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Original article

A retrospective study of the clinical and economic burden during hospitalizations among cancer patients with febrile neutropenia

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Abstract

Objective:
The objective of this study was to provide up-to-date estimates of the clinical and economic burden that occurs during inpatient treatment of cancer patients with febrile neutropenia (FN).

Methods:
A retrospective cohort study was conducted using 2007–2010 hospital discharge data from the Premier database. The study population included adult patients with discharge diagnoses of neutropenia (ICD-9 code 288.0x) with fever or infection and receipt of intravenous antibiotics and female breast cancer, lung cancer, colorectal cancer, ovarian cancer, non-Hodgkin lymphoma (NHL), or Hodgkin lymphoma. Primary study outcomes were inpatient mortality, hospital length of stay (LOS), and total hospitalization cost for each patient's first FN-related hospitalization. Logistic regressions (for mortality) and multivariate linear regressions (for LOS and cost) were conducted to assess the effect of comorbidities and infection types on study outcomes, adjusting for other patient and hospital characteristics.

Results:
Among 16,273 cancer patients hospitalized with FN, the inpatient case fatality rate was 10.6%, mean LOS was 8.6 days, and mean total hospitalization cost was $18,880. Lung cancer patients had the highest inpatient case fatality rate (15.7%), and NHL patients had the longest LOS (10.1 days) and the highest cost ($24,218). Multivariate analyses showed that most comorbidities were associated with a greater risk of mortality, longer LOS, and higher cost. Septicemia/bacteremia and pneumonia were associated with a greater risk of mortality, and most types of infection were associated with a longer LOS and higher cost.

Limitations:
The total burden of FN may be under-estimated in this study because outpatient treatment and any patient deaths or costs that occurred outside of Premier hospitals could not be captured.

Conclusions:
FN-related hospitalizations among cancer patients are costly and accompanied by considerable mortality risk. Substantial differences in the clinical and economic burden of FN exist depending on cancer types, comorbidities, and infection types.

Introduction

Chemotherapy-induced febrile neutropenia (FN) is a common, life-threatening side-effect of myelosuppressive chemotherapy[1,2] that often requires immediate hospitalization and administration of empiric, broad-spectrum antibiotics[3].

Each year, conservative estimates project that 60,000–100,000 cancer patients in the US are hospitalized with neutropenic complications[4].

Significant risk of mortality and substantial costs are often seen during hospitalization of cancer patients with FN[3,5,6]. The clinical and economic burden of FN-related hospitalizations among cancer patients have been examined in two large US studies. Using discharge data from hospital databases from seven states in 1999, Caggiano *et al.*[5] reported an inpatient case fatality rate of 6.8%, mean hospital length of stay (LOS) of 9.2 days, and mean total cost for hospitalization of $13,372 (1999 US dollars). Similarly, Kuderer *et al.*[3] used hospital discharge data from 1995–2000 from 115 academic medical centers and reported an inpatient case fatality rate of 9.5%, mean hospital LOS of 11.5 days, and mean total cost for hospitalization of $20,290 (2000 US dollars). In a more recent study (2005–2008), Schilling *et al.*[6] used a hospital database maintained by ASPEN Healthcare Metrics and reported an inpatient case fatality rate of 13.7%, a mean LOS of 10.7 days, and mean hospitalization cost of $22,839 (2009 US dollars) for cancer patients with neutropenia and fever or infection. However, the size of the Schilling *et al.* study was relatively small ($n = 1809$) compared with the previous studies ($n = 20,780$ and $n = 41,779$)[3,5,6].

Cost data from these previous studies are now more than 10 years old or based on a relatively small study size. Additionally, clinical management of FN has changed considerably with incorporation of new antimicrobial drugs, better tailoring of antimicrobial therapy to the risk of complications, and increased outpatient management of low-risk FN patients[7–9]. These changes may affect the clinical and economic burden of FN-related hospitalizations. This retrospective cohort study used discharge data of cancer patients hospitalized with FN from one of the largest hospital databases in the US to provide up-to-date information on the clinical and economic burden of FN.

Patients and methods

Study population

This retrospective cohort study included adult patients ≥18 years of age with FN and a primary cancer type of female breast cancer, lung cancer, colorectal cancer, ovarian cancer, non-Hodgkin lymphoma (NHL), or Hodgkin lymphoma who were discharged from January 1, 2007–December 31, 2010 from a US hospital participating in the database maintained by Premier. Patients were excluded if they had received a hematopoietic stem cell transplant at any time before or during the index hospitalization or if they had diagnoses of multiple primary cancer types based on relevant Current Procedural Technology (CPT), International Classification of Disease, 9th edition (ICD-9), or Healthcare Common Procedure Coding System (HCPCS) codes.

FN was identified based on a discharge diagnosis of neutropenia (principal or secondary ICD-9 diagnosis code 288.0x), fever (principal or secondary ICD-9 diagnosis code 780.6x), or infection (codes listed in Supplemental Table 1), and receipt of any intravenous antibiotic agent recommended by the Infectious Disease Society of America (IDSA)[8,10] (Supplemental Table 2) for initial empirical therapy. Initial empirical therapy was defined as the receipt of such agents on 2 or more consecutive days during the hospitalization (or anytime before death if death occurred within 1 day after admission) when the first injection of such agent(s) occurred within the first 5 days after admission. Cancer type was ascertained based on a corresponding discharge diagnosis ICD-9 code (Supplemental Table 1).

Premier database

The Premier database includes extensively validated discharge files from all inpatients and visit records of hospital-based outpatients from over 400 geographically diverse US hospitals. Compared with the 2007 American Hospital Association (AHA) statistics[11], hospitals covered by Premier's database in 2008 were more likely to have larger size (300+ beds), be located in the South rather than the Northeast region, and be teaching hospitals. In addition to the data elements available in most standard hospital discharge files (e.g., demographics, diagnoses, discharge status, and physician and hospital characteristics), the Premier database also contains a date-stamped log of all cost items including procedures, medications, laboratory, and diagnostic and therapeutic services at the individual patient level. Data were fully de-identified and compliant with the 1996 Health Insurance Portability and Accountability Act (HIPAA).

Study outcomes

For any cancer patient with multiple FN-related hospitalization episodes during the study period, the first hospitalization episode of the patient (index hospitalization) was selected for the analysis. The primary study outcomes were inpatient mortality, hospital LOS, and total hospitalization cost, all of which were based on the index hospitalization. Mortality risk was reported as a simple inpatient case fatality rate (number of deaths divided by the number of admissions). All LOS calculations were based on the relevant admission and discharge dates. Total hospitalization cost was determined from clinical and billing records. All costs represent the hospital's internal assessment of the actual cost to the hospital of delivering goods and services (not amount charged or reimbursed) and were reported to

Premier in accordance with accepted accounting standards. These costs were not further standardized or adjusted when recorded in the Premier database. However, for the analyses presented here, costs from the database were adjusted to 2010 US dollars according to the hospital and related services component of the Consumer Price Index (CPI). Patient's discharge and survival outcomes (discharged alive, died before being discharged, or still in hospital and alive) on each day within 30 days after the start of the index hospitalization were also examined. Additionally, patient demographics, patient clinical characteristics, hospital characteristics, and hospitalization characteristics were summarized for each hospital episode included in the study.

Secondary outcomes included use of antimicrobial agents, detailed components of cost and resource use (e.g., use of the intensive care unit [ICU] and ICU LOS), and incidence, cost, and clinical outcomes for FN-related re-hospitalizations. Only re-hospitalizations more than 2 days after discharge from the index hospitalization were examined as re-admission outcomes. Re-admission within 2 days of the discharge from the index hospitalization was considered as an extended part of the index hospitalization.

Statistical analyses

Means, medians, standard deviations (SD), and 95% confidence intervals (CI) were reported as appropriate for continuous variables, and percentages and 95% CI were reported for all indicator variables. Descriptive analyses were used to summarize the mortality risk outcomes, utilization, cost, and all the other study variables (patient demographic and clinical characteristics, hospital characteristics, and hospitalization characteristics). All analyses were undertaken for the overall patient population, by whether the patient died during the index hospitalization, and by cancer type (female breast cancer, lung cancer, colorectal cancer, ovarian cancer, NHL, and Hodgkin lymphoma).

