Chronic lymphocytic leukemia and associated chronic lung diseases

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Abstract

Infections are a significant cause of morbidity and mortality in chronic lymphocytic leukemia (CLL), with respiratory tract infections being predominant. This study evaluated the incidence of chronic lung diseases (asthma, chronic obstructive pulmonary disease [COPD], and bronchiectasis) among 4,532 patients with CLL and their association with infection complications and outcomes. We found that bronchiectasis (5%), asthma (12.2%), and COPD (6.6%) were prevalent among CLL patients and were associated with an increased hazard ratio (HR) for pneumonia (HR=1.7). Bronchiectasis and COPD were significantly associated with higher rates of hospitalization due to pneumonia. Preventive measures, such as Prevenar vaccination and intravenous immunoglobulin therapy, reduced pneumonia-related hospitalizations. These findings underscore the importance of early diagnosis and management of chronic lung diseases in CLL patients.

Introduction

Chronic lymphocytic leukemia (CLL) is the most common leukemia in Western countries.[1] The disease is characterized by dysfunction in both B and T lymphocytes, which may be intrinsic to the disease itself or a result of its therapy.[2,3] A frequent immune defect observed in CLL patients is hypogammaglobulinemia, which occurs in 20-60% of cases at diagnosis and is associated with an increased incidence of infections.[4-6] Infection-related complications are a major cause of morbidity and mortality in CLL patients, primarily affecting the respiratory tract, but also involving the skin, urinary tract, and gastrointestinal tract.[6,7]

Chronic lung diseases, such as bronchial asthma, chronic obstructive pulmonary disease (COPD),[8] and bronchiectasis, are all linked to an increased risk of respiratory infections.[9] The exact mechanisms connecting immunosuppression with chronic lung disease or bronchiectasis remain to be fully elucidated. However, it is well-established that patients with immunodeficiencies, such as hypogammaglobulinemia, are at heightened risk for developing lung complications, including bronchiectasis and recurrent bronchial infections.[10,11] This association has been reported in patients with hematological malignancies, as well as those who have undergone bone marrow transplantation.[12,13] Notably, bronchiectasis in CLL patients contributes to increased morbidity, frequent hospitalizations, and higher mortality rates.[14]

The diagnosis of chronic lung diseases or bronchiectasis typically relies on pulmonary function testing and imaging, such as computed tomography (CT) scans. However, according to International Workshop on Chronic Lymphocytic Leukemia (IWCLL) guidelines, routine CT screening is not recommended for all newly diagnosed CLL patients. Furthermore, routine lung function testing is not generally performed or recommended in CLL patients.[1,15] Therefore, we do not have an accurate assessment of the prevalence of chronic respiratory disease in patients with CLL and whether it differs compared to the general population.

The current study aims to assess the incidence of chronic lung diseases - specifically asthma, COPD, and bronchiectasis - in CLL patients, as well as their association with infection-related complications, hospitalizations, and overall patient outcomes.

Methods

The cohort is based on data obtained from electronic medical records after receiving approval from the ethical committee for members of Maccabi-(MHS-O13-21),

the second-largest healthcare organization in Israel, with approximately 2.5 million insured patients. All patients included were diagnosed with CLL based on the IWCLL criteria,[1] between 1998 and 2022, of whom we had full data on clinical, laboratory and therapy given with special emphasis on vaccination and supportive care treatment as intravenous immunoglobulin therapy.

These patients were identified using the ICD9 coding system (204.10-12) that is added to the patient's medical record after confirmation of the diagnosis by an expert hematologist and in addition, the diagnosis was recorded in the MHS registry for hematologic neoplasm diseases. As with previous retrospective studies of CLL conducted on the MHS database,[15] to ensure the validity of the cohort, the patients had to meet in addition one of the following criteria: (i) have received anti-CLL therapy at least once since diagnosis, or (ii) if treatment-naive, at least one CBC result indicative of an absolute lymphocyte count above 5×10^9/L at any time during the study.

Next, we identified patients who received a diagnosis of bronchiectasis, COPD, or asthma from their family doctor or after having a pulmonologist visit. In particular, we define the following criteria for identifying the diseases of the respiratory system:

(i) Bronchiectasis: patients diagnosed with an ICD9 code of 494 by any physician.

(ii) Asthma: patients diagnosed with ICD9 code of 493 by an expert pulmonologist or patients that received an ICD9 code of 493 by any physician and in addition were treated for at least 6 months in a particular year by one of the following drugs: (A) Budesonide/Formoterol, (B) Fluticasone propionate/Salmeterol, (C) Fluticasone furoate/Vilanterol, (D) Tiotropium bromide, (E) Albuterol (Salbutamol) or (F) Ipratropium bromide.

(iii) COPD: patients diagnosed with ICD9 codes 490-492 or 496 by an expert pulmonologist. In addition, patients who received these ICD9 codes by any physician and in addition were treated for at least 6 months in a particular year by one of the drugs mentioned above or having a history of smoking and being included in MHS COPD registry.

If the same patient has multiple respiratory diagnoses, we define as the leading respiratory diagnosis to be mostly prone to lung infection (namely, bronchiectasis is prioritized over asthma, and asthma is prioritized over COPD).

