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## **ORIGINAL ARTICLE** Causation and Prevention

# **National Cancer Institute Cancer Center Designation** and 30-Day Mortality for Hospitalized, **Immunocompromised Cancer Patients**

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## **ABSTRACT**

Purpose: To examine 30-day mortality and National Cancer Institute (NCI) designation for cancer patients who are immunocompromised and hospitalized. Method: Secondary analysis of 1998 and 1999 hospital claims, cancer registry, and vital statistics (n = 10,370) linked to survey and administrative data from 160 Pennsylvania hospitals. Logistic regression models estimated the effects of NCI designation on the likelihood of 30-day mortality. Results: NCIdesignated centers were associated with a 33% reduction in the likelihood of death, after adjusting for patient, hospital, and nursing characteristics. Conclusions: Immunocompromised cancer patients have lower mortality in NCI-designated hospitals. Identification and adoption of care processes from these institutions may improve mortality.

## INTRODUCTION

Neutropenia related to the treatment of cancer is a frequent patient complication. A prospective observational study of patients undergoing active chemotherapy reported the frequency of febrile neutropenia at 10.4%, with significant variations observed based on tumor type, chemotherapy administered, and patient characteristics (1).

Febrile neutropenia—defined as the presence of fever at or above 38.0°C and an absolute neutrophil count below 1,000 cells/mm<sup>3</sup>—is considered an oncologic emergency (2).

Keywords: Outcomes research, Supportive care and symptom control, Health services research

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For several decades, clinical instruction to physicians, nurses, and pharmacists stressed the necessity of prompt assessment, performance of diagnostic studies, such as blood cultures, and the administration of broad-spectrum anti-infectives (3). Despite these efforts, complications and mortality from this problem still occur with notable frequency. In two recent studies, the average inpatient mortality estimates for this complication were 6.8% (4) and 9.5% (5). Notable variation in mortality was observed based on the severity of illness.

In 2007, the Oncology Nursing Society convened a stateof-the-knowledge symposium on the management of febrile neutropenia (6, 7). The goals of this symposium were to understand the clinical and research advances in the understanding of neutropenia in patients with cancer, to summarize the current clinical landscape, and to disseminate evidence-based preventive and management strategies to clinicians throughout the United States. Salient findings from this symposium were (a) an underdeveloped research infrastructure to study the problem, (b) strong evidence for the use of risk assessment models to estimate probabilities of febrile neutropenia and related complications, and (c) a wide variation in practice standards for prevention and management of neutropenia in the United States.

Variation in clinical practice and quality outcomes is a widely recognized problem in cancer care. The National Cancer



Quality Board has described the cancer care in the United States as "uneven" (8). Health service researchers have sought to explain variations in outcomes by an array of patient and hospital characteristics. One such endeavor, by our research team, elucidated the relationships among mortality, characteristics of hospitals (e.g., bed size, teaching intensity), and characteristics of nurses (e.g., staffing, educational preparation). In a sample of surgical oncology patients, we identified significant associations between 30-day mortality and characteristics of hospitals and nursing care (9). Other investigators have identified hospital characteristics associated with surgical oncology outcomes (10, 11). Similar investigations have not yet been published for patients with cancer who are hospitalized and immunocompromised.

From a conceptual perspective, researchers have hypothesized that patients with significant clinical complexity, as well as relatively frequent use of health care services, are most likely to benefit from organizational characteristics that foster excellent care delivery (12). Below, we present data to examine this hypothesis in a sample of patients with cancer, who are hospitalized and immunocompromised. For purposes of this analysis, we define immunocompromised patients as those with a confirmed cancer diagnosis, and either a diagnosis of agranulocytosis on inpatient claims or the combination of fever and leucopenia (<3,000/mm<sup>3</sup>). These findings have implications for the current state of health care delivery for these patients, as well as informing a future research agenda on reducing needless variation in mortality from cancer-related complications.

