

Incidence and Predictors of Community-Acquired Pneumonia in Patients With Hematological Cancers Between 2016 and 2019

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Background. Patients with hematological cancers (HC) are at high risk of infections, in particular community-acquired pneumonia (CAP). Recent data on incidence and predictors of CAP among patients with HC are scarce.

Methods. We performed a cohort study (2016–2019) in 2 hospitals in the Netherlands among adults with HC to calculate incidence rates (IRs) of CAP. In addition, we performed a nested case-control study to identify predictors of CAP.

Results. We identified 275 CAP cases during 6264 patient-years of follow-up. The IR of CAP was 4390/100 000 patient-years of follow-up. Compared with the general population, IR ratios ranged from 5.4 to 55.3 for the different HCs. The case fatality and intensive care unit (ICU) admission rates were 5.5% and 9.8%, respectively. Predictors for CAP in patients with HC were male sex, anemia, lymphocytopenia, chronic kidney disease, cardiovascular disease, autologous and allogeneic stem cell transplantation, treatment with immunosuppressive medication for graft-vs-host disease, treatment with rituximab in the past year, and treatment with immunomodulators (lenalidomide, thalidomide, pomalidomide and/or methotrexate) in the past month. Independent predictors of a severe disease course (death or ICU admission) included neutropenia (odds ratio, 4.14 [95% confidence interval, 1.63–10.2]), pneumococcal pneumonia (10.24 [3.48–30.1]), chronic obstructive pulmonary disease (6.90 [2.07–23.0]), and the use of antibacterial prophylaxis (2.53 [1.05–6.08]).

Conclusions. The burden of CAP in patients with HC is high, with significant morbidity and mortality rates. Therefore, vaccination against respiratory pathogens early in the disease course is recommended, in particular before starting certain immunosuppressive therapies.

Keywords. pneumonia; immunocompromised patients; hematological cancers; vaccine-preventable diseases.

Patients with hematological cancers (HCs) are immunocompromised, owing both to the nature of their disease and to the immunosuppressive antineoplastic treatments they receive. Therefore, these patients are at high risk of infectious complications. Community-acquired pneumonia (CAP) is a frequent and severe complication in patients with HC, causing substantial morbidity, with a case fatality rate of 16% among patients with HC, as well as a high burden of healthcare costs [1, 2]. *Streptococcus pneumoniae* is the most frequently isolated pathogen causing CAP (about 20% of cases), which often precedes invasive pneumococcal disease [3]. Our group

recently observed a high disease burden of invasive pneumococcal disease in patients with HC (482 cases per 100 000) [4].

A prior study estimated the incidence rate (IR) of CAP in patients with HC between 2011 and 2015 at 2977 cases per 100 000 patient-years of follow-up (PYFU) [2]. More recent epidemiological data are lacking. In addition, studies identifying risk factors for CAP in patients with HC are limited. Treatment advances for patients with HC, such as the increased use of novel immunomodulators and the use of rituximab for indolent lymphomas, may have changed the risk of respiratory infections, including CAP, in recent years [5, 6]. Considering the burden of CAP in this population, it is crucial to obtain accurate and recent data, regarding both the incidence and microbiological causes of CAP, as well as predisposing and protective factors.

The primary objective of this study was to determine the incidence of CAP among patients with HC, stratified by disease subtype. Secondary objectives were to investigate microbiological causes of CAP and to determine predictors of (severe) CAP. We hypothesized that the disease burden of CAP is much

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higher among patients with HC than in the general population but differs widely depending on the underlying HC and current and past antineoplastic treatments. With the current study, we aimed to provide a more solid scientific base for vaccination recommendations and other preventive strategies against respiratory infections among patients with HC.

METHODS

We performed a retrospective cohort study combined with a nested case-control study at the Amsterdam University Medical Center (UMC), 2 large tertiary care hospitals in Amsterdam, the Netherlands.

Cohort Study

The cohort consisted of all adult patients with a registered *International Classification of Disease, Tenth Revision (ICD-10)* diagnosis of HC in care of the Amsterdam UMC, between 1 January 2016 and 31 December 2019. Episodes of CAP among patients with HC in the same period were identified using CTcue, a software program that enables searching based on *ICD-10* codes and keywords in the electronic patient files. Only CAP diagnoses made in the hospital were included. A case of CAP was defined as the presence of radiological (radiographic or computed tomographic) findings consistent with pneumonia, and ≥ 1 of the following clinical criteria: (1) temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$; (2) cough; (3) increased sputum production; (4) hypoxemia, defined as partial oxygen pressure <60 mm Hg while breathing ambient air; or (5) findings on auscultation/percussion of the lungs consistent with pneumonia. Cases were not included if they fell into the CAP definition but a final noncommunicable diagnosis, such as pulmonary embolism, was made. Cases of hospital-acquired pneumonia were excluded by filtering out patients who had been hospitalized or had resided in a long-term care facility for >48 hours immediately before the onset of symptoms.

