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ORIGINAL RESEARCH

Thrombotic Thrombocytopenic Purpura and Evans Syndrome: Validating and Exploring 20 Years of Routine Hospital Care

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Purpose: Few patients scattered among centers complicate investigation of thrombotic thrombocytopenic purpura (TTP) and Evans syndrome (ES). Routinely collected Danish register data captures the total population and includes lifelong follow-up. We aimed to validate registered TTP and ES diagnoses and to explore clinical characteristics.

Patients and Methods: We identified all patients in Denmark with diagnosis registrations indicative of TTP or ES in the Danish National Patient Registry 2000–2019, validated diagnoses through medical record review, and extracted and presented data on initial treatment and complications.

Results: Diagnoses for patients registered with TTP and ES were confirmed for 46% and 59%, respectively. Among validated TTP patients the most widespread complications at time of diagnosis were neurological symptoms or deficits, observed in 81% of cases. Other frequent types of complications in TTP patients were any organ failure (32%) and infection (25%). Initial management and complications did not change for patients diagnosed between 2000 and 2009 and 2010 and 2019, and survival remained constant (overall mortality 26%, median follow up of 8.4 years). Treatments and complications also remained unchanged for ES patients.

Conclusion: Overall, diagnostic accuracy, complications and prognosis have remained relatively constant for patients over the study period. These now validated cohorts of Danish TTP and ES patients will be utilized in future studies to examine long-term health outcomes.

Keywords: validation, thrombotic microangiopathy, TTP, ADAMTS13

Introduction

Thrombotic thrombocytopenic purpura (TTP) is a thrombotic microangiopathy (TMA) characterized by mechanical hemolysis and consumptive thrombocytopenia. In most cases TTP is an acquired autoimmune disorder due to immune reactions against the von Willebrand factor cleaving protease ADAMTS13 (immune TTP (iTTP)) but can also be congenital (cTTP) in patients with two pathogenic ADAMTS13 gene variants.[1] Both result in ADAMTS13 deficiency,[2] triggering a cascade involving accumulation of ultra large von Willebrand factor multimers, platelet adhesion, aggregation, and consumption, and formation of microthrombi in the circulation. Platelet consumption leads to thrombocytopenia

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and bleedings, and microthrombi result in potentially life-threatening organ ischemia. The formation of ultra large von Willebrand factor multimers also leads to hemolytic anemia due to mechanical fragmentation of red blood cells. Before testing of ADAMTS13 activity became widely available, it was difficult to differentiate TTP from Evans syndrome (ES), the combination of autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP), as both disorders are characterised by concurrent haemolysis and thrombocytopenia.[3,4]

TTP most commonly presents in adults and just 10% of patients emerge in childhood or adolescence.[5–7] An estimated 5% of all TTP cases are attributed to cTTP, which debuts at any age, but is more common in younger patients.[5,8] Clinically, iTTP and cTTP are indistinguishable from each other.[9] Common clinical presentation is bleeding and neurological symptoms, and biochemical findings are unexpected severe thrombocytopenia and nonimmune hemolysis.[10] Accompanying symptoms often tend to be vague, such as abdominal pain, nausea, vomiting or weakness[7,10–14] making it challenging to diagnose and in particular distinguish TTP from other types of TMAs. Generalizable symptoms and presence of both thrombocytopenia and hemolysis can lead to misdiagnoses with autoimmune cytopenias.[3,4] We have previously observed TTP patients registered as ES patients in the Danish National Patient Registry,[4] although the magnitude of misclassification is unknown. Early recognition is crucial for prognosis of TTP, and misclassification as ES may have serious consequences.

The PLASMIC score is a clinical scoring system which determines likelihood of severe ADAMTS13 deficiency, developed and validated to assist in efficient identification of likely TTP, as laboratory testing of ADAMTS13 is time intensive and results are rarely available before treatment initiation is required.[15] TTP prognosis is entirely dependent on early diagnosis and immediate treatment.[9,12,16,17] Plasma exchange (PEX) is usually given daily until platelet count stabilizes,[18] acting predominantly by removing ultra large von Willebrand factor, anti-ADAMTS13 antibodies and cytokines, and increasing ADAMTS13 levels.[1,9,19] Additionally, recent guidelines from the International Society of Thrombosis and Haemostasis recommend adding corticosteroids, rituximab and caplacizumab to the treatment of first and relapsing episodes.[20]

Since the introduction of routine PEX 30 years ago, survival in TTP has improved considerably, and 30-day mortality is reduced to just 4–7%.[17,21,22] More than half of survivors face a range of debilitating complications including seizures, visual disturbances, transient ischemic attacks (TIA), and headaches.[7,11,23] Elucidating the full spectrum of long-term complications of TTP is a relatively underexplored area with very few studies investigating unselected patients.

Reports of annual incidence are around 3/1,000,000 individuals, while estimates of prevalence range from 13–20/1,000,000 individuals.[7,24,25] Investigating TTP has proven difficult due to the limited number of patients at individual centers, as well as the cost of gathering sufficient data for rare diseases.[18] Large population-based registries with long and complete follow-up are the best option to capture health events such as recurrence and late effects. Although TTP registries exist, they often describe cross-sectional data only and are generally unable to ensure complete follow-up for clinical health outcomes, socio-economic events and death.[7,12,14,24,26,27]

ES is another rare disorder with low prevalence (10–20/1,000,000 individuals) and incidence (1.5/1,000,000 person years) in Denmark.[4] The biggest developments in treatment of ES patients over the past decades has been the introduction of rituximab and TPOs as therapy options,[28] although prognosis for ES patients remains poor. There is a lack of evidence for this patient group, which calls for targeted longer term investigations.[4,29]

The aim of our study was to first validate registered diagnoses of TTP and ES in Danish nationwide health registries over a period of 20 years. We also aimed to provide up-to-date insights on initial treatment and clinical outcomes for confirmed TTP and ES patients in a Danish setting and examine the number of misclassified TTP patients first registered with an ES diagnosis.[4] Based on our findings, we ultimately aim to establish two nationwide validated patient cohorts to track immediate and long-term complications using established algorithms.