## **METHODS**

After human subjects exempt review by the University of Pennsylvania's institutional review board, we performed secondary analysis of linked data created by merging inpatient claims from the Pennsylvania Health Care Cost Containment Council (PHC4), the Pennsylvania Cancer Registry, and the American Hospital Association annual survey data. The list of National Cancer Institute's (NCI) (13) clinical and comprehensive cancer centers available from their Web site was used to identify hospitals in the sample with those designations in 1998–1999. Details of the linkage procedure have been reported elsewhere (9). Consistent with prior studies, we identified patients with neutropenia by an International Classification of Diseases, 9th edition (ICD-9) diagnosis code of 288.0 present in the claims record (4, 5). Because of augmentation of our claims data with elements abstracted from the clinical chart (described in more detail below), we included 1,309 patients with a combination of a white blood cell count value below 3,000/mm<sup>3</sup> and the presence of a temperature >38.0°C, both recorded in the medical record within the first three days of admission (granulocyte counts were not available). Because we could not identify with certainty these patients were neutropenic, the term immunocompromised will be used to describe the sample.

Our analytic sample included 10,370 adults with a confirmed cancer diagnosis treated in 160 acute care hospitals in 1998 and 1999. To clarify examination of outcome differences attributable to organizational characteristics, we excluded 65 patients who died on the day of admission, and 722 patients who were hospitalized in facilities with missing organizational variables.

## Definition of variables

# 30-day mortality

We obtained dates of death through the linkage of death records to the cancer registry and inpatient claims records. We defined 30-day mortality as the number of patients who died within 30 days following the date of hospital admission. When available, 30-day mortality rates are preferred to inpatient mortality rates, as the latter may be biased due to known differences in hospital length-of-stay and discharge profiles.

# Patient characteristics

Adjustment for patients' underlying severity of illness is necessary to examine the effects of organizational characteristics on mortality. To accomplish this task, variables to measure patient characteristics were obtained from the hospital claims file, the cancer registry record, and from the clinical data abstracted during the first three days of hospitalization.

On the basis of an existing approach to measure patient characteristics (14), we constructed an algorithm to detect comorbidities from claims data up to 90 days preceding the studied admission, and each comorbidity was treated as a dichotomous variable. To improve model fit, age at the time of hospitalization was measured as both a linear and quadratic term. We obtained pathologically confirmed tumor diagnoses from the cancer registry record, and tumor type was treated as a categorical variable for the range of tumors studied.

By state regulations, each hospital admission in Pennsylvania was abstracted routinely by trained medical record coders for key clinical findings (KCFs) to construct the Atlas<sup>TM</sup> (formerly known as MEDISGRPS) severity of illness score (15, 16). KCFs are data elements obtained from the first three days of the inpatient medical record; these reflect abnormal physical signs, laboratory values, and radiology or diagnostic cardiology results. In contrast to usual methods of measuring severity using solely diagnosis and procedure codes, an oncology nurse and an oncologist identified KCFs relevant to cancer patients and created a series of binary variables. For example, a patient may have had a KCF value that reflected a hemoglobin level of 10.0 g/dL during the first three days of admission. This was converted to a binary variable of anemia = yes.

## Hospital characteristics

Hospital characteristics data were obtained by the Commonwealth of Pennsylvania's annual state survey of health care facilities. Whenever possible, we selected variables studied frequently in the literature that examines outcomes related to organizational variables, and measured them similarly. Hospital beds set up and staffed were categorized as 100 beds or fewer, 101–250 beds, 251 beds or higher (17). Hospitals that performed solid organ transplants or open-heart operations in 1999 were

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coded as providers of "advanced procedures" (18). Prior studies have suggested that the provision of advanced technological resources may have spillover benefits for other conditions (19). We used the ratio of medical residents or fellows per bed set up and staffed to categorize teaching status: Non-teaching hospitals had no residents/fellows per bed; minor teaching hospitals had a lower than 1:4 resident/fellow to bed ratio; major teaching hospitals had at least one resident/fellow per four beds (20). A dichotomous variable was created to identify hospitals designated by the NCI as a clinical cancer center, comprehensive cancer center, or neither. At the time of this study, the NCI conferred clinical cancer center designation to facilities with clinical programs to support clinical trials, robust basic science research programs with a cancer focus, and the satisfactory completion of peer and site reviews. Comprehensive cancer center designation shared features of clinical cancer centers, with the addition of required shared research resources, and an interdisciplinary cancer control and population science research program.

# Nursing characteristics

The data from claims and hospital administrative files were compiled as part of a larger study originally designed to investigate the relationship between nursing organizational characteristics and patient outcomes. Data regarding nursing characteristics were obtained from a mailed survey to a 50% random sample registered nurses working in Pennsylvania between 1998 and 1999 (17). The overall response rate was 52%, which is similar to the response rates to anonymous surveys of health care professionals. Three characteristics of hospital nursing were measured in the current study: the nurse practice environment, nurse staffing, and the educational preparation of registered nurses. These measures were identical to those previously reported (9).

