Mental health and use of psychotropic prescription drugs in adult patients with primary immune thrombocytopenia: a nationwide population-based cohort study

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Abstract

Patients with primary immune thrombocytopenia (ITP) suffer from reduced survival and quality of life, but the underlying reasons for this are largely undescribed. Mental health and the use of psychotropic drugs in ITP is unknown. We investigated the risk of hospital-registered mental health events including fatigue and the use of psychotropic drugs in adult patients with ITP compared with the general population, using nationwide registry-data. We identified 3,749 patients with ITP and 149,849 age- and sex-matched general population comparators in the Danish Health Registries in the period 1997-2016. The median age was 60 years (interquartile range [IQR], 40-73) and 53% were women. We followed the individuals for incident mental health events and estimated the use of psychotropic drugs over calendar-years and in temporal relation to diagnosis of ITP. The first year cumulative incidence of any mental health event was 2.3% (95% confidence interval [CI]: 1.9-2.9) in patients and 0.7% (95% CI: 0.6-0.7) in comparators, yielding an adjusted cause-specific hazard ratio (csHR) of 3.57 (95% CI: 2.84-4.50). The corresponding estimates for depression were 1.2% (95% CI: 0.9-1.6) and 0.3% (0.3-0.4) respectively, with an adjusted csHR of 3.53 (95% CI: 2.56-4.85). We found similar findings for anxiety and fatigue, but risks generally diminished after 1-5 years. The use of opioids, antidepressants, and benzodiazepines increased in temporal relation to diagnosis of ITP. The risk of mental health events and the use of psychotropic drugs is higher in adult patients with ITP compared with the general population, and has a temporal relation to diagnosis of ITP emphasizing that mental health in ITP is a concern.

Introduction

Primary immune thrombocytopenia (ITP) is a disease characterized by accelerated autoimmune destruction of platelets and impaired bone marrow platelet production, and requires a diagnostic process to exclude other causes of thrombocytopenia.[1-3] Both the incidence and prevalence of ITP increases with age and has increased during the past decades, making ITP an increasing health burden in Western populations.[4,5]

Both survival and quality of life is reduced in patients with ITP compared to the general population, but apart from bleeding tendency, the underlying mechanisms behind most health events in ITP are not well understood.[6-10] Studies suggest that this effect is mediated both by ITP disease in itself and associated factors, as well as immediate and late effects from treatments, e.g., the psychiatric side effects of high-dose corticosteroids.[11-15] Patients with ITP suffer from complications such as pronounced fatigue and social isolation, with the latter known to be associated with depression and lower quality of life.[16,17] The risk of major bleeding in ITP is low, but the fear of bleeding is present in many patients with ITP and associated with a large decline in quality of life.[18,19] Despite major gains in the number of available treatments for ITP over the past decades, the health-related quality of life in ITP is generally reduced and comparable to that of cancer patients.[7] This results in impaired physical and mental health, and affects social relations and work life.[7,10] The cross-sectional I-WISH worldwide study reported of high prevalence of fatigue in ITP and low levels of emotional well-being, arising from both low energy levels and fear of the ITP disease aggravating.[20,21] Fatigue is also known as a common symptom in ITP occurring in up to 39% of adult patients, and cor-

related with the severity of the ITP disease in terms of low platelet counts as well as the levels of inflammation.[22,23] The mechanisms underlying fatigue specifically in ITP and autoimmune disease in general are not well-understood, but likely involve multiple physiological processes.[24] The socioeconomic impact of ITP in terms of reduced working hours, work productivity, and increased risk of future unemployment could also worsen mental health in ITP.[20,25] Taken together it is unknown how these factors may affect mental health, or if the use of psychotropic drugs is increased in adults with ITP. Providing clinicians with such knowledge and identifying potential mental health risk factors could improve management and quality of life in patients with ITP.

We assessed the risk of mental health events and the mental health burden by studying hospital-registered mental health events including fatigue, and the use of psychotropic drugs in adult patients with ITP compared with the general population, using a large nationwide population-based cohort study with full follow-up.

Methods

Data sources

We used the public Danish health registries to identify patients, comparators, covariates and outcomes. Details on the application of each registry and an overview of data extraction can be found in the *Online Supplementary Appendix (Online Supplementary Figure S1)*. In general, the methods applied are described in detail in previous studies by us.[8,26]

Identification of patients, comparators, mental health events and drug use

We identified patients with ITP in the Danish National Patient Registry (DNPR) during 1997-2016, and assigned each patient with up to 40 age- and sex-matched comparators without ITP from the general population through the Danish Civil Registration System (DCRS). Matched individuals had the same sex and year of birth as their respective index patient. Patients with secondary ITP, Evans syndrome, and thrombocytopathies were excluded. All individuals were followed for the incident of mental health events: schizophrenia/psychosis, depression, mania and bipolarity, anxiety/obsessive-compulsive disorder (OCD), fatigue, and a first-ever category with the first registration of any of the five aforementioned (*Online Supplementary Table S1*). We acknowledge that fatigue is not a psychiatric disorder *per se*, but patients often complain of fatigue, which is potentially a significant mental health burden. Therefore, we opted to include fatigue in the category "any mental health event". We also estimated the use of the psychotropic drugs: antidepressants, antipsychotics, benzodiazepines, opioids, and a first-ever category (*Online Supplementary Table S1*). The prevalence of both mental health events and psychotropic drug use prior to ITP diagnosis was also estimated.

We identified mental health events including fatigue in the DNPR, and psychotropic drug use was estimated through reimbursed prescriptions in the Danish National Prescription Registry (NPR), using this as a proxy measure of mental health burden.

The prevalent comorbidity was based on diagnoses registered in the DNPR before or on index date.

