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Survival after Stevens–Johnson Syndrome or Toxic Epidermal Necrolysis: A United Kingdom–Based Cohort Study



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TO THE EDITOR

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare mucocutaneous adverse drug reactions (Ferrandiz-Pulido and Garcia-Patos, 2013; Frey et al., 2017a, 2017b; Harr and French, 2012; Hsu et al., 2016; Martín-Merino et al., 2015; Mockenhaupt, 2012; Mockenhaupt et al., 2005). In the European Registry of Severe Cutaneous Adverse Reactions, 23% of patients died within 6 weeks after the onset of SJS and/or TEN (SJS: 12%, SJS and TEN overlap: 29%, TEN: 46%, 2003–2007). After 1 year, 34% of patients had died (Sekula et al., 2013). In a United States–based inpatient database study, 8.4% of patients died during the initial hospitalization for SJS and/or TEN (SJS: 4.8%, SJS and TEN overlap: 19.4%, TEN: 14.8%, 2009–2012) (Hsu et al., 2016).

We performed an observational study to evaluate absolute and relative short-term and long-term (5-year) mortality after SJS and/or TEN diagnosis. To quantify absolute short-term mortality after SJS and/or TEN, we conducted a cross-sectional study using Hospital Episode Statistics-Admitted Patient Care data, which capture information on all admissions at National Health Service hospitals in England. Of 434 patients with a first-time inpatient diagnosis of SJS and/or TEN ($n = 378$ for SJS [International Classification of Diseases 10th Revision L51.1], $n = 56$ for TEN [International Classification of Diseases 10th Revision L51.2]) between 1995 and 2013, 32 patients (7.4%) died during the index hospitalization (SJS: 5.0%, TEN: 23.2%; age ≥ 65 years:

25.0%, age < 65 years: 2.4%). Sex and body mass index ($< 65 \text{ kg/m}^2$ or $\geq 65 \text{ kg/m}^2$) were not associated with the risk of death (Table 1).

We further conducted a longitudinal cohort study to quantify long-term mortality after SJS and/or TEN compared with not having SJS and/or TEN using the United Kingdom–based Clinical Practice Research Datalink (CPRD) GOLD, which contains longitudinal primary care data (Herrett et al., 2010). These two study populations were analyzed separately because Hospital Episode Statistics-Admitted Patient Care data are only available for approximately 50% of all the general practitioner practices contributing data to CPRD GOLD (Clinical Practice Research Datalink, 2020). We included 477 patients with a first diagnosis of SJS and/or TEN and a referral to secondary care in CPRD GOLD (1995–2013). Diagnoses of SJS and/or TEN in this cohort were previously validated (positive predictive value = 87%) (Frey et al., 2017a). We conducted a propensity score matching of four comparator patients (nearest-neighbor matching; caliper = 0.025) without a diagnosis of SJS and/or TEN to each patient with SJS and/or TEN ($n = 1,908$). To minimize bias by differential healthcare utilization, comparator patients had to have ≥ 1 general practitioner visit within 30 days of a randomly assigned cohort entry date between 1995 and 2013. All patients had to be enrolled in CPRD GOLD for ≥ 180 days before the cohort entry date (date of first SJS and/or TEN in cases or randomly assigned date in

comparators). The propensity score included 15 covariates measured before the cohort entry date (demographics, lifestyle factors, body mass index, healthcare utilization, selected comorbidities). The mean age was 38 years in both groups, and covariate balance was achieved (Supplementary Table S1). We followed patients for a maximum of 5 years from cohort entry date until the first of the following occurred: death (primary endpoint), loss to follow-up, end of data collection, or completion of 5 years of follow up. The mean follow-up was 3.5 years (SD = 1.7) in patients with SJS and/or TEN and 3.2 years (SD = 1.8) in the comparator group (Figure 1: Kaplan–Meier curves). Of the 477 patients with SJS and/or TEN, 23 (4.8%, 95% CI = 4.4–5.2) died within 90 days after SJS and/or the cohort entry date, and 36 (7.5%, 95% CI = 5.2–10.0) died between day 91 and the end of follow-up. The hazard ratio, using time-specific Cox proportional hazard regression, for death in the first 90 days after SJS and/or TEN compared with that for SJS- and/or TEN-free controls was 4.86 (95% CI = 2.65–8.92) and 0.80 (95% CI = 0.56–1.16), respectively, for death after day 90. Results were not meaningfully different in subgroup analyses by sex, age (< 65 years or ≥ 65 years), body mass index ($< 28 \text{ kg/m}^2$ or $\geq 28 \text{ kg/m}^2$), and Charlson Comorbidity Score (≤ 2 and/or > 2 , Table 1).

