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Background. Febrile neutropenia (FN) is a common complication to chemotherapy, associated with increased short-term morbidity and mortality. However, the long-term outcomes after FN are poorly elucidated. We examined the long-term risk of infection and mortality rates in cancer patients with and without FN.

Methods. Patients aged >16 years treated with firstline chemotherapy were followed from 180 days after initiating chemotherapy until first infection, a new treatment with chemotherapy, death, or end of follow-up. Risk factors for infections were analyzed by competing risks regression, with death or another treatment with chemotherapy as competing events. Adjusted incidence rate ratios (aIRRs) of infection and death were analyzed using Poisson regression. In analyses of mortality, infection was included as a time-updated variable.

Results. We included 7190 patients with a median follow-up (interquartile range) of 0.58 (0.20–1.71) year. A total of 1370 patients had an infection during follow-up. The aIRRs of infection were 1.86 (95% confidence interval [CI], 1.56–2.22) and 2.19 (95% CI, 1.54–3.11) for patients with 1 or >1 episode of FN compared with those without FN. Mortality rate ratios were 7.52 (95% CI, 6.67–8.48) <1 month after, 4.24 (95% CI, 3.80–4.75) 1–3 months after, 2.33 (95% CI, 1.63–3.35) 3–6 months after, and 1.09 (95% CI, 0.93–1.29) >6 months after an infection, compared with the time before infection.

Conclusions. FN during chemotherapy is associated with a long-term increased risk of infection. Mortality rates are substantially increased for 6 months following an infection.

Keywords. cancer; chemotherapy; febrile neutropenia; infection; long-term complications.

Neutropenia is a frequent and potentially serious complication to myelosuppressive chemotherapy among patients treated for malignant disease. Patients with moderate or severe neutropenia (absolute neutrophil count [ANC], $0.5–1.0 \times 10^9$/L or $<0.5 \times 10^9$/L) have considerably increased risk of serious infections during the neutropenic episode [1, 2]. Fever (temperature >38°C), in addition to neutropenia or febrile neutropenia (FN), can be a life-threatening condition in patients on chemotherapy as infections in this patient group can progress rapidly.

A number of studies have examined the incidence of chemotherapy-induced FN and the associated short-term consequences in terms of treatment delays and dose reductions in delivered chemotherapy [3, 4], increased hospital mortality, length of hospital stay, and hospital costs [5, 6]. FN is associated with poorer cancer outcomes, presumably due to reduced dose intensity of chemotherapy [7]. However, it has not been

elucidated whether patients who develop FN during chemotherapy have an increased risk of infections in the long term.

It is well recognized that among patients who receive the same type and intensity of chemotherapy, only some develop serious infections during treatment, indicating that not only treatment-related but also patient-related factors are important for the short-term risk of infectious complications [8]. We hypothesized that FN is a marker of reduced immune competence and increased susceptibility to infectious complications and that this vulnerability also leads to an excess risk of infections after the chemotherapy has been completed. To test this hypothesis, we examined the risk of infection from 180 days after initiation of firstline chemotherapy among patients who had experienced 1 or more episodes of FN vs patients with no FN within the first 180 days after starting chemotherapy. Secondarily, we assessed whether the timing of FN in relation to initiation of chemotherapy was a predictor of long-term risk of infections.

Short-term mortality associated with FN has been studied. One study including almost 42 000 patients found the overall in-hospital mortality to be 9.5% [5]. However, there are no data on mortality associated with late infections emerging in the period after chemotherapy. Therefore, we compared mortality rates in patients with vs without infectious events that occurred after completion of chemotherapy.

Such information may be used to guide the intensity of long-term monitoring and prophylactic interventions for patients with a fragile phenotype and could potentially result in more appropriate management of these patients.

METHODS

Study Design and Setting
We conducted a cohort study of patients treated with chemotherapy for malignant diseases at Rigshospitalet, University of Copenhagen, Denmark, in the period from January 2010 to September 2015.

