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TRANSFUSION

Survival in adult patients with chronic primary and secondary immune thrombocytopenia: A population-based study

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Abstract

Background: Few studies have investigated long-term survival in patients with primary immune thrombocytopenia (pITP). Further, changes in prognosis over the past decades and prognosis of secondary immune thrombocytopenia (sITP) are largely unstudied. Our objectives were to study comorbidity-adjusted prognostic changes and causes of death in chronic pITP and sITP patients.

Study Design/Methods: Using nationwide Danish health registries 1980–2016, we identified 1762 patients with chronic pITP (median age 58 (IQR, 37–73) years) and 128 with chronic sITP (median age 59 (IQR, 40–73) years). Patients were age-sex-matched to 74,781 general population comparators. Comorbidity was assessed using Charlson Comorbidity Index (CCI).

Results: Overall median survival was reduced by 5.1 years (95% CI, 0.7–9.4) ($p < .001$) for pITP and 11.1 years (95% CI, 5.8–16.4) ($p < .001$) for sITP. 5-year survival increased from 69% (95% CI, 59–78) in 1980–89 to 80% (95% CI, 75–83) in 2010–16 for pITP, and decreased from 100% (95% CI, 89–98) to 64% (95% CI, 87–91) for sITP. However, numbers were small for sITP. 5-year survival for pITP with high CCI was 41% (95% CI, 32–49), and 85% (95% CI, 83–87) for low CCI.

Bleeding, infection and hematological cancer were relatively frequent causes of death with adjusted subhazard ratios of 3.25 (95% CI, 2.33–4.52), 1.53 (95% CI, 1.08–2.16) and 2.16 (95% CI, 1.12–4.16) in pITP respectively, and 10.52 (95% CI, 1.43–77.36) for hematological cancer in sITP.

Abbreviations: CCI, Charlson Comorbidity Index; CPR, Civil Personal Register; CI, confidence interval; cITP, chronic ITP; DNPR, Danish National Patient Registry; DCRS, The Danish Civil Registration System; DCRD, The Danish Regsiter of Causes of Death; ICD, international classification of diseases; ITP, immune thrombocytopenia; IQR, interquartile range; HR, hazard ratio; pITP, primary immune thrombocytopenia; sITP, secondary immune thrombocytopenia; subHR, subhazard ratio; TE, thromboembolic events; TPO-RA, thrombopoietin receptor agonist.

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Conclusions: Long-term survival is reduced in chronic ITP but seems to be improving. Comorbidity and sITP are associated with a poor prognosis.

KEYWORDS
causes of death, epidemiology, immune thrombocytopenia, long-term survival

1 | INTRODUCTION

Immune thrombocytopenia (ITP) is an autoimmune disorder where immune reactions against platelets and megakaryocytes lead to abnormal low platelet count and increased risk of bleeding.[1–4] Diagnosis of primary ITP (pITP) is a diagnosis of exclusion, and involves the exclusion of secondary ITP (sITP) caused by underlying conditions such as infection or autoimmune disease.[1,5,6] pITP is a defined diagnostic entity,[7] whereas definitions and distribution of diagnoses underlying sITP is less clear.[8]

The majority of patients with ITP suffers a chronic course with ongoing medical treatments[9] and impaired quality of life.[10,11] Reductions in quality of life involve physical and mental issues following persistent bleeding symptoms, fatigue,[11] risk of thromboembolic events (TE),[12–14] and side effects of treatments.[15]

Only a few studies on long-term survival in patients with pITP exist,[16,17] but recent studies have documented an increased mortality in patients with pITP compared with the general population.[18,19] This has been attributed to an increased risk of death from infection, bleeding and cancer,[18–22] but estimates of long-term survival and additional data on the underlying causes-of-death are sparse. Furthermore, the prognosis for patients with sITP is largely unstudied, with lack of studies comparing survival among sITP with survival in pITP and the general population.

The current cornerstones in the treatment of both pITP and sITP remain immunosuppressants and agents stimulating thrombopoiesis[23,24] but the management of the underlying disorder is also important in sITP.[5,7] Medical treatment options have generally improved over the past decades.[9] Rituximab[25,26] and thrombopoietin-receptor agonists were introduced in the 2000s[23,24] and have gained traction since, while splenectomy has declined.[27] The changing landscape of treatment options may potentially have impacted survival of both pITP and sITP over time, but this has to our knowledge not been investigated previously. Additionally, comorbidity has been shown to be more prevalent among patients with ITP,[18] but the effect on mortality is sparsely investigated.

In this study, we provide nationwide data about long-term survival, comorbidity, and causes of death among patients with pITP and sITP compared with the general population.

2 | METHODS

2.1 | Data sources

The Danish nationwide health registries comprise unique sources of data with high completeness, validity and follow-up.[28] They have universal coverage and are continuously updated. The registries hold information regarding hospitalization since 1977 and hospital outpatient and emergency department registrations since 1994 for inhabitants in Denmark.[29–31]

We used data from these registries to construct a nationwide cohort of patients with ITP and matched comparators. In Denmark, patients with hematological conditions are solely managed in public hospitals.

All hospital contacts in Denmark are assigned a diagnosis code by the physician using the international classification of diseases (ICD) and registered in the Danish National Patient Registry (DNPR).[29,32] We retrieved data from the DNPR on in-patient and outpatient hospital contacts (outpatient contacts from 1994 and onwards) and associated ICD-codes. The Danish Civil Registration System (DCRS)[30] provided data on sex, dates of birth, emigration, and death while we retrieved causes of death for deceased patients and comparators from the Danish Register of Causes of Death (DRCD).[31] All inhabitants in Denmark are assigned a unique and permanent 10-digit Civil Personal Register (CPR) number. This consists of six digits indicating date and year of birth and four digits as unique identifiers, and allows individual-level-record linkage between Danish registries.[30]

2.2 | Identification & selection of patients and comparisons

Patients with ITP were identified through ICD-codes classifying ITP in the DNPR, using the ICD-8 (1977–1993) and ICD-10 (1994–2016) (Table S1). We included patients with two or more registrations of ITP with a minimum of 12 months apart thereby fulfilling criteria for chronic ITP (cITP).[7]

We categorized patients as having secondary ITP (sITP) if they fulfilled cITP criteria and a registration of at least one underlying qualifying diagnosis any time

before or up to 12 months after the first registration of ITP (Table S2). Figure S1 illustrates the steps in the selection process of patients fulfilling the above criterias.

