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Healthcare resource utilization in patients with myeloproliferative neoplasms: A Danish nationwide matched cohort study

Sarah Friis Christensen[1] | Lise Skovgaard Svingel[2] | Anders Kjærsgaard[2] | Anna Stenling[3] | Bianka Darvalics[2] | Björn Paulsson[3] | Christen Lykkegaard Andersen[4,5] | Christian Fynbo Christiansen[2] | Jesper Stentoft[6] | Jørn Starklint[7] | Marianne Tang Severinsen[8] | Mette Borg Clausen[4] | Morten Hagemann Hilsøe[9] | Hans Carl Hasselbalch[1] | Henrik Frederiksen[10] | Ellen Margrethe Mikkelsen[2] | Marie Bak[1,4]

[1]Department of Hematology, Zealand University Hospital, Roskilde, Denmark

[2]Department of Clinical Epidemiology, Department of Clinical Medicine, Aarhus University Hospital and Aarhus University, Aarhus, Denmark

[3]Novartis Sverige AB, Kista, Sweden

[4]Department of Hematology, Copenhagen University Hospital, Rigshospitalet, Denmark

[5]The Research Unit for General Practice and Section of General Practice, Department of Public Health, University of Copenhagen, Copenhagen, Denmark

[6]Department of Hematology, Aarhus University Hospital, Aarhus, Denmark

[7]Department of Hematology, Holstebro Hospital, Holstebro, Denmark

[8]Department of Hematology, Aalborg University Hospital, Aalborg, Denmark

[9]Department of Hematology, Hospital South West Jutland, Esbjerg, Denmark

[10]Department of Hematology, Odense University Hospital, Odense, Denmark

Correspondence
Sarah Friis Christensen, Department of Hematology, Zealand University Hospital, Vestermarksvej 9, 4000 Roskilde, Denmark.
Email: safc@regionsjaelland.dk

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Novartis

Abstract

Few studies have assessed healthcare resource utilization (HRU) in patients with Philadelphia-negative myeloproliferative neoplasms (MPN) using a matched cohort design. Further, no detailed assessment of HRU in the years preceding an MPN diagnosis exists. We conducted a registry-based nationwide Danish cohort study, including patients with essential thrombocythemia, polycythemia vera, myelofibrosis, and unclassifiable MPN diagnosed between January 2010 and December 2016. HRU data were summarized annually from 2 years before MPN diagnosis until emigration, death, or end of study (December 2017). We included 3342 MPN patients and 32 737 comparisons without an MPN diagnosis, matched on sex, age, region of residence, and level of education. During the study period, the difference in HRU (rate ratio) between patients and matched comparisons ranged from 1.0 to 1.5 for general practitioner contacts, 0.9 to 2.2 for hospitalizations, 0.9 to 3.8 for inpatient days, 1.0 to 4.0 for outpatient visits, 1.3 to 2.1 for emergency department visits, and 1.0 to 4.1 for treatments/examinations. In conclusion, MPN patients had overall higher HRU than the matched comparisons throughout the follow-up period (maximum 8 years). Further, MPN patients had substantially increased HRU in both the primary and secondary healthcare sector in the 2 years preceding the diagnosis.

KEYWORDS
ambulatory care, case–control studies, early diagnosis, epidemiology, general practice, health resources, healthcare costs, hospitalization, myeloproliferative disorder, registries

Sarah Friis Christensen, Lise Skovgaard Svingel, Ellen Margrethe Mikkelsen, and Marie Bak contributed equally to this work.

1 | INTRODUCTION

The myeloproliferative neoplasms (MPNs), comprising essential thrombocythemia (ET), polycythemia vera (PV), myelofibrosis (MF), and MPN, unclassifiable (MPN-U), are acquired hematopoietic stem cell cancers.[1,2] The clinical presentation of patients with MPN ranges from nearly asymptomatic patients managing full-time jobs to debilitated patients in need of frequent hospitalization. Prevalent symptoms include fatigue, pruritus, constitutional symptoms, abdominal discomfort, and early satiety, largely attributable to splenomegaly—a common manifestation of PV and MF.[3,4] Besides splenomegaly, MPN complications encompass thrombosis, hemorrhage, infections, bone marrow failure, and progression to acute myeloid leukemia.[4,5] In addition, recent research has documented an increased risk of several chronic diseases (e.g., cardiovascular diseases, age-related macular degeneration, chronic kidney disease, and inflammatory bowel disease) and second cancers in MPN patients.[6–15] The development of targeted treatment (JAK1/2 inhibitors) has significantly improved constitutional symptoms and splenomegaly in some MPN patients, but for many patients, the symptom burden persists despite treatment.[16] Bone marrow transplantation is a potentially curative treatment, but only few patients undergo transplantation due to high treatment-related mortality.[2,17] Given the chronic nature of the MPNs and the substantial morbidity burden, MPN patients have a continuous need for health care during the lifelong course of disease.

Only two studies have examined healthcare resource utilization (HRU) in patients with MPN and compared with matched individuals without MPN.[18,19] In a cross-sectional study using US claim databases, Mehta et al. found that all aspects of HRU, including outpatient consultations, inpatient days, emergency room visits, and pharmacy costs (e.g., number of prescriptions), were higher among MPN patients compared with matched comparisons without MPN.[18] Similarly, in a population-based retrospective study using data from Ontario's administrative health databases, Bankar et al. showed that MPN patients had a higher HRU than matched comparisons for all examined HRU measures, except long-term care.[19]

However, so far, no studies reporting HRU from nationwide cohorts of MPN patients exist, and neither of the two prior studies determined the HRU of all four MPN subtypes. Furthermore, accumulating research demonstrates that MPN-associated driver mutations, complications, and symptoms are often present several years before patients are diagnosed with MPN.[20–22] Hence, it seems plausible that HRU might increase in the years prior to the time of MPN diagnosis as well. In support of this theory, the study by Bankar et al. reported that, based on a comorbidity score calculated from pre-diagnostic characteristics, MPN patients were more likely than comparisons to have high HRU around time of diagnosis.[19] However, individual-level data by MPN subtype and type of HRU (e.g., outpatient consultations, inpatient days, hospital treatments, emergency department [ED] visits, and general practitioner [GP] contacts) were not collected in the years preceding the MPN diagnosis.

Up-to-date real-world data on HRU is essential for healthcare planning, health economic analysis, and decisions on implementation of new treatments. Hence, we aimed to assess pre- and post-diagnostic HRU in nationwide cohorts of Danish MPN patients and matched comparisons without MPN.

2 | MATERIALS AND METHODS

2.1 | Study design and setting

In this descriptive, matched cohort study, we used data from population-based Danish registries (Figure S1). The Danish healthcare system provides egalitarian, tax-funded health care for all citizens (approximately 5.7 million),[23] enabling us to study HRU across diagnoses and healthcare sectors.

2.2 | Study population

The study population comprised eight cohorts: four MPN cohorts and four $_{non}$MPN cohorts. The MPN cohorts included all patients aged ≥18 years with a first-time diagnosis of ET, PV, MF, or MPN-U recorded in the Danish National Chronic Myeloid Neoplasia Registry (DCMR) in the period from January 1, 2010 to December 31, 2016 (Figure S2).[24] Patients were diagnosed according to the prevailing World Health Organization diagnostic criteria at time of diagnosis (Table S1). Patients with chronic myeloid leukemia or prefibrotic myelofibrosis were not eligible for inclusion (Figure S3). The $_{non}$MPN cohorts ($_{non}$ET, $_{non}$PV, $_{non}$MF, and $_{non}$MPN-U) were randomly sampled without replacement by matching patients to population comparisons by 1:10 (when data allowed) on sex, age (year of birth), region of residence, and level of education. The index date for patients and their matched comparisons was defined as the date of MPN diagnosis in the DCMR. Patients and comparisons contributed person-time from index date until emigration, death, or end of study on December 31, 2017 (i.e., maximum 8 years), whichever came first. In addition, we applied a 2-year pre-diagnosis period preceding the index date.

