Loss of life expectancy in patients with myeloproliferative neoplasms in Sweden

Yuliya Leontyeva,[1] Anna Ravn Landtblom,[2,3] Malin Hultcrantz,[4,5] Mats Lambe,[1] Hannah Bower,[6] Paul C. Lambert[1,7] and Therese M.-L. Andersson[1]

[1]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; [2]Center for Hematology and Regenerative Medicine, Department of Medicine, Huddinge, Karolinska Institutet, Stockholm, Sweden; [3]Department of Hematology, Karolinska University Hospital, Stockholm, Sweden; [4]Department of Medicine, Myeloma Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [5]Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden; [6]Clinical Epidemiology Division, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden and [7]Cancer Registry of Norway, Norwegian Institute of Public Health, Oslo, Norway

Correspondence: Y. Leontyeva
yuliya.leontyeva@ki.se

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Abstract

Myeloproliferative neoplasms (MPN) are chronic bone marrow malignancies. While the prognosis is generally good, patients can face complications leading to reduced life expectancy. However, no population-based studies have quantified the life expectancy (LE_C) and loss in life expectancy (LLE) following MPN. In this population-based study, we included individuals diagnosed with MPN in Sweden aged 50 years and older between 2002 and 2021, with follow-up until 2022. We used flexible parametric relative survival models with a period analysis (2012-2021) to estimate LE_C and LLE. We also estimated 15-year restricted mean survival time (RMST) and the loss in 15-year restricted mean survival time (LRMST) for each MPN subtype: polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). The average LE_C was 11.4 years (95% confidence interval [CI]: 11.2-11.7) and LLE was 4.3 years (95% CI: 4.1-4.6). For the MPN subtypes, the average 15-year LRMST was 1.8 (95% CI: 1.7-2.0) in PV, 1.3 (95% CI: 1.1-1.4) in ET, and 4.4 years (95% CI: 4.0-4.8) in PMF. Our study shows that life expectancy is lower in all MPN subtypes compared to the general population. By quantifying LE_C and LLE, our research offers insights into the impact of MPN on an individual's lifespan beyond the diagnosis.

Introduction

Myeloproliferative neoplasms (MPN) represent a group of blood cancers characterized by abnormal development and functioning of bone marrow cells, resulting in varying levels of the overproduction of erythrocytes, thrombocytes, leukocytes, and bone marrow fibrosis. The three primary subtypes of MPN are polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). In Sweden, approximately 600 new MPN cases are diagnosed each year,[1,2] but the prevalence is higher due to the relatively indolent clinical course of the disease. Despite a generally good prognosis, individuals diagnosed with MPN are at risk of experiencing a range of symptoms, e.g., fatigue, abdominal discomfort, and pruritus,[3] and complications associated with the disease, including thromboembolism, infections, bleeding, and secondary malignancies.[4-7] Also, converging evidence indicate that the life expectancy is lower in individuals with MPN compared to the general population both due to the disease itself and various possible complications.[8-11]

Determining expected survival to MPN patients poses a complex challenge. While comprehensive cohort studies have provided insights into survival patterns among individuals with MPN,[7] there remains a notable gap in population-based studies quantifying the life expectancy (LE_C) of individuals with MPN, and the impact of MPN on reduction of their LE_C. The concept of LE_C and loss in life expectancy (LLE) are valuable measures for summarising cancer survival data. Estimating these measures involves extrapolating the all-cause survival curve which is best done by splitting this quantity into cancer-related mortality (excess hazard) and underlying mortality unrelated to MPN,[12] and conducting the extrapolation of these separately. However, this separate extrapolation has primarily been evaluated for cancer types where the excess mortality decreases over time.[12,13] In contrast, in MPN the excess mortality persists over an extended period and may not necessarily decrease, which makes it challenging to quantify LE_C and LLE.