We excluded patients registered with Evans syndrome (defined as a registration of both ITP and autoimmune hemolysis[33]), congenital platelet disorders, ITP prevalent before 1980, or <18 years of age at diagnosis of cITP (Table S1).

Index date marked the start of follow-up, and was defined as the date of fulfillment of the cITP criteria for both pITP and sITP. Patients and comparators were categorized according to decade of diagnosis (1980–89, 1990–99, 2000–09 and 2010–16) and age at inclusion (18–39, 40–59, 60–69, 70+ years).

Each patient was assigned up to 40 unique age and sex-matched comparators from the general population. All comparators were allotted the same index date as patients, and both patients and comparators were followed from index date to the first of death, emigration, or end of study period December 31st, 2016.

Comorbidity at time of study inclusion was based on diagnoses registered in the DNPR before or on index date, and aggregated in 12 categories after the Quan 2011 updated Charlson Comorbidity Index (CCI).[34] A Charlson Comorbidity Score of 0 was considered low, a score of 1–2 intermediate, and a score of >2 high. For sITP patients, we computed CCI scores disregarding pre-existing diagnoses that mandated sITP grouping. Details regarding included diagnosis codes are provided in Table S3.

Granular data on treatment were generally lacking or incomplete, but registration of thrombopoietin-receptor agonist (TPO-RA) or Rituximab treatment (present vs. absent) was retrieved using designated procedure codes from DNPR (Table S3).

2.3 | Statistical analysis

Baseline characteristics were presented as median age at diagnosis including interquartile range (IQR), and percentage with 95% confidence intervals (95% CI) for distributions of sex, treatments and comorbidity.

Median, 1-, 5-, and 10-year survival were estimated using the Kaplan–Meier estimator. Differences in survival were tested using the log-rank test for equality of survivor functions.[35]

Causes of death were aggregated into six pre-specified categories: bleeding, hematological malignancy, solid malignancy, cardiovascular disease, infection and other/unspecified (Table S4). We used Cox proportional hazard regression to estimate unadjusted and adjusted hazard ratios for death comparing overall mortality between patients and comparators, as well as unadjusted and adjusted cause-specific hazard ratios for each group of cause of death. Hazard ratios were adjusted for age, sex, decade of diagnosis, prevalent CCI-score, splenectomy performed, TPO-RA-treatment, and Rituximab-treatment. Analyses treating other causes of death as competing events were applied to estimate unadjusted and adjusted subdistribution hazard ratios by the Fine-Gray proportional subdistribution hazard regression, as well as cumulative incidence proportions of the different causes of death.[36,37]

All analyses were done separately for a set of patients with pITP or sITP and their respective general population comparators. All p-values and confidence intervals provided together with effect or point estimates were not adjusted for multiplicity.

The precision of Cox regression models to describe data was tested for goodness of fit by plotting Cox-Snell residuals, showing more than 99% of observation with no or minimal deviation for both pITP and sITP models.[38]

All data-management and statistical analyses were performed using Stata 16.1 (StataCorp, 4905 Midtown Dr., College Station, TX 77845, USA).

2.4 | Sensitivity analysis

We performed a sensitivity analysis, doing selected analyses including only patients with certain combinations of ICD-codes. This included ICD-10 codes D693, D693A and D694, and ICD-8 code 287.10.

2.5 | Ethics & approval

Registry-based research does not require Ethic Committee approval according to Danish law. All data were anonymized and without access to detailed patient medical files.

2.6 | Data sharing & availability

It is prohibited to share national health data publicly according to Danish law. Access to data can be made upon request through relevant applications and contacts to Research Service at Statistics Denmark.

3 | RESULTS

3.1 | Inclusion and characteristics

We included 1762 patients with chronic pITP, 128 with chronic sITP, and 74,781 age-sex-matched comparators.

TABLE 1 Baseline characteristics of patients with chronic primary and secondary ITP and general population age-sex-matched comparators