Pooled analysis

Summary statistics for the primary outcomes of the study (inpatient mortality risk, hospital LOS, and total hospitalization cost) were reported for index hospitalizations with different characteristics at the patient, hospital, or hospitalization level.

Multivariate analysis

Multivariate regression analysis was conducted separately for female breast cancer, lung cancer, and NHL to quantify the effect of patient comorbidity (i.e., congestive heart failure, other heart disease, lung disease, liver disease, renal disease, diabetes, cerebrovascular disease, peripheral vascular disease, deep venous thrombosis, pulmonary embolism, and anemia) and infection type (i.e., septicemia/bacteremia, pneumonia, urinary tract infection, intravenous site infection, candidiasis, bacterial infection–site unspecified, and other miscellaneous infection) on the primary study outcomes. Comorbidities were defined on the basis of discharge diagnosis from the index hospitalization and any previous hospitalizations within 180 days prior to the index hospitalization. Infection types were defined on the basis of discharge diagnosis from the index hospitalization. ICD-9 codes used to identify comorbidities and types of infection are listed in Supplemental Table 1. Logistic regression was used to estimate inpatient mortality risk, and ordinary least squares linear regression was used to estimate hospital LOS and total hospitalization cost. Each model included two alternative specifications. The first included indicator variables for comorbidities of interest; the second included the total number of comorbidities. The following potentially confounding variables were controlled: patient characteristics (i.e., age, gender, race/ethnicity, and primary payer) and hospitalization characteristics (i.e., discharge year and admission source). Hospital characteristics (i.e., region, urban/rural, teaching status, and bed size) were also controlled to account for variability in costs of FN due to region and type of hospital.

Linked claims data analysis

To estimate the percentage of hospitalizations for FN that were preceded by chemotherapy use in the 30 days before the FN episode, the Premier database was linked to the OptumInsight database, a large outpatient research database that incorporates de-identified medical and pharmacy claims, lab results, and enrollment data covering more than 35 million patients for a national managed care population. The linking process required hospital-level matching (based on the hospital's Medicare provider number and other hospital details) and discharge-level matching (based on admission date, discharge data, DRG [diagnosis related groups] or MS-DRG [Medicare severity diagnosis related groups], patient gender, and patient birth date). Only discharges with exactly matched records in both databases could be used in the linked claims data analysis. Previous analysis has shown that 2.7% of discharges with cancer as the principal ICD-9 diagnosis in the Premier database were linked to the OptumInsight database[12], which is likely a result of different populations captured in each database. The OptumInsight database includes a single payer and represents commercially-insured individuals, who tend to be younger. Older patients, in whom cancer is more prevalent, are less likely to be covered in any commercial insurance database. The Premier database

represents all payers and is more likely to capture the older patients.

Results

Patient demographics and hospitalization characteristics

A total of 16,273 index hospitalizations for adult cancer patients with evidence of neutropenia and fever/infection and administration of intravenous antibiotics were identified in the Premier database (Supplemental Table 3). Overall, patients had a mean (SD) age of 62.7 (13.5) years, and 60.1% of patients were female. The most common primary cancer types identified were NHL ($n = 5437$; 33.4%), lung cancer ($n = 4792$; 29.4%), and female breast cancer ($n = 3279$; 20.1%). Most patients had two or more comorbidities ($n = 10,384$; 63.8%), and the most common comorbidities were anemia ($n = 10,102$; 62.1%), lung disease ($n = 6037$; 37.1%), heart disease (congestive heart failure: $n = 1217$; 7.5% and other heart disease: $n = 9441$; 58.0%), and renal disease ($n = 3392$; 20.8%). Additional patient demographics are shown in Table 1.

Approximately half of the patients were treated by an attending physician with an oncology specialty ($n = 7937$; 48.8%). All patients had some type of infection, with septicemia/bacteremia ($n = 4657$; 28.6%) and pneumonia ($n = 3552$; 21.8%) being the most common types specified. Consistent with the study definition of FN, all patients received antibiotics. A total of 6666 patients (41.0%) received antifungals and 2822 (17.3%) received antivirals. Additional hospitalization characteristics are shown in Table 1.

Hospital providers were geographically distributed across the US, with 2955 patients (18.2%) treated at hospitals in the Northeast, 2709 (16.6%) treated at hospitals in the West, 7131 (43.8%) treated at hospitals in the South, and 3478 (21.4%) treated at hospitals in the Midwest. The majority of patients were treated at hospitals in urban locations ($n = 14,558$; 89.5%), with only a small sub-set treated at rural hospitals ($n = 1715$; 10.5%). Nearly half of the patients were treated at a teaching hospital ($n = 7263$; 44.6%). Most patients were treated at larger hospitals, with 36.6% of patients treated at hospitals having 300–499 beds, and 36.6% of patients treated at hospitals with 500+ beds.

Clinical and economic outcomes

Overall, 14,555 patients (89.4%) were discharged alive. Most patients were discharged to home ($n = 12,273$; 75.4%). The remainder of patients were discharged to another healthcare facility ($n = 2140$; 13.2%) or discharged to a different or unknown destination ($n = 142$; 0.9%).

Altogether 1718 patients died; the inpatient case fatality rate was 10.6% (95% CI: 10.1–11.0) overall and differed among cancer types (Table 2). The inpatient case fatality rate was highest for patients with lung cancer ($n = 750$; 15.7%; 95% CI = 14.6–16.7) and lowest for patients with female breast cancer ($n = 182$; 5.6%; 95% CI = 4.8–6.3). At the end of 30 days after admission to the hospital, 86.8% of patients had been discharged alive, 3.5% were still hospitalized, and 9.8% had died before being discharged (Figure 1).

For the index hospitalization, mean LOS across all cancer types was 8.6 days (95% CI = 8.5–8.8). A total of 3101 patients (19.1%) were treated in an ICU setting during their index hospitalization, with a mean LOS of 5.2 days spent in ICU. Hospital LOS varied among cancer types (Table 2). Patients with NHL had the longest mean LOS (10.1 days; 95% CI = 9.8–10.4), and patients with female breast cancer had the shortest mean LOS (5.9 days; 95% CI = 5.7–6.1).

Total hospitalization cost for the index hospitalization was available for 16,268 patients. Mean hospitalization cost across all cancer types was $18,880 (95% CI = 18,479–19,281); the mean cost per day of hospitalization was $2169 (95% CI = 2150–2189). Consistent with hospital LOS, cost was variable based on cancer type. NHL had the highest mean cost ($24,218; 95% CI = 23,328–25,109), and female breast cancer had the lowest mean cost ($11,132; 95% CI = 10,649–11,615). However, mean cost per day was similar among cancer types ($1901–$2348). Detailed components of hospital costs are available in Table 2.

Mean total hospitalization cost was lower and LOS was shorter for patients who were discharged alive than for patients who were discharged dead (Table 3). For patients discharged alive, mean cost was $17,322 (95% CI = 16,939–17,704) and mean LOS was 8.3 days (95% CI = 8.2–8.5). For patients who died while they were in the hospital, mean cost was $32,088 (95% CI = 30,219–33,956), and mean LOS was 11.0 days (95% CI = 10.4–11.6).

Re-admissions

Re-admission to the hospital was fairly common. In the 30 days following hospital discharge, 3460 patients (23.8%) were re-admitted to the hospital for any reason, and 853 patients (5.9%) were re-admitted to the hospital for FN-related reasons (Table 2). The FN-related re-admission rate was higher for patients with NHL (9.9%) and for patients with Hodgkin lymphoma (8.6%) than for patients with other tumor types (2.3–4.1%).

A total of 2220 patients (15.3%) were re-admitted for FN-related reasons at any time. For re-admissions among

Table 1. Patient sample.