To further improve the understanding of outcomes in individuals with MPN, we conducted a population-based study

to estimate LEc and LLE under different assumptions regarding the long-term excess mortality of individuals with MPN. Additionally, we estimated the 15-year restricted mean survival time (RMST) and the corresponding loss in 15-year restricted mean survival time (LRMST), as complementary measures not requiring extrapolation.

Methods

The cohort included individuals diagnosed with MPN identified through the Swedish Cancer Register (SCR) between 2002 and 2021. Since indolent disorders like MPN may be under-reported,[14-16] additional cases were included from the Swedish National Patient Register. Death dates were retrieved from the Cause of Death Register up to December 31, 2022. The study focused on individuals diagnosed at age 50 years or older to enhance the precision and stability of our results. The study was approved by the Swedish Ethical Review Authority and conducted in accordance with the Declaration of Helsinki.

LLE was defined as the difference between the life expectancy of MPN-diagnosed individuals (LE_C) and their expected life expectancy derived from general population life tables (LEp). We calculated LE_C and LLE using a relative survival approach, separately extrapolating excess mortality and underlying mortality unrelated to MPN,[12] assuming that the latter matched the general population mortality. General population mortality rates and LE_P were obtained from Swedish life tables stratified by age, sex, and year up to 2022,[17] with constant mortality rates assumed beyond 2022.

A period analysis was applied to estimate LE_C and LLE for cases diagnosed after 2011, covering the years 2012-2021.[18-20] Short-term survival was estimated based on individuals diagnosed within this period window, while long-term survival was estimated from those diagnosed earlier. Using a flexible parametric relative survival model,[21-23] we estimated excess mortality. The model incorporated age at diagnosis and sex using time since diagnosis as the timescale with a maximum follow-up of 15 years. To avoid assumption about proportional excess hazards over time, our model included time-varying effects for age and sex. Three scenarios were applied to extrapolate long-term excess mortality beyond the 15-year follow-up. In the (i) default scenario, extrapolation was based on the mod-

Table 1. Demographic characteristics of patients with myeloproliferative neoplasms (MPN) diagnosed in Sweden during the years from 2002 to 2021 by MPN subtypes: polycythemia vera, essential thrombocythemia, primary myelofibrosis and MPN-unclassifiable.

	MPN subtypes				
	PV	ET	PMF	MPN-U	Total
	Calendar period 2002-2011				
N (%)	3,158 (40.5)	2,429 (31.1)	374 (4.8)	1,842 (23.6)	7,803 (100.0)
Age at diagnosis, years, median (Q1-Q3)	73.4 (64.5-81.0)	72.0 (62.9-80.4)	73.3 (65.1-80.4)	75.1 (65.7-82.3)	73.4 (64.3-81.1)
Categories of age, years, N (%)					
50-59	479 (15.2)	459 (18.9)	39 (10.4)	252 (13.7)	1,229 (15.8)
60-69	772 (24.4)	608 (25.0)	110 (29.4)	396 (21.5)	1,886 (24.2)
70-79	1,022 (32.4)	732 (30.1)	129 (34.5)	594 (32.2)	2,477 (31.7)
80-99	885 (28.0)	630 (25.9)	96 (25.7)	600 (32.6)	2,211 (28.3)
Sex, N (%)					
men	1,690 (53.5)	920 (37.9)	221 (59.1)	905 (49.1)	3,736 (47.9)
women	1,468 (46.5)	1,509 (62.1)	153 (40.9)	937 (50.9)	4,067 (52.1
	Calendar period 2012-2021				
N (%)	3,523 (40.2)	3,351 (38.2)	712 (8.1)	1,185 (13.5)	8,771 (100.0)
Age at diagnosis, years, median (Q1-Q3)	72.6 (65.1-79.6)	72.3 (64.1-79.9)	73.3 (65.9-79.7)	74.5 (67.3-82.0)	72.8 (65.1-80.1)
Categories of age, years, N (%)					
50-59	510 (14.5)	527 (15.7)	86 (12.1)	123 (10.4)	1,246 (14.2)
60-69	926 (26.3)	875 (26.1)	183 (25.7)	272 (23.0)	2,256 (25.7)
70-79	1,240 (35.2)	1,120 (33.4)	275 (38.6)	423 (35.7)	3,058 (34.9)
80-99	847 (24.0)	829 (24.7)	168 (23.6)	367 (31.0)	2,211 (25.2)
Sex, N (%)					
men	1,886 (53.5)	1,307 (39.0)	419 (58.8)	567 (47.8)	4,179 (47.6)
women	1,637 (46.5)	2,044 (61.0)	293 (41.2)	618 (52.2)	4,592 (52.4)