Name	Primary ITP ($n = 1762$) [95% CI]	Comparators pITP ($n = 69{,}684$) [95%CI]	Secondary ITP ($n = 128$) [95%CI]	Comparators sITP ($n = 5097$) [95%CI]
Women, %	60 [58–63]	61 [60–61]	64 [55–72]	64 [63–66]
Age, years (median, IQR)	58 [37–73]	57 [36–73]	59 [40–73]	59 [40–73]
Underlying causes of secondary ITP, %				
Autoimmunity	N/A	N/A	57 [48–66]	N/A
Hematologic malignancy	N/A	N/A	27 [20–36]	N/A
Immunodeficiency	N/A	N/A	<3	N/A
Infection	N/A	N/A	15.6 [9.8–23.1]	N/A
Year of diagnosis, %				
1980–1989	5.4 [4.4–6.6]	5.4 [5.2–5.6]	<3	2.4 [2.0–2.8]
1990–1999	18 [17–20]	18 [18–18]	16 [10–23]	16 [15–16]
2000–2009	35 [33–37]	35 [34–35]	45 [37–54]	45 [44–47]
2010–2016	41 [39–44]	42 [41–42]	37 [28–46]	37 [35–31]
Splenectomized, %	20 [18–22]	0.20 [0.17–0.24]	30 [23–39]	0.08 [0.02–0.20]
Comorbidity, %				
No registered comorbidity	66 [63–68]	81 [81–81]	59 [50–68]	82 [80–83]
AIDS	<0.2	0.05 [0.04–0.07]	<3	<3
Chronic pulmonary disease	8.1 [6.8–9.4]	5.9 [5.7–6.1]	10.2 [5.5–16.8]	5.69 [5.1–6.4]
Congestive heart failure	4.3 [3.4–5.4]	2.6 [2.5–2.7]	6.3 [2.7–12.0]	2.5 [2.1–3.0]
Connective tissue disease	9.4 [8.0–10.8]	2.6 [2.5–2.7]	3.9 [1.3–8.9]	2.2 [1.8–2.6]
Dementia	1.5 [1.0–2.2]	1.4 [1.3–1.5]	<3	1.3 [1.0–1.6]
Diabetes mellitus	2.8 [2.1–3.7]	1.6 [1.5–1.7]	3.9 [1.3–8.9]	1.7 [1.4–2.1]
Hemiplegia	0.51 [0.23–0.97]	0.26 [0.22–0.30]	<3	0.20 [0.09–0.36]
Metastatic solid tumor	0.79 [0.44–1.33]	0.53 [0.47–0.58]	0.78 [0.02–4.28]	0.67 [0.46–0.93]
Mild liver disease	3.52 [2.71–4.49]	0.62 [0.57–0.68]	5.5 [2.2–10.9]	0.71 [0.50–0.98]
Moderate–severe liver disease	1.7 [1.1–2.4]	0.20 [0.17–0.24]	<3	0.24 [0.12–0.41]
Moderate–severe renal disease	3.0 [2.3–3.9]	1.3 [1.2–1.4]	4.7 [1.7–9.9]	1.2 [0.9–1.5]
Solid tumor, lymphoma or leukemia	13 [11–14]	7.4 [7.2–7.6]	9.4 [4.9–15.8]	7.4 [6.7–8.1]
Comorbidity score				
Comorbidity-score (mean)	0.44 [0.41–0.47]	0.23 [0.23–0.23]	0.50 [0.38–0.62]	0.22 [0.21–0.23]
Novel treatments, %				
TPO-RA exposure	1.7 [1.2–2.4]	<0.1 [0.0;0.2]	<3	0.00 [0.00–0.07]
Rituximab exposure	22 [20–24]	0.29 [0.25–0.33]	34 [26–43]	0.37 [0.22–0.58]

Note: Table 1 All estimates are provided as percentage proportions with 95% confidence intervals except age which is presented as median with interquartile ranges (IQR) and comorbidity-score presented as means. In order not to violate Danish rules for microdata, some estimates are not presented with exact numbers.

Abbreviations: pITP, primary ITP; sITP, secondary ITP; N/A, not available, and (n=), number of patients or comparators.

The most frequent underlying cause of sITP was autoimmune diseases, comprising 57% (95% CI, 48–66) of all secondary cases (3.9% of all ITP cases) (Table 1).

Total follow-up time was 13,970 person-years for patients (average 7.4 years), and 641,749 person-years for comparators (average 8.6 years).

Women constituted 60% (95% CI, 58–63) of patients with pITP and 64% (95% CI, 55–72) of sITP patients. Median age was 58 years (IQR, 37–73) for patients with pITP and 59 years (IQR, 40–73) for sITP. Comorbidity was generally registered more frequent among patients (Table 1). Patients with pITP had a mean comorbidity-

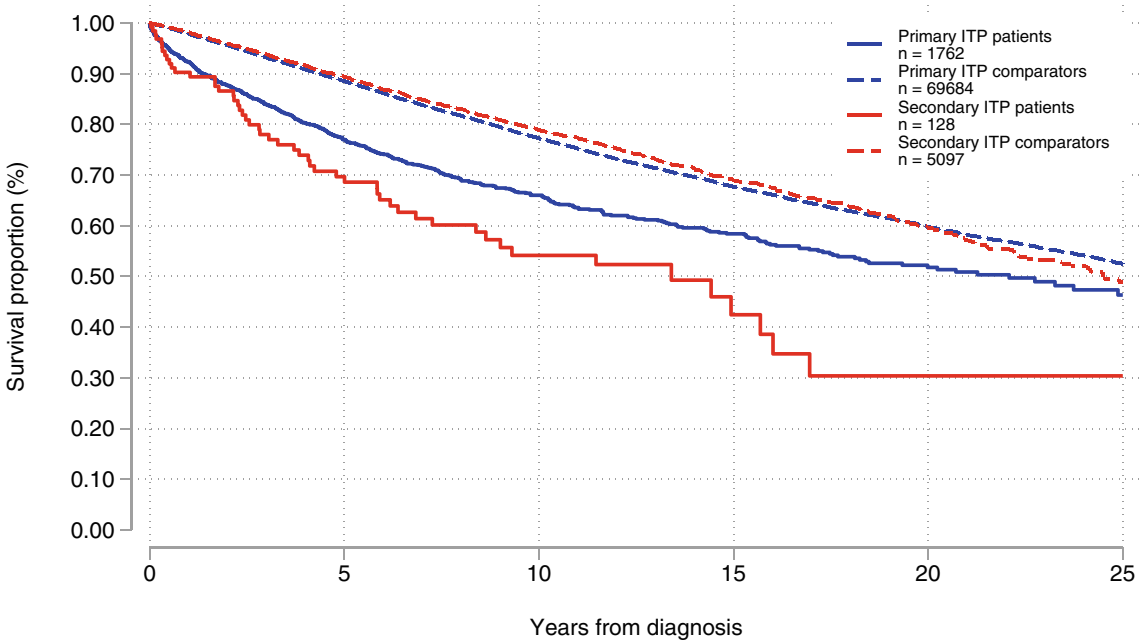

FIGURE 1 Kaplan–Meier overall survival curves for patients with chronic primary ITP and secondary ITP. Solid lines represent patients and dashed lines are comparators. Survival was reduced compared with age-sex-matched general population comparators for both groups. [Color figure can be viewed at wileyonlinelibrary.com]

score of 0.44 (95% CI, 0.41–0.47) compared to 0.23 (95% CI, 0.23–0.23) in comparators, while corresponding numbers for sITP were 0.50 (95% CI, 0.38–0.62) and 0.22 (95% CI, 0.21–0.23) respectively.