We calculated the IRs of CAP per 100 000 PYFU for each year for the entire inpatient and outpatient hospital population and derived from the same hospitals (general hospital population) and for patients with HC, stratified by disease subtype. Differences in CAP IRs over time between patients with HC and the general hospital population, and between the different HC disease subtypes, were compared by calculating IR ratios (IRRs) and 95% confidence intervals (CIs).

Case-Control Study

Controls were matched in a 1:1 ratio based on the HC subtype. Controls had to be in the care of the Amsterdam UMC during the same period as the corresponding case patients and to not have had a CAP between 1 January 2016 and 31 December 2019. Controls were randomly selected using CTcue software, based on the *ICD-10* code of the HC. Controls were included only in the absence of radiological findings consistent with CAP

as well as the absence of a CAP diagnosis (*ICD-10* code) during the study period. Through record review, clinical data were retrieved, including age, sex, comorbid conditions, current and previous antineoplastic therapies, previous vaccinations, use of antimicrobial prophylaxis, and substance use, as well as laboratory parameters, including blood cell counts, immunoglobulin G levels, and creatinine levels from all case patients and controls. Additional data collected from cases were CAP-related hospital admission, ICU admission and death, length of stay, microbiological tests performed, and pathogens identified.

Outcomes and Analysis

The primary outcome was the incidence of CAP per 100 000 PYFU, stratified by subtype of HC. Secondary outcomes were microbiological causes of CAP, as well as predictors for CAP and for severe disease outcome, defined as CAP-related death within 30 days and/or CAP-related ICU admission.

To identify predictors of CAP, conditional multivariable logistic regression analysis was performed, using stepwise backward selection based on likelihood ratio. The analysis was adjusted for matching of case patients and controls, based on type of underlying cancer. Variable entry was set at $P < .05$, and variable removal at $P > .1$. The following predefined variables were entered in the model: age, sex, comorbid condition (cardiovascular disease, chronic obstructive pulmonary disease, chronic kidney disease), type of antimicrobial prophylaxis (antiviral, antibacterial, and/or antifungal), prior pneumococcal vaccination, history of stem cell transplantation (SCT; allogeneic or autologous), presence of graft-vs-host disease (GVHD), immunosuppressive treatment for GVHD, treatment with cytotoxic chemotherapy (defined as alkylating agents, purine analogues, anthracycline derivatives and/or vinca alkaloids), the use protein kinase inhibitors, immunomodulators (defined as the use of thalidomide, lenalidomide, pomalidomide, or methotrexate), and/or steroids in the month before CAP, the use of rituximab in the 12 months before CAP, the use of intravenous immunoglobulins as well as the presence of anemia (hemoglobin level, <7.5 mmol/L), lymphocytopenia (lymphocyte count, $<1.0 \times 10^9/\text{L}$), neutropenia (neutrophil count, $<1.5 \times 10^9/\text{L}$), and thrombocytopenia (platelet count, $<150 \times 10^9/\text{L}$).

In addition, we performed multivariable binary logistic regression analysis, using stepwise backward selection to determine predictive factors for a severe disease outcome among the CAP case patients. The same predefined variables were entered in the model we used to establish risk factors for CAP, along with the type of underlying HC and the microbiological cause of pneumonia (pneumococcal, bacterial, viral, fungal, or no pathogen found). Because the CURB-65 score was not available for all CAP cases in this study, the association between the CURB-65 score and severe disease outcome was assessed only by univariate logistic regression to avoid loss of data. We applied an α level of 5% to indicate statistical significance. For all statistical

analyses, SPSS statistical software version 26 (IBM SPSS) was used. Cases with missing data were excluded from the analysis.

Ethical Considerations

For this noninterventional study, a waiver for medical ethical approval was granted by the Medical Ethics Committee of the Amsterdam UMC, Location Academic Medical Center (reference no. W19_467#19.540). No patient consent was required.