The diagnosis of pneumonia was based on the association of ICD-9 codes entered by the family doctor into the patients' files, in combination with corresponding antibiotic prescriptions for outpatients. In hospitalized patients, the diagnosis also included imaging.

Statistical analysis

We used multivariable-adjusted Cox regression with time-dependent Covariates to estimate hazard ratios (HR) (95% confidence intervals [CI]) for the events of pneumonia, and hospitalization due to pneumonia, first treatment for CLL and death. The index date was defined as the time of CLL diagnosis. Except for sociodemographic factors, all other covariates were defined as time-dependent covariates, allowing for variations in a patient's exposure status throughout the follow-up period. This approach enhances statistical power for detecting moderate effects and reduces the likelihood of biases, such as immortal time bias. Note that the chronic respiratory diagnosis can vary over time (because some patients develop them during the follow-up period).

We used variance inflation factor (VIF) to test for multicollinearity and exclude collinear variables. Then Schoenfeld's global test was applied to test the proportional-hazards assumption for those variables. The Mantel-Byar test was used to ensure statistical significance after adjustment for immortal time bias.

We use inverse probability of treatment weighting (IPTW)[16] to create a pseudo-population that equalizes the distribution of confounding variables between the patients that suffers from chronic respiratory diseases or those that are not.

All statistical analyses were performed using the R statistical software 4.3.3 (February, 2024) (Foundation for Statistical Computing, Vienna, Austria).

Results

We identified 4,532 patients with CLL, of which 184 patients (5%) were diagnosed with bronchiectasis, 446 patients (12.2%) were diagnosed with asthma, and 242 patients (6.6%) were diagnosed with COPD (Figure 1).

The patients' characteristics are analyzed using univariate analysis and are summarized in Tables 1 and 2, grouped according to their primary respiratory disease (patients diagnosed with a respiratory condition during the follow-up period were also included in their corresponding diagnosis group). The development of bronchiectasis was more frequent among smokers or former smokers compared to non-smokers ($P<0.001$). It was also more common in patients who received more frequent CLL-directed therapy or more lines of therapy, as well as in patients with hypogammaglobulinemia (low levels of immunoglobulin [Ig] G, IgA, and IgM).

No association was found between other chronic diseases, such as diabetes mellitus, chronic renal failure, or hypertension, and the presence of bronchiectasis. Notably, elevated body mass index (BMI) and morbid obesity were less common in patients without bronchiectasis compared to those with bronchiectasis. Additional details are provided in Table 1.

Among the 184 patients with both CLL and bronchiectasis, 128 patients (70%) were diagnosed with bronchiectasis after their CLL diagnosis, while 56 patients (30%) were diagnosed with bronchiectasis prior to their CLL diagnosis.

Asthma was more common in females, while COPD was

statistically more frequent in males. Both asthma and COPD were more common in smokers or former smokers. Hypogammaglobulinemia, particularly low IgG levels, was associated with COPD. Additional data are summarized in Table 2.

In CLL patients, the diagnosis of asthma, COPD, and, particularly, bronchiectasis was associated with a higher HR of 1.7 for pneumonia. Among the 128 patients who developed bronchiectasis after their CLL diagnosis, 44 (34%) had pneumonia in the year preceding the diagnosis of bronchiectasis. Of these, approximately ten patients had multiple episodes of pneumonia during this period.

Other conditions associated with a higher HR for pneumonia included male sex, Binet Stage C, chronic renal failure, a history of pneumonia in the previous year, and treatment with antiviral agents or penicillin in the last 12 months.

In terms of hospitalization, both bronchiectasis and COPD were associated with a higher hazard ratio for hospitalization due to pneumonia. Older age (>65 years), male sex, and Binet Stage C were also associated with a higher risk of hospitalization due to pneumonia. Figure 2 presents the cumulative hazard for hospitalization due to pneumonia, grouped according to the leading chronic respiratory disease. Patients with bronchiectasis were most prone to hospitalization due to pneumonia.

Next, we conducted a multivariate analysis to evaluate the impact of vaccinations and respiratory complications in patients with CLL. The vaccines evaluated included the influenza vaccine, pneumococcal vaccine, Prevenar 13, and COVID-19 vaccines. Only Prevenar 13, administered to 817 patients (22.3%) in our cohort, demonstrated a statistically significant reduction in the HR for hospitalization due to pneumonia (Table 3).

We also investigated the effect of IVIG as a monthly infusion for infection prevention in patients with hypogammaglobulinemia below 500 mg/L and recurrent infections (2 infection in 6 months or 3 in 1 year).

IVIG was administered to 326 CLL patients (8.9%), and these patients showed a significantly lower hazard ratio (HR=0.69; *P*=0.026) for pneumonia-related hospitalizations. The incidence of pneumonia decreased significantly as early as the second month of IVIG administration. However, nine patients developed bronchiectasis while receiving IVIG, and there was no evidence that IVIG administration reduced the risk of bronchiectasis.

We also assessed whether achieving a target IgG level during IVIG treatment had any clinical impact. For those who were tested for IgG levels, values above 700/500/600 mg/dL did not significantly reduce the risk of pneumonia. Over the course of 1 year, 11% of patients not receiving IVIG developed pneumonia, compared to only 4% of those receiving IVIG, which was a statistically significant difference (*P*=0.02).

We explored multiple white blood cell (WBC) cut-offs (10, 20, 50, and 100) and found that a threshold of 50.000 was also informative for predicting hospitalization due to pneumonia.

