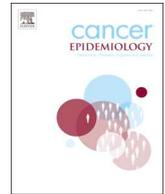




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Trends of incidence and survival of patients with chronic myelomonocytic leukemia between 1999 and 2014: A comparison between Swiss and American population-based cancer registries

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ABSTRACT

Background: Chronic myelomonocytic leukemia (CMML) is a rare hematopoietic malignancy. Treatment with hypomethylating agents (HMA) was introduced between 2004 and 2006 but its impact on population-based survival remains controversial. The aim of this study was to investigate epidemiological characteristics and survival before and after introduction of HMA treatment.

Methods: We performed a population-based analysis of CMML cases reported to the *Cantonal Cancer Registries* in Switzerland (SWISS) and the Surveillance, Epidemiology, and End Results (SEER) Program from the United States for 1999–2006 (before HMA) and 2007–2014 (after HMA). Time trends were compared for these two time periods.

Results: 423 and 4144 new CMML cases were reported to the SWISS and SEER registries, respectively. We observed an increasing proportion of older patients ≥ 75 years in the SWISS (50.3%–62.3%) compared to a decreasing one in the SEER population (59.1%–55.1%). Age standardized incidence-rates were similar and remained stable in both countries (0.32–0.38 per 100'000 py). Relative survival (RS) improved significantly in the SEER (3 years 27%–37%; 5 years 19%–23%; $p < 0.001$ for both) but remained stable in the SWISS population (3 years 48% to 40%; 5 years 34% to 26%; n.s. for both).

Conclusions: With the exception of opposing age-trends, epidemiologic characteristics are similar in both countries and comparable to other population-based registries. RS remains poor and different time trends of population-based survival cannot be faithfully explained by HMA but most likely by changes in diagnostic accuracy within prognostically distinct age-groups.

Abbreviations: AML, acute myeloid leukemia; allo HSCT, allogenic hematopoietic stem cell transplantation; ASR, age-standardized incidence-rate; AZA, 5-Azacitidine; CC, conventional care; CI, confidence interval; CCR, cantonal cancer registries; CMML, chronic myelomonocytic leukemia; CIR, crude incidence-rate; DEC, decitabine; ESA, erythropoiesis stimulating agents; FDA, food and drug administration; HMA, hypomethylating agents; MD-CMML, MDS-type CMML; MDS, myelodysplastic syndromes; MP-CMML, MPN-type CMML; MPN, myeloproliferative neoplasms; NICER, National Institute for Epidemiology and Cancer Registration; OS, observed survival; py, person-years; RS, relative survival; SC, supportive care; SEER, surveillance, epidemiology, and end results program; SFSO, Swiss Federal Statistics Office; SWISS, cantonal cancer registries in Switzerland

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1. Introduction

Chronic myelomonocytic leukemia (CMML) is a rare hematopoietic malignancy characterized by peripheral monocytosis with overlapping features between myeloproliferative neoplasms (MPN) and myelodysplastic syndromes (MDS). Depending on the predominant presentation, CMML can be sub-classified into a myelodysplastic (MD-CMML, $WBC < 13 \times 10^9/L$) or myeloproliferative (MP-CMML, $WBC \geq 13 \times 10^9/L$) subtype [1]. Reactive monocytosis may be difficult to distinguish from CMML. Therefore, several follow-up investigations may be required for the correct diagnosis with integration of quantitative and qualitative features of peripheral blood and bone marrow. Multiparameter flow cytometry can contribute to find the correct diagnosis, but plays a minor role. Also conventional cytogenetics frequently reveal a normal karyotype at initial stages of the disease, whereas molecular genetics contributes increasingly to the identification of clonality. Difficulties may as well arise in the discrimination of CMML from other myeloid malignancies, such as advanced MDS, secondary acute myeloid leukemia (s-AML), or other MDS/MPN overlap syndromes.