RESULTS

Cohort Study

Between 2016 and 2019, a total of 275 CAP cases occurred during 6264 PYFU. The IR of CAP in patients with HC was 4390/100 000 PYFU, compared with 275/100 000 PYFU for the general hospital population (Table 1 and Figure 1). The risk of CAP was significantly increased compared with the general in-hospital population for all subtypes of HC, with IRRs ranging between 5.4 and 55.3, depending on HC subtype and treatment status (Table 1). The highest IRs of CAP were observed for patients who had undergone autologous or allogeneic SCT, as well as those with acute myeloid leukemia, acute lymphoblastic leukemia, or multiple myeloma (Table 1 and Figure 1). The IRs of CAP in patients with HC and in the general hospital population did not change over time between 2016 and 2019 (IRR, 0.9 [95% CI, .6–1.3] and 1.0 [.9–1.2], respectively).

Microbiological Testing and Diagnoses

The distribution of causative agents of microbiologically confirmed CAP is depicted in Figure 2. The most frequently identified pathogen was *S. pneumoniae* (24 cases), followed by rhinovirus, parainfluenza virus, and *Haemophilus influenzae* (Supplementary Materials and Supplementary Table 2). In 37 of 121 cases in which no pathogen was found, no diagnostic

testing had been performed. In the remaining 87 cases, no pathogen had been found despite diagnostic testing. However, sputum cultures were done less frequently in this group than in the other CAP cases (25.6% vs 39.8%, respectively; $P = .02$). In addition, pneumococcal urinary antigen tests were performed in only 7.2% of these cases, compared with up to 50% in the pneumococcal CAP group ($P = .01$).

Predictors for Severe Disease Outcome

The hospital admission, ICU admission, and case fatality rates for CAP were 67.4%, 9.8%, and 5.5% respectively. An overview of baseline and clinical characteristics of CAP stratified by causative infectious agent can be found in Supplementary Table 1 (Supplementary Materials). Rates of hospitalization and ICU admission differed among the subtypes of CAP, with pneumococcal pneumonia having higher rates of admission than other types of CAP (ICU admission, 35% vs 7.7%, respectively [$P < .01$]; hospitalization, 88% vs 66% [$P = .03$]). The CURB-65, which was available for 186 of 275 case patients (67.6%), was a statistically significant predictor of a severe disease course (odds ratio, 2.19 [95% CI, 1.41–3.41]). Pneumococcal pneumonia, chronic obstructive pulmonary disease as a comorbid condition, the presence of neutropenia, and the use of antibacterial prophylaxis before the CAP episode were independent predictors of a severe disease course in a multivariable analysis (Table 2).

Case-Control Study

Baseline clinical characteristics of the case patients and controls are summarized in Table 3. Of the 275 CAP case patients, 49 (17.9%) had received pneumococcal vaccination before CAP, compared with 39 controls (14.2%). Hematopoietic SCT (HSCT) recipients represented a larger proportion of vaccinated individuals—88%, compared with 43% among unvaccinated individuals ($P < .001$). The overall mortality rate was higher

Table 1. Incidence Rates (IRs) of Community-Acquired Pneumonia Stratified by Type of Underlying Cancer and Hematopoietic Stem Cell Transplantation and IR Ratios Compared With the General Hospital Population and Other Hematological Cancers

Diagnosis	No. of Cases (n = 275)	PYFU	IR/100 000 (2016–2019)	IRR vs General Population	95% CI Lower	95% CI Upper	IRR for Diagnosis vs Other HCs	95% CI Lower	95% CI Upper
All HCs	275	6264	4390	23.3	20.4	24.6	NA	NA	NA
ALL	15	235	6383	23.2	13.8	39.0	1.48	.88	1.79
CLL	38	821	4629	16.8	12.0	23.6	1.06	.75	1.23
AML	49	665	7368	26.8	19.8	36.3	1.82	1.33	2.11
CML	8	261	3065	11.1	5.5	22.5	0.69	.34	.88
Hodgkin lymphoma	11	473	2326	8.5	4.6	15.5	0.51	.28	.63
Non-Hodgkin lymphoma	70	1919	3648	13.3	10.2	17.2	0.77	.59	.89
Multiple myeloma	55	880	6250	22.7	17.0	30.4	1.52	1.13	1.77
MDS	19	340	5588	20.3	12.8	32.3	1.29	.81	1.53
Other	10	670	1493	5.4	2.9	10.2	0.31	.17	.39
auto-HSCT	55	816	6740	24.5	18.3	32.7	1.66	1.24	1.93
allo-HSCT	85	559	15 206	55.3	43.4	70.5	4.54	3.52	5.30

Abbreviations: ALL, acute lymphoblastic leukemia; allo-HSCT, allogeneic hematopoietic stem cell transplantation (HSCT); AML, acute myeloblastic leukemia; auto-HSCT, autologous HSCT; CI, confidence interval; CLL, chronic lymphocytic leukemia; CML, chronic myelocytic leukemia; HC, hematological cancer; IR, incidence rate; IRR, IR ratio; MDS, myelodysplastic syndrome; NA, not applicable; PYFU, patient-years of follow-up.

