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Survival in Primary Myelofibrosis: A Population-based Analysis in the Netherlands

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Therapeutic options for myelofibrosis have changed substantially over the last decades, especially following the discovery of driver mutations like those in the tyrosine kinase Janus kinase 2 (JAK2). Ruxolitinib was the first JAK1/2 kinase inhibitor that was approved for myelofibrosis management. Besides significant symptom reduction, long-term follow-up of randomized clinical trials indicated a survival benefit after ruxolitinib treatment in selected patients with intermediate-2 or high-risk disease according to the International Prognostic Scoring System (IPSS).[1–4] Currently, limited data are available on how the introduction of ruxolitinib has impacted the survival of primary myelofibrosis (pMF) patients at the population level.

As the median age at diagnosis of pMF is 67 years, it is essential to account for nondisease related mortality. Relative survival (RS) is a net survival measure representing MF survival in the absence of other causes of death. For (p)MF patients, previous population-based studies have reported 5-year RS rates of 35%–58%.[5–10] Unfortunately, treatment details and data on disease severity in these studies were lacking. Also, follow-up time since the availability of ruxolitinib was generally short. In a more recent study, 4-year RS in ruxolitinib-treated patients was 52%, but this was not compared to the overall pMF population and risk scores were unknown.[11] Therefore, in our nationwide, population-based study, we aimed to evaluate the RS of pMF patients in the Netherlands over time, and more specifically before and after the availability of ruxolitinib.

We selected all patients diagnosed with pMF between 2001 and 2018 from the Netherlands Cancer Registry (NCR), which relies on case notification through the Nationwide Histopathology and Cytopathology Data Network and Archive and the National Registry of Hospital Discharges. Patients with secondary MF—that is, in case of preceding essential thrombocythemia or polycythemia vera—were not included in the study. After case notification, registrars of the NCR verify the diagnosis as noted by the treating physician and collect basic information on patient and disease characteristics, and type of primary treatment (ie, the initial treatment that was started after diagnosis, including a "wait-and-see policy"). The exact therapeutic regimen and IPSS scores were registered for patients diagnosed from 2014 onward. Patients were passively followed until the date of death or emigration, or end of follow-up (ie, December 31, 2019). Death dates were retrieved from the Nationwide Population Registries Network. The NCR Privacy Review Board approved the use of anonymous data for this study.

RS was defined as the ratio of the proportion of observed MF survivors to the proportion of expected survivors in a comparable set of individuals assumed to be free of MF (matched to the patients by age, sex, and calendar year). RS rates with 95% confidence intervals were calculated according to the cohort method. The expected survival was estimated according to the Ederer II method from Dutch population life tables. RS was calculated for 2 age categories (18–65 y and >65 y) and 2 calendar periods (2001–2010 and 2011–2018). The age categories were based on expected differences in both treatment strategies and prognosis. The calendar periods were based on the first availability of ruxolitinib in the Netherlands since 2011. Multivariable evaluation using Poisson regression was performed to assess linear trends in RS over time and to model the effect of calendar period of diagnosis, sex, and prior malignancy on the excess mortality ratio within 5 years after pMF diagnosis. The European standard population was used for age-standardization of incidence rates. Additional details on the statistical analyses are presented in the Supplementary Material (http://links.lww.com/HS/A160).

Incidence rates and the characteristics of 1913 pMF patients diagnosed between 2001 and 2018 are shown in Supplementary Table S1 (http://links.lww.com/HS/A160). Our standardized incidence rate of 0.49/100,000 person-years is comparable to recent literature.[9,12] Supplementary Figures S1 and S2 (http://links.lww.com/HS/A160) show an increase in incidence over time and with age, respectively. Median age and distribution of sex were comparable across patients in the 2 calendar periods (Supplementary Table S1, http://links.lww.com/HS/A160).

