RESEARCH ARTICLE

Mortality, Length of Stay, and Cost Associated with Hospitalized Adult Cancer Patients with Febrile Neutropenia

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Abstract

Background: Febrile neutropenia (FN) is a serious complication following chemotherapy and is associated with significant mortality and financial expenditure. The aim of this study was to evaluate risk factors for longer length of stay (LOS) and mortality and cost of treatment among hospitalized adults with cancer who developed febrile neutropenia in Thailand. Materials and Methods: Information on illness of inpatients and casualties came from hospitals nationwide and from hospital withdrawals from the 3 health insurance schemes in fiscal 2010. The data covered 96% of the population and were analyzed by age groups, hospital level, and insurance year schemes in patients with febrile neutropenia. Results: A total of 5,809 patients were identified in the study. The mortality rate was 14%. The median LOS was 8.67 days and 69% of patients stayed for longer than 5 days. On bivariate analysis, age, cancer type, and infectious complications (bacteremia/sepsis, hypotension, fungal infections, and pneumonia) were significantly associated with longer LOS and death. On multivariate analysis, acute leukemia and infectious complications were linked with longer LOS and death significantly. The median cost of hospitalized FN was THB 33,686 (USD 1,122) with the highest cost observed in acute leukemia patients. Conclusions: FN in adult patients results in significant mortality in hospitalized Thai patients. Factors associated with increased mortality include older age (>70), acute leukemia, comorbidity, and infectious complications.

Keywords: Agranulocytosis - cancer complication - cost of illness - length of stay - Thailand

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Introduction

Febrile neutropenia (FN) is a serious and life-threatening condition after administration of intravenous chemotherapy. In 1966, Bodey observed that the mortality of most patients who had infection and neutropenia was 90% or 100% if the bone marrow was unable to recover (Bodey et al., 1966). Nowadays, with the improvement of antibiotics and the use of colony-stimulating growth factor, the mortality rate has been lowered to about 10%. Nevertheless, invasive fungal infections still carry a significant rate of mortality (Kuderer et al., 2006).

FN in turn is a major dose-limiting toxicity of chemotherapy, often requiring prolonged hospitalization and broad-spectrum antibiotic use. These measures can prompt dose reductions or treatment delay in subsequent chemotherapy cycles and compromise clinical outcome (Ellis, 2008).

Development of FN often leads to a longer hospital stay and an increase in diagnostic and treatment costs. The expenses include intravenous antibiotics, myeloid growth factor, increased laboratory data, radiological imaging and intravenous devices.

The median cost per episode of FN ranged from USD 12,000-19,000 in the studies conducted in the United States (Elting et al., 2008; Stokes et al., 2009; Schilling et al., 2011). No study evaluating the cost of treatment of FN in Thailand was found. This study was a retrospective analysis of clinical data from the national hospitalization database. This study focused on the burden of FN in Thailand to better understand factors associated with longer length of stay and mortality in adults.

Materials and Methods

Data source

The hospitalization database is derived from inpatient Medical Expensing Forms from the National Health Security Office (NHSO), Thailand, and inpatient data from the Civil Servants Benefit System from the Comptroller General's Department and the Social Security Office in the fiscal year 2010. Health institutions across the

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country from all provinces were included. Laboratory data, radiological studies, and cause of death are not in the database. Hospital costs were derived from charges reported on the patient's insurance scheme.

Patient population

All adult cancer patients (≥15 years old) hospitalized with FN between October 1, 2009 and September 30, 2010 (fiscal year 2010) were included in the study. Clinical and cost data were analyzed. Data received by the analyst team was checked for accuracy by looking for (a) overlapping information (b) visit dates (c) missing items (d) incorrect coding and (e) dating with the correct fiscal year.

Inclusion criteria were based on the tenth revision of the International Classification of Diseases (ICD-10). All subjects had to have at least one diagnosis for malignancy (ICD-10 C00-C85 and C91-C95) and agranulocytosis (ICD-10 D70). Bone marrow transplant patients were excluded from the study. Some of the patients admitted with FN do not receive the principal diagnosis of FN, instead, they usually receive a diagnosis of other infections if the source could be identified such as pneumonia, fungal infections or complication such as septic shock. Hence, patients with either a principal or secondary diagnosis of FN were included.