Statistical analyses

Baseline characteristics were presented as medians with interquartile range (IQR) for age, and percentages with 95% confidence intervals (95% CI) for distributions of sex, age groups, prevalent comorbidities, prevalent mental health events, and prevalent use of psychotropic drugs. Comorbidity score was calculated as means with 95% CI of all prevalent comorbidity covariates.

We used Cox proportional hazard and Fine-Gray regression to estimate unadjusted and adjusted cause-specific hazard ratios (csHR) and subdistribution hazard ratios for mental health events including fatigue in patients with ITP compared with the general population. We adjusted analyses for the effects of calendar decade of diagnosis, the defined comorbidities as dichotomous variables, and the residual confounding of age and sex.[27] The absolute risk of mental health events was estimated as cumulative incidences. Death and emigration served as competing events.

For psychotropic drug use, we estimated the monthly incidence rates (IR) per 100-person-years (PY), incidence rate ratios (IRR), and incidence rate differences (IRD). We also estimated the prevalence proportions of patients and comparators receiving a minimum of one prescription in a given year within each category of psychotropic drugs. This was done for both calendar years and for each year in a period 5 years prior to and 10 years after diagnosis of ITP. All analyses were done separately for each outcome for the set of patients with ITP and their respective general population comparators.

Please refer to the *Online Supplementary Appendix* for details regarding methodical approaches and considerations.

Ethics approval

Registry-based research does not require Ethic Committee approval according to Danish law.

Results

We included 3,749 patients with ITP and 149,849 age- and sex-matched general population comparators, yielding a total of 153,598 individuals (Table 1). The total follow-up time was 21,753 PY (median 4.9 years) for ITP and 1,031,241 PY (median 6.2 years) for comparators.

Women comprised 53% and median age was 60 years (IQR, 40-73) in both patients and comparators. The age groups (18-59 years, 60+ years) were equally distributed between patients and comparators, and 39% were diagnosed with ITP in the period 1997-2006 and 61% in 2007-2016.

The mean comorbidity score was 0.52 (95% CI: 0.50-0.55) for ITP and 0.29 (95% CI: 0.28-0.29) for comparators. Among patients, 3.5% (95% CI: 2.9-4.1) had a comorbidity score >2 while this only applied for 1.3% (95% CI: 1.2-1.3) of the comparators (Table 1).

At the time of ITP diagnosis, depression was prevalent among 3.9% (95% CI: 3.3-4.6) of patients *versus* 2.8% (95% CI: 2.7-2.9) in comparators; 2.0% (95% CI: 1.6-2.5) of patients and 0.8% (95% CI: 0.8-0.9) of comparators had prevalent fatigue. Any mental health event was prevalent in 7.2% (95% CI: 6.4-8.1) of patients and 5.1% (95% CI: 5.0-5.2) of comparators (Table 1).

With the exception of antipsychotics, the prevalent use of psychotropic drugs up to 24 months prior to diagnosis of ITP was higher for all drug-groups in patients compared with comparators, with the highest use found in benzodiazepines (21% in patients and 16% in comparators) (Table 1).

Cumulative incidences and risk of mental health events

Mental health events and fatigue were more frequently registered in patients with ITP compared with the general population after index date, but differences generally diminished or equalized over time. The first year cumulative incidence of any mental health event was 2.3% (95% CI: 1.9-2.9) in patients and 0.7% (95% CI: 0.6-0.7) in comparators (Figure 1; *Online Supplementary Table S3*), with the highest subgroup incidence found in depression (1.2% [95% CI: 0.9-1.6] in patients and 0.3% [95% CI: 0.3-0.4] in comparators). The remaining subgroups also differed significantly during first year. Most cumulative incidence differences diminished (Figure 1; *Online Supplementary Table S3*), but persisted throughout the 5th year for depression and the 10th year for anxiety/OCD and fatigue.

The first year cumulative incidence of any mental health event in males with ITP was 2.1% (95% CI: 1.5-2.8) and 2.6%

Table 1. Baseline characteristics of patients with primary immune thrombocytopenia and general population age- and sex-matched comparators.

Characteristics	Primary ITP N=3,749	Comparators N=149,849
Women, % (95% CI)	53 (52-55)	53 (53-53)
Age in years, median (IQR)	60 (40-73)	60 (40-73)
Period of diagnosis, % (95% CI)		
1997-2006	39 (37-40)	39 (39-39)
2007-2016	61 (60-63)	61 (61-61)
Age groups, % (95% CI)		
18-59 years	50 (49-52)	50 (50-50)
60+ years	50 (48-51)	50 (50-50)
Prevalent comorbidity		
Comorbidity-score, mean (95% CI)	0.52 (0.50-0.55)	0.29 (0.28-0.29)
Low 0, % (95% CI)	64.4 (62.8-65.9)	78.2 (78.0-78.4)
Intermediate 1-2, % (95% CI)	32.1 (30.6-33.6)	20.6 (20.4-20.8)
High >2, % (95% CI)	3.5 (2.9-4.1)	1.3 (1.2-1.3)
Prevalent drug prescription <24 months before ITP, % (95% CI)		
Antidepressants	14.3 (13.2-15.4)	11.1 (11.0-11.3)
Antipsychotics	3.7 (3.2-4.4)	3.2 (3.2-3.3)
Opioids	20.3 (19.0-21.6)	13.8 (13.6-14.0)
Benzodiazepines	21.0 (19.7-22.4)	16.1 (15.9-16.3)
Any psychotropic drug	38.7 (37.2-40.3)	30.2 (30.0-30.5)
Prevalent mental health events including fatigue, % (95% CI)		
Schizophrenia/psychosis	1.2 (0.9-1.6)	0.9 (0.9-1.0)
Depression	3.9 (3.3-4.6)	2.8 (2.7-2.9)
Mania/bipolarity	0.2 (0.1-0.4)	0.4 (0.4-0.4)
Anxiety/OCD	0.9 (0.7-1.3)	1.2 (1.1-1.2)
Fatigue	2.0 (1.6-2.5)	0.8 (0.8-0.9)
Any mental health event	7.2 (6.4-8.1)	5.1 (5.0-5.2)
Number of mental health events >1, % (95% CI)	1.0 (0.7-1.4)	0.9 (0.8-0.9)

The category “any mental health event” included the first-ever hospital registration of schizophrenia/psychosis, depression, mania/bipolarity, anxiety/obsessive compulsive disorder (OCD) or fatigue. ITP: immune thrombocytopenia; IQR: interquartile range; CI: confidence interval.