MPN: myeloproliferative neoplasms; PV: polycythemia vera; ET: essential thrombocythemia; PMF: primary myelofibrosis; MPN-U: MPN-unclassifiable.

el parameters, as is most often used for other cancer sites.[24-27] The (ii) constant scenario assumed the 15-year excess mortality rate remained steady, maintaining the value it reaches at 15 years after MPN diagnosis; while the (iii) zero scenario assumed excess mortality equals general population mortality after 15 years follow-up. Although the default and constant scenarios are clinically relevant, the zero scenario was included as a sensitivity analysis, to highlight the differences in estimates under clinically plausible and implausible assumptions.

LEc was calculated by summing restricted mean survival times up to 15 years post diagnosis and from 15 to 75 years after diagnosis for each scenario. Ninety-five percent confidence intervals (95% CI) for LEc and LLE were derived using bootstrap resampling.

To assess the disease course during the first years following diagnosis, we calculated 15-year restricted mean survival time (RMST) and the corresponding loss (LRMST) without extrapolation. RMST and LRMST were estimated for all MPN cases and separately for PV, ET, and PMF subtypes.

Marginal values of LE_C, LLE, 15-year RMST, and LRMST were estimated by averaging values for all MPN cases within 2012-2021.[28] Marginal values of 15-year RMST and LRMST were also estimated for each MPN subtype.

Further statistical details and additional figures are presented in the *Online Supplementary Appendix*. All analyses were performed with Stata 18 software packages stpm3 and standsurv.[29,30]

Results

Myeloproliferative neoplasm cohort

The entire MPN cohort included a total of 16,574 individuals diagnosed with MPN between 2002 and 2021. MPN patient demographics, MPN subtypes, age, and sex among patients diagnosed during two distinct time periods: 2002-2011 and 2012-2021 are presented in Table 1. A shift in the distribution of MPN subtypes was observed between these two time periods, for example, PMF represented 8.1% of registered cases in 2012-2021 compared to 4.8% in 2002-2011. The median age at diagnosis for all MPN subtypes combined was 73.4 years in 2002-2011 and 72.8 years in 2012-2021, slightly higher than earlier reports due to the age truncation. The age distribution varied slightly across all MPN subtypes and the two time periods.

Estimates of life expectancy and loss in life expectancy

The estimates of LE_C and LLE are shown for the two above-mentioned scenarios, namely the default and constant. The results from the zero scenario are presented in the *Online Supplementary Appendix*. The default scenario and the constant scenario yielded comparable estimates across various ages, while the zero scenario led to higher values of LE_C and, thus, lower values of LLE. For individuals diagnosed with MPN at older ages, the estimates were similar across all scenarios. Figure 1 presents estimates of LE_C and LLE along with 95% CI for women and men with