Next, we examined factors influencing time to first treatment in our cohort. The presence of acute respiratory diseases (e.g., sinusitis or bronchitis) in the last 12 months or treatment with macrolides or penicillin in the last 12 months was associated with a shorter time to first treatment. How-

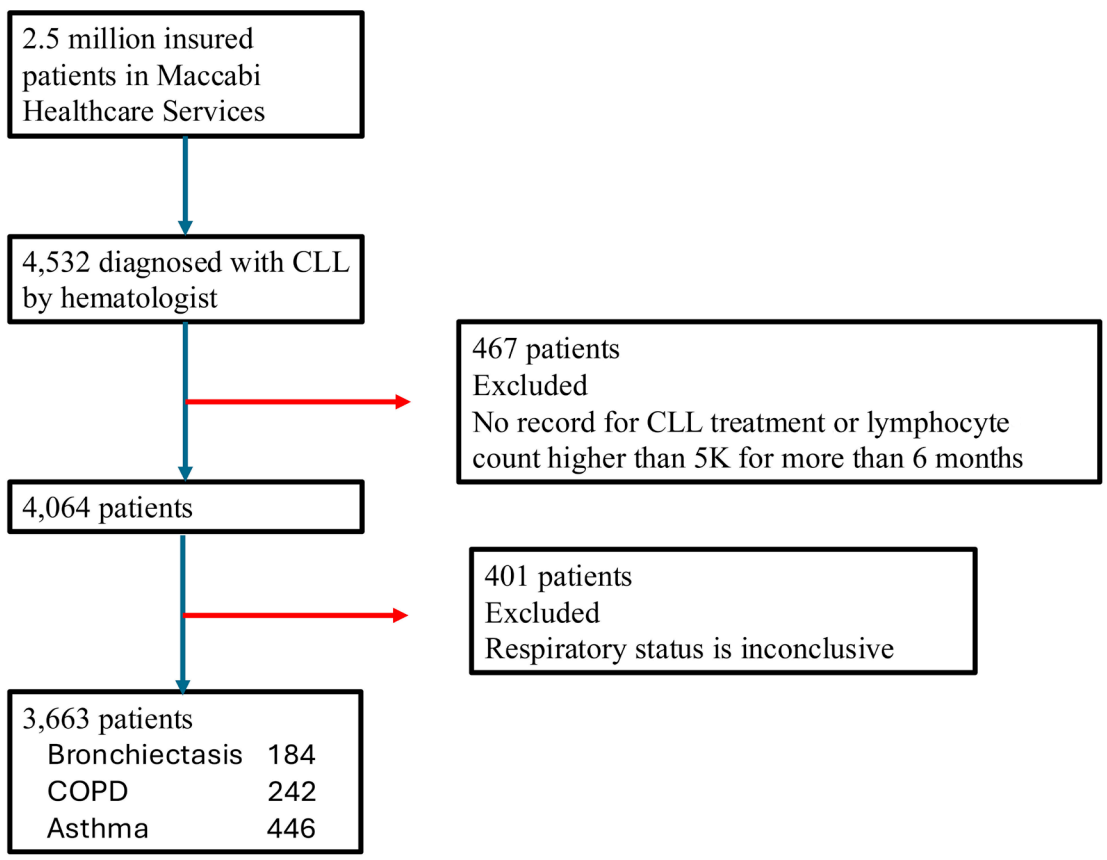

Figure 1. Flowchart depicting the process of identifying and selecting eligible patients for inclusion in our study cohort. CLL: chronic lymphocytic leukemia; CODP: chronic obstructive lung disease.

ever, bronchiectasis and COPD were not associated with a shorter time to first treatment or overall survival.

Using multivariate analysis, we also examined the effects of various CLL treatments on lung complications. Anti-CD20 treatment was associated with a higher HR ratio for pneumonia and hospitalization due to pneumonia. Chemotherapy regimens, including bendamustine and rituximab (BR) and fludarabine, cyclophosphamide, and rituximab (FCR), were also associated with a higher HR for pneumonia. Treatment with venetoclax plus anti-CD20 increased the risk of pneumonia in our cohort, though it was not statistically significant. Acalbrutinib treatment was associated with an increased risk of pneumonia but this observation should be taken with caution due to possible bias as treatment was approved and started during the COVID-19 pandemia, a period that we have seen increased

Table 1. A univariate analysis was performed to demonstrate the characteristics of patients assigned to groups based on their leading respiratory diagnosis.