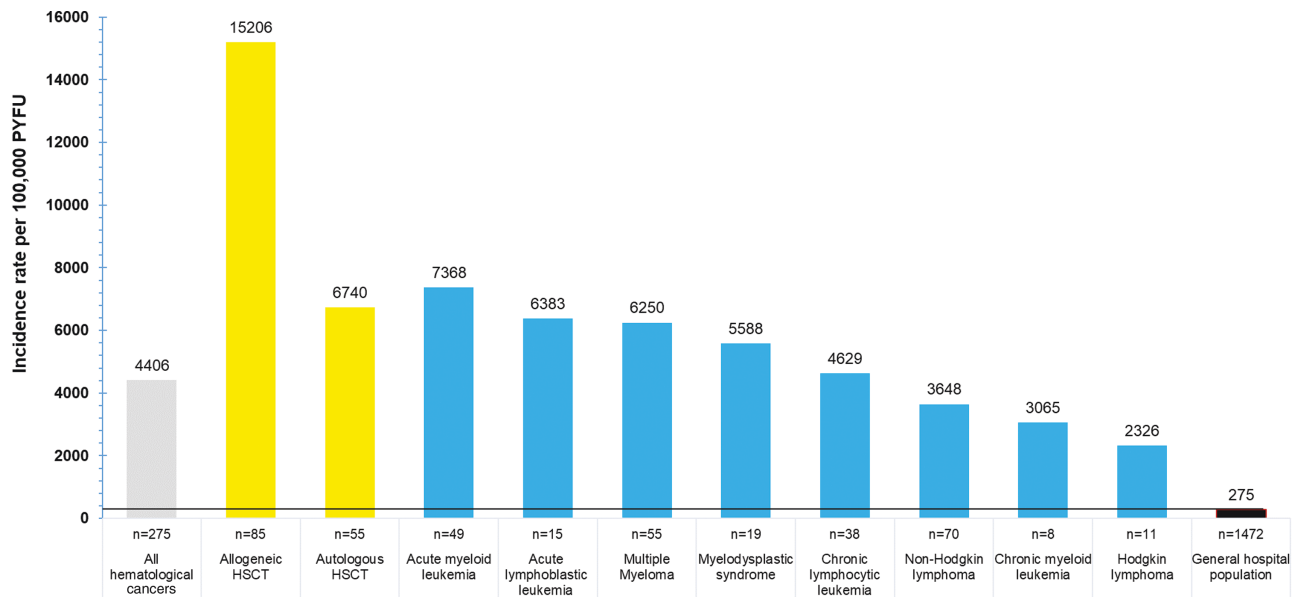


Figure 1. Incidence rate (IR) of community-acquired pneumonia (CAP) (2016–2019), stratified according to hematological cancer compared with the general hospital population (*black line*). Abbreviations: HSCT, hematopoietic stem cell transplantation; PYFU, patient-years of follow-up.

in patients with CAP than in controls (odds ratio, 6.85 [95% CI, 3.83–12.25]). Statistically significant predictors of CAP in the final multivariable model included male sex, anemia, lymphocytopenia, cardiovascular disease, chronic kidney disease, a history of allogeneic or autologous HSCT, use of immunosuppressive medication for GVHD, treatment with rituximab in the year before CAP, and treatment with immunomodulators in the month before CAP (Table 4).

DISCUSSION

We report a high burden of CAP hospital presentations among patients with HC than in those without HC (IRR, 16.0 [95% CI,

13.5–18.9]). The IR of CAP was 4390/100 000, much higher than what was reported in a previous study (2976.7/100 000 PYFU) [2]. One of the possible explanations is the higher rate of HSCT in the present study—51% versus 5.4% in the aforementioned study. In addition, a different definition of CAP was used in the prior study, which included cases based on CAP-related ICD-10 insurance claims rather than a combination of clinical and radiological findings. This could also explain the lower CAP-related mortality rate reported in the present study (5.5% vs 16% in the earlier study), because a case definition based only on ICD-10 codes may have led to selection of more severe CAP cases. Another explanation for the lower mortality rate in our study could be the increased use of computed tomography in more recent years, resulting in more timely diagnosis and treatment [7, 8].