Methods

In this retrospective cohort study, we identified patients in the Danish National Patient Registry (DNPR),[30] and extracted relevant details from medical records to validate and describe diagnoses.

Every individual in Denmark is assigned a unique 10-digit civil registration number at birth or immigration, recorded in the Civil Registration System.[31] Healthcare providers note civil registration number alongside relevant health information for all patient contacts, enabling linkage between nationwide registries. All hospital contacts are registered in the DNPR with diagnoses based on International Classification of Disease (ICD)-10 codes.[32] Nine hematology departments at public hospitals provide all hematological care in Denmark; hence, all known hematology patients are identifiable through the DNPR.

The cohort includes all patients in the DNPR from January 1st 2000 to December 31st 2019 with a registered ICD-10 code for TTP (M311A) or two diagnostic codes suggestive of Evans syndrome (D693 and one of - D591/D594/D594C/D598/D599/D599A). Patients whose diagnostic work up occurred <18 years of age or before 01/01/2000 were excluded. Analyses were stratified by diagnosis period (2000–2009; 2019–2019) to assess temporal changes.

Local investigators at each Danish hematology department reviewed medical records including clinical and paraclinical data, in order to categorize diagnoses as TTP (iTTP/cTTP if confirmed by genetic testing), ES, hemolytic uremic syndrome, transient abnormal myelopoiesis, preeclampsia, HELLP syndrome, malignant hypertension, cancer–associated TMA, other TMA, ITP, or other.

Diagnoses were evaluated and confirmed/rejected by the local investigating hematologist based on clinical information and medical definition. Medical definition of TTP was thrombocytopenia, hemolysis, schistocytosis in peripheral blood smear and ADAMTS13 activity <10%. Testing of ADAMTS13 activity was not undertaken in all cases. In the absence of ADAMTS13 testing a TTP diagnosis could still be assigned if the local investigator determined TTP the most likely cause of TMA using best clinical judgement. Definition of ES was absence of TTP combined with presence of both ITP and AIHA. Positive predictive value (PPV) was calculated as confirmed diagnoses as a fraction of registered cases, and proportion of patients misdiagnosed with ES instead of TTP and vice versa were calculated.

For patients validated with either TTP or ES relevant clinical and paraclinical data on the presenting episode (symptoms, findings, complications, initial treatment and PLASMIC score variables (platelet count, hemolysis, active cancer, history of transplant (solid organ or stem cell), MCV, INR, creatinine level)),[15] possible relapse and survival was entered in a secure RedCap database.[33]

Descriptive characteristics, initial diagnosis variables and health outcomes were described as medians (interquartile range (IQR)) for continuous variables, and proportions (%, 95% confidence interval (CI)) for categorical variables. We compared confirmed and rejected patient populations and diagnosis periods using Wilcoxon rank-sum tests for medians and tests of equality of proportions for proportions. For confirmed TTP patients, PLASMIC scores[15] were calculated, and neurological symptoms described.

Patients with validated TTP or ES were followed specifically for episodes of relapse and mortality from initial diagnosis period until loss to follow-up (migration), end of study period (31st May 2022) or death, whichever occurred first. Analyses were stratified by diagnosis period to assess temporal changes in diagnosis and treatment. Survival data was analyzed using Kaplan–Meier methods. For data protection, specific values for patient groups ≤3 and groups that can be used to identify patient groups ≤3 have been censored. All analysis was performed in STATA 16 (StataCorp LLC, USA).

Permission to extract from medical records was granted by the Danish Authority of Patient Safety (3–3013-2980/1) and Danish Regions (20/44380 and 20/25,503). Data was stored and handled in accordance with Danish data protection laws (Databeskyttelsesloven), ensuring privacy and protection.

Results

Of the 407 patients identified in the DNPR registered with either a TTP or ES diagnosis, 259 patients (149 registered TTP; 110 registered ES) remained after assessing medical record availability and applying exclusion criteria (Figure 1). Inaccessible medical records were largely from 2000 to 2009, and half (54%) of the eligible cohort received their first diagnosis code at a specialized hematology department.

Patients were predominantly diagnosed during the latter half of the study period, 2010–2019 (Table 1). Median age for registered TTP patients was 54 years of age, and just over half (54%) of the patients were women. From 2000–2009 to 2010–2019, the proportion of registered TTP patients investigated for ADAMTS13 enzyme activity and presence of an

