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ORIGINAL PAPER

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Risk of fractures and use of bisphosphonates in adult patients with immune thrombocytopenia—A nationwide population-based study

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Summary

Corticosteroids remain the first-line treatment of immune thrombocytopenia (ITP), but increase the risk of osteoporosis and fractures. Bisphosphonates are used for the treatment of osteoporosis, but their usage among patients with ITP has not been systemically described. We investigated the risk of fractures and the use of bisphosphonates in adult patients with primary (pITP) and secondary ITP (sITP) compared with matched comparators in a nationwide registry-based cohort study. We identified 4030 patients with pITP (median age 60 years [IQR, 40–74]), 550 with sITP (median age 59 years [IQR, 43–74]) and 182 939 age–sex-matched general population comparators. All individuals were followed for incident fractures. Bisphosphonate use was estimated for calendar-years and in temporal relation to the ITP diagnosis. Adjusted cause-specific hazard ratio (csHR) for any fracture was 1.37 (95% confidence interval [CI] 1.23; 1.54) for pITP and 1.54 (1.17; 2.03) for sITP. The first-year csHR was 1.82 (1.39; 2.40) for pITP and 2.78 (1.58; 4.91) for sITP. Bisphosphonate use over calendar-years and in the early years following ITP diagnosis was higher among patients with ITP diagnosis compared with the general population. In conclusion, the risk of fractures and the use of bisphosphonates are higher in patients with ITP compared with the general population.

KEYWORDS
bisphosphonates, bone disease, corticosteroids, epidemiology, immune, thrombocytopenia

INTRODUCTION

Immune thrombocytopenia (ITP) is an autoimmune disorder where an immune reaction against platelets causes isolated thrombocytopenia and a subsequent elevated risk of bleeding.[1] Adult patients with ITP suffer from reduced survival and quality of life,[2–5] as well as increased risks of thrombosis, infection and cancer.[2,6–8] Mechanisms behind these health events are not well understood, but it has been suggested that both immune dysfunction of the ITP disease as well as immediate or late effects from treatment contribute.[3,7,9]

The preferred first-line treatment of ITP remains high-dose corticosteroids, either as a short course of prednisolone or pulsed dexamethasone.[10,11] Patients with ITP are generally exposed to corticosteroids for a short period, but accumulated doses over time still remain high due to long exposure time, repeated courses or combination treatment regimens including low-dose corticosteroids.[11,12]

Exposure to corticosteroids is associated with bone-related morbidity, such as osteoporosis and fractures, even in low-dose regimens.[13–16] Furthermore, the majority of patients with ITP are female and >50 years of age[2,17] with a biologically elevated risk of osteoporosis, making considerations regarding bone-related side-effects of treatment relevant.[18,19] Hip fractures are also known to be associated with increased mortality.[14,20] However, it has not been investigated whether patients with ITP suffer from an increased risk of fractures.

The cumulative doses of corticosteroids used in patients with ITP and other patients are generally high.[21,22] Previous studies have shown a decrease in bone mineral density (BMD) and a high prevalence of glucocorticoid-induced osteoporosis in ITP, but with the beneficial effects of bisphosphonates.[23] Bisphosphonates are key elements in the treatment of osteoporosis,[24] but the general use of bisphosphonates in relation to the diagnosis of ITP and whether it differs from its use in the general population have not been investigated.

In this nationwide study, we present data quantifying the risk of fractures and the use of bisphosphonates over calendar-years and in temporal relation to the diagnosis of ITP.

MATERIALS AND METHODS

Data sources

The Danish health registries comprise valid and nationwide data with continuous updates.[25–28] They contain information regarding hospitalizations since 1977, hospital outpatient and emergency room (ER) registrations since 1994 and data on prescription drugs dispensed since 1995 for all inhabitants of Denmark and allow individual-level record linkage across them.[25–27,29,30]

Patients with haematological conditions are solely managed in public hospitals, and all hospital contacts in Denmark are assigned a diagnosis code by physicians using the International Classification of Diseases (ICD) and registered in the Danish National Patient Registry (DNPR).[26,30]

We retrieved data from the DNPR on inpatient and outpatient hospital contacts and associated ICD codes. The Danish Civil Registration System (DCRS)[27] provided data on sex, date of birth, migration and death. Data on redeemed prescriptions for bisphosphonates from 1995 and onwards were retrieved from The Danish National Prescription Registry.[31]

Identification of patients, comparators and health events

We used the designated codes for ITP in the ICD-8 (287.10) (1977–1993) and ICD-10 (D69.3) (1994–2016) for identification of patients in the DNPR (Table S1). Patients were categorized as having secondary ITP (sITP) if they were registered with at least one underlying qualifying diagnosis before or up to 30 days after registration of ITP (Table S2).[28–31] This approach was similar to another study by our group (Figure S1).[2] Index data was the first registration of ITP in the DNPR, and each patient was assigned up to 40 age–sex-matched comparators from the general population. The comparators were allotted the same index date as the patients, and all individuals were followed until the first of: fracture (emergency room or in-hospital), emigration, death or the end of December 2016. Individuals with a history of fractures before the index date were excluded from the incidence analyses. Fractures were aggregated in five categories: hip and femoral, humeral, distal antebrachial, axial (costal, vertebral or pelvic fracture) and a category with the first registration of any of the four aforementioned (Table S3). Fractures were identified in the DNPR using previously applied methods (Table S3).[32] Procedural codes and dates for dual X-ray absorptiometry (DXA) scans were identified in the DNPR.

Prevalent comorbidity at inclusion was based on diagnoses registered in the DNPR before or at the index date and categorized into nine groups. We mainly used the Quan 2011 updated Charlson Comorbidity Index (CCI),[33] while other categories were defined solely on registrations of specific ICD-codes in the DNPR (Table S4). The applied Quan 2011 categories were: metastatic solid cancer/tumour, chronic pulmonary disease, diabetes mellitus, dementia, congestive heart failure and myocardial infarction (the latter two joined in the category 'heart disease'). The remaining categories were: alcohol-related diagnoses, autoimmune disease, hyperparathyroidism and osteoporosis (Tables S3 and S4). This approach of classifying individual-level comorbidity in longitudinal studies through the DNPR has been proven to be valid.[34] However, many patients with osteoporosis are diagnosed and treated in the primary sector, hence not registered in the DNPR. We therefore also included a covariate with the prevalent use of bisphosphonates as a proxy measure for potential non-registered bone-demineralizing disorder.

