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ORIGINAL ARTICLE

Cardiovascular disease in chronic myelomonocytic leukemia: do monocytosis and chronic inflammation predispose to accelerated atherosclerosis?

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Abstract

Patients with chronic myelomonocytic leukemia (CMML) have monocytosis and likely a state of chronic inflammation. Both have been associated with an increased risk of atherosclerosis. The aim of the study was to test the hypothesis that CMML patients are at increased risk of developing cardiovascular disease (CVD) due to persistent monocytosis and sustained chronic inflammation. In a retrospective cohort study, we assessed hazards for cardiovascular events after diagnosis in 112 CMML patients and 231 chronic lymphocytic leukemia (CLL) patients. Analyses were carried out on restricted cohorts (CMML = 84, CLL = 186), excluding patients with a prior history of CVD, as well as on unrestricted cohorts. In the restricted cohorts, a significant effect of cardiovascular event occurrence did not remain after adjustment (HR 2.49, 95% CI 0.94–6.60). In unrestricted cohorts, we found a more than twofold increased rate of cardiovascular events in CMML (HR 2.34, 95% CI 1.05–5.20). Our results indicate an increased risk of CVD after the diagnosis in CMML patients.

Keywords Chronic myelomonocytic leukemia · MPN/MDS · Cardiovascular disease · Atherosclerosis · Chronic inflammation

Abbreviations

AMI	Acute myocardial infarction
AML	Acute myeloid leukemia
CHIP	Clonal hematopoiesis of indeterminate potential
CI	Confidence interval
CLL	Chronic lymphocytic leukemia
CMML	Chronic myelomonocytic leukemia
DRG	Diagnosis-related group
CVD	Cardiovascular disease
DM-II	Type II diabetes
HR	Hazard ratio
IHD	Ischemic heart disease
MDS	Myelodysplastic syndrome
MPN	Myeloproliferative neoplasm
NO	Nitric oxide
OR	Odds ratio
SNOMED	Systematized Nomenclature of Medicine – Clinical Terms
TCI	Transitory cerebral ischemia

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Introduction

Chronic myelomonocytic leukemia (CMML) is a chronic myeloid hematopoietic stem cell disorder classified as a myelodysplastic/myeloproliferative neoplasm. According to the 2016 WHO classification of myeloid neoplasms, it is characterized by absolute peripheral monocytosis ($> 1 \times 10^9$/L) with monocytes accounting for ≥ 10% of the white blood cell (WBC) count and the presence of dysplasia in one or more myeloid lineages in the bone marrow [1]. According to blast excess, CMML is sub-divided into CMML-0, CMML-1, and CMML-2 [1].

Monocytes play a crucial role in the pathogenesis and prognosis of atherosclerosis [2, 3]. In mice, it has been shown that decreased numbers of circulating monocytes inhibit

atherosclerosis [4]. Similarly, monocytosis is an independent risk factor for the development of subclinical carotid atherosclerosis [5], coronary artery disease and acute myocardial infarction (AMI) [3], and as the atherosclerotic lesions worsen the number of circulating monocytes rises [6].

Chronic inflammation is considered a risk factor for development of atherosclerosis [7]. This is supported by the findings of a recent clinical trial that concluded that anti-inflammatory therapy targeting IL-1β reduced the risk of recurrent cardiovascular events compared to placebo [8]. Furthermore, patients with chronic inflammatory and autoimmune diseases have an increased burden of CVD [9], which is thought to involve immunologic abnormalities and inflammation as well as modifiable and commonly known risk factors for atherosclerosis like smoking, hypertension, and overweight [9, 10]. Two studies have suggested an increased prevalence of autoimmune diseases prior to CMML diagnosis [11, 12], indicating that patients with CMML have a high load of chronic inflammation. This association has been further substantiated by the findings of elevated levels of inflammatory cytokines such as IL-6 and TNFα in CMML patients [13].

