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Relationship between co-morbidities at diagnosis, survival and ultimate cause of death in patients with chronic lymphocytic leukaemia (CLL): a prospective cohort study

Paolo Strati, **Sameer A. Parikh**, **Kari G. Chaffee**, **Neil E. Kay**, **Timothy G. Call**, **Sara J. Achenbach**, **James R. Cerhan**, **Susan L. Slager**, and **Tait D. Shanafelt**

Mayo Clinic College of Medicine, Rochester, MN, USA

Summary

The ultimate cause of death for most patients with newly diagnosed chronic lymphocytic leukaemia (CLL) and its relationship to co-morbid health conditions is poorly defined. We conducted a prospective cohort study that systematically followed 1143 patients diagnosed with CLL between June 2002 and November 2014. Comorbid health conditions at the time of CLL diagnosis and their relationship to survival and cause of death were evaluated. Collectively, 1061 (93%) patients had at least one co-morbid health condition at the time of CLL diagnosis (median number 3). Despite this, 89% of patients had a low-intermediate Charlson Comorbidity Index score (CCI) at diagnosis. After a median follow-up of 6 years, 225 patients have died. Death was due to CLL progression in 85 (46%) patients, infection in 14 (8%) patients, other cancer in 35 (19%) patients and comorbid health conditions in 50 (27%) patients. Higher CCI score and a greater number of major comorbid health conditions at the time of CLL diagnosis was associated with shorter non-CLL specific survival, but not with shorter CLL-specific survival on multivariate analysis. In conclusion, CLL and CLL-related complications (infections and second cancers) are the overwhelming cause of death in patients with CLL, regardless of CCI score and number of comorbid health conditions at diagnosis.

Keywords

chronic lymphocytic leukaemia; comorbidities; causes of death

Chronic lymphocytic leukaemia (CLL) is a disease of the elderly (median age at diagnosis ~72 years) and typically occurs in individuals with coexistent health problems (Satram-Hoang *et al*, 2014), which may affect survival (Charlson *et al*, 1987). Over the last 15 years, a number of genetic, biological and molecular characteristics of CLL B-cells that are associated with survival have been identified (Di Giovanni *et al*, 1989; Dohner *et al*, 2000;

Correspondence: Tait Shanafelt, MD, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA. shanafelt.tait@mayo.edu.

Author contributions

TDS designed the study, analysed the data, provided clinical care to patients and wrote the paper; PS designed the study, analysed data and wrote the paper; TGC, SAP and NEK provided clinical care to patients and co-authored the paper; KGC, SJA, JRC and SLS collected and analysed the data and co-authored the paper.

Conflict-of-Interest

The authors declare no conflicts of interest.

Rassenti *et al*, 2008) Although comprehensive approaches to integrate clinical and biological factors into a single risk score have been developed (Wierda *et al*, 2007; Pflug *et al*, 2014), they have not yet integrated the impact of comorbidities and competing causes of death. These facts make accurate risk stratification and counselling of newly diagnosed patients challenging.

It is already known that traditional prognostic factors play a more limited role for predicting outcome among patients aged 75 years or older (Shanafelt *et al*, 2010). However, how to account for the impact of concomitant medical conditions on patient outcome in newly diagnosed CLL patients remains unclear (Thurmes *et al*, 2008; Goede *et al*, 2014; Nabhan *et al*, 2014). Conflicting data are available in the literature as to whether comorbid conditions predict prognosis in newly diagnosed patients with CLL (Thurmes *et al*, 2008; Reyes *et al*, 2012), whereas they more clearly play an independent prognostic role at time of first treatment (Goede *et al*, 2014; Manda *et al*, 2014).

Here we report the findings of a prospective cohort study that evaluated the cause of death in newly diagnosed patients with CLL and evaluated whether the number of comorbidities predicts the cause of death and survival of newly diagnosed patients.

Methods

Study population

The Molecular Epidemiology Resource (MER) of the University of Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence (SPORE) was used for this study. The MER is a prospective cohort study of non-Hodgkin lymphoma and CLL outcomes that was initiated in 2002 (Thompson *et al*, 2011; Maurer *et al*, 2014). Newly diagnosed patients with CLL who were evaluated at Mayo Clinic, Rochester, MN, within 9 months of CLL diagnosis, were aged 18 years or older, resident in the United States and enrolled in MER between June 2002 and November 2014, were included in this cohort. Exclusion criteria included human immunodeficiency virus infection, non-English speaking, and inability to provide written informed consent. At baseline, patients provided data on personal and family history, comorbidities and functional status. Patients were prospectively and systematically contacted every 6 months during the first 3 years after initial diagnosis to assess vital status, disease progression and new treatments. Patients then continued to be followed until death or last to follow-up. The study was approved by the Institutional Review Board of Mayo Clinic and was conducted in accordance with the principles of the Declaration of Helsinki.

