Original Article

Yonsei Med J 2021 Jun;62(6):479-486
https://doi.org/10.3349/ymj.2021.62.6.479

Yonsei Medical Journal
YMJ
pISSN: 0513-5796 · eISSN: 1976-2437

Incidence and Clinical Outcomes of Febrile Neutropenia in Adult Cancer Patients with Chemotherapy Using Korean Nationwide Health Insurance Database

Dalyong Kim[1*], Soohyeon Lee[2*], Taemi Youk[3,4], and Soojung Hong[5]

[1]Division of Hematology & Medical Oncology, Department of Internal Medicine, Dongguk University Ilsan Hospital, Goyang;
[2]Division of Oncology/Hematology, Department of Internal Medicine, Korea University, Seoul;
[3]Department of Statistics, Korea University, Seoul;
[4]Research Institute, National Health Insurance Service Ilsan Hospital, Goyang;
[5]Division of Oncology-Hematology, Department of Internal Medicine, National Health Insurance Service Ilsan Hospital, Goyang, Korea.

Purpose: The aim of this study was to evaluate the episodes of febrile neutropenia (FN) in patients with gastric cancer (GC), colorectal cancer (CRC), lung cancer (LC), and breast cancer (BC); and to identify the incidence and trends of admission rates, as well as factors affecting mortality.

Materials and Methods: Using nationwide claims data, all new admissions to hospitals for FN were selected. We evaluated the incidence of FN and mortality-related clinical factors in adult cancer patients who received cytotoxic chemotherapy from January 2004 to December 2013.

Results: While the incidence of FN increased, the length of hospitalization decreased in Korea. The incidence of FN was 19.8% in LC patients, 15.5% in GC patients, 13.3% in BC patients, and 9.5% in CRC patients. The overall in-hospital mortality of FN was 12.9% and showed a decreasing trend. Admission rates to intensive care units and in-hospital mortality were the highest for lung cancer (15.2% and 19.3%, respectively). Age and sepsis syndrome were risk factors for in-hospital mortality for all cancer types.

Conclusion: Careful observation and active prophylaxis should be considered for patients at high risk of FN.

Key Words: Chemotherapy, febrile neutropenia, national health insurance

INTRODUCTION

Cancer incidence is increasing globally and in Korea. According to the annual report of cancer statistics in Korea, 37% of people are expected to develop cancer at some time in life.[1] Cancer survival has been continuously improving, and the 5-year relative survival rates of all newly diagnosed cancer patients between 2011 and 2015 was 70.7%. Early detection of cancer and development of new anti-cancer drugs are important factors for improving the survival of cancer patients. Although new therapeutic options, such as targeted agents and biologics, have been introduced since 2000, most cancer patients are still treated with conventional cytotoxic chemotherapy.

Bone marrow suppression is a common adverse event of cytotoxic chemotherapy. Bone marrow suppression is a common adverse event of cytotoxic chemotherapy and induces febrile neutropenia (FN). FN is defined when the absolute neutrophil count is expected to drop to less than 500 cells/mm^3 or less than 500 cells/mm^3, and the body temperature is above 38.3°C or continuously above 38.0°C over a 1-hour period.[2] FN can be life-threatening, and affects the schedule and dose of chemotherapy. In some patients, chemotherapy may be discontinued due to FN. Chemotherapy regimen and dose intensity are risk factors for FN. According to a review of clinical trials of

Received: December 4, 2020 **Revised:** February 5, 2021
Accepted: April 5, 2021
Corresponding author: Soojung Hong, MD, Division of Oncology-Hematology, Department of Internal Medicine, National Health Insurance Service Ilsan Hospital, 100 Ilsan-ro, Ilsandong-gu, Goyang 10444, Korea.
Tel: 82-31-900-0967, Fax: 82-31-900-3366, E-mail: suzzy901@nhimc.or.kr

*Dalyong Kim and Soohyeon Lee contributed equally to this work.
•The authors have no potential conflicts of interest to disclose.

breast cancer and non-Hodgkin's lymphoma, hematologic toxicity data and dose-intensity data were not reported in about 40% of the studies included in that review.[3] Also, prophylactic use of granulocyte colony stimulating factor (G-CSF) varied and was inconsistent. In addition, the degree of bone marrow suppression is very different according to the risk of each patient treated with the same chemotherapy, making it difficult to estimate the incidence of FN in the real world. Since 2014, reimbursement of long-acting G-CSF for prevention of FN has been available to some patients who have high risk of FN, but the risk factors of each patient have not been sufficiently considered for insurance coverage. Therefore, many patients still do not receive prophylactic G-CSF in Korea.