Many fractures are treated without hospitalization in the ER. Since ER registrations were available in the DNPR from 1994 and prescription data only were available from 1995 onwards, we excluded patients diagnosed before 1995.

Statistical analyses

Baseline characteristics were presented as medians with an interquartile range (IQR) for age and proportions with 95% confidence intervals (95% CIs) for distributions of sex, age groups, study periods, prevalent comorbidity, prevalent fracture and use of bisphosphonate.

We estimated 1st, 2–5th, 6–10th year and overall incidence rates (IRs) and 95% CIs for each type of fracture among patients and comparators. IRs were estimated as the number of fractures per 1000 persons per year (1000 PY).

Corresponding incidence rate ratios (IRRs) and 95% CIs were estimated for comparison of incidences in patients and comparators. We applied the Altman–Bland method to test for interaction between subgroup estimates.[35]

We used Cox proportional hazard regression to estimate unadjusted and adjusted cause-specific hazard ratios (csHR) for fractures in patients with ITP compared with the general population. We adjusted for effects of age, sex, calendar decade of diagnosis, comorbidity and the presence of prevalent bisphosphonate use. Fine–Gray proportional subdistribution hazard regression treating death and emigration as competing events was applied to estimate unadjusted as well as adjusted subdistribution hazard ratios. The cumulative incidence proportions of fractures were also estimated.[36,37] Time-split analyses estimating overall, 1st year, 2–5th year and 6–10th year estimates after the index date were performed for both Cox and Fine–Gray regressions. Cumulative incidence proportions were stratified by age groups and calendar-years.

Since individuals could receive multiple prescriptions over time, descriptive data on bisphosphonates were estimated as prevalence proportions of patients and comparators receiving a minimum of one prescription in a year with full follow-up. This was done for both calendar-years and for each year in a period of 5 years prior to and 10 years after the diagnosis of ITP.

All analyses were done separately for set of patients with pITP or sITP and their respective general population comparators.

As sensitivity analyses, we estimated the csHRs of fractures using only individuals with no history of fractures and in individuals previously treated with bisphosphonates.

All data management and statistical analyses were performed using Stata 17.0 (StataCorp, 4905 Midtown Dr., College Station, TX 77845, USA).

RESULTS

We included 4030 patients with pITP, 550 with sITP and 182 959 age–sex-matched comparators (Table 1).

Total follow-up time was 27 732 PY for patients (median 5.3 years), while comparators were followed for 1 298 141 PY (median 6.6 years).

Women comprised 53% of pITP and 63% of sITP. The median age was 60 years (IQR 40–74) for pITP and 59 years (IQR 43–74) for sITP. Age groups were equally distributed (18–59 years, 60+ years) (Table 1).

The mean comorbidity score was 0.35 (95% CI 0.34; 0.37) for pITP and 0.35 (95% CI 0.31; 0.40) for sITP. Comparators had a mean score of 0.23 (95% CI 0.23; 0.23) and 0.22 (95% CI 0.22; 0.23) for pITP and sITP respectively (Table 1). The proportions of prevalent osteoporosis, DXA-scans and bisphosphonate users were higher in patients with pITP and sITP compared with the general population (Table 1).

Incidences of fractures

The overall IR for any fracture was 12/1000 PY (95% CI 11; 14) for pITP and 10/1000 PY (95% CI 10; 10) for comparators, corresponding to an IRR of 1.2/1000 PY (95% CI 1.1; 1.4). The first-year IRR was 1.8 (95% CI 1.4; 2.4), but diminished in the following years (Table 2).

The overall IRR for hip and femoral fractures was 1.2 (95% CI 1.0; 1.4) and elevated to 2.3 (95% CI 1.5; 3.2) in the first year, but diminished thereafter (Table 2).

The overall IR of any fracture was 15 (95% CI 11; 20) for sITP and 11 (95% CI 11; 12) for comparators, corresponding to an IRR of 1.4 (95% CI 1.0; 1.8). The IRR remained significantly elevated 5 years after the diagnosis of ITP (Table 2).

The first-year cumulative incidences for any fracture were 1.5% (95% CI 1.2; 2.0) for pITP and 0.91% (95% CI 0.86; 0.96) for comparators (Table 3; Figure 1). Differences remained until the end of the fifth year.

For hip and femoral fractures, first-year cumulative incidences were 0.84% (95% CI 0.59; 1.18) for pITP and 0.39% (95% CI 0.36; 0.42) for comparators.

For sITP, the first-year cumulative incidences for any fracture were 2.7% (95% CI 1.5; 4.5) in patients and 1.0% (95% CI 0.9; 1.2) in comparators (Table 3; Figure 1). Again, differences remained until the end of the fifth year.

Differences between patients and comparators generally evened out over time for both pITP and sITP (Table 3; Figure 1).

Risk of fractures

The overall risk of any fracture for pITP was elevated with an adjusted csHR of 1.37 (95% CI 1.23; 1.54) and 1.54 (95% CI 1.17; 2.03) for sITP. The first-year overall adjusted csHR was 1.82 (95% CI 1.39; 2.40) for pITP and 2.78 (95% CI 1.58; 4.91) for sITP, and remained elevated through the 2–5th year (Table S5; Figure 2).

This was mainly driven by an increased risk of distal antebrachial and hip and femoral fractures in both pITP and sITP, while the risk of humeral and axial fractures was slightly elevated for pITP (Table S5; Figure 2).

The general trend for most types of fractures was that the risk diminished over time (Figure 2).

Stratifications

We found an increased risk of any fracture for patients with pITP aged 18–59 years with an overall adjusted csHR of 1.47 (95% CI 1.19; 1.80) and with the risk persisting over time (Table S5; Figure 2; Figure S2). The corresponding estimates for 60+ years were 1.36 (95% CI 1.19; 1.56) in pITP.

Both men and women with pITP had an increased risk of any fracture, but the risk did not differ across sexes.

TABLE 1 Baseline characteristics of included patients with primary (pITP) and secondary ITP (sITP) and general population age–sex-matched comparators.