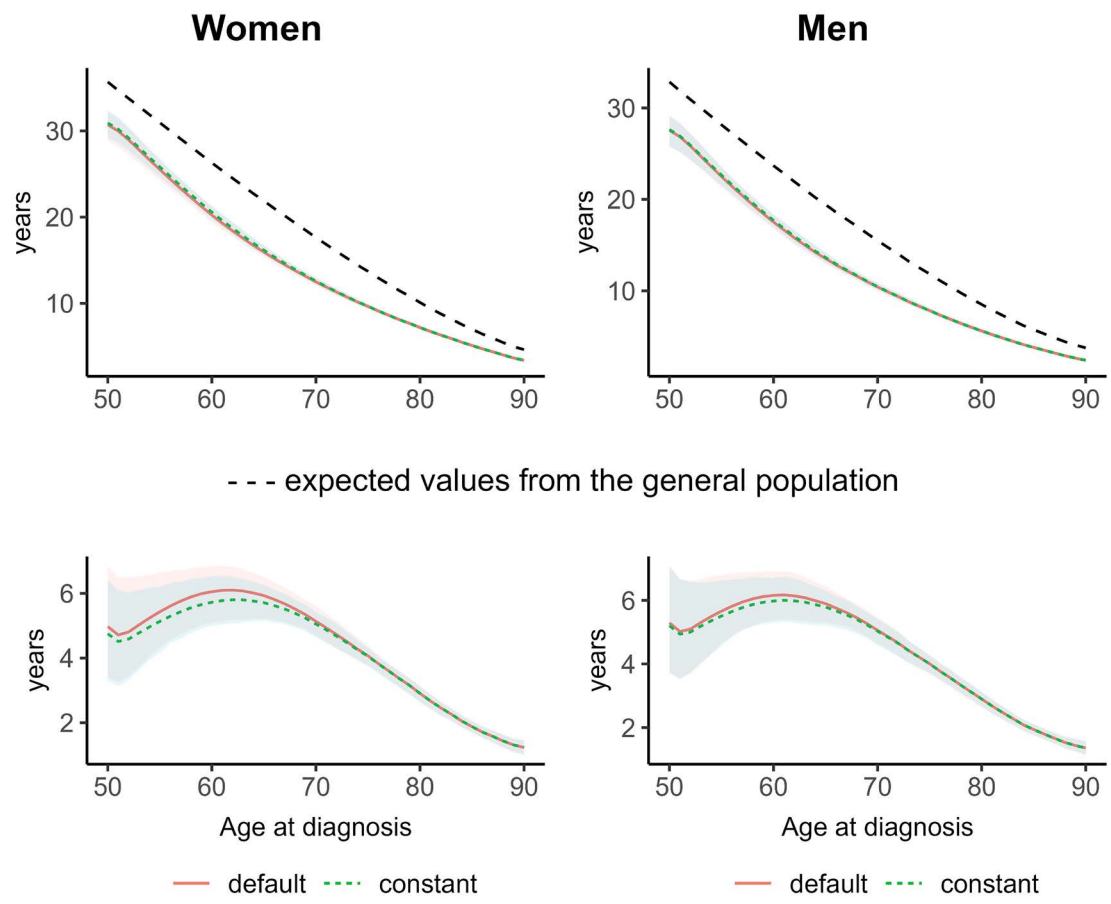

Figure 1. Life expectancy (above) and loss in life expectancy (below) in myeloproliferative neoplasms, with 95% confidence intervals, obtained with two assumptions about the behavior of the extrapolated excess hazard. Default refers to linear log cumulative excess hazard and constant refer to a constant excess hazard after the follow-up period. Results are shown for women and men based on a period analysis with period window from 2012 to 2021, using diagnoses from 2002 to 2021 in Sweden. The values are presented in years.

