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Evans Syndrome: Analysis of 1255 Adult Cases in US Hospitals, Revealing Demographics, Associations, and Outcomes

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ABSTRACT

Background: Evans syndrome (ES) is a rare immune disorder characterized by immune thrombocytopenia and warm autoimmune hemolytic anemia (wAIHA), with the possibility of autoimmune neutropenia (AIN). Limited data due to its rarity led us to perform a descriptive analysis of demographics, outcomes, and comorbidities.

Materials and Methods: This study used the National Inpatient Sample database to identify Evans syndrome hospitalizations (ICD-10 code D69.41) from 2016 to 2019, with national estimates. We collected demographic data, examined outcomes, and assessed patient comorbidity. STATA Version 17 was used for data analysis.

Results: In our study of 1,255 ES hospitalizations, the mean age was 50.13 years, with a relatively even gender distribution. The racial breakdown included White (59.6%), Black (17.1%), and Hispanic (14.6%). Most had Medicare (41.8%), Medicaid (20.4%), or private insurance (33.5%). Charlson Comorbidity Index scores varied, with 36.6% scoring 3 or more. Non-elective admissions accounted for 90.2% of cases, coming from various U.S. Census Divisions, with East North Central (16.2%) and Pacific (16.1%) leading. Large urban teaching hospitals handled 84.1% of cases. Mortality was 5.5%, the mean stay was 7.8 days, with total charges averaging $114,696. Notable associations included SLE (15.63%), ITP (37%), and anemia (53.5%). Inpatient risks included AKI (22.47%) and sepsis (15.33%). Interventions included red blood cell transfusion (18.65%) and platelet transfusion (10.44%).

Conclusion: This study offers key insights into ES in hospitalized adults, emphasizing demographic trends and important associations with other conditions. More research is required to enhance our understanding of ES and enhance outcomes for those affected.

Keywords: Evans Syndrome; Immune thrombocytopenia; Autoimmune hemolytic anemia; Autoimmune neutropenia; Demographics; Associations

INTRODUCTION

Evans syndrome (ES) is a rare immune disorder where a single patient experiences the simultaneous or sequential development of immune thrombocytopenia (ITP) and warm autoimmune hemolytic anaemia (wAIHA), sometimes with or without autoimmune neutropenia (AIN)[1]. ES is an uncommon condition, accounting for approximately 7% of AIHA cases and roughly 2% of ITP cases [2]. While ES has traditionally been considered an "idiopathic" condition and primarily a diagnosis of exclusion, it can also be associated with other diseases or

conditions such as systemic lupus erythematosus (SLE), lymphoproliferative disorders, or primary immunodeficiencies. Depending on the presence or absence of these associated conditions, ES is classified as primary or secondary[3]. The occurrence of autoimmune hemolytic anaemia has been reported in a range of 37% to 73% of patients with ES. Thrombocytopenia is also common, with the detection of antibodies against platelets (PA-IgG) documented in 35% of individuals, primarily of the anti-IIb-IIIa type[4]. As ES is a diagnosis of exclusion, it's necessary to rule out common causes such as cold agglutinin disease, thrombotic thrombocytopenic purpura (TTP) through careful evaluation of the peripheral blood smear, infectious causes (such as HIV and Hepatitis C), other autoimmune conditions, and malignancies before confirming an ES diagnosis[4]. The clinical features of ES include fatigue, pallor, jaundice, weakness, as well as skin and mucosal bleeding. These symptoms may exhibit an intermittent pattern throughout a person's lifetime and occasionally result in catastrophic bleeding and massive hemolysis[5]. In a previous study involving 68 ES patients, mostly women, it was found that immune thrombocytopenia (ITP) and/or warm autoimmune hemolytic anemia (AIHA) typically began at an average age of 52 ± 33 years. In over half of the cases, these conditions were presented simultaneously[6]. Studying Evans syndrome, a complex disorder, is crucial for enhancing patient care and clinical practice. The limited inpatient data available underscores the need for comprehensive research on patient demographics, outcomes, and comorbidities using descriptive statistics.