Several studies on the incidence of FN and healthcare cost have been reported in the United States, Australia, UK, and Asian countries such as Singapore and Thailand,[4-12] but there is no available data in Korea. Therefore, this study aimed to evaluate the incidence of FN in patients with gastric cancer (GC), colorectal cancer (CRC), lung cancer (LC), and breast cancer (BC) who were treated with chemotherapy before prophylactic G-CSF was covered, as well as the trends for admission rates, and factors affecting mortality using the nationwide claims data from the Korean National Health Insurance Service (NHIS) database (DB). The five most commonly diagnosed types of cancer in Korea were GC, CRC, thyroid cancer, LC, BC. These four cancers, except thyroid cancer, accounted for 47% of all cancer deaths, and healthcare expenditure was higher than those for other cancers. For this reason, these four common cancers of interest were analyzed.

MATERIALS AND METHODS

Data source

In Korea, almost all citizens are covered by the NHIS as a single national insurance. As of 2013, the NHIS included 97.2% (n=49989620) of the country's total population, and the medical aid system included the remaining 2.8% (n=1458871) of the population. NHIS claims data include a qualification DB, treatment DB, and clinic DB. The treatment DB contains details of treatment, type of disease, and prescriptions.

Study population

The subjects of this retrospective study were adult cancer patients (aged >18 years) with FN from Jan. 2004 to Dec. 2013 in the NHIS DB. Patients with newly diagnosed cancer were selected by diagnostic codes (Korean Standard Classification of Diseases based on International Classification of Diseases-10) as follows: GC (C16), CRC (C18-20), LC (C34), and BC (C50). Patients treated with chemotherapy were defined as those with anti-cancer drug classification codes after the first claims with cancer codes.

Since patients admitted with FN often do not receive a major diagnostic code of FN (R508) in real practice, we could not obtain appropriate data. Therefore, we used an operational definition of FN. The medical insurance system of Korea is a single-payer system. Korean doctors have no choice but to obey the insurance standards based on international guidelines, since the country does pay back the benefits if it is confirmed that treatment has not been made by the insurance coverage standards. Most patients with FN tend to be hospitalized and treated in Korea. Therefore, among cancer patients selected from the NHIS DB, patients with FN were defined as those who were hospitalized and received G-CSF and antibiotics after chemotherapy. The first FN episode after chemotherapy was selected in individual patients. We excluded patients with multiple primary cancer, Acquired Immune Deficiency Syndrome (AIDS), or hematopoietic stem cell transplants.

Data collection and operational definition of variables

Due to the possibility of dividing a bill for medical expenses during one hospitalization period, if the interval between requests for hospitalization was less than 7 days, it was considered as one admission based on the date of treatment commencement and termination. The following were considered to be past medical history that may affect FN if their diagnostic codes were used repeatedly for 5 years before chemotherapy initiation: diabetes (E10–E14), heart failure (I11.0, I13.0, I13.2, I15.0, I15.1, I15.9), ischemic heart disease (I20–I25), liver cirrhosis (K74, K70.4, K71.7), chronic obstructive pulmonary disease (COPD, J40-J44), and renal failure (N17–N19). Since healthcare claims data do not indicate the cancer stage, early stage and late stage were distinguished based on operation before chemotherapy. Anthracycline, taxane, platinum, and fluoropyrimidine were given priority, and a representative chemotherapeutic agent group was defined. For example, docetaxel plus adriamycin treatment was assigned to the anthracycline group, and fluorouracil plus irinotecan therapy was assigned to the fluoropyrimidine group. Hypotension (I95), shock (R57.9), septic shock (R57.2), sepsis (R65.1, A40–A41), pneumonia (J10.0, J11.0, J12-J18, J20.0, J69, J17), urinary tract infection (N39.0), candidiasis (B37), and other fungal infection (B44, B49, B59, J17.3) were considered complications of FN, and were confirmed using the claimed diagnostic code within 3 months after chemotherapy. Any code of hypotension, shock, septic shock, or sepsis was judged to be sepsis syndrome. The use of the intensive care unit (ICU) was confirmed by the existence of a claim for admission to the ICU.

Statistical analysis

We examined the proportion of patients with FN by gender, age, region, income, comorbidities, and operation status. If a statistical test was needed to determine whether there was a difference in the factor of interest, chi-square (or Fisher's exact) test was performed. A logistic regression model and a Cox proportional hazard model were established to analyze the fac-

https://doi.org/10.3349/ymj.2021.62.6.479

tors related to ICU treatment and in-hospital mortality in patients with FN, respectively. In the Cox proportional hazard model, the time from the occurrence of NF to death was used as the time scale. All analyses were performed using SAS v 9.4 (SAS Institute, Cary, NC, USA) and R3.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

Statement of ethics

This retrospective nationwide study was reviewed and approved by the Institutional Review Board of the National Health Insurance Service Ilsan Hospital (NHIMC 2015-02-020). This study adhered to the tenets of the Declaration of Helsinki, and written informed consent was waived.

