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

Michael Asger Andersen,[1] Casper Tabassum Eriksen,[1] Christian Brieghel,[1] Jorne Lionel Biccler,[2] Caspar da Cunha-Bang,[1] Marie Helleberg[3] and Carsten Utoft Niemann[1]

[1]Department of Hematology, Rigshospitalet, Copenhagen University Hospital; [2]Department of Hematology, Aalborg University Hospital and [3]Department of Infectious Diseases, Rigshospitalet, Copenhagen University Hospital, Denmark

Correspondence: carsten.utoft.niemann@regionh.dk
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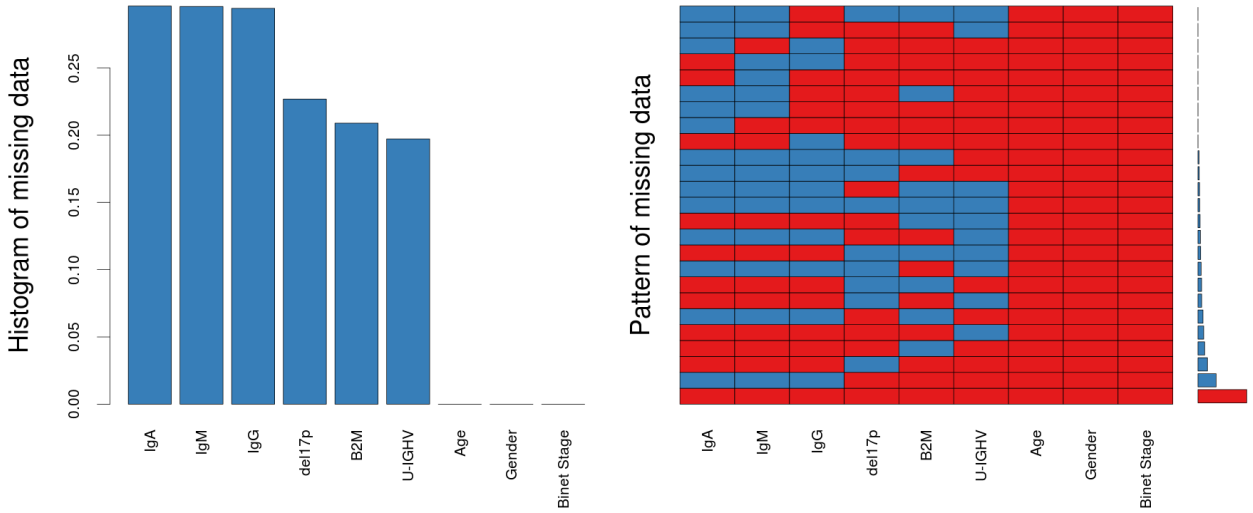
Supplementary methods

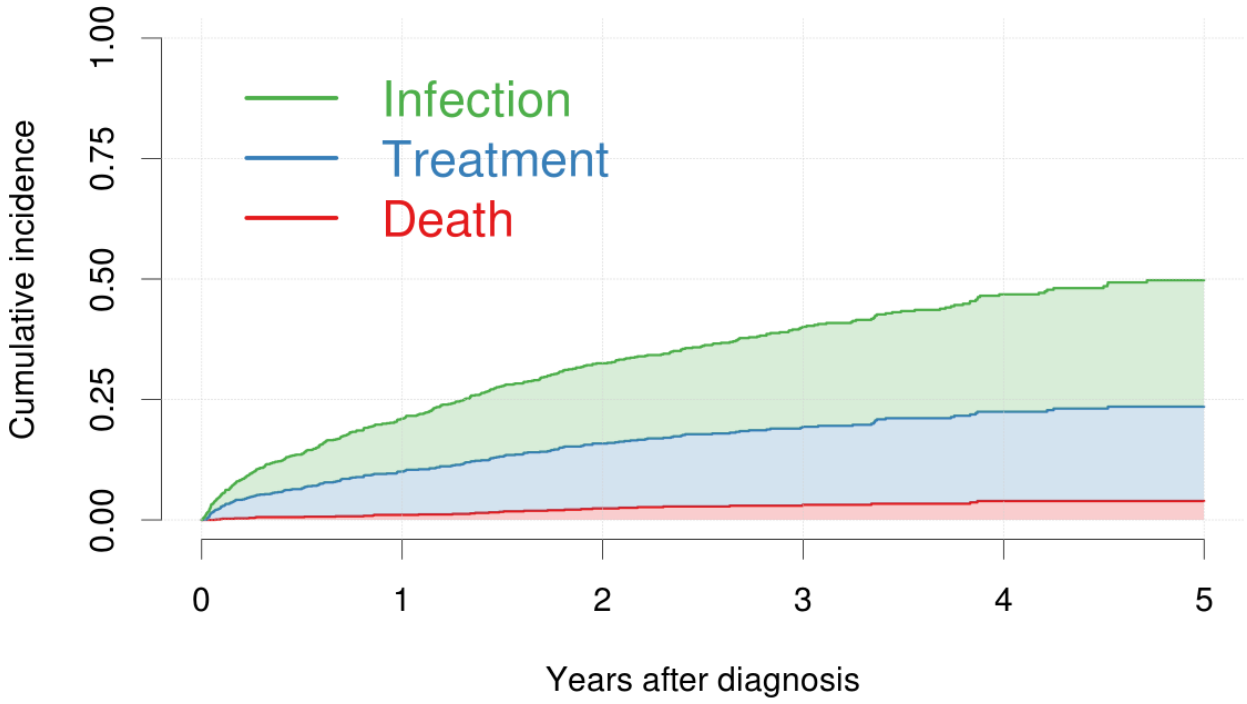
Study population and data source: All patients diagnosed with CLL in Denmark between January 1st 2010 and July 1st 2016, which was also the end of follow-up. The CLL-IPI variables and data on treatment and survival were retrieved from the Danish National CLL registry. Indication of CLL treatment were 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.