Comorbidity and mortality assessment

Comorbidities diagnosed prior to or simultaneously with CLL diagnosis were recorded at the time of first CLL evaluation at Mayo Clinic. Comorbidities were assigned to one of 15 categories: stroke, cardiovascular disease (including coronary artery disease, peripheral vascular disease, cardiomyopathy, valve heart disease and atrial fibrillation), hypertension, respiratory disease, diabetes mellitus, other endocrinological disease, dyslipidaemia, rheumatological disease, gastrointestinal disease, genitourinary disease, psychiatric disease, history of deep venous thrombosis or pulmonary embolism, alcohol abuse, sexually

transmitted disease, and other cancers (excluding non-melanoma skin cancer). For other analyses, baseline comorbidities were further analysed as major comorbid conditions (e.g. cerebrovascular disease, cardiovascular disease, respiratory disease, diabetes mellitus and other cancer). The Charlson Comorbidity Index (CCI) was also calculated for each patient, based on comorbid health conditions present at the time of diagnosis (Deyo *et al*, 1992). The CCI is an age-weighted prognostic score based on 17 disease categories, which has been validated over the last 25 years and has reliably predicted survival in any patient population (Charlson *et al*, 1987). A CCI score ≤3 was considered low, 4–5 was moderate, 6–7 was high and ≥8 was very high.

Information on cause of death was also collected from electronic records. For patients in whom cause of death could be accurately determined, the cause of death was classified into one of four categories: (i) progressive CLL, (ii) infection, (iii) other cancers or (iv) comorbid health condition (in absence of CLL progression). When the cause of death could not be accurately determined, the cause of death was categorized as 'unknown'.

Statistical analysis

Descriptive statistics were used to summarize baseline clinical characteristics. The relationship between baseline categorical or continuous variables and ultimate cause of death were compared using the χ^2 or Fisher exact tests and the Kruskal–Wallis test, as appropriate. Comorbidity categorical indices were modelled as continuous variables. Survival was modelled using the Kaplan–Meier method using a log-rank test to compare each comorbidity index. Overall survival (OS) was defined as time from diagnosis to death or last follow-up. CLL-specific survival was defined as time from diagnosis to death from a CLL-related cause. CLL progression, infection and second cancer were considered CLL-related causes of death for this analysis. Patients who died due to other causes were treated as a competing risk. Non-CLL specific survival was defined as time from diagnosis to death from a cause unrelated to CLL. Patients who died due to CLL progression, infection, and second cancer were treated as a competing risk at the time of death for this analysis. Patients with unknown cause of death were excluded for both the CLL-specific and non-CLL specific survival analyses. Logistic regression was used to compare comorbidities at baseline by cause of death (i.e., CLL-specific *versus* non-CLL specific). Survival was displayed using a cumulative incidence function with competing risks for CLL- and non-CLL specific analyses using Gray's test to compare groups.

Multivariate analyses (MVA) to identify characteristics independently associated with mortality were performed using Cox regression analysis, accounting for competing risks (when appropriate) using Fine-Gray models. Each model contained age (10-year increments), sex and Rai stage; we then added one of the comorbidity measures (e.g. CCI or number of major co-morbidities) to the model. Due to the number of missing values for molecular CLL prognostic factors [e.g. fluorescence *in situ* hybridization (FISH), *IGHV*], we were unable to include these factors in the multivariate models. All *P*-values were 2-sided and considered significant if ≤0·05. Analyses were performed using SAS version 9·4 (SAS Institute, Cary, NC, USA).

Results

Baseline characteristics and comorbidities

One thousand and forty-three patients were included in the study. Baseline characteristics are shown in Table I. Median age was 63 years and two-thirds were men. Among those patients with CLL prognostic testing available, 44% had unmutated *IGHV* and 14% had unfavourable genetic characteristics on FISH analysis (del17p or del11q).