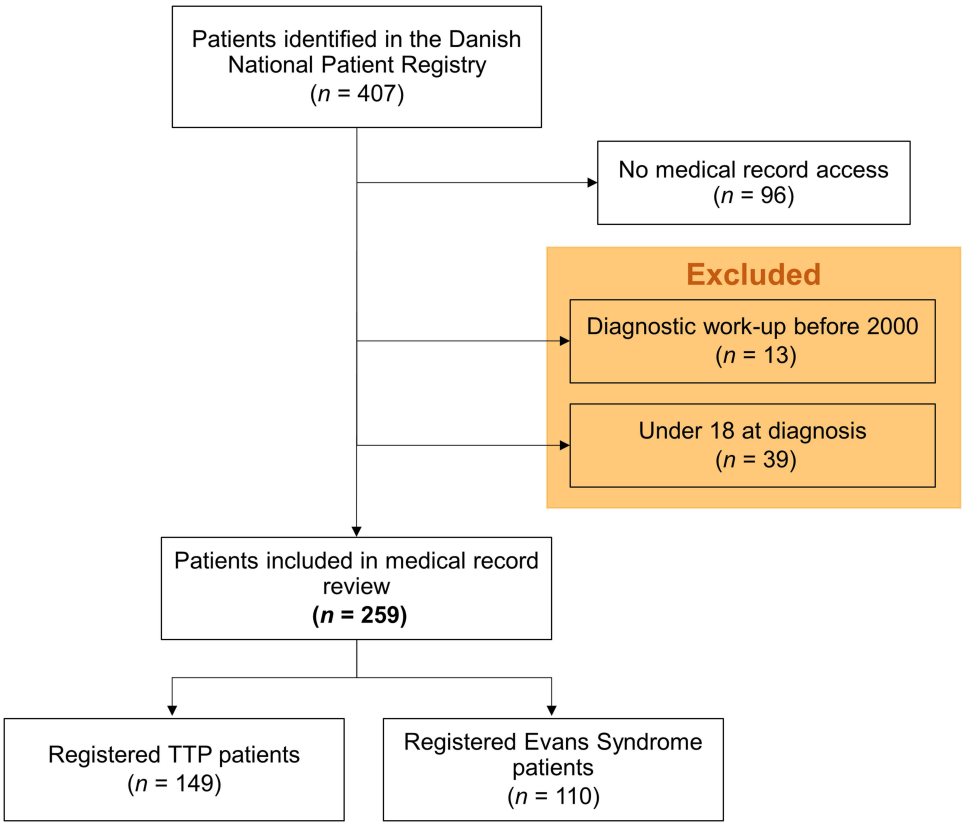

Figure 1 Flowchart indicating participation in study after inclusion and exclusion criteria.
Abbreviation: TTP, thrombotic thrombocytopenic purpura.

ADAMTS13 inhibitor surged from 29% to 68% and 26% to 62%, respectively. Registered ES patients had a median age of 65 years, increasing from 58 to 68 years between the two diagnosis periods, and 45% were women. Nearly all registered TTP and ES patients initially presented with thrombocytopenia (>93%).

Just under half (PPV 46%) of all patients registered with TTP in the DNPR were validated with a TTP diagnosis in this investigation, and the PPV remained constant between 2000–2009 and 2010–2019 (Table 2). The PPV of ES was higher (59%), and this improved between 2000–2009 and 2010–2019 (41% vs 67%). Less than 2.0% of TTP registered

Table 1 Descriptive Characteristics and Comparisons of Registered TTP and Evans Syndrome Patients Diagnosed 2000–2019

	Overall	Diagnosed between	
		2000–2009	2010–2019
Registered TTP	**n=149**	**n=27**	**n=122**
Age at diagnosis, median [IQR]	54.0 [40.6–69.9]	52.4 [39.3–65.3]	54.7 [41.8–70.4]
Female	54.4 [46.0–62.5]	66.7 [46.0–83.5]	51.6 [42.4–60.8]
ADAMTS13 enzyme activity investigated	61.3 [52.7–69.3]	29.2 [12.6–51.1]	67.8 [58.6–76.1]
ADAMTS13 inhibitor investigated	55.7 [47.1–64.1]	26.1 [10.2–48.4]	61.5 [52.1–70.4]
DAT investigated	78.3 [70.4–84.8]	69.6 [47.1–86.8]	80.0 [71.5–86.9]
Schistocytes investigated	81.3 [73.8–87.4]	69.6 [47.1–86.8]	83.6 [75.6–89.8]

(*Continued*)

Table 1 (Continued).

	Overall	Diagnosed between	
		2000–2009	2010–2019
Thrombocytopenia	≥98.0†	≥88.9†	≥97.5†
Hemolysis	80.4 [72.8–86.7]	60.9 [38.5–80.3]	84.3 [76.4–90.5]
First diagnosis at hematology department	43.6 [35.5–52.0]	25.9 [11.1–46.3]	47.5 [38.4–56.8]
Death during follow-up	43.6 [35.5–52.0]	44.4 [25.5–64.7]	43.4 [34.5–52.7]
Registered Evans syndrome	**n=110**	**n=34**	**n=76**
Age at diagnosis, median [IQR]	64.8 [49.9–75.4]	57.8 [37.0–68.3]	68.3 [52.7–77.0]
Female	44.5 [35.1–54.3]	41.2 [24.6–59.3]	46.1 [34.5–57.9]
ADAMTS13 enzyme activity investigated	17.5 [10.7–26.2]	12.9 [3.6–29.8]	19.4 [11.1–30.5]
ADAMTS13 inhibitor investigated	13.1 [7.2–21.4]	≤8.8†	16.0†
DAT investigated	91.3 [84.1–95.9]	87.1 [70.2–96.4]	93.1 [84.5–97.7]
Schistocytes investigated	47.1 [37.2–57.2]	37.5 [21.1–56.3]	51.4 [39.3–63.3]
Thrombocytopenia	93.3 [86.6–97.3]	≥91.2†	96.0†
Hemolysis	79.8 [70.8–87.0]	59.4 [40.6–76.3]	88.9 [79.3–95.1]
First diagnosis at hematology department	67.3 [57.7–75.9]	58.8 [40.7–75.4]	71.1 [59.5–80.9]
Death during follow-up	50.0 [40.3–59.7]	50.0 [32.4–67.6]	50.0 [38.3–61.7]

Notes: Reported values expressed as proportions with 95% confidence intervals (% [95% CI]), unless otherwise stated. †In the interest of data protection, specific values for patient groups ≤3 and groups that can be used to identify patient groups ≤3 are censored.
Abbreviations: TTP, thrombotic thrombocytopenic purpura; IQR, interquartile range; ADAMTS13, von Willebrand factor-cleaving protease; DAT, direct antiglobulin test.