Name	Primary ITP (%) (95% CI) ($n = 4030$)	Comparators pITP (%) (95% CI) ($n = 161\,020$)	Secondary ITP (%) (95% CI) ($n = 550$)	Comparators sITP (%) (95% CI) ($n = 21\,939$)
Women	53 (52; 55)	53 (53; 54)	63 (59; 67)	63 (62; 63)
Age (years, median [IQR])	59.8 (39.6; 73.5)	59.8 (39.6; 73.5)	58.9 (42.8; 73.6)	58.9 (42.6; 73.7)
Mean age at death (years)	76.9 (76.2; 77.7)	83.0 (82.8; 83.1)	74.7 (73.0; 76.4)	81.3 (81.0; 81.6)
Age groups				
18–59 years	50.2 (48.6; 51.8)	50.2 (50.0; 50.5)	51.3 (47.0; 55.5)	51.4 (50.7; 52.0)
60+ years	49.8 (48.2; 51.4)	49.8 (49.5; 50.0)	48.7 (44.5; 53.0)	48.6 (48.0; 49.3)
Calendar-years				
1995–2005	38.6 (37.1; 40.2)	38.6 (38.4; 38.9)	44.5 (40.3; 48.8)	44.4 (43.8; 45.1)
2006–2016	61.4 (59.8; 62.9)	61.4 (61.1; 61.6)	55.5 (51.2; 59.7)	55.6 (54.9; 56.2)
Comorbidities				
Alcohol consumption	6.05 (5.34; 6.84)	3.22 (3.13; 3.30)	5.64 (3.86; 7.91)	2.82 (2.61; 3.05)
Autoimmune disease	9.43 (8.54; 10.37)	4.18 (4.08; 4.28)	5.45 (3.71; 7.70)	4.54 (4.27; 4.83)
Cancer (solid, metastatic)	1.17 (0.86; 1.55)	0.48 (0.44; 0.51)	0.36 (0.04; 1.31)	0.52 (0.43; 0.63)
Chronic pulmonary disease	7.84 (7.03; 8.71)	5.86 (5.75; 5.98)	9.82 (7.46; 12.62)	5.67 (5.37; 5.99)
Dementia	1.84 (1.44; 2.30)	1.49 (1.43; 1.55)	0.91 (0.30; 2.11)	1.44 (1.29; 1.61)
Diabetes mellitus	3.10 (2.59; 3.68)	1.85 (1.78; 1.91)	4.00 (2.52; 5.99)	1.73 (1.56; 1.91)
Heart disease	9.50 (8.62; 10.45)	5.85 (5.74; 5.97)	8.91 (6.66; 11.61)	4.94 (4.66; 5.24)
Hemiplegia	0.45 (0.26; 0.70)	0.27 (0.24; 0.29)	0.73 (0.20; 1.85)	0.24 (0.18; 0.32)
Hyperparathyroidism	0.15 (0.05; 0.32)	0.24 (0.22; 0.26)	1.09 (0.40; 2.36)	0.22 (0.17; 0.30)
Comorbidity score				
Comorbidity score (mean)	0.35 (0.34; 0.37)	0.23 (0.23; 0.23)	0.36 (0.31; 0.40)	0.22 (0.22; 0.23)
Bone disease				
Prevalent fracture any type	10.67 (9.73; 11.66)	9.93 (9.78; 10.07)	10.91 (8.43; 13.82)	9.91 (9.52; 10.32)
Prevalent osteoporosis	2.56 (2.09; 3.09)	1.78 (1.71; 1.84)	5.09 (3.41; 7.27)	2.07 (1.89; 2.27)
Prevalent use of bisphosphonates	3.85 (3.27; 4.49)	3.04 (2.95; 3.12)	5.45 (3.71; 7.70)	3.72 (3.47; 3.98)
Prevalent DXA scan	6.03 (5.31; 6.81)	4.61 (4.50; 4.71)	7.82 (5.72; 10.39)	5.21 (4.92; 5.51)
Incident DXA scan	13.28 (12.24; 14.36)	8.80 (8.66; 8.94)	22.73 (19.29; 26.46)	11.24 (10.83; 11.67)

Note: Baseline table with characteristics of patients with primary and secondary ITP (columns 2 and 4) and their comparators (columns 3 and 5). Numbers are percentages, unless otherwise stated. The proportion of women was higher in secondary ITP compared to primary ITP, and comorbidity was generally more pronounced among patients compared with the general population. The category 'autoimmune disease' included connective tissue disease, inflammatory bowel disease and rheumatoid arthritis.

Abbreviations: DXA, dual X-ray absorptiometry; ITP, immune thrombocytopenia.

The risk across calendar-years increased for pITP with a csHR from 1.26 (95% CI 1.09; 1.46) in 1995–2005 to 1.56 (95% CI 1.31; 1.86) in 2006–2016 (Table S5; Figure S2).

Similar findings were found for sITP in all subgroups.

Use of bisphosphonates

The use of bisphosphonates was significantly elevated in patients with pITP from 1998 to 2008 compared with the general population, but equalized in more recent years (Figure 3). For sITP, significant differences were found in the period from 2007 to 2016.

We also found that the use of bisphosphonates was not elevated prior to, but rose significantly in a 5-year period following pITP (Figure 3). The same applied to sITP, but with an elevated use prior to sITP, although not significantly.

Sensitivity analysis

We performed two sensitivity analyses. The first one excluded all individuals with any type of prevalent fracture, and the second included only individuals previously treated with bisphosphonates. This did not change the overall results (Tables S6 and S7).

TABLE 2 Incidence rates in measures as number of fractures per 1000 person-years and incidence rate ratios of fractures in patients with primary and secondary ITP and general population age–sex-matched comparators.