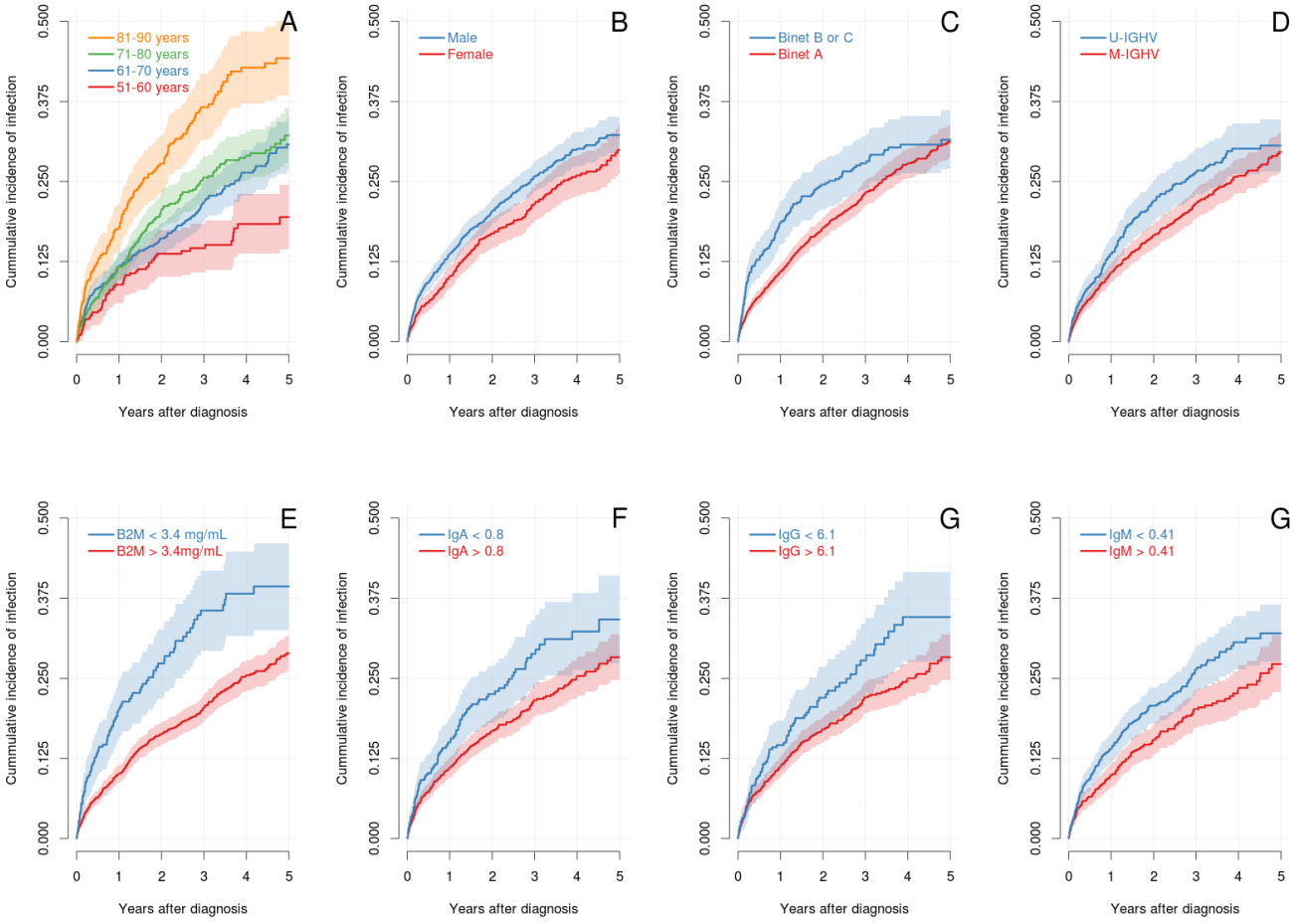
Supplementary figures



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.