Patient demographics and clinical characteristics

Baseline characteristics of FN patients including age, gender, type of cancer, and comorbidities were captured from enrollment data.

Outcome measures

Inpatient mortality, length of stay and hospital costs were the primary outcomes. Bivariate and multivariate analysis of clinical factors predicting longer length of stay (≥5 days) and mortality were conducted.

Statistical analysis

The explanation of variables, tables of frequency enumeration and interrelationships were written using the SPSS program and checked before analyzing. After analyzing the data, the research team passed the primary analysis to ten medical specialists in order to check the validity of the information. Upon confirmation of validity, the data were compared to the Ministry of Public Health's Statistics Report 2010 for trend congruence as well as the hospital's mortality reporting for each age and disease group for comparison with the national Death Registration of the Registry Administration, Ministry of Interior Affairs (Hollenberg, 1996).

Ethics approval was provided by the Ethics Committee of the Faculty of Medicine, Khon Kaen University, under the guidelines of the Helsinki Declaration and Good Clinical Practice.

Results

Patient population

A total of 5,809 adult cancer patients with FN were reported in 2010 in the nationwide hospitals of Thailand. The sample consisted of 3,485 (60%) female and 2,324 (40%) male patients. In the study population, 3,687 (63.5%) were adults between the ages of 15 and 60 years, and 2,122 (36.5%) subjects were older than 60 years.

Acute leukemia was the most common type of cancer and occurred in 22% of patients. Other cancers are non-Hodgkin lymphoma (16%) and breast cancer (12%). There were 1,226 (21%) patients with a diagnostic code for hypotension, 639 (11%) patients with pneumonia, 403 (7%) subjects with bacteremia or sepsis, and 316 (5%) with fungal infections.

Length of stay (LOS)

The median LOS was 8.67 days (1-320 days). There were 1,822 (31%) patients with a LOS of 5 days or less and 3,987 (69%) patients with a LOS longer than 5 days (Table 1). Gender of subjects hospitalized for more than 5 days was significantly different from those with a shorter LOS. Men required a longer admission time than women. Age group was also a risk factor for longer LOS. Patients aged less than 40 years were more likely to need hospitalization for more than 5 days as compared with those aged 40-80 years. Acute leukemia was the greatest risk of longer LOS compared with other cancer diagnoses. Patients who suffered from pneumonia, bacteremia/sepsis, fungal infections, and hypotension were found to have a significant likelihood of being hospitalized for longer than 5 days as compared with those without these diagnoses (Table 1).

Mortality

The mortality rate was 14.0% from 815 deaths reported in the study time. Male patients were more likely to die compared with females. Subjects who were older than 70 years old were at higher risk of death than those younger patients. Acute leukemia was the greatest risk of death compared with other cancer types (Table 2). Renal disease, COPD, and congestive heart failure significantly increased the risk of death. A diagnosis of hypotension significantly increased the risk of death: 37% of patients with hypotension died, as compared with 7.8% mortality rate among patients without hypotension. The incidence of hypotension among patients who died was 56% as compared with 15% among survivors. Likewise, pneumonia, bacteremia/sepsis, and fungal infections were significantly associated with an increased risk of death (Table 2).

Multivariate analysis

Table 3 presents the results of a multivariate logistic regression analysis for inpatient mortality and longer length of stay (>5 days). Age group and cancer type significantly increased risk for both mortality and longer length of stay. Bacteremia/sepsis, hypotension, pneumonia, renal disease and congestive heart failure were all found to be significantly associated with the risk of death, while diabetes mellitus, pneumonia, bacteremia/sepsis, fungal infection and hypotension increased the risk for longer LOS significantly.