Chronic inflammation in the Philadelphia-negative myeloproliferative neoplasms (MPNs) has recently been proposed to increase the risk of premature atherosclerosis [7]. The increased thrombotic risk in patients with MPNs is caused by elevated hematocrit, platelet count, and leukocyte count, but CVD and thrombotic complications may also be related to chronic inflammation contributing to atherosclerosis development [7]. Chronic inflammation in MPNs, and likely also in CMML, may be elicited and driven by the malignant clone continuously releasing inflammatory products and accordingly sustaining a vicious inflammatory circle and a chronic inflammatory state. Furthermore, atherosclerosis is considered an immune-mediated process causing a state of chronic inflammation that involves both the humoral and the adaptive immune system [10, 14, 15] and thereby may participate in the self-perpetuating state of chronic inflammation and clonal evolution as mentioned above. In this context, the TET2 and JAK2V617F mutations are highly relevant. Firstly, the TET2 mutation, which is the most frequent mutation in CMML [16], has been described as an "inflammatory" mutation closely associated with the development of cardiovascular diseases [17]. Secondly, by generating reactive oxygen species, the JAK2V617F mutation [18], which is present in about 10% of CMML patients [19], is considered an important inflammatory driver in MPNs and is associated with an increased risk of ischemic heart disease in MPNs [20].

The aim of this study was to test the hypothesis that patients with CMML have an increased risk of CVD due to accelerated atherosclerosis evoked by persistent monocytosis and sustained chronic inflammation. Only one very recent register-based study [21] has been presented on this topic, and they found a markedly increased risk for atherosclerotic disease-related mortality in 4699 CMML patients compared to breast and prostate cancer patients. We tested the hypothesis in CMML patients by comparing them to a reference cohort of patients with chronic lymphocytic leukemia (CLL) in a retrospective cohort study.

Materials and methods

Study population

We conducted a retrospective cohort study including 112 CMML patients and a reference population of 231 patients with chronic lymphocytic leukemia (CLL).

CMML patients were identified in two regions of Denmark (Region Zealand and The Capital Region of Denmark) from lists of pathology SNOMED (Systematized Nomenclature of Medicine–Clinical Terms) codes for CMML and CMML obs. pro. ($n = 200$). We assessed patients who were treated at three hematological departments (Roskilde Hospital, Rigshospitalet and Herlev Hospital) between January 1, 2003, and August 31, 2013, and whose medical records could be located ($n = 159$). Diagnosis was verified according to the WHO 2008 criteria [22] and patients for whom the criteria could not be verified were excluded ($n = 47$). Ultimately, 112 CMML patients were included (Fig. 1). Date of diagnosis was defined as the date of a bone marrow biopsy consistent with a diagnosis of CMML. For a small number of patients, the biopsy was consistent with CMML, but persistent peripheral monocytosis emerged later. For those patients, the date of diagnosis was defined as the onset date of persistent monocytosis with a prior biopsy consistent with CMML.

CLL patients were diagnosed at the Department of Hematology at Roskilde Hospital January 1, 2003–August 13, 2012, and identified by the use of computer-generated lists of all patients given the DRG (diagnosis-related group) code for CLL within that period ($n = 237$). Six patients from the initial list were excluded as they did not meet the diagnostic criteria for CLL, and ultimately 231 CLL patients were included as references (Fig. 2). They were originally used as a reference population in a study investigating the impact of smoking on Philadelphia-negative MPNs [23].

Inclusion started on the date of CMML/CLL diagnosis, and follow-up ended with occurrence of a cardiovascular event, death, or end of data collection.

Analyses were carried out on restricted cohorts (CMML = 84 and CLL = 186), in which patients with prior CVD were excluded, and on unrestricted cohorts (CMML = 112 and CLL = 231).

The study was reported to The Danish Data Protection Agency, approved by The Danish Health and Medicines Authority, and it was conducted in accordance with the ethical principles stated in the Declaration of Helsinki.