RESULTS

Characteristics of patients with febrile neutropenia

Between 2004 and 2013, a total of 759168 patients were newly diagnosed with GC, CRC, LC, or BC. Patients without chemotherapy, patients with AIDS or hematopoietic stem cell transplants, and patients with multiple cancer codes were excluded from the analysis. Among 313316 patients who received chemotherapy, 14.2% were hospitalized due to FN (Fig. 1). The overall incidence of FN was 19.8% (LC), 15.5% (GC), 13.3% (BC), and 9.5% (CRC). Baseline characteristics of inpatients with FN are shown in Table 1. The incidence of FN was the highest in patients in their 60s for GC, CRC, and LC. In patients with breast cancer, the largest proportion of FN was found in patients in their 40s (33.2%) due to the epidemiologic characteristics of the young BC population in Korea. In LC, male patients had more frequent FN (20.6% vs. 17.3%, $p<0.01$), but the incidence of FN was higher in female patients with GC (14.9% vs. 17%, $p<0.01$) and CRC (8.5% vs. 11.2%, $p<0.01$). LC patients had more underlying diseases, while COPD was the most common underlying disease in all cancer patients.

Hospitalization due to febrile neutropenia

The number of FN patients showed an increasing trend over the 10 years, while the incidence of FN did not (Fig. 2). The mean length of hospitalization gradually decreased (Fig. 3). Hospitalization days were longer in FN patients with LC compared to patients with other cancer types. Pneumonia was the most common complication in patients with FN (13.4–38.2%), and other complications were identified in less than 5% of patients (Table 2). ICU unit utilization was also higher in FN pa-

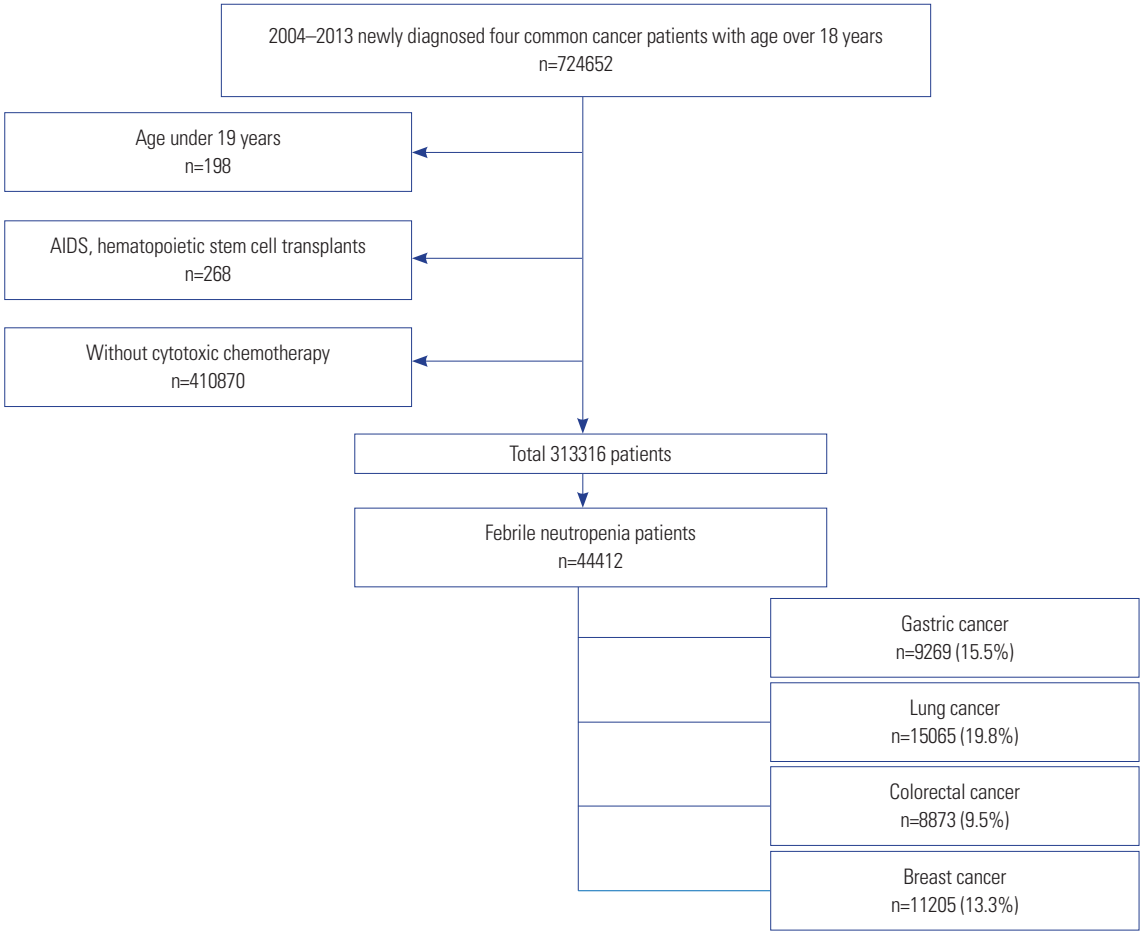

Fig. 1. Consort diagram for the patient selection process. AIDS, Acquired Immune Deficiency Syndrome.