The prevalence of various comorbid health conditions present at the time of CLL diagnosis are shown in Fig 1. Rheumatological diseases (primarily osteoarthritis, 42% of patients), dyslipidaemia (41%) and hypertension (40%) were the three most common comorbid health conditions present at the time of CLL diagnosis. The CCI score was low (0–3) at the time of CLL diagnosis in 831 (73%) patients, intermediate (4–5) in 185 (16%), high (6–7) in 76 (7%) and very high (8+) in 51 (4%). While 548 (48%) patients had no major comorbidities at time of CLL diagnosis, 394 (34%) had one major comorbidity and 201 (18%) had two or more major comorbidities.

Cause of death

After a median follow-up of 6 years, 225 patients had died. The cause of death could be accurately determined in 184 (82%) of these patients: CLL progression in 85 (46%) patients, infection in 14 (8%), other cancer in 35 (19%) and comorbid health conditions in 50 (27%). The relationship between causes of death and baseline characteristics is shown in Table II. Patients with unmutated *IGHV* had a greater likelihood of experiencing a CLL-related death (odds ratio [OR] 219, 95% confidence interval [CI] 106–454; $P = 004$). No other CLL-related prognostic parameters had a statistically significant association with a CLL-related cause of death, although power was limited for some comparisons (e.g., high-risk FISH). With respect to comorbid health conditions at the time of CLL diagnosis, patients with a history of stroke (OR 574, 95% CI 102–3238; $P = 0048$), history of cardiac disease (OR 202, 95% CI 104–393; $P = 004$), higher CCI (OR 146, 95% CI 107–198; $P = 002$) and higher number of major comorbidities (OR 173, 95% CI 113–265; $P = 001$) had a higher likelihood of dying due to non-CLL related causes. No other co-morbid health conditions had a statistically significant association with a non-CLL related cause of death on univariate analysis.

Overall survival

After a median follow-up of 6 years, the median OS had not been reached. On univariate analysis, both a higher CCI score (Fig 2A) and a higher number of major comorbidities at diagnosis (Fig 2B) were significantly associated with a shorter OS (both $P < 0001$). On MVA, after adjusting for age, sex and Rai stage, a higher CCI score appeared to correlate with OS although this difference was not statistically significant (Table IIIA; HR = 114; 95% CI 098–132; $P = 010$). A greater number of major comorbidities at diagnosis were significantly associated with OS in the MVA (Table III; HR = 127; 95% CI 106–152; $P = 0009$).

CLL-specific and non-CLL specific mortality

Median CLL-specific and non-CLL specific mortality have not been reached with current follow-up. On univariate analysis, higher CCI score was associated with a higher CLL-specific mortality (Fig 3A; $P < 0001$). A greater number of major comorbidities at diagnosis had a non-significant trend toward higher CLL-specific mortality (Fig 3B; $P = 0066$). Both a higher CCI score and higher number of major comorbidities were associated with higher non-CLL specific mortality (Figs 3C and D, respectively; $P < 0001$ for both).

After adjusting for age, sex and Rai stage, MVA identified no statistically significant associations between CCI score or the number of major comorbidities at the time of diagnosis and CLL-specific mortality (Tables IIIA,B). In contrast, both higher CCI score (Table IIIA; HR = 137; 95% CI 102–182; $P = 0035$) and higher number of major comorbidities (Table III; HR = 161; 95% CI 111–233; $P = 0012$) were significantly associated with increased non-CLL specific mortality.

Finally, when the analyses were repeated either (i) censoring deaths of unknown cause or (ii) assigning patients with deaths of unknown cause to one of the death groups (CLL-related and unrelated), no significant difference in the above findings were observed.

Discussion

Limited information is available regarding cause of death in patients with CLL and its relationship to baseline comorbidities. The dogma is generally that patients with CLL are elderly, frequently have comorbid health conditions, and are likely to ultimately die from causes unrelated to CLL. Here we report one of the few studies to evaluate cause of death in a cohort of newly diagnosed patients with CLL followed prospectively and to evaluate their relationship with comorbidity.

Although comorbidities were common, a majority of patients died directly from CLL (46%) or infection (8%). An additional ~20% died of other cancers that may be at least indirectly related to CLL given the increased risk of non-hematologic cancer associated with this condition. The CCI and the number of comorbidities at diagnosis were associated with survival in MVA and appeared to mediate this effect through an influence on non-CLL specific mortality, but not on CLL-specific mortality. These results indicating that most patients with CLL die directly of CLL or CLL related complications challenge many traditionally held paradigms.