The highest IRs of CAP were observed for patients with a history of allogeneic or autologous HSCT and patients with a diagnosis of acute myeloid leukemia, acute lymphoblastic leukemia, or multiple myeloma, who often undergo HSCT (63.3%, 53.3% and 66.7% of cases in this study, respectively). While HSCT is a life-saving treatment for HC, it also leads to a period

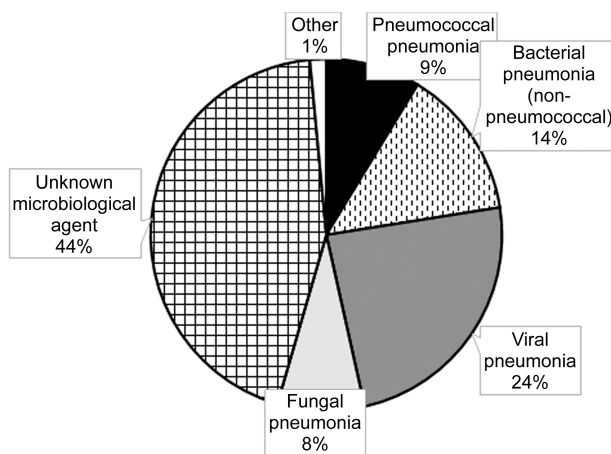


Figure 2. Distribution of causative infectious agents of community-acquired pneumonia.

Table 2. Multivariable Regression Analysis With Predictors of Severe Disease (n = 235)

Predictor	Adjusted OR	95% CI
COPD	6.90	2.07–23.0
Neutropenia	4.14	1.63–10.2
Pneumococcal pneumonia	10.24	3.48–30.1
Antibacterial prophylaxis	2.53	1.05–6.08

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; OR, odds ratio.