Similar to our cross-sectional study, a United States–based database study of patients with SJS and/or TEN identified through hospital discharge diagnoses reported a mortality of 8.4% during the initial hospitalization (7.4% in our cross-sectional study) (Hsu et al., 2016). However, we cannot rule out that some false-positive diagnoses were included in either of these database studies. On the other hand, the

Abbreviations: CI, confidence interval; CPRD, Clinical Practice Research Datalink; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis

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Table 1. Mortality Among Patients With SJS/TEN Overall and Within Subgroups. Cross-Sectional Study: Mortality During Initial Hospitalization Using HES APC Data. Longitudinal Cohort Study: Mortality During Short-Term (day 1-90) and Long-Term (Day 91 Until 5 Years) Follow-Up Using CPRD GOLD Data

Subgroup of SJS/ TEN Patients	Cross-Sectional Study (HES APC)		Longitudinal Cohort Study (CPRD GOLD)				
	n (SJS and/ or TEN)	n (Death among SJS and TEN) (%)	n (SJS and/ or TEN)	Early Follow-Up Period (≤90 d after CED)		Late Follow-Up Period (>90 d and ≤5 y after CED)	
				HR ¹ (95% CI)	n (Death among SJS and TEN) (%)	HR ¹ (95% CI)	n (Death among SJS and TEN) (%)
Overall	434	32 (7.4)	477	4.86 (2.65–8.92)	23 (4.8)	0.80 (0.56–1.16)	36 (7.5)
SJS (ICD-10 L51.1)	378	19 (5.0)	N/A	N/A	N/A	N/A	N/A
TEN (ICD-10 L51.2)	56	13 (23.2)	N/A	N/A	N/A	N/A	N/A
Women	210	16 (7.6)	246	6.89 (2.71–17.50)	12 (4.9)	0.96 (0.59–1.58)	20 (8.1)
Men	224	16 (7.6)	231	4.90 (2.03–11.83)	11 (4.8)	0.74 (0.43–1.28)	16 (6.9)
Aged <65 y	330	8 (2.4)	386	6.25 (2.04–19.09)	8 (2.1)	0.90 (0.44–1.81)	10 (2.6)
Aged ≥65 y	72	24 (25.0)	91	5.43 (2.54–11.61)	15 (16.5)	0.97 (0.64–1.49)	26 (28.6)
BMI <28 kg/m ² ²	176	18 (10.2)	183	4.85 (2.10–11.23)	12 (6.6)	0.81 (0.46–1.42)	15 (8.2)
BMI ≥28 kg/m ² ²	72	8 (10.0)	95	2.65 (0.75–9.40)	NR ³	1.46 (0.76–2.61)	14 (14.7)
BMI missing	178	6 (3.4)	199	6.91 (2.02–23.59)	7 (3.5)	0.56 (0.25–1.26)	7 (3.5)
Charlson Comorbidity Score ≤2 ²	N/A	N/A	404	7.40 (2.95–18.56)	13 (3.2)	0.91 (0.54–1.53)	18 (4.6)
Charlson Comorbidity Score >2 ²	N/A	N/A	73	2.84 (1.28–6.33)	10 (13.7)	1.20 (0.71–2.03)	18 (24.7)

Abbreviations: BMI, body mass index; CED, cohort entry date; CI, confidence interval; CPRD, Clinical Practice Research Datalink; HES APC, Hospital Episode Statistics-Admitted Patient Care; HR, hazard ratio; ICD-10, International Classification of Disease 10th Revision; N/A, not available; NR, not reportable; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

¹Compared to matched patients without SJS/TEN.

²Last recording before CED.

³Cells counting of <5 patients are not shown owing to ethics regulations to preserve confidentiality.