Predicting the most likely cause of death following diagnosis becomes crucial for the management of these patients, particularly when therapy is needed. Currently, many patients are excluded from standard therapy or clinical trials because of concomitant comorbid conditions. Our results, however, demonstrate that CLL and its complications remain the main cause of death in these patients, and that comorbidities don’t affect CLL-specific survival. These results highlight the importance of effective CLL therapy regardless of the presence of concomitant health conditions. In addition, it prompts the need for new therapies that can be employed in elderly patients with comorbid conditions. Ultimately, this may translate into longer survival and lower healthcare-associated costs.

In our study, despite a younger median age than typically reported in CLL (63 vs. 72 years), comorbid health conditions were very common at time of CLL diagnosis, with rheumatological diseases, hypertension and dyslipidaemia each being observed in 40% or more of patients. Their high incidence in this elderly population may just be secondary to aging. However, several studies have shown a significant association between CLL and chronic illnesses, such as renal disease (Strati *et al*, 2015), dyslipidaemia (Mulas *et al*, 2011) and hypovitaminosis D (Shanafelt *et al*, 2011). While both direct organ infiltration and microenvironment activity may be contributing factors to some of these other health conditions, the specific mechanisms underlying such associations remain unclear.

Despite the high frequency of comorbidities at time of CLL diagnosis, the majority of patients showed a low-intermediate CCI and had fewer than two major comorbidities, pointing toward a relatively low burden of comorbid health conditions in our cohort. While a high CCI at time of CLL diagnosis may predict poor survival, there is limited evidence regarding the effects of multiple comorbidities on treatment outcomes (Fried *et al*, 2014). In fact, although data is limited, some studies suggest CLL and related complications are the cause of death for about 50% of patients with this disease (Thurmes *et al*, 2008; Goede *et al*, 2014; Nabhan *et al*, 2014; Satram-Hoang *et al*, 2014). In our study, we found an even higher rate, in which 73% died of CLL progression or CLL related complications, such as infections or other cancers (Tsimberidou *et al*, 2009; Royle *et al*, 2011; Solomon *et al*, 2013). Of interest, this is a cohort of patients diagnosed in the chemoimmunotherapy era; while the latter remains the standard of care for fit previously untreated patients, ongoing changes in therapy standards, with the potential introduction of newer biological agents as frontline regimens, may alter this scenario in the near future.

Not surprisingly, the presence of unmutated *IGHV* was significantly associated with CLL-related mortality, with 77% of unmutated patients dying of CLL-related causes vs. 61% of *IGHV* mutated patients, as previously observed (Wierda *et al*, 2007; Fried *et al*, 2014; Pflug *et al*, 2014; Kutsch *et al*, 2015). The presence of stroke or cardiac disease at time of CLL diagnosis was associated in our study with a higher rate of non-CLL related mortality, despite appropriate secondary prevention. In fact, 33% of patients with history of stroke had a CLL-related death *versus* 74% of patients without it, and 64% of patients with a cardiac disease history died of CLL-related causes *versus* 78% of patients without it. However, beyond these few associations, CLL progression and complications remained the main cause of death, irrespective of baseline characteristics and comorbidities.

In our study, while associated with a shorter non-CLL specific survival, a higher CCI and a higher number of major comorbidities did not associate with a shorter CLL-specific survival on MVA. Our group had already demonstrated that baseline comorbidities are less relevant than age and Rai stage in predicting survival at time of CLL diagnosis (Thurmes *et al*, 2008). A more recent study, however, showed that the presence of comorbidities at time of first treatment is an independent prognostic factor for survival (Goede *et al*, 2014), highlighting the prognostic role played by chronic illnesses when CLL requires therapy. The lack of association between baseline comorbidities and CLL-specific mortality highlights the predominant roles played by CLL progression and complications in the survival of CLL patients. This is a relevant point, as comorbidities can limit therapeutic options for patients

with CLL and frequently represent exclusion criteria in clinical trials. As a consequence, both less toxic agents and clinical trials evaluating treatments that are designed to be tolerated by patients who do not meet traditional clinical trial eligibility criteria are needed.

Our study has some limitations. This is a single centre study, employing 2 specific scales to assess comorbidities, and causes of death could not effectively be collected for all patients. In addition, the investigated cohort was younger than the average CLL population, potentially affecting the observed results.