The incidence rate of CMML ranges from 0.3 to 0.7 per 100,000 person-years (py) with a median age at diagnosis above 70 years (yrs) and a male predominance [2–6]. Due to the demographic ageing of the general population, an increasing number of CMML patients is expected in the future with a growing impact on health system resources [7]. Population-based outcome data was recently reported from the *Surveillance Epidemiology and End Results* (SEER) database including 2238 CMML patients diagnosed between 2003 and 2013. Median survival declined with increasing age, ranging from 25 (age 20–29 yrs) to 11 months (age > 80 yrs), and the main causes of death comprised progression into secondary acute myeloid leukemia (AML), bleeding and infection [3].

Prognostic factors for transformation into secondary AML and survival include peripheral blood cell counts, serum lactate dehydrogenase, percentage of bone marrow blasts, specific cytogenetic abnormalities as well as somatic mutations in myeloid driver genes (e.g. *ASXL1*) [8,9]. By next-generation sequencing (NGS), molecular mutations are detectable in > 90% of CMML patients. The somatic mutation patterns in patients with CMML are heterogeneous and include markers, which are also encountered in other myeloid malignancies such as *SRSF2*, *CBL*, *EZH2*, *JAK2V617F*, *KRAS/NRAS*, *RUNX1*, and *TET2* [10].

At present, the only curative treatment remains intensive chemotherapy followed by allogeneic hematopoietic stem cell transplantation (allo HSCT). Due to the toxicity of this approach, including infections, severe graft versus host disease, and other organ toxicities, allo HSCT remains reserved for a minority of fit and mostly younger patients [11]. Treatment recommendations for CMML patients are mainly extrapolated from experiences gained in MDS and MPN patients, as randomized trials are scarce and difficult to perform in this rare disease. Palliative treatment options include supportive care with transfusions and erythropoiesis stimulating agents (ESA) as well as cytoreductive treatment with hydroxyurea [12]. Other experimental therapies, such as the JAK inhibitor ruxolitinib, are currently under investigation [13]. In the presence of excess of blasts > 5% or other poor prognostic factors, treatment with hypomethylating agents (HMA), such as 5-azacitidine (AZA) or decitabine (DEC), are used for CMML patients. The recommendation of HMA treatment is based on results of three clinical MDS trials, which cumulatively comprise about 20 CMML patients that were finally randomized to HMA therapy [14–16]. In the United States (US) AZA and DEC were approved by the Food and Drug Administration (FDA) for the treatment of all subtypes of MDS, including CMML in 2004 and 2006, respectively [17]. DEC is not approved for treatment of MDS or CMML in Europe or Switzerland. So far, only one small phase 1 study has been published that specifically investigated DEC in CMML patients [18]. Additional efficacy data derives from aggregated evidence of several phase 2 studies [19,20] as well as retrospective

analyses in cohorts and population-based cancer registries [21–24]. Overall, responses to HMA range from 35 to 70% in CMML patients with improvement of survival of 6 months in responders [24]. Both HMA have similar response rates, with higher complete responses reported for DEC compared to AZA (58% vs 20%) in retrospective studies [23,24]. However, it remains controversial, whether introduction of HMA treatment improved survival of CMML patients on a population-based level.

Here we report demographic characteristics, annual cases, incidence and survival of CMML patients from population-based cancer registries in Switzerland (SWISS) and the SEER program from the US. Trends were compared for 1999–2006 and 2007–2014, representing time periods before and after introduction of HMAs for treatment of CMML patients, respectively.

2. Methods

2.1. Study design

We performed a comparative study from two population-based cancer registry databases from Switzerland and the US. CMML (ICD-O-3 code 9945/3) cases reported to the *Cantonal Cancer Registries* (CCRs) in Switzerland [25] and the SEER database in the US [26] between 1999 and 2014 were included. In both databases, cases diagnosed prior to the introduction of the third revision of the ICD-O classification published in 2000, were recoded from ICD-O-2 to ICD-O-3. The ICD-O classification does not provide different codes for CMML-0, -1 and -2. Data was stratified for the two time periods 1999–2006 (before HMAs) and 2007–2014 (after HMAs), based on the approval status of HMAs in the US (2004 and 2006) and Switzerland (2006). Data from both registries was analysed equivalently by the *National Institute for Epidemiology and Cancer Registration* (NICER) as described below.