(95% CI: 1.9-3.4) in females (*Online Supplementary Table S3*). The corresponding numbers for comparators were 0.6% (95% CI: 0.5-0.6) and 0.7% (95% CI: 0.7-0.8), respectively. Similar differences during first year were found across age groups (18-59 and 60+ years) and calendar years (*Online Supplementary Table S3*).

For all stratified groups, significant differences between patients and comparators persisted up to 10 years after diagnosis of ITP, with the largest differences found in the period 2007-2016 (*Online Supplementary Table S3*).

The overall risk of any mental health event was elevated with an adjusted csHR of 1.56 (IQR, 1.38-1.76), and most pronounced during the first year where csHR was 3.57 (IQR, 2.84-4.50) (Figure 2; *Online Supplementary Table S4*). The largest overall risk was found in fatigue with an adjusted csHR of 1.86 (IQR, 1.56-2.22), and significantly elevated overall estimates were also found for depression and anxiety/OCD.

The risk during the first year was elevated for all subgroups. Fatigue was most pronounced with a first year adjusted csHR of 4.31 (IQR, 2.97-6.97) followed by depression with a csHR of 3.53 (IQR, 2.56-4.85). Risks declined to that of the general population for depression over time, but remained elevated for both anxiety/OCD and fatigue even after 10 years (Figure 2; *Online Supplementary Table S4*).

The overall risk of any mental health event in ITP did not differ across sex or age groups (Figure 2; *Online Supplementary Table S4*). Calendar year stratified analyses showed

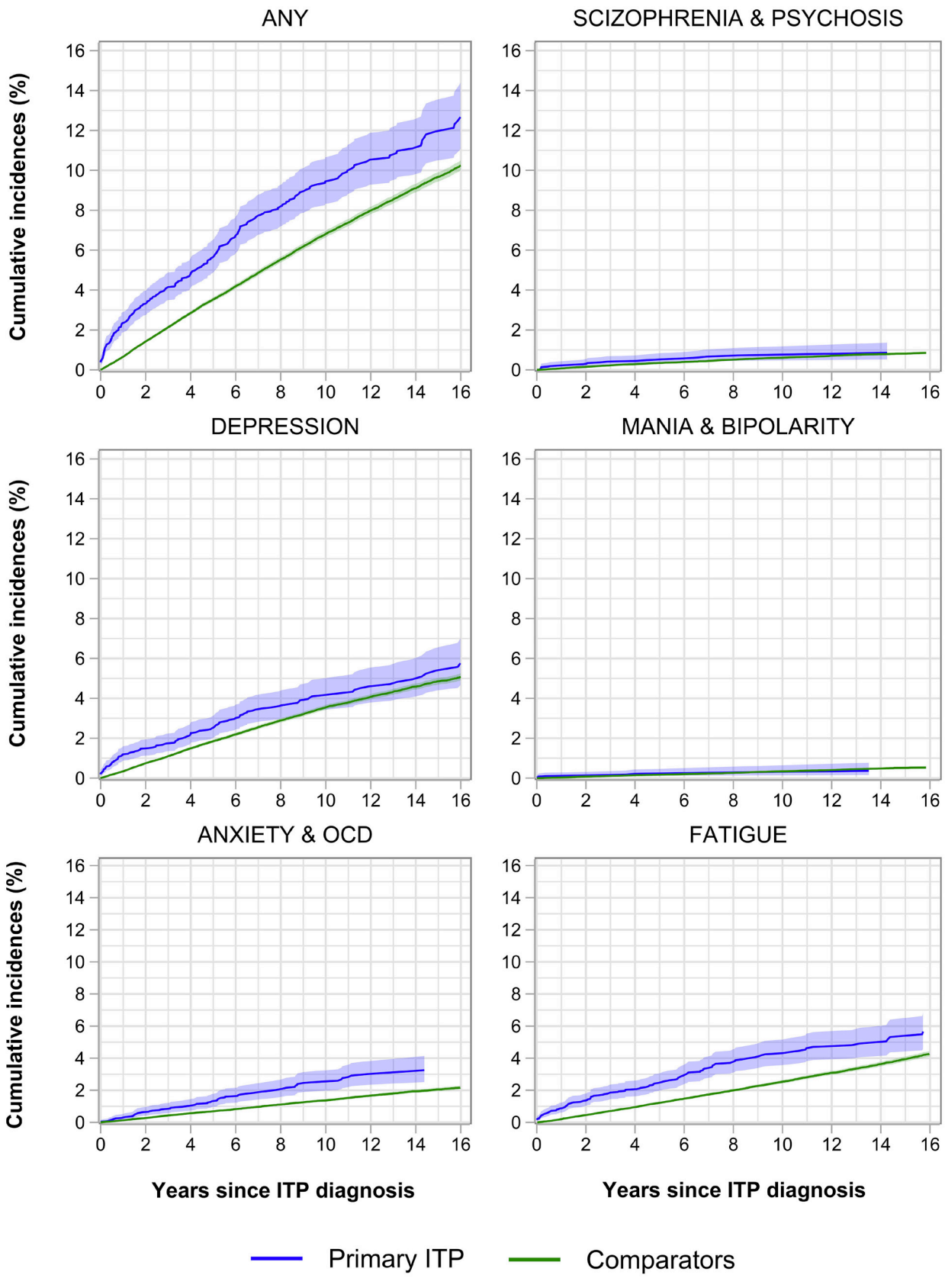

Figure 1. Cumulative incidence proportions for mental health events including fatigue. Cumulative incidences for different mental health events including fatigue. The category "any" was the first-ever hospital registration of any of the other 5 groups. Cumulative incidences for patients with immune thrombocytopenia (ITP) were elevated for depression, anxiety or obsessive-compulsive disorder (OCD), and fatigue compared with the general population.