We previously assessed rates of FN among patients treated with chemotherapy for malignant disease at our center and found incidence rates of 5.7% during the first cycle [9] and 2.1% [10] during the following cycles.

Patients and Study Size
We included patients who were >16 years of age and alive 180 days after initiating standard firstline chemotherapy. Patients were either treated for solid malignant tumors or for diffuse large B-cell lymphoma. Exclusion criteria were having been included in a trial protocol, treatment regimens with <10 patients per protocol, watch-and-wait regimens, and treatment with regimens other than firstline (ie, relapse, second- or third-line therapy) (Figure 1).

Data Sources
Data were obtained from electronic health records retrieved from the PERSIMUNE data repository (PERSIMUNE Datawarehouse [11]). Data on chemotherapy for patients with diffuse large B-cell lymphoma were retrieved from the LYFO database [12]. The PERSIMUNE Datawarehouse contains nationwide data on biochemistry, microbiology, and pathology from all national labs and data on diagnoses, hospital admissions, outpatient visits, and causes of death from national registries, as well as data on vital signs and medication from central regional databases. As such, there is complete ascertainment of outcomes. The LYFO database is a nationwide database that has been collecting data

prospectively since 1982 regarding diagnostics and treatment of malignant lymphoma in Denmark [12].

Study Exposure, Outcomes, and Variables
The exposure was FN before baseline. Patients were then grouped based on the number of FN episodes (1 or >1). The primary outcomes of interest were (1) time to first severe infection, defined as collection of a blood culture, which was used as a proxy for an infection, regardless of whether the culture was positive or negative, and (2) mortality associated with infectious events.

Secondary Analyses
In a secondary analysis, we grouped the patients according to in which cycle of chemotherapy they experienced FN (FN in the first cycle, FN in later cycles, or no FN) to test the hypothesis that patients who experienced an episode of FN in the first cycle have a more fragile phenotype and poorer long-term outcomes than patients who experienced FN in later cycles.

Definitions
We defined FN by:

1a. a neutrophilocyte count $\leq 0.5 \times 10^9$/L;
or
1b. a leukocyte count $\leq 2.0 \times 10^9$/L, where a neutrophilocyte count was not measured on the same day (sensitivity, specificity, and positive and negative predictive values for total leucocyte count as a predictor of neutropenia are provided in the Supplementary Data: Supplementary Table 1 and Supplementary Figure 1);

and

2. either collection of a blood culture, regardless of whether the culture was positive or negative, or death within 3 days of neutropenia.

Only episodes of FN that occurred at least 7 days after a prior episode of FN were considered a new event.
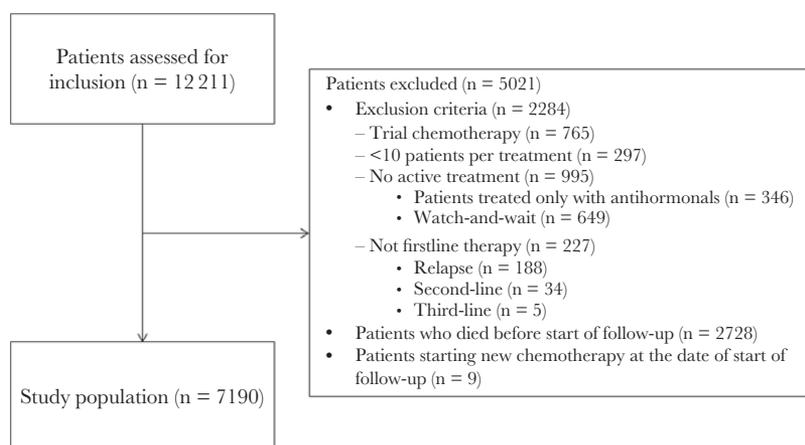
Figure 1. Flowchart showing patient exclusion criteria.