2.2. Data source from Swiss and US population-based cancer registries

During our observation period the population increased similarly in Switzerland from 7.2 to 8.2 million [27] and in the US from 279.0 to 318.6 million (+14% for both) [26]. Over the course of the study period, an increasing number of cantons in Switzerland opened cancer registries providing incidence data to the Swiss data pool. The time-periods covered by each canton are shown in *Supplementary Table 1*. In 1999, 13 out of 26 cantons registered cancers, covering 57.7% of the Swiss population. As of 2014, this number increased to 23 cantons, covering 88.2%. Age and sex distribution from the population covered by the CCRs was shown to be identical to the general Swiss population [28]. Vital status follow-up was provided by all CCRs. Vital status information was collected by passive (linkage with federal mortality data) and active follow-up (verification of vital status with the cantonal registration offices). The *Swiss Federal Statistics Office* (SFSO) provided canton-specific mid-year estimates of the general population and mortality statistics referring to all persons with permanent residence status in Switzerland according to age, sex, and calendar year. The microscopically verified cases were mainly reported by pathologists and accounted for 94.2% and 97.4% for the two time periods, respectively. CMML was reported on death certificates in only two patients for the whole observation time. The Swiss data were compared to data extracted from the SEER database for 1999–2006 [29] and 2007–2014 [30], respectively. Details on the SEER data source are published elsewhere [26].

2.3. Statistical analysis

Crude and age-specific incidence-rates were calculated using mid-year population estimates provided by the SFSO or SEER, stratified by sex and age, as defined. The estimated annual CMML cases for all of Switzerland and US were extrapolated by applying the observed

incidence rates to the population of all cantons/states under the assumption of homogeneity between cantons/states. Mortality statistics were not analyzed because of the limited number of reported deaths due to CMML in Switzerland. Age-standardized incidence-rates were calculated using the old *European Standard Population* as reference for the Swiss and US population [31,32]. Observed survival (OS) was estimated using the Ederer II method [33]. Relative survival (RS) and corresponding 95% confidence intervals (95% CI) were calculated from CMML cases reported to the SWISS CCRs and SEER for consecutive time intervals up to 5 years after diagnosis. RS was calculated as the ratio of the OS of cancer cases and the expected survival of people in the general population using the period approach [34]. Relative survival estimates were age-standardized using weights (standard 1) from the International Cancer Survival Standards [35]. Age-stratified analyses were performed for the age categories < 75 years and 75+ years. Significance test for RS was applied according to the method described by Parkin and Hakulinen [36]. Statistical analysis of SWISS data was performed with Stata/MP version 15 (STAT Corp., TX, USA). The SEER data was analyzed using the SEER*Stat software version 8.3.5 [37].

3. Results

3.1. Study population

In total, 423 and 4144 new CMML cases were registered in the SWISS and SEER population-based registries during the complete observation time (Table 1): 155 and 1280 cases for the years 1999 to 2006, and 268 and 2864 cases for the years 2007 to 2014, respectively. The male predominance of CMML was confirmed and was slightly more prominent in the SWISS than the SEER population (65.0% vs 62.8%). Median age at diagnosis in the different time-periods ranged from 74 to 77 yrs in the SWISS compared to 75–79 yrs in the SEER population. Time-trends over the two time periods were different, with an increasing trend of older patients ≥ 75 yrs in the SWISS (50.3% to 62.3%) compared to a decreasing trend in the SEER population (59.1% to 55.1%). This resulted in a general increase of median age at diagnosis of 2 years in the SWISS and a decrease of 1 year in the SEER population,

respectively. In general, females were diagnosed more frequently at higher age compared to males (females vs males 75+ yrs; SWISS: 60.1% vs 56.7%; SEER: 61.8% vs 53.2%). In summary, age and sex distribution were generally comparable between the two registries, with the exception of opposite age trends at diagnosis in the SWISS (increasing) and the SEER (decreasing) during the observation time.