Table 2 Positive Predictive Value of TTP and Evans Syndrome Diagnoses in the DNPR 2000–2019

	Overall	Diagnosed between	
		2000–2009	2010–2019
TTP	**n=149**	**n=27**	**n=122**
Confirmed TTP	46.3 [38.1–54.7]	44.4 [25.5–64.7]	46.7 [37.6–56.0]
Registered TTP: opposite evaluated diagnosis	≤2.0†		
Evans syndrome	**n=110**	**n=34**	**n=76**
Confirmed Evans syndrome	59.1 [49.3–68.4]	41.2 [24.6–59.3]	67.1 [55.4–77.5]
Registered Evans syndrome: opposite evaluated diagnosis	≤2.7†		

Notes: †In the interest of data protection, specific values for patient groups ≤3 and groups that can be used to identify patient groups ≤3 are censored.
Abbreviation: TTP, thrombotic thrombocytopenic purpura.

patients were wrongly classified ES patients, and less than 2.7% vice versa. Less than 4.2% of confirmed TTP patients had a cTTP diagnosis, all of whom were confirmed with genetic testing.

Confirmed TTP patients had a median age of 50 years and 64% were women, while rejected patients were older and less likely to be female, with a median age of 63 years (Table S1).

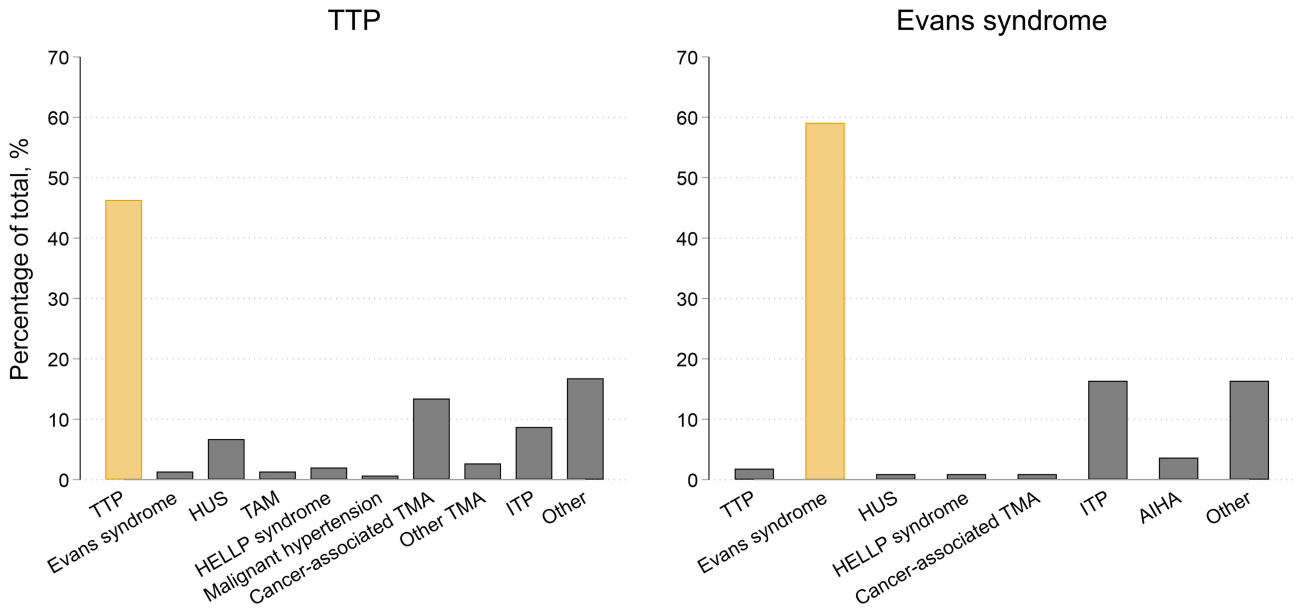

Figure 2 Confirmed diagnoses of patients registered with TTP and Evans syndrome in the Danish National Patient Registry 2000–2019.
Abbreviations: TTP, thrombotic thrombocytopenic purpura; HUS, hemolytic-uremic syndrome; TAM, transient abnormal myelopoiesis; HELLP, hemolysis, elevated liver enzymes and low platelets; TMA, thrombotic microangiopathy; ITP, immune thrombotic thrombocytopenia; AIHA, autoimmune hemolytic anemia.

ADAMTS13 enzyme activity and inhibitor presence were tested for a higher proportion of confirmed TTP patients versus rejected diagnoses, 78% vs 45% for enzyme activity and 79% vs 33%, for inhibitor presence (Table S1). Confirmed TTP patients were also more likely to have received their original diagnosis at a specialized hematology department (65% vs 25%) (Table S1). Confirmed ES patients were over 10 years older than their rejected counterparts.

The most common diagnoses for rejected TTP patients were cancer associated TMA's, ITP, and HUS (Figure 2). ITP without hemolytic anemia was also a common diagnosis amongst rejected patients registered with ES.