Statistical Analysis

Baseline was defined as 180 days after initiation of chemotherapy, and patients were followed until date of first infection, date of death, date of another treatment with chemotherapy, or September 29, 2015, whichever came first. Patients were stratified into 3 groups based on the number of FN episodes they had experienced before baseline (none, 1, or >1) on firstline chemotherapy. We then estimated the relative risk of infection among patients with either 1 or >1 episodes of FN vs those without FN. The cumulative risk of infection was assessed using competing risks regression based on Fine and Gray's proportional subdistribution hazards model [13], with death or another treatment with chemotherapy as competing events. The relative risks of infection and death were assessed using multivariate Poisson regression analyses adjusted for baseline variables: age, sex, diagnosis, calendar year, leucocyte count, hemoglobin, serum albumin, body surface area (BSA), comorbidities (Charlson's Comorbidity Index [CCI] [14, 15]), and stage of disease. In the analysis of risk of death, date of infection was included as a time-updated variable. Missing data were included as a separate category in the multivariate analyses.

All statistical analyses were performed using the Stata/IC statistical package, version 14.

The study was approved by the Danish Data Protection Agency (RH-2015-04, I-suite 03605) and the Danish National Board of Health (3-3013-1060/1/).

RESULTS

Patient Characteristics

A total of 12211 potentially eligible patients diagnosed with 1 of 26 types of cancers were evaluated. We excluded 2284 patients who received treatment other than standard firstline chemotherapy, 2728 patients who died within 180 days of initiation of chemotherapy, and 9 patients who received another treatment with chemotherapy at the date of start of follow-up, leaving 7190 patients in the study (Figure 1). The median age at baseline (interquartile range [IQR]) was 64 (54–71) years, and 3656 (50.9%) were women (Table 1). The most frequent diagnoses were breast cancer (889, 12.4%), colon cancer (850, 11.8%), gastric cancer (829, 11.5%), non–small cell lung cancer (713, 9.9%), primary malignant brain tumor (509, 7.1%), nasopharyngeal cancer (490, 6.8%), and ovarian cancer (449, 6.2%). There were 287 (4.0%) patients with diffuse large B-cell lymphoma.

Overall, 736 (10.2%) patients experienced at least 1 episode of FN during the first 180 days after initiation of chemotherapy. Of those, 617 (8.6%) patients experienced 1 FN episode, and 119 (1.6%) patients experienced more than 1 FN episode before baseline. Out of the 2728 patients who died within 180 days of initiation of chemotherapy, 374 (13.7%) had experienced at least 1 episode of FN.

Risk of and Risk Factors for Infection

Among the 7190 patients, who were followed for 8486 person-years, with a median follow-up time (IQR) of 0.58 (0.20–1.71) years, a total of 1370 patients had at least 1 infectious event during follow-up. The incidence rates were 15.3 (95% confidence interval [CI], 14.5–16.2), 24.3 (95% CI, 20.7–28.5), and 26.7 (95% CI, 19.2–37.2) per 100 person-years for the patients with no, 1, and >1 FN episode before baseline, respectively. Baseline characteristics of patients with and without an infection during follow-up are presented in the Supplementary Data (Supplementary Table 2). Out of the 1370 collected blood cultures, 139 (10.1%) had a positive result (Supplementary Table 3).

The cumulative incidence rates of infection 3 years after baseline were 21%, 31%, and 34% for the group with no, 1, or >1 FN episode, respectively (Figure 2). The adjusted incidence rate ratio (aIRR) of infection was 1.86 (95% CI, 1.56–2.22) and 2.19 (95% CI, 1.54–3.11) among patients with 1 FN episode and those with >1 FN episode compared with those with no FN, respectively (Table 2). The excess risk of infection among patients with prior FN compared with those without prior FN was constant over the time after start of follow-up (data not shown).

Age 60–79 years, hypoalbuminemia, anemia or leukocytosis at baseline, BSA ≥2 m^2, a CCI score ≥3, and disseminated disease were other independent risk factors for infection (Table 2).