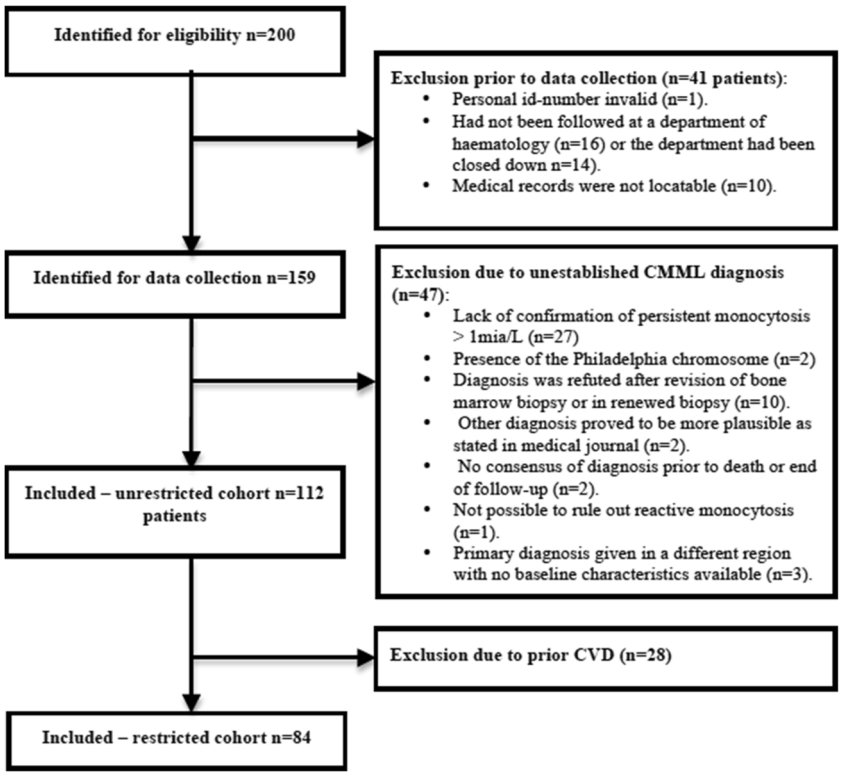

Fig. 1 Identification of CMML patients in unrestricted and restricted cohorts

Clinical end points

Information on baseline characteristics and cardiovascular endpoints was collected by systematically reviewing electronic and paper medical records. The data collection was performed between September and December 2013 for CMML and during 2012 for CLL.

Baseline characteristics (Table 1) were retrieved from the first visit to the department of hematology. For patients not diagnosed initially after the first visit, baseline characteristics were retrieved from records in relation to diagnosis.

The composite primary endpoint consisted of surrogate parameters of atherosclerosis as listed in Tables 2, 3, and 4.

Statistical analysis

Cox regression and 95% confidence intervals (CI) were used to analyze the difference in rate of occurrence of CVD within