This study used the Practice Environment Scale of the Nursing Work Index (PES-NWI) to measure the perceived working conditions of registered nurses in acute care hospitals (21). Items on this scale reflect a nurse's agreement that the selected characteristic is present in their current job (1 = strongly disagree, 2= disagree, 3 = agree, and 4 = strongly agree). Five subscales comprising 31 items describe the practice environment of registered nurses in hospitals: Nurse Participation in Hospital Affairs (e.g. "staff nurses have the opportunity to participate on hospital and nursing committees"); Nursing Foundations for Quality of Care ("active inservice/continuing education programs for nurses"); Nurse Manager Ability, Leadership, and Support of Nurses ("a supervisory staff that is supportive of the nurses"); Staffing and Resource Adequacy ("enough registered nurses to provide quality patient care"); and Collegial Nurse-Physician Relations ("physicians and nurses have good working relationships").

We aggregated values on PES-NWI items from individual nurse responses to calculate hospital-level means of the PES-NWI subscales. Hospitals were then assigned to one of three categories: unfavorable nurse practice environments (scores above 2.5 on zero or one subscale), mixed, (scores above 2.5 on 2–3 subscales), or favorable (scores above 2.5 on 4-5 subscales). This classification has been supported by both validity and latent class analysis (22).

To measure nurse staffing, survey responses from eligible registered nurses were used to calculate a mean workload (number of patients cared for on the last shift) per hospital. Consistent with prior analyses, outlier values on this measure (more than 6 patients cared for in intensive care units and 20 patients cared for outside of intensive care units) were excluded. The mean value of the number of patients cared for on the last shift was used as a continuous measure in the final models.

To measure educational preparation of nurses, each eligible staff nurse's response to the question "what is the highest nursing degree you have?" was used for analysis. For each hospital, we calculated the proportion of nurses who held a baccalaureate degree or higher. The proportion was treated as a continuous measure.

# Statistical analysis

First, we tested bivariate relationships for 30-day mortality and characteristics of patients, hospitals, and nurses using the appropriate t, F, or chi-square test. We examined correlation matrices to identify high correlations, and calculated variance inflation factors and tolerance values to diagnose multicollinearity among nursing and hospital characteristics.

To construct severity of illness models, we first estimated logistic regression models to predict 30-day mortality using the available patient characteristics. Split-sampling methodology was used to increase the stability of obtained parameter estimates. In a random 50% sample of study patients, 192 logistic regression models were estimated to predict 30-day mortality for each candidate patient characteristic. We used the purposeful selection algorithm described by Bursac and colleagues (23) to guide the final variable selection. Briefly described, univariate models were estimated to identify variables significantly associated with 30-day mortality at p < .25. Iterative multivariate models were then estimated for evidence of significance at p < .10 and changes to parameter estimates that exceeded 20%. The model was finally replicated in the remaining 50% of the sample, with no corresponding differences in parameter estimates and statistical significance observed. The retained 63 variables reflected demographics, clinical findings on admission, comorbidities, and cancer information. The C statistic enabled us to compare the discriminatory power of our severity of illness models (24). The C statistic of our final severity of illness model was 0.82. The variables and the corresponding odds ratios for the likelihood of 30-day mortality are available in the Appendix. Briefly summarized, these variables may be categorized into age, tumor type, conditions present on admission, comorbidities, abnormal laboratory values, vital signs, or physical examination findings.

Following the estimation and validation of the severity adjustment model, we then performed a patient-level analysis and estimated a series of logistic regression models to predict 30-day mortality. First, models estimated the effect of each hospital and nursing characteristic with the patient characteristics selected



Table 1.

days of admission)

from the severity adjustment model. After these models were examined for significant results, our final models considered all patient severity measures described above, plus a reduced set of nursing and hospital characteristics simultaneously. Robust, cluster methods were specified in STATA version 10.0 (STATA Corp, College Station, Texas) to adjust standard errors and account for patient clustering in hospitals (25, 26). Coefficients were transformed to odds ratios (OR), and 95% confidence intervals (95% CI) were calculated for all parameter estimates. Finally, we compared hospital and nursing characteristics by organizational characteristics of significance in our final model by calculating means and frequencies.