Older adults (≥70 years old) were at a significantly higher risk for death as compared with young adults (15-40 years) with the OR of 1.71 in 70-79 year-old group and 1.90 in ≥80 year-old group, but the length of stay was not

Table 1. Bivariate Association between Each Predictor Variable and Length of Stay

Variable	Mean LOS	Median LOS	LOS (days) ≤5	LOS (days) >5	OR	95%CI	p-value
Total	15.14	8.67	1822	3987			
Sex							
Male	17.71	11	583	1741	1.65	1.46-1.85	<0.001
Female	13.42	7.7	1239	2246	1		
Age group							
15-40	19.53	14	214	874	1		
40-60	14.63	8	907	1692	0.46	0.39-0.54	<0.001
60-70	13.84	8	435	828	0.47	0.39-0.56	<0.001
70-80	12.66	8	229	485	0.52	0.42-0.64	<0.001
≥80	14.92	9	37	108	0.71	0.48-1.07	0.102
Cancer type							
Leukemia	21.78	18	166	1103	1		
HL	14.46	9.5	13	34	0.39	2.04-0.76	0.006
NHL	13.74	9	244	669	0.41	0.33-0.51	<0.001
Head and neck	22.83	11	75	180	0.36	0.26-0.49	<0.001
Esophagus	21.49	11	8	31	0.58	0.26-1.29	0.183
Stomach	13.50	7.6	22	46	0.31	0.18-0.54	<0.001
Colorectal	10.30	6	134	147	0.17	0.12-0.22	<0.001
Hepatobiliary	7.94	6	50	51	0.15	0.10-0.23	<0.001
Lung	9.52	7	92	145	0.24	0.17-0.32	<0.001
Bone	15.83	8.5	10	24	0.36	0.17-0.77	0.008
Sarcoma	10.25	8.5	6	14	0.35	0.13-0.93	0.035
Breast	8.40	6.9	283	433	0.23	0.18-0.29	<0.001
Cervix	17.80	6	99	110	0.17	0.12-0.23	<0.001
Ovary	6.06	4	125	74	0.01	0.06-0.12	<0.001
Other gynecological cancer	12.24	6.3	26	34	0.20	0.11-0.34	<0.001
Testis	10.30	6	7	8	0.17	0.06-0.48	0.001
Bladder	13.97	9	8	10	0.19	0.07-0.48	0.001
CUP	12.62	7.5	46	76	0.25	0.17-0.37	<0.001
Other cancer	15.25	9	32	59	0.27	0.17-0.37	<0.001
Multiple cancers	15.97	8	376	739	0.30	0.24-0.36	<0.001
Pneumonia							
Yes	20.59	15	114	525	2.27	1.84-2.83	<0.001
No	14.46	8	1708	3462	1		
Bacteremia/sepsis							
Yes	22.11	18	42	361	4.22	3.04-5.98	<0.001
No	14.62	8	1780	3626	1		
Fungal infections							
Yes	27.36	21.6	19	297	7.64	4.78-12.91	<0.001
No	14.44	8	1803	3690	1		
Hypotension							
Yes	16.84	12	264	962	1.88	1.61-2.19	<0.001
No	14.68	8	1558	3025	1		

*HL: Hodgkin lymphoma, NHL: non-Hodgkin lymphoma, CUP: cancer of unknown primary, LOS: length of stay, OR: Odds ratio, CI: confidence interval, p-value significant<0.05

higher in elderly (Table 3).

Patients with esophageal, testicular and bladder cancers were at higher risk for death as compared with subjects with acute leukemia, but not statistically significantly, while patients with breast and cervical cancer were at a significantly lower risk of death. Acute leukemia patients were at higher risk for longer LOS as compared to other cancer patients.

The complications of bacteremia/sepsis, hypotension, and pneumonia were all significantly associated with death and these three conditions along with fungal infections increased the risk of longer LOS significantly. Patients with hypotension had an almost 6-fold increase in the risk of death as compared to those without hypotension. And patients with fungal infections had an increase in the risk of longer LOS for 4.5 times compared with those without fungal complications.