Continued efforts are needed to determine the optimal approach to assess co-morbidity and functional status in patients with CLL, and integrate these measures with established prognostic tools at different time-points in the course of the disease including at the time of and the time of first treatment.

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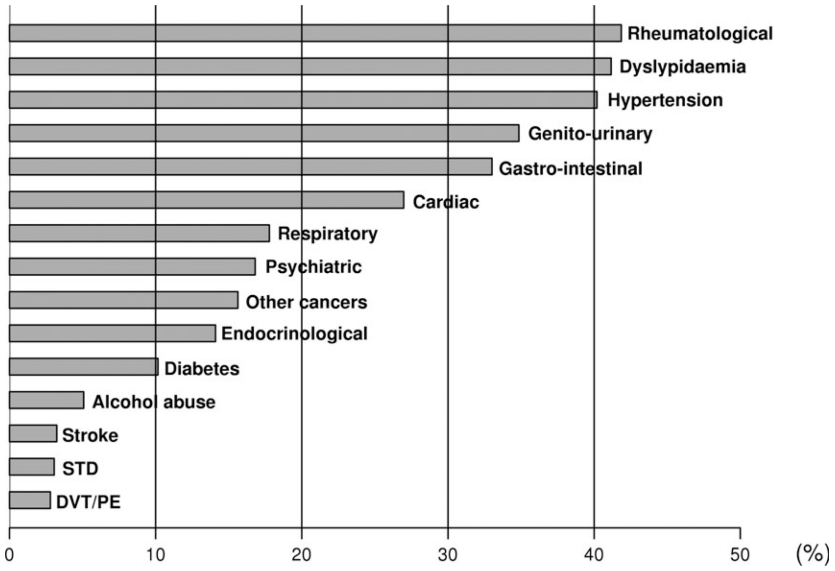

Fig 1.

Baseline comorbid health conditions in 1143 CLL patients. DVT, deep venous thrombosis; PE, pulmonary embolism; STD, sexually transmitted disease. ‘Other cancers’ did not include non-melanoma skin cancers.

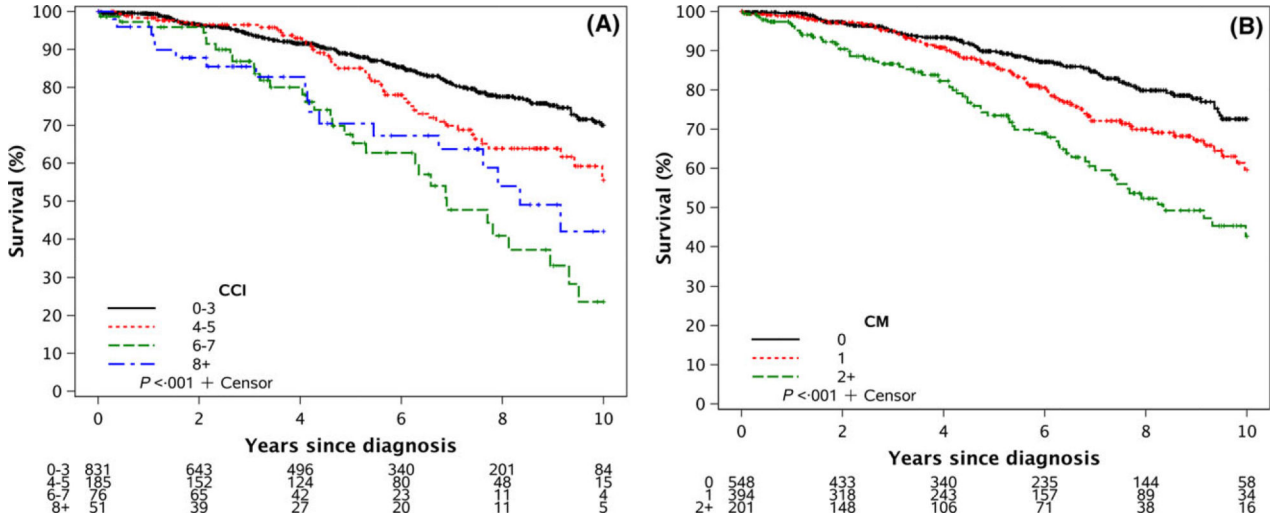

Fig 2.

Overall survival. (A) Overall survival by Charlson Comorbidity Index (CCI) score at the time of CLL diagnosis. (B) Overall survival by number of major comorbidities (CM) at time of CLL diagnosis. Events included all types of death, both CLL-related, non-CLL related, and of unknown cause.