The rates of infection varied between patients with different cancer types, with incidence rates (IRs) of 3.35/100PY (95% CI, 2.59–4.35) to 48.8/100 PY (95% CI, 37.1–64.3) for patients with breast cancer and prostate cancer, respectively. However, the relative risk of infection for patients with vs without FN before baseline showed the same tendency across the different types of cancers, with a substantially increased risk among patients with prior FN (Supplementary Table 4). Among patients with diffuse large B-cell lymphoma, the IR of infection was 12.0/100PY (95% CI, 9.45–15.1), which was similar to the pooled group of patients with solid tumors (IR, 16.5/100PY; 95% CI, 15.6–17.4). For the group of patients with diffuse large B-cell lymphoma, the IRR of infection was 1.91 (95% CI, 1.03–3.53) and 1.93 (95% CI, 0.98–3.83) among patients with 1 FN episode and those with >1 FN episode compared with those with no FN, respectively. For the pooled group of patients with solid tumors, the IRR of infection was 1.59 (95% CI, 1.34–1.90) and 2.00 (95% CI, 1.35–2.98) among patients with 1 FN episode and those with >1 FN episode compared with those with no FN, respectively.

Risk of Death After Infectious Events

There was an increased risk of death after an infectious event, and the increased mortality persisted up to 6 months after the infection. The adjusted mortality rate ratio (aMRR) was 7.52 (95% CI, 6.67–8.48) for the first month, 4.24 (95% CI, 3.80–4.75) for 1–3 months after, 2.33 (95% CI, 1.63–3.35) for 3–6 months after, and 1.09 (95% CI, 0.93–1.29) for >6 months

