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Incidence and predictors of infection among patients prior to treatment of chronic lymphocytic leukemia: a Danish nationwide cohort study

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TITLE PAGE

Title: Incidence and predictors of infection among patients prior to treatment of chronic lymphocytic leukemia: a Danish nationwide cohort study

Running title: Infectious risk in chronic lymphocytic leukemia

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With the international prognostic index (CLL-IPI) for patients with CLL, we have a tool to identify patients with a high risk of progression.[1,2] Despite improved supportive care, infections are a significant cause of morbidity and mortality prior to treatment; one third of patients with CLL will die following an infection.[3]

Though infections in CLL have been a subject of interest in many studies, reporting incidences between 0.13-0.19 per patient-year, there is still no consensus on how to identify patients at an increased risk of infection. Studies on infectious risk prior to treatment in CLL are scarce and very heterogeneous in terms of study population.[4] Consequently, identification of prognostic markers for risk of infections are warranted.

Infections in patients with CLL are believed to correlate with the progressive immune dysfunction. The progressive immune dysfunction in CLL is characterized by a cell-mediated and an antibody-mediated dysfunction.[5] The CLL-microenvironmental interaction may play a major role in this progressive immune dysfunction. The neoplastic B-cells co-evolve together with the microenvironmental changes, which promotes the leukemia cell survival and growth while inhibiting normal B-cell and T-cell function as well as causing hypogammaglobulinemia and cytokine changes.[6]

The rate, severity and prognostic factors for infections in CLL prior to treatment constitute a gap in our knowledge of the infection-prone nature of CLL. By means of the unique Danish National CLL registry, a nationwide cohort of all patients diagnosed with CLL in Denmark between 2008 to 2016, and a national Danish Microbiology database, we conducted a retrospective study to address this issue.[7,8]

All patients diagnosed with CLL in Denmark between January 1st 2010 and July 1st 2016, which was also the end of follow-up, were included. The CLL-IPI variables and data on treatment and survival were retrieved from the Danish National CLL registry.[7] Information on immunoglobulin levels was included if data were available within 6 months of diagnosis. Information on blood cultures was retrieved from the Danish Microbiology Database.

The event of the first blood culture prior to CLL therapy was used as a proxy for severe infection, regardless of whether an infectious agent was identified. Time to event was calculated from date of diagnosis or first date of measurement of immunoglobulin at or after diagnosis, whichever came last. Patients were followed until date of infection, initiation of CLL-specific treatment, death or end of follow-up, whichever came first. Estimates of cumulative incidence for each of the competing risks were calculated using the Aalen Johansen estimator. We examined difference in

cumulative incidence of infection using Gray's test. We fitted a cause-specific hazard model and a Fine-Gray model.[9] All models were compared to the non-parametric Aalen Johansen curves. Martingale residuals and Schoenfeld residuals were visualized for diagnostic purposes. Statistical tests were two-sided and P-values of 0.05 were considered significant. All analyses were performed in R. Source code is available on request.

In total, 2905 CLL patients were diagnosed in Denmark between 2010 and 2016. Of these, 1204 patients had complete data on CLL-IPI variables, gender and immunoglobulin levels available within six months of diagnosis. Cohort characteristics of the study population are summarized in Table 1. The median age was 70 years at time of diagnosis, 61 % were male. Eighty-two percent were Binet A, 13 % Binet B and 4.7 % Binet C stage. Based on the patients with available CLL-IPI variables, 55 % were low risk (CLL-IPI score 0-1), 30 % were intermediate risk (CLL-IPI score 2-3), 12 % were high risk (CLL-IPI score 4-6) and 2.6 % were very high risk (CLL-IPI score 7-10). Regarding the immunoglobulin levels, 54 % of the patients had immunoglobulin deficiency, with 19 %, 17 % and 46 % having low levels of IgA, IgG and IgM respectively.

In the entire cohort of 2905 patients, a total of 1239 patients had an event: infection, treatment initiation or death. The median time of follow-up was 2.9 years (IQR: 1.53-4.57). Having a blood culture drawn prior to treatment or death was the most common event, which occurred in 662 patients; 482 patients received treatment without first having had an infection, and 95 patients died without having had an infection or having received treatment. The cumulative incidence of infection prior to treatment was 12% after one year. For treatment initiation prior to having a blood culture drawn, the cumulative incidence was 11 % after one year; for death prior to treatment or infection: 1 % after one year (Table 1 and Figure 1). Of the patients with an infection, Sixty-five patients (9.8%) died within 30 days after the infection, 163 (25 %) died within one year after the infection and 74 (11 %) received treatment for CLL within one year.