European Registry of Severe Cutaneous Adverse Reactions previously reported a mortality of 28% within 90 days (Sekula et al., 2013), but strict case definition may have led to an under-representation of mild cases. Our longitudinal cohort study revealed that compared with SJS- and TEN-free controls, the risk of death returned to baseline once the patient survived the acute phase of the disease. Short-term

mortality during the first 3 months of follow-up was lower in our cohort study (4.8%) than mortality during hospitalization for SJS and/or TEN in our cross-sectional study (7.4%) and has to be interpreted carefully. CPRD GOLD data capture 98.2% of all deaths (Gallagher et al., 2019), but our data show that they did not capture SJS and/or TEN diagnoses for several patients with severe SJS and/or TEN, especially if

patients died during the initial hospitalization. In our cross-sectional analysis of Hospital Episode Statistics-Admitted Patient Care data, we observed that of 434 patients with an inpatient diagnosis of SJS and/or TEN, only 40% had a diagnosis for SJS and/or TEN recorded in CPRD GOLD within the 180 days before or after hospital discharge. Mortality during the initial hospitalization among those without a subsequent diagnosis in CPRD GOLD ($n = 260$, $n = 28$ for deaths) was 10.8% versus 2.3% among those with a subsequent diagnosis for SJS and/or TEN in CPRD GOLD ($n = 174$, $n = 4$ for deaths). Nevertheless, such under-recording of SJS and/or TEN diagnoses in CPRD GOLD does not affect the validity of our comparative analysis on long-term mortality after SJS and/or TEN.

The population-based longitudinal nature of CPRD GOLD data allowed us to follow patients with SJS and/or TEN over several years to evaluate short-term and long-term mortality and to compare them with SJS- and TEN-free controls. This study has several limitations. First, we could not evaluate mortality by disease

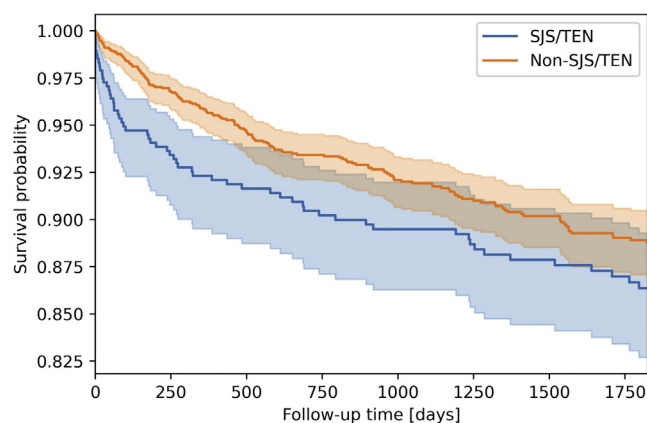


Figure 1. Survival after the diagnosis of SJS and/or TEN. Survival after the diagnosis of SJS and/or TEN and survival in the comparator group (non-SJS and/or non-TEN) with 95% confidence intervals during 5 years of follow-up. SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

severity in our longitudinal cohort study because differentiation between SJS and TEN is insufficient in CPRD GOLD (Frey et al., 2017b). Second, owing to the rarity of SJS and TEN, statistical power was low despite the large size of the databases. Third, delayed recording of SJS and TEN diagnoses may occur in CPRD GOLD if a patient enters the healthcare system through a hospital. For this reason, we chose 90 days to evaluate short-term mortality rather than 6 weeks, as was done in the Registry of Severe Cutaneous Adverse Reactions study (Sekula et al., 2013). In addition, although death recording is nearly complete in CPRD GOLD, a delayed recording may occur in 30% of patients (mostly <30 days delay) (Gallagher et al., 2019). However, a sensitivity analysis evaluating death during the first 120 days did not change our results (two extra deaths between days 91 and 120 in patients with SJS and/or TEN). In summary, our results revealed an absolute risk of death of 7.4% among patients hospitalized with SJS and/or TEN in England. Long-term mortality of up to 5 years was not increased compared with that to patients free of SJS- and TEN.

Data availability statement

Owing to official regulations by the data provider, the sharing of analytical data is strictly prohibited. Any analytical data has to be stored on a pre-specified and agreed-on server with strict access control. Data can be requested through an official data request submitted to the Clinical Practice Research Datalink.

Data for this study were derived from Clinical Practice Research Datalink primary care data obtained under license from the United Kingdom Medicines and Healthcare products Regulatory Agency. The data are provided by patients and collected by the National Health Service as part of their care and support. The interpretation and conclusions contained in this study are those of the authors alone. Hospital Episode Statistics-Admitted Patient Care data copyright (2020) were reused with

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CONFLICT OF INTEREST

The authors state no conflict of interest. The authors confirm that they have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. This study was approved by the Independent Scientific Advisory Committee for Medicines and Healthcare products Regulatory Agency database research (protocol number: 14_009RA, made available to reviewers).

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SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at <https://doi.org/10.1016/j.jid.2020.09.034>.