Name	Primary ITP (95% CI)	Comparators pITP (95% CI)	IRR pITP (95% CI)	Secondary ITP (95% CI)	Comparators sITP (95% CI)	IRR sITP (95% CI)
Fracture rates overall						
Any fracture 18–59 years	5.81 (4.75; 7.10)	4.00 (3.86; 4.15)	1.45 (1.17; 1.78)	6.59 (4.04; 10.76)	4.84 (4.44; 5.27)	1.36 (0.77; 2.23)
Any fracture 60+ years	27.15 (23.75; 31.03)	20.88 (20.45; 21.32)	1.30 (1.13; 1.49)	34.99 (25.24; 48.50)	22.06 (20.91; 23.27)	1.59 (1.11; 2.21)
Any fracture 1995–2005	11.89 (10.28; 13.75)	10.66 (10.42; 10.90)	1.12 (0.96; 1.29)	13.51 (9.50; 19.22)	10.91 (10.33; 11.53)	1.24 (0.84; 1.77)
Any fracture 2006–2016	14.25 (11.99; 16.94)	9.75 (9.46; 10.06)	1.46 (1.22; 1.74)	18.06 (11.77; 27.70)	11.28 (10.41; 12.22)	1.60 (0.98; 2.47)
Hip and femur	5.65 (4.82; 6.64)	4.61 (4.50; 4.74)	1.23 (1.04; 1.44)	6.46 (4.36; 9.56)	4.42 (4.12; 4.73)	1.46 (0.94; 2.17)
Humerus	2.74 (2.18; 3.45)	2.18 (2.09; 2.26)	1.24 (0.97; 1.57)	3.38 (1.96; 5.82)	2.50 (2.28; 2.73)	1.35 (0.72; 2.34)
Distal antebrachium	4.41 (3.67; 5.30)	3.70 (3.59; 3.81)	1.18 (0.97; 1.43)	5.90 (3.88; 8.95)	4.38 (4.09; 4.70)	1.34 (0.84; 2.05)
Axial	2.88 (2.30; 3.60)	2.31 (2.22; 2.39)	1.25 (0.98; 1.57)	3.92 (2.36; 6.51)	2.55 (2.33; 2.79)	1.54 (0.86; 2.57)
Any fracture	12.77 (11.43; 14.27)	10.33 (10.14; 10.52)	1.24 (1.10; 1.38)	15.04 (11.46; 19.74)	11.03 (10.54; 11.54)	1.36 (1.01; 1.80)
Fracture rates 1st year						
Hip and femur	8.95 (6.33; 12.66)	3.94 (3.64; 4.27)	2.27 (1.54; 3.24)	8.13 (3.05; 21.67)	3.76 (3.01; 4.69)	2.17 (0.58; 5.77)
Humerus	1.95 (0.93; 4.10)	1.72 (1.52; 1.94)	1.14 (0.45; 2.38)	2.05 (0.29; 14.52)	2.44 (1.85; 3.21)	0.84 (0.02; 4.89)
Distal antebrachium	6.61 (4.39; 9.95)	3.70 (3.40; 4.02)	1.79 (1.12; 2.71)	14.82 (7.06; 31.08)	4.59 (3.75; 5.63)	3.23 (1.26; 6.92)
Axial	2.78 (1.50; 5.17)	1.83 (1.62; 2.05)	1.52 (0.72; 2.84)	4.13 (1.03; 16.53)	2.25 (1.69; 3.00)	1.84 (0.22; 7.01)
Any fracture	16.45 (12.60; 21.47)	9.13 (8.64; 9.64)	1.80 (1.35; 2.37)	29.31 (17.02; 50.48)	10.23 (8.90; 11.77)	2.86 (1.50; 5.01)
Fracture rates 2–5th year						
Hip and femur	5.27 (4.05; 6.87)	4.74 (4.55; 4.94)	1.11 (0.84; 1.45)	8.04 (4.57; 14.16)	4.31 (3.84; 4.83)	1.87 (0.95; 3.31)
Humerus	3.15 (2.24; 4.43)	2.28 (2.15; 2.42)	1.38 (0.95; 1.95)	4.71 (2.25; 9.88)	2.51 (2.16; 2.92)	1.88 (0.74; 3.95)
Distal antebrachium	4.13 (3.05; 5.58)	3.65 (3.48; 3.83)	1.13 (0.81; 1.53)	4.20 (1.89; 9.35)	4.46 (3.98; 5.00)	0.94 (0.34; 2.08)
Axial	3.04 (2.15; 4.30)	2.32 (2.18; 2.46)	1.31 (0.89; 1.86)	4.77 (2.27; 10.01)	2.53 (2.18; 2.94)	1.89 (0.75; 3.97)
Any fracture	13.29 (11.17; 15.82)	10.58 (10.28; 10.89)	1.26 (1.04; 1.50)	18.22 (12.22; 27.19)	11.17 (10.37; 12.03)	1.63 (1.04; 2.45)
Fracture rates 6–10th year						
Hip and femur	4.77 (3.43; 6.65)	4.68 (4.46; 4.91)	1.02 (0.71; 1.42)	6.38 (3.04; 13.39)	4.97 (4.41; 5.59)	1.28 (0.51; 2.68)
Humerus	3.13 (2.08; 4.71)	2.25 (2.10; 2.41)	1.39 (0.88; 2.10)	2.75 (0.89; 8.52)	2.36 (1.99; 2.80)	1.16 (0.24; 3.48)
Distal antebrachium	4.05 (2.82; 5.83)	3.69 (3.50; 3.90)	1.10 (0.73; 1.58)	5.67 (2.55; 12.62)	4.31 (3.79; 4.91)	1.32 (0.48; 2.91)
Axial	2.44 (1.54; 3.87)	2.29 (2.14; 2.45)	1.06 (0.63; 1.69)	2.75 (0.89; 8.54)	2.49 (2.11; 2.94)	1.11 (0.23; 3.30)
Any fracture	10.44 (8.26; 13.20)	10.41 (10.07; 10.77)	1.00 (0.78; 1.27)	10.21 (5.49; 18.97)	10.85 (9.97; 11.80)	0.94 (0.45; 1.74)

Note: Incidence rates (IRs) and incidence rate ratios (IRRs) in patients with primary and secondary ITP. Rates and ratios were generally higher for patients early in the study period, but differences diminished over time for most groups. The p-value for the Altman–Bland test of interaction in the decline in rates of any fracture between the 1st and 2–5th year was $p = 0.035$.[35] The corresponding p-value for the increase in rates from 1995–2005 to 2006–2016 was $p = 0.024$.

Abbreviations: DXA, dual X-ray absorptiometry; ITP, immune thrombocytopenia.