Rituximab exposure was almost exclusively registered in patients with 22% (95% CI, 20–24) in pITP and 34% (95% CI, 26–43) in sITP. The same accounted for TPO-RA exposure with 1.7% (95% CI, 1.2–2.4) in pITP and 1.6% (95% CI, 0.2–5.5) in sITP, while both Rituximab and TPO-RA exposure was <0.40% for comparators.

3.2 | Survival

Survival was lower in patients with pITP and sITP than matched comparators (Figure 1). The median survival of patients with pITP was 22.1 years (95% CI, 18.1–26.2) and 13.4 years (95% CI, 7.3–16.0) in patients with sITP, compared with 27.1 years (95% CI, 26.2–27.9) and 24.5 years (95% CI, 22.8-.) in comparators, respectively (Figure 1; Table S5).

Overall adjusted hazard ratios (HRs) for death were 1.79 (95% CI, 1.62–1.97) for pITP and 3.60 (95% CI, 2.50–5.17) for sITP compared to the general population (Table S5).

Survival was impaired in the first years after diagnosis of cITP (Figure 1). The 5-year survival of patients with pITP was 77% (95% CI, 75–79) and 89% (95% CI, 88–89) in comparators (Table S5). Corresponding numbers for sITP were 70% (95% CI, 60–78) and 89% (95% CI, 88–90).

Higher comorbidity at diagnosis of chronic ITP was associated with reduced survival. Patients with pITP and low comorbidity had a 5-year survival of 85% (95% CI, 83–87) compared with 41% (95% CI, 32–49) in pITP patients with high comorbidity (Table S6; Figure S3). Corresponding numbers for patients with sITP were 80% (95% CI, 68–88) and 26% (95% CI, 4–56). Adjusted HRs for death looked similar across the various groups of comorbidity scores (Table S6).

The 5-year survival in pITP increased from 69% (95% CI, 59–78) in 1980–89 to 80% (95% CI, 75–83) in 2010–16, compared to an increase from 88% (95% CI, 87–89) to 90% (95% CI, 89–90) for comparators.

The 5-year survival in sITP decreased from 100% (95% CI, not estimable) in 1980–89 to 64% (95% CI, 38–81) in 2010–16, compared to a decrease from 95% (95% CI, 89–98) to 89% (95% CI, 87–91) for comparators (Figure 2; Table S5). Mortality rates did not change significantly for neither pITP nor sITP across decades (Table S7).

The risk of death did not change across decades. Adjusted hazard ratios changed from 1.47 (95% CI, 1.08–2.00) in 1980–89 to 1.67 (95% CI, 1.33–2.10) in 2010–2016 for pITP, and from 3.82 (95% CI, 1.87–7.78) in 1990–99 (few observations in 1980–89) to 1.42 (95% CI, 0.57–3.52) in 2010–2016 for sITP (Figure 3; Table S5).

Survival stratified by age showed the largest survival differences between patients and comparators aged 70+.

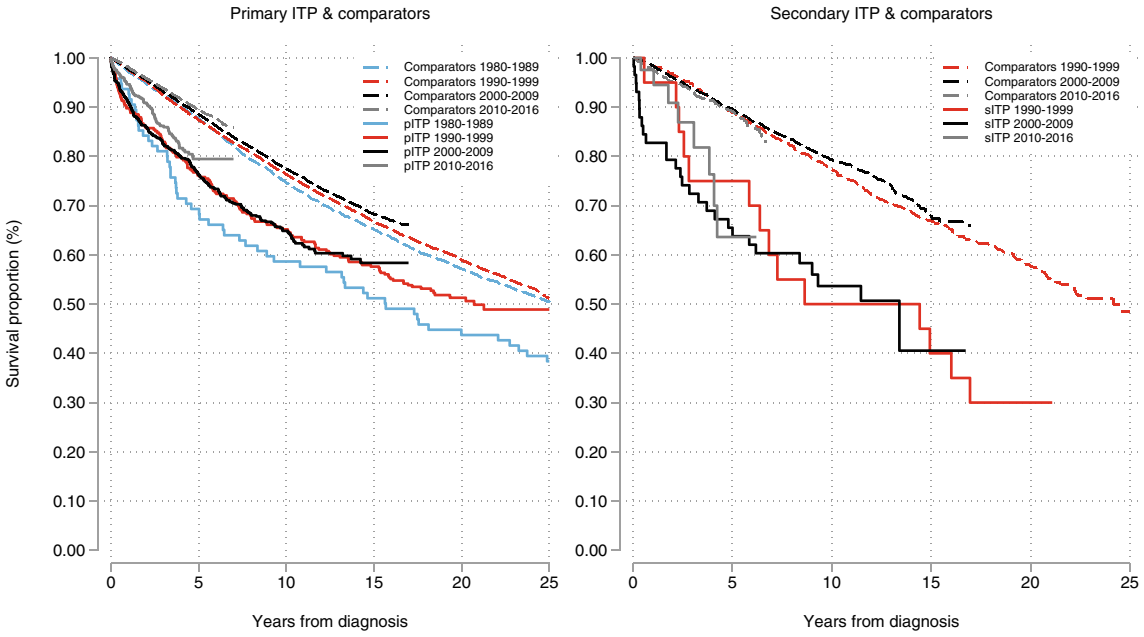

FIGURE 2 Kaplan–Meier survival curves for chronic primary and secondary ITP illustrating the development in survival over the decades. Survival generally improved across decades, particularly from the 1980s and forward. Abbreviations: pITP, primary ITP; sITP, secondary ITP. [Color figure can be viewed at wileyonlinelibrary.com]