a significant increase in csHR from 1.28 (IQR, 1.08-1.53) in 1997-2006 to 1.93 (IQR, 1.63-2.27) in 2007-2016 (P<0.001 when applying the Altman-Bland test of interaction) (Figure 2; *Online Supplementary Table S4*).

Adjusted subdistribution hazard ratios taking competing events (death and emigration) into account generally lowered estimates towards the null-association, but remained significantly elevated for most subgroups and calendar time periods (*Online Supplementary Table S4*).

Use of psychotropic drugs

Psychotropic drugs usage was elevated for patients with ITP compared with the general population, both in temporal relation to diagnosis of ITP, and over calendar years. The use of benzodiazepines was significantly elevated in patients in the year preceding diagnosis of ITP, and remained elevated in the first year after diagnosis (Figure 3). The 6-month IRR between the incidences of new benzodiazepine prescriptions in patients and comparators were significantly elevated the entire period 24 months before and after diagnosis of ITP, with the largest difference in 0-6 months after diagnosis with an IRR of 1.85 (IQR, 1.69-2.02) (Table 2). The IRD peaked 0-6 months after ITP with 15.3 (IQR, 12.5-18.2) more prescriptions/100-PY in patients *versus* comparators, while the general use of benzodiazepines for both patients and comparators declined continuously over calendar years by approximately 50% (Figure 3).

For antidepressants, the IRR was slightly elevated in the period 6 months before to 18 months after diagnosis of ITP, with a peak of 1.24 (IQR, 1.03-1.45) during 12-18months after ITP. The IRD was 1.67 (IQR, 0.34-2.99) in favor of the patients in the 6 months preceding ITP diagnosis, and remained elevated throughout 18 months after diagnosis. The overall use of antidepressants increased slightly over calendar years, but diminished after 2010 (Figure 3).

For opioids, the IRR between patients and comparators was significantly elevated in the 18 months preceding diagnosis of ITP, and peaking at 2.19 (IQR, 1.95-2.44) in the 0-6-month interval after diagnosis (Table 2). The IRD also peaked in this interval with 11.11 (IQR: 8.89-13.33) more pre-