	All ($n=16,273$)	Female Breast ($n=3279$)	Lung ($n=4792$)	Colorectal ($n=1542$)	Ovarian ($n=754$)	Non-Hodgkin Lymphoma ($n=5437$)	Hodgkin Lymphoma ($n=469$)
Age, years							
Mean (SD)	62.7 (13.5)	57.1 (11.9)	66.5 (10.0)	63.6 (12.1)	62.6 (13.2)	63.6 (15.0)	49.2 (20.1)
Median	64	57	67	64	63	66	49
Age group, years, *n* (%)							
18–44	1600 (9.8)	510 (15.6)	94 (2.0)	98 (6.4)	63 (8.4)	621 (11.4)	214 (45.6)
45–64	6692 (41.1)	1854 (56.5)	1786 (37.3)	688 (44.6)	332 (44.0)	1911 (35.1)	121 (25.8)
65–74	4758 (29.2)	694 (21.2)	1845 (38.5)	438 (28.4)	201 (26.7)	1508 (27.7)	72 (15.4)
75–84	2802 (17.2)	199 (6.1)	983 (20.5)	280 (18.2)	141 (18.7)	1151 (21.2)	48 (10.2)
85+	421 (2.6)	22 (0.7)	84 (1.8)	38 (2.5)	17 (2.3)	246 (4.5)	14 (3.0)
Gender, *n* (%)							
Female	9778 (60.1)	3279 (100.0)	2261 (47.2)	869 (56.4)	754 (100.0)	2409 (44.3)	206 (43.9)
Male	6495 (39.9)	NA	2531 (52.8)	673 (43.6)	NA	3028 (55.7)	263 (56.1)
Race/ethnicity, *n* (%)							
White	11,461 (70.4)	2174 (66.3)	3562 (74.3)	1049 (68.0)	555 (73.6)	3811 (70.1)	310 (66.1)
Black	1495 (9.2)	413 (12.6)	393 (8.2)	149 (9.7)	51 (6.8)	432 (7.9)	57 (12.2)
Hispanic	699 (4.3)	163 (5.0)	113 (2.4)	76 (4.9)	37 (4.9)	281 (5.2)	29 (6.2)
Other	2618 (16.1)	529 (16.1)	724 (15.1)	268 (17.4)	111 (14.7)	913 (16.8)	73 (15.6)
Comorbidities, *n* (%)							
Congestive heart failure	1217 (7.5)	116 (3.5)	438 (9.1)	72 (4.7)	46 (6.1)	512 (9.4)	33 (7.0)
Other heart disease	9441 (58.0)	1554 (47.4)	3293 (68.7)	848 (55.0)	410 (54.4)	3131 (57.6)	205 (43.7)
Lung disease	6037 (37.1)	672 (20.5)	2903 (60.6)	408 (26.5)	218 (28.9)	1712 (31.5)	124 (26.4)
Liver disease	774 (4.8)	152 (4.6)	158 (3.3)	97 (6.3)	28 (3.7)	316 (5.8)	23 (4.9)
Renal disease	3392 (20.8)	356 (10.9)	1109 (23.1)	409 (26.5)	182 (24.1)	1263 (23.2)	73 (15.6)
Diabetes	2991 (18.4)	482 (14.7)	939 (19.6)	275 (17.8)	121 (16.0)	1106 (20.3)	68 (14.5)
Cerebrovascular disease	347 (2.1)	46 (1.4)	137 (2.9)	28 (1.8)	20 (2.7)	105 (1.9)	11 (2.3)
Peripheral vascular disease	395 (2.4)	22 (0.7)	234 (4.9)	25 (1.6)	13 (1.7)	93 (1.7)	8 (1.7)
Deep venous thrombosis	92 (0.6)	18 (0.5)	28 (0.6)	6 (0.4)	3 (0.4)	35 (0.6)	2 (0.4)
Pulmonary embolism	282 (1.7)	41 (1.3)	110 (2.3)	33 (2.1)	23 (3.1)	70 (1.3)	5 (1.1)
Anemia	10,102 (62.1)	1700 (51.8)	3119 (65.1)	951 (61.7)	472 (62.6)	3564 (65.6)	296 (63.1)
Number of comorbidities, *n* (%)							
0	1834 (11.3)	676 (20.6)	246 (5.1)	179 (11.6)	104 (13.8)	552 (10.2)	77 (16.4)
1	4055 (24.9)	1086 (33.1)	813 (17.0)	436 (28.3)	185 (24.5)	1375 (25.3)	160 (34.1)
2	4311 (26.5)	831 (25.3)	1304 (27.2)	405 (26.3)	209 (27.7)	1463 (26.9)	99 (21.1)
3	3254 (20.0)	422 (12.9)	1240 (25.9)	288 (18.7)	145 (19.2)	1086 (20.0)	73 (15.6)
4+	2819 (17.3)	264 (8.1)	1189 (24.8)	234 (15.2)	111 (14.7)	961 (17.7)	60 (12.8)
Fever as primary or secondary diagnosis, *n* (%)	10,797 (66.3)	2473 (75.4)	2759 (57.6)	934 (60.6)	462 (61.3)	3836 (70.6)	333 (71.0)
Any infection, *n* (%)	16,273 (100.0)	3279 (100.0)	4792 (100.0)	1542 (100.0)	754 (100.0)	5437 (100.0)	469 (100.0)
Septicemia/bacteremia	4657 (28.6)	656 (20.0)	1458 (30.4)	452 (29.3)	210 (27.9)	1757 (32.3)	124 (26.4)
Pneumonia	3552 (21.8)	353 (10.8)	1747 (36.5)	192 (12.5)	108 (14.3)	1067 (19.6)	85 (18.1)
Urinary tract infection	2384 (14.7)	470 (14.3)	617 (12.9)	320 (20.8)	200 (26.5)	738 (13.6)	39 (8.3)
Intravenous site infection	280 (1.7)	59 (1.8)	52 (1.1)	27 (1.8)	18 (2.4)	114 (2.1)	10 (2.1)
Candidiasis	2161 (13.3)	414 (12.6)	713 (14.9)	170 (11.0)	73 (9.7)	734 (13.5)	57 (12.2)
Bacterial infection, site unspecified	2101 (12.9)	406 (12.4)	466 (9.7)	229 (14.9)	153 (20.3)	793 (14.6)	54 (11.5)
Other miscellaneous infection	6412 (39.4)	1679 (51.2)	1467 (30.6)	635 (41.2)	277 (36.7)	2132 (39.2)	222 (47.3)
Antimicrobial treatment, *n* (%)							
Any antibiotics	16,273 (100.0)	3279 (100.0)	4792 (100.0)	1542 (100.0)	754 (100.0)	5437 (100.0)	469 (100.0)
Any antifungals	6666 (41.0)	1060 (32.3)	1840 (38.4)	568 (36.8)	235 (31.2)	2751 (50.6)	212 (45.2)
Any antivirals	2822 (17.3)	347 (10.6)	416 (8.7)	156 (10.1)	54 (7.2)	1713 (31.5)	136 (29.0)

Primary payer, *n* (%)							
Medicare	8267 (50.8)	1052 (32.1)	2979 (62.2)	791 (51.3)	369 (48.9)	2936 (54.0)	140 (29.9)
Medicaid	1474 (9.1)	404 (12.3)	402 (8.4)	123 (8.0)	50 (6.6)	422 (7.8)	73 (15.6)
Other government provider	181 (1.1)	42 (1.3)	44 (0.9)	25 (1.6)	1 (0.1)	61 (1.1)	8 (1.7)
Managed care	4604 (28.3)	1354 (41.3)	966 (20.2)	423 (27.4)	248 (32.9)	1443 (26.5)	170 (36.2)
Non-managed care commercial	1226 (7.5)	335 (10.2)	279 (5.8)	127 (8.2)	62 (8.2)	380 (7.0)	43 (9.2)
Other payer*	521 (3.2)	92 (2.8)	122 (2.5)	53 (3.4)	24 (3.2)	195 (3.6)	35 (7.5)
Discharge year, *n* (%)							
2007	3814 (23.4)	771 (23.5)	1098 (22.9)	346 (22.4)	184 (24.4)	1306 (24.0)	109 (23.2)
2008	4093 (25.2)	859 (26.2)	1210 (25.3)	373 (24.2)	187 (24.8)	1362 (25.1)	102 (21.7)
2009	4369 (26.8)	850 (25.9)	1289 (26.9)	425 (27.6)	196 (26.0)	1474 (27.1)	135 (28.8)
2010	3997 (24.6)	799 (24.4)	1195 (24.9)	398 (25.8)	187 (24.8)	1295 (23.8)	123 (26.2)
Admission source, *n* (%)							
Emergency room	9099 (55.9)	1846 (56.3)	2884 (60.2)	878 (56.9)	427 (56.6)	2817 (51.8)	247 (52.7)
Physician referral	6322 (38.8)	1314 (40.1)	1649 (34.4)	600 (38.9)	290 (38.5)	2266 (41.7)	203 (43.3)
Transfer from another facility	690 (4.2)	91 (2.8)	206 (4.3)	43 (2.8)	27 (3.6)	307 (5.6)	16 (3.4)
Other/unknown	162 (1.0)	28 (0.9)	53 (1.1)	21 (1.4)	10 (1.3)	47 (0.9)	3 (0.6)

*Includes charity, indigent, self-pay, worker's compensations, and other.
SD, standard deviation; NA, not allowed.

these patients, the inpatient case fatality rate was 7.5% ($n = 167$; 95% CI = 6.4–8.6), mean LOS was 8.0 days (95% CI = 6.4–8.6), and mean cost was $17,235 (95% CI = 16,128–18,342).