2.3 | Variables and data sources

The DCMR is a national quality registry with ≥98% national coverage and 89%–100% completeness of data on patients with MPN.[24–27]

We linked individual-level data from the DCMR with data from other registries using a unique personal identification number issued by the Danish Civil Registration System to all citizens.[28] From the Danish Civil Registration System, we obtained information on sex, age, region of residence, date of emigration, and vital status. Information on level of education was acquired from educational data from Statistics Denmark and classified as short, medium, long, or missing (including no education) according to highest completed education (Table S1).[29,30] We obtained information on the conditions included in the Charlson Comorbidity Index (CCI) score (Table S1) from 5 years prior to index date from the Danish National Patient Registry (DNPR).[31,32] The DNPR holds clinical data (according to International Classification of Diseases, 10th revision since 1994) on all somatic hospital admissions since 1977 and all outpatient

TABLE 1 Baseline characteristics of the study population including comparison cohorts

	ET	nonET	PV	nonPV	MF	nonMF	MPN-U	nonMPN-U
Total number, *n*	1140	11 181	1109	10 873	533	5217	560	5466
Year of diagnosis, *n* (%)								
2010	129	1229	128	1208	64	629	72	707
	(11.3)	(11.0)	(11.5)	(11.1)	(12.0)	(12.1)	(12.9)	(12.9)
2011	130	1298	129	1301	73	723	77	750
	(11.4)	(11.6)	(11.6)	(12.0)	(13.7)	(13.9)	(13.8)	(13.7)
2012	158	1560	146	1425	82	818	75	730
	(13.9)	(14.0)	(13.2)	(13.1)	(15.4)	(15.7)	(13.4)	(13.4)
2013	171	1671	155	1549	97	952	73	714
	(15.0)	(14.9)	(14.0)	(14.2)	(18.2)	(18.2)	(13.0)	(13.1)
2014	169	1664	204	1994	66	610	84	824
	(14.8)	(14.9)	(18.4)	(18.3)	(12.4)	(11.7)	(15.0)	(15.1)
2015	191	1878	178	1725	79	788	85	832
	(16.8)	(16.8)	(16.1)	(15.9)	(14.8)	(15.1)	(15.2)	(15.2)
2016	192	1881	169	1671	72	697	94	909
	(16.8)	(16.8)	(15.2)	(15.4)	(13.5)	(13.4)	(16.8)	(16.6)
Age, mean (SE)	65.1	64.9	68.1	67.9	71.6	71.4	69.7	69.7
	(14.6)	(14.7)	(12.6)	(12.6)	(11.4)	(11.5)	(13.4)	(13.4)
Age, median (IQR)	67	67	69	69	73	73	72	71
	(55, 76)	(55, 76)	(61, 77)	(61, 77)	(66, 79)	(66, 79)	(63, 80)	(63, 80)
Age groups, *n* (%)								
<40	67	682	24	239	9	90	11	109
	(5.9)	(6.1)	(2.2)	(2.2)	(1.7)	(1.7)	(2.0)	(2.0)
40–50	137	1368	88	884	17	180	50	470
	(12.0)	(12.2)	(7.9)	(8.1)	(3.2)	(3.5)	(8.9)	(8.6)
51–69	444	4318	453	4477	168	1675	189	1873
	(38.9)	(38.6)	(40.8)	(41.2)	(31.5)	(32.1)	(33.8)	(34.3)
≥70	492	4813	544	5273	339	3272	310	3014
	(43.2)	(43.0)	(49.1)	(48.5)	(63.6)	(62.7)	(55.4)	(55.1)
Sex, *n* (%)								
Female	689	6746	552	5439	223	2168	291	2847
	(60.4)	(60.3)	(49.8)	(50.0)	(41.8)	(41.6)	(52.0)	(52.1)
Male	451	4435	557	5434	310	3049	269	2619
	(39.6)	(39.7)	(50.2)	(50.0)	(58.2)	(58.4)	(48.0)	(47.9)
Level of education, *n* (%)								
Short	355	3537	419	4184	192	1917	221	2203
	(31.1)	(31.6)	(37.8)	(38.5)	(36.0)	(36.7)	(39.5)	(40.3)
Medium	430	4305	446	4471	234	2347	224	2217
	(37.7)	(38.5)	(40.2)	(41.1)	(43.9)	(45.0)	(40.0)	(40.6)
Long	319	3159	203	2001	84	831	99	974
	(28.0)	(28.3)	(18.3)	(18.4)	(15.8)	(15.9)	(17.7)	(17.8)
Missing	36	180	41	217	23	122	16	72
	(3.2)	(1.6)	(3.7)	(2.0)	(4.3)	(2.3)	(2.9)	(1.3)
CCI score,[a] *n* (%)								
0	713	8425	668	7958	301	3544	324	3923
	(62.5)	(75.4)	(60.2)	(73.2)	(56.5)	(67.9)	(57.9)	(71.8)

TABLE 1 (Continued)

	ET	nonET	PV	nonPV	MF	nonMF	MPN-U	nonMPN-U
1	230	1312	242	1350	109	755	116	706
	(20.2)	(11.7)	(21.8)	(12.4)	(20.5)	(14.5)	(20.7)	(12.9)
>1	197	1444	199	1565	123	918	120	837
	(17.3)	(12.9)	(17.9)	(14.4)	(23.1)	(17.6)	(21.4)	(15.3)
Region of residence, *n* (%)								
Capital Region of Denmark	418	4129	310	3025	185	1823	107	1032
	(36.7)	(36.9)	(28.0)	(27.8)	(34.7)	(34.9)	(19.1)	(18.9)
Region Zealand	164	1594	199	1948	150	1475	82	806
	(14.4)	(14.3)	(17.9)	(17.9)	(28.1)	(28.3)	(14.6)	(14.7)
Region of Southern Denmark	229	2235	281	2712	106	1031	121	1186
	(20.1)	(20.0)	(25.3)	(24.9)	(19.9)	(19.8)	(21.6)	(21.7)
North Denmark Region	49	481	93	926	43	416	141	1364
	(4.3)	(4.3)	(8.4)	(8.5)	(8.1)	(8.0)	(25.2)	(25.0)
Central Denmark Region	280	2742	226	2262	49	472	109	1078
	(24.6)	(24.5)	(20.4)	(20.8)	(9.2)	(9.0)	(19.5)	(19.7)
Follow-up, years								
Mean (95% CI)	3.8	3.9	3.8	3.9	3.1	3.9	3.3	3.9
	(3.7–4.0)	(3.8–3.9)	(3.7–4.0)	(3.9–3.9)	(3.0–3.3)	(3.9–4.0)	(3.1–3.4)	(3.8–4.0)
Median (IQR)	3.6	3.7	3.6	3.6	2.8	3.9	2.8	3.6
	(2.1–5.3)	(2.2–5.4)	(2.3–5.3)	(2.3–5.5)	(1.5–4.7)	(2.2–5.5)	(1.7–4.8)	(2.1–5.6)
Individuals who died, *n* (%)	157	1319	173	1420	222	1006	198	882
	(13.8)	(11.8)	(15.6)	(13.1)	(41.7)	(19.3)	(35.4)	(16.1)

[a]Charlson Comorbidity Index score, excluding non-melanoma skin cancer (ICD-10: C44).

and ED visits since 1995. Furthermore, it holds clinical data on surgical procedures, examinations, and certain hospital-administered treatments, including medical treatments in relation to blood cancer.

The HRU study outcome was defined as number of GP contacts (including telephone, email, and in-person contacts with GP) and hospital contacts, hospitalizations (i.e., inpatient episodes), inpatient days, outpatient visits, ED visits, and treatments/examinations as defined in Table S2. Data on number and type of hospital contacts were retrieved from the DNPR.

Information on all types of GP contacts was obtained from the Danish National Health Service Registry, which includes nationwide data on primary care services.[33]

HRU was assessed in two observation periods: a 2-year pre-diagnosis period (year −2 and year −1 relative to the index date) and a post-diagnosis follow-up period of maximum 8 years (year 1–8 relative to the index date) (Figure S2).

2.4 | Statistical analysis

Demographic characteristics were described for the MPN and comparison cohorts using frequency (*n*), proportion (%), median and interquartile range (IQR), and mean and standard error. The Wald method with continuity correction was used to calculate the associated 95% confidence intervals (CIs). In addition, median follow-up time and the number of patients who died (all-cause mortality) or emigrated during follow-up were reported.

We described HRU as the annual number of GP contacts and of all types of hospital contacts by median and IQR to describe the distribution of data. This median HRU was calculated for each year of the observation periods as the median number of contacts per person at risk in the cohort on 1 January of each respective year. This was supplemented with computation of the intensity of HRU as mean number of contacts per person-years at risk with 95% CIs for each year of the observation periods. In this way, individuals provided person-time until the date of a censoring event (emigration, death, or end of follow-up). Finally, we calculated and graphically presented rate ratios (RRs) of the intensity of HRU, comparing the four patient cohorts and their respective comparison cohort.

The study was registered by Aarhus University according to Danish and European regulations for data protection (Aarhus University record number 2016-051-000001, # 886).

Data management and analyses of the pseudonomized data were performed on secured servers at Statistics Denmark using SAS 9.4.