MPN across ages. The default scenario gave an LE_C for women diagnosed with MPN at age 55 of 25.5 years (95% CI: 24.2-26.7), and an LLE of 5.4 years (95% CI: 4.3-6.7). Meanwhile, a 75-year-old woman had LEc of 9.7 years (95% CI: 9.4-9.9) and an LLE of 4.1 (95% CI: 3.8-4.3). LE_C in men was lower than in women of corresponding ages, while LLE was similar between men and women. For example, in men diagnosed with MPN at the age of 55, LE_C was 22.5 years (95% CI: 21.4-23.6) and LLE was 5.7 years (95% CI: 4.6-6.8). Meanwhile, in men diagnosed at the age 75, LE_C was 7.8 years (95% CI: 7.6-8.1) and LLE was 4.0 years (95% CI: 3.7-4.3). Detailed results of LE_P, LE_C, and LLE with 95% CI for women and men at selected ages (55, 65, 75 and 85 years) are presented in *Online Supplementary Table S1*. Marginal estimates of LE_C and LLE with 95% CI for individuals with MPN across the three scenarios are presented in Table 2. Marginal values are averaged across the sex and age distributions for individuals diagnosed with MPN in 2012-2021. Using the default scenario, the marginal (average) LLE was 4.3 years (95% CI: 4.1-4.6).

Estimates of 15-year restricted mean survival time and loss in 15-year restricted mean survival time

Figure 2 illustrates 15-year LRMST in women and men diagnosed with MPN at four selected ages: 55, 65, 75, and 85 years. Women diagnosed with PV at age 55 had a 15-year LRMST 0.8 years (95% CI: 0.5-1.1). Women diagnosed with PV at 75 years of age had 15-year LRMST of 2.4 years (95% CI: 2.0-2.7). Fifteen-year LRMST for women diagnosed with ET at 55 and 75 years old was of 0.6 years (95% CI: 0.4-