Table 1. Baseline Characteristics of Febrile Neutropenic Inpatients

	GC	CRC	LC	BC
Sex				
Male	6257 (67.5)	4804 (54.1)	11842 (78.6)	40 (0.4)
Female	3012 (32.5)	4069 (45.9)	3223 (21.4)	11165 (99.6)
Age (yr)				
<40	827 (8.9)	394 (4.4)	248 (1.6)	1900 (17.0)
40–49	1661 (17.9)	1131 (12.7)	971 (6.4)	3719 (33.2)
50–59	2673 (28.8)	2424 (27.3)	3176 (21.1)	3542 (31.6)
60–69	2820 (30.4)	3111 (35.1)	6052 (40.2)	1678 (15.0)
≥70	1228 (13.2)	1813 (20.4)	4618 (30.7)	366 (3.3)
Operation				
Yes (early stage)	2837 (30.6)	5600 (63.1)	1552 (10.3)	6668 (59.5)
No (late stage)	6432 (69.4)	3273 (36.9)	13513 (89.7)	4537 (40.5)
Comorbidities*				
Diabetes	1524 (22.7)	1768 (26.5)	3407 (29.2)	1187 (13.4)
Heart failure	545 (8.1)	719 (10.8)	1483 (12.7)	514 (5.8)
Ischemic heart disease	776 (11.6)	835 (12.5)	2245 (19.3)	669 (7.6)
Liver cirrhosis	156 (2.3)	156 (2.3)	281 (2.4)	72 (0.8)
Chronic obstructive pulmonary disease	1904 (28.4)	1990 (29.8)	7020 (60.2)	2606 (29.5)
Chronic kidney disease	99 (1.5)	130 (1.9)	261 (2.2)	102 (1.15)
Anticancer drugs				
Anthracycline	742 (8)	257 (2.9)	796 (5.3)	10271 (91.7)
Taxane	3299 (36)	51 (0.6)	5851 (38.8)	564 (5.0)
Platinum	4345 (47)	5992 (67.5)	7897 (52.4)	56 (0.5)
Fluoropyrimidine	823 (9)	2549 (28.7)	11 (0.1)	253 (2.3)
Other	60 (1)	24 (0.3)	510 (3.4)	61 (0.5)
Use of intensive care unit	874 (9.4)	721 (8.1)	2296 (15.2)	613 (5.5)
In-hospital mortality	1399 (15.1)	792 (8.9)	2903 (19.3)	659 (5.9)

GC, gastric cancer; CRC, colorectal cancer; LC, lung cancer; BC, breast cancer.
Data are presented as n (%).
*According to the definition of past medical history, data on the study subject's underlying diseases were searched between 2007 and 2013.

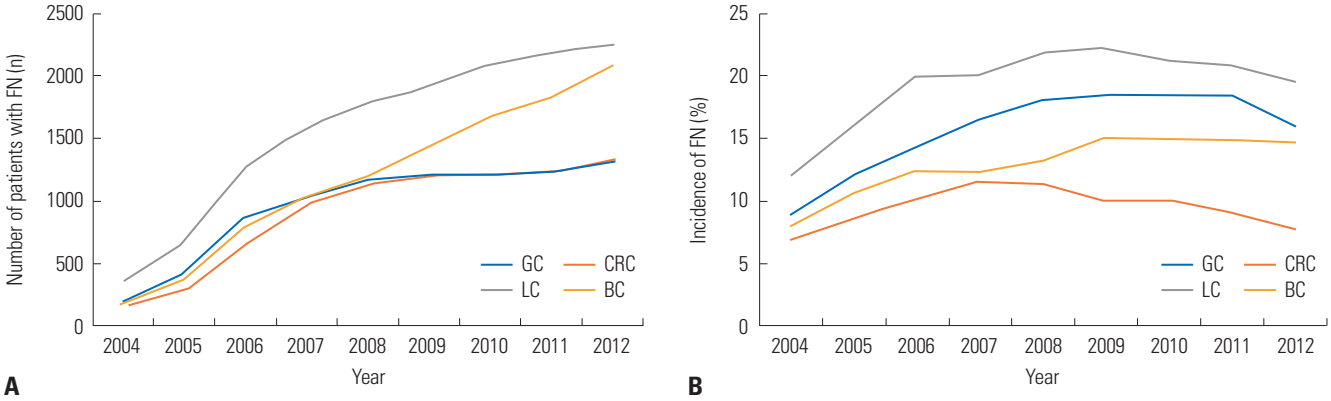

Fig. 2. Trends of hospitalization for FN. (A) Number of patients with FN. (B) Incidence of FN. FN, febrile neutropenia; GC, gastric cancer; CRC, colorectal cancer; LC, lung cancer; BC, breast cancer.