## **RESULTS**

### Patient characteristics

Table 1 shows the characteristics of the study sample (n =10,370 in 160 hospitals). The mean age was approximately 62 years, with a range between 21 and 98 years of age. A relatively low proportion of non-white patients were in this sample, which is characteristic of Pennsylvania's demographics. Nearly half of all patients had metastatic disease at the time of

Patient Characteristics of the Study Sample, N = 10,370

Range Mean (SD) Age (years) 61.6 (14.2) 21-98 % 5,600 54.0 Female Year of hospitalization 1998 5,621 54.2 1999 4,749 45.8 Non-white ethnicity 1,161 11.2 21.2 Cancer stage Regional 2,183 4,870 47.0 Distant Tumor type Lung 1,911 18.4 1,686 16.3 Leukemia Lymphoma 1,373 13.2 1.289 **Breast** 12.4 Colorectal and anal 959 9.3 7.0 Other GI tumor 715 Ovarian 428 4.1 382 3.7 Prostate 2.6 Other gynecological 266 Other genitourinary 238 2.3 Head, neck, larynx 248 2.4 Esophagus 169 1.6 706 Other 6.8 Patients with both 3,000 28.9 fever > 38.0°C and leucocyte < 3,000/mm<sup>3</sup> documented in first three days of admission 1,460 14.1 30-day mortality (death within 30

diagnosis. While a third of patients had hematological malignancies, 18% had lung cancer, and over 12% had breast cancer. Approximately 14% of the sample died within 30 days of admission.

The association between 30-day mortality and nursing and hospital characteristics is shown in Table 2. The left-hand-side panel displays calculated ORs and 95% confidence intervals (95% CIs) calculated from seven separate multivariate logistic regression models. Each characteristic displayed was entered into a model with all 63 patient variables to estimate the likelihood of 30-day mortality. (To conserve space, the calculated ORs for each patient characteristic were suppressed from the table, but these are available from the authors.) Receipt of care in an NCI-designated comprehensive cancer center was associated with a 37% decrease in the likelihood of mortality within 30 days of admission, after adjusting for all 63 patient characteristics (Model I). In Model II, care received in a minor teaching hospital—when compared with a non-teaching hospital—was associated with a significant decrease in the likelihood of mortality (OR 0.81, 95% CI 0.67–0.98). The other characteristics studied, namely nurse staffing, nurse educational preparation, nursing practice environment, performance of advanced procedures, and bed size, were not significantly associated with mortality.

The right-hand side of Table 2 shows results from one logistic regression (Model VIII) estimating the likelihood of mortality with a reduced set of hospital and nursing characteristics, plus all 63 patient characteristics from the severity of illness model (output suppressed). The only characteristic significantly associated with mortality was receipt of care in an NCI-designated cancer center (OR 0.67, 95% CI 0.47-0.93).

Given the significant effects of NCI cancer centers observed, we compared the hospital and nursing characteristics by NCI status (Table 3). Inferential statistics are not provided because of the imbalance in the exposure variable. All NCI cancer centers in the sample performed advanced procedures, such as solid organ transplant or coronary artery bypass graft surgery, compared with 35% of non-NCI hospitals. Nurses in NCI hospitals reported more favorable working conditions, as measured by the PES-NWI subscales, than those in non-NCI hospitals. Similarly, staffing and educational preparation were higher in NCI facilities. NCI-designated hospitals were larger and had substantially higher proportions of fellows and residents per bed.

In a further attempt to explain our primary significant finding, we also examined differences in patient characteristics by NCI cancer center status. We observed a significant age difference (mean 62.1 years in non-NCI hospitals versus 54.0 in NCI hospitals, p < .001). More cases of regional cancer stage were found in non-NCI hospitals (21.5% versus 17.5%, respectively, p <.01). However, no significant difference in distant or metastatic stage was observed (46.7% in non-NCI versus 49.8% in NCI hospitals, p = .06). Of the 61 other deleterious patient characteristics used for risk adjustment, 20 were significantly more frequent in non-NCI hospital patients, while 7 were significantly more frequent in NCI hospital patients.