Variable, N (%)	Bronchiectasis N=184	None N=2,791	*P*
Age at diagnosis, years			0.004
<=65	62 (33.7)	1,246 (44.6)	
>65	122 (66.3)	1,545 (55.4)	
Sex			0.590
Male	110 (59.8)	1,605 (57.5)	
Binet stage			0.7596
A or B	105 (57.1)	1,557 (55.8)	
C	79 (42.9)	1,234 (44.2)	
Smoking status			<0.001
Quit smoking	32 (17.6)	215 (8.0)	
Currently smoking	12 (6.6)	304 (1.4)	
No smoking	140 (76)	2,272 (81.4)	
Treatment lines			< 0.001
Treatment naive	102 (55.4)	1,982 (71.0)	
1st	49 (26.6)	589 (21.1)	
2nd	24 (13.0)	185 (6.6)	
3rd or more	9 (4.9)	35 (1.3)	
Other chronic conditions			
Diabetes mellitus	31 (16.8)	493 (17.7)	0.842
Hematologic neoplasm	14 (7.6)	166 (5.9)	0.339
Ulcerative colitis	2 (1.1)	9 (0.3)	0.145
Kidney failure	47 (25.5)	681 (24.4)	0.724
Obesity: BMI >30 kg/m^2	11 (6.0)	315 (11.3)	0.027
Ischemic heart disease	20 (10.9)	276 (9.9)	0.613
Overweight: BMI >25-<30 kg/m^2	11 (6.0)	366 (13.1)	0.004
Hypertension	75 (40.8)	1099 (39.4)	0.756
Baseline blood work			
Albumin g/dL < LNL	6 (3.3)	46 (1.6)	0.1339
β2 microglobulin >3.5 mg/dL	17 (9.2)	153 (5.5)	0.0467
CRP mg/dL			<0.001
High 0.5-1	21 (11.4)	181 (6.5)	
Very high >1	22 (12.0)	228 (8.2)	
Eosinophils x µL, high >UNL	6 (3.3)	52 (1.9)	<0.001
Ig A mg/dL < LNL	15 (8.2)	89 (3.2)	<0.001
Ig G mg/dL <LNL	37 (20.1)	272 (9.7)	<0.001
Ig M mg/dL <LNL	69 (37.5)	616 (22.1)	<0.001

BMI: body mass index; CRP: C-reactive protein; UNL: upper normal limits; LNL: lower normal limits; Ig: immunoglobulin.

incidence of pneumonias. Table 4 presents a multivariant analysis for the number of months of exposure to main CLL treatments and the corresponding hospitalization events due to pneumonia.

Regarding the association of blood tests with pneumonia, Table 2 presents the most recent blood test results taken

Table 2. Demographic, clinical, and laboratory characteristics of chronic lymphocytic leukemia patients with chronic respiratory diseases (asthma, chronic obstructive lung disease) compared to those without chronic respiratory disease employing univariant analysis.

Variable, N (%)	Asthma N=446	*P*	COPD N=242	None N=2,791	*P*
	Bronchiectasis N=184	0.999			0.46
Age at diagnosis, years <=65 >65	 247 (55.4)		 114 (47.1) 128 (52.9)	 1,246 (44.6) 1,545 (55.4)	
Sex Male	 229 (51.3)	0.016	 182 (75.2)	 1,605 (57.5)	<0.001
Binet stage A or B C	 250 (56.1) 196 (43.9)	< 0.001	 168 (69.4) 74 (30.6)	 1,557 (55.8) 1,234 (44.2)	<0.001
Smoking status Quit smoking Currently smoking No smoking	 70 (15.9) 53(12.0) 323 (72.4)	< 0.001	 64 (27.4) 94 (40.2) 84 (34.7)	 215 (8.0) 304 (1.4) 2,272 (81.4)	<0.001
Treatment lines Treatment naive 1st 2nd 3rd or more	 317 (71.1) 74 (16.6) 45 (10.1) 10 (2.2)	0.005	 158 (65.3) 58 (24.0) 20 (8.3) 6 (2.5)	 1,982 (71.0) 589 (21.1) 185 (6.6) 35 (1.3)	0.13
Other chronic conditions					
Diabetes mellitus	95 (21.3)	0.074	52 (21.5)	493 (17.7)	0.138
Hematologic neoplasm	34 (7.6)	0.169	6 (2.5)	166 (5.9)	0.02
Ulcerative colitis	3 (0.7)	0.223	1 (0.4)	9 (0.3)	0.565
Kidney failure	116 (26.0)	0.478	54 (22.3)	681 (24.4)	0.532
Obesity: BMI >30 kg/m^2	67 (15.0)	0.027	21 (8.7)	315 (11.3)	0.241
Ischemic heart disease	60 (13.5)	0.024	28 (11.6)	276 (9.9)	0.434
Overweight: BMI >25-<30 kg/m^2	72 (16.1)	0.086	34 (14.0)	366 (13.1)	0.692
Hypertension	213 (47.8)	<0.001	93 (38.4)	1,099 (39.4)	0.784
Baseline blood work					
Albumin g/dL <LNL	15 (3.4)	0.0222	5 (2.1)	46 (1.6)	0.5988
β2 microglobulin >3.5 mg/dL	27 (6.1)	0.6559	16 (6.6)	153 (5.5)	0.464
CRP mg/dL High 0.5-1 Very high >1	 47 (10.5) 41 (9.2)	<0.001	 29 (12.0) 20 (8.3)	 181 (6.5) 228 (8.2)	 <0.001
Eosinophils x μL, high >UNL	17 (3.8)	0.0127	12 (5.0)	52 (1.9)	0.0039
IgA mg/dL < LNL	15 (3.4)	0.7742	8 (3.3)	89 (3.2)	0.8493
IgG mg/dL <LNL	54 (12.1)	0.1273	35 (14.5)	272 (9.7)	< 0.001
IgM mg/dL <LNL	114 (25.6)	0.1125	68 (28.1)	616 (22.1)	0.0368+