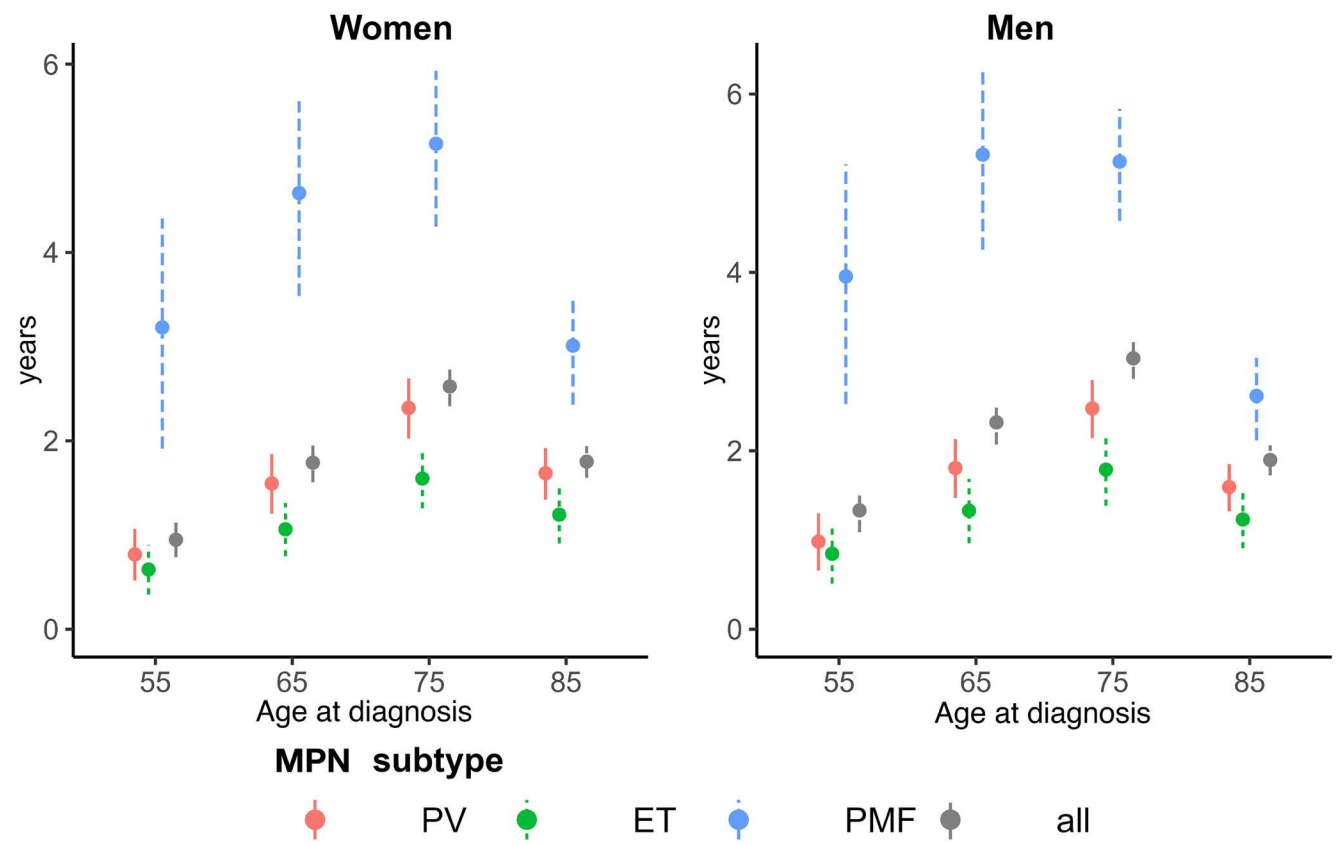

Figure 2. Loss in 15-year restricted mean survival time in myeloproliferative neoplasms, with 95% confidence intervals. Results are shown for women and men aged 55, 65, 75 and 85 years at myeloproliferative neoplasms (MPN) diagnosis based on a period analysis with period window from 2012 to 2021, using diagnoses from 2002 to 2021 in Sweden. Loss in 15-year restricted mean survival time (LRMST) is presented in years. The results are presented by MPN subtypes: polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF) as well as for all MPN subtypes combined (including MPN-unclassifiable).

Table 2. Marginal estimates of life expectancy in the absence of myeloproliferative neoplasms (MPN), life expectancy for individuals with MPN and the loss in life expectancy with 95% confidence intervals obtained with 3 assumptions about the behavior of the extrapolated excess hazard.

Scenario	LE_P	LE_C	LLE
Default, years (95% CI)	15.7	11.4 (11.2-11.7)	4.3 (4.1-4.6)
Constant, years (95% CI)	15.7	11.5 (11.3-11.7)	4.2 (4.0-4.5)
Zero, years (95% CI)	15.7	12.1 (12.0-12.3)	3.6 (3.4-3.7)

Default refers to linear log cumulative excess hazard, constant and zero refer to a constant and a zero-excess hazard, respectively, after the follow-up period. The results are for MPN cases aged 50 years and above based on a period analysis with period window from 2012 to 2021 using diagnoses from 2002 to 2021 in Sweden. LE_P: life expectancy in the absence of MPN; LE_C: life expectancy for individuals with MPN; LLE: loss in life expectancy; CI: confidence interval.

Table 3. Marginal 15-year restricted mean survival time in the absence of myeloproliferative neoplasms (MPN), 15-year restricted mean survival time for individuals with MPN and the loss in 15-year restricted mean survival time with 95% confidence intervals for MPN cases aged 50 years and above based on a period analysis with period window from 2012 to 2021 using diagnoses from 2002 to 2021 in Sweden.

MPN subtype	$RMST_P$	$RMST_C$	LRMST
PV, years (95% CI)	11.0	9.2 (9.1-9.4)	1.8 (1.7-2.0)
ET, years (95% CI)	11.2	9.9 (9.7-10.1)	1.3 (1.1-1.4)
PMF, years (95% CI)	10.9	6.5 (6.2-6.9)	4.4 (4.0-4.8)
All subtypes combined, years (95% CI)	11.1	8.9 (8.8-9.0)	2.7 (2.1-2.3)

The estimates are given by MPN subtypes: polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF) as well as for all MPN subtypes combined (including MPN-unclassifiable [MPN-U]). $RMST_P$: 15-year restricted mean survival time in the absence of MPN; $RMST_C$: 15-year restricted mean survival time for individuals with MPN; LRMST: loss in 15-year restricted mean survival time; CI: confidence interval.