Table 2. Results From Multivariable Logistic Regression Models Estimating the Likelihood of 30-Day Mortality

	Variable NCI designation	Marginal Models			Partial Model			
Model I		OR 0.63	95% CI		Model	OR	95% CI	
			0.45	0.96	VIII	0.67	0.47	0.93
II	Teaching							
	Non-teaching	_	_	_		_	_	_
	Minor teaching	0.81	0.67	0.98		0.83	0.69	1.01
	Major teaching	0.80	0.62	1.02		0.94	0.65	1.38
III	Number of RNs/patient	1.05	0.98	1.14		1.01	0.93	1.09
IV	≥ 50% RNs with BSN or higher	0.88	0.72	1.07		0.97	0.74	1.26
V	Nursing practice environment							
	Unfavorable	_	_	_		_	_	_
	Mixed	1.00	0.68	1.46		0.97	0.65	1.46
	Favorable	0.87	0.56	1.35		0.89	0.58	1.38
VI	Performed advanced procedures	0.87	0.73	1.04				
VII	Size							
	<100 beds	_	_	_				
	100-250 beds	1.21	0.88	1.65				
	> 250 beds	1.09	0.80	1.50				

Note: Marginal models estimate the effect of each hospital or nursing characteristic on the likelihood of 30-day mortality, with 63 patient characteristics from the severity model as covariates. The partial model estimates the effects of hospital, nursing, and 63 patient characteristics on the likelihood of 30-day mortality simultaneously. Odds ratios from patient characteristics are suppressed. OR = Odds ratio; CI = Confidenceinterval; NCI = National Cancer Institute; RNs = Registered nurses; BSN = Bachelor's of science in nursing

## DISCUSSION

In this state-based sample of adults hospitalized with cancer who are immunocompromised, the calculated 30-day mortality rate exceeded 14%. After considering severity of illness with 63 patient characteristics, significant mortality variations were observed by NCI cancer center designation and hospital teaching status. However, when these characteristics were examined simultaneously, and in conjunction with other characteristics of hospitals and of nurses, NCI cancer center designation

Table 3. Characteristics of Nurses and Hospitals by NCI Cancer Center Designation

Characteristic	NCI Designation				
	No $(n = 156)$	Yes $(n=4)$			
	n (%	(a)			
Performs advanced procedures	55 (35.3)	4 (100.0)			
Nursing practice environment					
Unfavorable	12 (7.7)	_			
Mixed	113 (72.4)	2 (50.0)			
Favorable	31 (19.9)	2 (50.0)			
	Mean (SD)				
Number of RNs/patients	5.6 (1.2)	4.2 (0.4)			
RNs who hold bachelor's degree or higher	35.7% (12.2)	61.1% (20.8)			
Number of beds	216.7 (130.3)	526.0 (305.3)			
Residents and fellows/beds (%)	7.0 (13.7)	70.5 (52.5)			

Note: Inferential statistics not provided due to imbalance between comparison groups

remained significantly associated with mortality. An examination of hospital, nursing, and patient characteristics suggests that NCI hospitals differed notably from the rest of the sample on the variables available for analysis.

Our mortality estimates are close, if not slightly higher than previously published reports. This is most likely due to our availability to examine death within 30 days of hospital admission, which will include a number of patients who die outside of the hospital. These data are not routinely available in claims data, unless they are linked to vital statistics. Health service researchers have examined both in-hospital and 30-day mortality, and generally recommend the latter measure, to account for differences by hospital in length of stay and disposition patterns (27).

While mortality associated with cancer-related neutropenia has been studied extensively, we were not able to find any studies that attempt to explain the variation in mortality by treating institutions. In our analysis, we identified one characteristic—NCI cancer center designation—that was persistently and significantly associated with a lower likelihood of death. There are several potential explanations for our findings. First, while we attempted to measure the hospital and nursing characteristics that pervade the hospital outcomes literature, additional characteristics of hospitals may be important to consider. The depth of support from pharmacy, emergency medicine, infectious disease, radiology, and microbiology departments may be important considerations for this specific patient population. In addition, we were unable to measure the quality of care delivered prior to the hospital episode. This care is likely to have occurred in outpatient settings, where claims data are not routinely available. It is also likely that patients who were clinically unstable and live remotely may not be able to travel to the NCI centers



for care, thus increasing the likelihood for poor outcomes in non-NCI centers.