+Despite its *P* value, the variable "Immunoglobulin (Ig) M <LNL" did not remain statistically significant after applying the Benjamini–Hochberg correction and may be subject to false discovery. COPD: chronic obstructive pulmonary disease; BMI: body mass index; CRP: C-reactive protein; UNL: upper normal limits; LNL: lower normal limits.

at least 1 month before the event to identify potential predictors of pneumonia. High LDH was associated with an increased risk of pneumonia and shorter overall survival. Very high leukocyte count (greater than 50) was linked to an increased risk of pneumonia, hospitalization, and shorter time to first treatment and overall survival. Low neutrophil count was also associated with an increased risk of pneumonia, hospitalization, and shorter time to first treatment. Low platelets (<15x10^9/L) and very low platelets (<10x10^9/L) were associated with a higher risk of hospitalization. Very low eGFR (less than 30) was associated with an increased risk of pneumonia. Although CRP is elevated during active pneumonia, our results suggest it is not a reliable predictor of future pneumonia events. Additional details are provided in Tables 1 and 2.

Finally, we conducted a multivariate analysis of the sub-cohort of patients with chronic respiratory disease. Bronchiectasis was associated with a significantly higher risk of pneumonia compared to COPD and asthma (HR=1.38; *P*<0.001). Male sex, age over 65, and Binet Stage C were all associated with an increased risk of pneumonia. Importantly, IVIG treatment decreased the risk of pneumonia (HR=0.68; *P*=0.031). Figure 3 shows the incidence of pneumonia among patients with bronchiectasis, comparing those receiving monthly IVIG with those who are not.

Discussion

CLL, is known for its impact on the immune system, leading to significant immunosuppression and increased susceptibility to infections.[7] Respiratory infections are a major cause of morbidity and mortality in CLL patients, particularly due to underlying hypogammaglobulinemia.[4,5] In the current study, we examined the incidence and impact of chronic respiratory diseases - specifically asthma, COPD, and bronchiectasis - in a cohort of patients with CLL, revealing important associations between these conditions and infection-related complications, hospitalizations, and patient outcomes.

Our results indicate that bronchiectasis is the most significant chronic respiratory condition associated with increased morbidity in CLL patients. We found that 5% of CLL patients in our cohort were diagnosed with bronchiectasis, a condition that has been previously reported to be more prevalent in immunocompromised populations.[10,11,16] Notably, the incidence of bronchiectasis was higher among CLL patients who had undergone frequent treatments or multiple lines of therapy, and those with hypogammaglobulinemia. This aligns with findings from other studies, which have highlighted the role of impaired immune function in the development of bronchiectasis and recurrent respiratory infections.[10,17] In particular, hypogammaglobulinemia, characterized by low IgG, IgA, and IgM levels, is frequently observed in CLL and is a known risk factor for respiratory complications, as these patients have reduced antibody responses to infections.[4,5]

Our study also demonstrated that CLL patients with bronchiectasis had a significantly higher risk of developing pneumonia. The association between lung disease and pneumonia has been well-documented in various immunocompromised populations, including those with hematologic malignancies.[12,16] In our cohort, 34% of patients diagnosed with bronchiectasis had a history of pneumonia in the year leading up to the diagnosis, emphasizing the potential for chronic lung damage as a consequence of recurrent infections.

The impact of CLL treatment on lung health is another important consideration. We found that treatment regimens, particularly anti-CD20 monoclonal antibodies and chemotherapy agents such as fludarabine, cyclophosphamide, and bendamustine, were associated with an increased risk of pneumonia. This aligns with other studies that have demonstrated an increased risk of infections in patients undergoing chemotherapy or immunotherapy for CLL.[18] The use of venetoclax and acalbrutinib, both of