MATERIALS AND METHODS

This retrospective study employed data extracted from the National Inpatient Sample (NIS), which is sponsored by the Agency for Healthcare Research and Quality (AHRQ) and constitutes part of the Health Care Cost and Utilization Project (HCUP)[7]. The NIS database represents an approximate 20% stratified sample of discharges across nearly 1000 U.S. hospitals in the 50 states of the United States. Notably, the NIS database is the largest publicly available all-payer inpatient care database in the United States. For this analysis, the study specifically utilized the National Inpatient Sample (NIS) database spanning the years 2016 to 2019, encompassing hospitalizations from January 1, 2016, to December 31, 2019, and with records of over 24 million hospital stays. Furthermore, since the NIS data is deidentified, this study was exempt from requiring Institutional Review Board (IRB) approval.

Study population

In this study, the NIS database was used to identify patients with a clinical diagnosis of Evans syndrome (ICD-10 code D69.41) over a four-year period, from 2016 to 2019. A 'weight' variable was used to allow the sample to be extrapolated into regional or national estimates. Weight calculations are based on census data, hospital location, census division, teaching status, and bed size. Patient demographics, diagnoses, payer information, length of stay, procedures, and hospital charges are collected in the NIS database. Data was weighted to provide a national estimate of the prevalence. Demographic information was collected on age, sex, race, household income, hospital size, hospital location, primary payer source, associated diagnoses, procedures, and outcomes.

Patients are categorized into six groups based on race: White, Black, Hispanic, Asian or Pacific Islander, Native American, and Other. Primary insurance provider categories (primary expected payer) included Medicare, Medicaid, private insurance, and no insurance. The median household income national quartile for patient ZIP code (ZIPINC-quartile) was used as a proxy measure for socioeconomic status. Hospital characteristics identified consisted of hospital location, census division, and teaching status.

Outcomes of interest and analysis

Our outcomes of interest included in-hospital mortality, length of stay, total hospitalization charges, as well as complications and associations linked with Evans syndrome. All analyses were conducted using appropriate stratifying, clustering, and weighting samples provided by Healthcare Cost and Utilization Project regulations[8]. We used the Charlson Comorbidity Index score to predict the severity and comorbidity in patients [9]. For mortality,

we utilized the NIS variable "DIED." The length of stay was determined using the NIS variable "LOS." Total hospitalization charges were assessed using the variable "TOTCHG." Common comorbidities and associations with Evans syndrome were identified by ICD-10 diagnosis codes that were utilized at the time of discharge (Supplemental Table 1). Procedures or interventions were identified via ICD-10 procedure codes, and these were also aggregated to demonstrate the most commonly performed inpatient interventions in this patient population (Supplemental Table 2). Data analysis was performed using STATA Version 17, College Station, TX: Stata Corp LLC. Descriptive statistics were used to summarize the data.

RESULT

Table 1 summarizes the baseline characteristics of 1,255 hospitalizations with Evans syndrome. The mean age was 50.13 years, with a fairly balanced distribution by gender (47.8% male and 52.2% female). The racial composition consists primarily of White (59.6%), followed by Black (17.1%), Hispanic (14.6%), and other groups. Income levels vary across percentiles, with Medicare (41.8%), Medicaid (20.4%), and private insurance (33.5%) being the predominant insurance types. Charlson Comorbidity Index scores indicate a range of comorbidity levels, with 36.6% having a score of 3 or more. Most admissions are non-elective (90.2%). Patients come from various U.S. Census Divisions, with the highest percentage in the East North Central (16.2%) and Pacific (16.1%) divisions. Hospital bed sizes vary, with large hospitals accounting for the majority (62.0%), and the majority of patients are admitted to urban teaching hospitals (84.1%).

Table 2 focuses on mortality, length of stay, and total charges. Among 1255 hospitalizations, 69 (5.5%) patients died in the hospital. The average length of stay and total charges were 7.8 days and $ 114,696 respectively, for each hospitalization.

Table 3 presents the common disease associations with Evans syndrome. The most frequently reported was SLE at 15.63%, followed by lymphoma at 7.01%, antiphospholipid syndrome at 4.70%, and common variable immunodeficiency at 4.31%. Sjögren's syndrome was observed in 2.87% of cases, while hepatitis C and autoimmune lymphoproliferative syndrome (ALPS) were noted in 1.83% and 1.12%, respectively. The least common association was IgA deficiency at 0.48%.