We observed significant differences in patient characteristics between NCI and non-NCI hospitals. However, these characteristics were included in our final analyses as covariates. It is also possible that there may be differences in patients for characteristics (such as depth and duration of neutropenia, do-notresuscitate status, election for palliative care, cause of death) that are not available in these data. Thus, selection bias in patients cannot be excluded as an explanation for our findings. However, it is likely that patients in NCI cancer centers are more likely to receive chemotherapy at higher dose intensities than non-NCI centers. Confirmation of our findings with datasets that possess more granular patient detail would be a welcome addition to the literature. An analytic approach to address unmeasured patient severity of illness would include the use of instrumental variable analysis to identify characteristics that increase the proclivity of care receipt in NCI hospitals, yet are not associated with mortality. An example of this would be a patient's geographic distance to an NCI cancer center. Regrettably, geographic location was not available in our patient dataset.

Another reason for our principal finding is that the patients studied were too ill at presentation to benefit from organization-outcomes relationships, contrary to the previous hypothesis. If so, the emphasis for research and practice should be on studying processes of care (e.g., prompt antibiotics, astute assessment and interventions for aberrant findings, and evidence-based sepsis management), rather than organizational characteristics. Strengthening efforts by training providers to identify patients at risk for this complication, and providing early intervention, may also mitigate poor outcomes.

When the persistent and significant effect of NCI cancer centers is considered, we attempted to examine possible correlates of this designation. On average, NCI hospitals were larger, better staffed, had more nurses holding at least a bachelor's degree, had a tenfold higher teaching intensity, and performed advanced procedures. However, these variables explained very little of the outcome variation. This compels researchers to study the organizational and clinical processes in place in NCIs that enable them to have better outcomes for this problem. It appears that hospitals with extensive human resources perform better for this patient population, suggesting that the additional investments to support NCI designation convey a benefit to patients. However, the majority of patients in the United States are not able to receive care in an NCI-designated center, and a part of the original mission was to disseminate cancer research findings to community clinicians (28). We are unable to examine the extent that knowledge regarding management of these patients is shared between NCI and other settings; this is a ripe area for future research.

One clinical practice recommendation is a more careful decision analysis to admit patients to the hospital for this complication in the first place. Despite a strong body of evidence that supports outpatient management of febrile neutropenia for patients at low risk for complications (29–36), this evidence-based approach has not been widely adopted in the United States (6, 7). Redesigned care models that incorporate outpatient management may reduce the risk of iatrogenic complications, with an indirect reduction on mortality related to adverse events.

#### Limitations

A significant limitation to our analysis is the age of the data. We studied patients admitted to hospitals between 1998 and 1999 because of a fortuitous linkage of claims, cancer registry, vital statistics, hospital characteristics, and access to nurse survey data that are rarely available. Between then and now, the speciation of organisms, the anti-infective agents used, the patient populations at risk, and the use of colony-stimulating factors to ameliorate neutropenia may have changed, but inpatient management of febrile neutropenia has not changed appreciably since the time of the study (37, 38). In addition, the NCI-designated hospitals are identical between 1998 and 2010. However, our findings should be interpreted cautiously and warrant investigation in more recent patient populations.

Because our primary data source was inpatient claims, we did not have access to data regarding chemotherapy, receipt of colony-stimulating factors or anti-infectives. Important clinical covariates, such as performance and functional status, are also missing. Our use of a state database restricted us to only four hospitals that held NCI designation. These limitations are presented alongside a sizeable patient sample, a sample of hospitals that is large and diverse, careful attention to risk adjustment of the patient population, and an important inclusion of patients below the age of 65 years that are rarely studied in claims-based quality of cancer care studies.

Finally, because of the original study design, the measures of nurse staffing, educational preparation, and practice environment were aggregated to the hospital level. Data specific to oncology units or ambulatory clinics were not available. However, because of capacity problems, immunocompromised cancer patients with fever are often admitted to non-oncology units. Thus, we feel that nursing measures aggregated to the hospital level are appropriate for this study.

## **CONCLUSIONS AND SUMMARY**

Mortality related to infectious complications is a significant problem for patients with cancer. Understandably, characteristics of individual patients are strongly associated with mortality. Yet after adjusting for these clinical characteristics, patients who received care in NCI-designated cancer centers were less likely to die following this common complication. Not all patients can or should be treated in NCI cancer centers, however. To improve outcomes for these vulnerable patients, future studies should first identify processes of care in place in high-performing centers and implement these efficacious interventions to other hospitals and clinics.

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design, analysis, or manuscript preparation. The study was designed, executed, and written solely by the authors.