Table 3. Baseline Characteristics of Case Patients and Controls

Characteristic		No./Total (%) ^a		OR ^b	95% CI	P Value	
		Case Patients (n = 275)	Controls (n = 275)				
Sex	Male sex	167/275 (60.72)	135/275 (49.09)	0.62	.44–.88	.007 ^c	
Age	Age, median, y	64 (n = 275)	66 (n = 275)	1.02	1.00–1.03	.02 ^c	
	18–64 y	128/275 (46.54)	143/275 (52.00)	0.82	.59–1.13	.22	
	≥65 y	147/275 (53.45)	132/275 (48.00)	1.23	.89–1.69	.22	
Mortality	Deaths (all causes)	95/275 (34.5)	19/275 (6.9)	6.85	3.83–12.3	<.001 ^c	
Comorbid conditions	Total	194/275 (70.54)	128/275 (46.54)	2.74	1.89–3.97	<.001 ^c	
	Cardiovascular disease	116/274 (42.3)	79/273 (28.9)	1.75	1.24–2.46	.002 ^c	
	COPD	28/274 (10.2)	6/275 (2.2)	5.40	2.08–14.0	.001 ^c	
	Asthma	14/274 (5.1)	4/275 (1.5)	3.50	1.15–10.6	.03 ^c	
	Diabetes	33/274 (12.0)	25/274 (9.1)	1.36	.79–2.36	.27	
	Asplenia	6/275 (2.2)	2/275 (0.7)	3.00	.61–14.9	.18	
	History of solid organ tumor	43/275 (15.6)	38/272 (13.9)	1.18	.71–1.95	.52	
	Chronic kidney disease	54/274 (19.7)	24/275 (8.7)	2.36	1.44–3.89	.001 ^c	
	Liver cirrhosis	4/273 (1.5)	1/275 (0.4)	65.29	.01–702.391	.38	
	Immunodeficiency disorder	12/274 (4.4)	13/275 (4.7)	0.92	.42–2.02	.84	
	Race/ethnicity	White	238/272 (87.5)	238/267 (89.14)	1.00	.62–1.62	>.99
		Asian	7/272 (2.57)	3/267 (1.12)	2.33	.60–9.02	.22
		Black	18/272 (6.62)	21/267 (7.87)	0.84	.43–1.64	.61
Substance use	Current smoker	27/254 (10.63)	15/177 (8.47)	1.46	.68–3.13	.34	
	Former smoker	111/209 (53.11)	55/124 (44.35)	1.04	.59–1.82	.89	
	Current alcohol use	83/224 (37.05)	81/151 (53.64)	0.56	.34–.91	.02 ^c	
	Current drug use	10/218 (4.59)	5/126 (3.97)	2.00	.50–7.99	.33	
Vaccination	Pneumococcal	49/271 (18.08)	39/275 (14.18)	1.37	.83–2.25	.21	
	Influenza	22/101 (21.78)	21/154 (13.63)	2.40	.85–6.81	>.99	
HSCT ^c	All HSCT	140/275 (50.91)	85/275 (30.91)	2.72	1.81–4.08	<.001 ^c	
	Allogeneic	85/275 (30.9)	44/275 (16.0)	2.86	1.76–4.65	<.001 ^c	
	Autologous	55/275 (20.0)	41/275 (14.9)	1.64	.96–2.78	.07	
	≤24 mo since HSCT or shorter	49/138 (35.5)	21/82 (25.6)	2.25	.98–5.18	.056	
GVHD	Total	46/275 (16.73)	10/275 (3.64)	5.50	2.59–11.7	<.001 ^c	
	Use of immunosuppressives	53/275 (19.27)	8/275 (2.91)	12.25	4.42–33.9	<.001 ^c	
Treatment	None treatment	151/275 (54.91)	224/275 (81.45)	0.26	.16–.39	<.001 ^c	
	Protein kinase inhibitors (past month)	18/275 (6.55)	12/275 (4.36)	1.60	.73–3.53	.24	
	Cytotoxic chemotherapy (past month)	41/275 (14.9)	15/275 (5.5)	3.17	1.65–6.06	<.001 ^c	
	Immunomodulators (past month)	44/275 (16.00)	17/275 (6.18)	5.50	2.31–13.1	<.001 ^c	
	Steroids (past month)	43/275 (15.64)	25/275 (9.09)	2.06	1.15–3.68	.02 ^c	
	Rituximab (past 12 mo)	44/275 (16.0)	10/275 (3.6)	9.50	3.39–26.6	<.001 ^c	
	Hypomethylating agents (past month)	15/275 (5.45)	1/275 (0.36)	15.0	1.98–113	.009 ^c	
	Other	29/275 (10.55)	26/275 (9.45)	1.13	.65–1.95	.68	
Prophylaxis	Antiviral	106/275 (38.5)	32/275 (11.6)	5.35	3.19–8.99	<.001 ^c	
	Antibacterial ^d	83/275 (30.2)	27/275 (9.8)	5.00	2.81–8.88	<.001 ^c	
	Antifungal	33/275 (12.0)	10/275 (3.6)	3.30	1.63–6.70	.001 ^c	
	Intravenous Ig	18/275 (6.55)	3/275 (1.09)	6.00	1.77–20.4	.004 ^c	
Laboratory values ^d	Leukocyte count, median, ×10 ⁹ /L	6.90 (n = 260)	6.70 (n = 246)	0.99	.99–1.01	.65	
	Leukopenia (leukocytes <4 × 10 ⁹ /L)	70/260 (26.9)	30/246 (12.2)	2.36	1.44–3.89	.001 ^c	
	Neutrophil count, median, ×10 ⁹ /L	3.55 (n = 246)	3.63 (n = 235)	0.99	.98–1.02	.82	
	Neutropenia (neutrophils <1.5 × 10 ⁹ /L)	54/246 (21.9)	18/235 (7.7)	8.67	2.62–28.7	<.001 ^c	
	Lymphocyte count, median, ×10 ⁹ /L	1.48 (n = 239)	1.89 (n = 226)	0.99	.98–1.00	.07	

Table 3. Continued

Characteristic	No./Total (%) ^a		OR ^b	95% CI	P Value
	Case Patients (n = 275)	Controls (n = 275)			
Lymphocytopenia (lymphocytes <1 × 10 ⁹ /L)	75/239 (31.4)	34/226 (15.0)	2.85	1.71–4.74	<.001 ^c
Hb, median, mmol/L	7.40 (n = 259)	8.30 (n = 248)	0.59	.49–.70	<.001 ^c
Anemia (Hb <7.5 mmol/L)	144/275 (52.4)	74/275 (26.9)	3.41	2.26–5.16	<.001 ^c
Thrombocyte count, median, ×10 ⁹ /L	182.50 (n = 258)	212.50 (n = 248)	0.99	.99–1.00	.07
Thrombocytopenia (thrombocytes <150 × 10 ⁹ /L)	101/258 (39.1)	51/248 (20.6)	2.59	1.66–4.04	<.001 ^c
IgG, median, g/L	8.00 (n = 142)	8.30 (n = 125)	1.03	.98–1.07	.27
IgM, median, g/L	0.39 (n = 116)	0.60 (n = 108)	0.98	.78–1.23	.86

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; Hb, hemoglobin; HSCT, hematopoietic stem cell transplantation; Ig, immunoglobulin; OR, odds ratio.
^aCase patients had hematological cancer (HC) with community-acquired pneumonia (CAP); controls, HC without CAP. Data represent no./total (%) of case patients or controls, unless otherwise specified.