Table 2. Bivariate Association between Each Predictor Variable and Mortality

Variable	Alive	Dead	%	OR	95%CI	p-value
Total	4994	815	14			
Sex						
Male	1910	414	17.8	1.67	1.43-1.94	<0.001
Female	3084	401	11.5	1		
Age group						
15-40	935	153	14.1	1		
40-60	2287	312	12.0	0.83	0.68-1.03	0.086
60-70	1087	176	13.9	0.99	0.78-1.25	0.929
70-80	572	142	19.9	1.52	1.18-1.95	0.001
≥80	113	32	22.1	1.73	1.12-2.66	0.012
Cancer type						
Leukemia	970	299	23.6	1		
HL	45	2	4.3	0.14	0.03-0.60	0.008
NHL	732	181	19.8	0.80	0.65-0.99	0.038
Head and neck	241	14	5.5	0.19	0.11-0.33	<0.001
Esophagus	33	6	15.4	0.59	0.24-1.42	0.239
Stomach	61	7	10.3	0.37	0.17-0.82	0.015
Colorectal	259	22	7.8	0.28	0.17-0.43	<0.001
Hepatobiliary	92	9	8.9	0.32	0.16-0.64	0.001
Lung	195	42	17.7	0.70	0.49-1.00	0.050
Bone	33	1	2.9	0.10	0.13-0.72	0.023
Sarcoma	19	1	5.0	0.17	0.02-1.28	0.086
Breast	693	23	3.2	0.11	0.07-0.17	<0.001
Cervix	206	3	1.4	0.05	0.02-0.15	<0.001
Ovary	188	11	5.5	0.19	0.10-0.35	<0.001
Other gyne cancer	53	7	11.7	0.43	0.19-0.92	0.038
Testis	13	2	13.3	0.50	0.11-2.22	0.362
Bladder	14	4	2.2	0.93	0.30-2.84	0.894
CUP	109	13	10.7	0.39	0.21-0.70	0.002
Other cancer	78	13	14.3	0.55	0.30-1.00	0.050
Multiple cancers	960	155	13.9	0.52	0.42-0.65	<0.001
Diabetes mellitus						
Yes	382	77	16.8	1.26	0.96-1.63	0.078
No	4612	738	13.8	1		
Renal disease						
Yes	290	217	42.8	5.87	4.81-7.19	<0.001
No	4704	598	11.3	1		
COPD						
Yes	25	15	37.5	3.73	1.82-7.38	<0.001
No	4969	800	13.9	1		
Pulmonary embolism						
Yes	9	4	30.8	2.73	0.61-9.81	0.082
No	4985	811	14.0	1		
CHF						
Yes	39	26	40.0	4.19	2.43-7.10	<0.001
No	4955	789	13.7	1		
Pneumonia						
Yes	402	237	37.1	4.68	3.89-5.64	<0.001
No	4592	578	11.2	1		
Bacteremia/sepsis						
Yes	268	135	33.5	3.50	2.78-4.39	<0.001
No	4726	680	12.6	1		
Fungal infections						
Yes	237	79	25.0	2.15	1.63-2.83	<0.001
No	4726	680	12.6	1		
Hypotension						
Yes	767	459	37.4	7.11	6.05-8.35	<0.001
No	4227	356	7.8	1		

*HL: Hodgkin lymphoma, NHL: non-Hodgkin lymphoma, CUP: cancer of unknown primary, COPD: chronic obstructive pulmonary disease, CHF: congestive heart failure, OR: Odds ratio, CI: confidence interval, p-value significant<0.05

Cost of treatment

Overall, the mean and median costs of hospitalization were THB 76,484 (USD 2,549) and THB 33,686 (USD 1,122). There was a wide range of hospital costs among various types of cancer. Acute leukemia was associated with the highest hospitalization cost with the median of THB 90,239 (USD 3,008) and cervical cancer

Table 3. Factors Associated with Longer LOS and Mortality on Multivariate Analysis