## REFERENCES

- Crawford, J.; Dale, D.C.; Kuderer, N.M.; Culakova, E.; Poniewierski, M.S.; Wolff, D.; Lyman, G.H. Risk and timing of neutropenic events in adult cancer patients receiving chemotherapy: the results of a prospective nationwide study of oncology practice. J Natl Compr Canc Netw 2008, 6, 109-118.
- Larson, E.; Nirenberg, A. Evidence-based nursing practice to pre-2. vent infection in hospitalized neutropenic patients with cancer. Oncol Nurs Forum 2004, 31, 717-723.
- Bodey, G.P. The changing face of febrile neutropenia-from monotherapy to moulds to mucositis. Fever and neutropenia: the early years. J Antimicrob Chemother 2009, 63(Suppl. 1), i3-i13.
- Caggiano, V.; Weiss, R.V.; Rickert, T.S.; Linde-Zwirble, W.T. Incidence, cost, and mortality of neutropenia hospitalization associated with chemotherapy. Cancer 2005, 103, 1916-1924.
- Kuderer, N.M.; Dale, D.C.; Crawford, J.; Cosler, L.E.; Lyman, G.H. Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. Cancer 2006, 106, 2258-2266.
- Friese, C.R.; Wicklin Gillespie, T.; Rice, R.D. Neutropenia: state of the knowledge part II. Oncol Nurs Forum 2006, 33, 1202-
- Nirenberg, A.; Bush, A.P.; Davis, A.; Friese, C.R.; Gillespie, T.W.; Rice, R.D. Neutropenia: state of the knowledge part I. Oncol Nurs Forum 2006, 33, 1193-1201.
- Hewitt, M.; Simone, J.V. (eds.) Ensuring Quality Cancer Care. Washington, DC: National Cancer Policy Board, Institute of Medicine, 1999.
- Friese, C.R.; Lake, E.T.; Aiken, L.H.; Silber, J.H.; Sochalski, J. Hospital nurse practice environments and outcomes for surgical oncology patients. Health Serv Res 2008, 43, 1145-1163.
- Birkmeyer, J.D.; Dimick, J.B.; Birkmeyer, N.J. Measuring the quality of surgical care: structure, process, or outcomes? J Am Coll Surg 2004, 198, 626-632.
- Birkmeyer, N.J.O.; Goodney, P.P.; Stukel, T.A.; Hillner, B.E.; Birkmeyer, J.D. Do cancer centers designed by the National Cancer Institute have better surgical outcomes? Cancer 2005, 103, 435-441.
- Mitchell, P.H.; Shortell, S.M. Adverse outcomes and variations in organization of care delivery. Med Care 1997, 35(Suppl. 11), NS19-NS32.
- National Cancer Institute. Cancer Centers Program Cancer Centers List. Bethesda, MD: National Cancer Institute. 2010. Available at http://cancercenters.cancer.gov/cancer\_centers/cancercenters-names.html. Accessed January 26, 2010.
- Silber, J.H.; Romano, P.S., Rosen, A.K.; Wang, Y.; Even-Shoshan, O.; Volpp, K.G. Failure-to-rescue: comparing definitions to measure quality of care. Med Care 2007, 45, 918-925.
- Brewster, A.C.; Karlin, B.G.; Hyde, L.A.; Jacobs, C.M.; Bradbury, R.C.; Chae, Y.M. MEDISGRPS: a clinically based approach to classifying hospital patients at admission. Inquiry 1985, 22, 377-387.
- 16. lezzoni, L.I.; Moskowitz, M.A. A clinical assessment of Medis-Groups. JAMA 1988, 260, 3159-3163.
- Aiken, L.H.; Clarke, S.P.; Sloane, D.M.; Sochalski, J.; Silber, J.H. Hospital nurse staffing and patient mortality, nurse burnout, and job dissatisfaction. JAMA 2002, 288, 1987-1993.
- Hartz, A.J.; Krakauer, H.; Kuhn, E.M.; Young, M.; Jacobsen, S.J.; Gay, G.; Muenz, L.; Katzoff, M.; Bailey, R.C.; Rimm, A.A. Hospital characteristics and mortality rates. N Engl J Med 1989, 321, 1720-1725
- Silber, J.H.; Rosenbaum, P.R.; Schwartz, J.S.; Ross, R.N.; 19. Williams, S.V. Evaluation of the complication rate as a measure