Neurological symptoms or deficits were common at presentation (81%) amongst TTP patients (Table 3). Of those, TIA was most common, while confusion and headaches were both reported present for over a quarter of all patients (Figure 3). Almost all confirmed TTP patients received plasma exchange for a median 12 days, which remained constant over the two diagnosis periods (Table 3). Median first steroid course duration increased from 49 to 90 days from

Table 3 Clinical Characteristics of Confirmed TTP and Evans Syndrome Patients 2000–2019

	Diagnosed between	
	2000–2009	**2010–2019**
TTP	**n=12**	**n=57**
Clinical Presentation		
Pregnant[a]	0.0 [0.0–45.9]	≤8.1[†]
Sepsis	≤25.0[†]	≤5.3[†]
Fever	50.0 [18.7–81.3]	30.4 [18.8–44.1]
Hypertension[b]	44.4 [13.7–78.8]	30.4 [17.7–45.8]
Proteinuria[b]	100.0 [2.5–100.0]	55.6 [30.8–78.5]
Neurological symptom/deficit[c]	≥75.0[†]	80.4 [67.6–89.8]

(*Continued*)

Table 3 (Continued).

	Diagnosed between	
	2000–2009	**2010–2019**
Management		
PEX	100.0 [71.5–100.0]	94.7 [85.4–98.9]
PEX treatment days, median [IQR]	12.5 [6.0–17.0]	12.0 [7.0–19.0]
Steroid course	≥75.0[†]	91.2 [80.7–97.1]
Steroid period 1 treatment days, median [IQR]	49.0 [13.0–96.0]	90.0 [45.0–143.0]
Rituximab	41.7 [15.2–72.3]	61.4 [47.6–74.0]
IVIG	0.0 [0.0–26.5]	≤5.3[†]
Other treatment[d]	0.0 [0.0–26.5]	22.8 [12.7–35.8]
Intensive care	27.3 [6.0–61.0]	28.6 [16.6–43.3]
Complications		
Organ failure[e]	50.0 [21.1–78.9]	28.1 [17.0–41.5]
CNS failure	33.3 [9.9–65.1]	17.5 [8.7–29.9]
Heart failure	≤25.0[†]	8.8 [2.9–19.3]
Kidney failure	≤25.0[†]	17.5 [8.7–29.9]
Bleeding	33.3 [9.9–65.1]	17.5 [8.7–29.9]
Allergic reaction to PEX	0.0 [0.0–26.5]	14.0 [6.3–25.8]
Infection	41.7 [15.2–72.3]	22.8 [12.7–35.8]
Other complication[f]	≤25.0[†]	35.1 [22.9–48.9]
Relapse		
Relapse	27.3 [6.0–61.0]	14.5 [6.5–26.7]
Evans syndrome	**n=14**	**n=51**
Management		
Steroid course	≥78.6[†]	90.2 [78.6–96.7]
Steroid period 1 treatment days, median [IQR]	144.5 [30.0–306.0]	96.5 [38.0–169.0]
Rituximab	57.1 [28.9–82.3]	54.9 [40.3–68.9]
IVIG	28.6 [8.4–58.1]	25.5 [14.3–39.6]
TPO-RA[g]	≤21.4[†]	13.7 [5.7–26.3]
Other treatment[d]	28.6 [8.4–58.1]	9.8 [3.3–21.4]
Intensive care	0.0 [0.0–30.8]	≤5.9[†]
Complications		
Organ failure	0.0 [0.0–23.2]	≤5.9[†]
Bleeding	≤21.4[†]	19.6 [9.8–33.1]

(*Continued*)

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Table 3 (Continued).

	Diagnosed between	
	2000–2009	**2010–2019**
Infection	≤21.4[†]	21.6 [11.3–35.3]
Other complication[f]	≤21.4[†]	11.8 [4.4–23.9]
Relapse		
Relapse	33.3 [9.9–65.1]	37.3 [24.1–51.9]

Notes: Reported values expressed as proportions with 95% confidence intervals (% [95% CI]), unless otherwise stated. [†]In the interest of data protection, specific values for patient groups ≤3 and groups that can be used to identify patient groups ≤3 are censored. [a]Calculated for women only. [b]Reported for percentage of those tested. Only 20/69 patients tested for proteinuria, resulting in high estimates. [c]Neurological symptoms and deficits primarily include transient ischemic attacks, confusion, headaches, seizures, vision impairment, stroke, and coma. [d]Other treatments primarily include chemotherapy and ciclosporin for TTP, and splenectomy and mycophenolate for ES. [e]Organ failure consists of the subcategories CNS, heart and kidney failure, detailed in the following rows for TTP. [f]Other complications primarily include allergic reactions and diabetes. [g]TPO-RAs include romiplostim and eltrombopag.

Abbreviations: TTP, thrombotic thrombocytopenic purpura; PEX, plasma exchange; IQR, interquartile range; IVIG, intravenous immunoglobulin; CNS, central nervous system; TPO-RA, thrombopoietin receptor agonists.

2000–2009 to 2010–2019. We observed an increased usage of other treatments in the 2010–2019 period, including chemotherapy, primarily cyclophosphamide and vincristine. Any organ failure occurred in 32% of confirmed TTP patients, while the second most common complication, infections, was seen in a quarter all TTP of patients. The proportion of confirmed TTP patients who relapsed in the follow-up period numerically dropped over time (2000–2009 27%; 2010–2019 15%) (Table 3). PLASMIC scores could be calculated for 80% of confirmed TTP patients and scores grouped at the upper end of the scale (Figure 4).