3.2. Incidence

The estimated annual numbers of new CMML cases increased from 32.75 to 48 (+46.6%) in Switzerland and from 1281.2 to 1372.9 (+7.1%) in the US over the observation period (Table 2). Age-specific crude incidence-rate (CIR) of CMML cases reported to SWISS and SEER cancer registries showed a similar pattern with a steep increase after the age of 50 yrs and a peak at the age > 80 yrs (Fig. 1). Age-specific CIR increased markedly in the SWISS over the study period, but remained virtually unchanged for the SEER population. Accordingly, the CIR increased in Switzerland from 0.45 to 0.61 per 100'000 py but remained stable in the US at 0.4 per 100,000 py (Table 2). In contrast, the age-standardized incidence rates (ASR) were comparable in both countries and remained stable during the observation period (SWISS: 0.32 (95%-CI: 0.27 – 0.37) and 0.38 (0.34-0.43) per 100,000 py; SEER 0.37 (0.35-0.39) and 0.35 (0.33-0.36) per 100,000 py). In concordance with the male predominance, the ASR were higher for males compared to females in both countries (0.51-0.57 vs 0.14-0.22 per 100'000 py). In summary, the increase of annual cases and age-specific CIR was more prominent in Switzerland compared to the US but the ASR was comparable in both countries and remained stable during the observation period.

3.3. Observed and relative survival

The OS and RS were better in the SWISS compared to the SEER population in the first period 1999–2006 and reached similar values in the second period 2007–2014 (Supplementary tables 2 and 3, Fig. 2 for RS). No significant change in RS at 3 yrs and 5 yrs was found between the two time-periods in the SWISS population (3 yrs: 48% vs 40%; 5 yrs:

Table 1
Characteristics of CMML cases reported to SWISS and SEER cancer registries for 1999–2006 and 2007–2014.

A) SWISS	1999 – 2006			2007 – 2014			1999-2014		
	n	%	median age [*]	n	%	median age [*]	n	%	median age [*]
Males	104	67.1	74 [67-80]	171	63.8	77 [71-82]	275	65.0	76 [70-82]
0-74 years	55	52.9		64	37.4		119	43.3	
75+ years	49	47.1		107	62.6		156	56.7	
Females	51	32.9	76 [68-81]	97	36.2	77 [69-84]	148	35.0	77 [69-83]
0-74 years	22	43.1		37	38.1		59	39.9	
75+ years	29	56.9		60	61.9		89	60.1	
Both sexes	155	100	75 [67-81]	268	100	77 [71-83]	423	100	76 [70-82]
0-74 years	77	49.7		101	37.7		178	42.1	
75+ years	78	50.3		167	62.3		245	57.9	
B) SEER	1999 – 2006			2007 – 2014			1999-2014		
	n	%	median age [*]	n	%	median age [*]	n	%	median age [*]
Males	790	61.7	76 [69-81]	1,813	63.3	74 [67-82]	2,603	62.8	75 [67-82]
0-74 years	355	44.9		864	47.7		1,219	46.8	
75+ years	435	55.1		949	52.3		1,384	53.2	
Females	490	38.3	79 [71-84]	1,051	36.7	77.5 [69-84]	1,541	37.2	78 [70-84]
0-74 years	168	34.3		421	40.1		589	38.2	
75+ years	322	65.7		630	59.9		952	61.8	
Both sexes	1,280	100	76 [70-82]	2,864	100	75 [68-83]	4,144	100	76 [68-83]
0-74 years	523	40.9		1,285	44.9		1,808	43.6	
75+ years	757	59.1		1,579	55.1		2,336	56.4	

* Median age in years with inter-quartile ranges.

Table 2
Incidences of CMML reported to SWISS and SEER cancer registries for 1999–2006 and 2007–2014.