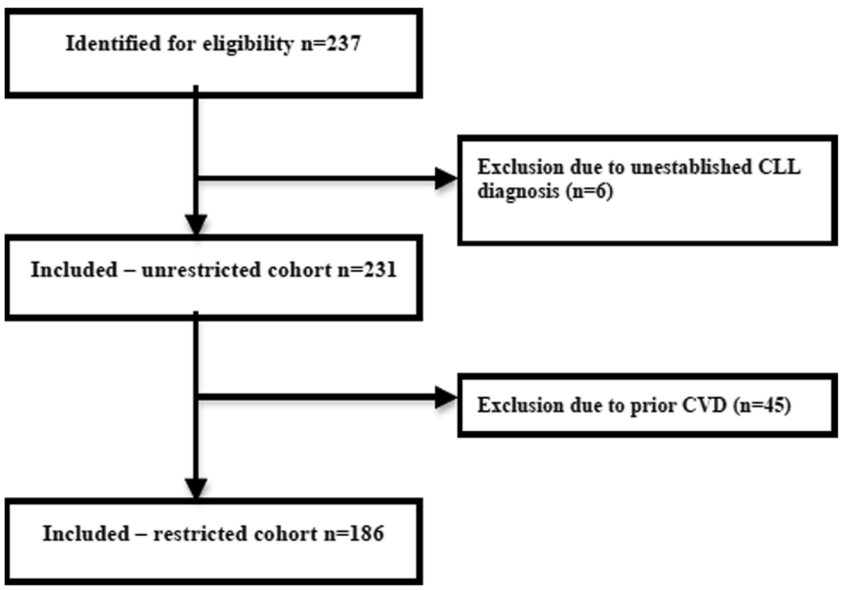

Fig. 2 Identification of CLL patients in unrestricted and restricted cohorts

Table 1 Baseline characteristics for restricted and unrestricted cohorts

Characteristics	Unrestricted cohort		Restricted cohort	
	CMML $n = 112$	CLL $n = 231$	CMML $n = 84$	CLL $n = 186$
CMML-1	82 (74)		63 (75)	
CMML-2	30 (26)		21 (25)	
Sex, *n* (%)				
Male	73 (65.2)	135 (58.4)	53 (63.3)	96 (51.6)
Female	39 (34.8)	96 (41.6)	31 (36.9)	90 (48.4)
Mean age (years) at diagnosis ± SD	73.6 ± 10.6	68.6 ± 10.3	72.3 ± 11.2	68.3 ± 10.5
Smoking status, *n* (%)				
Never	33 (31.4)	122 (54.0)	27 (34.6)	103 (56.9)
Former	45 (42.9)	46 (20.4)	32 (41.0)	34 (18.8)
Current	27 (25.7)	58 (25.7)	19 (24.4)	44 (24.3)
Missing	7	5	6	5
Alcohol intake, units/week, *n* (%)				
0–7	77 (74.8)	169 (76.1)	54 (71.1)	135 (75.8)
8–14	11 (10.7)	21 (9.5)	9 (11.8)	17 (9.6)
15–21	5 (4.9)	11 (5.0)	5 (6.6)	10 (5.6)
> 21	7 (6.8)	15 (6.8)	5 (6.6)	12 (6.7)
Former misuse	3 (2.9)	6 (2.7)	3 (3.6)	4 (2.2)
Missing	9	9	8	8
DM-II, *n* (%)	13 (11.6)	20 (8.2)	8 (9.5)	13 (7.0)
Hypertension, *n* (%)	35 (31.3)	82 (35.5)	22 (26.2)	63 (33.9)
Statin treatment, *n* (%)	20 (17.9)	51 (22.1)	5 (6.0)	17 (9.1)
Person years of follow-up	179	759	151.9	613.5
Follow-up (months), median (IQR)	10 (19.3)	30.7 (44.3)	10.8 (21.7)	30.5 (46.0)

CMML chronic myelomonocytic leukemia, *CLL* chronic lymphatic leukemia, *SD* standard deviation, *DM-II* type II diabetes, *IQR* interquartile range

the respective cohorts. Whichever of the cardiovascular endpoints occurring first in a patient was used in the statistical analyses. HRs were adjusted for sex, age at diagnosis, and baseline cardiovascular risk factors: smoking status, alcohol consumption, statin treatment, hypertension, and type II diabetes (DM-II).

Logistic regression was performed in the unrestricted cohorts in order to investigate a potential difference in the history of prior cardiovascular events between the groups.

Statistical analyses were carried out using IBM SPSS Statistics version 20, and in all analyses, alpha level of statistical significance was 0.05. Missing values for smoking status and alcohol consumption (see Table 1) were treated using the "Replace Missing Values" option and the method "Replace by mean of two nearby points."

Results

Baseline characteristics are shown in Table 1. The characteristics of the unrestricted cohorts were similar to those of the restricted cohorts except that there was a slight male predominance in the CLL group (M/F = 1.4), which was not present in the unrestricted cohort (M/F = 1.1).

In the analysis of the restricted cohorts, 9 (11%) CMML patients developed a cardiovascular event during 152 person years of follow-up, and during 614 person years of follow-up, 9 (5%) CLL patients developed a cardiovascular event (Table 2). Patients with CMML had an increased risk of developing CVD compared to patients with CLL, HR 3.39 (95% CI 1.36–8.43). However, after adjustment for possible confounders, no statistically significant difference was observed, HR 2.49 (95% CI 0.94–6.60). We also did the analysis excluding aortic aneurysms in the CVD category as they may be random findings, but this did not change the result, HR 2.44 (95% CI 0.84–6.91).

There was no statistically significant difference in the prevalence of CVD among CMML and CLL patients prior to diagnosis when adjusted for sex, age at diagnosis, and cardiovascular risk factors (Table 3).

We also analyzed occurrence of CVD in the unrestricted cohorts, which included patients with prior CVD. This was done in order not to underestimate a potential effect of monocytosis prior to diagnosis in patients diagnosed at an

Table 2 Rate of cardiovascular event occurrence after diagnosis of CMML compared to CLL in restricted cohorts

Cardiovascular diseases	CMML $n = 84$		CLL $n = 186$			
	n^a	%	n^a	%	Unadjusted HR (95% CI)	Adjusted[b] HR (95% CI)
Any CVD	9	10.7	10	5.4	3.39 (1.36–8.43)	2.49 (0.94–6.60)
IHD	1	1.2	2	1.1		
AMI	1	1.2	1	0.5		
Coronary stenosis	0	0	1	0.5		
Ischemic stroke	5	6	2	1.1		
TCI	2	2.4	1	0.5		
Claudicatio intermittens	0	0	4	2.2		
Aortic aneurysm	1	1.2	1	0.5		