Significantly higher risk of infection was demonstrated for the following variables: 1) older compared to younger patients (p-value < 0.001), 2) male patients (p-value = 0.02), 3) patients with Binet stage B or C (p-value= 0.04), 4) patients with unmutated IGHV (p-value = 0.04), 5) patients with high levels of β-2-microglobulin (B2M>4mg, p-value < 0.001), 6) patients with low levels of IgA (p-value = 0.004), 7) patients with low levels of IgG (p-value = 0.009) and 8) patients with low levels of IgM (p-value = 0.008) (Supplementary Figure 3). We fitted multivariate models on data from 1204 patients with all variables available. The cumulative incidences of infection, treatment and death for these patients were somehow lower than for patients with missing variables (Table 1).

The cause-specific hazard and Fine-Gray models are summarized in Tables 2 for all three competing outcomes. From the cause-specific model, we found that patients with low IgA levels compared to those with normal/high IgA levels had a hazard rate for infection of 1.61; 95 % CI [1.19-2.19]; p<0.001. For the variables age, gender, Binet stage and B2M the hazard rates were estimated to 1.03 per year; 95 % CI [1.01-1.04]; p < 0.001, 1.38; 95 % CI [1.05-1.81]; p=0.02, 1.73; 95 % CI [1.24-2.41]; p < 0.001 and 1.46; 95 % CI [1.03-2.09]; p=0.04, respectively.

In this nationwide cohort, we have assessed the incidence and prognostic factors for infections prior to any CLL treatment as well as the outcomes after such infections in patients prior to treatment of CLL. Severe infections were very common prior to treatment with a five year cumulative incidence of 31 % among 2905 CLL patients. Age, gender, Binet stage, B2M and IgA levels were significantly associated with the cause-specific hazards rate of infection.

Compared to previously published studies, we here present the largest and most homogeneous cohort for analysis of prognostic factors for risk of infection. We did not find del(17p) nor unmutated IGHV to be associated with rate of infection. This might be due to the small numbers of patients with del(17p) and the fact that these prognostic factors are highly associated with the risk of treatment, thus in a competing risk scenario, they do not correlate with infection before treatment (Table 2).

For this registry-based study, we used the event of a blood culture as a proxy for the event of a severe infection. According to the Danish national guidelines, a blood culture is drawn when a sepsis is suspected, and the patients should always receive intravenous antibiotics afterwards.[10] The here demonstrated cumulative incidence of severe infection in patients with untreated CLL within the first year after diagnosis of 12 %, is within the range of previously reported 0.13-0.19 infections pr. patient-year.[5] The previously reported rates allow multiple events per patient year while the cumulative incidence only counts one event per patient, which may explain the slightly lower rate in our study. Also, we only included untreated patients, who have a lower infectious burden. [5] The 30-days post-infection mortality rate of 9.8 % demonstrated here is comparable to a previous study on hematological malignancies.[13]

Immunoglobulin deficiency is common at diagnosis and occurs spontaneously throughout the natural course of the disease and is related to disease duration and stage. [14] In this study we found IgA to be the best predictor of the rate of infections, however IgG and IgM were also associated with the rate of infection in the univariate analysis. IgA is especially important on mucosal surfaces where it binds and prevents translocations of pathogens.[13] Most patients with IgA deficiency are asymptomatic, and the IgA mucosal immunity is often considered superfluous.[13] When multiple

facets of the immune system are dysfunctional, e.g. in CLL, IgA may either itself play a greater role in protection or it may merely serve as a proxy for the degree to which the CLL cells inhibit the immune system. Sun et al. showed that upon treatment with ibrutinib, patients experienced an increase in IgA. After six months, patients had fewer infections although their levels of IgG remained low while the decrease in infectious risk correlated with improved IgA levels in this study.[14]

Due to the registry-based design, we did not have any information on comorbidities. As multiple medical conditions add to the infectious risk of patients with CLL, we were unable to assess whether this confounded our results. The lack of data on comorbidities may overestimate the role of aging rather than recognizing the relevance of comorbidities. [15]

The data presented here thus represent the first step for identification of further risk factors for infection at time of CLL diagnosis. Exploration of prophylactic or pre-emptive treatment strategies for this population in clinical trials is warranted. This should include investigation of risk factors for infections in treated patients as well. Validation of the here presented data in independent cohorts is encouraged.

