

Unique Clinical Characteristics and Prognosis of Allopurinol-Induced Severe Cutaneous Adverse Reactions



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What is already known about this topic? Allopurinol can lead to severe cutaneous adverse reactions (SCARs) with the frequency of 0.05% to 0.5% and is the most common cause of SCARs in Korea due to the relatively high prevalence of the HLA-B*58:01 genotype (8% to 13%).

What does this article add to our knowledge? Allopurinol-induced SCARs have unique characteristics and poor prognoses with important predictive factors (chronic renal insufficiency, blood urea nitrogen levels, eosinophil counts, creatinine levels, alanine aminotransferase levels, and platelet counts) of death compared with other drug-induced SCARs.

How does this study impact current management guidelines? This information will encourage clinicians to identify allopurinol-induced SCAR patients with poor prognosis using unique predictive factors so that early intensive treatment and close monitoring can be implemented to prevent death.

BACKGROUND: Allopurinol is the most common cause of severe cutaneous adverse reactions (SCARs) in Korea due to the relatively high prevalence of the HLA-B*58:01 genotype (8%-13%).

OBJECTIVE: We aimed to reveal the clinical characteristics and risk factors for death in allopurinol-induced SCARs in Korea.

METHODS: We retrospectively reviewed the medical records of 106 subjects with allopurinol-induced SCARs and 639 subjects with other drug-induced SCARs who were enrolled in the Korean SCARs Registry (collected from 34 nationwide medical institutions) from January 2010 to December 2015.

RESULTS: Subjects with allopurinol-induced Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) were older and had more comorbidities, longer latent periods, longer disease durations, more deranged laboratory findings, and increased disease severity resulting in a higher mortality rate (17.6% vs 7.6%; $P = .020$) compared with the subjects with other drug-induced SCARs. There was no significant difference in age or mortality in drug reaction with eosinophilia and systemic symptoms (DRESS). Subjects with allopurinol-induced SJS/TEN were older and had shorter latent periods and a higher mortality

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Abbreviations used

AGEP- Acute generalized exanthematous pustulosis
 ALT- Alanine aminotransferase
 BUN- Blood urea nitrogen
 CI- Confidence interval
 DRESS- Drug reaction with eosinophilia and systemic symptoms
 ICU- Intensive care unit
 OR- Odds ratio
 ROC- Receiver operation characteristic
 SCAR- Severe cutaneous adverse reaction
 SJS- Stevens-Johnson syndrome
 TEN- Toxic epidermal necrolysis

rate (17.6% vs 3.7%; $P = .044$) than those with allopurinol-induced DRESS. In allopurinol-induced SJS/TEN, significant risk factors for death included chronic renal insufficiency, intensive care unit (ICU) admission, increased blood urea nitrogen levels on admission day, serum peak eosinophil counts, baseline and peak creatinine levels, baseline and peak alanine aminotransferase levels, and decreased lowest platelet counts. In allopurinol-induced DRESS, significant risk factors for death included ICU admission and increased glucose levels on admission day.

CONCLUSIONS: Allopurinol-induced SCARs have unique characteristics and poor prognoses with important predictive factors of death. © 2019 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:2739-49)

Key words: Allopurinol; Drug reactions with eosinophilia and systemic symptoms; Severe cutaneous adverse reaction; Stevens-Johnson syndrome; Toxic epidermal necrolysis

Allopurinol, a xanthine oxidase inhibitor, has been widely used to manage hyperuricemia and gout. Although alternative agents such as febuxostat and probenecid have been developed, allopurinol is still the mostly commonly prescribed hypouricemic drug.^{1,2} However, allopurinol can induce severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS). Although allopurinol-induced SCARs occur only in 0.05% to 0.5% of those exposed, SCARs can result in permanent multiorgan injuries, prolonged hospitalization, and death.³⁻⁵ The HLA-B*58:01 allele has been shown to be a critical risk factor for allopurinol-induced SCARs. HLA-B*58:01 screening is recommended in areas of high allele frequency to prevent allopurinol-induced SCARs.^{6,7} Renal insufficiency is considered to be another major risk factor for allopurinol-induced SCARs⁸ and is also a significant risk factor for poor prognosis.⁹ In addition, coadministration of diuretics and higher doses of allopurinol are considered to be risk factors for allopurinol-induced SCARs.^{10,11} The latter risk factor results in higher oxypurinol concentrations, implying that the drug concentration plays an important role. However, it is not clear whether other risk factors, apart from the drug concentration, are prognostically useful. It is also unclear whether allopurinol-induced SCAR patients have unique clinical characteristics or whether they have distinctive prognostic factors compared with individuals with other drug-induced SCARs.