CMML chronic myelomonocytic leukemia, *CLL* chronic lymphatic leukemia, *HR* hazard ratio, *CI* confidence interval, *CVD* cardiovascular disease (includes IHD, ischemic stroke, TCI, claudicatio intermittens, aortic aneurysm), *IHD* ischemic heart disease (AMI and treatment-requiring coronary artery stenosis), *TCI* transitory cerebral ischemia

[a] Number of patients with the given event

[b] HR adjusted for sex, age at diagnosis, DM-II, smoking, alcohol consumption, statin treatment, and hypertension

advanced disease state. In the unrestricted cohorts, 12 (11%) CMML patients and 16 (7%) CLL patients developed their first cardiovascular event after diagnosis within 179 and 759 person years of follow-up, respectively. This analysis resulted in an unadjusted HR of 3.01 (95% CI 1.41–6.44), and after adjustment, the effect remained significant with a HR of 2.34 (95% CI 1.05–5.20) (Table 4).

Baseline median monocyte count in the CMML group was 3.5×10^9/L ($1.0–67.5 \times 10^9$/L), and in the CLL group, 0.5×10^9/L (0–3.1) (data only available for 68% of CLL patients). We found no significant association between baseline degree of monocytosis and CVD in the restricted CMML cohort, HR 1.67 (95% CI 0.83–3.36).

Discussion

In this retrospective cohort study, we found a more than two-fold increased risk of developing CVD in CMML compared to CLL in unrestricted cohorts. These findings support the hypothesis that CMML patients have an increased risk of accelerated atherosclerosis evoked by persistent monocytosis

Table 3 History of cardiovascular events prior to diagnosis in CMML and CLL

Cardiovascular diseases	CMML $n = 112$		CLL $n = 231$			
	n^a	%	n^a	%	OR, unadjusted (95% CI)	OR, adjusted[b] (95% CI)
Any CVD	28	25	45	19.5	1.28 (0.81–2.36)	1.02 (0.56–1.84)
IHD	16	14.3	30	13		
AMI	12	10.7	21	9.1		
Coronary stenosis	4	3.6	9	3.9		
Ischemic stroke	8	7.1	9	3.9		
TCI	4	3.6	4	1.7		
Claudicatio intermittens	2	1.8	6	2.6		
Aortic aneurysm	3	2.68	2	0.9		

CMML chronic myelomonocytic leukemia, *CLL* chronic lymphatic leukemia, *OR* odds ratio, *CI* confidence interval, *CVD* cardiovascular disease (includes IHD, ischemic stroke, TCI, claudicatio intermittens, aortic aneurysm), *IHD* ischemic heart disease (AMI and treatment-requiring coronary artery stenosis), *TCI* transitory cerebral ischemia

[a] Number of patients with the given event. Note that some patients had more than one event, and therefore, the columns do not add up to the number of "Any CVD"

[b] OR adjusted for sex, age at diagnosis, DM-II, smoking status, alcohol consumption, statin treatment, and hypertension

Table 4 Rate of cardiovascular event occurrence after diagnosis of CMML compared to CLL in unrestricted cohorts

Cardiovascular diseases	CMML $n = 112$		CLL $n = 231$			
	n[a]	%	n[a]	%	Unadjusted HR (95% CI)	Adjusted[b] HR (95% CI)
Any CVD	12	10.7	16	6.9	3.01 (1.41–6.44)	2.34 (1.05–5.20)
IHD	2	1.7	6	2.6		
AMI	2	1.7	5	2.2		
Coronary stenosis	0	0	1	0.4		
Ischemic stroke	6	5.4	2	0.9		
TCI	2	1.8	2	0.9		
Claudicatio intermittens	0	0	4	1.7		
Aortic aneurysm	2	1.8	2	0.9		

CMML chronic myelomonocytic leukemia, *CLL* chronic lymphatic leukemia, *HR* hazard ratio, *CI* confidence interval, *CVD* cardiovascular disease (includes IHD, AMI, ischemic stroke, TCI, claudicatio intermittens, aortic aneurysm), *IHD* ischemic heart disease (AMI and treatment-requiring coronary artery stenosis), *TCI* transitory cerebral ischemia

[a] Number of patients with the given event

[b] HR adjusted for sex, age at diagnosis, DM-II, smoking, alcohol consumption, statin treatment, and hypertension

and sustained chronic inflammation. When we analyzed the restricted cohorts with exclusion of patients with cardiovascular events prior to diagnosis of CMML or CLL, no significant association was observed after adjustment for potential confounders. Our results from the unrestricted cohorts are in line with the findings by Molenaar et al. [21], who find increased risks of heart disease-related mortality and cardiovascular disease-related mortality in CMML patients.