Table 1. Patient Characteristics

	No FN	1 FN Episode	>1 FN Episode	Total Population	P Value
Total, No. (%)	6454 (100.0)	617 (100.0)	119 (100.0)	7190 (100.0)	
Female, No. (%)	3220 (49.9)	362 (58.7)	74 (62.2)	3656 (50.9)	<.0001
Age, median (IQR), y	64 (54–71)	64 (54–71)	65 (59–72)	64 (54–71)	
Age groups, No. (%)					.60
<40 y	422 (6.54)	48 (7.78)	9 (7.56)	479 (6.66)	
40–59 y	2064 (32.0)	198 (32.1)	26 (21.9)	2288 (31.8)	
60–79 y	3675 (56.9)	355 (57.5)	79 (66.4)	4109 (57.2)	
80+ y	293 (4.54)	16 (2.59)	5 (4.20)	314 (4.37)	
Baseline leukocyte count, No. (%)					.06
<3.5	633 (9.81)	91 (14.8)	24 (20.2)	748 (10.4)	
3.5–8.8	4368 (67.7)	409 (66.3)	65 (54.6)	4842 (67.3)	
>8.8	1278 (19.8)	117 (19.0)	27 (22.7)	1422 (19.8)	
Missing values	175 (2.71)	0 (0.0)	3 (2.52)	178 (2.48)	
Baseline hemoglobin, No. (%)					<.0001
<lower limit of normal[a]	3750 (58.1)	435 (70.5)	79 (66.4)	4264 (59.3)	
≥lower limit of normal	2.539 (39.3)	182 (29.5)	36 (30.3)	2757 (38.3)	
Missing values	165 (2.56)	0 (0.00)	4 (3.36)	169 (2.35)	
Baseline albumin, No. (%)					
<lower limit of normal[b]	1084 (16.8)	154 (25.0)	43 (36.1)	1281 (17.8)	
≥lower limit of normal	3020 (46.8)	290 (47.0)	49 (41.2)	3359 (46.7)	
Missing values	2.350 (36.4)	173 (28.0)	27 (22.7)	2550 (35.47)	
Body surface area, No. (%)					.05
<2 m^2	4694 (72.7)	462 (74.9)	81 (68.1)	5237 (72.8)	
≥2 m^2	1542 (23.9)	111 (18.0)	13 (10.9)	1666 (23.2)	
Missing	218 (3.38)	44 (7.13)	25 (21.0)	287 (3.99)	
Charlson Comorbidity Index, No. (%)					<.0001
2	5167 (80.1)	455 (73.7)	79 (66.4)	5701 (79.3)	
3	448 (6.94)	55 (8.91)	13 (10.9)	516 (7.18)	
4+	839 (13.0)	107 (17.3)	27 (22.7)	973 (13.5)	
Stage of disease at start of chemotherapy, No. (%)					<.0001
Adjuvating	1342 (20.8)	112 (18.2)	15 (12.6)	1469 (20.4)	
Neo-adjuvating/concomitant	2360 (36.6)	184 (29.8)	18 (15.1)	2562 (35.6)	
Inoperable/disseminated/metastatic	2016 (31.2)	219 (35.5)	51 (42.9)	2286 (31.8)	
Missing/unknown	736 (11.4)	102 (16.5)	35 (29.4)	873 (12.1)	
Diagnosis, No. (%)					<.0001
Breast cancer	782 (12.1)	92 (14.9)	15 (12.6)	889 (12.4)	
Primary malignant brain tumor	502 (7.78)	7 (1.13)	0 (0.00)	509 (7.08)	
Anal cancer	13 (0.20)	2 (0.32)	0 (0.00)	15 (0.21)	
Cholangiocarcinoma	25 (0.39)	1 (0.16)	1 (0.84)	27 (0.38)	
Colon cancer	833 (12.9)	17 (2.76)	0 (0.00)	850 (11.8)	
Esophageal cancer	273 (4.23)	25 (4.05)	2 (1.68)	300 (4.17)	
Liver cancer	24 (0.37)	1 (0.16)	0 (0.00)	25 (0.35)	
Rectum cancer	163 (2.53)	0 (0.00)	0 (0.00)	163 (2.2)	
Gastric cancer	758 (11.7)	54 (8.75)	17 (14.3)	829 (11.5)	
Diffuse large B-cell lymphoma	218 (3.38)	44 (7.13)	25 (21.0)	287 (3.99)	
Penis cancer	9 (0.14)	0 (0.00)	0 (0.00)	9 (0.13)	
Prostate cancer	143 (2.22)	20 (3.24)	5 (4.20)	168 (2.34)	
Testicular cancer	145 (2.25)	18 (2.92)	6 (5.04)	169 (2.35)	
Bladder cancer	172 (2.67)	15 (2.43)	0 (0.00)	187 (2.60)	
Cervical cancer	212 (3.28)	16 (2.59)	0 (0.00)	228 (3.17)	
Uterine cancer	131 (2.03)	2 (0.32)	1 (0.84)	134 (1.86)	
Ovary cancer	355 (5.50)	76 (12.3)	18 (15.1)	449 (6.24)	
Vulvar cancer	11 (0.17)	0 (0.00)	0 (0.00)	11 (0.15)	
Nasopharyngeal cancer	402 (6.23)	81 (13.1)	7 (5.88)	490 (6.82)	
Soft tissue sarcoma	5 (0.08)	0 (0.00)	1 (0.84)	6 (0.08)	
Neuroendocrine tumor	119 (1.84)	19 (3.08)	3 (2.52)	141 (1.96)	
Non–small cell lung cancer	628 (9.73)	76 (12.3)	9 (7.56)	713 (9.92)	

Table 1. Continued

	No FN	1 FN Episode	>1 FN Episode	Total Population	P Value
Malignant pleural mesothelioma	284 (4.40)	13 (2.11)	0 (0.00)	297 (4.13)	
Small cell lung cancer	162 (2.51)	29 (4.70)	9 (7.56)	200 (2.78)	
Thymoma	19 (0.29)	7 (1.13)	0 (0.00)	26 (0.36)	
Cancer of unknown primary	66 (1.02)	2 (0.32)	0 (0.00)	68 (0.95)	

Abbreviations: FN, febrile neutropenia; IQR, interquartile range.