A) SWISS	1999-2006			2007-2014		
	Cases*	CIR	ASR [95% CI]	Cases*	CIR	ASR [95% CI]
Males	22.8	0.62	0.51 [0.42-0.62]	30.9	0.79	0.57 [0.48-0.66]
0-74 years		0.35	0.31[0.24-0.41]		0.32	0.26[0.20-0.33]
75+ years		5.29	5.26[3.88-6.98]		8.04	7.96[6.51-9.64]
Females	10.6	0.29	0.17 [0.13-0.24]	17	0.43	0.25 [0.20-0.31]
0-74 years		0.14	0.11[0.07-0.17]		0.18	0.14[0.10-0.20]
75+ years		1.75	1.76[1.17-2.54]		2.78	2.80[2.12-3.64]
Both sexes	32.75	0.45	0.32 [0.27-0.37]	48	0.61	0.38 [0.34-0.43]
0-74 years		0.24	0.20[0.16-0.25]		0.25	0.20[0.16-0.24]
75+ years		3.01	3.01[2.38-3.77]		4.79	4.83[4.11-5.63]

B) SEER	1999-2006			2007-2014		
	Cases*	CIR	ASR [95% CI]	Cases*	CIR	ASR [95% CI]
Males	787.8	0.51	0.56 [0.52-0.60]	869.8	0.53	0.51 [0.49-0.54]
0-74 years		0.24	0.30[0.27-0.34]		0.27	0.28[0.26-0.30]
75+ years		6.70	6.61[6.00-7.27]		6.22	6.11[5.73-6.53]
Females	493.4	0.31	0.23 [0.21-0.26]	503.0	0.30	0.22 [0.20-0.3]
0-74 years		0.11	0.12[0.10-0.14]		0.13	0.12[0.10-0.14]
75+ years		3.03	2.91[2.60-3.25]		2.68	2.54[2.34-2.75]
Both sexes	1281.2	0.40	0.37 [0.35-0.39]	1372.9	0.41	0.35 [0.33-0.36]
0-74 years		0.17	0.21[0.19-0.22]		0.20	0.20[0.19-0.21]
75+ years		4.42	4.32[4.01-4.64]		4.08	3.96[3.77-4.17]

ASR: age-standardized incidence-rates per 100,000 py (old European standard).

* Cases: Extrapolated number of annual cases on nationwide level derived from extrapolation of regional data. CIR: crude incidence-rates per 100'000 py.

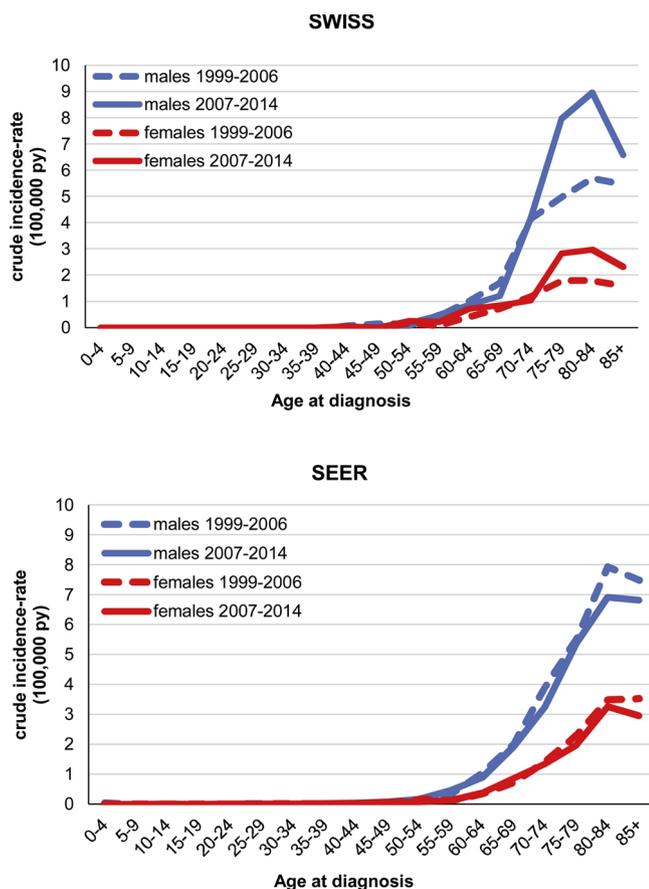


Fig. 1. Age-specific crude incidence-rates of CMML cases reported to SWISS and SEER cancer registries for 1999–2006 and 2007–2014.