TABLE 3 Cumulative incidences of different types of fractures after 1, 5 and 10 years after diagnosis of ITP, and end of study time in patients with primary and secondary ITP and general population age–sex-matched comparators.

Name	Primary ITP (%) (95% CI)	Comparators pITP (%) (95% CI)	Secondary ITP (%) (95% CI)	Comparators sITP (%) (95% CI)
End of 1st year				
Hip and femur	0.84 (0.59; 1.18)	0.39 (0.36; 0.42)	0.76 (0.26; 1.85)	0.37 (0.30; 0.46)
Humerus	0.18 (0.08; 0.37)	0.17 (0.15; 0.19)	<0.70	0.24 (0.18; 0.32)
Distal antebrachium	0.62 (0.40; 0.91)	0.37 (0.34; 0.40)	1.39 (0.62; 2.72)	0.46 (0.37; 0.56)
Axial	0.26 (0.14; 0.47)	0.18 (0.16; 0.20)	<0.70	0.22 (0.17; 0.30)
Any fracture	1.54 (1.18; 2.00)	0.91 (0.86; 0.96)	2.74 (1.54; 4.51)	1.02 (0.88; 1.16)
End of 5th year				
Hip and femur	2.56 (2.07; 3.14)	2.16 (2.08; 2.24)	3.35 (1.99; 5.26)	1.99 (1.80; 2.20)
Humerus	1.21 (0.88; 1.63)	1.02 (0.96; 1.07)	1.66 (0.78; 3.12)	1.18 (1.04; 1.35)
Distal antebrachium	1.97 (1.54; 2.50)	1.72 (1.65; 1.79)	2.78 (1.56; 4.59)	2.12 (1.92; 2.34)
Axial	1.24 (0.90; 1.66)	1.04 (0.99; 1.10)	1.92 (0.95; 3.49)	1.18 (1.03; 1.34)
Any fracture	5.84 (5.05; 6.71)	4.80 (4.68; 4.92)	8.39 (6.03; 11.23)	5.15 (4.83; 5.49)
End of 10th year				
Hip and femur	4.14 (3.44; 4.93)	4.06 (3.94; 4.18)	5.50 (3.56; 8.04)	4.07 (3.77; 4.40)
Humerus	2.31 (1.78; 2.94)	1.92 (1.84; 2.01)	2.64 (1.37; 4.59)	2.17 (1.95; 2.41)
Distal antebrachium	3.37 (2.72; 4.11)	3.20 (3.09; 3.31)	4.69 (2.89; 7.14)	3.89 (3.59; 4.20)
Axial	2.06 (1.58; 2.65)	1.96 (1.88; 2.05)	2.85 (1.54; 4.84)	2.23 (2.00; 2.47)
Any fracture	9.28 (8.19; 10.45)	8.89 (8.71; 9.07)	11.78 (8.77; 15.26)	9.52 (9.05; 10.01)
End of study period				
Hip and femur	6.54 (5.46; 7.76)	7.39 (7.13; 7.66)	6.51 (4.22; 9.46)	8.88 (5.89; 12.62)
Humerus	3.47 (2.57; 4.56)	3.49 (3.30; 3.68)	4.23 (2.04; 7.65)	4.07 (3.59; 4.59)
Distal antebrachium	5.60 (4.34; 7.08)	5.94 (5.63; 6.26)	5.98 (3.78; 8.87)	7.00 (6.29; 7.76)
Axial	3.79 (2.86; 4.90)	3.91 (3.69; 4.14)	4.55 (2.46; 7.62)	5.15 (3.49; 7.25)
Any fracture	15.27 (13.33; 17.33)	16.17 (15.73; 16.62)	14.59 (10.85; 18.86)	20.18 (15.99; 24.73)

Note: Cumulative incidence proportions of subgroups of fractures at time points after diagnosis of ITP. The competing events were death and emigration. For a corresponding graphic illustration, please see Figure 1.

Abbreviations: DXA, dual X-ray absorptiometry; ITP, immune thrombocytopenia.

DISCUSSION

The risk of fractures was elevated for both pITP and sITP, in particular hip and femoral fractures. The risks were highest in the first years after diagnosis but diminished in the following years. The use of bisphosphonates over calendar-years and in temporal relation to the diagnosis of ITP was elevated for both pITP and sITP compared with the general population.

Patients with both pITP and sITP had significantly more comorbidities than the comparators, but all analyses were adjusted for potential confounding factors and effect modifiers. We also estimated the subhazard ratios for fractures with death as a competing event. This resulted in lower and insignificant estimates compared to csHRs, indicating the presence of competing risk events.

The largest fracture risks were found in hip and femoral fractures for both pITP and sITP. Patients with hip and femoral fractures are usually admitted to a hospital for treatment, while the other groups of fractures are often managed at an ER. However, fractures treated at an ER are still recorded correctly with updated codes after discharge, but these data were only available from 1994 and onwards. Axial fractures may be associated with unspecific symptoms and diagnostic delay, and many are not diagnosed.[38,39] In spite of this, the risk was elevated in pITP. Patients with pITP are often in a hospital follow-up, and therefore health events, such as a fracture, are more likely to be captured. An elevated risk of vertebral fractures in other autoimmune diseases, such as rheumatoid arthritis, has also been found.[40] Specific reasons for this are unknown, but the varying severity and chronicity of the diseases could explain this.