[a]Lower limit for normal hemoglobin level was 8.3 for men and 7.3 for women.

[b]Lower limit for normal albumin level was <36 if age <70 years and <34 if age >70 years.

after an infection, compared with the time before infection (Table 3). The increase in risk of death after an infectious event was similar among patients with vs without a prior episode of FN (Supplementary Table 5).

Among the 139 patients with positive blood cultures, 39 (28.1%) and 84 (60.4%) died within 1 and 6 months of the infection, respectively. For the 1231 patients with negative blood cultures, 240 (19.5%) and 570 (46.3%) died within 1 and 6 months, respectively.

Secondary Analyses

We found no significant difference in risk of infection according to timing of the episode of FN. The incidence rate of infection was 15.3 (95% CI, 14.5–16.2) per 100 person-years for the patients with no FN, 23.5 (95% CI, 18.8–29.3) for the patients with FN in the first cycle of chemotherapy, and 25.7 (95% CI, 21.3–30.9) for patients with first FN in later cycles of chemotherapy. The aIRR of infection was 1.82 (95% CI, 1.43–2.31) and 1.98 (95% CI, 1.62–2.42) for the groups with FN in the first cycle and later cycles, respectively, compared with the group with no FN.

DISCUSSION

In a large cohort study using nationwide data from electronic health records, we examined if FN within 180 days after initiation of chemotherapy is a predictor of long-term risk of
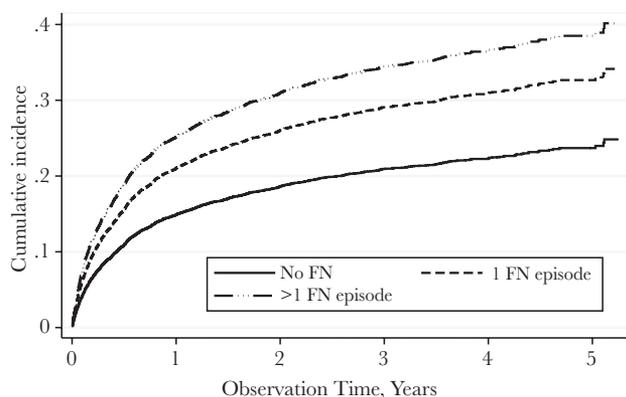
Figure 2. Cumulative incidence of infection in the period from 180 days after initiation of chemotherapy, stratified by episodes of febrile neutropenia before baseline. Abbreviation: FN, febrile neutropenia.

infection and poor outcomes among cancer patients. We found that FN following chemotherapy was associated with a long-term increased risk of infection, with an approximately 2-fold increase in risk among patients who had experienced FN compared with patients who had not developed FN within 180 days after initiation of chemotherapy. An infectious event after completion of chemotherapy was associated with a markedly increased risk of death in the following month, and the increased risk of death persisted up to 6 months after the infection. Associations between infection and risk of death did not differ between patients with vs without prior episodes of FN.

The observational design of the study precludes assessment of causality, but the association between FN and increased long-term risk of infection may suggest that patients with FN represent a fragile phenotype with a generally increased risk of infectious complications and poor long-term outcomes following chemotherapy. The association between FN and long-term risk of infection was independent of other indicators of a more vulnerable phenotype, such as older age, anemia, low albumin, disseminated disease, and comorbidity. In fact, the estimate of the relative risk of infection associated with FN increased slightly after adjustment for these factors.

Existing literature in this area focus on short-term complications of FN in terms of in-hospital mortality, length of hospital stay, and hospital costs [2, 5, 7]. Major factors associated with inpatient mortality, length of stay, and costs include patient characteristics, type of malignancy, comorbidities, and infectious complications [5]. Identification of well-defined risk factors of poor outcome on the long term is equally essential for optimizing the management of these patients, which is the rationale for this study. However, the literature on long-term complications of FN is scarce.