Supplementary information is available on Leukemia's website.

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Tables

Table 1

	All patients	Patients included in the multivariable model	Patients with missing data
Characteristic, unit	n (%) or median (range)	n (%) or median (range)	Number of patients with missing data
Number of patients	2905	1204	1701
Age, years	70 (30-98)	69 (32-96)	0
Male gender	1779 (61.0)	719 (59.7)	0
Binet Stage (B or C)	516 (18.0)	181 (15.0)	0
Unmutated IGHV (unmutated)	743 (31.9)	360 (29.9)	573
β-2-microglobulin (>4mg/mL)	330 (14.4)	173 (14.4)	607
Del17p	148 (6.6)	79 (5.9)	659
IgA (<0.8 g/L)	389 (19.0)	234 (19.4)	860
IgG (<6.1 g/L)	342 (16.7)	207 (17.2)	855
IgM (<0.41 g/L)	948 (46.3)	584 (48.5)	859
Any Ig deficiency	1105 (54,4)	677 (56.3)	864
	Cumulative incidence (95 % CI)	Cumulative incidence (95 % CI)	Cumulative incidence (95 % CI)
5-year cumulative incidence of infection (%)	31.2 (29.0-33.6)	26.0 (22.6-29.4)	34.5 (31.5-37.5)
5-year cumulative incidence of treatment (%)	21.9 (20.0-24.0)	19.6 (16.7-22.5)	23.3 (20.7-25.9)
5-year cumulative incidence of death (%)	4.9 (3.8-6.0)	3.9 (2.5-5.4)	5.4 (3.9-6.9)

Table 1 Cohort description: Cohort characteristics of patients in the study and the 5-year cumulative incidences of infection, treatment and death for 1) all patients, 2) patients included in the multivariable models and 3) patients excluded from the analysis. Number of patients with missing data is stated for each variable. Gray test showed a significantly higher risk of infection and treatment for patients missing one or more variable as compared to patients with data on all variables available (p-value<0.001 and p-value = 0.03), but not for death (p-value = 0.24).

A) Cause-specific proportional hazard regression model

	INFECTION				TREATMENT				DEATH			
	HR	Lower CI	Upper CI	P-value	HR	Lower CI	Upper CI	P-value	HR	Lower CI	Upper CI	P-value
Age, per year	1.03	1.01	1.01	0.00	0.99	0.98	0.98	0.16	1.07	1.03	1.03	0.00
Male gender	1.37	1.04	1.04	0.02	0.96	0.69	0.69	0.79	1.20	0.58	0.58	0.62
Binet B or C	1.30	0.92	0.92	0.14	3.68	2.63	2.63	0.00	0.33	0.08	0.08	0.11
U-IGHV	1.08	0.81	0.81	0.59	3.08	2.23	2.23	0.00	0.52	0.20	0.20	0.19
Del17p	0.83	0.46	0.46	0.55	1.66	0.94	0.94	0.08	1.90	0.61	0.61	0.27
B2M (> 4mg/mL)	1.25	0.87	0.87	0.24	1.54	1.03	1.03	0.04	2.28	1.03	1.03	0.04
IgA < 0.80 g/L	1.39	1.02	1.02	0.04	1.82	1.30	1.30	0.00	1.28	0.59	0.59	0.52