Table 4 outlines documented hematological associations with Evans syndrome. Hemolytic anemia was documented in 15.7% of cases, followed by ITP at 37%, neutropenia at 4.22%, anemia at 53.5%, thrombocytopenia at 18%, and pancytopenia at 14.5%.

Table 5 describes documented inpatient risks and outcomes associated with Evans syndrome. Acute Kidney Injury (AKI) was documented in 22.47% of cases, followed by sepsis at 15.33%, acute respiratory failure at 13.86%, pneumonia at 8.94%, Congestive Heart Failure (CHF) at 15.94%, Acute Myocardial Infarction (MI) at 2.31%, and Disseminated Intravascular Coagulation (DIC) at 1.04%.

Table 6 details the inpatient interventions and procedures associated with Evans syndrome. Red blood cell transfusion was the most common, administered in 18.65% of cases, followed by platelet transfusion at 10.44% and IVIG (intravenous immunoglobulin) infusion at 7%. Intubation and mechanical ventilation were required in 8.29% of cases, while splenectomy was performed in 2%.

Table 1: Baseline characteristics of Evans syndrome hospitalizations

	Total hospitalizations (N=1255)	Percentage (%)
Mean age	50.13 years	
Sex		
Male	600	47.8%
Female	655	52.2%
Race		
White	748	59.6%
Black	214	17.1%
Hispanic	183	14.6%
Asian or Pacific Islander	57	4.6%
Native American	8	0.7%
Other	40	3.2%
Median household income		
0-25th percentile	282	22.5%
26th to 50th percentile	277	22.1%
51st to 75th percentile	318	25.4%
76th to 100th percentile	311	24.8%
Insurance status		
Medicare	524	41.8%
Medicaid	256	20.4%
Private insurance	420	33.5%
No insurance	51	4.1%
Charlson Comorbidity Index score		
0	323	25.8%
1	236	18.8%
2	234	18.7%
3 or more	459	36.6%
Admission Type		
Non-elective	1144	90.2%
Elective	122	9.8%
Census Division		
New England	99	7.9%
Middle Atlantic	170	13.6%
East North Central	203	16.2%
West North Central	71	5.7%
South Atlantic	204	16.3%
East South Central	74	5.9%
West South Central	155	12.4%
Mountain	69	5.5%
Pacific	202	16.1%

Hospital Bed-Size		
Small	181	14.5%
Medium	293	23.4%
Large	778	62.0%
Hospital Location/Teaching Status		
Rural	45	3.6%
Urban nonteaching	152	12.1%
Urban teaching	1055	84.1%

Table 2: Mortality, Length of stay and Total charges

In-patient Mortality rate	5.5% (69/1255)
The average length of stay	7.8 days
Average total charges	$ 114,696

Table 3: Common diseases associations with Evans syndrome

Condition	Total hospitalizations(n)	Percentage (%)
Autoimmune lymphoproliferative syndrome (ALPS)	14	1.12%
SLE (Systemic lupus erythematosus)	196	15.63%
Antiphospholipid syndrome	59	4.70%
Sjögren's syndrome	36	2.87%
Common variable immunodeficiency	54	4.31%
IgA deficiency	6	0.48%
Lymphoma	88	7.01%
Hepatitis C	23	1.83%
HIV (Human immunodeficiency virus)	2	0.16%

Table 4: Hematological associations with Evans syndrome

Condition	Total hospitalizations (n)	Percentage (%)
Hemolytic anemia	197	15.7%
ITP	463	37%
Neutropenia	53	4.22%
Anemia	672	53.5%
Thrombocytopenia	227	18%
Pancytopenia	182	14.5%

Table 5: Common inpatient risks/outcomes associations with Evans syndrome

Condition	Total hospitalizations (n)	Percentage (%)
AKI (Acute kidney injury)	282	22.47%
Sepsis	192	15.33%
Acute respiratory failure	174	13.86%
Pneumonia	112	8.94%
CHF (Congestive heart failure)	200	15.94%
Acute MI (Myocardial infarction)	29	2.31%
DIC (Disseminated intravascular coagulation)	13	1.04%

Table 6: In-Patient Interventions / Procedures associated with Evans syndrome

Interventions/ Procedures	Total hospitalizations (n)	Percentage (%)
Red blood cell transfusion	234	18.65%
Platelets transfusion	131	10.44%
IVIG (Intravenous immunoglobulin) infusion	87	7%
Splenectomy	25	2%
Intubation/Mechanical ventilation	104	8.29%