Variable	Death			Longer LOS		
	OR	95%CI	p-value	OR	95%CI	p-value
Age group						
15-40	1			1		
40-60	1.19	0.94-1.53	0.149	0.65	0.54-0.78	<0.001
60-70	1.23	0.93-1.63	0.146	0.62	0.50-0.76	<0.001
70-80	1.71	1.26-2.32	0.001	0.66	0.52-0.84	0.001
≥80	1.90	1.15-3.14	0.012	0.85	0.56-1.30	0.458
Cancer type						
Leukemia	1			1		
HL	0.26	0.06-1.11	0.069	0.49	0.25-0.95	0.035
NHL	0.89	0.70.1.14	0.353	0.51	0.40-0.64	<0.001
Head and neck	0.38	0.21-0.69	0.001	0.51	0.37-0.71	<0.001
Esophagus	1.05	0.40-2.76	0.928	0.81	0.36-1.82	0.618
Stomach	0.81	0.34-1.90	0.626	0.51	0.30-0.87	0.014
Colorectal	0.51	0.31-0.85	0.010	0.25	0.19-0.34	<0.001
Hepatobiliary	0.54	0.25-1.20	0.130	0.27	0.17-0.42	<0.001
Lung	0.83	0.54-1.26	0.371	0.32	0.23-0.44	<0.001
Bone	0.22	0.03-1.67	0.144	0.47	0.22-1.01	0.052
Sarcoma	0.43	0.05-3.35	0.420	0.51	0.19-1.36	0.179
Breast	0.23	0.14-0.36	<0.001	0.39	0.31-0.50	<0.001
Cervix	0.11	0.03-0.35	<0.001	0.30	0.22-0.42	<0.001
Ovary	0.51	0.26-0.99	0.045	0.15	0.11-0.22	<0.001
Other gyne cancer						
	0.75	0.30-1.84	0.526	0.34	0.20-0.58	<0.001
Testis	1.03	0.21-4.96	0.969	0.18	0.06-0.51	0.001
Bladder	1.12	0.34-3.67	0.851	0.23	0.09-0.61	0.003
CUP	0.67	3.35-1.28	0.222	0.36	0.24-0.54	<0.001
Other cancers	0.87	3.45-1.69	0.677	0.35	0.22-0.56	<0.001
Multiple cancers	0.89	0.69-1.15	0.385	0.43	0.35-0.54	<0.001
Comorbidity						
Diabetes mellitus	1.08	0.79-1.47	0.629	1.30	1.04-1.62	0.022
Renal disease	3.17	2.53-3.98	<0.001	0.79	0.63-0.99	0.043
COPD	1.83	0.85-3.94	0.124	0.87	0.43-1.76	0.697
Pulmonary embolism						
	2.43	0.62-9.47	0.202	1.46	0.38-5.57	0.581
CHF	2.34	1.31-4.20	0.004	2.16	1.00-4.68	0.050
Cirrhosis	0.95	0.31-2.95	0.933	0.52	0.27-1.00	0.051
Infections						
Pneumonia	2.33	1.88-2.88	<0.001	1.49	1.19-1.88	0.001
Bacteremia/sepsis	3.34	2.56-4.36	<0.001	2.71	1.93-3.81	<0.001
Fungal infections	0.99	0.72-1.36	0.932	4.48	2.78-7.24	<0.001
Hypotension	5.60	4.69-6.68	<0.001	1.44	1.23-1.70	<0.001

*HL: Hodgkin lymphoma, NHL: non-Hodgkin lymphoma, CUP: cancer of unknown primary, COPD: chronic obstructive pulmonary disease, CHF: congestive heart failure. LOS: length of stay, OR: Odds ratio, CI: confidence interval, p-value significant<0.05

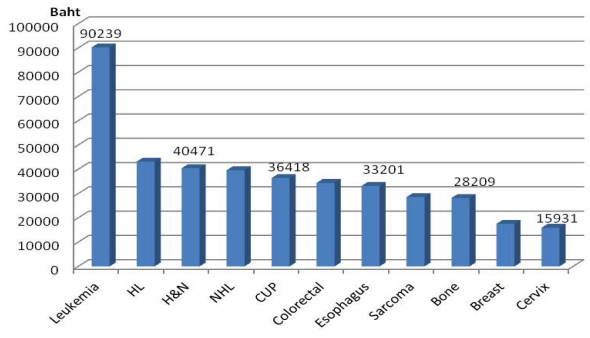

Figure 1. Median Cost of FN by Cancer Type

hospitalization cost was the lowest with the median of THB 15,931 (USD 531) (Figure 1).