Patients with confirmed ES had similar treatment and complications in both diagnosis periods (Table 3). Most ES patients were treated with steroids, for a median period of 145 days in the earlier diagnosis period, and 97 days in the

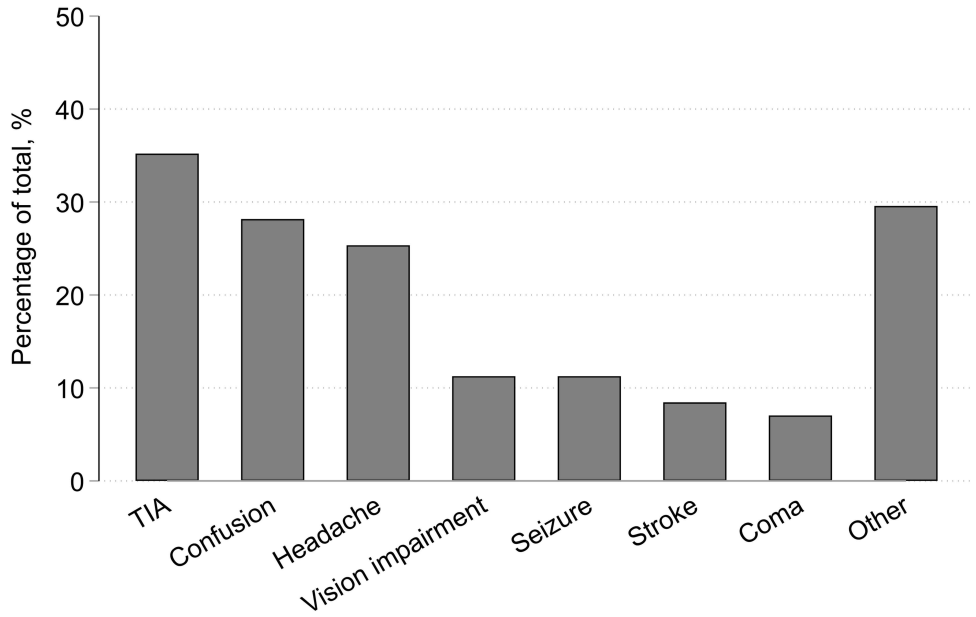

Figure 3 Neurological symptoms and deficits at presentation for confirmed TTP patients in the Danish National Patient Registry 2000–2019.
Abbreviations: TTP, thrombotic thrombocytopenic purpura; TIA, transient ischemic attack.

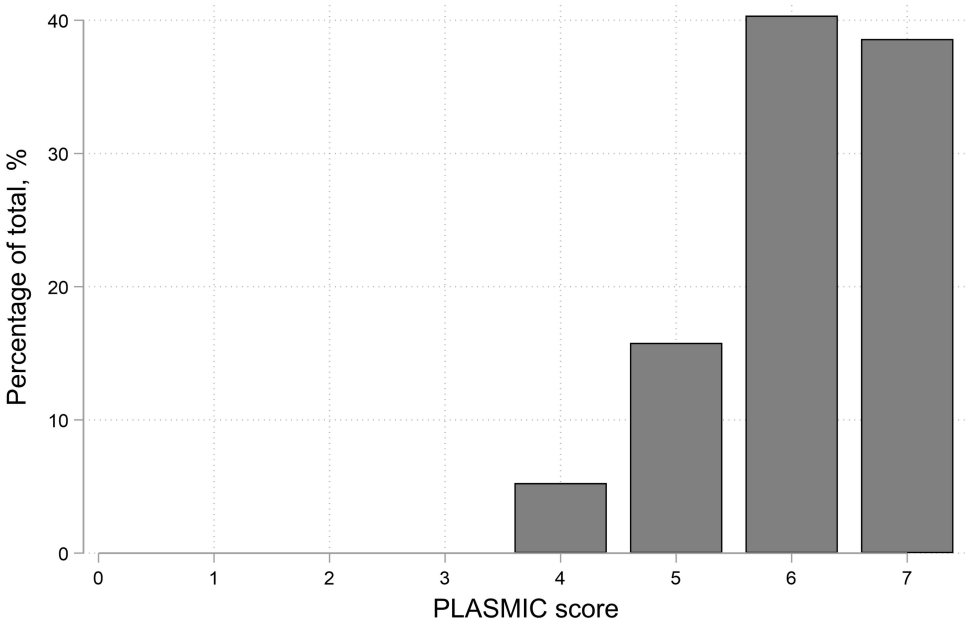

Figure 4 PLASMIC score frequencies for confirmed TTP patients registered in the Danish National Patient Registry 2000–2019.
Abbreviation: TTP, thrombotic thrombocytopenic purpura.

later. A quarter of confirmed ES patients received IVIG treatment, consistent between 2000–2009 and 2010–2019. Bleeding and infection were the most common complications, both observed in a fifth of ES patients, and approximately a third of ES patients relapsed during follow-up.

Kaplan-Meier analysis suggests there was no improvement in survival for TTP patients, and ES patients diagnosed later may have worse survival compared to their earlier diagnosed peers, although a small sample size limits statistical power (Figure 5). Median survival for this population of TTP patients was not reached during the study period, and median follow-up was 8.4 years. Thirty-day mortality was 8.4% for TTP patients and 1.5% for ES patients.