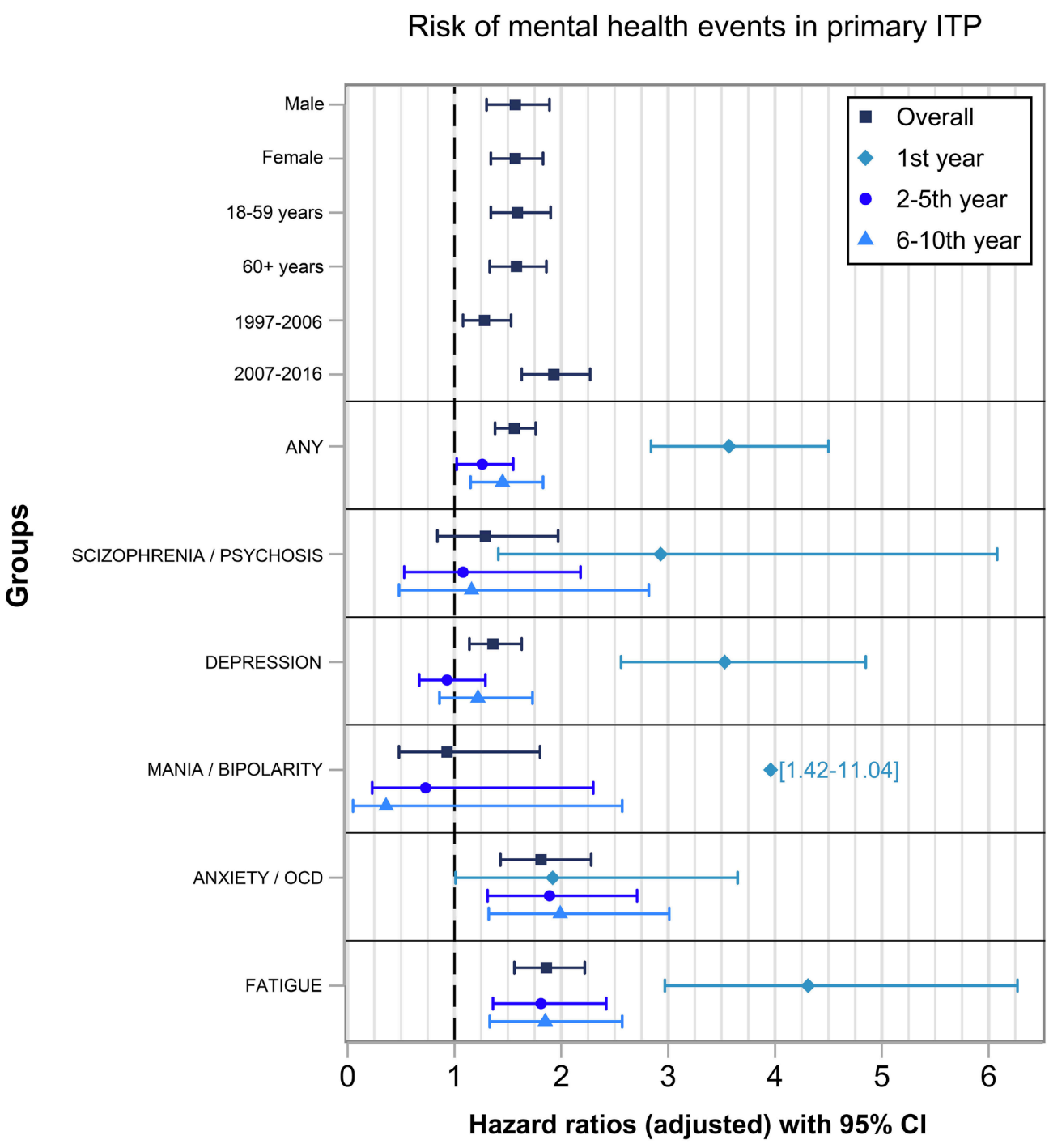

Figure 2. Hazard ratios for mental health events including fatigue in immune thrombocytopenia compared with the general population. Graphic illustrations of hazard ratios for mental health events including fatigue, illustrating overall and time split estimates as well as overall estimates stratified on age, sex and calendar years. Risk was generally increased for most mental health events, with largest risk estimates in the first years. Please note that the confidence intervals for some 1st year risk estimates due to high right outliers are provided as text, in order to optimize the visual information in the graph. ITP: immune thrombocytopenia; OCD: obsessive-compulsive disorder; CI: confidence interval.

scriptions/100-PY among patients *versus* comparators, and remained elevated >5.0 throughout all 24 months after ITP. We did not find any differences between patients and comparators with regards to distribution of subgroups of drugs based on their ATC-codes and modes of action (*Online Supplementary Figure S2*).

Sensitivity analyses

The two sensitivity analyses (*Online Supplementary Appendix*) excluding either all individuals with any history of any mental health event including fatigue or all individuals with any prior use of psychotropic drugs up to 24 months before index date, did not change results significantly (*Online Supplementary Table S5*). We also repeated the estimates of the category any mental health event with prior exclusion of fatigue in the definition of any mental health event. This lowered the adjusted csHR from 1.56 (IQR, 1.38-1.76) to 1.47 (IQR, 1.27-1.70) (*Online Supplementary Table S4*).

We found that comparators sampled by affiliation to departments of pulmonology and rheumatology were more likely to have a higher use of psychotropic drugs than patients with ITP (*Online Supplementary Figure S3*).