In accordance with previous literature, RS was markedly worse in older patients (Figure 1).[5,7,9,13,14] In the subgroup of patients with known IPSS scores (diagnosed between 2014 and 2018), a clear association between RS and the IPSS risk category was found (Figure 1). Furthermore, the multivariable

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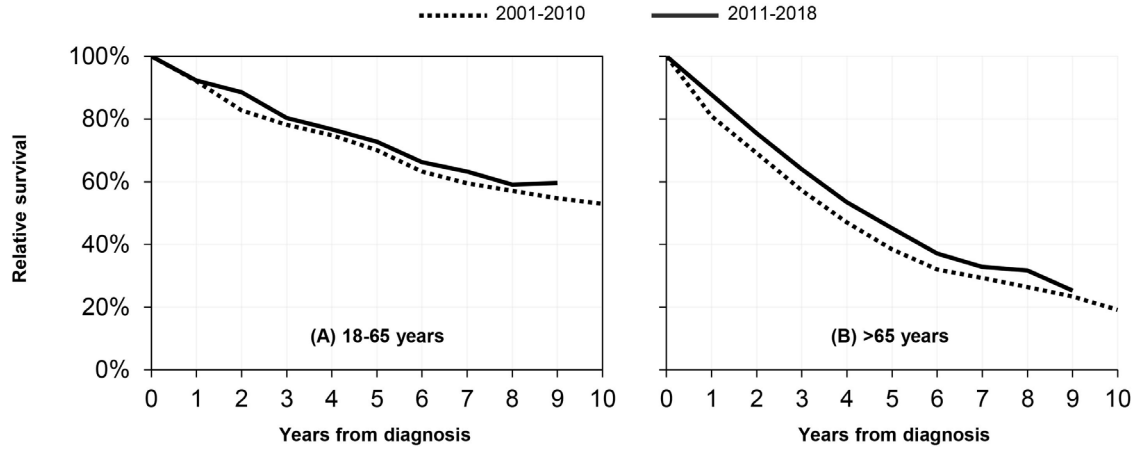
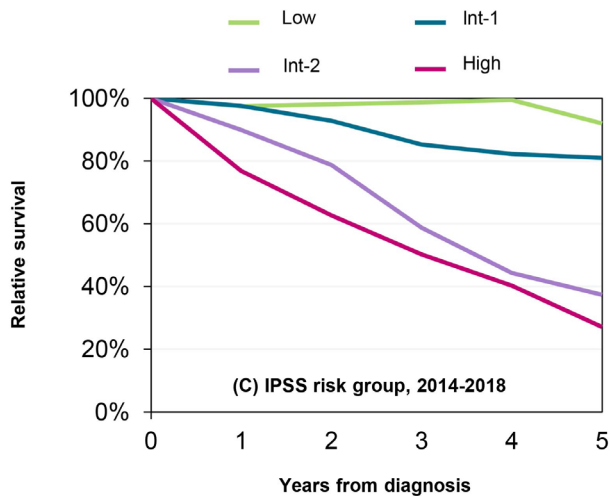
analysis indicated higher excess mortality ratios both in males and in patients with a prior malignancy (Supplementary Table S2, http://links.lww.com/HS/A160). Overall, we found a slight increase in 5-year RS over time, from 51% in 2001–2011 to 55% in 2011–2018 (P = 0.04). The increase was most pronounced in patients aged >65 years at diagnosis, namely from 38% to 45% (P = 0.01; Figure 1).

Primary treatment details are presented in Figure 2 and Supplementary Table S3 (http://links.lww.com/HS/A160), Supplementary Table S5 (http://links.lww.com/HS/A160), and Supplementary Table S6 (http://links.lww.com/HS/A160). The majority of patients initially received a wait-and-see policy. Early allogeneic stem cell transplantation was mainly performed in patients aged <65 years, with only a slight increase over time (from 8% in patients diagnosed between 2001 and 2010, to 11% of those diagnosed between 2011 and 2018). Other systemic therapy was increasingly prescribed in all age groups (from 3% to 14% in patients diagnosed between 2001–2010 and 2011–2018, respectively). This mainly concerned JAK1/2 inhibitor therapy, with a small percentage of other drugs



RS	Calendar period: 2001-2010	Calendar period: 2011-2018	*P* for trend*
	RSR (in%) with 95% CI		
5-year	70 (64-75)	73 (67-78)	0.415
10-year	53 (47-59)	-	-

Calendar period: 2001-2010	Calendar period: 2011-2018	*P* for trend*
RSR (in%) with 95% CI		
38 (34-43)	45 (40-50)	0.014
19 (15-24)	-	-



RS	IPSS risk group: Low	Int-1	Int-2	High	Unk
	RSR (in%) with 95% CI				
5-year	98 (89-100)	93 (87-97)	79 (71-85)	63 (54-70)	78 (62-89)
10-year	92 (73-99)	81 (70-90)	37 (26-49)	27 (16-41)	37 (15-62)