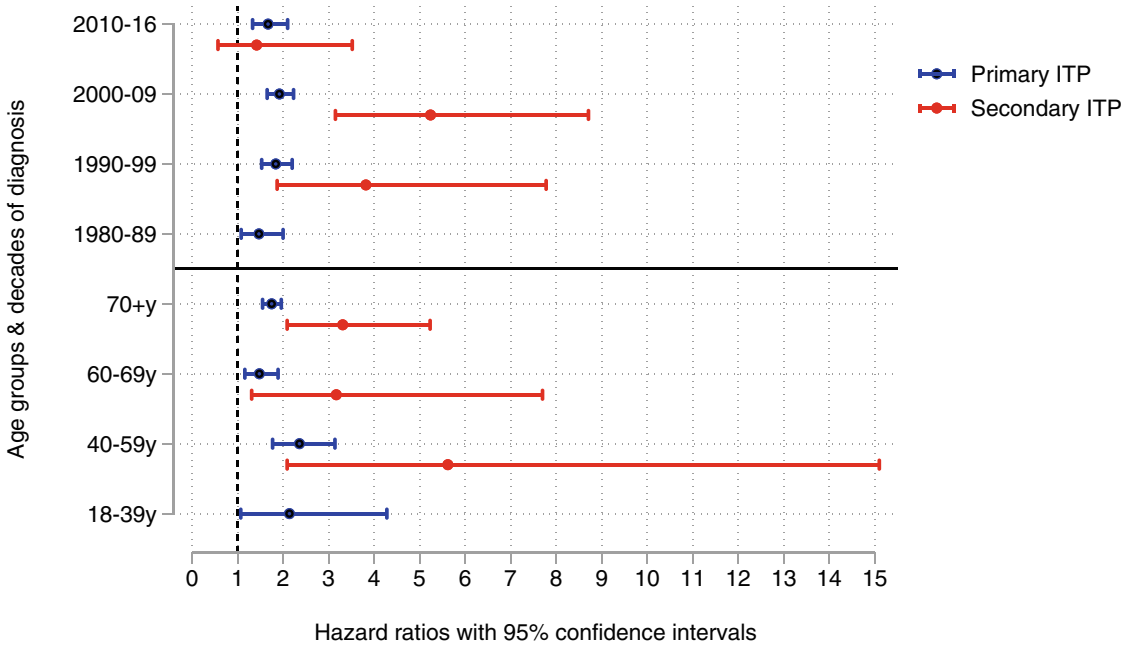

FIGURE 3 Illustration of the development in hazard ratio for death across age-groups and study periods. Blue lines represent primary and red lines represent secondary ITP. There was no significant change in risk over study decades for neither primary nor secondary ITP. Younger age < 60 years was associated with increased risk of death for patients with primary ITP. [Color figure can be viewed at wileyonlinelibrary.com]

For pITP, the 5-year survival was 46% (95% CI, 41–51) for patients and 68.7% (95% CI, 68–69) for comparators. For sITP, the 5-year survival was 36.3% (95% CI, 20–52) in patients and 71.6% (95% CI, 69–74) for comparators (Table S5, Figure S2).

Adjusted HRs stratified by age showed that the relative instantaneous risk of death was higher in younger patients with pITP. Patients aged 40–59 year had an HR of 2.36 (95% CI, 1.77–3.14) compared to 1.75 (95% CI, 1.55–1.96) in patients aged 70 + years (Figure 3;