3 | RESULTS

3.1 | Participants

We identified 3342 MPN patients in the DCMR resulting in four patient cohorts comprising 1140 ET, 1109 PV, 533 MF, and 560 MPN-U patients (Figure S3). The matched comparison cohorts

TABLE 2 Healthcare resource utilization in ET patients and $_{non}$ET comparisons pre- and post-diagnosis

Year relative to index	Persons at-risk, *n*		GP contacts				Hospitalizations				Inpatient days			
	ET	$_{non}$ET	ET		$_{non}$ET		ET		$_{non}$ET		ET		$_{non}$ET	
			Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]
−2	1140	11 181	8 (4–14)	9.8 (9.6–10.0)	7 (3–12)	8.8 (8.8–8.9)	1 (1–2)	1.5 (1.3–1.7)	1 (0–1)	1.0 (1.0–1.0)	2 (1–7)	7.4 (7.1–7.8)	1 (0–4)	4.2 (4.1–4.3)
−1	1140	11 181	12 (7–18)	13.5 (13.3–13.7)	7 (3–13)	9.0 (9.0–9.1)	1 (1–2)	1.5 (1.4–1.7)	1 (0–1)	1.1 (1.0–1.1)	4 (1–9)	8.5 (8.2–8.8)	1 (0–4)	4.9 (4.8–4.9)
1	1140	11 181	11 (5–18)	13.1 (12.9–13.3)	7 (3–13)	9.3 (9.3–9.4)	1 (1–2)	1.9 (1.8–2.0)	1 (0–1)	1.2 (1.2–1.3)	2 (1–8)	8.1 (7.8–8.4)	1 (0–6)	5.9 (5.8–6.0)
2	1140	10 832	10 (5–16)	13.0 (12.8–13.3)	7 (3–13)	10.2 (10.2–10.3)	1 (1–2)	2.0 (1.8–2.2)	1 (0–1)	1.2 (1.2–1.3)	3 (1–11)	10.9 (10.5–11.3)	1 (0–5)	5.7 (5.6–5.8)
3	889	8741	9 (5–15)	12.9 (12.6–13.2)	7 (3–13)	10.6 (10.5–10.7)	1 (1–2)	2.0 (1.8–2.3)	1 (0–1)	1.3 (1.3–1.4)	3 (1–11)	8.8 (8.3–9.2)	1 (0–6)	6.1 (6.0–6.2)
4	673	6762	9 (4–15)	12.6 (12.3–12.8)	7 (3–13)	10.7 (10.6–10.8)	1 (1–2)	2.2 (2.0–2.5)	1 (0–1)	1.3 (1.3–1.4)	4 (1–11)	9.4 (8.9–10.0)	1 (0–5)	6.1 (6.0–6.2)
5	500	5068	9 (4–14)	12.7 (12.4–13.0)	7 (3–13)	11.0 (10.9–11.1)	1 (1–2)	2.3 (2.0–2.6)	1 (0–2)	1.4 (1.3–1.4)	3 (1–10)	8.4 (7.9–9.0)	1 (0–6)	6.1 (5.9–6.2)
6	343	3468	9 (4–14)	13.8 (13.3–14.2)	7 (3–13)	12.2 (12.1–12.3)	1 (1–2)	2.4 (2.0–2.8)	1 (0–2)	1.4 (1.3–1.5)	3 (1–9)	8.9 (8.1–9.7)	1 (0–5)	6.4 (6.2–6.6)
7	194	2046	9 (4–16)	15.1 (14.5–15.7)	7 (4–14)	13.1 (12.9–13.3)	1 (1–2)	2.1 (1.6–2.7)	1 (0–2)	1.5 (1.4–1.7)	3 (1–8)	8.1 (7.1–9.2)	1 (0–6)	6.5 (6.2–6.8)
8	89	965	7 (4–15)	21.1 (19.8–22.5)	7 (3–13)	18.9 (18.5–19.3)	1 (1–2)	2.4 (1.6–3.6)	1 (0–1)	2.1 (1.8–2.4)	2 (1–5)	9.3 (7.5–11.5)	1 (0–6)	7.7 (7.1–8.3)

Year relative to index	Persons at-risk, *n*		Outpatient visits				ED visits				Treatments/examinations			
	ET	$_{non}$ET	ET		$_{non}$ET		ET		$_{non}$ET		ET		$_{non}$ET	
			Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]
−2	1140	11 181	2 (1–4)	3.7 (3.5–3.8)	1 (1–3)	2.9 (2.9–3.0)	1 (1–1)	1.2 (1.1–1.4)	1 (0–1)	0.7 (0.7–0.7)	3 (1–6)	5.6 (5.4–5.8)	2 (1–5)	5.0 (4.9–5.0)
−1	1140	11 181	3 (2–6)	4.5 (4.3–4.6)	2 (1–4)	3.6 (3.6–3.6)	1 (1–2)	1.3 (1.2–1.5)	1 (0–1)	0.7 (0.7–0.8)	4 (2–8)	7.0 (6.8–7.1)	2 (1–6)	5.5 (5.5–5.6)
1	1140	11 181	9 (5–13)	10.1 (9.9–10.3)	2 (1–4)	3.7 (3.7–3.8)	1 (1–1)	1.3 (1.2–1.5)	1 (0–1)	0.9 (0.8–0.9)	12 (6–18)	14.6 (14.3–14.8)	2 (1–6)	6.0 (6.0–6.1)
2	1140	10 832	5 (2–8)	6.9 (6.7–7.1)	2 (1–4)	3.6 (3.6–3.7)	1 (1–2)	1.5 (1.3–1.7)	1 (0–1)	0.9 (0.9–0.9)	6 (3–12)	10.3 (10.1–10.5)	2 (1–6)	5.8 (5.7–5.9)
3	889	8741	4 (2–8)	6.4 (6.2–6.7)	2 (1–4)	3.8 (3.8–3.9)	1 (1–2)	1.5 (1.3–1.8)	1 (0–1)	0.9 (0.9–1.0)	6 (3–11)	10.4 (10.1–10.6)	2 (1–6)	6.1 (6.1–6.2)

TABLE 2 (Continued)

Year relative to index	Persons at-risk, *n*		Outpatient visits				ED visits				Treatments/examinations			
	ET	nonET	ET		nonET		ET		nonET		ET		nonET	
			Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]
4	673	6762	4 (2–7)	6.5 (6.2–6.7)	2 (1–4)	3.8 (3.8–3.9)	1 (1–1)	1.5 (1.3–1.8)	1 (0–1)	1.0 (0.9–1.0)	5 (2–11)	10.2 (9.9–10.5)	2 (1–6)	6.1 (6.0–6.2)
5	500	5068	4 (2–7)	6.1 (5.8–6.4)	2 (1–4)	3.8 (3.7–3.9)	1 (1–2)	1.6 (1.4–2.0)	1 (0–1)	1.0 (1.0–1.1)	5 (2–9)	9.2 (8.9–9.6)	2 (1–6)	6.2 (6.1–6.3)
6	343	3468	3 (2–7)	5.7 (5.4–6.1)	2 (1–4)	3.7 (3.6–3.8)	1 (1–1)	1.7 (1.3–2.1)	1 (0–1)	1.1 (1.0–1.2)	4 (2–10)	8.9 (8.5–9.4)	2 (1–6)	6.0 (5.9–6.2)
7	194	2046	2 (1–4)	4.5 (4.0–4.9)	2 (1–3)	3.6 (3.5–3.8)	1 (1–2)	2.0 (1.5–2.7)	1 (0–1)	1.2 (1.1–1.3)	3 (1–6)	7.8 (7.2–8.4)	2 (1–6)	6.2 (6.0–6.4)
8	89	965	2 (1–3)	3.9 (3.2–4.7)	1 (1–3)	3.8 (3.5–4.1)	1 (1–1)	2.5 (1.1–4.8)	1 (0–1)	1.6 (1.3–1.9)	2 (1–4)	7.4 (6.3–8.5)	2 (1–4)	7.0 (6.6–7.3)

[a]Median healthcare resource utilization was defined by the median number of contacts, episodes, days, visits, or treatments/examinations per person at risk in the cohort on January 1 of the respective year.
[b]Mean healthcare intensity was calculated as number of contacts, episodes, days, visits, or treatments/examinations divided by person-years at risk (each individual provided person-time to every year until date of a censoring event).

included 11 181 nonET, 10 873 nonPV, 5217 nonMF, and 5466 nonMPN-U comparisons, yielding 32 737 nonMPN comparisons.

Median age at MPN diagnosis was 67 years (IQR: 55–76) for ET, 69 years (IQR: 61–77) for PV, 72 years (IQR: 63–80) for MPN-U, and 73 years (IQR: 66–79) for MF patients (Table 1). Women comprised 60% of ET, 52% of MPN-U, 50% of PV, and 42% of MF patients. In all cohorts, most patients had an education of medium length (38%–45% across cohorts). Across MPN subtypes, a smaller proportion of patients (ranging from 57% in MF to 63% in ET) than comparisons (ranging from 68% in nonMF to 75% in nonET) had not been diagnosed with any comorbidity according to CCI at the time of index.

The median follow-up was 3.6 years (IQR: 2.1–5.3) in ET, 3.6 years (IQR: 2.3–5.3) in PV, 2.8 years (IQR: 1.5–4.7) in MF, and 2.8 years (IQR: 1.7–4.8) in MPN-U patients (Table 1). The median follow-up was 3.6–3.9 years across comparison cohorts. During follow-up, 750 MPN patients (22%) and 4627 nonMPN comparisons (14%) died (all-cause mortality). The proportion of deaths among ET patients (14%) and PV patients (16%) was similar to that observed in their comparisons, while the proportion of deaths among MPN-U patients (35%) and MF patients (42%) was twofold that in their comparisons (Table 1).