Fracture risk was more pronounced during the first year after ITP diagnosis. Guidelines for the treatment of ITP with corticosteroids recommend short courses with fast tapering,[10] but despite this, accumulated doses may reach 2–3 g of prednisolone[11] during induction therapy. Furthermore, corticosteroids can be administered as concomitant therapy in addition to later-line therapies.[10] Whether this early increased risk of fracture is causally related to the use of high-dose corticosteroids in ITP remains unelucidated, but one study found that exposure to corticosteroids causes a rapid

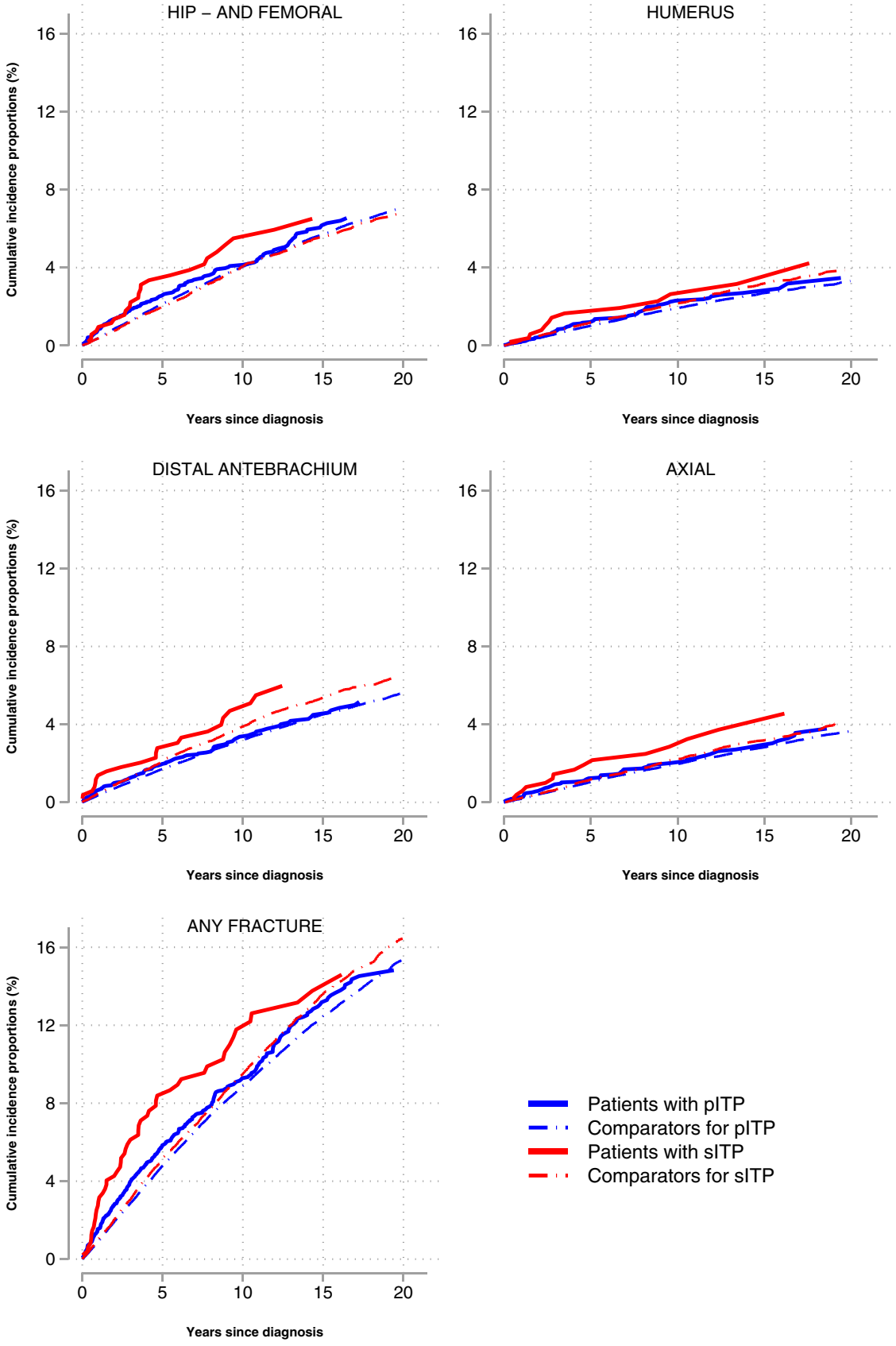

FIGURE 1 Cumulative incidences for different types of fractures. Graphs illustrating the cumulative incidences, including 95% confidence intervals, for different types of fractures in primary and secondary ITP and general population age–sex-matched comparators. Blue lines represent primary ITP, and red lines represent secondary ITP. Solid lines represent patients, and dashed lines represent comparators. ITP, immune thrombocytopenia.