tients with LC (15.2%), followed by GC (9.4%), CRC (8.1%), and BC (5.5%). In-hospital mortality rate was 19.3% in LC, 15.1% in GC, 8.9% in CRC, and 5.9% in BC. The cost of G-CSF increased yearly (Table 3). The frequency and cost of G-CSF use were higher in FN patients with BC.

Factors related to ICU treatment and in-hospital mortality

Sepsis syndrome was the most important factor for ICU care in patients with FN (Table 4). The risk of treatment in the ICU for sepsis syndrome was 3.30 times higher in GC, 3.83 times in

https://doi.org/10.3349/ymj.2021.62.6.479

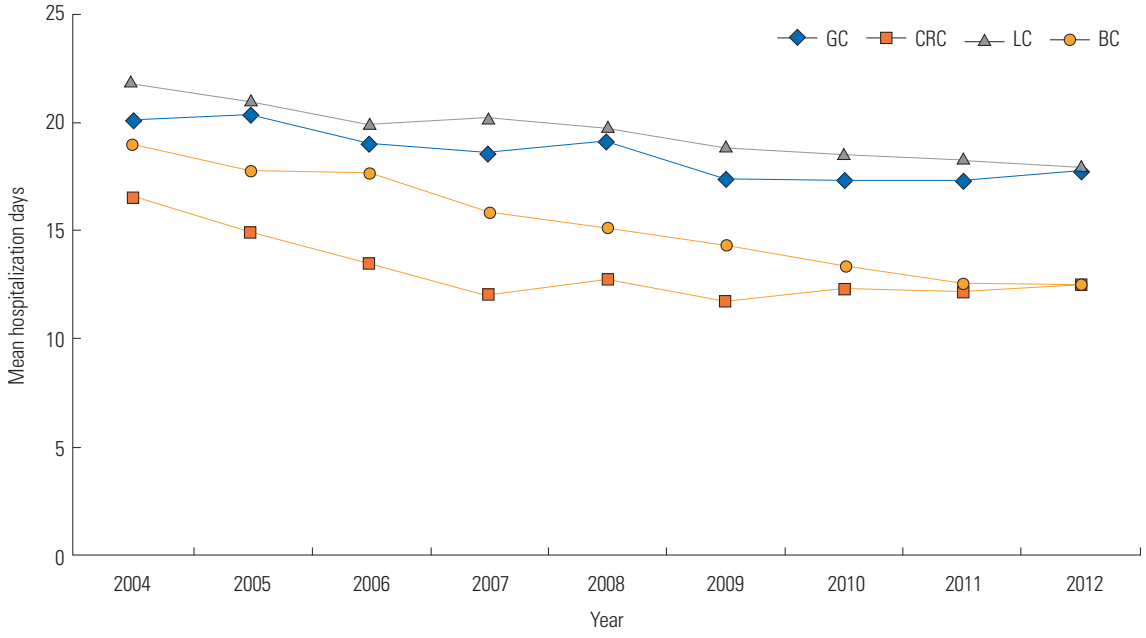

Fig. 3. Trends of mean hospitalization days for febrile neutropenia. GC, gastric cancer; CRC, colorectal cancer; LC, lung cancer; BC, breast cancer.

Table 2. Complications* in Patients with Febrile Neutropenia

	GC	CRC	LC	BC
Hypotension	14 (0.15)	14 (0.16)	40 (0.27)	14 (0.12)
Shock	10 (0.11)	2 (0.02)	9 (0.06)	3 (0.03)
Septic shock	5 (0.05)	2 (0.02)	12 (0.08)	4 (0.04)
Sepsis	155 (1.67)	84 (0.95)	285 (1.89)	84 (0.75)
Pneumonia	1243 (13.41)	1299 (14.64)	5753 (38.19)	1975 (17.63)
Urinary tract infection	90 (0.97)	133 (1.5)	136 (0.9)	137 (1.22)
Candidiasis	252 (2.72)	129 (1.45)	458 (3.04)	355 (3.17)
Aspergillosis	7 (0.08)	2 (0.02)	19 (0.13)	6 (0.05)
Undefined fungal infection	3 (0.03)	3 (0.03)	13 (0.09)	3 (0.03)
Pneumocystosis	2 (0.02)	1 (0.01)	5 (0.03)	4 (0.04)

GC, gastric cancer; CRC, colorectal cancer; LC, lung cancer; BC, breast cancer.
Data are presented as n (%).
*Complications were identified using the diagnostic codes.