3.2 | Healthcare resource utilization

3.2.1 | Pre-diagnosis period

In the pre-diagnosis period, MPN patients in all cohorts had higher median number of all types of HRU than their matched comparisons (Tables 2–5). Accordingly, the mean number of all types of HRU per person-years at risk, that is, the intensity, was higher among MPN patients than among their comparisons during the 2 years preceding diagnosis, corresponding to RRs >1 (Figure 1 and Table S3). In the pre-diagnosis period, especially during the year preceding diagnosis, the discrepancy between patients and comparisons in terms of RR was greatest for inpatient days (year −1 relative to index: ET, 1.7 [95% CI: 1.6–1.9]; PV, 1.7 [95% CI: 1.6–1.8]; MF, 1.8 [95% CI: 1.7–2.0]; and MPN-U, 3.1 [95% CI: 2.8–3.4]) and ED visits (year −1 relative to index: ET, 1.8 [95% CI: 1.7–1.9]; PV, 1.9 [95% CI: 1.8–2.0]; MF, 1.6 [95% CI: 1.4–1.7]; and MPN-U, 1.8 [95% CI: 1.7–2.0]).

In all four patient cohorts, there was an increase in the median number and intensity of GP contacts, hospital inpatient days, hospital outpatient visits, and hospital treatments/examinations from 2 years before diagnosis to 1 year before diagnosis (Tables 2–5). This pattern was not as pronounced in the four comparison cohorts. Median number and intensity of hospitalizations and ED visits remained stable during the pre-diagnosis period in all cohorts.

3.2.2 | Post-diagnosis period

A common trait for all patient and comparison cohorts was that the median number and intensity of hospitalizations and ED visits remained relatively stable throughout follow-up (Tables 2–5).

TABLE 3 Healthcare resource utilization in PV patients and $_{non}$PV comparisons pre- and post-diagnosis

Year relative to index	Persons at-risk, *n*		GP contacts				Hospitalizations				Inpatient days			
	PV	$_{non}$PV	PV		$_{non}$PV		PV		$_{non}$PV		PV		$_{non}$PV	
			Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]
−2	1109	10 873	8 (3–13)	9.7 (9.5–9.8)	7 (3–13)	9.0 (9.0–9.1)	1 (1–2)	1.4 (1.2–1.6)	1 (0–1)	1.0 (1.0–1.0)	3 (1–6)	5.5 (5.1–5.8)	1 (0–4)	4.3 (4.3–4.4)
−1	1109	10 873	11 (7–17)	12.7 (12.5–13.0)	7 (3–13)	9.4 (9.3–9.4)	1 (1–2)	1.5 (1.4–1.6)	1 (0–1)	1.1 (1.0–1.1)	4 (1–9)	8.4 (8.1–8.6)	1 (0–5)	4.9 (4.9–5.0)
1	1109	10 873	11 (6–18)	13.5 (13.3–13.7)	7 (3–13)	9.7 (9.6–9.7)	1 (1–2)	1.8 (1.7–2.0)	1 (0–1)	1.2 (1.2–1.2)	3 (1–8)	7.5 (7.2–7.7)	1 (0–6)	6.0 (5.9–6.1)
2	1080	10 499	10 (5–16)	13.3 (13.0–13.5)	7 (3–13)	10.5 (10.5–10.6)	1 (1–2)	1.8 (1.6–1.9)	1 (0–1)	1.3 (1.2–1.3)	3 (1–7)	9.0 (8.6–9.4)	1 (0–5)	5.9 (5.8–6.0)
3	883	8612	10 (5–16)	13.1 (12.9–13.4)	7 (3–14)	10.7 (10.6–10.8)	1 (1–2)	2.0 (1.8–2.2)	1 (0–1)	1.4 (1.3–1.4)	4 (1–11)	8.7 (8.3–9.2)	1 (0–6)	6.4 (6.2–6.5)
4	685	6748	9 (5–15)	13.5 (13.2–13.8)	7 (3–13)	11.2 (11.1–11.3)	1 (1–2)	2.0 (1.8–2.3)	1 (0–2)	1.4 (1.3–1.5)	4 (1–10)	9.0 (8.5–9.6)	1 (0–6)	6.4 (6.3–6.5)
5	465	4766	10 (5–15)	13.6 (13.2–13.9)	8 (3–14)	11.7 (11.6–11.8)	1 (1–2)	2.3 (2.0–2.6)	1 (1–2)	1.5 (1.4–1.5)	4 (1–13)	11.8 (11.1–12.5)	1 (0–7)	7.6 (7.4–7.8)
6	317	3259	9 (5–14)	13.8 (13.4–14.3)	8 (3–14)	12.3 (12.2–12.5)	1 (1–2)	2.2 (1.8–2.6)	1 (1–2)	1.4 (1.4–1.5)	6 (1–11)	12.7 (11.8–13.6)	1 (1–6)	6.3 (6.1–6.5)
7	189	1998	9 (4–15)	15.5 (14.9–16.2)	8 (3–14)	13.2 (13.0–13.4)	1 (1–2)	2.3 (1.9–2.9)	1 (1–1)	1.5 (1.4–1.6)	4 (1–10)	15.2 (14.0–16.5)	2 (1–6)	7.4 (7.1–7.7)
8	83	927	10 (6–14)	23.7 (22.3–25.3)	8 (3–14)	21.4 (21.0–21.8)	1 (1–3)	3.5 (2.4–5.0)	1 (0–1)	1.8 (1.5–2.2)	9 (2–35)	28.6 (25.2–32.4)	1 (0–4)	7.5 (6.9–8.2)

Year relative to index	Persons at-risk, *n*		Outpatient visits				ED visits				Treatments/examinations			
	PV	$_{non}$PV	PV		$_{non}$PV		PV		$_{non}$PV		PV		$_{non}$PV	
			Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]
−2	1109	10 873	2 (1–4)	3.4 (3.2–3.5)	2 (1–3)	2.9 (2.9–3.0)	1 (1–1)	1.3 (1.1–1.5)	1 (0–1)	0.7 (0.7–0.7)	3 (1–6)	5.0 (4.9–5.2)	2 (1–5)	4.9 (4.9–5.0)
−1	1109	10 873	3 (2–6)	4.5 (4.4–4.7)	2 (1–4)	3.5 (3.5–3.6)	1 (1–2)	1.4 (1.3–1.6)	1 (0–1)	0.7 (0.7–0.8)	4 (2–9)	7.1 (6.9–7.3)	2 (1–6)	5.4 (5.3–5.4)
1	1109	10 873	12 (7–17)	13.0 (12.8–13.3)	2 (1–4)	3.8 (3.8–3.9)	1 (1–2)	1.5 (1.3–1.7)	1 (0–1)	0.8 (0.8–0.9)	16 (9–23)	18.0 (17.7–18.3)	2 (1–6)	6.1 (6.0–6.2)
2	1080	10 499	6 (3–10)	7.9 (7.7–8.1)	2 (1–4)	3.8 (3.8–3.9)	1 (1–1)	1.5 (1.3–1.6)	1 (0–1)	0.8 (0.8–0.9)	8 (4–13)	11.3 (11.1–11.5)	2 (1–6)	6.1 (6.0–6.1)
3	883	8612	5 (2–9)	7.0 (6.8–7.2)	2 (1–4)	3.9 (3.8–3.9)	1 (1–2)	1.6 (1.4–1.9)	1 (0–1)	1.0 (0.9–1.0)	7 (3–13)	10.8 (10.5–11.0)	2 (1–6)	6.3 (6.2–6.3)

TABLE 3 (Continued)

Year relative to index	Persons at-risk, *n*		Outpatient visits				ED visits				Treatments/examinations			
	PV	nonPV	PV		nonPV		PV		nonPV		PV		nonPV	
			Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]
4	685	6748	5 (2–8)	7.0 (6.8–7.3)	2 (1–4)	4.0 (3.9–4.0)	1 (1–2)	1.5 (1.3–1.8)	1 (0–1)	1.0 (1.0–1.1)	6 (3–12)	10.6 (10.3–10.9)	2 (1–6)	6.3 (6.2–6.4)
5	465	4766	4 (2–8)	7.4 (7.1–7.8)	2 (1–4)	4.0 (3.9–4.1)	1 (1–2)	1.8 (1.4–2.1)	1 (0–1)	1.1 (1.1–1.2)	6 (3–12)	11.7 (11.3–12.1)	2 (1–6)	6.7 (6.6–6.8)
6	317	3259	4 (2–8)	8.2 (7.7–8.6)	2 (1–4)	4.0 (3.9–4.1)	1 (1–2)	1.9 (1.5–2.4)	1 (0–1)	1.2 (1.1–1.3)	6 (3–12)	12.7 (12.2–13.2)	2 (1–6)	6.5 (6.4–6.7)
7	189	1998	3 (2–6)	8.7 (8.1–9.3)	2 (1–4)	3.6 (3.4–3.7)	1 (1–1)	1.8 (1.2–2.6)	1 (0–1)	1.3 (1.1–1.4)	5 (2–11)	14.6 (13.8–15.4)	2 (1–6)	6.3 (6.1–6.4)
8	83	927	3 (1–6)	9.8 (8.6–11.2)	1 (1–3)	3.7 (3.4–4.0)	1 (1–2)	2.7 (1.6–4.3)	1 (0–1)	1.4 (1.1–1.7)	5 (1–10)	20.6 (18.8–22.5)	2 (1–4)	6.2 (5.8–6.5)

[a]Median healthcare resource utilization was defined by the median number of contacts, episodes, days, visits, or treatments/examinations per person at risk in the cohort on January 1 of the respective year.
[b]Mean healthcare intensity was calculated as number of contacts, episodes, days, visits, or treatments/examinations divided by person-years at risk (each individual provided person-time to every year until date of a censoring event).