Previous studies have shown that dose reductions and treatment delays in chemotherapy, which are often consequences of FN, are associated with reduced long-term survival, presumably due to progression of cancer secondary to suboptimal chemotherapy [16]. In recent years, the importance of the immune system in controlling cancer has been highlighted [17]. The impact of chemotherapy dose intensity and of immunological parameters on associations between FN after chemotherapy and risk of progression of cancer should be explored in future studies.

Table 2. Incidence Rates and Incidence Rate Ratios of Infection

	No. of Events	IR[a] (95% CI)	IRR (95% CI)	aIRR (95% CI)
FN groups				
No FN	1182	15.3 (14.5–16.2)	1 (ref.)	1 (ref.)
1 FN episode	153	24.3 (20.7–28.5)	1.59 (1.34–1.88)	1.86 (1.56–2.22)
>1 FN episode	35	26.7 (19.2–37.2)	1.75 (1.25–2.44)	2.19 (1.54–3.11)
Sex				
Female	567	11.4 (10.5–12.3)	1 (ref.)	1 (ref.)
Male	803	22.9 (21.4–24.6)	2.02 (1.81–2.25)	1.11 (0.97–1.28)
Age groups, y				
<40	63	7.71 (6.02–9.86)	0.71 (0.54–0.93)	1.05 (0.79–1.41)
40–59	347	10.9 (9.77–12.1)	1 (ref.)	1 (ref.)
60–79	892	21.4 (20.0–22.8)	1.97 (1.74–2.23)	1.16 (1.02–1.33)
>80	68	23.1 (18.2–29.3)	2.13 (1.64–2.76)	1.20 (0.92–1.58)
Baseline leukocyte count				
<3.5	119	12.4 (10.3–14.8)	0.86 (0.71–1.04)	0.74 (0.60–0.90)
3.5–8.8	865	14.3 (13.4–15.3)	1 (ref.)	1 (ref.)
>8.8	346	29.3 (26.3–32.5)	2.04 (1.80–2.31)	1.65 (1.45–1.88)
Missing	40	13.3 (9.76–18.13)	0.93 (0.68–1.28)	1.26 (0.45–3.57)
Baseline hemoglobin				
<lower limit of normal[b]	876	18.9 (17.7–20.2)	1.48 (1.32–1.66)	1.26 (1.11–1.43)
≥lower limit of normal	456	12.8 (11.7–14.0)	1 (ref.)	1 (ref.)
Missing	38	13.2 (9.60–18.1)	1.03 (0.74–1.44)	0.83 (0.29–2.41)
Baseline albumin				
<lower limit of normal[c]	269	30.5 (27.1–34.4)	2.03 (1.76–2.35)	1.26 (1.11–1.43)
≥lower limit of normal	635	15.0 (13.9–16.2)	1 (ref.)	1 (ref.)
Missing	466	13.8 (12.6–15.1)	0.92 (0.82–1.04)	0.83 (0.29–2.41)
Body surface area, m²				
<2	916	15.1 (14.1–16.1)	1 (ref.)	1 (ref.)
≥2	384	21.1 (19.1–23.3)	1.40 (1.25–1.58)	1.23 (1.08–1.40)
Missing	70	12.0 (9.45–15.1)	0.79 (0.62–1.01)	1
Charlson Comorbidity Index				
2	1028	14.4 (13.5–15.3)	1 (ref.)	1 (ref.)
3	127	27.1 (22.8–32.3)	1.89 (1.57–2.27)	1.48 (1.23–1.80)
4+	215	25.0 (21.9–28.6)	1.74 (1.50–2.02)	1.29 (1.10–1.52)
Stage of disease at start of chemotherapy				
Adjuvating	141	5.15 (4.36–6.06)	1 (ref.)	1 (ref.)
Neo-adjuvating/concomitant	479	17.6 (16.1–19.2)	3.41 (2.83–4.12)	2.53 (1.93–3.32)
Inoperable/disseminated/metastatic	530	26.6 (24.4–28.9)	5.17 (4.29–6.23)	4.05 (3.18–5.16)
Missing/unknown	220	21.5 (18.9–24.6)	4.19 (3.39–5.18)	4.79 (3.06–7.50)

Univariate and multivariate Poisson regression analyses. All variables were included in the multivariate model, including all diagnoses.