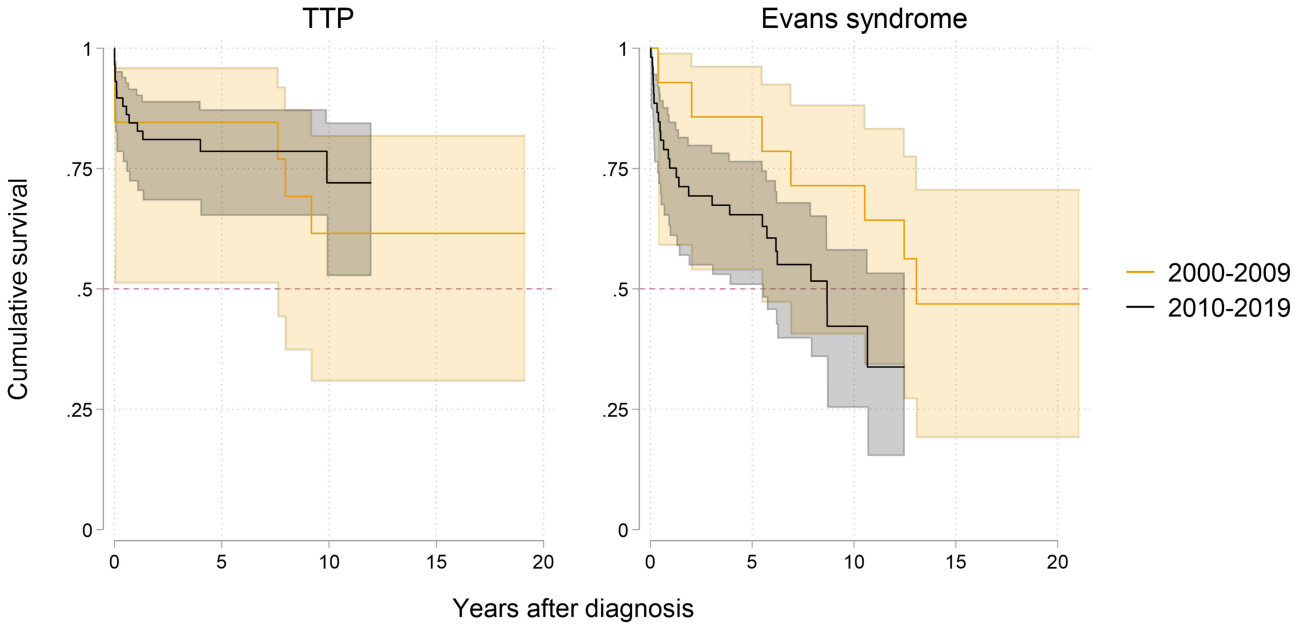

Figure 5 Kaplan-Meier survival estimates and 95% confidence intervals for confirmed TTP and ES patients registered in the Danish National Patient Registry 2000–2019 by diagnosis period.
Abbreviations: TTP, thrombotic thrombocytopenic purpura; ES, Evans syndrome.

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Discussion

Of the 149 TTP and 110 ES patients registered in the DNPR, 69 and 65 patients had their diagnoses confirmed, respectively. A PPV for TTP diagnosis of 46% suggests a moderate diagnostic reliability in the DNPR. This level of PPV aligns with findings from a 2010 validation study by Wahl et al[34] which also reported a PPV of 46% for iTTP diagnoses, based on administrative codes in an American insurance database. This consistency across different healthcare systems and settings underscores the challenges in accurately diagnosing TTP using administrative data alone. While the number of patients registered with an ICD code indicative of TTP increased over time in our study, PPV remained constant, indicating no improvement in the accuracy of registered TTP diagnoses in Denmark since 2000. Future register-based studies must be backed by medical record verification, as ICD code alone will lead to largely skewed estimates, through inclusion of a large proportion of patients without TTP.

The DNPR showed a higher reliability for ES diagnoses with an overall PPV of 59%. Furthermore, the PPV for ES diagnoses improved from 41% to 67% over time. The diagnoses that contribute to ES, AIHA and ITP, have been independently validated and registered ICD codes proved reliable, with all estimates of PPV sitting around 80%.[35–37] Although we had previous experience with TTP patients classified as ES patients,[4] we found no reason for this concern.

Our study identified significant differences between patients with confirmed TTP diagnoses and those with registered TTP diagnoses that were ultimately rejected. Confirmed TTP patients were younger, more likely to be female, and more likely to present with hemolysis than their rejected counterparts. Median age of diagnosis for TTP patients was 50 years, and there was a female preponderance, consistent with previous findings.[6,7] Moreover, confirmed patients were more likely to have received their first diagnosis code at a hematology department (65% vs 25%).

Less than 4% of Danish TTP patients diagnosed between 2000 and 2019 were congenital, in line with worldwide estimates.[5] We did not find evidence that cTTP is more common in Denmark, indicating this is not a Scandinavian trend even though high rates have been reported in Norway.[38] This may be a stand-alone phenomenon and investigation of TTP over a longer period in Denmark and the rest of Scandinavia would provide more insight into distribution.

ADAMTS13 enzyme activity alongside hemolytic anemia, thrombocytopenia, and clinical presentation with multi-visceral ischemic symptoms completes the diagnostic criteria for TTP.[2,5,39–41] ISTH guidelines recommend results of ADAMTS13 testing should be available within 3 days for efficient diagnosis, although an acceptable timeframe is within 7 days.[20] We observed increased measurement of ADAMTS13 enzyme and inhibitor activity over time, a positive trend in diagnosis of TTP, although increased testing did not result in a higher PPV. Still, approximately one third of registered TTP patients were not tested. TTP patients remain difficult to identify, likely due to ambiguity of disease presentation. PLASMIC scores could be calculated for most TTP patients, and all patients had a score ≥4, the large majority ≥5. The cut-off for "low risk for severe ADAMTS13 deficiency" is <5,[42] yet results presented here suggest that patients with a PLASMIC score of 4 should also be considered for ADAMTS13 investigation. Sensitivity of PLASMIC scores decreases with age,[43] which may have contributed to the observed scores.