Pooled analysis

When data were pooled across all cancer types studied and analyzed based on different sub-groups (e.g., by patient age), several factors were associated with increased mortality, LOS, and/or cost (Table 4). Of note, older age was associated with a higher mortality, with patients 18–44 years of age having an inpatient case fatality rate of 5.1% (95% CI = 4.0–6.1) and patients $\geq$75 years of age having an inpatient case fatality rate of 15.8% (95% CI = 14.6–17.1). However, LOS and cost were comparable among age groups. Males had higher mortality (12.6% vs 9.2%), a slightly longer LOS (9.1 vs 8.3 days), and higher cost ($21,038 vs $17,447) than did females. Compared with the average across all patients, most specific comorbidities were associated with higher mortality, longer LOS, and higher cost (Table 4). Finally, the inpatient case fatality rate in patients with septicemia/bacteremia (25.1%; 95% CI = 23.9–26.4) or pneumonia (20.3%; 95% CI = 19.0–21.6) was higher than the rate across the entire population (Table 4).

Multivariate analysis

Multivariate analyses were performed for female breast cancer, lung cancer, and NHL because these cancer types had a sufficient number of patients to perform meaningful analyses. First, specific types of comorbidities and infection were evaluated as potential risk factors for inpatient mortality and higher economic burden (i.e., longer LOS and higher hospitalization cost). Most comorbidities were associated with a higher risk of in-hospital mortality (Table 5), longer LOS (Table 6), and higher cost (Table 7). For example, for patients with NHL and lung disease, the risk of mortality was higher (risk ratio [RR] as approximated by the odds ratio = 4.5; 95% CI = 3.6–5.7), LOS was 3.6 days longer (95% CI = 3.0–4.2), and cost was $13,268 higher (95% CI = 11,441–15,095) than in NHL patients without lung disease. Similarly, for patients with NHL and liver disease, the risk of mortality was higher (RR = 2.3; 95% CI = 1.6–3.2), LOS was 4.7 days longer (95% CI = 3.6–5.9), and cost was $14,634 higher (95% CI = 11,239–18,029) than in NHL patients without liver disease. For patients with NHL and renal disease, the risk of mortality was higher (RR = 3.1; 95% CI = 2.5–3.8), LOS was 2.3 days longer (95% CI = 1.7–3.0), and cost was $10,408 higher (95% CI = 8391–12,425) than in NHL patients without renal disease. Similar results were seen for patients with other cancer types (Tables 5–7).

Table 2. Economic and clinical outcomes.

	All ($n=16,273$)	Female Breast ($n=3279$)	Lung ($n=4792$)	Colorectal ($n=1542$)	Ovarian ($n=754$)	Non-Hodgkin Lymphoma ($n=5437$)	Hodgkin Lymphoma ($n=469$)
Inpatient case fatality rate							
n (%)	1718 (10.6)	182 (5.6)	750 (15.7)	173 (11.2)	63 (8.4)	513 (9.4)	37 (7.9)
95% CI	10.1–11.0	4.8–6.3	14.6–16.7	9.6–12.8	6.4–10.3	8.7–10.2	5.4–10.3
LOS—all index patients, days							
n	16,273	3279	4792	1542	754	5437	469
Mean	8.6	5.9	8.4	9.6	9.0	10.1	8.6
Median	5	4	6	6	6	6	6
95% CI	8.5–8.8	5.7–6.1	8.2–8.7	9.0–10.1	8.2–9.7	9.8–10.4	7.6–9.6
Use of ICU							
n (%)	3101 (19.1)	347 (10.6)	1099 (22.9)	299 (19.4)	122 (16.2)	1133 (20.8)	101 (21.5)
ICU LOS, days							
Mean	5.2	3.8	4.9	5.6	5.5	5.8	6.3
Median	3	2	3	3	3	3	4
95% CI	5.0–5.5	3.3–4.2	4.6–5.3	4.8–6.5	4.0–6.9	5.3–6.2	5.1–7.5
Total hospitalization cost—all index patients, $*							
n	16,268	3278	4790	1542	754	5435	469
Mean	18,880	11,132	17,689	19,667	18,958	24,218	20,622
Median	10,396	6807	11,505	11,269	10,588	12,197	11,119
95% CI	18,479–19,281	10,649–11,615	17,129–18,249	18,365–20,969	17,000–20,917	23,328–25,109	17,746–23,498
Average cost per day of hospitalization, $							
n	16,268	3278	4790	1542	754	5435	469
Mean	2169	1901	2207	2096	2074	2317	2348
Median	1890	1687	1922	1796	1892	2018	2064
95% CI	2150–2189	1863–1939	2172–2242	2026–2165	2004–2144	2280–2354	2216–2481
Room and board costs, $							
n	15,886	3206	4701	1520	741	5268	450
Mean	8348	5381	7985	9390	8930	10,047	8929
95% CI	8169–8528	5138–5624	7710–8260	8710–10,069	8002–9858	9678–10,417	7604–10,254
ICU costs, $							
n	3017	341	1082	295	120	1088	91
Mean	9125	6592	8423	9637	10,524	10,195	10,687
95% CI	8680–9571	5632–7552	7780–9065	8207–11,066	7568–13,479	9345–11,045	8249–13,125
Non-ICU costs, $							
n	15,290	3135	4450	1472	721	5081	431
Mean	6873	4786	6387	7765	7426	8234	7066
95% CI	6732–7015	4591–4980	6184–6590	7172–8357	6721–8132	7946–8522	5949–8182
Laboratory costs, $							
n	16,223	3271	4776	1537	753	5419	467
Mean	976	634	873	983	958	1262	1110
95% CI	948–1004	606–662	845–901	926–1039	873–1044	1189–1336	970–1251
Pharmacy costs, $							
n	16,212	3265	4775	1539	751	5415	467
Mean	4122	2324	3386	4058	3933	5870	4465
95% CI	4005–4239	2198–2450	3265–3506	3768–4347	3318–4548	5584–6156	3537–5394
Antibiotics costs, $							
n	15,651	3169	4599	1485	718	5231	449
Mean	733	517	641	751	644	949	792
95% CI	702–764	470–563	614–668	663–838	512–775	871–1026	651–933