CRC, 3.75 times in LC, and 5.32 times in BC than in those without septic syndrome. The odds ratio (OR) of patients aged over 65 years was significantly higher in all cancer types except LC. Female patients with FN were at low risk for intensive care. Patients with a history of surgery for CRC or BC had significantly lower ORs than patients who did not undergo surgery.

In the Cox proportional hazard model, old age and sepsis syndrome were common factors affecting in-hospital mortality in FN patients with any types of cancer (Table 5). The risk of in-hospital death due to FN was about 1.3 to 2.1 times higher in patients older than 65 years compared to those under the age of 65 years. Patients with sepsis syndrome had higher risk of death by approximately 1.9 to 2.5 times compared to those without sepsis syndrome.

DISCUSSION

We used the operational definition of FN cases that were hospitalized and received G-CSF and antibiotics after chemotherapy. In other studies, using claims data, some researchers used the diagnostic code for agranulocytosis[6,8] and others used the diagnostic codes for neutropenia or neutropenia with fever.[4,7,9,13] Weycker suggested that FN patients can be identified in claims data with positive predictive value higher than 80% using the diagnostic codes.[14] Although we tried to retrieve the FN cases by using the term of FN and/or agranulocytosis, we only captured a limited number of the cases. In Korea, the therapeutic use of G-CSF is covered by insurance only if the solid cancer patients treated with chemotherapy have agranulocytosis (ANC below 500 cells/mm^3) or neutropenia (ANC below 1000 cells/mm^3) with fever. Therefore, we searched for patients using G-CSF and antibiotics drug codes. Although the operational definition is different from previous research, we thought it would not be significantly different from the operational definitions of other studies, due to the strict standard of insurance payment in Korea.

The incidence of FN in Korean cancer patients was 14.2%, and patients with FN increased from 2004 to 2012. This increase appears to be associated with an increase in the overall number of cancer patients. Chemotherapy regimen also affected the development of FN. In patients with BC who commonly used anthracycline, the incidence of FN was higher than that in other cancer patients. With CRC, the incidence of FN increased significantly between 2005 and 2006. This was related to the rapid increase in the use of doublet chemotherapy, since 5-fluorouracil and oxaliplatin (FOLFOX) and 5-fluorouracil, irinotecan (FOLFIRI) were covered by national health insurance

Table 3. Use of Granulocyte-Stimulating Factors

	Year								
	2004	2005	2006	2007	2008	2009	2010	2011	2012
Use of granulocyte-stimulating factors									
Gastric	388	880	1778	2141	2296	2255	2260	2364	2365
Colorectal	373	658	1636	2502	2851	2800	2554	2643	2711
Lung	635	1215	2463	2904	3472	3417	3829	3908	3952
Breast	605	1307	2627	3674	4548	4844	5101	5572	5575
Cost of granulocyte-stimulating factors ($)									
Gastric	72284	165589	369755	437162	502618	463075	460932	475173	447929
Colorectal	62535	129048	253685	402883	499169	454707	429072	454412	420779
Lung	142531	297209	553351	699489	789064	788533	881344	901856	859089
Breast	128082	290818	640212	823229	926687	1092214	1172591	1218723	1147884

Table 4. Risk Ratio of the Use of Intensive Care Unit in Cancer Patients with Febrile Neutropenia