DISCUSSION

Data on Evans syndrome is limited due to the rare nature of this disease and its status as a diagnosis of exclusion. This study identified 1255 hospitalizations with Evans syndrome in the NIS database over a four-year period from 2016 to 2019. The median age was found to be 50.13 years. There was a slight female predominance, and these findings are consistent with previous studies where the incidence was reported to be higher in female patients compared to their male counterparts[6]. The age and gender distribution variables related to Evans syndrome are in accordance with both autoimmune hemolytic anemia (AIHA) and immune thrombocytopenic purpura (ITP), both of which have a median age distribution of 50 years[10, 11].

Our analysis showed that the racial distribution indicated a greater number of reported cases in the Caucasian population, followed by Black, Hispanic, Asian, and Native American individuals, and, finally, those belonging to other racial categories. In our study, the census divisions of South Atlantic, Pacific, and East North Central had a higher distribution of cases compared to other geographic divisions. However, we could not find any other epidemiological studies related to Evans syndrome given the rare occurrence of this disease, especially in the adult population.

The diagnosis of Evans Syndrome is still one of exclusion. Profound immune dysregulation is seen in Evans Syndrome[12]. Hence, it is increasingly recognized that we should look for other associated autoimmune or hematological conditions that will influence both the management and outcome[1]. Thus, it is classified as primary (or idiopathic) and secondary (associated with other conditions). Increased mortality is seen in secondary Evans syndrome compared to primary Evans syndrome[13].

In our study, we identified associations between Evans syndrome and various other conditions. Common autoimmune conditions were reported in 29.11% of hospitalizations, while hematological malignancies such as lymphoma were reported in 7% of these cases. Additionally, HCV was reported in 1.83%, and HIV was reported in 0.16% of the studied populations. Among the autoimmune conditions, the most significant association was reported with systemic lupus erythematosus (SLE) at 15.63%, with approximately 4% exhibiting associations with common variable immunodeficiency (CVID) and antiphospholipid syndrome. These findings are in line with several other studies that have found similar associations[2]. These conclusions emphasize the importance of an extensive diagnostic workup that is advised to find underlying conditions based on patients' characteristics, such as chest, abdomen, and pelvis CT scans to detect lymph nodes, serum protein electrophoresis, immunoglobulin concentration, antibodies specific to SLE, Sjogren's syndrome, antiphospholipid syndrome, and tests for viral infections like HIV and HCV.

In our study, red blood cell transfusion emerged as the most common intervention, occurring in 234 cases (18.65%), followed by platelet transfusion in 131 cases (10.44%), IVIG (intravenous immunoglobulin) infusion in 87 cases (7%), and splenectomy (surgical removal of the spleen) in 25 cases (2%). These findings provide a clear overview of the prevalence of these medical interventions in the treatment of Evans syndrome, offering valuable insight into therapeutic patterns for healthcare professionals and researchers.

Limitations

Our study's scope is limited due to the lack of follow-up information beyond hospital discharge, which hinders our ability to evaluate long-term outcomes beyond the hospital context. Our analysis only implies when patients with Evans syndrome get hospitalized for any reason. Essential particulars like basic lab values, pathological data, imaging data, treatment methodologies, and analyses of causes of death are missing from the NIS dataset. Only a single ICD-10 code is available for Evans syndrome, so it is not possible to divide the patient population into primary and secondary Evans syndrome. It is also important to acknowledge that our analyses were performed using retrospective registry data, introducing the potential for selection bias due to potential selective reporting and the use of ICD codes for forming the patient group.

Despite these limitations, utilizing this extensive database remains a valuable asset in achieving our primary research goal: obtaining insights into real-

world practices and associations concerning Evans syndrome. While errors in coding and variations in documentation are feasible within the NIS database, it has undergone thorough validation and has been widely employed in research undertakings. Our study, which examines a substantial sample from this database, encompasses a diverse population across the United States and integrates data from numerous medical centers.

CONCLUSION

This study offers a wealth of valuable information about Evans syndrome in hospitalized adults. It reveals distinct demographic patterns and associations between ES and various other medical conditions. It is evident that additional research is necessary to gain a deeper understanding of the intricate nature of ES, ultimately leading to enhanced outcomes for patients with this condition.

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