Anti-fungal costs, $							
n	6425	1026	1780	550	221	2646	202
Mean	553	332	363	549	443	748	931
95% CI	501–606	260–405	320–406	409–690	286–599	637–859	497–1366
Antiviral costs, $							
n	2696	333	401	150	52	1628	132
Mean	282	181	256	273	291	294	468
95% CI	250–313	144–218	169–344	162–384	151–431	255–333	172–764
Other drugs, $							
n	16,182	3252	4775	1539	750	5399	467
Mean	3110	1683	2571	3076	3132	4452	3106
95% CI	3015–3204	1582–1784	2474–2669	2843–3308	2627–3638	4219–4684	2477–3736
Non-drug pharmacy costs, $							
n	2891	428	827	272	121	1142	101
Mean	256	186	234	200	241	311	290
95% CI	224–289	135–238	192–277	134–265	125–358	240–382	114–465
Central supply costs, $							
n	12,688	2272	4002	1210	567	4290	347
Mean	726	426	693	869	842	868	622
95% CI	695–758	376–476	650–737	717–1022	683–1000	806–931	507–737
Surgery supply costs, $							
n	7167	958	2370	687	350	2605	197
Mean	626	484	514	478	537	808	933
95% CI	590–662	404–564	477–551	416–540	459–614	727–889	582–1284
Total discharged alive[†]							
n	14,555	3097	4042	1369	691	4924	432
Any FN-related re-admission within 30 days							
n (%)	853 (5.9)	127 (4.1)	149 (3.7)	32 (2.3)	20 (2.9)	488 (9.9)	37 (8.6)
95% CI	5.5–6.2	3.4–4.8	3.1–4.3	1.5–3.1	1.6–4.1	9.1–10.7	5.9–11.2
Any all-cause re-admission within 30 days							
n (%)	3460 (23.8)	422 (13.6)	886 (21.9)	260 (19.0)	151 (21.9)	1631 (33.1)	110 (25.5)
95% CI	23.1–24.5	12.4–14.8	20.6–23.2	16.9–21.1	18.8–24.9	31.8–34.4	21.4–29.6

All costs were adjusted to 2010 US dollars.
* Hospitals vary on how costs are assigned to sub-categories. This variability does not affect total cost.
[†]Incidences of FN-related and all-cause readmissions were calculated relative to the total number of patients discharged alive.
CI, confidence interval; LOS, length of stay; ICU, intensive care unit; FN, febrile neutropenia.

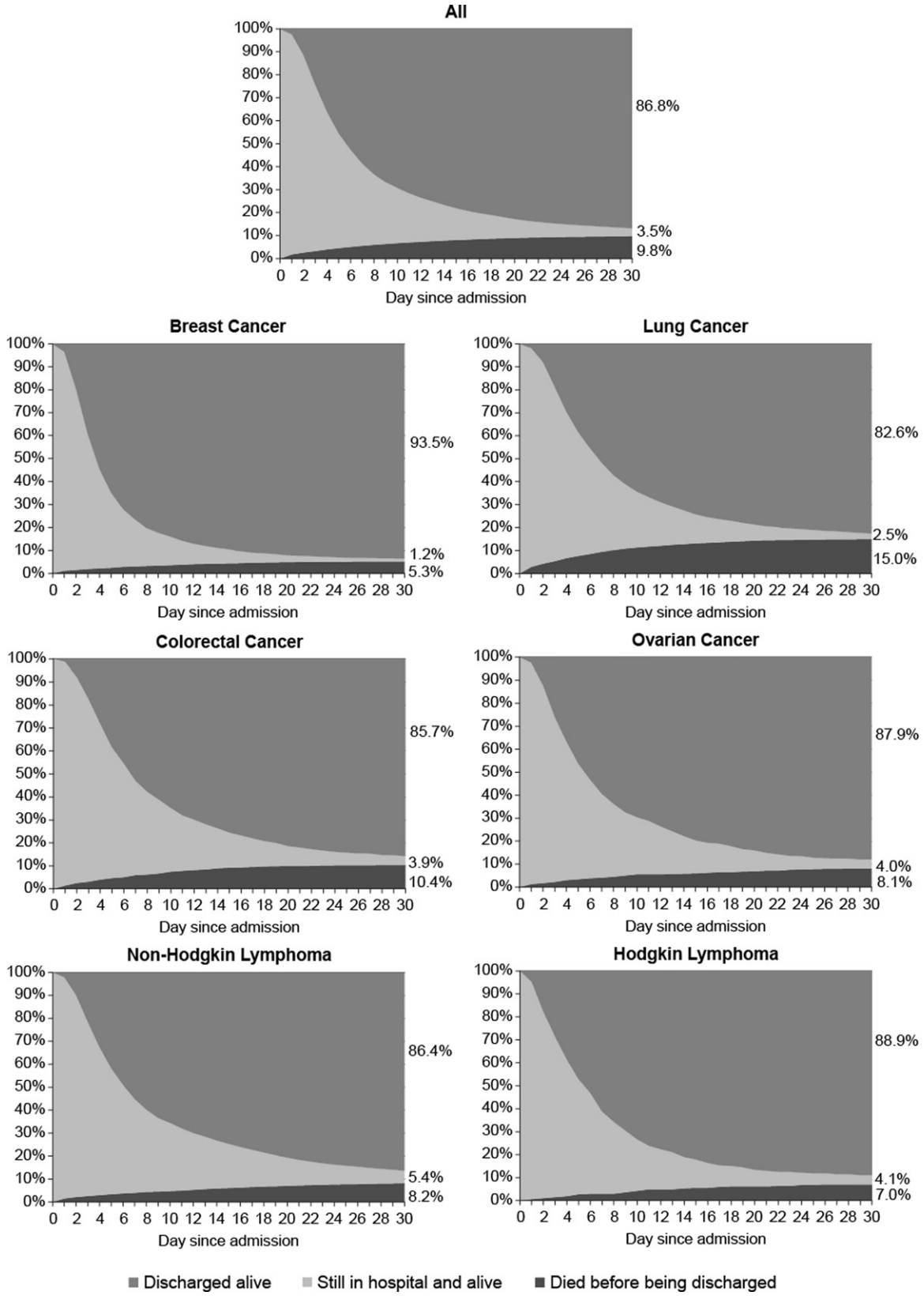

Figure 1. Mortality and discharge outcomes by day since admission. The percentages on the right margin of each graph represent the proportion of patients classified as ''discharged alive,'' ''still in hospital and alive,'' and ''died before being discharged'' during the 30 days following admission. For patients who were discharged alive, survival status after discharge date is unavailable in the hospital database.

Table 3. Cost and LOS by discharge status.

	All ($n = 16,273$)	Female Breast ($n = 3279$)	Lung ($n = 4792$)	Colorectal ($n = 1542$)	Ovarian ($n = 754$)	Non-Hodgkin Lymphoma ($n = 5437$)	Hodgkin Lymphoma ($n = 469$)
Inpatient case fatality rate							
n (%)	1718 (10.6)	182 (5.6)	750 (15.7)	173 (11.2)	63 (8.4)	513 (9.4)	37 (7.9)
95% CI	10.1–11.0	4.8–6.3	14.6–16.7	9.6–12.8	6.4–10.3	8.7–10.2	5.4–10.3
LOS for patients discharged alive, days							
n	14,555	3097	4042	1369	691	4924	432
Mean	8.3	5.7	8.4	9.3	8.8	9.6	8.0
Median	5	4	6	6	5	6	5
95% CI	8.2–8.5	5.5–5.9	8.2–8.6	8.8–9.8	8.0–9.5	9.4–9.9	7.1–8.9
LOS for patients discharged dead, days							
n	1718	182	750	173	63	513	37
Mean	11.0	9.4	8.6	11.3	11.0	14.6	15.8
Median	7	6	6	7	8	10	10
95% CI	10.4–11.6	7.9–10.9	7.9–9.2	9.0–13.6	7.9–14.1	13.3–15.9	8.8–22.8
Total hospitalization cost—patients discharged alive, $							
n	14,551	3096	4041	1369	691	4922	432
Mean	17,322	10,450	16,609	18,396	17,950	21,810	17,687
Median	9859	6640	11,089	10,861	10,125	11,615	10,286
95% CI	16,939–17,704	9990–10,909	16,041–17,176	17,142–19,651	16,077–19,823	20,964–22,656	15,646–19,727
Total hospitalization cost—patients discharged dead, $							
n	1717	182	749	173	63	513	37
Mean	32,088	22,743	23,517	29,722	30,016	47,325	54,889
Median	18,639	15,697	14,564	18,033	16,561	28,295	32,656
95% CI	30,219–33,956	19,309–26,177	21,711–25,322	23,868–35,575	18,796–41,235	42,982–51,668	28,682–81,096

All costs were adjusted to 2010 US dollars.
CI, confidence interval; LOS, length of stay.

Table 4. Pooled analysis.