- of quality of care in coronary artery bypass graft surgery. JAMA **1995**. 274. 317-323.
- 20. Ayanian, J.Z.; Weissman, J.S. Teaching hospitals and quality of care: a review of the literature. Milbank Q 2002, 80, 569-593.
- 21. Lake, E.T. Development of the practice environment scale of the nursing work index. Res Nurs Health 2002, 25, 176-188.
- Lake, E.T., Friese, C.R. Variations in nursing practice environments: relation to staffing and hospital characteristics. Nurs Res **2006**, *55*, 1-9.
- 23. Bursac, Z.; Gauss, C.H.; Williams, D.K.; Hosmer, D.W. Purposeful selection of variables in logistic regression. Source Code Biol Med
- Hanley, J.A.; McNeil, B.J. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 1982, 143, 29-36,
- 25. Rogers, W.H. Regression standard errors in clustered samples. Stata Tech Bull 1993, 13, 19-23.
- 26. Huber, P.J. The behavior of maximum likelihood estimates under non-standard conditions. Proceedings of the Fifth Berkeley Symposium on Mathematical Statistics and Probability. Vol 1. Berkeley, CA: University of California Press, 1967, 221-233.
- Jencks, S.F.; Williams, D.K.; Kay, T.L. Assessing hospitalassociated deaths from discharge data: the role of length of stay and comorbidities. JAMA 1988, 260, 2240-2246.
- 28. Nathan, D.; Benz, E.J. Comprehensive cancer centres and the war on cancer. Nat Rev Cancer 2001, 1, 240-245
- Klastersky, J.; Paesmans, M.; Rubenstein, E.B.; Boyer, M.; Elting, L.; Feld, R.; Gallagher, J.; Herrstedt, J.; Rapoport, B.; Rolston, K.; Talcott, J. The multinational association for supportive care in cancer risk index: a multinational scoring system for identifying low-risk febrile neutropenic cancer patients. J Clin Oncol 2000, 18, 3038-3051.
- 30. Escalante, C.P.; Rubenstein, E.B.; Rolston, K.V. Outpatient antibiotic treatment in low-risk febrile neutropenic cancer patients. Support Care Cancer 1996, 4, 358-363.
- Escalante, C.P.; Rubenstein, E.B.; Rolston, K.V. Outpatient antibiotic therapy for febrile episodes in low-risk neutropenic patients with cancer. Cancer Invest 1997. 15. 237-242.
- Escalante, C.P.; Weiser, M.A.; Manzullo, E.; Benjamin, R.; Rivera, E.; Lam, T.; Ho, V.; Valdres, R.; Lee, E.L.; Badrina, N.; Fernandez, S.; DeJesus, Y.; Rolston, K. Outcomes of treatment pathways in outpatient treatment of low risk febrile neutropenic cancer patients. Support Care Cancer 2004, 12, 657-662.
- Rubenstein, E.B.; Rolston, K.; Benjamin, R.S. Outpatient treatment of febrile episodes in low-risk neutropenic patients with cancer. Cancer 1993, 71, 3640-3646.
- 34. Chamilos, G.; Bamias, A.; Efstathiou, E.; Zorzou, P.M.; Kastritis, E.; Kostis, E.; Papadimitriou, C.; Dimopoulos, M.A. Outpatient treatment of low-risk neutropenic fever in cancer patients using oral moxifloxacin. Cancer 2005, 103, 2629-2635.
- 35. Malik, I.A.; Khan, W.A.; Karim, M.; Aziz, Z.; Khan, M.A. Feasibility of outpatient management of fever in cancer patients with low-risk neutropenia: results of a prospective randomized trial. Am J Med **1995**, *98*, 224–231.
- Sipsas, N.V.; Bodey, G.P.; Kontoyiannis, D.P. Perspectives for the 36. management of febrile neutropenic patients with cancer in the 21st century. Cancer 2005, 103, 1103-1113.
- Pizzo, P.A. The changing face of febrile neutropenia-from monotherapy to moulds to mucositis. Where do we go from here? J Antimicrob Chemother 2009, 63(Suppl. 1), i16-i17.
- National Comprehensive Cancer Network. Practice Guidelines in Oncology: Prevention and Treatment of Cancer-Related Infections. Fort Washington, PA: National Comprehensive Cancer Network, 2008 (Retrieved July 15, 2009, from http://www.nccn.org).

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