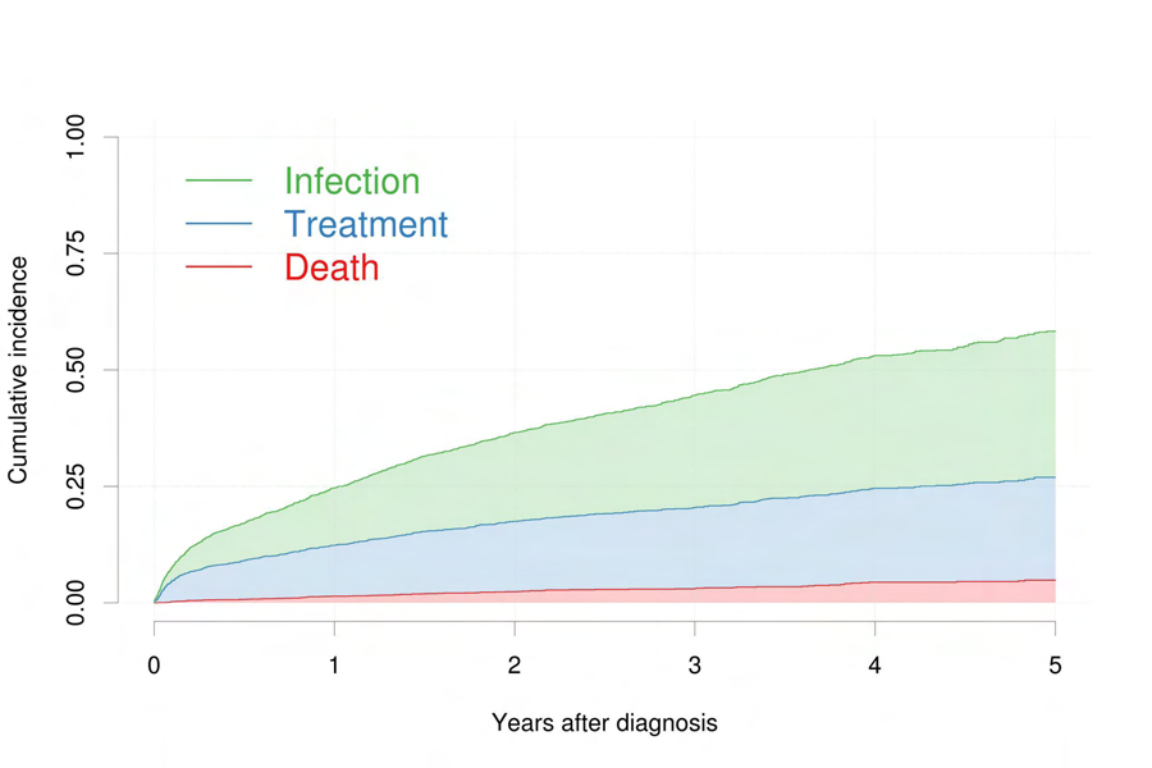
B) Fine-Gray regression model

	INFECTION				TREATMENT				DEATH			
	HR	Lower CI	Upper CI	P-value	HR	Lower CI	Upper CI	P-value	HR	Lower CI	Upper CI	P-value
Age, per year	1.03	1.01	1.04	0.00	0.99	0.98	1.01	0.23	1.08	1.04	1.13	0.00
Male gender	1.38	1.05	1.81	0.02	1.03	0.75	1.40	0.87	1.27	0.61	2.62	0.52
Binet B or C	1.73	1.24	2.41	0.00	4.20	3.06	5.75	0.00	0.50	0.12	2.14	0.35
U-IGHV	1.29	0.97	1.71	0.08	3.30	2.42	4.49	0.00	0.66	0.27	1.65	0.38
Del17p	1.05	0.59	1.90	0.86	2.02	1.18	3.47	0.01	1.79	0.59	5.39	0.30
B2M (> 4mg/mL)	1.46	1.03	2.09	0.04	1.69	1.16	2.45	0.01	2.68	1.14	6.26	0.02
IgA < 0.80 g/L	1.61	1.19	2.19	0.00	2.18	1.59	3.01	0.00	1.53	0.67	3.53	0.31

Table 2 Results of the regression models: Results of the a) cause-specific proportional hazard regression models and b) Fine-Gray regression models for CLL with infection, treatment and death as outcomes.

Figures

Figure 1 Cumulative incidence for all outcomes: Aalen Johansen cumulative incidence estimates for the three outcomes stacked on top of each other. Each patient could only have one event, that being the event whichever came first. Thus, infections subsequent to treatment and vice versa were not included. Time zero being time of diagnosis for all patients.