Variable	*n*	Inpatient case fatality rate		LOS, days		Cost per hospitalization, $*	
		%	95% CI	Mean	95% CI	Mean	95% CI
All patients	16,273	10.6	10.1–11.0	8.6	8.5–8.8	18,880	18,479–19,281
Age, years							
18–44	1600	5.1	4.0–6.1	8.9	8.4–9.5	21,567	19,844–23,291
45–64	6692	8.7	8.0–9.4	8.3	8.1–8.5	18,609	17,961–19,257
65–74	4758	11.4	10.5–12.3	8.6	8.4–8.9	18,271	17,609–18,933
75+	3223	15.8	14.6–17.1	9.1	8.8–9.4	19,007	18,235–19,779
Gender							
Female	9778	9.2	8.6–9.8	8.3	8.1–8.5	17,447	16,967–17,927
Male	6495	12.6	11.8–13.4	9.1	8.8–9.3	21,038	20,344–21,732
Race/ethnicity							
White	11,461	10.1	9.6–10.7	8.3	8.2–8.5	18,143	17,686–18,600
Black	1495	11.8	10.2–13.5	10.0	9.5–10.6	21,401	19,982–22,820
Hispanic	699	10.2	7.9–12.4	8.5	7.8–9.2	20,273	18,214–22,331
Other	2618	11.8	10.6–13.1	9.2	8.8–9.6	20,296	19,181–21,411
Primary payer							
Commercial	5830	7.8	7.2–8.5	7.8	7.5–8.0	17,995	17,289–18,702
Government	9922	12.2	11.5–12.8	9.1	8.9–9.3	19,296	18,810–19,782
Other Payer[‡]	521	10.2	7.6–12.8	9.2	8.2–10.1	20,858	17,948–23,767
Hospital area: urban/rural							
Rural	1715	8.7	7.4–10.0	7.3	7.0–7.7	14,537	13,693–15,381
Urban	14,558	10.8	10.3–11.3	8.8	8.6–8.9	19,392	18,956–19,828
Hospital region							
Midwest	3478	8.9	7.9–9.8	7.8	7.5–8.1	16,423	15,724–17,123
Northeast	2955	12.2	11.1–13.4	9.9	9.5–10.3	24,529	23,285–25,773
South	7131	10.3	9.6–11.0	8.6	8.4–8.8	17,134	16,609–17,658
West	2709	11.6	10.4–12.8	8.4	8.1–8.8	20,473	19,391–21,555
Hospital teaching status							
Teaching	7263	10.4	9.7–11.1	9.2	9.0–9.4	21,222	20,552–21,892
Non-teaching	9010	10.7	10.0–11.3	8.2	8.0–8.3	16,992	16,513–17,470
Hospital bed size							
1–199	1912	9.0	7.7–10.3	7.0	6.7–7.3	15,117	14,301–15,933
200–299	2457	10.8	9.6–12.0	8.0	7.7–8.4	16,777	15,837–17,717
300–499	5948	11.3	10.5–12.1	8.6	8.4–8.9	18,193	17,595–18,791
500+	5956	10.2	9.4–11.0	9.4	9.1–9.6	21,643	20,858–22,427
Discharge year							
2007	3814	10.0	9.1–11.0	8.6	8.3–8.9	18,635	17,818–19,452
2008	4093	11.1	10.2–12.1	9.0	8.7–9.3	20,010	19,175–20,845
2009	4369	11.1	10.1–12.0	8.6	8.3–8.9	19,368	18,574–20,161
2010	3997	9.9	9.0–10.8	8.2	8.0–8.5	17,423	16,669–18,178
Admission source							
Emergency room	9099	11.8	11.1–12.4	8.4	8.2–8.6	18,532	18,014–19,050
Other admission	7174	9.0	8.4–9.7	8.9	8.7–9.1	19,321	18,693–19,950
Comorbidities							
Congestive heart failure	1217	21.4	19.1–23.8	12.5	11.8–13.1	29,827	27,792–31,862
Other heart disease	9441	13.2	12.5–13.9	9.4	9.2–9.6	21,001	20,426–21,576
Lung disease	6037	21.4	20.3–22.4	11.1	10.8–11.4	26,643	25,781–27,505
Liver disease	774	21.7	18.8–24.6	13.8	12.8–14.7	33,620	30,800–36,440
Renal disease	3392	25.8	24.4–27.3	12.1	11.7–12.5	30,594	29,342–31,846
Diabetes	2991	12.0	10.8–13.2	9.7	9.3–10.0	21,347	20,294–22,399
Cerebrovascular disease	347	21.9	17.5–26.3	13.1	11.9–14.4	31,233	27,672–34,795
Peripheral vascular disease	395	17.2	13.5–21.0	10.8	9.7–11.9	25,077	21,501–28,654
Deep venous thrombosis	92	7.6	2.1–13.1	14.6	11.9–17.2	33,914	25,405–42,424
Pulmonary embolism	282	23.0	18.1–28.0	13.9	12.4–15.4	34,362	30,078–38,646
Anemia	10,102	11.0	10.4–11.6	9.8	9.6–10.0	21,719	21,166–22,272
Number of comorbidities							
0	1834	2.5	1.8–3.2	4.9	4.7–5.2	9313	8813–9813
1	4055	3.6	3.0–4.2	6.3	6.1–6.5	12,575	12,087–13,062
2	4311	7.9	7.1–8.7	8.3	8.0–8.6	16,971	16,313–17,629
3	3254	14.4	13.2–15.6	10.2	9.8–10.5	22,664	21,691–23,636
4+	2819	25.4	23.8–27.0	13.0	12.6–13.5	32,733	31,306–34,160
Infections[†]							
Septicemia/bacteremia	4657	25.1	23.9–26.4	11.4	11.1–11.8	27,941	26,935–28,947
Pneumonia	3552	20.3	19.0–21.6	11.0	10.7–11.4	26,148	25,066–27,230
Urinary tract infection	2384	9.9	8.7–11.1	11.2	10.7–11.7	24,260	22,939–25,581
Intravenous site infection	280	7.5	4.4–10.6	15.0	13.3–16.7	35,076	30,570–39,581
Candidiasis	2161	11.8	10.5–13.2	11.5	11.0–12.0	24,705	23,508–25,903

Bacterial infection, site unspecified	2101	7.0	5.9–8.1	11.7	11.2–12.2	25,258	23,825–26,692
Other miscellaneous infection	6412	2.4	2.1–2.8	6.0	5.8–6.1	11,968	11,563–12,374

All costs were adjusted to 2010 US dollars.
*Cost information was available for 16,268 patients.
†Types of infection are not mutually exclusive.
‡Includes charity, indigent, self-pay, worker's compensations, and other.
CI, confidence interval.

Table 5. Multivariate analysis of in-hospital mortality by specific comorbidities and infection types.

	Female Breast Cancer ($n = 3279$)		Lung Cancer ($n = 4792$)		Non-Hodgkin Lymphoma ($n = 5437$)	
	Risk ratio	95% CI	Risk ratio	95% CI	Risk ratio	95% CI
Comorbidities						
Congestive heart failure	2.0	1.0–3.8	1.0	0.8–1.3	1.0	0.7–1.4
Other heart disease	0.9	0.6–1.4	1.1	0.9–1.4	1.1	0.9–1.5
Lung disease	3.9	2.7–5.7	2.9	2.4–3.7	4.5	3.6–5.7
Liver disease	2.0	1.1–3.7	1.6	1.0–2.4	2.3	1.6–3.2
Renal disease	5.2	3.4–7.8	2.5	2.1–3.1	3.1	2.5–3.8
Diabetes mellitus	0.6	0.4–1.0	0.9	0.7–1.2	0.8	0.6–1.0
Cerebrovascular disease	1.3	0.4–3.6	1.4	0.9–2.2	1.6	0.9–2.8
Peripheral vascular disease	0.4	0.0–3.5	1.1	0.7–1.6	1.1	0.6–2.2
Deep venous thrombosis	1.1	0.1–10.3	0.4	0.1–1.9	0.5	0.1–2.5
Pulmonary embolism	4.4	1.6–11.9	1.8	1.1–3.0	1.5	0.7–2.9
Anemia	0.6	0.4–0.9	0.7	0.6–0.9	0.8	0.6–1.0
Infection						
Septicemia/bacteremia	4.1	2.6–6.5	3.8	3.1–4.7	4.7	3.6–6.3
Pneumonia	2.1	1.3–3.3	1.2	1.0–1.5	1.5	1.1–1.9
Urinary tract infection	0.8	0.5–1.4	0.7	0.5–1.0	0.7	0.5–1.0
Intravenous site infection	0.3	0.1–1.1	0.1	0.0–0.5	0.3	0.1–0.6
Candidiasis	0.8	0.5–1.4	0.9	0.7–1.2	0.9	0.7–1.3
Bacterial infection, site unspecified	0.3	0.2–0.6	0.5	0.4–0.7	0.7	0.5–0.9
Other miscellaneous infection	0.2	0.1–0.5	0.4	0.3–0.6	0.5	0.4–0.9

CI, confidence interval.
The following potentially confounding variables were controlled: patient characteristics (i.e., age, gender, race/ethnicity, and primary payer), hospitalization characteristics (i.e., discharge year and admission source), and hospital characteristics (i.e., region, urban/rural, teaching status, and bed size).

