patients with cancer.

## Limitations

Comparisons across the studies are impeded by the heterogeneity of diagnoses and of the various parameters used to obtain and classify blood glucose values and ranges, suggesting the need for standardized blood glucose measurement parameters and treatment plans. The majority of studies used serum blood glucose values. The exclusion of point-of-care testing in all studies but one (Derr et al., 2008) limited the ability to accurately measure the ebb and flow of glycemia. The majority of the studies in this review were retrospective in design, limiting the ability to demonstrate a causal relationship between hyperglycemia and poor outcomes, with only one study using a glucose control intervention. Each study assessed malglycemia and its relationship to multiple outcomes; however, none of the studies evaluated all five outcomes.

## Conclusion

The impact of malglycemia on disease progression, treatment, and outcomes in patients with cancer is important to investigate. Management of malglycemia has had a limited focus in the research for or treatment of those patients. Few studies have examined the relationship among malglycemia and clinical outcomes. The empirical literature in this review primarily consisted of retrospective studies. Those types of studies, although valuable, provide weak evidence on which to base recommendations for practice. The current review suggests that malglycemia is significantly related to poorer outcomes in patients with cancer; however, prospective studies are needed to determine whether a causal relationship exists. Additional research also is needed to elucidate the physiologic processes influencing malglycemia and its subsequent impact on hospitalized patients with cancer. Understanding the phenomena can facilitate management of malglycemia and could potentially influence disease progression, disease response to treatment, and severity of side effects. In addition, studying malglycemia in conjunction with the symptom profile can expedite earlier implementation of interventions to prevent untoward outcomes. Finally, identifying malglycemia as a primary area of concern for patients with cancer could instigate the development of interventions to manage variations in blood glucose and, potentially, alleviate symptom toxicities and improve quality of life for those patients.

## Implications for Nursing

Oncology nurses should understand that malglycemia may affect disease progression, response to treatment, and severity of side effects. Oncology nurses can facilitate mitigation of the deleterious effects of malglycemia through assessment, monitoring, and integration of evidence-based interventions such as glycemia protocols, activity, and dietary changes. Effective management of malglycemia could potentially decrease infections, mortality, length of stay, and treatment-related toxicities, resulting in improved quality of life and survival in hospitalized patients with cancer.

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