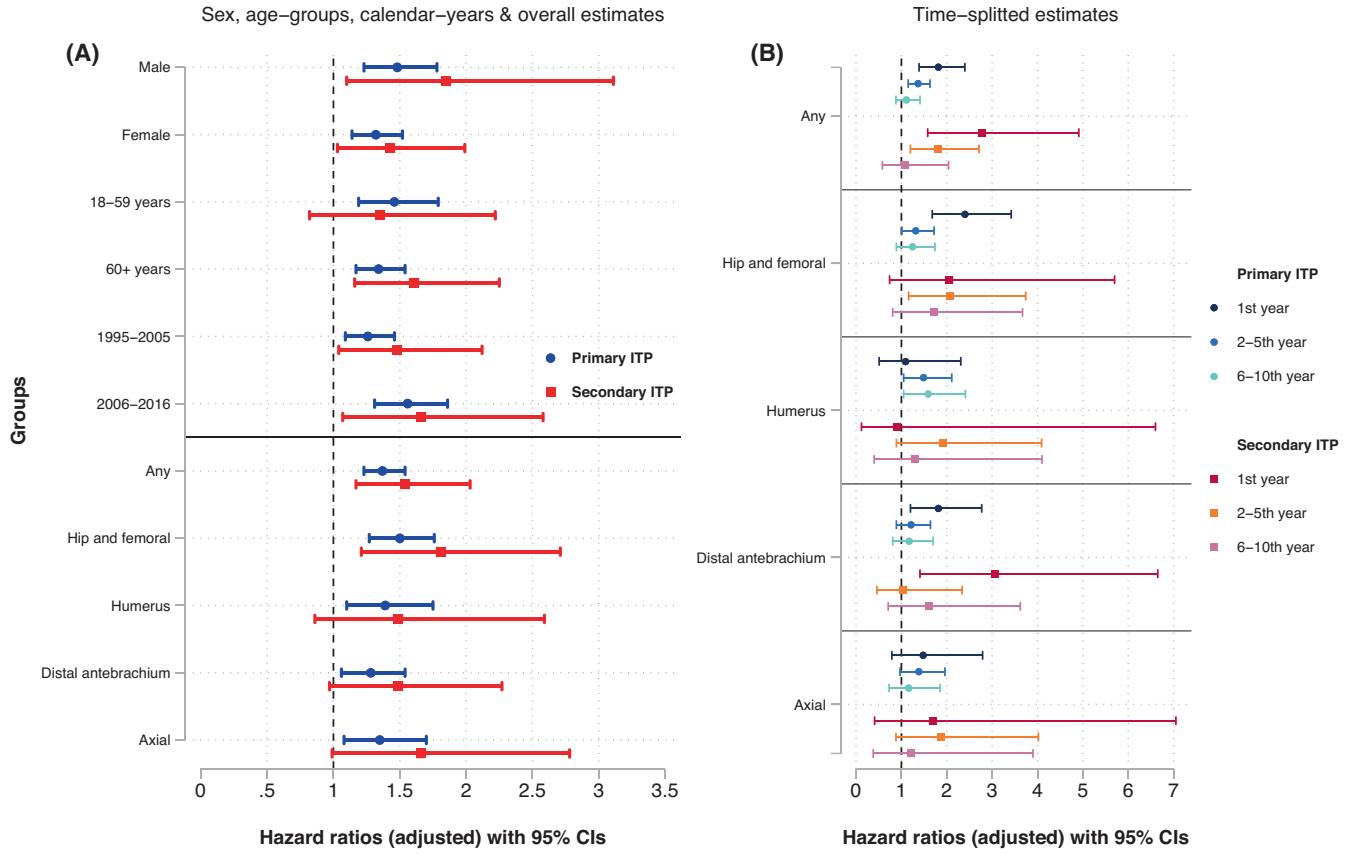

FIGURE 2 Hazards ratio plot with 95% confidence intervals for fractures. A graphic illustration of adjusted hazard ratios for fracture risks for both primary and secondary ITP. (A) represents the overall fracture risk for each fracture group and stratifications by age and sex. (B) represents the time-split estimates of 1st year, 2–5th year and 6–10th year risks. CIs, confidence intervals; ITP, immune thrombocytopenia.

and early decreasing BMD.[40] Fear of bleeding and fatigue are widespread symptoms in ITP and correlate to disease severity.[41] This could constrain patients from participating in sports and exercises, thereby reducing BMD and increasing the first-year risk of fracture due to inactivity.[42] The gradual fracture risk reduction in the following years could, conversely, be correlated to a better acceptance and treatment control of the ITP disease. Furthermore, the autoimmune features underlying the ITP disease itself[9] could also enhance the effect of pro-inflammatory cytokines associated with decreasing BMD, such as in rheumatoid arthritis (RA), where[43–45] patients also suffer from an elevated risk of hip and vertebral fractures independent of corticosteroid use due to disease inflammation.[44] Another study found a HR of 1.8 for fracture in a 5-year period following the diagnosis of monoclonal gammopathy of undetermined significance, similar to our estimates.[46]

Patients aged 18–59 years had a relatively higher and persisting risk of fractures compared with patients aged 60+ years. Since corticosteroids are the greatest risk factor for developing secondary osteoporosis in individuals <50 years, clinical focus on osteoporosis in this young patient group is of great importance.[47]

Other haematological diseases not treated with corticosteroids are also associated with an increased risk of fractures. Farmer et al. found an elevated risk of osteoporotic femoral fractures for some myeloproliferative neoplasms, which are associated with chronic inflammation.[32,48,49] Some types of lymphoma are underlying sITP,[50,51] and are associated with an increased risk of both fractures and osteoporosis following treatment.[52–54] This could contribute to an elevated fracture risk in sITP.

The use of bisphosphonates rose in the years following ITP, possibly indicating a clinical awareness of bone-demineralizing disease following treatment with corticosteroids. Comorbidities associated with a prior high cumulative use of corticosteroids (e.g. chronic pulmonary disease, autoimmune disease) were more prevalent in ITP in general, particularly for sITP, with a 2.5-fold increased proportion of prevalent osteoporosis and a 1.5- and 2.0-fold increased use of prevalent incident DXA-scans respectively.[22] The use over calendar-years diminished for pITP but persisted for sITP. This could indicate a persisting clinical focus on bone-demineralizing disease in sITP, as well as an awareness of sITP being characterized by high comorbidity and associated with poor prognosis.[2,55] Whether these findings should increase the use of bisphosphonates in ITP is unknown, but one study found a significant increase in BMD following treatment with concomitant bisphosphonates in patients with ITP exposed to corticosteroids.[56]