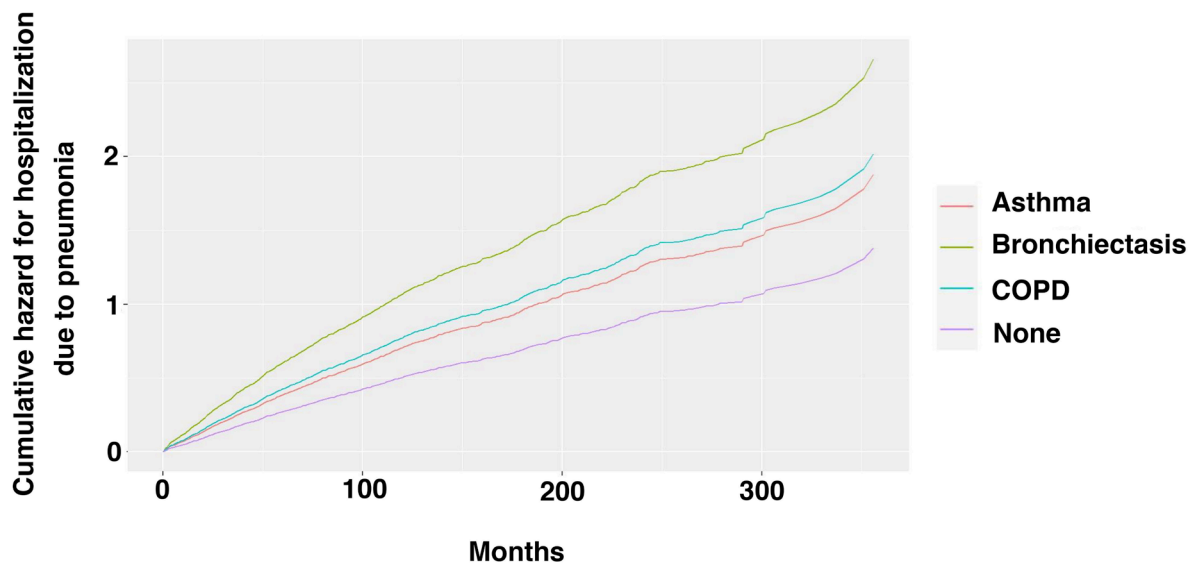

Figure 2. Cumulative hazard for hospitalization due to pneumonia, stratified by the leading chronic respiratory diagnosis in patients with chronic lymphocytic leukemia. CODP: chronic obstructive lung disease.

which are increasingly used in CLL treatment regimens, also appears to increase the risk of pneumonia, though this was not statistically significant in our cohort. Other studies have similarly reported increased infection rates with the use of novel therapies like BCL2 or Bruton tyrosine kinase inhibitors, highlighting the importance of balancing treatment efficacy with the potential for immune suppression.[19,20]

Another possible explanation for the increased incidence of bronchiectasis in CLL patients may be bronchopulmonary infiltration, as reported by Carmier *et al.*[21] but this is probably rare event.

Smoking is known to be associated with an increased risk of lung complications, especially infections, and may contribute to the pathogenesis and development of bronchiectasis.[17] Smoking was a key factor in the development of bronchiectasis in our cohort of patients with CLL, with smokers or former smokers showing a higher frequency

Table 3. Multivariate analysis of the association between confounding variables, pneumonia, and hospitalization.

Variable	Pneumonia		Hospitalization due to pneumonia	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age >65 years	1.18 (0.99-1.4)	0.071	1.47 (1.15-1.89)	0.002
Male	1.33 (1.12-1.59)	0.001	1.52 (1.2-1.91)	<0.0001
Binet stage C	1.7 (1.42-2.02)	<0.0001	2.18 (1.68-2.82)	<0.0001
Chronic lung disease				
Asthma	1.29 (1.07-1.55)	0.008	1.17 (0.9-1.51)	0.235
Bronchiectasis	1.7 (1.35-2.15)	<0.0001	2.13 (1.81-2.57)	0.048
COPD	1.38 (1.09-1.76)	0.008	1.41 (1.03-1.92)	0.03
Pulmonologist consultation last year	1.06 (0.94-1.18)	0.337	1.06 (0.92-1.22)	0.418
Smoking status				
Never smoked	1.08 (0.57-2.06)	0.807	0.86 (0.41-1.8)	0.688
Quit smoking	1.21 (0.62-2.36)	0.58	1 (0.46-2.19)	0.992
Currently smoking	1.34 (0.69-2.6)	0.382	1.14 (0.53-2.44)	0.735
Other conditions				
Renal failure	1.23 (1.04-1.45)	0.014	1.55 (1.25-1.93)	<0.0001
Obesity BMI, kg/m^2 >UNL	0.92 (0.73-1.16)	0.484	0.95 (0.7-1.28)	0.724
Albumin, g/dL >UNL	0.02 (0.01-0.04)	<0.0001	0.1 (0.04-0.24)	<0.0001
Albumin g/dL <LNL	1.34 (0.94-1.92)	0.106	1.48 (0.97-2.26)	0.067
Acute phase reactant and Ig levels				
CRP, mg/dL >UNL	1.18 (0.91-1.54)	0.214	0.96 (0.67-1.38)	0.835
Eosinophils x μL >UNL	1.41 (0.98-2.03)	0.066	1.6 (0.97-2.64)	0.064
Ferritin ng/mL >UNL	1.03 (0.74-1.43)	0.881	1.17 (0.82-1.66)	0.396
Hemoglobin, g/dL High	0.02 (0.01-0.04)	<0.0001	0.08 (0.05-0.15)	<0.0001
IgA, mg/dL<LUL	1.05 (0.78-1.4)	0.767	1.05 (0.75-1.47)	0.79
IgG, mg/dL <LNL	1.01 (0.81-1.25)	0.947	1.12 (0.85-1.47)	0.423
IgG <500 mg/dL	1.18 (0.76-1.82)	0.47	1.11 (0.69-1.79)	0.662
IgM, mg/dL<LNL	1.12 (0.92-1.36)	0.246	1.13 (0.88-1.46)	0.343
WBC >50x10^9/L i.e., very high	1.37 (1.04-1.82)	0.027	1.79 (1.26-2.54)	0.001

All variables were defined as time-dependent covariates. The table includes only variables that met the criteria for the proportional hazards assumption on the basis of the results of Schoenfeld's global test. A *P* value lower than 5% are considered to be statistically significant. HR: hazard ratio; CI: confidence interval; COPD: chronic obstructive lung disease; BMI: body mass index; CRP: C-reactive protein; UNL: upper normal limits; LNL: lower normal limits; Ig: immunglobulin.