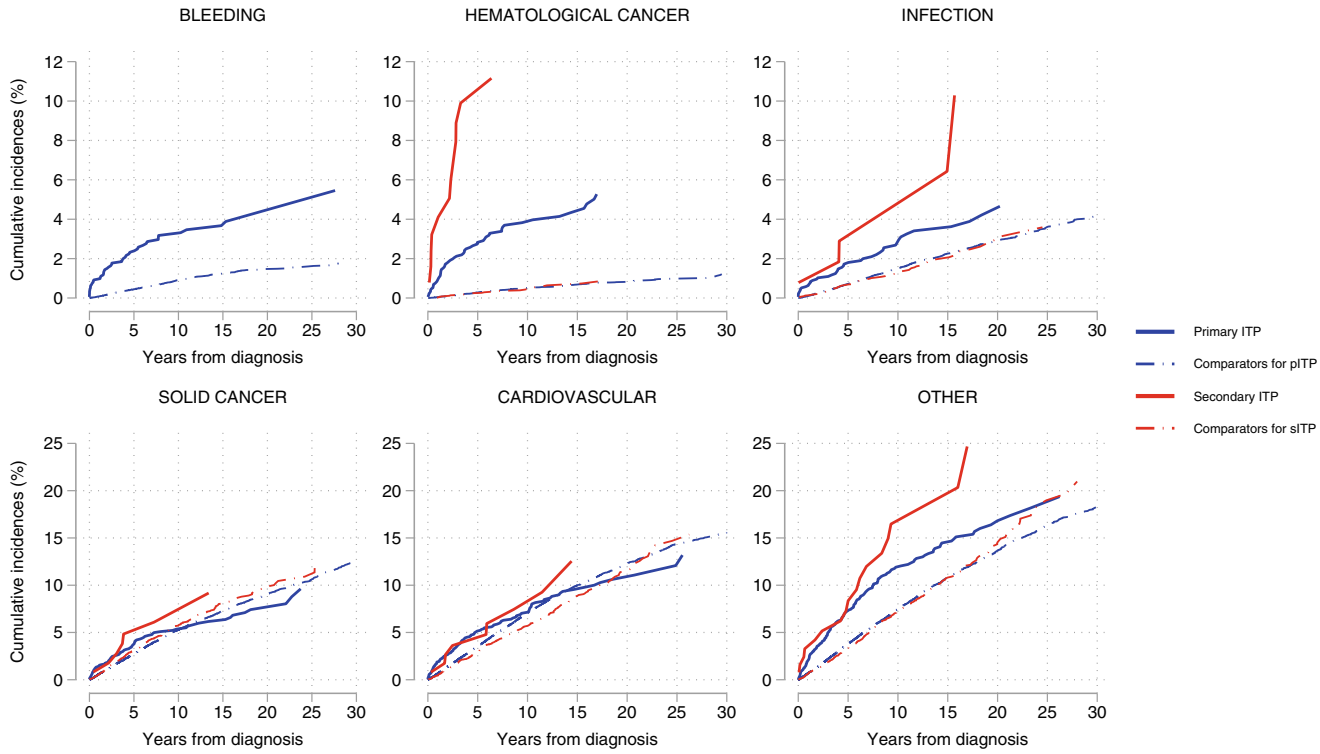

FIGURE 4 Categorized cumulative incidence curves for causes of death. Blue lines illustrate primary ITP and comparators while red lines illustrate secondary ITP and comparators. Bleeding, hematological cancer and infection were relatively frequent causes of death in patients with chronic ITP. Some groups had too few observations and were omitted. [Color figure can be viewed at wileyonlinelibrary.com]

Table S5). No differences in HR were observed for patients with sITP between different age groups, where the numbers of patients were generally small.

3.3 | Causes of death

Cumulative incidences of causes of death in patients and comparators are depicted in Figure 4.

The cumulative mortality due to bleeding, hematological cancer, and infection differed from the general population both at 1, 5, 10 years after diagnosis, and at end of study period for pITP. Cumulative mortality from cardiovascular disease and solid cancer only differed during the first years (Figure 4; Table 2).

Within the first 5 years after diagnosis of pITP, cumulative mortalities of bleeding and hematological cancer were 2.3% (95% CI, 1.7–3.2) and 2.8% (95% CI, 2.1–3.8) respectively. Corresponding numbers for comparators were 0.44 (95% CI, 0.39–0.50) and 0.28 (95% CI; 0.24–0.33). The 5-year cumulative mortality from infections was 1.7% (95% CI, 1.2–2.5) among patients and 0.71 (95% CI, 0.64–0.78) in comparators, but differences were attenuated with time (Table 2). Mortality of both cardiovascular disease and solid cancer were similarly higher in pITP patients versus comparators during the first 5 years.

For sITP, hematological cancer was a pronounced cause of death during the first years. The 5-year cumulative mortality due to hematological cancer was 9.9% (95% CI, 5.2–16.3) versus 0.24% (95% CI, 0.12–0.43) in patients versus comparators, and similar differences were seen for death from infection (Figure 4; Table 2).

Adjusted cause-specific Cox proportional hazard ratios (csHR) for death in pITP compared with the general population showed increased relative risk of death from bleeding with a csHR of 4.42 [3.15–6.20] and 2.93 [1.98–4.36] for hematological cancer (Table 3). For sITP, the greatest relative risks were found in death from hematological cancer with a csHR of 16.18 [5.15–50.79] and bleeding with a csHR of 8.56 [1.88–38.98].

We used Fine-Gray subhazard ratios (subHR) to account for competing risk events. This yielded an adjusted subHR of 3.25 [2.33–4.52] for death from bleeding and 2.16 [1.12–4.16] for death from hematological cancer in pITP. For sITP, adjusted subHR for death from hematological cancer was 10.52 [1.43–77.36] (Table 3).

TABLE 2 Cumulative incidences for causes of death for chronic primary and secondary ITP and general population comparators

Name	Primary ITP (%) ($n = 1762$) [95% CI]	Comparators pITP (%) ($n = 69{,}684$) [95% CI]	Secondary ITP (%) ($n = 128$) [95% CI]	Comparators sITP (%) ($n = 5097$) [95% CI]
End of 1st year				
Bleeding	0.92 [0.55–1.46]	0.08 [0.06–0.10]	<3	<3
Hematological cancer	0.88 [0.52–1.42]	0.05 [0.03–0.07]	3.22 [1.06–7.47]	<3
Solid cancer	1.35 [0.88–1.98]	0.55 [0.50–0.61]	<3	0.52 [0.35–0.76]
Cardiovascular	1.88 [1.32–2.62]	0.69 [0.63–0.75]	<3	0.44 [0.28–0.66]
Infection	0.58 [0.30–1.03]	0.11 [0.08–0.13]	<3	0.12 [0.05–0.26]
Other/unspecified	2.02 [1.42–2.77]	0.70 [0.64–0.76]	3.28 [1.08–7.60]	0.63 [0.44–0.89]
End of 5th year				
Bleeding	2.32 [1.65–3.17]	0.44 [0.39–0.50]	<3	0.33 [0.19–0.54]
Hematological cancer	2.82 [2.07–3.75]	0.28 [0.24–0.33]	9.90 [5.23–16.33]	0.24 [0.12–0.43]
Solid cancer	3.70 [2.83–4.75]	2.74 [2.61–2.87]	4.84 [1.79–10.22]	3.06 [2.57–3.61]
Cardiovascular	5.15 [4.10–6.35]	3.51 [3.36–3.66]	3.62 [1.18–8.36]	2.92 [2.45–3.46]
Infection	1.72 [1.15–2.48]	0.71 [0.64–0.78]	2.89 [0.77–7.59]	0.66 [0.45–0.94]
Other/unspecified	7.29 [6.04–8.70]	3.80 [3.64–3.96]	7.29 [3.38–13.20]	3.38 [2.86–3.96]
End of 10th year				
Bleeding	3.18 [2.34–4.21]	0.91 [0.82–1.00]	1.77 [0.34–5.69]	0.57 [0.37–0.86]
Hematological cancer	3.83 [2.88–4.96]	0.51 [0.45–0.58]	11.15 [6.05–18.00]	0.43 [0.25–0.69]
Solid cancer	5.36 [4.22–6.68]	5.29 [5.09–5.50]	6.09 [2.47–12.06]	5.74 [5.01–6.53]
Cardiovascular	7.03 [5.71–8.52]	7.06 [6.83–7.30]	7.45 [3.21–14.08]	5.68 [4.96–6.47]
Infection	2.69 [1.88–3.71]	1.49 [1.38–1.60]	2.89 [0.77–7.59]	1.30 [0.97–1.72]
Other/unspecified	11.90 [10.15–13.81]	7.48 [7.24–7.73]	16.48 [9.54–25.06]	7.37 [6.53–8.27]
End of study				
Bleeding	5.46 [2.82–9.34]	1.92 [1.56–2.35]	1.77 [0.34–5.69]	2.02 [0.95–3.78]
Hematological cancer	5.27 [3.92–6.90]	1.28 [1.03–1.58]	11.15 [6.05–18.00]	0.85 [0.52–1.33]
Solid cancer	13.47 [6.92–22.22]	13.42 [12.55–14.31]	9.17 [3.47–18.29]	11.81 [9.78–14.05]
Cardiovascular	13.18 [9.83–17.04]	17.37 [16.22–18.56]	12.54 [5.48–22.68]	15.36 [12.81–18.13]
Infection	4.66 [3.19–6.52]	4.39 [3.83–5.00]	10.29 [3.02–22.81]	3.59 [2.46–5.04]
Other/unspecified	19.37 [15.59–23.46]	19.84 [18.73–20.97]	24.68 [13.28–37.92]	20.97 [17.21–24.99]