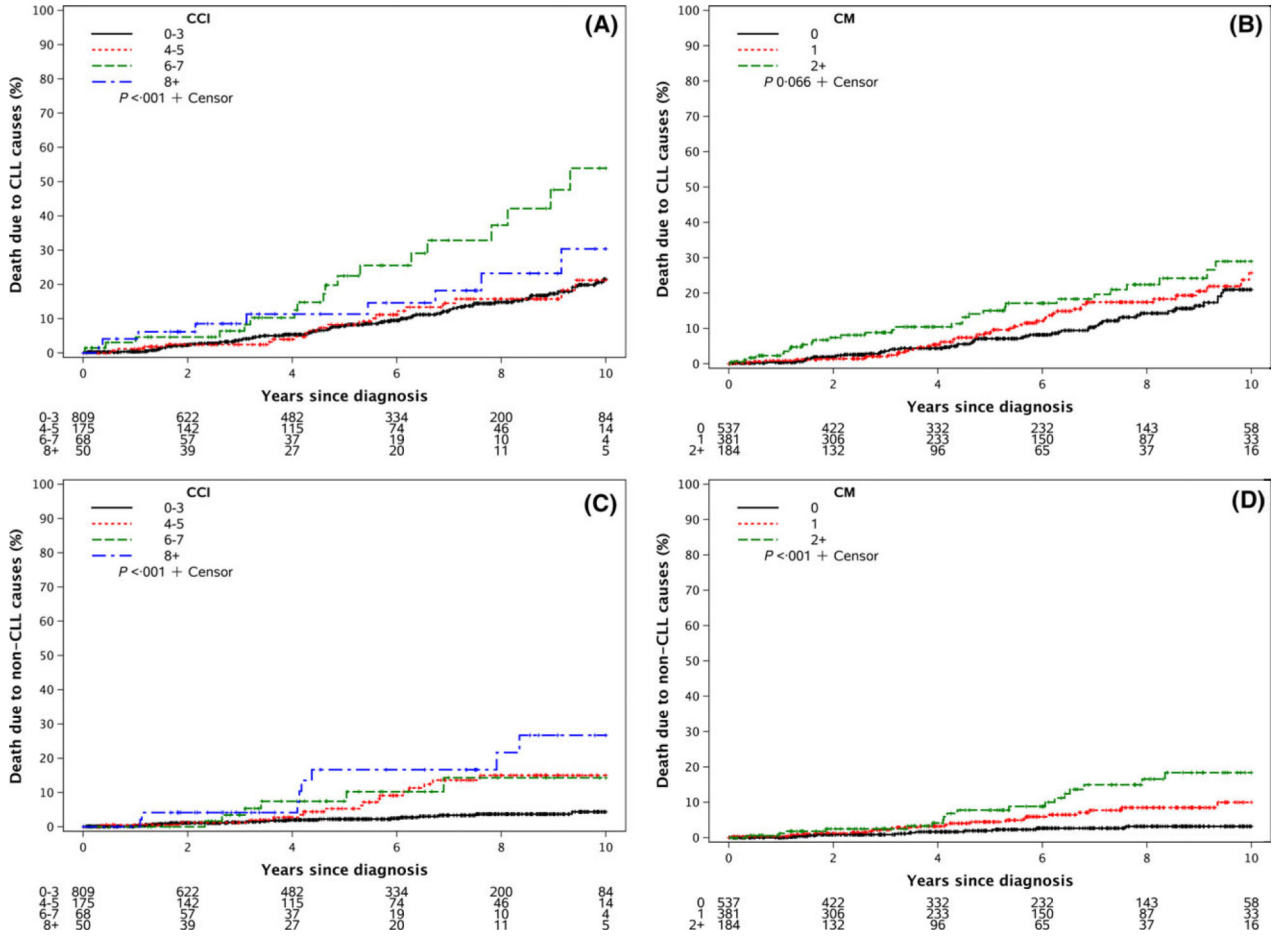

Fig 3.

CLL-specific and non-CLL specific mortality. (A) CLL-specific-mortality by Charlson Comorbidity Index (CCI) score at time of CLL diagnosis. (B) CLL-specific-mortality by number of major comorbidities (CM) at time of CLL diagnosis. (C) Non-CLL specific mortality by Charlson Comorbidity Index score at time of CLL diagnosis. (D) Non-CLL specific mortality by number of major comorbidities at time of CLL diagnosis.