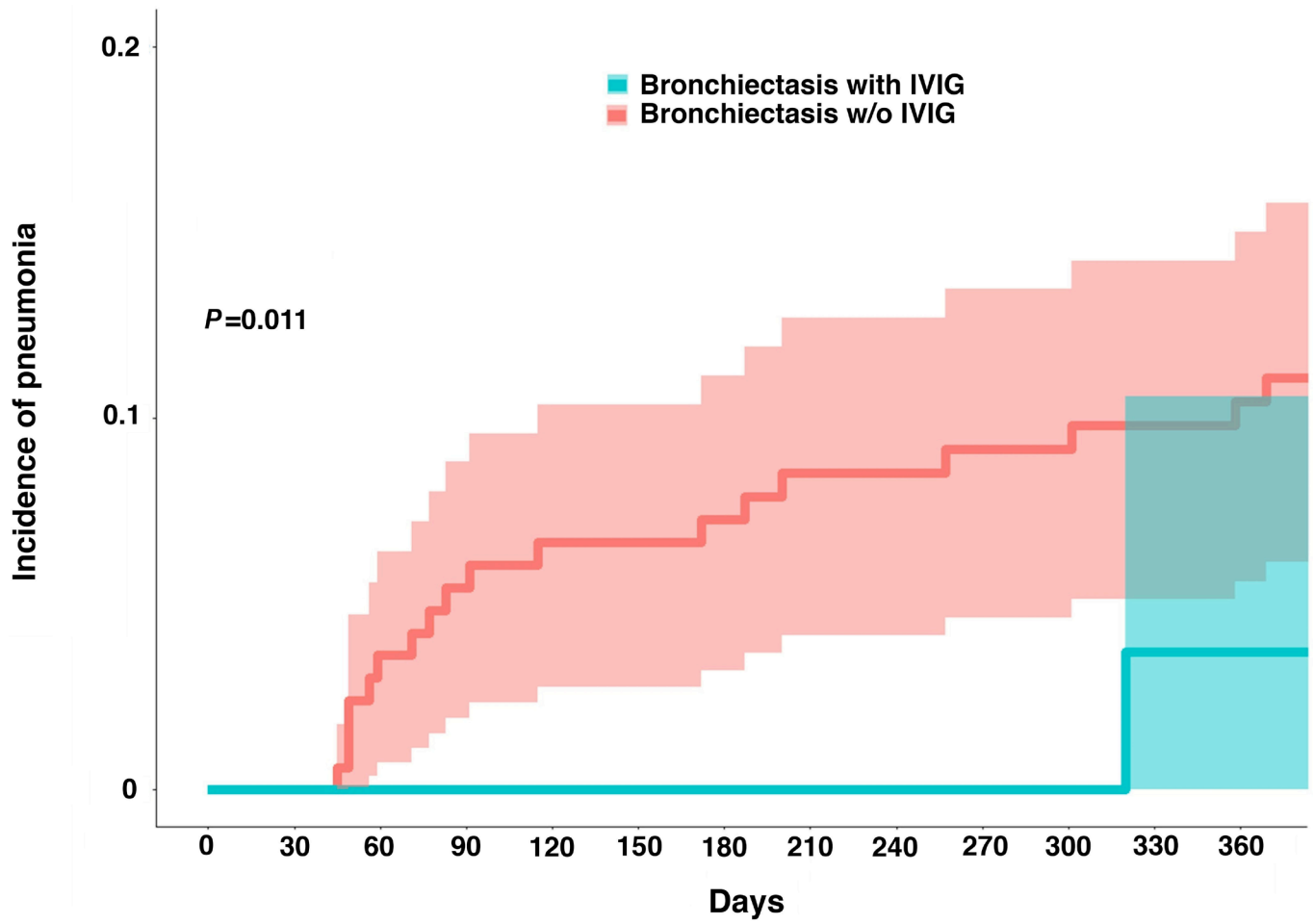

Figure 3. Cumulative hazard for hospitalization due to pneumonia, stratified by the leading chronic respiratory diagnosis in patients with chronic lymphocytic leukemia. IVIG: intravenous immunoglobulin, w/o: without.

Table 4. Multivariate analysis of the association between chronic lymphocytic leukemia treatment regimens and the risk of pneumonia and hospitalization due to pneumonia.

Variable	N of patients	N of months	Pneumonia		Hospitalization due to pneumonia	
			HR (95% CI)	*P*	HR (95% CI)	*P*
Anti CD20*	934	11,969	1.46 (1.13-1.9)	0.004531	1.4 (1.01-1.94)	0.044369
Acalabrutinib+	143	1,347	1.78 (0.74-4.33)	0.2	2.91 (1.49-5.69)	0.001783
Bendamustin + anti CD20	211	1,123	1.23 (1.06-0.95)	0.042	2.09 (0.84-5.2)	0.11
Chlorambucil + anti CD20	29	206	1.38 (0.71-2.68)	0.338	1.73 (0.77-3.86)	0.182
FC	116	596	0.3 (0.04-2.12)	0.23	0.49 (0.06-4.18)	0.512
FCR	678	3,864	2.51 (1.7-3.71)	<0.0001	1.96 (1.27-3.42)	0.017
Ibrutinib	360	10,192	1.29 (0.83-2)	0.255	1.18 (0.74-1.83)	0.489
Venetoclax + anti-CD20	160	1,703	1.25 (0.43-2.96)	0.81	1.84 (0.86-3.99)	0.12
Pneumonia last year	NA	NA	1.25 (1.13-1.49)	<0.0001	1.66 (1.48-1.9)	0.009
IVIG administration as prophylaxis	326	7,736	0.74 (0.43-1.29)	0.289	0.69 (0.46-0.92)	0.026
COVID-19 vaccine coverage	2,600	54,903	0.88 (0.69-1.12)	0.303	0.53 (0.18-2)	0.2
Influenza vaccine coverage	3,202	212,609	0.99 (0.84-1.16)	0.889	0.85 (0.69-1.05)	0.139
Pneumovax coverage	1,731	24,827	0.84 (0.61-1.15)	0.273	0.75 (0.47-1.18)	0.214
Prevnar coverage	879	9,893	0.87 (0.54-1.4)	0.564	0.87 (0.17-0.98)	0.009