ET patients versus nonET comparisons

During the years after diagnosis, ET patients had a higher annual median HRU than nonET comparisons regarding GP contacts, inpatient days, outpatient visits, as well as treatments/examinations (Table 2). The median number of GP contacts (11 [IQR: 5–18]), outpatient visits (9 [IQR: 5–13]), and treatments/examinations (10 [IQR: 5–16]) peaked in the first year post-diagnosis. Accordingly, we observed higher intensity of HRU among ET patients than among their comparisons regarding all types of HRU, corresponding to RRs varying from 2.7 (95% CI: 2.6–2.9) for outpatient visits in the first year post-diagnosis down to 1.0 (95% CI: 0.8–1.3) for outpatient visits in the eighth year post-diagnosis (Figure 1 and Table S3).

PV patients versus nonPV comparisons

In all years of follow-up, PV patients had a higher median number of GP contacts, inpatient days, outpatient visits, and treatments/examinations than their comparisons (Table 3). In PV patients, the median number of outpatient visits (12 [IQR: 7–17]) and treatments/examinations (16 [IQR: 9–23]) peaked in the first year of follow-up. In contrast, the median number of inpatient days increased during follow-up from 3 days (IQR: 1–8) in the first year post-diagnosis to 9 days (IQR: 2–35) in the eighth year, while remaining stable at 1–2 days in nonPV comparisons. The largest differences in the intensity of HRU between PV and nonPV were observed in the last year of follow-up for most types of HRU: hospitalizations (RR = 1.9 [95% CI: 1.5–2.4]), inpatients days (RR = 3.8 [95% CI: 3.0–4.8]), ED visits (RR = 2.0 [95% CI; 1.6–2.5]), and treatments/examinations (RR = 3.3 [95% CI: 2.7–4.2]) (Figure 1 and Table S3).

MF patients versus nonMF comparisons

MF patients had a higher median number than nonMF comparisons regarding hospitalizations, inpatient days, outpatient visits, and treatments/examinations (Table 4). In MF patients, the median number of outpatient visits (13 [IQR: 8–20]) and treatments/examinations (17 [IQR: 10–32]) was particularly high in the first year of follow-up. For MF patients, the median number of inpatient days peaked with 12 days (IQR: 7–27) in the sixth year post-diagnosis, while it remained at 2–3 days in nonMF comparisons. Correspondingly, we observed a first peak in RR for both GP contacts (1.4 [95% CI: 1.3–1.6]) and hospital-related HRU types, including ED visits (1.8 [95% CI: 1.6–1.9]) in the first year after MPN diagnosis (Figure 1 and Table S3). This was followed by a second peak in all types of hospital contacts in the sixth year post-diagnosis with RRs ranging from 1.8 (95% CI: 1.5–2.1) for ED visits to 2.9 (95% CI: 2.4–3.6) for inpatient days.

MPN-U patients versus nonMPN-U comparisons

In line with the findings in the other MPN subtypes, patients registered with MPN-U had a higher median number of GP contacts, inpatient days, outpatient visits, and treatments/examinations than nonMPN-U comparisons (Table 5). In addition, a peak in median HRU was seen in MPN-U in the first year following diagnosis regarding GP contacts (13 [IQR: 7–21]), outpatient visits (10 [IQR: 5–16]), and treatments/examinations (14 [IQR: 6–26]). The largest discrepancies in the

TABLE 4 Healthcare resource utilization in MF patients and $_{non}$MF comparisons pre- and post-diagnosis

Year relative to index	Persons at-risk, *n*		GP contacts				Hospitalizations				Inpatient days			
	MF	$_{non}$MF	MF		$_{non}$MF		MF		$_{non}$MF		MF		$_{non}$MF	
			Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]
−2	533	5217	9 (4–14)	10.5 (10.2–10.8)	7 (3–14)	9.7 (9.6–9.8)	1 (1–2)	1.7 (1.4–1.9)	1 (0–1)	1.2 (1.1–1.2)	4 (1–11)	7.8 (7.3–8.4)	1 (0–6)	5.8 (5.6–5.9)
−1	533	5217	12 (7–19)	14.0 (13.7–14.4)	8 (3–14)	10.0 (9.9–10.1)	1 (1–2)	1.8 (1.6–2.0)	1 (0–2)	1.2 (1.2–1.3)	6 (2–16)	11.5 (11.1–11.9)	1 (0–7)	6.2 (6.0–6.3)
1	533	5217	11 (6–19)	15.0 (14.7–15.4)	8 (4–14)	10.4 (10.4–10.5)	2 (1–4)	3.2 (3.0–3.4)	1 (1–2)	1.4 (1.4–1.5)	7 (2–24)	20.2 (19.6–20.7)	2 (1–8)	7.3 (7.2–7.5)
2	462	4990	10 (5–17)	14.5 (14.2–14.9)	8 (4–14)	11.2 (11.1–11.2)	2 (1–3)	3.3 (3.0–3.6)	1 (0–2)	1.5 (1.4–1.5)	9 (2–22)	21.4 (20.7–22.1)	2 (0–8)	7.4 (7.2–7.5)
3	338	4107	10 (4–17)	14.1 (13.6–14.5)	8 (4–15)	11.7 (11.6–11.8)	2 (1–3)	2.8 (2.5–3.1)	1 (1–2)	1.7 (1.6–1.7)	6 (2–15)	13.4 (12.7–14.1)	2 (1–9)	8.1 (8.0–8.3)
4	249	3236	10 (4–18)	14.3 (13.8–14.8)	8 (4–15)	11.7 (11.6–11.8)	2 (1–3)	2.6 (2.3–3.0)	1 (1–2)	1.7 (1.6–1.7)	5 (1–14)	12.1 (11.4–12.8)	2 (1–8)	8.3 (8.1–8.5)
5	184	2545	9 (5–17)	15.0 (14.4–15.6)	8 (4–15)	12.8 (12.7–13.0)	2 (1–2)	2.5 (2.1–3.0)	1 (1–2)	1.7 (1.6–1.8)	5 (1–14)	13.7 (12.7–14.7)	2 (1–9)	8.0 (7.8–8.2)
6	114	1688	8 (3–15)	15.8 (14.9–16.7)	9 (4–16)	14.2 (14.0–14.4)	2 (1–4)	4.0 (3.1–5.0)	1 (1–2)	2.0 (1.8–2.1)	12 (7–27)	28.0 (25.7–30.6)	3 (1–10)	9.5 (9.2–9.8)
7	51	995	9 (5–15)	16.1 (14.8–17.5)	9 (4–15)	16.1 (15.8–16.4)	2 (1–3)	2.4 (1.6–3.4)	1 (1–2)	2.0 (1.8–2.2)	5 (1–13)	8.6 (7.1–10.4)	3 (1–8)	9.2 (8.8–9.7)
8	26	434	12 (6–23)	30.4 (27.6–33.4)	10 (4–16)	23.5 (22.8–24.1)	2 (1–2)	2.4 (0.9–5.2)	1 (1–1)	2.8 (2.3–3.4)	4 (2–18)	15.6 (11.1–21.4)	2 (1–7)	10.4 (9.4–11.5)

Year relative to index	Persons at-risk, *n*		Outpatient visits				ED visits				Treatments/examinations			
	MF	$_{non}$MF	MF		$_{non}$MF		MF		$_{non}$MF		MF		$_{non}$MF	
			Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]
−2	533	5217	2 (1–5)	4.5 (4.3–4.8)	2 (1–4)	3.2 (3.1–3.3)	1 (1–1)	1.2 (0.9–1.4)	1 (0–1)	0.9 (0.8–0.9)	3 (2–7)	7.1 (6.8–7.4)	2 (1–6)	5.4 (5.4–5.5)
−1	533	5217	4 (2–7)	6.3 (6.0–6.5)	2 (1–5)	4.1 (4.0–4.1)	1 (1–1)	1.4 (1.2–1.6)	1 (0–1)	0.9 (0.8–0.9)	6 (2–11)	9.3 (9.0–9.5)	3 (1–7)	6.2 (6.1–6.3)
1	533	5217	13 (8–20)	17.0 (16.6–17.3)	2 (1–5)	4.2 (4.2–4.3)	1 (1–2)	1.7 (1.4–1.9)	1 (0–1)	0.9 (0.9–1.0)	17 (10–32)	26.9 (26.4–27.3)	3 (1–7)	6.6 (6.5–6.7)
2	462	4990	7 (4–12)	12.2 (11.8–12.6)	2 (1–5)	4.1 (4.0–4.2)	1 (1–2)	1.7 (1.4–2.0)	1 (0–1)	1.0 (1.0–1.1)	10 (5–23)	20.5 (20.0–21.0)	3 (1–6)	6.7 (6.6–6.8)
3	338	4107	6 (3–12)	9.8 (9.4–10.2)	2 (1–5)	4.4 (4.3–4.5)	1 (1–2)	1.6 (1.3–2.0)	1 (0–1)	1.1 (1.0–1.2)	8 (4–19)	16.1 (15.6–16.6)	3 (1–7)	7.0 (6.9–7.1)