Factors	GC			CRC			LC			BC		
	OR	95% CI	*p* value	OR	95% CI	*p* value	OR	95% CI	*p* value	OR	95% CI	*p* value
Female (reference: male)	0.769	0.667–0.886	<0.001	0.872	0.776–0.981	0.022	0.782	0.704–0.868	<0.001	0.417	0.177–0.983	0.046
Age over 65 years (reference: <65)	1.498	1.310–1.713	<0.001	1.185	1.050–1.337	0.006	1.076	0.988–1.172	0.092	2.335	1.923–2.837	<0.001
Diabetes	1.098	0.946–1.275	0.220	1.100	0.963–1.257	0.161	1.068	0.976–1.169	0.155	1.079	0.884–1.317	0.454
Ischemic heart disease	1.078	0.891–1.305	0.439	1.046	0.878–1.246	0.615	1.098	0.990–1.218	0.077	1.310	1.030–1.666	0.028
Liver cirrhosis	1.083	0.726–1.615	0.697	1.229	0.856–1.765	0.263	0.867	0.662–1.137	0.302	2.844	1.630–4.962	<0.001
Chronic obstructive pulmonary disease	0.933	0.809–1.075	0.338	0.932	0.818–1.062	0.291	0.914	0.839–0.996	0.041	0.878	0.749–1.029	0.107
Chronic kidney disease	1.258	0.781–2.027	0.345	1.309	0.886–1.934	0.177	1.280	0.983–1.665	0.066	3.784	2.398–5.971	<0.001
Sepsis syndrome	3.300	2.268–4.804	<0.001	3.833	2.343–6.271	<0.001	3.754	2.895–4.869	<0.001	5.316	3.297–8.572	<0.001
Candidiasis	1.102	0.743–1.634	0.629	0.949	0.573–1.572	0.839	1.268	1.006–1.598	0.044	0.857	0.553–1.330	0.492
Pneumonia	1.116	0.938–1.329	0.216	1.097	0.933–1.290	0.263	1.197	1.100–1.303	<0.001	1.081	0.904–1.292	0.393
Operation (reference: unoperated)	1.136	0.995–1.298	0.060	0.888	0.789–0.999	0.048	1.130	0.988–1.292	0.075	0.500	0.434–0.575	<0.001

OR, odds ratio; CI, confidence interval; GC, gastric cancer; CRC, colorectal cancer; LC, lung cancer; BC, breast cancer.

in 2006. Although it was not desirable to make a direct comparison between different study populations, the incidence of FN seemed to be higher compared to other studies. Before 2014, the prophylactic use of G-CSF was not covered by the national health insurance, which could have led to a higher incidence of FN. Weycker, et al.[13] reported that FN occurred in 13.1% to 20.6% of patients with metastatic solid tumors during chemotherapy. Similar to our data (19.8%), FN was most frequently observed in patients with LC (20.6%). Unlike these data, the incidence of FN in non-small cell lung cancer was 6.9% in a German prospective study.[15] In CRC, 1.8% of patients treated with adjuvant FOLFOX had FN.[16] The incidence of FN was 5.7% to 12.3% when chemotherapy was performed in metastatic CRC patients.[17,18] Notably, we reported the incidence of FN in patients with GC. There have been few articles about FN in GC due to the low incidence in Western populations, and no article on FN using claims data in Asian patients with GC. In a multicenter prospective observational study conducted in Europe, the incidence of FN in gastric cancer was 7% (14/199),[19] whereas that in our data was 15.5%. Since chemotherapy regimens used in Europe differ from those used in East Asia, the frequency of FN might be different.

The ICU admission rate depending on cancer type ranged from 5.5% to 15.2%, whereas Australian data showed that 5.9% of the patients with solid tumor were treated for FN in the ICU.[9] The ICU utilization rate of patients with FN in the US was higher than ours (10.1% in whole FN inpatients) as follows: 10.6% in BC, 22.9% in LC, and 19.4% in CRC.[20] Consistent with the results of other studies, the cost of therapeutic use of G-CSF steadily increased.

The number of patients who died of FN was the highest in LC. Regardless of cancer type, old age and sepsis syndrome due to FN were risk factors of in-hospital death. In a study conducted by Dulisse, et al.,[20] sepsis was an important risk factor for FN [OR: 4.1, 95% confidence interval (CI): 2.6–6.5 in female BC; OR: 3.8, 95% CI: 3.1–4.7 in LC]. The greater the number of past

https://doi.org/10.3349/ymj.2021.62.6.479

Table 5. Hazard Ratio of In-Hospital Mortality in Cancer Patients with Febrile Neutropenia

Factors	GC			CRC			LC			BC		
	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
Female (reference: male)	0.798	0.692–0.920	0.002	0.815	0.683–0.972	0.023	0.906	0.811–1.012	0.080	0.389	0.120–1.257	0.116
Age over 65 years (reference: <65)	1.438	1.251–1.653	<0.001	1.330	1.117–1.584	0.001	1.377	1.259–1.506	<0.001	2.243	1.707–2.947	<0.001
Diabetes	0.991	0.846–1.160	0.913	1.026	0.847–1.243	0.792	0.987	0.898–1.084	0.792	0.918	0.700–1.205	0.539
Ischemic heart disease	1.188	0.973–1.450	0.091	0.985	0.771–1.258	0.906	0.902	0.809–1.006	0.066	1.555	1.087–2.224	0.016
Liver cirrhosis	1.232	0.815–1.862	0.323	0.867	0.575–1.307	0.497	0.897	0.677–1.188	0.450	2.288	1.138–4.599	0.020
Chronic obstructive pulmonary disease	1.054	0.909–1.222	0.487	1.050	0.855–1.289	0.641	0.963	0.881–1.052	0.405	1.077	0.864–1.343	0.511
Chronic kidney disease	0.755	0.447–1.275	0.294	1.381	0.839–2.273	0.205	1.099	0.858–1.408	0.454	1.434	0.762–2.699	0.265
Sepsis syndrome	2.126	1.488–3.038	<0.001	1.959	1.237–3.102	0.004	2.018	1.661–2.452	<0.001	2.060	1.130–3.754	0.019
Candidiasis	1.019	0.618–1.681	0.941	0.461	0.223–0.951	0.037	0.880	0.688–1.125	0.308	0.700	0.403–1.217	0.206
Pneumonia	0.974	0.813–1.167	0.778	0.968	0.768–1.221	0.783	1.039	0.950–1.136	0.403	0.806	0.620–1.049	0.110
Operation (reference: Unoperated)	0.926	0.805–1.065	0.283	0.941	0.794–1.115	0.486	0.984	0.835–1.160	0.848	1.070	0.871–1.314	0.518