Septicemia/bacteremia and pneumonia were also associated with higher risk of mortality (Table 5), longer LOS (Table 6), and higher cost (Table 7) across all three cancer types studied. For patients with female breast cancer who had septicemia or bacteremia, the risk of mortality was higher (RR = 4.1; 95% CI = 2.6–6.5), LOS was 1.7 days longer (95% CI = 1.0–2.3), and cost was $5664 higher (4233–7095) than for patients with female breast cancer who did not have septicemia or bacteremia. Similarly, for female breast cancer patients with pneumonia, the risk of mortality was higher (RR = 2.1; 95% CI = 1.3–3.3), LOS was 2.5 days longer (95% CI = 1.8–3.2), and cost was $6593 higher (95% CI = 4949–8237) than for patients with female breast cancer who did not have pneumonia.

When the number of comorbidities was included in the multivariate models rather than specific comorbidities, higher numbers of comorbidities were associated with higher risk of mortality and higher cost. For example, for patients with female breast cancer, the risk of mortality was greater for patients with two comorbidities (RR = 3.5; 95% CI = 1.5–8.1) than for patients with no comorbidities. The risk of mortality continued to increase as the number of comorbidities increased. Relative to patients with no comorbidities, the RR of mortality for female breast cancer patients with three comorbidities was 5.2 (95% CI = 2.2–12.2), and the RR for patients with four or more comorbidities was 9.6 (95% CI = 4.0–22.7). Mean cost for patients with NHL who had one comorbidity was $4084 higher (95% CI = 1107–7061) than cost for NHL patients who had no comorbidities. Similarly, cost for patients with NHL who had two comorbidities was $9627 higher (95% CI = 6626–12,628), cost for patients with three comorbidities was $16,949 higher (95% CI = 13,765–20,133), and cost for patients with four

Table 6. Multivariate analysis of length of stay by specific comorbidities and infection types.

	Female Breast Cancer ($n = 3279$)		Lung Cancer ($n = 4792$)		Non-Hodgkin Lymphoma ($n = 5437$)	
	Estimated mean additional LOS (days)	95% CI	Estimated mean additional LOS (days)	95% CI	Estimated mean additional LOS (days)	95% CI
Comorbidities						
Congestive heart failure	2.7	1.7–3.8	1.1	0.3–1.8	1.2	0.3–2.2
Other heart disease	0.2	−0.2–0.6	0.2	−0.3–0.7	0.9	0.3–1.5
Lung disease	1.6	1.1–2.1	1.8	1.3–2.3	3.6	3.0–4.2
Liver disease	2.5	1.6–3.4	2.6	1.4–3.8	4.7	3.6–5.9
Renal disease	2.2	1.6–2.9	1.0	0.4–1.5	2.3	1.7–3.0
Diabetes mellitus	0.1	−0.4–0.7	0.3	−0.2–0.8	0.8	0.1–1.4
Cerebrovascular disease	0.1	−1.6–1.7	2.8	1.5–4.1	4.8	2.8–6.7
Peripheral vascular disease	−0.9	−3.2–1.5	1.2	0.2–2.2	−0.4	−2.5–1.6
Deep venous thrombosis	1.8	−0.8–4.4	5.7	2.9–8.5	5.5	2.2–8.8
Pulmonary embolism	4.1	2.4–5.9	1.4	0.0–2.9	7.0	4.7–9.4
Anemia	1.5	1.1–1.9	1.5	1.1–2.0	1.9	1.3–2.5
Infection						
Septicemia/bacteremia	1.7	1.0–2.3	0.8	0.2–1.3	3.4	2.6–4.1
Pneumonia	2.5	1.8–3.2	1.9	1.3–2.4	2.4	1.6–3.3
Urinary tract infection	1.8	1.2–2.5	2.1	1.4–2.9	2.3	1.4–3.2
Intravenous site infection	1.6	0.1–3.1	4.0	1.9–6.1	3.8	1.9–5.7
Candidiasis	1.8	1.1–2.6	2.6	2.0–3.3	3.9	3.1–4.8
Bacterial infection, site unspecified	0.9	0.2–1.6	1.1	0.3–1.9	2.9	2.1–3.8
Other miscellaneous infection	0.2	−0.5–0.9	−0.2	−0.9–0.5	0.8	−0.1–1.7

CI, confidence interval; LOS, length of stay.
The following potentially confounding variables were controlled: patient characteristics (i.e., age, gender, race/ethnicity, and primary payer), hospitalization characteristics (i.e., discharge year and admission source), and hospital characteristics (i.e., region, urban/rural, teaching status, and bed size).

Table 7. Multivariate analysis of hospitalization cost by specific comorbidities and infection types.

	Female Breast Cancer ($n = 3278$)		Lung Cancer ($n = 4790$)		Non-Hodgkin Lymphoma ($n = 5435$)	
	Estimated mean additional cost (2010 $)	95% CI	Estimated mean additional cost (2010 $)	95% CI	Estimated mean additional cost (2010 $)	95% CI
Comorbidities						
Congestive heart failure	4402	1997–6807	2517	628–4405	2754	−81–5588
Other heart disease	11	−937–959	1234	27–2442	3133	1374–4893
Lung disease	5274	4149–6400	5606	4478–6734	13,268	11,441–15,095
Liver disease	3795	1716–5875	5169	2218–8119	14,634	11,239–18,029
Renal disease	6469	4990–7948	4215	2896–5533	10,408	8391–12,425
Diabetes mellitus	188	−1078–1454	957	−395–2309	877	−1148–2902
Cerebrovascular disease	281	−3422–3984	5978	2813–9144	12,656	6923–18,389
Peripheral vascular disease	−1387	−6678–3903	2752	295–5209	−399	−6492–5694
Deep venous thrombosis	1237	−4627–7100	7922	1020–14,825	16,727	6901–26,553
Pulmonary embolism	11,299	7383–15,215	5497	1981–9013	16,070	9061–23,079
Anemia	3154	2272–4036	3657	2535–4778	4532	2857–6207
Infection						
Septicemia/bacteremia	5664	4233–7095	4727	3354–6100	11,232	9003–13,461
Pneumonia	6593	4949–8237	4905	3455–6355	7678	5276–10,079
Urinary tract infection	4452	2904–6001	4998	3153–6842	6745	4099–9391
Intravenous site infection	3789	438–7140	7013	1879–12,147	10,029	4424–15,634
Candidiasis	4560	2943–6177	4971	3333–6609	8557	5961–11,153
Bacterial infection, site unspecified	1692	142–3243	1200	−767–3167	6891	4358–9425
Other miscellaneous infection	1673	77–3268	308	−1515–2131	3720	990–6450

CI, confidence interval.
The following potentially confounding variables were controlled: patient characteristics (i.e., age, gender, race/ethnicity, and primary payer), hospitalization characteristics (i.e., discharge year and admission source), and hospital characteristics (i.e., region, urban/rural, teaching status, and bed size).

or more comorbidities was $28,768 higher (95% CI = 25,429–32,107) than cost for patients with no comorbidities.