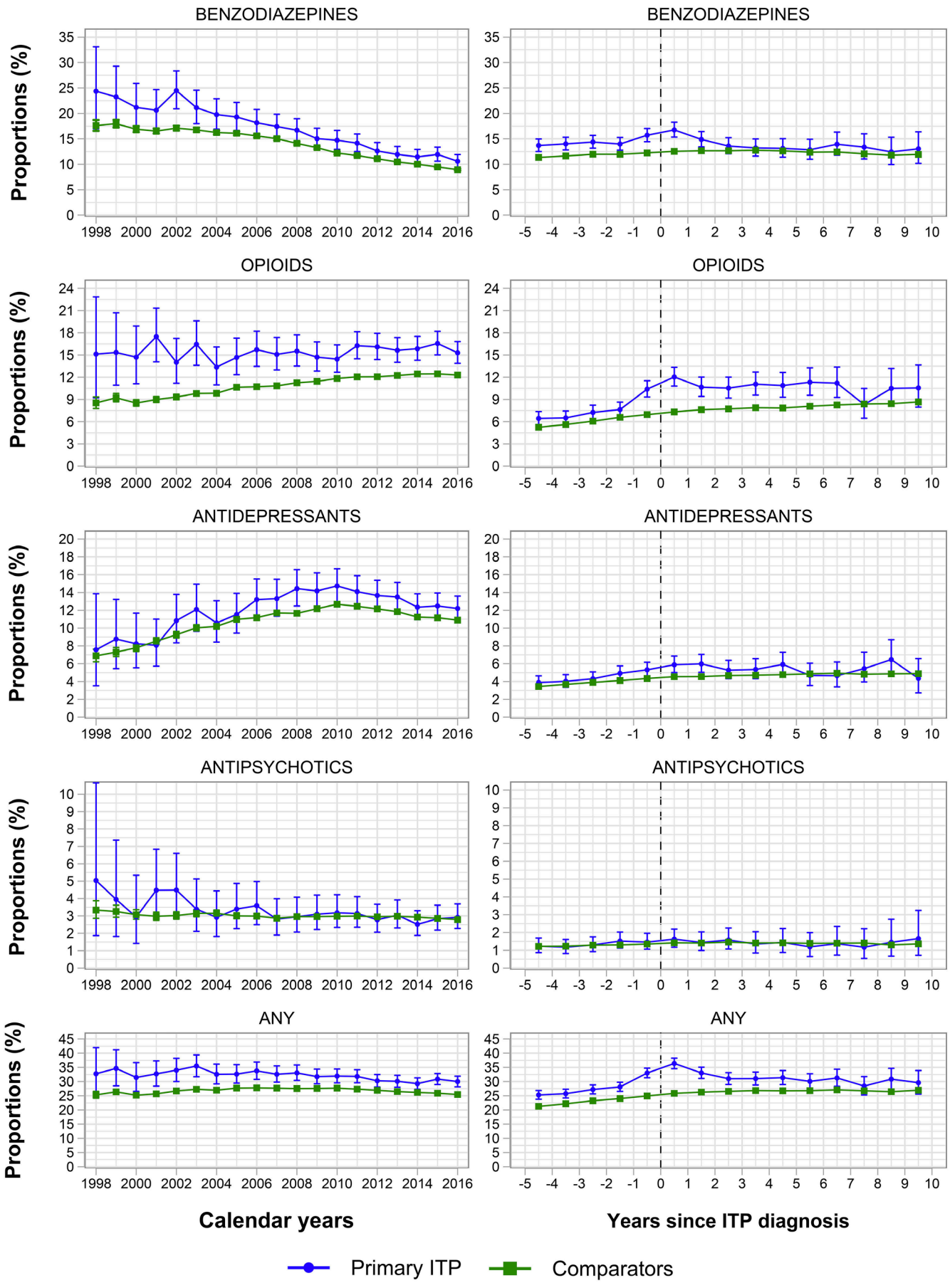

Figure 3. Prevalence proportions for psychotropic drugs in patients with primary immune thrombocytopenia and general population comparators. Illustration of the use of psychotropic drugs measured as proportions of patients with immune thrombocytopenia (ITP) and comparators receiving a minimum of 1 registered prescription within a given year with full follow-up. Blue represents primary ITP, while green represents comparators.

Table 2. Incidence rates per 100-person-years, incidence rate differences and incidence rate ratios for new psychotropic drug use in 6-month intervals in patients 2 years before and after diagnosis of primary immune thrombocytopenia compared with the general population.

	Primary ITP	Comparators	IRR (95% CI)	IRD (95% CI)
Incidence time point	**Incidence rate (95% CI)**	**Incidence rate (95% CI)**		
Year -2 to -1.5				
Antidepressants	6.22 (5.16-7.51)	5.56 (5.39-5.74)	1.12 (0.92-1.35)	0.66 (-0.52 to 1.85)
Antipsychotics	1.52 (1.05-2.20)	1.72 (1.63-1.82)	0.88 (0.58-1.28)	-0.20 (-0.77 to 0.37)
Opioids	7.71 (6.52-9.12)	6.77 (6.58-6.97)	1.14 (0.95-1.35)	0.94 (-0.37 to 2.24)
Benzodiazepines	20.78 (18.72-23.06)	16.79 (16.48-17.09)	1.24 (1.11-1.38)	3.99 (1.81-6.17)
Any psychotropic drug	52.50 (49.04-56.21)	45.09 (44.57-45.61)	1.16 (1.09-1.25)	7.41 (3.79-11.03)
Year -1.5 to -1				
Antidepressants	6.60 (5.50-7.93)	5.73 (5.55-5.91)	1.15 (0.95-1.39)	0.88 (-0.34 to 2.09)
Antipsychotics	1.74 (1.23-2.46)	1.71 (1.61-1.80)	1.02 (0.69-1.45)	0.03 (-0.58 to 0.65)
Opioids	8.98 (7.69-10.50)	7.17 (6.97-7.37)	1.25 (1.06-1.47)	1.81 (0.40-3.23)
Benzodiazepines	20.94 (18.87-23.23)	16.81 (16.51-17.12)	1.25 (1.12-1.38)	4.13 (1.93-6.32)
Any psychotropic drug	58.40 (54.70-62.34)	46.47 (45.94-47.00)	1.26 (1.17-1.34)	11.93 (8.08-15.78)
Year -1 to - 0.5				
Antidepressants	7.08 (5.93-8.44)	5.95 (5.78-6.14)	1.19 (0.99-1.42)	1.12 (-0.14 to 2.38)
Antipsychotics	1.68 (1.18-2.39)	1.71 (1.62-1.81)	0.98 (0.67-1.40)	-0.03 (-0.63 to 0.57)
Opioids	9.97 (8.60-11.56)	7.29 (7.09-7.49)	1.37 (1.17-1.59)	2.68 (1.19-4.17)
Benzodiazepines	20.46 (18.42-22.72)	16.83 (16.53-17.14)	1.22 (1.09-1.35)	3.63 (1.46-5.80)
Any psychotropic drug	59.78 (56.04-63.77)	48.04 (47.50-48.58)	1.24 (1.16-1.33)	11.75 (7.85-15.64)
Year -0.5 to 0				
Antidepressants	7.75 (6.55-9.18)	6.09 (5.91-6.27)	1.27 (1.06-1.51)	1.67 (0.34-2.99)
Antipsychotics	1.58 (1.10-2.27)	1.73 (1.64-1.83)	0.91 (0.61-1.31)	-0.16 (-0.74 to 0.43)
Opioids	13.58 (11.95-15.44)	7.60 (7.40-7.80)	1.79 (1.56-2.04)	5.98 (4.23-7.73)
Benzodiazepines	22.91 (20.74-25.31)	16.65 (16.35-16.95)	1.38 (1.24-1.52)	6.26 (3.97-8.56)
Any psychotropic drug	70.97 (66.84-75.35)	48.84 (48.30-49.39)	1.45 (1.37-1.54)	22.12 (17.83-26.41)
Year 0-0.5				
Antidepressants	8.34 (7.05-9.85)	6.90 (6.70-7.10)	1.21 (1.01-1.43)	1.44 (0.03-2.85)
Antipsychotics	2.54 (1.89-3.41)	1.89 (1.79-1.99)	1.34 (0.97-1.82)	0.65 (-0.11 to 1.41)
Opioids	20.47 (18.38-22.80)	9.37 (9.14-9.60)	2.19 (1.95-2.44)	11.11 (8.89-13.33)
Benzodiazepines	33.43 (30.67-36.43)	18.08 (17.77-18.41)	1.85 (1.69-2.02)	15.34 (12.45-18.24)
Any psychotropic drug	96.76 (91.68-102.13)	54.12 (53.54-54.70)	1.79 (1.69-1.89)	42.65 (37.39-47.90)
Year 0.5-1				
Antidepressants	8.68 (7.32-10.30)	7.11 (6.91-7.32)	1.22 (1.02-1.45)	1.57 (0.08-3.07)
Antipsychotics	2.36 (1.72-3.25)	1.97 (1.87-2.08)	1.20 (0.84-1.65)	0.39 (-0.37 to -1.15)
Opioids	17.44 (15.44-19.69)	10.25 (10.01-10.50)	1.70 (1.50-1.92)	7.18 (5.06-9.31)
Benzodiazepines	24.45 (22.06-27.10)	18.94 (18.61-19.27)	1.29 (1.16-1.43)	5.51 (2.97-8.05)
Any psychotropic drug	82.64 (77.85-87.73)	56.95 (56.35-57.56)	1.45 (1.36-1.54)	25.69 (20.71-30.66)
Year 1-1.5				
Antidepressants	9.06 (7.62-10.77)	7.32 (7.11-7.54)	1.24 (1.03-1.47)	1.73 (0.15-3.32)
Antipsychotics	1.86 (1.28-2.69)	2.01 (1.91-2.12)	0.92 (0.61-1.34)	-0.15 (-0.85 to 0.54)
Opioids	16.73 (14.73-19.02)	10.84 (10.58-11.10)	1.54 (1.35-1.76)	5.90 (3.74-8.05)
Benzodiazepines	23.49 (21.08-26.18)	19.12 (18.78-19.47)	1.23 (1.10-1.37)	4.38 (1.81-6.94)
Any psychotropic drug	78.47 (73.66-83.59)	58.35 (57.73-58.99)	1.34 (1.26-1.43)	20.12 (15.12-25.11)
Year 1.5-2				
Antidepressants	8.34 (6.93-10.05)	7.44 (7.22-7.66)	1.12 (0.92-1.35)	0.90 (-0.66 to 2.47)
Antipsychotics	2.27 (1.61-3.21)	2.10 (1.99-2.22)	1.08 (0.74-1.53)	0.17 (-0.63 to 0.96)
Opioids	16.50 (14.45-18.84)	11.14 (10.87-11.41)	1.48 (1.29-1.70)	5.37 (3.16-7.57)
Benzodiazepines	24.68 (22.13-27.52)	19.51 (19.16-19.87)	1.26 (1.13-1.41)	5.17 (2.45-7.88)
Any psychotropic drug	79.50 (74.52-84.81)	59.81 (59.16-60.47)	1.33 (1.24-1.42)	19.69 (14.51-24.87)