^bBased on univariate logistic regression analysis.

^cSignificant at P < .05.

^dLast laboratory values available before episode of CAP (of matched case), but no longer than 6 months before the episode (of matched case); medians were used instead of modes, owing to nonnormal distribution of variables (according to Kolmogorov-Smirnov test).

^eThe following antimicrobial agents were included: amoxicillin, amoxicillin + clavulanic acid (Augmentin), azithromycin, benzylpenicillin, levofloxacin, pheneticillin, and phenoxymethylpenicillin.

of profound pancytopenia, as well as to an eradication of the existing memory cell pool, leaving the recipient highly susceptible to infections [9]. In addition, GVHD is a frequent complication of allogeneic HSCT, which is often treated with high doses of immunosuppressive drugs, further increasing the infection risk. A prior study on invasive pneumococcal disease among oncological patients also identified multiple myeloma as one of the cancers with highest IR of CAP (along with non-Hodgkin lymphoma and chronic lymphocytic leukemia) [4]. Multiple myeloma is associated with B-cell, T-cell, dendritic cell, and natural killer cell abnormalities, and patients with this condition often mount poor responses to vaccinations [10, 11].

Table 4. Multivariable Regression Analysis With Predictors of Community-Acquired Pneumonia (n = 434)

Characteristic	Adjusted OR ^a	95% CI ^a
Male sex	2.81	1.41–5.60
Anemia (Hb <7.5 mmol/L)	3.19	1.52–6.71
Lymphocytopenia (lymphocytes <1.00 × 10 ⁹ /L)	2.74	1.10–8.82
Cardiovascular disease	2.60	1.30–5.20
Intravenous Ig use	4.02 ^b	.70–26.4 ^b
Chronic kidney disease	3.13	1.25–7.86
allo-HSCT	3.80	1.45–9.91
auto-HSCT	5.54	1.96–15.7
Use of immunosuppressives for GVHD	13.7	2.45–76.5
Rituximab (within 12 mo before pneumonia diagnosis)	346	8.15–14.5 × 10 ³
Use of immunomodulators ^c	7.78	1.48–40.9
Steroid treatment (within 1 mo)	0.26 ^b	.06–1.22 ^b

Abbreviations: allo-HSCT, allogeneic hematopoietic stem cell transplantation; auto-HSCT, autologous hematopoietic stem cell transplantation; CI, confidence interval; GVHD, graft-vs-host disease; Hb, hemoglobin; Ig, immunoglobulin; OR, odds ratio.

^aResults are statistically significant unless otherwise indicated.

^bNot significant.

^cImmunomodulators included thalidomide, lenalidomide, pomalidomide, and methotrexate.

In 44% of CAP cases in this study, no causative pathogen was found. This could have been caused by pretreatment with antibiotics by the general practitioner, the use of antibiotic prophylaxis, or incomplete diagnostic workup. Sputum cultures and pneumococcal urinary antigen tests were performed less frequently in patients in whom no pathogen was identified, possibly owing to less severe disease presentation. In CAP cases where a causative organism was determined, *S. pneumoniae* was the most commonly identified pathogen, in agreement with findings from earlier studies on CAP in immunocompromised individuals [1] and patients with human immunodeficiency virus [12]. In addition, the incidence of pneumococcal CAP has likely been underestimated in the current study owing to extensive use of antimicrobial prophylaxis and limited use of pneumococcal urinary antigen tests (10.3%) and sputum culture (35.5%) during the study period. Pneumococcal CAP was an independent risk factor for a severe disease course. This is likely caused by a combination of pathogen and host factors, such as the strong ability of *S. pneumoniae* to become invasive and cause sepsis [13], as well as the splenic dysfunction often found in patients with HC, which causes a particular vulnerability to encapsulated bacteria [14].

Independent risk factors for CAP in patients with HC were male sex, chronic kidney disease, a history of HSCT, use of immunosuppressive medication for treatment of GVHD, use of rituximab, use of immunomodulators, and reduced lymphocyte counts and hemoglobin levels. The implications of these findings for clinical practice could include advocating for vaccination against respiratory pathogens in patients with HC before starting rituximab, immunomodulators, or other immunosuppressive treatments.