TABLE 4 (Continued)

Year relative to index	Persons at-risk, *n*		Outpatient visits				ED visits				Treatments/examinations			
	MF	nonMF	MF		nonMF		MF		nonMF		MF		nonMF	
			Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]
4	249	3236	5 (2–11)	9.3 (8.9–9.7)	2 (1–5)	4.3 (4.2–4.4)	1 (1–2)	1.6 (1.2–2.0)	1 (0–1)	1.1 (1.1–1.2)	8 (4–20)	16.1 (15.6–16.7)	3 (1–8)	7.1 (7.0–7.2)
5	184	2545	5 (3–9)	8.5 (8.0–9.0)	2 (1–5)	4.5 (4.4–4.6)	1 (1–2)	1.7 (1.3–2.3)	1 (0–1)	1.3 (1.2–1.4)	8 (4–18)	15.2 (14.5–15.9)	3 (1–7)	7.2 (7.1–7.4)
6	114	1688	4 (2–9)	8.2 (7.5–8.9)	2 (1–5)	4.2 (4.1–4.4)	1 (1–2)	2.5 (1.6–3.7)	1 (1–1)	1.4 (1.3–1.6)	6 (3–17)	18.0 (17.0–19.1)	3 (1–8)	6.9 (6.7–7.1)
7	51	995	4 (1–6)	5.6 (4.7–6.6)	2 (1–4)	3.7 (3.5–3.9)	2 (1–4)	2.3 (1.2–3.9)	1 (1–2)	1.7 (1.5–1.9)	5 (2–15)	12.0 (10.7–13.4)	2 (1–6)	7.0 (6.7–7.2)
8	26	434	2 (1–4)	5.4 (3.9–7.2)	2 (1–3)	4.8 (4.4–5.3)	1 (1–2)	2.2 (0.9–4.6)	1 (1–1)	1.7 (1.3–2.2)	3 (2–6)	11.2 (9.2–13.5)	2 (1–5)	7.4 (6.8–7.9)

[a]Median healthcare resource utilization was defined by the median number of contacts, episodes, days, visits, or treatments/examinations per person at risk in the cohort on January 1 of the respective year.
[b]Mean healthcare intensity was calculated as number of contacts, episodes, days, visits, or treatments/examinations divided by person-years at risk (each individual provided person-time to every year until date of a censoring event).

intensity of HRU between MPN-U and nonMPN-U were observed for inpatient days (RR = 3.1 [95% CI: 2.8–3.4]) in the year preceding diagnosis; and for GP contacts (RR = 1.5 [95% CI: 1.4–1.7]), outpatient visits (RR = 3.7 [95% CI: 3.4–4.0]), ED visits (RR = 2.1 [95% CI: 1.9–2.3]), and treatments/examinations (RR = 3.8 [95% CI: 3.5–4.1]) in the first year following diagnosis (Figure 1 and Table S3).

4 | DISCUSSION

This is the first nationwide study to report detailed pre- and post-diagnostic data on HRU in patients with ET, PV, MF, and MPN-U. We found that, compared with matched comparisons, MPN patients had an overall higher HRU throughout the study period regardless of MPN subtype. Interestingly, our study also revealed substantial increases of most HRU measures from 2 years before the MPN diagnosis.

Overall, baseline characteristics of the Danish MPN patients, such as age at diagnosis, male-to-female ratio, and MPN subtype distribution, were comparable with the existing literature.[34–37] Further, in line with previous findings, Danish MPN patients had higher mortality than the matched comparisons during the study period, which was driven by a more than twofold higher mortality among MF and MPN-U patients relative to their comparisons.[36,38] Diverging results on mortality of patients with MPN-U exist.[36,39] In a Norwegian registered-based study,[36] standardized mortality rates were substantially elevated in patients with MPN-U (and MF) compared with the background population, thus similar to our study population. Conversely, a newly published retrospective study[39] investigating MPN-associated splanchnic vein thromboses, found that patients with MPN-U had a particularly indolent phenotype with low mortality.

When assessing HRU by MPN subtype, several results are worth highlighting. Even though ET is often considered indolent, we still observed that ET patients had an overall higher HRU than the matched nonET individuals throughout our study, which is in accordance with previous results.[18,19] Interestingly, we found that the intensity of outpatient visits and hospital treatments/examinations was highest in the first year after diagnosis. In line with our findings, Bankar et al. also reported the highest HRU around the time of diagnosis.[19] The high HRU in the first year after diagnosis is most likely explained by diagnostic work-up and frequent visits during treatment initiation, but it may also reflect attention drawn to comorbidity or complications. For example, Hultcrantz et al. showed a nearly 10-fold elevation in venous thrombosis rate 3 months after diagnosis in MPN patients.[8,40] We found no major fluctuations in RRs for HRU in the remaining years of follow-up (up to 8 years), which is in agreement with studies reporting that ET progression often occurs beyond the first decade post-diagnosis.[41]

In line with the existing literature, PV patients constituted a larger HRU burden than nonPV individuals in all years of follow-up.[18,19] Noteworthy, the increase in RRs for outpatient visits and treatments/examinations within the first year after diagnosis was even more pronounced for PV than for ET. This likely reflects the initial requirement of frequent phlebotomies, in addition to diagnostic work-up and initiation of cytoreductive therapy. Given the higher average age in PV

TABLE 5 Healthcare resource utilization in MPN-U patients and $_{non}$MPN-U comparisons pre- and post-diagnosis

Year relative to index	Persons at-risk, *n*		GP contacts				Hospitalizations				Inpatient days			
	MPN-U	$_{non}$MPN-U	MPN-U		$_{non}$MPN-U		MPN-U		$_{non}$MPN-U		MPN-U		$_{non}$MPN-U	
			Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]
−2	560	5466	9 (4–16)	11.3 (11.0–11.5)	7 (3–13)	9.4 (9.3–9.5)	1 (1–2)	1.7 (1.5–2.0)	1 (0–1)	1.0 (1.0–1.1)	5 (1–10)	8.5 (8.0–9.0)	1 (0–5)	4.9 (4.8–5.1)
−1	560	5466	13 (8–20)	14.9 (14.5–15.2)	8 (3–14)	10.0 (9.9–10.1)	1 (1–2)	1.8 (1.6–2.0)	1 (0–1)	1.1 (1.1–1.2)	8 (2–18)	15.9 (15.5–16.5)	1 (0–5)	5.1 (5.0–5.3)
1	560	5466	13 (7–21)	15.5 (15.2–15.9)	8 (3–14)	10.2 (10.1–10.3)	1 (1–3)	2.6 (2.4–2.8)	1 (0–2)	1.3 (1.2–1.3)	6 (2–21)	16.9 (16.4–17.5)	1 (0–7)	6.2 (6.1–6.4)
2	504	5265	11 (6–19)	15.5 (15.1–15.8)	8 (3–14)	11.1 (11.0–11.2)	1 (1–3)	2.6 (2.4–2.9)	1 (0–2)	1.3 (1.3–1.4)	6 (1–17)	13.8 (13.2–14.4)	1 (0–6)	6.1 (6.0–6.3)
3	377	4189	10 (6–18)	15.4 (15.0–15.8)	8 (3–14)	11.7 (11.6–11.8)	2 (1–3)	3.2 (2.9–3.6)	1 (0–2)	1.5 (1.4–1.5)	8 (2–17)	16.2 (15.5–17.1)	1 (0–7)	6.9 (6.8–7.1)
4	268	3284	9 (5–16)	14.2 (13.7–14.7)	8 (3–14)	11.8 (11.7–11.9)	1 (1–3)	2.8 (2.4–3.3)	1 (1–2)	1.5 (1.4–1.6)	7 (1–16)	16.1 (15.1–17.1)	2 (0–8)	7.3 (7.1–7.6)
5	185	2447	10 (5–18)	14.6 (14.0–15.2)	8 (4–14)	11.7 (11.5–11.8)	2 (1–2)	2.2 (1.8–2.7)	1 (1–1)	1.4 (1.3–1.5)	9 (2–16)	14.3 (13.1–15.5)	2 (1–7)	6.2 (6.0–6.5)
6	130	1788	11 (5–17)	15.8 (15.1–16.6)	8 (3–14)	12.7 (12.5–12.8)	1 (1–2)	2.0 (1.5–2.7)	1 (1–2)	1.5 (1.4–1.7)	2 (1–8)	8.8 (7.7–10.0)	2 (1–7)	7.1 (6.8–7.4)
7	73	1137	10 (6–15)	16.8 (15.7–17.9)	8 (3–14)	13.2 (12.9–13.4)	1 (1–2)	2.5 (1.8–3.4)	1 (1–2)	1.6 (1.4–1.8)	1 (1–7)	7.8 (6.5–9.3)	2 (1–6)	6.1 (5.7–6.4)
8	30	508	9 (6–15)	23.2 (20.9–25.7)	8 (3–14)	19.0 (18.4–19.5)	2 (1–2)	3.4 (1.1–8.0)	1 (1–1)	1.8 (1.4–2.2)	11 (1–13)	17.1 (11.1–25.3)	1 (1–5)	6.6 (5.9–7.4)
Year relative to index	Persons at-risk, *n*		Outpatient visits				ED visits				Treatments/examinations			
	MPN-U	$_{non}$MPN-U	MPN-U		$_{non}$MPN-U		MPN-U		$_{non}$MPN-U		MPN-U		$_{non}$MPN-U	
			Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]
−2	560	5466	2 (1–5)	3.8 (3.6–4.0)	2 (1–4)	2.9 (2.8–2.9)	1 (1–2)	1.3 (1.1–1.6)	1 (0–1)	0.7 (0.7–0.8)	3 (1–7)	7.1 (6.8–7.4)	2 (1–5)	4.8 (4.7–4.9)
−1	560	5466	3 (2–7)	5.5 (5.3–5.7)	2 (1–4)	3.5 (3.4–3.6)	1 (1–2)	1.4 (1.2–1.7)	1 (0–1)	0.8 (0.7–0.8)	5 (2–11)	10.1 (9.8–10.4)	2 (1–6)	5.4 (5.3–5.5)
1	560	5466	10 (5–16)	13.6 (13.3–13.9)	2 (1–4)	3.7 (3.6–3.8)	1 (1–2)	1.8 (1.5–2.0)	1 (0–1)	0.8 (0.8–0.9)	14 (6–26)	23.1 (22.7–23.5)	2 (1–7)	6.1 (6.0–6.2)
2	504	5265	5 (2–10)	9.0 (8.7–9.4)	2 (1–4)	3.9 (3.8–4.0)	1 (1–2)	1.7 (1.4–1.9)	1 (0–1)	1.0 (0.9–1.0)	8 (3–16)	15.0 (14.6–15.4)	2 (1–7)	6.4 (6.3–6.5)
3	377	4189	4 (2–9)	8.2 (7.9–8.6)	2 (1–4)	3.8 (3.7–3.9)	1 (1–2)	1.9 (1.6–2.3)	1 (0–1)	1.0 (0.9–1.1)	7 (3–16)	14.4 (14.0–14.9)	2 (1–7)	6.4 (6.3–6.5)