Note: Table 2 Cumulative incidences for the 6 groups of causes of death in patients and comparators. In order not to violate Danish rules of microdata, some estimates are not presented with exact numbers. Abbreviations are explained in Table 1.

3.4 | Sensitivity analysis

Results from sensitivity analysis are presented in Table S8 and Figure S4. Results did not change significantly compared to the main results presented.

4 | DISCUSSION

Using population-based Danish Health Registries we found that survival was reduced for patients with pITP and sITP compared to the general population, but seemed to improve for pITP. Patients with sITP had a particularly poor prognosis. Death from bleeding, infection, and hematological cancer, were relatively higher than in comparators. Death from cardiovascular disease and solid cancer was more common than among comparators during the first years after cITP diagnosis, but differences attenuated over time.

6.8% of patients were sITP which is lower than the 18–20% proportion suggested by others.[1,8] These differences are likely explained by our conservative selection algorithm including only chronic ITP, and our rigorous definition of the sITP-qualifying diagnoses

Comorbidity was associated with a worse prognosis, but adjusted hazard ratios for death remained constant

TABLE 3 Cox cause-specific hazard ratios and Fine-Gray subhazard ratios for risk of death comparing patients with chronic primary and secondary ITP with age-sex-matched comparators from the general population

Name	Primary ITP (adjusted/unadjusted) [95% CI]	Secondary ITP (adjusted/unadjusted) [95% CI]
Bleeding		
Fine-Gray subHR	3.25 [2.33–4.52]/3.60 [2.69–4.82]	4.20 [0.96–18.33]/2.88 [0.68–12.13]
Cox cause-specific HR	4.42 [3.15–6.20]/4.01 [3.00–5.35]	8.56 [1.88–38.98]/3.71 [0.88–15.58]
Hematological cancer		
Fine-Gray subHR	2.16 [1.12–4.16]/7.42 [5.63–9.78]	10.52 [1.43–77.36]/22.81 [11.29–46.07]
Cox cause-specific HR	2.93 [1.98–4.36]/8.19 [6.22–10.78]	16.18 [5.15–50.79]/26.34 [13.09–53.04]
Solid cancer		
Fine-Gray subHR	0.89 [0.69–1.14]/1.00 [0.81–1.24]	0.98 [0.37–2.62]/1.04 [0.49–2.20]
Cox cause-specific HR	1.22 [0.96–1.55]/1.13 [0.92–1.40]	1.95 [0.80–4.80]/1.33 [0.63–2.82]
Cardiovascular		
Fine-Gray subHR	1.03 [0.84–1.27]/1.03 [0.86–1.24]	1.15 [0.51–2.60]/1.23 [0.63–2.40]
Cox cause-specific HR	1.49 [1.22–1.81]/1.17 [0.97–1.40]	2.78 [1.20–6.43]/1.62 [0.83–3.15]
Infection		
Fine-Gray subHR	1.53 [1.08–2.16]/1.70 [1.25–2.30]	1.61 [0.48–5.33]/2.94 [1.19–7.26]
Cox cause-specific HR	2.22 [1.57–3.13]/1.92 [1.42–2.60]	3.73 [0.94–14.76]/3.88 [1.56–9.62]
Other/unspecified		
Fine-Gray subHR	1.38 [1.16–1.64]/1.47 [1.26–1.71]	1.82 [0.92–3.59]/1.98 [1.21–3.24]
Cox cause-specific HR	1.92 [1.63–2.26]/1.62 [1.39–1.87]	3.84 [2.03–7.27]/2.51 [1.54–4.08]

Note: Table 3 Subhazard ratios and Cox cause-specific hazard ratios for different causes of death. Risk of death from bleeding, hematological cancer or infection were higher in patients than comparators for both primary and secondary ITP.
Abbreviations: HR, hazard ratio; subHR, subhazard ratio.

between comorbidity scores. We used the updated Quan version from 2011 to compute comorbidity score,[34] but risk associated with various forms of comorbidities has changed over our long study period. Along with the inaccuracy in the ICD-8 compared to the ICD-10 system, this could potentially underestimate comorbidity of individuals included early in the study period, particularly among comparators who are not by exposure (ITP diagnosis) in routine hospital follow-up.