HR, hazard ratio; CI, confidence interval; GC, gastric cancer; CRC, colorectal cancer; LC, lung cancer; BC, breast cancer.

medical history, the higher the risk of death. Lung, liver, and kidney diseases were risk factors for FN in BC and LC. Our data showed that liver cirrhosis is a risk factor for in-hospital mortality due to FN in patients with breast cancer only. Although the criteria for elderly people are different, higher in-hospital mortality in elderly patients has been consistently reported in previous studies.[8,20] Based on the analysis of risk factors for in-hospital mortality, close observation and active prophylactic administration of G-CSF should be considered for patients aged 65 years or older and patients with a history of FN sepsis syndrome. Although the use of prophylactic long-acting G-CSF has been insured when chemotherapy regimens with a high risk of FN are used in Korea, it is not covered in LC, CRC, or GC. Patient risk factors such as age and underlying illness are not considered as components for determining the insurance coverage for prophylactic use of G-CSF.

Our study had some limitations. First, since we used the diagnostic and drug codes extracted from the national health claims data, the selection of patients with FN may not accurately represent the real situation. FN cases may include agranulocytosis without fever. However, we thought that the patients included in our study had FN, as afebrile neutropenia was not an indication for hospital admission. Therefore, we tried to capture the FN patients as accurately as possible using operational definitions. Second, detailed information of each patient, such as stage, performance status, type of chemotherapy, actual regimens, dose, dose intensity, and prophylactic use of G-CSF, were not collected in the claims DB. Third, in consideration of the limitation of Korean insurance data which did not include non-payment items in the claim data, only G-CSF costs were checked, and not the total expenses of FN. In addition, only inpatient claims data were used. However, we believe most patients with FN were included in this study. In Korea, doctors seem to prefer hospitalization for FN due to the relatively low medical costs compared to Western societies. Hospitalization rates for FN were 72% and 89–94% in German and US data, respectively.[13,15] Lastly, we only studied four common types of cancer in Korea, not all cancers.

Overall, this study demonstrated the incidence and mortality of FN in real clinical practice in Korea using nationwide claims data. The results provide meaningful insight about the epidemiology and economics of patients with FN. Moreover, the results of this study can be used to establish healthcare policies. Although the Korean government has reimbursed the cost of prophylactic G-CSF since 2014, it has only been partially covered, which still does not meet international standards. It should be considered that the use of prophylactic G-CSF for high-risk patient is more beneficial in the long run. To do so, more research is needed.

ACKNOWLEDGEMENTS

This study was funded by grants (NHIS-2015-20-018) from the National Health Insurance Service Ilsan Hospital.

AUTHOR CONTRIBUTIONS

Conceptualization: Soohyeon Lee and Soojung Hong. Data curation: Taemi Youk. Formal analysis: Taemi Youk. Funding acquisition: Soojung Hong. Investigation: Soojung Hong. Methodology: Taemi Youk. Project administration: Soohyeon Lee and Soojung Hong. Resources: Soojung Hong. Software: Taemi Youk. Supervision: Soojung Hong. Validation: Dalyong Kim, Soohyeon Lee, and Soojung Hong. Visualization: Taemi Youk. Writing—original draft: Dalyong Kim and Soohyeon Lee. Writing—review & editing: Dalyong Kim, Soohyeon Lee, and Soojung Hong. Approval of final manuscript: all authors.

ORCID iDs

Dalyong Kim https://orcid.org/0000-0003-0193-422X
Soohyeon Lee https://orcid.org/0000-0001-9665-062X
Taemi Youk https://orcid.org/0000-0002-4273-3777
Soojung Hong https://orcid.org/0000-0002-4350-2794

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https://doi.org/10.3349/ymj.2021.62.6.479