As expected, almost all TTP patients in this study received plasma exchange (96%), for a median of 12 days (IQR 6–19 days), with no change over time. Other commonly utilized therapies include steroids and rituximab. Over 90% of confirmed TTP patients were treated with steroids, which treat the underlying autoimmune processes of TTP.[9] An increase in median days of steroid treatment between 2000–2009 and 2010–2019 from 49 to 90 days suggests increased utilization of steroids for treatment of TTP patients in Denmark. Rituximab was given to 58% of patients, and both steroid and rituximab treated proportions were very similar to those described by Adeyemi et al[24] for iTTP patients in the United States (59% and 86%, respectively). Few patients were treated with other therapies investigated in this study, and no Danish patients identified were splenectomized.

With drastically improved survival for TTP patients[22] comes a new side of the disease: late effects of management and complications. Neurological symptoms are common amongst TTP patients,[44] and the overwhelming majority (81%) of Danish patients had at least one neurological symptom or deficit at clinical presentation, higher than previously reported estimates.[7,11,23] TIA, headaches and confusion were particularly common, which can have a big impact on quality of life. Regarding medical complications, organ failure of any severity was registered among one third of Danish patients. Central nervous system failure was particularly dominant. In one French study 40% of TTP patients had kidney

dysfunction, although only 1–2% required dialysis,[7] while kidney dysfunction of any severity was recorded in 16% of our patients. The proportion of patients receiving intensive care remained constant (28%). Overall, disease complications for TTP patients stayed constant over the 20-year study period, indicating a need for more concurrent efforts to improve patient outcomes. With treatment with PEX risk of relapse for TTP sat around 36–37%,[16] reduced to 10–14% following introduction of rituximab, as indicated by numerous small studies.[45] Consistent with these findings, relapse occurred for 17% of Danish TTP patients during the follow-up period.

Survival drastically improved at the introduction of PEX as first-line treatment,[17,21] and mortality estimates have remained stable since.[16] In a similar cohort study of the Oklahoma TTP registry (diagnosed 1989–2008) overall survival 30 days after cessation of PEX treatment was reported at 69%.[16] Adeyemi's 2022 study of iTTP patients in the United States presented a mortality rate of 25% with median follow-up of 11 years.[24] Similarly, our Danish patients with TTP had an unadjusted overall mortality rate of 26%, with median follow-up of 8 years, and this remained constant for patients diagnosed between 2000–2009 and 2010–2019. While cause of death was not examined, without treatment TTP is most often fatal, and death has been observed even without patients appearing critically ill.[10] It is highly likely a number of patients are unaccounted for, as death occurred before a TTP diagnosis could be established.[10] We observed a larger proportion of rejected TTP patients died during follow-up compared to confirmed TTP patients. These patients may have suffered from diseases that are more aggressive than treated TTP. Short follow-up and few data points restrict survival analysis, and accordingly, all interpretation is tentative.

Steroids are first line therapy for ES,[46] and accordingly were the most commonly reported treatment for patients, with over 90% receiving a steroid course, for a median duration of 111 days. The observed drop in median duration of steroid treatment (145 to 97 days between 2000–2009 and 2010–2019) is likely a result of the contemporary focus on shorter steroid treatment for patients with ITP in the American Society of Hematology treatment guidelines.[47] The next most commonly employed therapies were rituximab and IVIG treatment; over half of all ES patients received rituximab, and one quarter of patients received IVIG treatment, both constant throughout the study period. Previous concerns of diagnostic overlap between TTP and ES patients[4] are mitigated by our finding that no ES patients received plasma exchange, suggesting accurate diagnosis differentiation. In many instances, rituximab has replaced use of splenectomy in refractory patients.[46] Just 5.6% of Danish ES patients were splenectomized, also consistent between 2000–2009 and 2010–2019. Our results indicate treatment of ES patients has been consistent over the last two decades.

As this study is based on registered ICD diagnoses for TTP and ES we are limited to positive predictive value of the two diseases, and proportion of patients with TTP and ES misdiagnosed between the two specifically. Nearly a quarter of all medical records were inaccessible (96/407), and information bias may be introduced if these patients differed from those we had access to. Temporal changes observed in this study are hypothesis generating, but small patient groups may impact these results. Patients registered at other hospital departments without referral to hematological departments were not eligible for review. Testing of ADAMTS13 became standard diagnostic workup during the study period, meaning later diagnoses are likely more complete.

Long term follow-up of complications and comorbidities amongst patients with TTP has been called on.[1] Establishing this nationwide cohort of confirmed patients provides a framework to study TTP complications in comparison to general population with lifelong follow-up available using the Danish national health registries. While the focus of this study was to evaluate diagnoses and describe initial treatment at diagnosis for TTP and Evans syndrome patients, long term treatment and the effects of newly introduced treatments such as caplacizumab on outcomes and prognosis can be investigated in future studies.[48]

Conclusion

In conclusion, register based studies on TTP and ES in Denmark are feasible, but TTP diagnoses must be backed up by medical record validation, as a registered ICD code in the DNPR alone is unreliable. Registered ES diagnoses are sufficiently valid to stand alone in future studies. TTP remains a difficult diagnosis to pinpoint, due to variability and vagueness of symptoms. Prompt and efficient diagnosis and treatment of TTP is vital for a positive outcome.[1,9] While initial treatment and complications for Danish TTP and ES patients have remained relatively stable since 2000, future studies using these validated cohorts will be able to enlighten on long-term health outcomes of these patients.

Data Sharing Statement

Due to patient confidentiality, data used in this study cannot be made publicly available.

Ethics Approval

Permission to extract from medical records was granted by the Danish Authority of Patient Safety (3-3013-2980/1) and Danish Regions (20/44380 and 20/25503).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

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