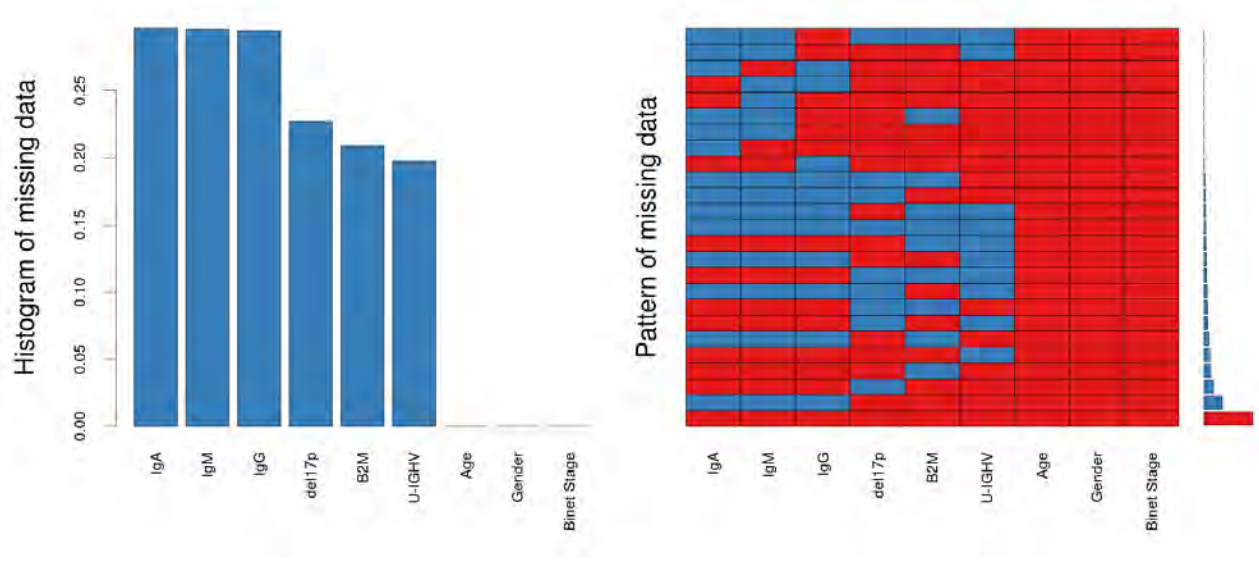

Infection
Treatment
Death
Cumulative incidence
0.00
0.25
0.50
0.75
1.00
0
1
2
3
4
5
Years after diagnosis

Supplementary methods

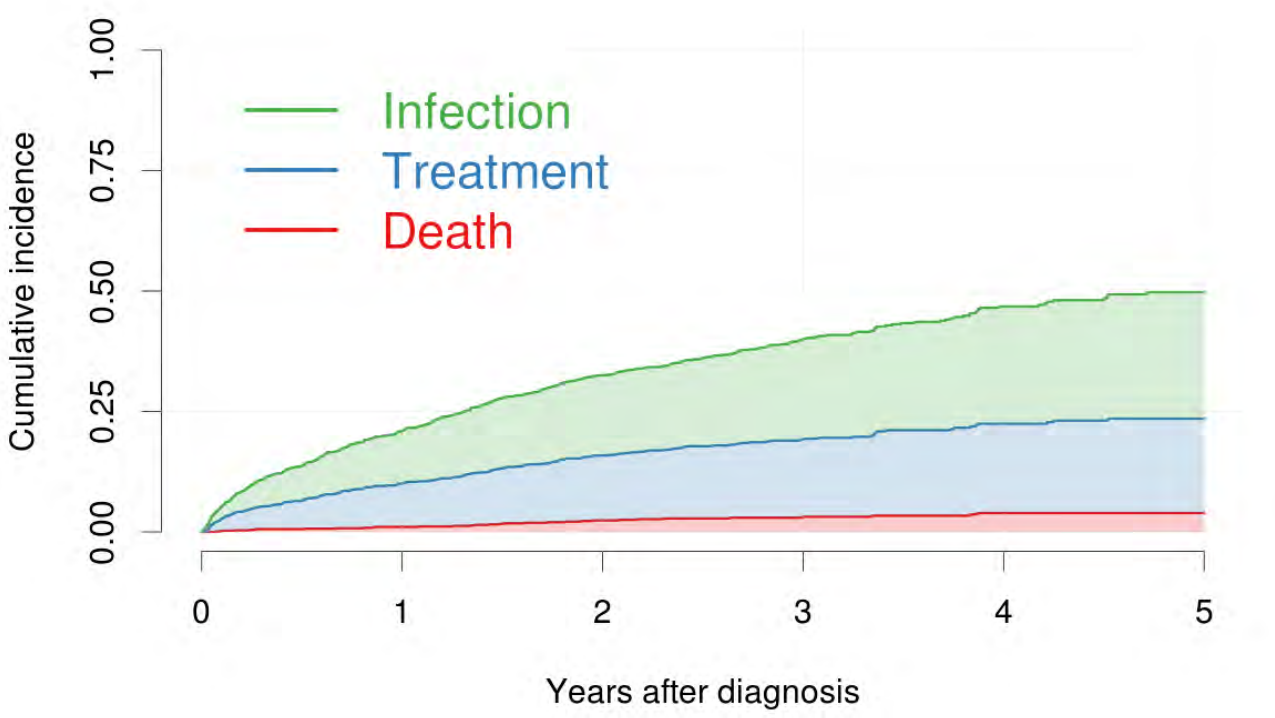
Study population and data source: All patients diagnosed with CLL in Denmark between January 1st 2010 and July 1st 2016, which was also the end of follow-up. The CLL-IPI variables and data on treatment and survival were retrieved from the Danish National CLL registry. Indication of CLL treatment were those recommended by iwCLL.[2] Laboratory results for immunoglobulins IgA, IgG and IgM and information of blood cultures were obtained from a nationwide and complete data infrastructure called PERSIMUNE (www.persimune.dk). Information on immunoglobulins was only included if samples were collected within 6 months of diagnosis. PERSIMUNE retrieves blood culture data from MIBA, which contains data on all microbiology laboratories in Denmark since 2010. We defined a blood culture as the first culture taken during the disease. A blood culture was drawn on the same day as diagnosis was censored. Definitions: The event of the first blood culture prior to CLL therapy was used as a proxy for severe infection, regardless of whether or not bacteria or fungi were identified in the blood. Immunoglobulin levels were dichotomized as low or normal/above normal based on the reference interval. The normal ranges were defined as IgG 6.1–14.9 g/L, IgA 0.8–4.9 g/L, and IgM 0.41–2.2 g/L. Time to event was calculated from date of diagnosis or first date of measurement of immunoglobulin at or after diagnosis whichever came last. Patients were followed until date of infection, initiation of CLL treatment, death or to end of follow-up whichever came first.