We considered several reasons for the difference between the results in the restricted and unrestricted cohorts. First, statistical power was lower in the analysis of the restricted cohorts. Second, median survival time in CMML patients was 16.9 months (results not shown), and it may be argued that the time of exposure to monocytosis was too short to result in CVD. On the other hand, undetected monocytosis prior to diagnosis, as discussed below, would result in a longer "true" exposure time, which may be reflected by the results in the unrestricted cohorts. Third, the monocytes increased in CMML are of the "classical monocyte" subset [24], whereas the monocyte subset related to atherosclerosis has not been clearly identified [14, 25, 26]. Fourth, the lack of an association in the restricted cohorts could reflect the course of events indicating that monocytosis identified as a risk factor for atherosclerosis might only be present secondary to plaque formation, and therefore, monocytosis per se may not induce plaque formation.

A number of CMML patients may possibly have had unrecognized CMML or even unexplained isolated monocytosis—"essential monocytosis"—for several years prior to diagnosis of CMML. An increased cardiovascular risk possibly appears with the occurrence of clonal hematopoiesis of indeterminate potential (CHIP), i.e., monocytosis, that may precede CMML, and therefore, we found it relevant to analyze unrestricted cohorts. Exclusion of patients with prior cardiovascular events would also exclude patients who may have had a cardiovascular event caused by the increased risk thought to evolve from unrecognized CMML or isolated monocytosis prior to the CMML diagnosis. Thus, the results from the restricted cohorts could underestimate the effect size. This is in line with the considerations by Molenaar et al. who find that their results suggest that CMML patients already have cardiovascular disease at the time of diagnosis [21]. On the other hand, patients with CVD prior to diagnosis already have atherosclerosis and are at increased risk of developing a second cardiovascular event. A higher percentage of CMML patients had prior CVD, and the results in the unrestricted cohorts could therefore overestimate the effect size if there is no actual effect of potentially undetected monocytosis on the formation of atherosclerosis. Indeed, the considerations of essential monocytosis prior to diagnosis are supported by the high number of mutations recorded at the time of diagnosis of CMML [27]. These mutations have likely evolved over several years, possibly along with undetected CHIP, similar to the biological continuum in MPNs evolving from JAK2V617F-positive essential thrombocythemia over polycythemia vera to the advanced myelofibrosis stage.

As reference group, we used CLL patients because they have a chronic hematological cancer and are likely more similar to CMML patients than healthy individuals. This is important if an unknown common association between CVD and cancer exists. It is also of great importance that both groups have been followed at hematological departments, making possible standardized data collection, which practically eliminates detection bias. However, it has been proposed that CLL is also associated with an inflammatory milieu [28]. A potential contribution from inflammation in CLL patients that may

make them more prone to develop cardiovascular events would only reduce the effect size. Importantly, to our knowledge, there are no studies reporting a negative association of CVD in CLL.

Patients were included according to the 2008 WHO criteria because they were applied during data collection. They differ from the 2016 criteria in requiring monocytes account for ≥ 10% of WBC count in addition to absolute peripheral blood monocytosis of > 1 mia/L [1]. When 2016 criteria were applied, 13 CMML patients had monocytosis accounting for ≤ 10% of WBC count. However, none of these patients had cardiovascular events neither before nor after diagnosis of CMML, and accordingly, we would have possibly found a stronger effect estimate had these patients not been included.

The strengths of this study include the fact that it was performed at only three institutions, and the two groups of patients were diagnosed within almost the same time period. Patients were identified from coding systems, which eliminates selection bias in the initial identification of patients. Recall bias is not an issue because data were retrieved from medical journals. Selection bias due to loss to follow-up practically does not exist, as patients were traceable via their electronic medical journal even if they changed hospitals.