34% vs 26%; n.s. for both). In contrast, a significant improvement of RS could be demonstrated at 3 yrs and 5 yrs in the SEER population (3 yrs: 27% vs 37%; 5 yrs: 19% vs 23%; $p < 0.001$ for both). The significant improvement of RS was mainly caused by younger patients with 0–74 yrs (3 yrs: 29% vs 41%; 5 yrs: 20% vs 28%; $p < 0.001$ for both), while changes in RS were modest and not significant in older patients with 75+ yrs (3 yrs: 23% vs 28%; 5 yrs: 14% vs 16%; n.s. for both) (*Supplementary tables 2 and 3, Fig. 3 for RS*). In summary, a significant improvement of RS in younger patients could be observed in the SEER but not in the SWISS population-based cancer registry over the observation period. Intriguingly, the RS were similar in both countries for the last time-period 2007–2014.

4. Discussion

In this study, we report population-based, epidemiologic data of CMML patients diagnosed in Switzerland and the US between 1999 and 2014. We compared the time-trends of demographic characteristics, annual cases, incidences and survival for the time-periods before (1999–2006) and after (2007–2014) introduction of HMAs for treatment of patients with CMML.

Our time trend analysis identified a disproportional increase of estimated annual cases in Switzerland (46.6%) compared to the US population (7.1%), based on a similar population growth of 14% in both countries. Median age at diagnosis, sex distribution and incidences from the SWISS and SEER populations are generally comparable to other reports from population-based registries, as summarized in *Supplementary table 4*. The demographic composition of both populations (age and sex) were comparable, with the exception of opposite time-trends of median age at diagnosis. We found an increasing median age at diagnosis in the SWISS in contrast to a decreasing in the SEER population. CMML is generally diagnosed at higher age [2–6]. The higher frequency of younger patients < 75 yrs of age observed in the SWISS population in 1999–2006 is, therefore, unusual and may explain the better OS and RS in Switzerland in the first time period. In contrast,

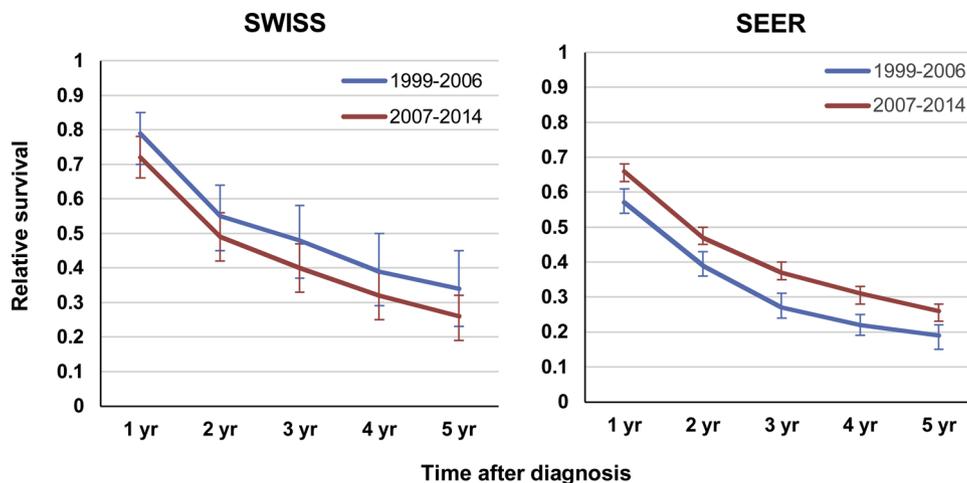


Fig. 2. Relative survival of CMML reported to SWISS and SEER cancer registries for 1999–2006 and 2007–2014.

an increasing proportion of patients < 75 yrs of age were observed in the SEER population in 2007–2014, which could have influenced the improvement of OS and RS in the US in the second time period. Based on the unusual predominance of CMML patients < 75 yrs of age in the SWISS population in the first time period, we conclude that a better case ascertainment and classification of CMML in the elderly population has contributed to the increase of annual cases and incidence in Switzerland for the second time period. On the contrary, more patients < 75 yrs were diagnosed in SEER in the second time period, suggesting an increased diagnostic awareness in younger CMML patients in the US over time. The ASRs remained comparable and stable for both populations, reflecting that differences in annual cases and CIR are mainly caused by population size, demographic composition (age and sex), or diagnostic accuracy, and not by new etiological factors.