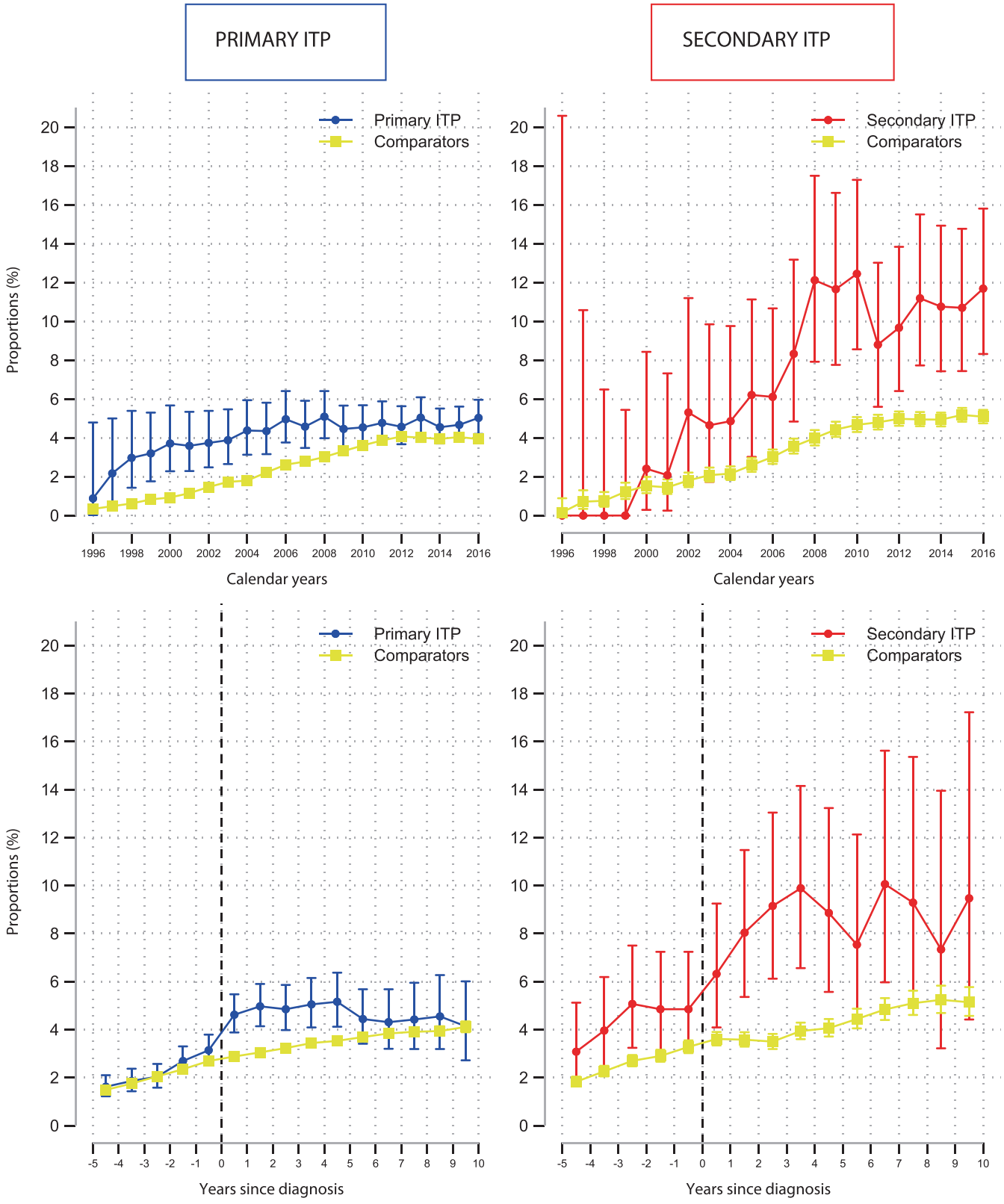

FIGURE 3 Use of bisphosphonates in patients with ITP and comparators. Illustration of the use of bisphosphonates measured as a minimum of one registered prescription within a year of full follow-up. Blue (left) represents point estimates and confidence intervals for primary ITP, while red (right) represents secondary ITP. Yellow represents comparators. Both developments over calendar-years (top) and the temporal relation to the diagnosis of ITP (bottom) are illustrated. ITP, immune thrombocytopenia.

Limitations

We categorized patients as suffering from primary and secondary ITP based on qualifying diagnoses that were either pre-existing or diagnosed within the first 30 days after ITP diagnosis. In spite of this, misclassifying sITP as pITP could occur since sITP is not a well-defined entity and an associated sITP-defining diagnosis may first become obvious later.[57] Patients with sITP are generally more burdened with comorbidity and have shorter survival than patients with pITP.[2] Some outcomes for sITP also lacked statistical power.

We investigated fractures that are usually associated with concomitant osteoporosis, but lacked data to determine whether fractures were indeed osteoporotic fractures. We also presumed an association between corticosteroids and fracture risk, but lacked granular treatment data to investigate this potential causality. Despite adjusting all analyses, we do not know the impact of other potential confounders or effect modifiers either.

Changes in registration practices in the DNPR over time could also influence results.

CONCLUSION

This study shows an elevated risk of fractures and a more frequent exposure to bisphosphonates in adult patients with pITP and sITP compared with the general population. The potential relationship between the increased risk of fractures and the immune dysfunction underlying ITP remains unknown. Further studies are needed to correlate this risk with the exposure to corticosteroids and ITP severity in order to identify patients who could benefit from bisphosphonates, and whether the use of bisphosphonates could prevent fractures in this population.

AUTHOR CONTRIBUTIONS

N. Mannering, D. L. Hansen and H. Frederiksen conceived the study idea. N. Mannering, D. L. Hansen, G. Moulis, W. Ghanima, A. Pottegård and H. Frederiksen designed the study. N. Mannering and H. Frederiksen applied for funding. N. Mannering and D. L. Hansen performed data analyses. N. Mannering wrote the first draft. All authors read and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

N.M. has received financial support from Novartis Healthcare for this work, received conference fees from AbbVie and Swedish Orphan Biovitrum (SOBI), guest speaker fees from Novartis and SOBI and served as Advisory Board member for SOBI outside this work. D.L.H. has received research grants from Alexion and Novartis >5 years ago, served as Advisory Board member for Janssen and Takeda and received conference fees from EUSA Pharma and Alexion outside this work. G.M. received meeting attendance grants from Amgen, Grifols and Novartis. He is the coordinator of research studies granted by Amgen, CSL Behring, Grifols, Novartis and Sanofi. He participated in educational sessions funded by Amgen, Grifols and Novartis and to boards for Amgen, Argenx, Novartis, Sanofi and Sobi. W.G. reports fees for participation on Advisory Boards from Amgen, Novartis, Pfizer, Principia Biopharma Inc., a Sanofi Company, Sanofi, SOBI, Grifols, UCB, Argenx, Cellphire, Alpine, Kedrion and HiBio. Lecture honoraria from Amgen, Novartis, Pfizer, Bristol Myers Squibb, Swedish Orphan Biovitrum, Grifols, Sanofi and Bayer. Research grants from Bayer, BMS/Pfizer and UCB. All outside this work. A.P. has participated in research projects funded by Alcon, Almirall, Astellas, Astra-Zeneca, Boehringer-Ingelheim, Novo Nordisk, Servier and LEO Pharma, all regulator-mandated phase IV studies, all with funds paid to the institution where he was employed (no personal fees) and with no relation to the work reported in this paper. H.F. received research support from Swedish Orphan Biovitrum outside this work. Novartis Healthcare supported the study but had no influence on the study design or results. None of the authors declare any other conflicts of interests.

ETHICS AND DATA AVAILABILITY STATEMENT

Registry-based research does not require Ethics Committee approval, according to Danish law. All analyses were performed without access to detailed patient medical files. The authors are prohibited from sharing national health data or grant access to the data according to Danish law. Access to data can be granted upon request through applications and contacts to the designated Danish authorities.

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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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