Figure 1. RS of patients with primary myelofibrosis in the Netherlands. (A) and (B), RSRs according to the calendar period of diagnosis for the age categories 18–65 y (A) and >65 y (B). The tables below (A) and (B) present the projected 5- and 10-y RSR with 95% CIs. The asterisk indicates the P value for the likelihood ratio test assessing linear trends in 5-y RS from the period 2001–2010 to the period 2011–2018. (C), RS as per the IPSS risk groups, among patients diagnosed during 2014–2018. The table below (C) presents the projected 2- and 5-y RSR with 95% CI. CI = confidence interval; Int = intermediate; IPSS = International Prognostic Scoring System; RS = relative survival; RSR = relative survival rates; Unk = unknown.

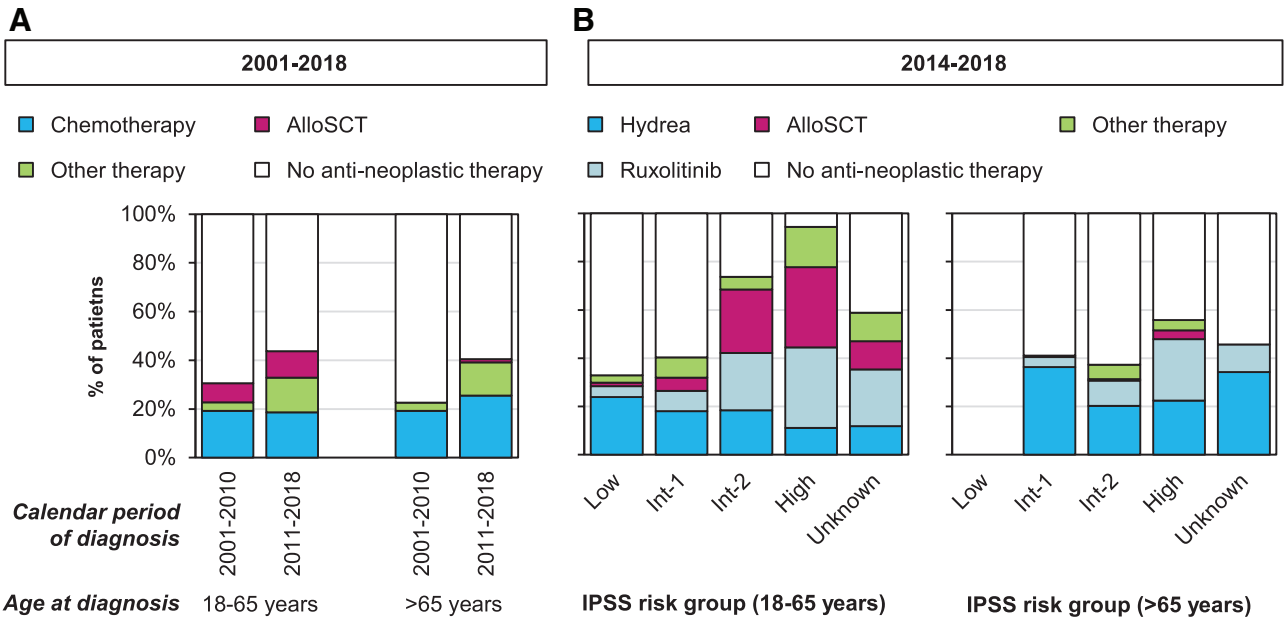


Figure 2. Primary treatment of patients with primary myelofibrosis in the Netherlands. (A), Information on primary therapy (ie, initial therapy started after diagnosis, including a "wait-and-see policy") according to age and at diagnosis and calendar period of diagnosis among patients diagnosed during 2001–2018. The absolute number and proportion of patients within a specific age group and period is shown in Supplementary Table S3 (http://links.lww.com/HS/A160). The group of other therapy encompasses immunomodulatory imide drugs, interferon-alpha, and ruxolitinib (as of 2011), among others. Of note, 6 patients with missing information on therapy were not included in this figure. (B), Specific type of primary therapy as per the IPSS risk group in the 2 age groups among patients diagnosed during 2014–2018. The absolute number and proportion of patients within a specific risk and age group is shown in Supplementary Table S5 (http://links.lww.com/HS/A160). The group of other therapy is delineated in Supplementary Table S6 (http://links.lww.com/HS/A160). alloSCT = allogeneic stem cell transplantation; Int = intermediate; IPSS = International Prognostic Scoring System.

including immunomodulatory imide drugs (ie, thalidomide) and interferon-alpha.