Table I.

Baseline characteristics of CLL patients.

Patients (*N* = 1143)	**Number (%), median [range]**
Age at diagnosis (years)	63.0 [23.7–89.5]
Age <60	464 (41%)
Age 60–69	372 (33%)
Age 70+	307 (27%)
Sex	
Male	769 (67)
Female	374 (33)
Race	
Caucasian	1066 (98)
Non-Caucasian	27 (2)
Missing	50
ALC ($\times 10^9$/l)	9.5 [0.4–958]
ALC <25	940 (83%)
ALC 25–50	88 (8%)
ALC >50	101 (9%)
Missing	14
Haemoglobin (g/l)	141 [49–179]
Missing	11
Platelet count ($\times 10^9$/l)	198 [19–675]
Missing	12
Creatinine clearance (ml/min)	85.4 [9.5–251.1]
Missing	287
Albumin (g/l)	37 [11–50]
Missing	246
Total bilirubin (μmol/l)	0.03 [0.005–1.3]
Missing	240
Rai stage	
0	629 (55)
I–II	458 (40)
III–IV	55 (5)
Missing	1
B2M	
< 35 mg/l	845 (81)
≥ 35 mg/l	194 (19)
Missing	104
CD49d	
Negative (<45%)	707 (69)
Positive (≥45%)	317 (31)
Missing	119

Patients (*N* = 1143)	**Number (%), median [range]**
CD49d	
Negative (<30%)	658 (64)
Positive (≥30%)	365 (36)
Missing	120
IGHV	
Mutated	559 (56)
Unmutated	436 (44)
Missing	148
High-Risk FISH	
No (negative, del13q, +12)	903 (86)
Yes (del11q, del17p)	148 (14)
Missing/Other	92

ALC, absolute lymphocyte count; B2M, beta-2-microglobulin; FISH, fluorescence *in situ* hybridization; *IGHV*, Immunoglobulin heavy chain variable region gene.

Table II.

Causes of mortality by baseline characteristics and comorbidities*

	Cause of death		
	CLL-related (*n* = 134)	**Unrelated to CLL (*n* = 50)**	***P*-value**
Age (years)	68 [39–87]	71 [44–89]	0.06
Age at diagnosis (years)			
Age <60	29 (22)	8 (16)	0.30
Age 60–69	47 (35)	14 (28)	
Age 70+	58 (43)	28 (56)	
Sex			
Males	103 (77)	41 (82	0.45
Females	31 (23)	41 (82) 9 (18)	
Laboratory parameters at diagnosis			
ALC at diagnosis ($\times 10^9$/l)	10.1 [0.4–958]	8.2 [1.0–115]	0.52
Creatinine clearance (ml/min)	80 [10–199]	74 [21–143]	0.16
Albumin (g/l)	37 [11–49]	36 [28–47]	0.32
Total bilirubin (lmol/l)	0.03 [0.01–1.3]	0.03 [0.02–0.1]	0.93
B2M			
≥35 mg/l	45 (41)	17 (39)	0.76
<35 mg/l	64 (59)	27 (61)	0.76
Missing	25	6	
CLL characteristics at diagnosis			
Rai stage			
0	53 (40)	24 (48)	0.16
I–II	62 (47)	24 (48)	
III–IV	18 (14)	2 (4)	
Missing	1	0	
CD49d			
Positive (≥45%)	51 (48)	14 (34)	0.13
Negative (<45%)	55 (52)	27 (66)	
Missing	28	9	
CD49d			
Positive (≥30%)	58 (55)	17 (41)	0.15
Negative (<30%)	48 (45)	24 (59)	
Missing	28	9	
IGHV			
Unmutated	78 (72)	23 (53)	**0.034**
Mutated	31 (28)	20 (47)	
Missing	25	7	
High-Risk FISH			
No (negative, del13q, +12)	76 (66)	37 (80)	0.06
Yes (del11q, del17p)	40 (34)	9 (20)	