TABLE 5 (Continued)

Year relative to index	Persons at-risk, *n*		Outpatient visits				ED visits				Treatments/examinations			
	MPN-U	$_{non}$MPN-U	MPN-U		$_{non}$MPN-U		MPN-U		$_{non}$MPN-U		MPN-U		$_{non}$MPN-U	
			Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]	Median (IQR)[a]	Mean (95% CI)[b]
4	268	3284	4 (2–9)	7.9 (7.5–8.4)	2 (1–4)	3.9 (3.8–4.0)	1 (1–2)	2.1 (1.6–2.7)	1 (0–1)	1.1 (1.0–1.2)	7 (3–17)	14.1 (13.6–14.7)	3 (1–7)	6.6 (6.5–6.7)
5	185	2447	4 (2–9)	7.0 (6.5–7.5)	2 (1–4)	3.8 (3.7–4.0)	1 (1–1)	1.5 (1.1–2.0)	1 (0–1)	1.1 (1.0–1.2)	6 (2–13)	11.7 (11.0–12.3)	3 (1–6)	6.3 (6.2–6.5)
6	130	1788	3 (1–7)	7.0 (6.4–7.8)	2 (1–4)	4.4 (4.2–4.5)	1 (1–1)	1.5 (0.9–2.3)	1 (0–1)	1.2 (1.1–1.4)	6 (2–9)	10.4 (9.6–11.2)	3 (1–7)	7.2 (7.0–7.4)
7	73	1137	2 (1–6)	5.9 (5.1–6.8)	2 (1–4)	4.2 (4.0–4.4)	1 (1–2)	2.6 (1.8–3.8)	1 (0–1)	1.3 (1.1–1.5)	3 (2–8)	10.3 (9.3–11.4)	3 (1–6)	6.7 (6.5–6.9)
8	30	508	3 (1–5)	4.9 (3.5–6.8)	1 (1–3)	3.5 (3.2–3.9)	1 (1–1)	2.5 (0.7–6.3)	1 (0–1)	1.6 (1.2–2.1)	5 (3–7)	11.8 (9.4–14.5)	2 (1–4)	6.0 (5.6–6.4)

[a]Median healthcare resource utilization was defined by the median number of contacts, episodes, days, visits, or treatments/examinations per person at risk in the cohort on January 1 of the respective year.
[b]Mean healthcare intensity was calculated as number of contacts, episodes, days, visits, or treatments/examinations divided by person-years at risk (each individual provided person-time to every year until date of a censoring event).

patients, differences in comorbidity may also in part explain this. In contrast to the nearly constant RRs between ET patients and $_{non}$ET comparisons during the subsequent years of follow-up, the discrepancy in HRU between PV and $_{non}$PV comparisons increased noticeably from the first to the eighth year after diagnosis. In particular, high RRs of inpatient days and treatments/examinations were present in the last year of follow-up. This increased difference in HRU between PV patients and $_{non}$PV comparisons toward the end of follow-up could reflect progression of PV and PV-associated comorbidity. However, cautious interpretation is necessary, as numbers were small and confidence intervals wide. Also important to notice is the considerably higher mean HRU intensity than median HRU, especially in the later years of follow-up. Such skewed distributions are common for HRU data and illustrate that a subgroup of patients have substantially higher HRU than the majority of patients.[42] In our study, this subgroup might represent patients with particularly debilitating symptoms, refractory disease, or transformation to acute myeloid leukemia. In addition, previous studies have shown that HRU is significantly higher in PV patients who encounter a thromboembolic event.[43,44]

We found the most marked differences in HRU between MF patients and $_{non}$MF comparisons, which substantiates previous findings.[2,4,45] Interestingly, the HRU of MF patients displayed a different pattern from the HRU of ET and PV patients, displaying a second peak in RRs of hospital-related HRU in the sixth year of follow-up. Especially, the intensity of inpatient days among MF patients was significantly higher than among $_{non}$MF comparisons. Conversely, much lower RRs for HRU were found in the last 2 years of follow-up. Given the poor prognosis of MF, the declined HRU in these years is probably a consequence of a longer survival in MF patients with low HRU, for example, patients with prefibrotic myelofibrosis categorized as MF before the prefibrotic myelofibrosis diagnosis was introduced (2016). Besides the substantial HRU of MF patients, a Spanish study indicated that MF entails considerable indirect and non-medical costs (e.g., lost productivity and informal care).[46]

Another novel finding from the present study was that MPN-U patients had a substantially higher HRU than $_{non}$MPN-U comparisons. MPN-U is a heterogeneous entity including a wide spectrum of patients. At one end patients not yet fulfilling the diagnostic criteria for ET, PV, and MF and at the other end patients with advanced stage MPN with pronounced fibrosis and increased blasts.[47] The observed high mortality of MPN-U patients in our study indicates that the MPN-U population in Denmark (overall) represents relatively advanced-stage MPN, which is in line with a Danish nationwide questionnaire study,[48] reporting that patients with MPN-U had the worst health-related quality of life of the MPN subtypes.

In most years of follow-up, MPN patients had more registered GP contacts than their comparisons. Compared with the existing literature, MPN patients in our study had more GP contacts than outpatient visits, whereas Bankar et al. found that outpatient care was equally divided between GPs and outpatient specialists (hematologist or oncologist) for ET and PV, while MF was more often seen by an outpatient specialist.[19] In our study, GP contacts included telephone and email consultations, while outpatient consultations only included visits, which may contribute to the observed difference.