Our reduced survival for patients with pITP is in line with previous studies.[18,19] Of note, even patients with pITP aged 40–59 years had a marked reduced 5-year survival of 87.5% versus 97.5% in comparators. Adjusted hazard ratios for death were also generally higher in younger patients with pITP. This could indicate that for younger people with a general preexisting low risk of death, chronic pITP is associated with a markedly increased relative risk of death. Possible explanations for this could be the increased risk of infection or other adverse outcomes following pITP.[21,22]

The overall 5-year survival in patients with sITP was 69.7% versus 89.4% in comparators. This is comparable to the prognosis in similarly aged patients with diffuse large B-cell lymphoma[39] or multiple myeloma,[40] and underlines the severity of sITP. No studies have to our knowledge investigated this previously, but the poor prognosis in secondary disease compared with primary is also known in for example, autoimmune hemolytic anemia.[41]

During the study period, there was an increase in survival among patients with pITP. However, the increase was not clearly better than expected from general improvements in survival in the general population. The non-parametric point estimate for 5-year survival increased from 69% to 80%, and corresponding numbers for comparators were 88% and 90%. The survival gap thereby narrowed, but the adjusted hazard ratio did not improve. The lack of improvement may be a consequence of population alteration, where older and more comorbid patients were diagnosed with ITP as study time progressed. While patients and comparators were age-matched, comorbidity was more prevalent in patients than among comparators. It is unknown to which extent the introduction of novel treatment options contributed positively to the overall changes of prognosis taking effects of aging and comorbidity into account. Survival did not seem to improve for sITP, but numbers were small and estimates insecure.

Bleeding, infection and hematological malignancy were predominantly causes of death. Other studies confirm these findings.[16,18] These events are all more frequent in patients with ITP[16,21,42] and also increased in similar autoimmune cytopenic blood disorders such as autoimmune hemolytic anemia and Evans syndrome.[33] Additionally, the generally high level of comorbidity could also indicate that an underlying diagnosis (e.g., chronic lymphocytic leukemia) and competing diagnoses alongside ITP partly explain the elevated mortality.

We noticed a large difference in the adjusted and unadjusted csHR and subHR estimates for relative risk of death from hematological cancer, with unadjusted estimates being higher when not controlling for rituximab exposure. This could indicate that some patients with ITP have an underlying lymphoproliferative disorder suppressed by exposure from anti-CD20 treatment.

Death from solid cancer was also relatively more frequent in patients, but with smaller differences between patients and the general population than other causes of death. Although immunosuppressive treatments can increase the risk of for example, skin cancer,[43] this observation could suggest that solid cancer and ITP can be coincidental and may not be causally linked.[44,45]

Cardiovascular csHR for death was 1.49 for pITP versus 2.78 for sITP. A comparable study found a 1.5-fold increased risk of death from cardiovascular disease[18] and cardiovascular thromboembolic disease generally occurs more frequently in patients with ITP.[13,14,46] However, subHR for death from cardiovascular disease approximated one for both pITP and sITP, indicating a higher risk of competing events. Both Fine-Gray and Cox regression models are recommended in the presence of competing risk events.[37]

Despite long and complete follow-up of patients and comparators our study has limitations. We identified patients using diagnosis registration in the DNPR which can lead to misclassification, particularly concerning comorbidities associated with thrombocytopenia for example, liver disease or malignant neoplasms. However, this approach has previously been found to be valid.[28] Validity of the registrations using the ICD-8 system applied in our earliest study period has not been validated. The high mortality in the early study period may therefore in part reflect that diagnostic procedures have become more accurate and that misclassification was higher.

Causes of death were retrieved using the DRCD, but the validity of this registry is not as high as other health registries due to changes in coding practice and decreased autopsy rates.[31] The impact of these changes on our results is unknown.

Analysis in some subgroups particularly in sITP lacked statistical precision due to low number of events. Our results emphasizes the utility of large registries and real-world data to track health events, and discover potential unmet needs in rare diseases like sITP. Misclassifying sITP as pITP could bias the estimate towards a worse prognosis for pITP, but since sITP is far less common than pITP this misclassification is probably minor. A misclassification of pITP as sITP could have a larger impact on results for sITP and is more likely since sITP is not a well-defined entity, and relies on poorly defined associated diagnoses. This misclassification would however be expected to bias the estimated prognosis in sITP towards a better prognosis.

We included only chronic ITP. Patients with pITP resolving after a short course of steroids, or cITP patients with subnormal but hemostatic safe platelet counts discharged from hospital follow-up may therefore not have been included. This would lead to inclusion of a disproportionate larger group of patients with severe ITP disease and our survival estimates may not apply to patients with more indolent ITP disease. However, patients with chronic ITP generally remain in clinical follow-up to prevent bleedings and manage complications, and therefore our results probably reflect risks in this group.

5 | CONCLUSION

These novel data show that survival is reduced, but seems to be improving over the past decades for patients with chronic ITP, and that comorbidity and sITP is associated with poorer survival. The increased risk of death from hematological malignancy, infection, and bleeding should direct clinical attention to recognize events and symptoms preceding or indicating these. Particularly considering the level of immunosuppression, elevation of platelets, and recognition of an underlying disease among patients suspected for sITP.

Detailed knowledge of the causal relationship between chronic pITP/sITP and mortality is lacking. Disentangling the impact of the underlying and complex immune dysfunction present in some cases of chronic ITP, and the effects of the disease itself and treatments, could potentially be beneficial for the future prevention of adverse events following chronic ITP.

AUTHOR CONTRIBUTIONS

Contribution: Nikolaj Mannering, Dennis Lund Hansen, Anton Pottegård and Henrik Frederiksen designed the study. Nikolaj Mannering and Henrik Frederiksen applied for funding. Nikolaj Mannering and Dennis Lund Hansen performed data analysis and result output. Nikolaj Mannering wrote first draft. All authors read and approved the final version of the manuscript.

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CONFLICT OF INTEREST

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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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