	Cause of death		
	CLL-related (*n* = 134)	**Unrelated to CLL (*n* = 50)**	***P*-value**
Missing/Other	18	4	
Comorbid conditions at diagnosis			
Other cancer[†]			
Yes	32 (24)	10 (20)	0.57
No	99 (76)	39 (80)	
Missing	3	1	
Stroke			
Yes	2 (1)	4 (8)	**0.047**
No	132 (99)	46 (92)	
Cardiac disease			
Yes	42 (31)	24 (48)	**0.036**
No	92 (69)	26 (52)	
Hypertension			
Yes	58 (43)	29 (58)	0.08
No	76 (57)	21 (42)	
Respiratory			
Yes	28 (21)	14 (28)	0.31
No	106 (79)	36 (72)	
Endocrinological			
Yes	22 (16)	6 (12)	0.46
No	112 (84)	44 (88)	
Diabetes			
Yes	15 (11)	11 (22)	0.06
No	119 (89)	39 (78)	
Dyslipidaemia			
Yes	47 (35)	25 (50)	0.07
No	87 (65)	25 (50)	
Rheumatological			
Yes	56 (42)	16 (32)	0.23
No	78 (58)	34 (68)	
Gastrointestinal			
Yes	47 (35)	13 (74)	0.24
No	87 (65)	37 (74)	
Genitourinary			
Yes	53 (40)	23 (46)	0.43
No	81 (60)	27 (54)	
Psychiatric			
Yes	17 (13)	5 (10)	0.62
No	117 (87)	45 (90)	
DVT/PE			
Yes	2 (1)	3 (6)	0.12

	Cause of death		
	CLL-related (*n* = 134)	**Unrelated to CLL (*n* = 50)**	***P*-value**
No	132 (99)	47 (94)	
Alcohol abuse			
Yes	8 (6)	3 (6)	1.00
No	126 (94)	47 (94)	
STD			
Yes	5 (4)	1 (2)	1.00
No	129 (96)	49 (98)	
CCI (median, range)	3 (0–17)	4 (0–12)	**0.019**
CCI score			
0–3	86 (64)	20 (40)	**0.006**
4–5	20 (15)	16 (32)	
6–7	19 (14)	6 (12)	
8+	9 (7)	8 (16)	
Major CM(median, range)	1 (0–4)	1 (0–4)	**0.011**
Major CM			
0	56 (42)	11 (22)	**0.032**
1	48 (36)	21 (42)	
2+	30 (22)	18 (36)	

ALC, absolute lymphocyte count; B2M, beta-2-microglobulin; CCI, Charlson Comorbidity Index; CLL, chronic lymphocytic leukaemia; CM, comorbidities; DVT, deep venous thrombosis; FISH, fluorescence *in situ* hybridization; IGHV, Immunoglobulin heavy chain variable region gene; PE, pulmonary embolism; STD, sexually transmitted disease.

*Deaths due to infection and other cancers are categorized as CLLrelated death. Deaths due to unknown cause are not included.

†'Other cancers' did not include non-melanoma skin cancers.

Table III.

Multivariate analysis of mortality.

	Overall mortality		CLL-specific mortality		Non-CLL specific mortality	
	HR [95% CI]	***P*-value**	**HR [95% CI]**	***P*-value**	**HR [95% CI]**	***P*-value**
(A) Including Charlson Comorbidity Index.						
Age (10 years)	1.82 [1.56–2.11]	<0.001	1.67 [1.37–2.05]	<0.001	1.81 [1.29–2.54]	<0.001
Males	1.68 [1.22–2.31]	0.001	1.47 [0.98–2.20]	0.06	2.00 [0.96–4.18]	0.06
Rai categories	2.21 [1.78–2.74]	<0.001	2.52 [1.91–3.33]	<0.001	1.38 [0.90–2.12]	0.14
CCI categories	1.14 [0.98–1.32]	0.10	1.00 [0.80–1.25]	0.99	1.37 [1.02–1.82]	0.035
(B) Including number of major comorbidities.						
Age (10 years)	1.81 [1.58–2.09]	<0.001	1.66 [1.38–1.99]	<0.001	1.90 [1.38–2.63]	<0.001
Males	1.58 [1.15–2.19]	0.005	1.45 [0.97–2.18]	0.07	1.74 [0.82–3.69]	0.15
Rai categories	2.21 [1.78–2.74]	<0.001	2.52 [1.91–3.34]	<0.001	1.31 [0.86–2.00]	0.21
Major CM	1.27 [1.06–1.52]	0.009	1.03 [0.82–1.30]	0.79	1.61 [1.11–2.33]	0.012

95% CI, 95% confidence interval; CCI, Charlson Comorbidity Index; CLL, chronic lymphocytic leukaemia; CM, comorbidities; HR, hazard ratio.