We did not find a protective effect of any type of antimicrobial prophylaxis or influenza or pneumococcal vaccination. However, this retrospective study was not designed or powered to investigate the efficacy of these interventions. In addition,

these interventions were given mainly to patients with HC with a higher baseline risk of CAP, including allogeneic HSCT recipients and patients with HC with recurrent respiratory infections, causing selection bias. Surprisingly, the use of antibacterial prophylaxis in this study was even associated with more severe disease outcome of CAP. This could be attributed to impaired susceptibility of bacteria to empiric antibiotic treatment. However, this finding could also have been biased by the fact that patients with HC who received antibacterial prophylaxis were also in the worst immunological condition. It is often thought that pneumocystis prophylaxis (trimethoprim-sulfamethoxazole) also protects against pneumococcal pneumonia, however this has never been demonstrated in randomized studies, nor in the present study. Antimicrobial stewardship and responsible use of antibiotics in this vulnerable population are important until further studies have been conducted.

To date, there are no Dutch national guidelines on routine vaccination of patients with HC, which explains the poor uptake of pneumococcal and influenza vaccines in our study. International guidelines do recommend vaccination with ≥ 1 dose of the 13-valent pneumococcal conjugate vaccine, in selected patients with HC, followed by the 23-valent polysaccharide vaccine, 2 months later [15, 16]. Our observations of a high burden of CAP in patients with HC, with *S. pneumoniae* the most commonly isolated pathogen and the one with the most severe disease course, support these recommendations. It is unlikely that randomized studies showing clinical efficacy of pneumococcal vaccination will ever be performed in patients with HC, because such studies require large numbers of participants and considerable financial resources and are generally precluded from ethical approval in view of current guidelines [3, 15, 16]. Therefore, vaccination recommendations for these patients must be based on a combination of studies showing a high disease burden and indirect evidence of vaccine effectiveness. Adequate serological response rates to pneumococcal vaccination have been described in patients with HC and in HSCT recipients [17, 18], and a strong reduction in pneumococcal disease after implementation of pneumococcal vaccination among allogeneic HSCT recipients was observed in an Australian observational cohort study [19]. Vaccine efficacy against respiratory pathogens is expected to be more impaired in patients using rituximab [20], another reason to provide vaccinations against respiratory pathogens before starting rituximab.

Future research is needed to determine the efficacy and immunogenicity of novel and existing vaccines against respiratory pathogens, such as the novel 20-valent pneumococcal conjugate vaccine [21], influenza vaccines, and COVID-19 vaccines. In addition, the efficacy of booster vaccinations, as well as the use of targeted antimicrobial prophylaxis and on-demand antibiotic treatment for high-risk patients with HC who do not respond to vaccination, should be further investigated in randomized studies. National vaccination recommendations tailored to

patients with HC as well as targeted information campaigns could aid in improving the currently poor vaccine uptake among patients with HC, such as for influenza and pneumococcal vaccines [22–24].

A limitation of the current study is that our data were collected at tertiary care hospitals and may thus not be representative of the general oncohematological population. In addition, patients with HC will also be more inclined than those without HC to contact their treating specialist for complaints. This may have introduced a bias toward a higher rate of CAP diagnoses in the hospital in patients with HC and less diagnoses by general physicians, compared with patients without HC for similar severity of pneumonia. Finally, we defined an episode of CAP based on both clinical and radiological signs. Because neutropenic patients do not always show typical radiological signs of pneumonia, cases could have been missed or diagnosed at a later stage [25, 26].

We conclude that patients with HC experience a high burden of CAP, with substantial morbidity and mortality rates. Our study identified HC groups and clinical predictors associated with the highest risk of (a severe disease course of) CAP. Based on our data, vaccination against respiratory pathogens such as *S. pneumoniae* should be promoted early in the disease course of patients with HC, before starting rituximab or immunomodulators when possible, because these therapies significantly increase the risk of CAP.

Supplementary Data

Supplementary materials are available at *Clinical 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.

Notes

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Author Contributions. H. M. G. G. and J. H. conceived the study. H. M. G. G., J. H., M. P. G., and A. G. wrote the study protocol. M. C., H. M. G. G., and G. W. collected the data, M. C. and H. M. G. G. analyzed the data, and all authors contributed to data interpretation. M. C. wrote the first version of the manuscript and H. M. G. G., J. H., M. P. G., and A. G. contributed to subsequent versions. All authors approved the final version of the manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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