Statistical analysis: Estimates of cumulative incidence for each of the competing risks were calculated using the Aalen Johansen estimator. Using Gray's test, subgroup analyses for infection were conducted. In the situation of competing risks, it is recommended to investigate cause-specific hazard models and Fine-Gray models of all competing events. Thus we fitted a cause-specific hazard model and a Fine-Gray model. IgA, IgG and IgM levels were highly correlated to each other, thus only IgA was included in the final model. All models were compared to the non-parametric Aalen Johansen curves. Martingale residuals and Schoenfeld residuals were visualized for diagnostic purposes. Statistical tests were two-sided and P-values of 0.05 were considered significant. All analyses were performed in R. using the packages pec, riskRegression, survival and cmprsk. Visualizations were created using the packages and ggplot2. Source code is available on request.

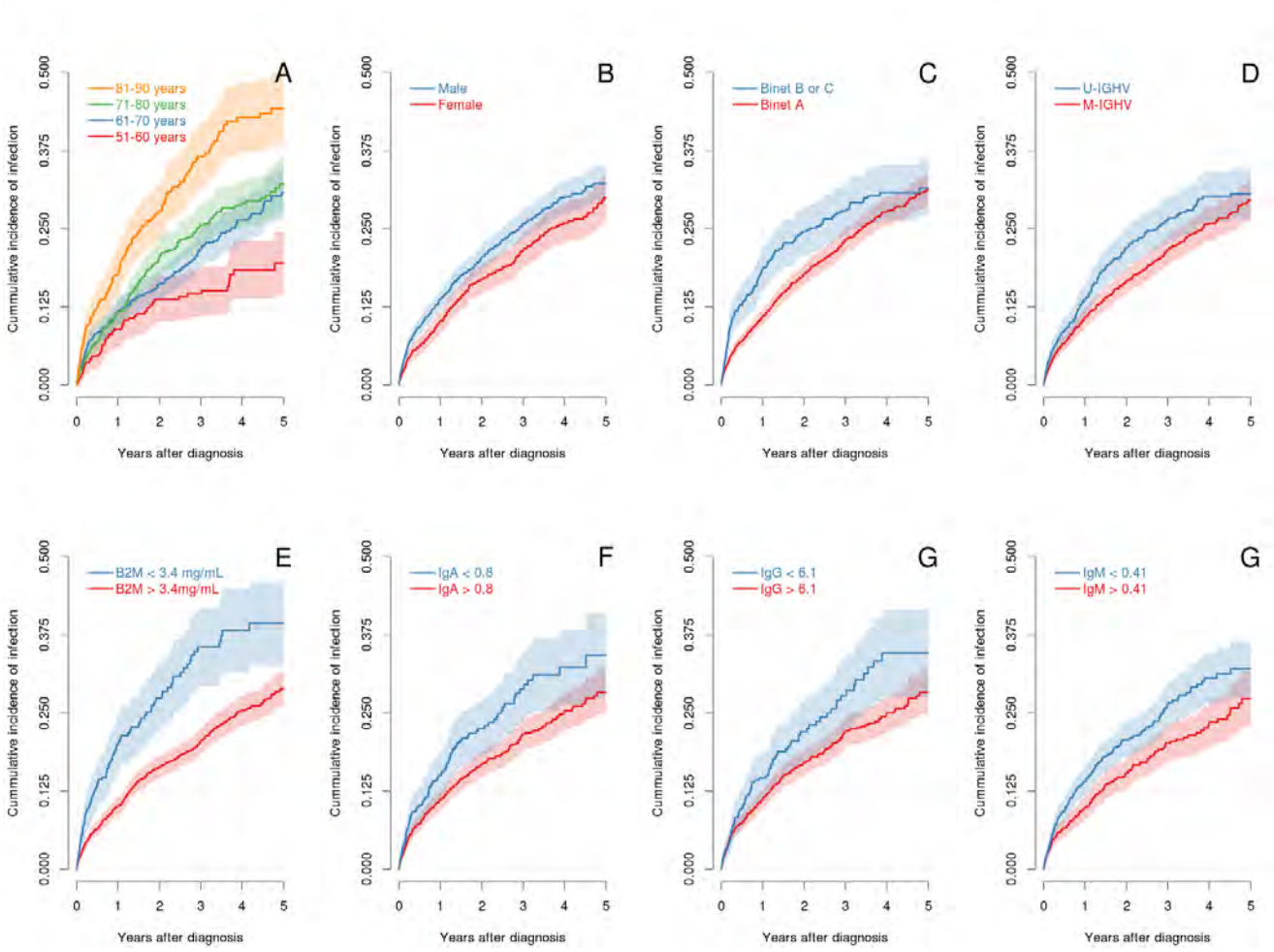
Supplementary figures



Supplementary figure 1 The histogram on the left shows the amount of missing data, each column present the percentage of patients with missing data for each variable. IgA is the most common missing variable. The heat map on the right illustrates the pattern of missing. The red are complete and blue are missing. A total of 44 % had complete data. The most common pattern of missing was to miss only the three immunoglobulin variables, which was the case for 13 %.