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Supplementary Table S1. Baseline Characteristics of Patients with and without SJS and/or TEN before and after PS Matching

Characteristics Displayed as n (%) Unless Otherwise Indicated	Before PS Matching		After PS Matching	
	SJS and TEN N = 477	Comparator Group N = 80,326	SJS and TEN N = 477	Comparator Group N = 1,908
Age, mean $\pm$ SD, y	38.6 $\pm$ 25.3	42.1 $\pm$ 25.4	38.6 $\pm$ 25.3	38.4 $\pm$ 25.7
Age, median, IQR, y	37.0 (43.0)	41.0 (41.0)	37.0 (43.0)	35.0 (46.0)
Women	246 (51.6)	46,670 (58.1)	246 (51.6)	977 (51.2)
Ethnicity				
White	208 (43.6)	24,017 (29.9)	208 (43.6)	890 (46.7)
Black	9 (1.9)	575 (0.7)	9 (1.9)	23 (1.2)
Asian	8 (1.7)	862 (1.1)	8 (1.7)	31 (1.6)
Mixed and other	6 (1.3)	626 (0.8)	6 (1.3)	30 (1.6)
Unknown	246 (51.6)	54,246 (67.5)	246 (51.6)	934 (49.0)
BMI (closest recording before CED)				
≥ 28 kg/m ²	95 (19.9)	15,162 (18.9)	95 (19.9)	383 (20.1)
< 28 kg/m ²	183 (38.4)	32,867 (40.9)	183 (38.4)	773 (40.5)
Unknown	199 (41.7)	32,297 (40.2)	199 (41.7)	752 (39.4)
Smoking status (closest recording before CED)				
Nonsmoker	189 (39.6)	29,954 (37.3)	189 (39.6)	785 (41.1)
Smoker	80 (16.8)	13,973 (17.4)	80 (16.8)	311 (16.3)
Ex-smoker	67 (14.1)	12,820 (16.0)	67 (14.1)	269 (14.1)
Unknown	141 (29.6)	23,579 (29.4)	141 (29.6)	543 (28.5)
Alcohol consumption (average units per wk for all recorded alcohol units before CED)				
0–7	212 (44.4)	38,212 (47.6)	212 (44.4)	860 (45.1)
> 8	67 (14.1)	9,991 (12.4)	67 (14.1)	294 (15.4)
Unknown	198 (41.5)	32,123 (40.0)	198 (41.5)	754 (39.5)
Comorbidities and proxies for polymorbidity before CED				
Charlson Comorbidity Score, mean $\pm$ SD	1.1 $\pm$ 1.9	0.8 $\pm$ 1.4	1.1 $\pm$ 1.9	1.1 $\pm$ 1.7
Charlson Comorbidity Score, median, IQR	0.0 (1.0)	0.0 (1.0)	0.0 (1.0)	0.0 (1.0)
Hospitalization within 365 d before CED	186 (39.0)	12,208 (15.2)	186 (39.0)	708 (37.1)
Emergency Department visit within 365 d before CED	50 (10.5)	2,164 (2.7)	50 (10.5)	174 (9.1)
GP visits within 180 d before CED				
0	5 (1.1)	4,705 (5.9)	5 (1.1)	17 (0.9)
1–4	110 (23.1)	29,447 (36.7)	110 (23.1)	448 (23.5)
≥ 4	362 (75.9)	46,174 (57.5)	362 (75.9)	1,443 (75.6)
Active cancer within 365 d before CED	17 (3.6)	947 (1.2)	17 (3.6)	63 (3.3)
Pneumonia within 180 d before CED	6 (1.3)	112 (0.1)	6 (1.3)	18 (0.9)
Chronic kidney disease ¹ at any time before CED	29 (6.1)	3,232 (4.0)	29 (6.1)	106 (5.6)
Acute kidney disease within 365 d before CED	< 5 (< 1.1) ⁷	50 (0.1)	NR ²	8 (0.4)
Antibiotics within 84 d before CED	245 (51.4)	12,479 (15.5)	245 (51.4)	1,008 (52.8)

Abbreviations: BMI, body mass index; CED, cohort entry date; GFR, glomerular filtration rate; GP, general practitioner; IQR, interquartile range; NR, not reportable; PS, propensity score; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

¹Defined as Read-code for chronic kidney disease or ≥ 2 recorded GFR values < 60 ml/min/1.73 m².

²Cells counting < 5 patients are not shown owing to ethics regulations to preserve confidentiality.