The OS and RS observed in the SWISS and SEER populations are generally comparable to other population-based registries (see

Supplementary table 4). As reported by others [3], our analysis of the SEER population confirmed a significant improvement of RS at 3 yrs as well as 5 yrs from 27% and 19% (1999–2006) to 37% and 26% (2007–2017), respectively. The improved RS remained significantly better in the subgroup analysis of the CMML patients < 75 yrs but not in the older CMML population. In contrast, no improvement of RS could be observed in our SWISS population, which is in analogy to a recent report from the Dutch population-based cancer registry comparing similar time-periods (2001–2006 vs 2007–2012) [5]. Intriguingly, RS in the SWISS and SEER population-based cancer registries reached the same range in 2007–2014. This observation may indicate that changes in diagnostic accuracy within prognostically distinct age-groups could explain the different time-trends of RS observed between the SWISS and SEER populations. However, we cannot exclude that differences may be related to inevitable fluctuations within the small Swiss CMML population caused by low case numbers and variable diagnostic accuracy.

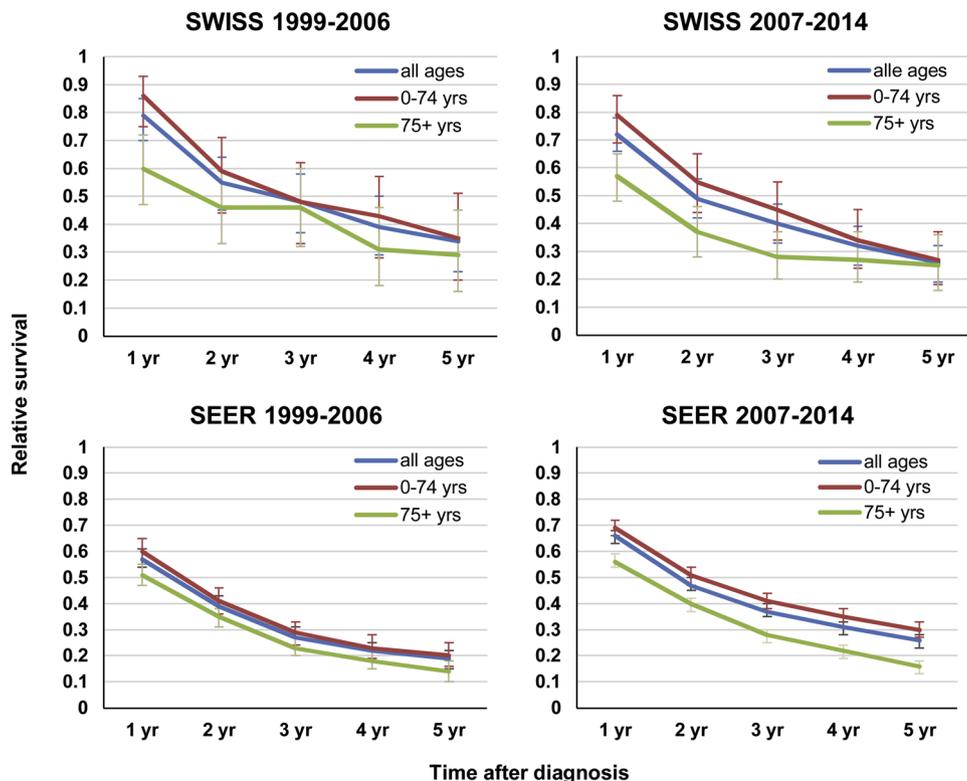


Fig. 3. Age-specific relative survival of CMML patients reported to SWISS and SEER cancer registries for 1999–2006 and 2007–2014.