IRR: incidence rate ratios; IRD: incidence rate differences; ITP: immune thrombocytopenia; CI: confidence interval.

Discussion

Using Danish nationwide health registries, we found an elevated risk of mental health events including fatigue among patients with ITP compared with the general population. The risks were most pronounced in the early years after diagnosis of ITP, however persisted for anxiety/OCD and fatigue. Patients with ITP also have an increased use of benzodiazepines, antidepressants and opioids, in temporal relation to diagnosis of ITP, mainly in the year preceding ITP diagnosis and in the following early years.

Comorbidity

Prevalent comorbidity was significantly more frequent among patients compared with the general population, but we adjusted all analyses for potential confounding and effect modifications. Previous studies have found that both prevalent and incident comorbidity is more frequent in patients with ITP than among the general population.[8] Comorbidity can impact both quality of life and mental health negatively, which could partly explain the increased prevalence of mental health events including fatigue, and prevalent use of psychotropic drugs in patients with ITP.[28,29]

Risks

We found an overall increased risk of hospital-diagnosed depression, anxiety/OCD and fatigue in patients with ITP, with the risk of the latter two persisting over the entire study period. Furthermore, the risks for all subgroups of mental health events including fatigue were significantly elevated in the first year after diagnosis of ITP. Possible explanations for this variation over time could be an increased clinical focus and intervention on mental health events following the diagnosis of ITP, or that the mental impact of both diagnosis and treatment materializes in the immediate aftermath. However, the persisting risk of anxiety/OCD and particularly fatigue indicates that this patient group suffers from long-term mental health burdens. ITP is often a chronic autoimmune disease with multiple relapses and remissions. This applies especially to the elderly and comorbid population, where both the ITP disease in itself, the treatment, and the pre-existing comorbidity burden could explain the reduced mental health and quality of life as seen in other chronic diseases.[30,31] Persistent fatigue has been described previously in ITP.[17,24,32] However, our outcome was based on a hospital-registered fatigue diagnosis possibly capturing a more severe entity. This could underestimate the true incidence of fatigue since many patients with ITP are not necessarily routinely screened for and registered with fatigue. Fatigue pathogenesis is unknown, but likely multifactorial.[32] A recent study argues that the immune suppression contributes to fatigue and does not alter the mechanisms underlying ITP, thereby not improving long-term outcomes such as quality of life and fatigue.[1] Platelets are involved in a plethora of immune reactions, and contain large amounts of circulating serotonin in their granules that they release in relation to both hemostasis and immune reactions.[33-35] Low levels of serotonin are related to both depression and fatigue.[36] This could indicate that low platelet counts are linked to low serotonin levels, causing both mental and immunological problems.[12] Whether patients with ITP and fatigue could benefit from therapy targeted at increasing levels of serotonin requires additional clinical studies, and the thrombotic risk associated with high serotonin levels should in that case also be considered.[37] Fatigue was included in the definition of the category "any mental health event", but our analysis excluding fatigue from this category did not change results.