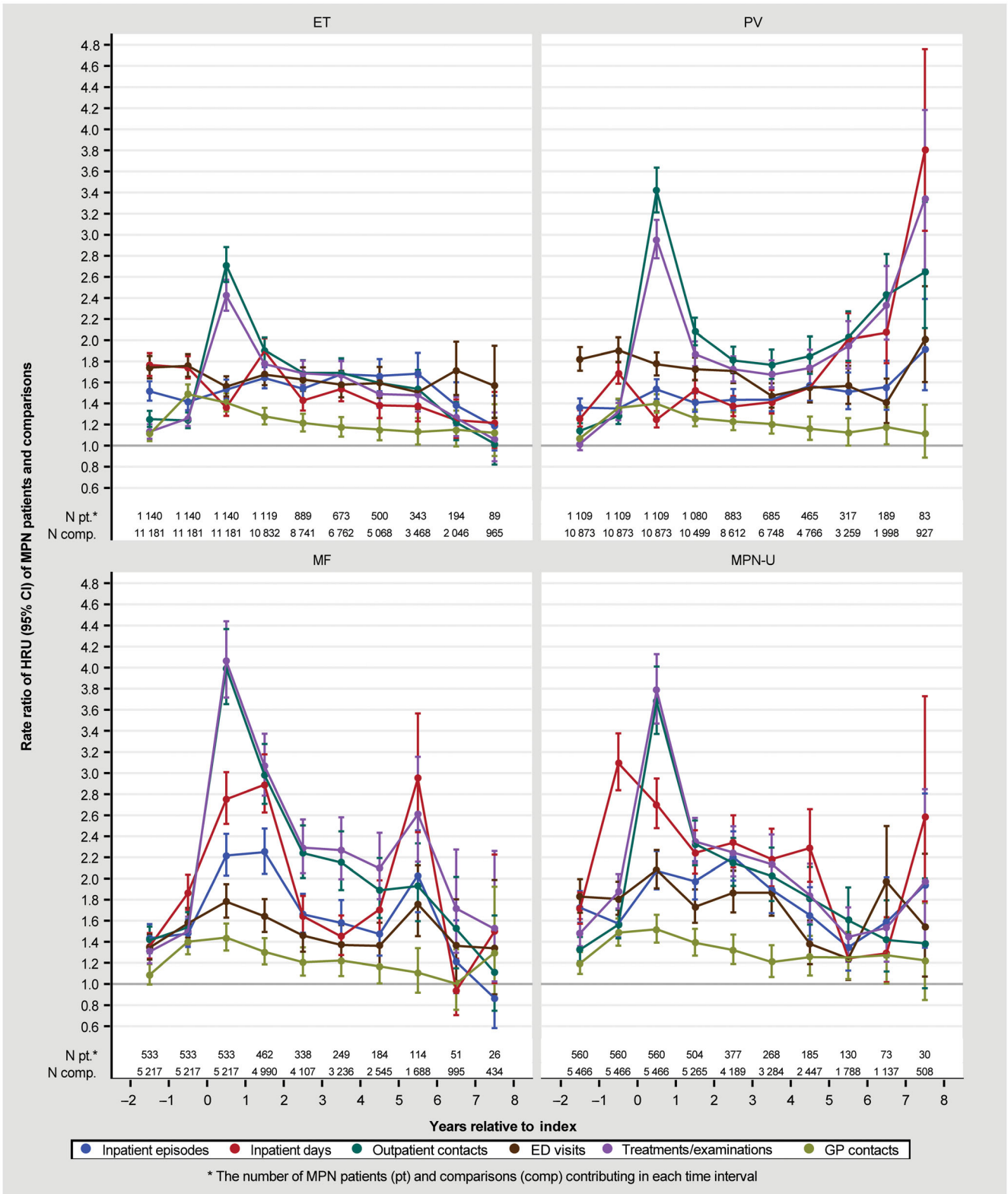

FIGURE 1 Rate ratios of healthcare resource utilization between ET, PV, MF, and MPN-U patients and their comparisons. comp, comparisons; ET, essential thrombocythemia; HRU, healthcare resource utilization; MPN, myeloproliferative neoplasms; MPN-U, unclassifiable myeloproliferative neoplasm; MF, myelofibrosis; pt, patients; PV, polycythemia vera

Of note, irrespective of MPN subtype, MPN patients were more often seen in the ED than $_{non}$MPN comparisons. In the study by Mehta et al., MPN patients also accounted for more ED visits than the matched comparisons.[18] The additional ED visits in MPN patients may represent acute MPN complications and side effects of MPN treatment.[5,7,8,11,13]

Assessing the pre-diagnostic period, MPN patients had a higher intensity of HRU than matched comparisons across HRU measures. For nearly all types of HRU, these differences were further augmented in the last year prior to diagnosis, possibly reflecting intensified diagnostic work-up. Interestingly, the highest RRs in the pre-diagnostic period were observed for inpatients days and ED visits, which might suggest that quite severe MPN manifestations, or MPN-associated comorbidity, are detectable at least 2 years before diagnosis. In support of these speculations, MPN patients have been found to have higher comorbidity than the background population before time of diagnosis,[19] which is in accordance with the baseline CCI scores found in the present study. The increased pre-diagnostic HRU was expected based on recent studies indicating that MPNs are often diagnosed months, or even years, after the first signs of MPN. For example, in the US Landmark Study, approximately half of the patients reported MPN-related symptoms ≥1 year before the diagnosis.[49] Further, a retrospective MPN study by Enblom et al. found that 66% of the vascular complications occurred during the 2 years preceding MPN diagnosis, and that blood test results frequently fulfilled the diagnostic criteria for MPN several months preceding diagnosis.[21] Lastly, a recent Danish screening study of cytosis and MPN driver mutations in the general population raised concerns about potential under-diagnosis of MPNs.[20]

Certain study limitations must be taken into consideration; First, despite a nationwide setting, limitations include small numbers toward the end of follow-up, as MPNs are rare diseases with an overall reduced survival. Moreover, patients diagnosed in the last part of the inclusion period did not have many years of follow-up. Second, misclassification within the MPN subtypes cannot be ruled out, as accurate classification can be difficult. However, in Denmark, all patients suspected of having a hematological disease are referred to hematology departments with equal access to diagnostic work-up like mutational analysis and bone marrow biopsy, which improves the diagnostic certainty. Third, the Danish National Health Service Registry has not yet been validated, but it does have an assumed high coverage as data collection is related to reimbursements of the GPs.[33] Fourth, we could not distinguish between HRU related to MPN and to comorbidity. However, as MPN patients had an increased comorbidity burden at baseline it is likely that comorbidity contributed to their augmented HRU. Finally, the matching of MPN patients and $_{non}$MPN comparisons might not have been balanced in the last years of follow-up due to longer survival of comparisons than patients.

A major strength of our study was the matched comparison design and the high quality of the Danish registries. Since 2010, it has been mandatory to report all newly diagnosed MPN patients to the DCMR. To ensure that no MPN patients are lost to follow-up, these reports are cross-merged with the DNPR.[24] This thorough registration, along with the nationwide design, diminishes selection bias. Another strength was the unambiguous linkage of data combined with the universal tax-funded healthcare system, ensuring close to complete data retrieval across healthcare sectors and accurate long-term follow-up. Finally, taking the demographic development[50] and the fact that MPNs, primarily, are cancers of the elderly into consideration, such HRU analyses are increasingly important for healthcare planning.

In conclusion, patients with MPN had a higher HRU than matched individuals without MPN. This was consistent across all MPN subtypes as well as different HRU measures. Our findings confirm a consistent HRU burden after the MPN diagnosis. Equally important, our study revealed substantially increased HRU in both the primary and secondary sectors 2 years before MPN diagnosis, warranting further exploration of the pre-diagnostic period, including the potential benefits of early detection.

AUTHOR CONTRIBUTIONS

Authors who contributed to the conceptualization, study design and/or protocol were Hans Carl Hasselbalch, Marie Bak, Henrik Frederiksen, Sarah Friis Christensen, Christian Fynbo Christiansen, Ellen Margrethe Mikkelsen, Lise Skovgaard Svingel, Björn Paulsson, and Anna Stenling. Data were analyzed and summarized by Anders Kjærsgaard, Bianka Darvalics, Ellen Margrethe Mikkelsen, Lise Skovgaard Svingel, whereas Hans Carl Hasselbalch, Henrik Frederiksen, Christen Lykkegaard Andersen, Jesper Stentoft, Mette Borg Clausen, Jørn Starklint, Marianne Tang Severinsen, and Morten Hagemann Hilsøe have contributed to data collection in DCMR. While the paper was written by Sarah Friis Christensen and Lise Skovgaard Svingel, the larger group of Christian Fynbo Christiansen, Anders Kjærsgaard, Bianka Darvalics, Ellen Margrethe Mikkelsen, Hans Carl Hasselbalch, Marie Bak, Henrik Frederiksen, Christen Lykkegaard Andersen, Jesper Stentoft, Mette Borg Clausen, Jørn Starklint, Marianne Tang Severinsen, Morten Hagemann Hilsøe, Anna Stenling, and Björn Paulsson have all actively contributed to the interpretation of the results and the revisions of the manuscript. All authors approved of the final version and are accountable for ensuring accuracy and integrity of the work.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

Individual patient data will not be shared.

ORCID

Sarah Friis Christensen https://orcid.org/0000-0003-2178-0440
Lise Skovgaard Svingel https://orcid.org/0000-0002-4938-037X
Marianne Tang Severinsen https://orcid.org/0000-0003-0996-1812
Hans Carl Hasselbalch https://orcid.org/0000-0003-3936-8032

Henrik Frederiksen https://orcid.org/0000-0001-8905-0220
Marie Bak https://orcid.org/0000-0002-1511-6749

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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