Discussion

Among 5,809 cancer patients who were hospitalized with FN during Oct 2009 to September 2010 at all hospitals in Thailand, the overall inpatient mortality was 14%. This figure is similar to the study from the United Kingdom (Schelenz et al., 2012) but slightly higher than the result from a few studies (Kuderer et al., 2006; Jin et al., 2010) mainly due to the higher proportion of the elderly and acute leukemia patients and the inclusion of all levels of hospital, not only tertiary hospital.

In addition to type of cancer, infectious complications, age group, and underlying disease increased mortality significantly. Hypotension, bacteremia/sepsis, and pneumonia were the most significant risk factors for inpatient mortality. Patients with hypotension were at 5-fold and those with pneumonia were at 2-fold increase in mortality. The elderly (>70 years) and those with renal disease were also at an increased risk for mortality but not longer LOS. The results are similar to other studies from various countries (Kuderer et al., 2006; Lal et al., 2008).

However, invasive fungal infection did not increase mortality as opposed to the study from Kuderer et al. The difficulty to obtain an accurate diagnosis was, since fungal cultures were not available in every hospital in Thailand, resulting in lower rates of diagnosis with only 5% of patients with fungal infection compared to 9% of patients from Kuderer et al study. The under report would explain the different results.

A diagnosis of acute leukemia was associated with longer LOS and mortality while breast cancer was associated with a significant reduction in the risk of both. This also corresponds to other published studies (Lal et al., 2008; Schelenz et al., 2012). The chemotherapy dose for acute leukemia is very high in order to completely eradicate cancer cells for the goal of complete remission, and as a result, the neutropenic period is prolonged and patients are at greater risk for developing infectious complications. Breast cancer patients, however, receive a lower dose of adjuvant and palliative chemotherapy compared to hematologic malignancy. Early diagnosis of breast cancer may lead to the reduction of the administration of high dose chemotherapy e.g. TAC (docetaxel, doxorubicin, and cyclophosphamide) regimen which contributed to a more than 20% risk of FN.

The LOS for all FN patients was 8.7 days, which collaborates with other studies of 6.5-9.2 days (Courtney et al., 2007; Innes et al., 2008; Schelenz et al., 2012). Surprisingly, patients who were younger than 40 years old were more likely to need longer hospitalization period compared to the older groups. A lower mortality rate and intensive treatment for infectious complications might contribute to the increased LOS.

FN results in a considerable burden on patients, caregivers, and payers. The median cost of FN was THB 33,686 (USD 1,122) per inpatient episode. Although it is much lower than other studies from the US and UK (Courtney et al., 2007; Liou et al., 2007; Innes et al., 2008; Schelenz et al., 2012), it is a huge burden for the payers, the Thai government. The three main reimbursement programs for Thai citizens are national coverage, government welfare for government officers, and social welfare for workers. In general, the government is responsible for more than two-thirds of the burden (Chindaprasirt et al., 2012).

According to recent studies, outpatient management of low-risk FN patients is safe and effective with a low failure rate in western countries (Elting et al., 2008; Teuffel et al., 2011). Thus, identifying patients who are low-risk is important. Nevertheless, outpatient management in the Thai setting is yet to be validated for effectiveness.

There are limitations of the present study. Firstly, there is the potential for misclassification of data collection wherein some patients were either inappropriately included or excluded based on ICD-10 codes. Secondly, some data associated with risk factors of death associated with FN were unavailable. The results of the present study need to be interpreted in the context of its limitations. Finally, the impact of FN on some aspects is lacking, such as long-term survival, caregiver burden, and post-hospital costs.

In conclusion, FN remains a serious cause of substantial morbidity, mortality, and cost as a whole. Elderly patients (>70 years), invasive fungal infection, bacteremia/sepsis, pneumonia, hypotension, multiple comorbid diseases, and acute leukemia should be considered as high risk factors in adults with FN. In order to improve the outcome and reduce the financial burden, risk stratification should be implemented in management of FN patients.

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