Supplementary figure 2) Cumulative incidence for complete case patients: Aalen Johansen cumulative incidence estimates for all possible outcomes stacked on top of each other. Each patient could only have one event, that being the event whichever came first. Thus, infection subsequent to treatment and vice versa would not be included. Time zero being time of diagnosis for all patients.



Supplementary figure 3) Aalen-Johansen cumulative incidence estimates for infection according to, A) Age group, B) Gender, C) Binet Stage, D) IGHV status, E) B2M, F) IgA, G) IgG, H), IgM. Time zero being time of diagnosis for all patients.

Supplementary table

	Infection				Treatment				Death			
Variable	HR	Lower CI	Upper CI	P-value	HR	Lower CI	Upper CI	P-value	HR	Lower CI	Upper CI	P-value
Age	1.03	1.01	1.04	0.00	0.99	0.98	1.00	0.20	1.08	1.04	1.13	0.00
Male	1.35	1.03	1.78	0.03	0.97	0.71	1.33	0.85	1.26	0.61	2.59	0.53
Binet BC	1.76	1.26	2.46	0.00	4.36	3.18	5.97	0.00	0.48	0.11	2.05	0.32
Unmutate	1.29	0.97	1.71	0.08	3.32	2.44	4.53	0.00	0.64	0.26	1.61	0.35

d IGHV												
Del17	1.06	0.59	1.90	0.85	1.89	1.10	3.24	0.02	1.85	0.62	5.56	0.27
B2M (> 4mg/mL)	1.56	1.09	2.22	0.01	1.85	1.27	2.68	0.00	2.79	1.20	6.49	0.02
IgG (<6.1 g/L)	1.53	1.12	2.09	0.01	1.61	1.14	2.28	0.01	2.13	0.94	4.83	0.07

Supplementary table 1) Results of the cause-specific proportional hazard regression models with IgG for CLL with infection, treatment and death as outcomes.