0.9) and 1.6 years (95% CI: 1.3-1.9), respectively, and the corresponding values for PMF were 3.2 years (95% CI: 1.9-4.4) in women aged 55 and 5.15 years (95% CI: 4.3-5.9) in women aged 75. Detailed results corresponding to Figure 2 are presented in *Online Supplementary Table S2*.

The marginal estimates of 15-year RMST and 15-year LRMST for each MPN subtype and all MPN subtypes combined, averaged across the sex and age distributions for individuals diagnosed with each MPN subtype in 2012-2021 are presented in Table 3. For PV the 15-year RMST was 9.2 years (95% CI: 9.1-9.4) and the 15-year LRMST was 1.8 years (95% CI: 1.7-2.0). In individuals diagnosed with ET the 15-year RMST was 9.9 years (95% CI: 9.8-10.1), while the 15-year LRMST was 1.3 years (95% CI: 1.1-1.4). PMF was the subtype associated with the lowest 15-year RMST of 6.5 years (95% CI: 6.2-6.9) and, consequently, the largest LRMST within the first 15 years after PMF diagnosis of 4.4 years (95% CI: 4.0-4.8).

Discussion

We found a reduced life expectancy in individuals with MPN diagnosed at or above the age of 50 compared to the general population. The reduction in life expectancy varied across age and sex, where women with MPN had slightly lower LLE than their male counterparts. Age is a strong predictor of the number of years lost due to MPN. Individuals diagnosed at younger ages generally have a longer life expectancy, and the largest LLE was observed in those diagnosed with MPN around age 60. We illustrated that all MPN subtypes had an inferior life expectancy compared to the general population within the first 15 years after diagnosis. Individuals with PMF had the lowest life expectancy and highest LLE within the first 15 years after diagnosis among the three MPN subtypes. This can be partly explained by differences in age and sex distribution between subtypes, reflected by an average 15-year RMST expected in the absence of MPN of 11.0, and 11.2, and 10.9 years for individuals with PV, ET, and PMF, respectively. However, the predominant factor contributing to the differences in 15-year RMST and the 15-year LRMST for individuals with PMF, in contrast to those for ET and PV, was a comparatively higher excess mortality for individuals with PMF[7].

Our findings are consistent with conclusions drawn from a large population-based study based on a cohort including more than 9,000 patients with MPN diagnosed in Sweden between 1973 and 2008[7,8]. There, all MPN subtypes had inferior survival compared with the general population. Our results revealed a notable pattern in LLE across ages. Individuals diagnosed with MPN between ages 50 and 60 experienced a smaller LLE compared to those diagnosed between 60 and 70. This is partly explained by the lower excess mortality among younger individuals over the 15-year follow-up period (*Online Supplementary Figure S5*) but can also reflect analytical limitations. The combination of the 15-year follow-up period, the need for specific extrapolation assumptions, and the relatively small number of observed deaths among patients diagnosed at younger ages introduces increased uncertainty and may lead to underestimation of the true LLE. We also found that starting around age 60 those diagnosed with MPN showed a greater LLE than those diagnosed at older ages. This is likely to reflect that individuals in their 60s generally have a longer life expectancy and, consequently, more potential years to lose than those at older ages. Assessing the LE_C and LLE thus contributes important individual prognostic information in addition to median survival.