Limitations to the study include the lack of systematically blinded clinical verification of diagnosis. Data collection for CLL and CMML patients was carried out by two different individuals giving rise to a possibility for selection bias, but we used the same system of medical records thereby minimizing the risk. Sample sizes were small due to disease rarity, cardiovascular events were rare, and follow-up time was relatively short, especially for CMML patients due to short survival time. Baseline monocyte levels were known for only 68% of CLL patients, and we did not use monocytosis in the CLL group as exclusion criteria. Persistent monocytosis in the reference group would possibly weaken the effect estimate, but as the mean monocyte count in the CLL group was 0.5×10^9/L, this type of bias seems unlikely. Baseline hemoglobin levels were known for only 72% of CLL patients, and we did not adjust the analyses for baseline hemoglobin levels. Median hemoglobin level at baseline was 10.8 g/dL (IQR 9.8–12.4 g/dL) for CMML and 13.7 g/dL (IQR 12.9–14.8 g/dL) for CLL, and it cannot be ruled out that the lack of adjustment for anemia could bias the results. However, hemoglobin levels possibly also reflect the state of disease progression in CMML; thus, the load of chronic inflammation and monocytosis, and adjustment for hemoglobin levels may therefore on the other hand hide an actual effect. The same considerations apply for CRP levels, which were only known for 76% of CMML patients (median 12 mg/L, IQR 3.9–55.5 mg/L) and 64% of CLL patients (median 2.1 mg/L, IQR 1.0–5.0 mg/L). Detailed treatment data was unfortunately not available, and therefore, we do not present data on that topic. Also, given the retrospective nature of the study, only limited data on molecular information was available. However, it is worth mentioning that JAK2V617F status had been analyzed in 40 CMML patients (35.7%) and 7 of those had positive JAK2V617F-status (17.5%). This higher percentage is most probably a result of selection bias, and other studies report lower occurrences [19, 29].

The perspectives of our findings in relation to the previous mentioned TET2 mutation are several. First, taking into account that the TET2 mutation is associated with the development of atherosclerosis [17], our findings may actually reflect this linkage between the TET2 mutation, chronic inflammation, and atherosclerosis in CMML. The TET2 mutation has been shown to give rise to impaired resolution of inflammation by fostering the production of several inflammatory cytokines such as IL-1β and IL-6 [30], which are elevated in CMML [13]. Second, in a murine model, loss of TET2 has been shown to worsen JAK2V617F-induced disease eliciting prolonged leukocytosis and extramedullary hematopoiesis with splenomegaly and a shorter survival. Of note, double mutant (JAK2V617F mutation and loss of TET2) myeloid cells were more likely to be in a proliferative state than JAK2V617F single-mutant myeloid cells [31]. Thus, loss of TET2 may be a disease accelerator in those CMML patients who also harbor the JAK2V617F mutation, and even in the absence of the JAK2V617F mutation, patients with TET2 mutation might represent a subgroup of CMML patients with a higher risk of CVD.

Conclusion

We found that CMML was associated with an increased relative risk of developing CVD. Our findings support the hypothesis that patients with CMML have a propensity to develop accelerated atherosclerosis due to persistent monocytosis and chronic inflammation. In this context, the assumption that patients with CMML may actually have carried their disease for several years prior to diagnosis, perhaps evolving from a state of essential monocytosis only, is highly relevant to consider.

Based on our findings and the findings by Molenaar et al. [21], it is interesting to consider if CMML patients would benefit from low-dose aspirin with regard to CVD and mortality rate similar to MPN patients [32].

Our considerations on essential monocytosis as a precursor stage of CMML existing several years before the CMML diagnosis as well as the impact of TET2 and JAK2V617F mutations in CMML patients call for further epidemiological studies investigating the possible link between chronic inflammation, monocytosis, and atherosclerosis in patients with CMML.

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Authors' contribution HCH and MVE provided the conception and design of the study, acquisition and interpretation of data, and drafting and revision of the article. ALS provided the acquisition of data, statistical assistance, and revision of the article. All authors gave their final approval of the version to be submitted.

Compliance with ethical standards

The study was reported to The Danish Data Protection Agency, approved by The Danish Health and Medicines Authority, and it was conducted in accordance with the ethical principles stated in the Declaration of Helsinki.

Conflict of interest ALS has received a grant from the Danish Cancer Society under Grant no. R54-A3264. HCS has received research funding from Novartis Oncology. MVE has no conflict of interest to declare.

The sources of funding had no involvement in the study design, collection, analysis, or interpretation of data; writing of the report; or the decision to submit the work for publication.

Ethical approval For this retrospective study, formal consent is not required.

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