In the subgroup of 711 patients in whom IPSS risk scores and exact therapeutic regimens were known (ie, those diagnosed between 2014 and 2018), the risk score was low in 9%, intermediate-1 in 31%, intermediate-2 in 27%, high in 26%, and unknown in 7%. As expected, since age is a risk factor in the IPSS, risk scores were significantly higher in older patients (Supplementary Table S4, http://links.lww.com/HS/A160). The main primary treatment strategies in low and intermediate-1 risk patients were a wait-and-see policy (applied in 67% and 59% of patients, respectively) and hydroxyurea (prescribed in 24% and 30%, respectively). Although these strategies were also commonly applied in patients with intermediate-2 and high-risk disease, more patients in these subgroups received early allogeneic stem cell transplantation (6% and 7%, respectively) or ruxolitinib (13% and 26%, respectively). The variation between age groups is shown in Supplementary Table S5 (http://links.lww.com/HS/A160).

While the RS in our cohort is congruent with reports concerning similar calendar periods,[7,9] we are among the first to present evidence of improving RS over time. To our knowledge, this finding was described by only 2 previous studies, with important uncertainties.[6,13] In a Norwegian study, 5-year RS increased from 50% to 59.5% between 2003–2007 and 2008–2012. However, this analysis was performed in male patients only.[6] The 2012 Swedish analysis did show a higher 5-year RS in the most recent time period, but statistical significance was not assessed and 10-year RS was not significantly altered.[13]

The parallel increase in RS and early use of "other therapy" (mainly concerning ruxolitinib) suggests effectiveness of the latter in our real-world population. Although the increase in the use of other therapy was similar in both age groups, the higher disease severity in patients aged >65 years might explain the greater effect size in this group. This is supported by the final overall survival analysis from the Controlled Myelofibrosis Study with Oral JAK inhibitor Treatment 1 trial. Although hazard ratios were similar among intermediate-2 and high-risk patients randomized to ruxolitinib,[2] the greater absolute mortality risk in the latter group could explain the greater impact on RS. Unfortunately, further evaluation in our cohort was complicated by unavailable treatment data at later stages during follow-up. Theoretically, an increased identification of lower-risk patients over time might form an alternative explanation for the observed increase in RS. Since IPSS scores were unavailable for patients diagnosed before 2014, we could not analyze this in our cohort. However, changes in diagnostic criteria are unlikely to have caused an increase in the proportion of low-risk patients, mainly since prefibrotic MF was described in all versions of the World Health Organization classification (ie, 2001, 2008, and 2016).[15,16] If any effect, an increase in higher-risk patients over time would seem more likely, due to reclassification of advanced-phase myeloproliferative neoplasms-unclassified patients as MF.[17] However, since no major changes were seen in the annual incidence rates directly following the publication of new diagnostic criteria (Supplemental Figure S1, http://links.lww.com/HS/A160), a significant effect of reclassifications seems improbable. Lastly, risk distribution in the patients diagnosed between 2014 and 2018 was comparable to that in a Spanish cohort of patients diagnosed between 2000 and 2017.[18]

The value of our study lies in the high nationwide coverage (>95% of all newly diagnosed malignancies in the Netherlands). Limitations include the lack of risk scores and detailed treatment information before 2014, and the lack of treatment data during follow-up. Also, like most population-based registries, we only identified patients with pMF, since patients with essential thrombocythemia and polycythemia vera are registered separately in the NCR and transformations to secondary myelofibrosis were not standardly registered before 2014.

In summary, our population-based analysis provides additional evidence for a slight increase in RS in pMF patients over

the last decades. We also demonstrate increasing early use of other therapy, mainly including ruxolitinib. We encourage future studies to validate and extend our study findings through analysis of population-based registry data. In addition, this study might compel forthcoming studies to assess the therapeutic value of ruxolitinib, as compared to other treatment strategies, in a real-world setting.

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Disclosures

PAWtB participates in the advisory board of Novartis B.V. and Celgene B.V. All the other authors have no conflicts of interest to disclose.

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