For the present study, direct information on treatments of patients was not available. Relevant interacting factors, such as median age at diagnosis and treatment allocation, can be corrected by propensity matching for the interpretation of population-based data. Zeidan et al. performed such an analysis using combined SEER-Medicare data from 1378 CMML patients (age ≥ 66 years) diagnosed between 2001 and 2011 [24]. The median OS of the entire cohort was 13 months (95% CI, 12–14 months). Regardless of the year of diagnosis, OS for patients receiving HMAs treatment was 17 months compared to 11 months for untreated patients. The use of HMAs was associated with a reduction of 28% in the risk of death, whereas supportive care remained without impact on OS [24]. Propensity matching eliminates known confounding factors but may be limited for the correction of other inconspicuous factors that may influence treatment allocation. This study from Zeidan et al. provides the most robust evidence from population-based, observational data for a survival benefit of HMAs treatment in CMML patients. However, treatment remains limited for CMML patients and only a minority of patients can proceed to the potentially curative treatment option of allo HSCT. Due to the rarity of CMML, clinical trials are difficult to perform exclusively in this entity. Nevertheless, collaborative clinical trials on an international level should be encouraged, in order to provide robust data on efficacy and safety of treatment, especially for the elderly population that is preferentially affected by the disease and is currently rarely offered treatment beyond supportive care.

In conclusion, our population-based study shows similar ASR and indicates that different incidences in CMML are mainly caused by population growth, demographic factors as well as changes in diagnostic awareness but not by additional etiological risk factors. Demographic factors are generally corrected for in the RS analysis [35] but differences of diagnostic accuracy in prognostically distinct age-groups may lead to earlier identification of cases and could influence population-based survival data [38]. Earlier performance of NGS within the current diagnostic workflow in patients with suspicious monocytosis may result in an earlier and more homogeneous diagnosis of CMML. However, difficulties in discriminating some CMML cases from other myeloid malignancies will persist, as the somatic mutation profiles do overlap between different myeloid entities. In addition, the physicians' reporting adherence of CMML cases to Cancer Registries may show variances. Our study underscores that survival of CMML patients remains generally poor and has not substantially improved over the last two decades, despite the introduction of HMA. The different time trends of population-based survival in CMML patients cannot be faithfully explained by introduction of HMA treatment but are most likely influenced by changes in diagnostic accuracy within prognostically distinct age-groups. This does not necessarily imply that single patients do not profit from HMA treatment but that the potential benefit of treatment has not reached a population-based impact.

Population-based studies have reported that only one fifth of all CMML patients receive disease modifying treatment and reasons for this observation remain unclear [5,7]. A potential explanation is that physicians may be reluctant in using treatment without sufficient evidence from clinical trials. Under these circumstances, more information on treatment allocation is indispensable to investigate the influence of HMA on population-based survival. Data on treatment is currently not available from the Swiss CCRs. Due to the restrictive data protection law in Switzerland, a correlation with patients' treatment information derived from health insurances, as performed by Zeidan et al. in the US, is currently not possible. The Swiss CCR data will be soon complemented with information on first line treatment, which will increase the utility. However, responses and side-effects will remain inaccessible. Therefore, a prospective registry was implemented in Switzerland that allows inclusion of patients with MDS and related disorders such as CMML.

Considering the limitations of our analysis of population-based data in Switzerland, we can frame general recommendations to improve data

collection and reporting for future health services research. Further systematic collection of longitudinal data not only on treatment but also comorbidities, side effects and outcomes of CMML patients is, therefore, urgently warranted.

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Conflict of interest

Authors declare no conflicts of interest for this study.

Author's contributions

SB: analyzed data and wrote the paper; MD: analyzed data and wrote the paper; AF: analyzed data and wrote the paper; VUB, ASK, AR, AH, AS, RB, MS and GS: critically reviewed the manuscript, VA: analyzed data and critically reviewed the manuscript; NB: initiated and designed the study, analyzed data and wrote the paper.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.canep.2019.01.003>.

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