	Infection				Treatment				Death			
variables	HR	Lower CI	Upper CI	P-value	HR	Lower CI	Upper CI	P-value	HR	Lower CI	Upper CI	P-value
Age	1.03	1.01	1.04	0.00	0.99	0.98	1.01	0.30	1.08	1.04	1.13	0.00
Male	1.29	0.99	1.70	0.06	0.92	0.67	1.26	0.60	1.20	0.58	2.46	0.62
Binet BC	1.74	1.25	2.44	0.00	4.34	3.17	5.93	0.00	0.51	0.12	2.21	0.37
Unmutated IGHV	1.29	0.97	1.71	0.08	3.35	2.46	4.57	0.00	0.66	0.26	1.65	0.37
Del17	1.00	0.55	1.79	0.99	1.79	1.05	3.06	0.03	1.60	0.53	4.83	0.40
B2M (> 4mg/mL)	1.53	1.07	2.18	0.02	1.76	1.22	2.55	0.00	2.77	1.19	6.45	0.02
IgM (<0.41 g/L)	1.36	1.05	1.78	0.02	1.63	1.19	2.23	0.00	1.46	0.72	2.97	0.29

Supplementary table 2) Results of the cause-specific proportional hazard regression models with IgM for CLL with infection, treatment and death as outcomes.

	Infection				Treatment				Death			
variables	HR	Lower CI	Upper CI	P-value	HR	Lower CI	Upper CI	P-value	HR	Lower CI	Upper CI	P-value
Age	1.03	1.01	1.01	0.00	0.99	0.97	0.97	0.15	1.07	1.03	1.03	0.00
Male	1.35	1.03	1.03	0.03	0.94	0.67	0.67	0.69	1.21	0.59	0.59	0.60
Binet BC	1.33	0.93	0.93	0.12	3.81	2.73	2.73	0.00	0.32	0.08	0.08	0.11
Unmutated IGHV	1.09	0.82	0.82	0.55	3.17	2.29	2.29	0.00	0.53	0.20	0.20	0.20
Del17	0.85	0.47	0.47	0.58	1.60	0.91	0.91	0.10	1.98	0.63	0.63	0.24
B2M (> 4mg/mL)	1.30	0.90	0.90	0.16	1.66	1.12	1.12	0.01	2.28	1.04	1.04	0.04
IgG (<6.1 g/L)	1.39	1.01	1.01	0.04	1.47	1.01	1.01	0.04	1.78	0.81	0.81	0.15

Supplementary table 3) Results of the Fine-Gray regression models with IgG for CLL with infection, treatment and death as outcomes.

	Infection				Treatment				Death			
variables	HR	Lower CI	Upper CI	P-value	HR	Lower CI	Upper CI	P-value	HR	Lower CI	Upper CI	P-value
Age	1.03	1.01	1.01	0.00	0.99	0.98	0.98	0.18	1.07	1.03	1.03	0.00
Male	1.32	1.00	1.00	0.05	0.88	0.63	0.63	0.43	1.15	0.57	0.57	0.70
Binet BC	1.35	0.95	0.95	0.09	3.76	2.70	2.70	0.00	0.33	0.08	0.08	0.13
Unmutated IGHV	1.09	0.82	0.82	0.56	3.13	2.27	2.27	0.00	0.52	0.20	0.20	0.19
Del17	0.82	0.46	0.46	0.52	1.53	0.86	0.86	0.15	1.83	0.58	0.58	0.30
B2M (> 4mg/mL)	1.30	0.90	0.90	0.15	1.62	1.08	1.08	0.02	2.36	1.06	1.06	0.04
IgM (<0.41 g/L)	1.25	0.96	0.96	0.10	1.46	1.05	1.05	0.03	1.38	0.67	0.67	0.38

Supplementary table 4) Results of the Fine-Gray regression models with IgM for CLL with infection, treatment and death as outcomes.