The results showed the impact of assumptions about the behavior of the excess hazard beyond the follow-up period on estimates of LE_C and LLE. Extrapolation based on the model parameters (the default scenario) and constant excess hazard beyond the follow-up period yielded similar estimates. Conversely, assuming zero excess hazard beyond the follow-up period resulted in substantial discrepancies to the by default estimates. Notably, the estimated LLE for older patients was similar across all three scenarios, primarily due to the prevailing expected mortality at these

ages and the shorter extrapolation length. It is important to note that the estimation of LE_C and LLE requires extrapolation beyond the observed data, and the results should be interpreted with this in mind. The default and constant scenarios are simplifications of a more complex reality. However, the fact that they produce almost identical results suggests that their assumptions about the behavior of the excess hazard rate beyond 15-year follow-up are similar. This is also supported by the fact that competing mortality from non-MPN causes tends to dominate over time. It should also be noted that if the excess hazard begins to increase after our chosen follow-up period of 15 years, this increase will not be captured by our modeling approach.

Strengths of our study included the population-based setting, the use of data from nationwide registers with generally high completeness and a virtually complete follow-up. However, some limitations need mentioning. Despite mandated reporting and a high completeness of the SCR, underreporting of MPN cannot be excluded. To address this, the MPN cohort also comprised individuals identified in the Patient Register, which includes nationwide data on all hospital discharge diagnoses since 1987, as well as information on patients receiving treatment in outpatient specialist care since 2001[31]. In total, 53% of MPN diagnoses were extracted from the SCR, 33% from the Inpatient Register, and 14% from the Outpatient Register (*Online Supplementary Table S3*). Cases recorded in the SCR rely on separate reporting from the clinician and pathologist. Reporting to the Patient Register is made by clinicians and may or not be based on pathology reports and other diagnostics. We conducted a sensitivity analysis using individuals diagnosed with MPN solely in the SCR. The results were broadly consistent with those from the full data set including all three cohorts (*Online Supplementary Tables S4-S7; Online Supplementary Figures S3-S5*).

In this study, we focused on individuals 50 years or older at MPN diagnosis, excluding younger individuals. One of the reasons was the increased difficulty in extrapolating survival for younger individuals. A possible solution would be to assume a consistent effect of age before 50 on excess hazard.[11] Given the longer life expectancy for younger individuals, the LLE may be higher for those diagnosed with MPN at ages below 50, but it may also be lower depending on the behavior of their excess mortality. Further, our analysis did not explore the influence of extrapolating covariates effects (e.g., age and sex) or considered more complex scenarios of the excess hazard after the follow-up period. Notably, due to convergence issues during bootstrapping, we could not estimate LLE for each MPN subtype separately. To the best of our knowledge, no previous study has estimated LLE for individuals diagnosed with MPN. Therefore, we deemed it important to present these combined results to advance the understanding of the prognosis among MPN patients. From a clinical perspective, estimating the LLE of individuals diagnosed with MPN and secondary myelofibrosis would be highly valuable. However, such information was unavailable in the dataset at hand.

To conclude, the clinical relevance of our results in the context of MPN is significant. Our study confirms that individuals diagnosed with MPN at or above the age of 50 have a moderately reduced life expectancy compared to the general population. In addition, patients within all MPN subtypes had a reduced restricted mean survival time within 15 years after diagnosis compared with the general population. The findings address a gap in population-based research by quantifying the life expectancy of individuals with MPN, thereby contributing to a more comprehensive and accurate understanding of survival outcomes. However, further research is needed, particularly in exploring survival and LLE in younger populations, as well as in relation to treatments, MPN subtypes, and genetic alterations. Overall, this study emphasizes the impact of MPN on survival and underscores the unmet need for optimized treatment strategies

Disclosures

No conflicts of interest to disclose.

Contributions

YL and TM-LA contributed to the conception of the work. YL and TM-LA implemented the methods, conducted the data analysis. YL and TM-LA wrote the original draft. ARL, MH, ML, HB, and PCL reviewed and edited the draft. All authors interpreted the findings, made critical revision of the article and approved the final manuscript to be published.

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Data-sharing statement

The data used for this study may not, according to the ethical permission granted for its use, be shared by the authors to a third party. Data are accessible by application to the Swedish authorities (The Swedish Cancer Registry).

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