The subdistribution hazard ratios for mental health events including fatigue were generally lower than the csHR estimates, but remained significant. This indicates the presence of death as competing risk albeit minor. The survival is reduced both in patients with ITP, and in severe psychiatric disorders requiring hospitalization.[6,8,38,39]

The risk of any hospital-registered mental health event including fatigue was higher in 2007-2016 compared with 1997-2006. The incidence of psychiatric disorders in Denmark has increased over the past decades, mainly due to earlier detection and awareness of psychiatric disorders.[40] Patients with ITP and pre-existing comorbidities in a clinical course could be more prone to referral to psychiatric assessment than comparators, and this could inflate our estimates of diagnoses, but is unlikely to affect the psychotropic drug usage.

Psychotropic drugs

The reasons for the increased use of benzodiazepines in the year preceding ITP are unclear. It could be early ITP symptoms (e.g., fatigue) related to the underlying immunological processes, misinterpreted as anxiety or depression by the patients' general practitioner. The increase in the years after diagnosis of ITP could be explained by the immediate mental health burden following diagnosis, or treating side effects from ITP treatment e.g., insomnia from corticosteroids.[41] The use and indications of benzodiazepines are generally broad, and associated with multiple side effects.[41,42] Long-term use is generally not recommended particularly in the elderly population in Denmark, and our data indicate that the use among patients with ITP declines to the levels of the general population.[42] We found that risk of anxiety/OCD was highest in the first years following diagnosis of ITP, which could explain why pharmacological treatment is only necessary in a limited period. The use of benzodiazepines generally declined over calendar years for both patients with ITP and comparators, probably attributable to increased regulation.[43]

The increased use of opioids prior to and after diagnosis of ITP could be due to the detection of conditions requiring analgesics during clinical follow-up for ITP, or pain associated with ITP itself, e.g., post-operative pain after splenectomy

or status bone marrow biopsies. Though decreasing in the recent years in Denmark, the use of opioids has generally increased over the past decades likely due to an aging and more comorbid population, accompanied by increasing prevalence of chronic pain and disease.[44,45]

The use of antidepressants in Denmark is generally high, and though declining since 2011, prescribed to approximately 9% of the Danish adult population, with SSRI being the most common drug.[46] This is in line with our findings of a declining trend over calendar years in both ITP and comparators since 2010. However, there could be multiple reasons for the increased use in the early years after diagnosis of ITP. Patients with ITP are more burdened with comorbidity, which in turn is associated with an increased the use of antidepressants.[46] Some comorbidities could also become overt in the aftermath of ITP. A depression arising in the immediate aftermath of an ITP diagnosis as response to the chronic health burden constituted by the ITP disease in itself, as well as treatment, and the social consequences (e.g., reduced sports activity and fear of bleeding[19]), is also likely. Remission or acceptance of the ITP disease over time could explain both the declines in incident risk of depression, and the use of antidepressants relative to comparators.

A similar study also found elevated prescription rates for psychotropic drugs and incident risk of depression and anxiety in the years following a diagnosis of lymphoma, but similar to our findings both declined over time.[47] Finally, autoimmune disease and the underlying inflammation in general is associated with depression.[48]

Comparators affiliated with other medical specialties had a generally higher use of some psychotropic drugs, e.g., the benzodiazepine use was higher in comparators affiliated with pulmonology than in ITP. The reasons for this could be that high comorbidity equals a higher mental health burden, or that being followed at a hospital in itself makes them more likely to receive a prescription. Whether this also could be the explanation for the higher use among patients with ITP remains unclear, but besides an increased number of prescriptions in general, the proportion of hospital opioid prescribers is also increasing.[45]

Limitations

Despite being a nationwide study based on valid registry data with full follow-up over 20 years, our study has limitations. We excluded secondary ITP, but some of these patients could potentially misclassify as ITP due to insufficient diagnostics of potential underlying disorders. However, we would expect this impact to be minor since secondary ITP constitutes a small proportion of patients with ITP.[8]

We lacked granular data on ITP treatment as well as biochemical data, e.g., accumulated corticosteroid exposure and platelet counts, and it is difficult to assess causality from our findings in general. Our study spanned a 20-year period where demographics clinical practice, perception and treatment of both ITP and comorbidities has changed. The impact of this on our results is unknown.

We only included the first event of interest in our time-to-event analyses. This approach does not track any potential future improvements after the first registration of an e.g., depression. We included all psychotropic drug prescriptions over time for each individual to partly compensate for this. A higher need for antidepressants and benzodiazepines in patients compared with the general population persisted for up to 2 years after ITP diagnosis. However, our prescription data has limitations too, and the NPR does not allow for assessing indications for the prescribed drugs except for more recent time periods, treatment duration, or dosage from the prescribing physician.[49,50] Furthermore, we were not able to clarify whether individuals indeed used the entire package of a given redeemed psychotropic drug.

Conclusion

We have shown that the risk of mental health events including fatigue and the use of psychotropic drugs is elevated in patients with ITP compared with the general population, and has a temporal relation to diagnosis of ITP. Reasons for this are likely both related to the ITP disease and the management, but also due to other factors such as comorbidity or complications associated with ITP. Clinicians treating patients with ITP should be aware of such mental health problems during follow-up, and psychotropic drug use should be well indicated. Further clinical studies are required to identify risk groups that could benefit from potential interventions.

Disclosures

No conflicts of interest to disclose.

Contributions

NM, DLH and HF conceived the study idea. NM, DLH, AP, KA and HF designed the study. NM and HF applied for funding. NM and DLH performed data analyses. NM wrote first draft. All authors read and approved the final version of the manuscript.

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Data-sharing statement

All analyses were performed without access to detailed patient medical files. The authors are prohibited to share national health data or grant access to the data according to Danish law. Access to data can be made upon request through applications and contacts to the relevant Danish authorities.

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