Abbreviations: aIRR, adjusted incidence rate ratio; CI, confidence interval; FN, febrile neutropenia; IR, incidence rate; IRR, incidence rate ratio.

[a]IR, per 100 person-years of follow-up.

[b]Lower limit for normal hemoglobin level was 8.3 mmol/L for men and 7.3 mmol/L for women.

[c]Lower limit for normal albumin level was <36 g/L if age <70 years and <34 g/L if age >70 years.

Our analyses show that older age (>60 years) and baseline anemia, hypoalbuminemia, and leukocytosis, as well as comorbidity and disseminated disease stage, are independent risk factors for infections. However, the aIRR for the 80+ age group did not reach statistical significance due to the small number of patients in this age group. Older age has been associated with poor outcomes in previous studies [5, 18]. Serum albumin is a commonly used marker for nutritional status in cancer patients. Malnutrition and inflammation suppress albumin synthesis, and low serum albumin level can therefore reflect the severity of disease and has also been shown to be a good predictor of

prognosis in previous studies [18, 19]. One prospective observational study also found low albumin (<35 g/L) at baseline to be associated with increased risk of FN in the first cycle of chemotherapy among patients with non-Hodgkin lymphoma [20]. Similarly, it is well known that anemia in cancer patients is a significant prognostic factor and has shown to be a strong predictor of poorer survival in this patient group [21].

The study has some limitations: We defined episodes of FN as collection of a blood culture during a neutropenic episode because data on temperature measurements at and during hospital admissions were only available from the most recent part

Table 3. Mortality Rates and Mortality Rate Ratios After an Infectious Event vs the Time Before/Without Infection

Time After Infection, mo	MR (95% CI)	aMRR[a] (95% CI)
0–1	3.35 (3.00–3.74)	7.52 (6.67–8.48)
1–3	1.62 (1.46–1.79)	4.24 (3.80–4.75)
3–6	0.76 (0.53–1.09)	2.33 (1.63–3.35)
> 6	0.28 (0.24–0.33)	1.09 (0.93–1.29)

Abbreviations: aMRR, adjusted mortality rate ratio; CI, confidence interval; MR, mortality rate.
[a]Mortality rate ratio adjusted for age, gender, diagnosis, calendar year, and baseline leukocyte count.

of the study period. We have tested the validity of this definition on the subgroup of patients with data on temperature measurements and found good agreement with the standard definition of FN [9]. We also used collection of a blood culture as a proxy for later infectious events. It is very difficult to find criteria that have both very high sensitivity and specificity for ascertainment of infectious events. Microbiological samples are only positive in a subset of patients with infections, and the sensitivity of analyses of microbiological samples is hampered when patients are treated with antibiotics before they present at the hospital.

Standard operating procedure in our center is to only collect blood cultures when there is clinical suspicion of infection. Thus, we believe that blood culture collection is a relevant proxy, which has also previously been used in a previous study to define infectious events [22].

We could not rule out that fever (eg, collection of a blood culture) was due to progression of cancer. In our analyses, patients were censored when they received another treatment with chemotherapy, and thus the infectious events during follow-up are unlikely to represent chemotherapy-induced FN episodes. We did not have access to data regarding patient performance status, but hemoglobin and albumin might be considered as surrogate markers of performance status [18, 19].

Major strengths of the study include the large cohort of patients with long-term follow-up and access to precise and complete nationwide data on study outcomes through electronic health records and nationwide registries that could be linked using the unique Danish civil registration number.

In conclusion, we found that FN is associated with a long-term increased risk of infection among patients treated with chemotherapy for malignant disease and that an infectious event is associated with increased mortality, persisting up to 6 months after the infection.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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