Linked claims data analysis

A total of 371 records (2.3% of all discharges in the study sample) from the Premier database could be linked to the OptumInsight database, with 105 patients with female breast cancer, 86 patients with lung cancer, 41 patients with colorectal cancer, 14 patients with ovarian cancer, 113 patients with NHL, and 12 patients with Hodgkin lymphoma having records in both databases. Most patients were documented to have received chemotherapy within 30 days before the index hospitalization for FN ($n = 291$; 78.4%). The percentage of patients who were documented to have received chemotherapy in the 30 days before their index hospitalization for FN was highest for patients with female breast cancer (90.5%; $n = 95$) and lowest for patients with NHL (59.3%; $n = 67$). Similar percentages of patients had prior chemotherapy among patients with lung cancer (82.6%; $n = 71$), colorectal cancer (87.8%; $n = 36$), ovarian cancer (85.7%; $n = 12$), and Hodgkin lymphoma (83.3%; $n = 10$).

Discussion

In this study of 16,273 cancer patients hospitalized with FN, the average inpatient case fatality rate for patients with all cancer types we studied was 10.6%, LOS was 8.6 days, and cost of hospitalization was $18,880. Several factors were associated with variability in these measures, including cancer type, discharge status, presence of comorbidities, and type of infection. Of note, LOS was longer and cost was higher among patients who died while hospitalized than among patients discharged alive. These results are consistent with Michels *et al.*[13], who reported that, among FN patients, those who died had higher mean per patient per month total cost than surviving FN patients ($21,214; 95% CI = 19,192–23,237 vs $8227; 95% CI = 7987–8466).

This study provides updated estimates of the inpatient case fatality rates, LOS, and cost that accompany FN treated in the hospital setting. Two large studies of US cancer patients conducted a decade ago reported inpatient case fatality rates of 6.8% and 9.5%, mean LOS of 9.2 days and 11.5 days, and mean total cost of hospitalization of $13,400 (1999 US dollars) and $20,290 (2000 US dollars)[3,5]. In a more recent study (2005–2008), the inpatient case fatality rate was 13.7%, mean LOS was 10.7 days, and mean hospitalization cost was $22,839 (2009 US dollars)[6]. Differences in the cancer types included in each study population may have contributed to differences seen among the studies. For example, treatment for patients with hematological cancers was generally accompanied by higher cost and a longer LOS than for patients with solid tumors, and the inpatient case fatality rate is often much greater among patients with lung cancer than among patients with female breast cancer[3,5,6]. The definitions of FN, healthcare facility types, patient comorbidities, types of infection, and changes in cost of care and treatment of FN over time may also have contributed to the differences seen among studies.

In addition to providing updated estimates on the impact of FN, several other factors differentiate this study. The National Comprehensive Cancer Network (NCCN)[14], European Organisation for Research and Treatment of Cancer (EORTC)[15], and Infectious Disease Society of America (IDSA) guidelines[8] all recommend prompt treatment of FN with broad-spectrum antibiotics. In light of these recommendations, receipt of intravenous antibiotics was incorporated into the definition of FN for this study, leading to a more refined definition of FN. Additionally, this study provides considerable detail on the economic and clinical burden of FN, including detailed cost components and resource utilization measures, day-by-day patient survival, and the incidence, cost, and the inpatient case fatality rate during re-admission. Finally, mean hospitalization cost in this study was determined based on the actual costs reported by each hospital rather than costs derived from charges (under certain assumption of cost-to-charge ratio), which were used in earlier studies[3,5]. Together, these details provide a more comprehensive assessment of the clinical and economic impact of FN than in previous studies.

This study also evaluated the impact of comorbidities and type of infections on mortality, LOS, and cost. The results from the pooled analysis and the multivariate analyses were similar for most comorbidities. However, in the pooled analysis, the inpatient case fatality rate for anemia (11.0%) was higher than the inpatient case fatality rate across all patients (10.6%), while the multivariate analyses indicated that anemia might be associated with lower risk of mortality (see Table 5). Several factors may have contributed to this discrepancy. First, the pooled analysis looked at results across all major cancer types examined in this study, while the multivariate analyses were conducted separately for female breast cancer, lung cancer, and NHL. Additionally, other comorbidities, infections, or other variables could confound the relationship between anemia and mortality.

The patients in this study may represent a population that is at high risk for serious complications of FN. Patients with FN can be categorized as high- or low-risk on the basis of validated risk models[16,17]. Low-risk patients are candidates for oral antibiotics in the inpatient setting or outpatient management of FN[14,16–20] and would not be captured in this study population. Little information is available about the incidence and treatment of low-risk

patients, but recent estimates suggest ~20% of patients may be treated for FN in the outpatient setting[21–23].

Hospitalization with intravenous antibiotics is the current standard of care for FN, but the clinical and economic burden of FN extends beyond the initial hospitalization. Among patients with FN, subsequent neutropenia-related care has been estimated to represent ~40% of the total healthcare costs for treating FN[2]. Finally, indirect costs of FN, such as lost productivity, care-giving burden, and cost of transportation to and from the healthcare facility, can increase cost estimates of FN[24–26]. These costs and changing treatment patterns should be considered when determining the impact of FN.

Determining the true cost of FN is an important factor in clinical decision-making, and estimates of FN cost can impact patient care. For example, initial estimates of the hospitalization cost for FN were $1000 per day[27]. In this setting, colony-stimulating factor (CSF) use was predicted to be cost-saving when the risk of hospitalization with FN was >40%[27]. More recent estimates that include a broader range of costs predicted that CSFs would be cost-saving when the risk of hospitalization with FN was ~20%[1,28]. These estimates are consistent with current NCCN and ASCO guidelines for use of CSFs to reduce the risk, duration, and severity of FN[29,30]. These guidelines recommend prophylactic use of CSFs in patients with a ≥20% risk of FN based on the chemotherapy regimen and treatment-related factors. Careful consideration of the risk and costs of FN is important to help inform appropriate and cost-effective patient care.

This study used inpatient data from over 400 hospitals included in the database maintained by Premier. A large number of cancer patients hospitalized with FN were identified, and data were extensively validated. One key limitation of this study is the possible under-estimation of the burden of FN because no outpatient management of FN was captured, any costs or patient deaths that occurred outside of Premier hospitals were not captured, and only re-admissions to the same facility as the index hospitalization could be identified in Premier's database. Additionally, absolute neutrophil count (ANC) and oral body temperature were not available in Premier's database, and the clinical definition of FN could not be used. Furthermore, no single ICD-9 code exists for FN, which can contribute to errors of omission and commission during coding of the data. As an operational definition of FN, hospitalization with a diagnosis of neutropenia has a sensitivity of 67–80% and a specificity of 94%[31,32] when compared with the clinical definition of FN, which is fever (a single oral temperature ≥38.3°C or ≥38.0°C for at least 1 hour) with neutropenia (<500 neutrophils/μL or <1000 neutrophils/μL and a predicted decline to <500 neutrophils/μL over the next 48 hours)[14]. To further validate the definition of FN, Premier records were linked to the OptumInsight database to determine the percentage of patients that had received chemotherapy before hospitalization for FN. Only 371 Premier records could be linked to the OptumInsight database. Additionally, the OptumInsight data extract used in the analysis might not comprehensively capture oral chemotherapy drugs, which could lead to under-representation of the percentage of patients who received chemotherapy, especially for patients with NHL. However, for all tumor types examined, except for NHL, 82.6–90.5% patients had evidence of chemotherapy within 30 days before the index hospitalization, which provides additional support for the validity of our FN definition.

Conclusion

FN-related hospitalizations among cancer patients remain costly and are accompanied by considerable mortality risk. Substantial differences in the clinical and economic burden of FN exist depending on type of cancer, comorbidities, and type of infection.

Transparency

Declaration of funding
This study was sponsored by Amgen Inc.

Declaration of financial/other relationships
X. Li, R. L. Barron, and J. C. Legg are employees of and stockholders in Amgen Inc. J. A. Gayle and F. R. Ernst are employees of Premier healthcare alliance, which received funding from Amgen Inc. B. Dulisse was an employee of Premier healthcare alliance at the time this study was conducted. K. J. Rothman and J. A. Kaye are employees of RTI Health Solutions, an independent, non-profit research organization which was engaged by Amgen Inc. to consult on the design of the study and interpretation of the results. JME Peer Reviewers on this manuscript have no relevant financial relationships to disclose.

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