All variable s were defined as time-dependent covariates. The table includes only variables that met the criteria for the proportional-hazards assumption on the basis of the results of Schoenfeld's global test. A *P* value lower than 5% are considered to be statistically significant. *Anti-CD 20 was considered still influential during 12 months following the last dose. +Acalabrutinib results might biased as it was given during the COVID-19 pandemia. HR: hazard ratio; CI: confidence interval; FC: fludarabine plus cyclophosphamide; FCR: fludarabine plus cyclophosphamide plus rituximab; IVIG: intravenous immunglobulin; NA: not applicable.

of bronchiectasis compared to non-smokers. This finding highlights the importance of smoking cessation in preventing respiratory complications in this cohort.

Lung functional assays are not performed routinely in patients with CLL. In an interesting study, Dhalla *et al*. recommended that pulmonary function tests and cross-sectional imaging of the lungs be considered for patients with CLL and hypogammaglobulinemia.[22] Based on our results, pulmonary function tests should be recommended in CLL patients, especially in those with a history of smoking or diagnosed with bronchiectasis, asthma, or COPD. This can help detect early changes in lung function and facilitate timely interventions.

The role of IVIG therapy in reducing infections in CLL patients with hypogammaglobulinemia has been the subject of several studies.[22,23] In our cohort, patients receiving IVIG had a significantly lower HR for pneumonia-related hospitalizations, supporting the use of IVIG as an effective intervention for preventing infections in this high-risk population. This is consistent with the findings of a recent study, which reported a significant reduction in the rate of respiratory infections in patients with CLL receiving IVIG therapy.[24] These results open the door to a series of questions regarding which indication holds the most clinically significant importance for the administration of IV IG: should IVIG only be used on those who develop infections or in all patients with low IgG levels since it is associated with lower risk of hospitalization for pneumonia? Should it be used regardless of IVIG levels? Based on our study, it would be imprudent to change the current recommendations. However, there will be a need for either a prospective study or a retrospective validation of these results, while also considering the economic toxicity and side effects of this treatment.

While IVIG administration reduced the incidence of pneumonia, it did not prevent the development of bronchiectasis in our study, suggesting that while IVIG can reduce infections, it does not address the chronic lung damage associated with conditions like bronchiectasis. This is an important distinction, as it suggests that other preventive strategies may be needed to address the long-term pulmonary complications in these patients.

Vaccination has also been shown to play a crucial role in reducing respiratory infections in CLL patients, but it should be taken in consideration that due to the immune dysfunction patients may not develop effective immune response.[25] In our study, the pneumococcal vaccine Prevenar 13 was associated with a significant reduction in hospitalization due to pneumonia. This supports the findings of several studies that have demonstrated the effectiveness of pneumococcal vaccination in reducing pneumonia incidence and improving outcomes in immunocompromised populations, including patients with CLL.[26,27] While influenza vaccination is commonly recommended for CLL patients,[28] our study found no statistically significant reduction in pneumonia incidence following the influenza vaccine, suggesting that other vaccines, such as Prevenar 13, may have a more significant impact on pneumonia prevention.

Additionally, we observed that older age, male sex, and advanced disease stage (Binet stage C) were associated with a higher risk of pneumonia and hospitalization due to pneumonia. These findings are in line with existing literature that has identified advanced age and disease stage as risk factors for poor outcomes in CLL patients.[29] The increased vulnerability of male patients to infections is also consistent with other studies in hematologic malignancy populations, which have suggested sex differences in immune responses and infection susceptibility.[30]

Our study had several limitations, including its retrospective design and reliance on electronic medical records. Additionally, the lack of routine pulmonary function testing or computed tomography screening in our cohort may have resulted in underdiagnosis of chronic respiratory conditions in some patients, potentially limiting the generalizability of our findings. Nevertheless, the data includes all hospitalizations, vaccinations, and medications purchased by the patients during the study period. Therefore, we believe that these data are highly representative of the patient population.

In conclusion, our study highlights the significant burden of chronic respiratory diseases, particularly bronchiectasis, in patients with CLL. These conditions are associated with an increased risk of pneumonia and hospitalization, emphasizing the need for close monitoring and early intervention. Vaccination and IVIG therapy are valuable tools in reducing respiratory infections, but further research is needed to identify strategies for preventing chronic lung damage in this population.

Disclosures

No conflicts of interest to disclose.

Contributions

HA and LR performed the research. TT and LR designed the research study. HA and LR contributed essential reagents or tools. LR analyzed the data. TT and GM and LR wrote the manuscript.

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Data-sharing statement

All relevant data is included in the manuscript.

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