The frequency of the HLA-B*58:01 allele is much higher (8% to 13%) in Korea than in western countries (1% to 6%).¹²⁻¹⁴ Although the incidence of allopurinol-induced SCARs is generally low (0.05% to 0.5%), the incidence of allopurinol-induced SCARs in chronic renal insufficiency in Korea is relatively high (2.0%), where all subjects have HLA-B*58:01, as reported in the previous study.¹³ Until now, HLA-B*58:01 screening before starting allopurinol is not routinely recommended in Korea. Allopurinol is also the most common cause of SCARs in Korea.¹⁵ In this study, we aimed to reveal the clinical characteristics and outcomes of allopurinol-induced SCARs compared with other drug-induced SCARs and identify the risk factors for death in allopurinol-induced SCARs in Korea using a retrospective, cross-sectional, multicenter registry study.

METHODS

Subjects and study design

This study was approved by the Institutional Review Board of Gangnam Severance Hospital (number: 3-2018-0289). We retrospectively reviewed the clinical characteristics and outcomes of 745 subjects who were enrolled in the Korean SCARs Registry from January 2010 to December 2015. The Korean SCARs Registry includes data obtained from 34 medical institutions throughout Korea. Data registered by allergy specialists after careful assessment of electronic medical records included culprit drugs, latent periods, clinical characteristics, and outcomes. The culprit drug was identified by the allergy specialists based on the World Health Organization-Uppsala Monitoring Center causality assessment system. Allopurinol-induced SCARs were defined by instances when allopurinol was assessed as a “certain” or “probable” culprit drug for the SCARs. Allopurinol was assessed to be the culprit drug in 106 subjects, whereas other culprit drugs induced SCARs in 639 subjects.

Definitions of SCARs, DRESS, SJS, TEN, and the SCORTEN score

SCARs are defined as severe cutaneous reactions caused by a drug, and they include DRESS, SJS, TEN, and acute generalized exanthematous pustulosis (AGEP). AGEP was excluded in this study as no allopurinol-induced SCAR patient had AGEP. We used diagnostic criteria suggested by the RegiSCAR study group.^{16,17} Patients with SJS and TEN presented with typical skin lesions including erythematous, macules, or flat atypical targets. The percentage of the total body surface area presenting skin detachment was used to classify SJS and TEN; if it was less than 10%, SJS was diagnosed, and if it was greater than 30%, TEN was diagnosed. If it was between 10% and 30%, the patient was diagnosed with SJS/TEN overlap syndrome. DRESS was diagnosed based on the presence of typical skin lesions, fever, enlarged lymph nodes, eosinophilia, and organ involvement as per RegiSCAR criteria, and those with 4 points (“probable”) or higher were included. Among subjects with SJS/TEN, some had systemic features such as lymphadenopathy and/or eosinophilia. However, as they did not meet the DRESS criteria, they were classified as SJS/TEN. Conversely, some subjects with DRESS had mucosal involvements such as oral mucositis, conjunctivitis, and/or anal mucositis, but as they did not meet SJS/TEN criteria, they were classified as DRESS. We used the original SCORTEN score (A severity-of-illness score for toxic epidermal necrolysis) suggested by Bastuji-Garin et al,¹⁸ which includes an assessment of age, heart rate, the presence of malignancy, total body surface area detached, serum urea level, bicarbonate level, and

glucose level. The score has been shown to predict mortality risk in SJS/TEN.

Statistical analyses

Only variables that did not exceed 30% of the missing values were included. Nonparametric methods were used for numerical data as the data did not follow a normal distribution. The median value (lower, 1/4; upper, 3/4) was described, whereas categorical data were expressed by percentage. The clinical characteristics of subjects were compared according to the culprit drug (allopurinol vs other drug), SCARs type (SJS/TEN vs DRESS), and outcome (recovery vs death). The Mann-Whitney *U* test, the χ^2 test, or Fisher's exact test was performed to compare the numerical and categorical data between the groups. Kaplan-Meier survival curves were drawn to compare the survival probability between the groups. Binary receiver operation characteristic (ROC) analysis and logistic regression analysis were used to find optimal variable cutoff values and their predictive power, respectively. We determined the odds ratio (OR) and 95% confidence interval (CI) using binary logistic regression. $P < .05$ was considered to be statistically significant. Statistical analyses were performed using SPSS version 16 (SPSS Inc., Chicago, Ill).

RESULTS

Clinical characteristics according to the culprit drugs in total SCAR subjects

Of the 745 SCAR subjects, allopurinol and other drugs were the culprit agents in 106 and 639 individuals, respectively. Other drugs included anticonvulsants (22.5%), β -lactam antibiotics (21.1%), and nonsteroidal anti-inflammatory drugs (10.3%) (Table I). Subjects with allopurinol-induced SCARs and other drug-induced SCARs exhibited different clinical characteristics (Table E1, available in this article's Online Repository at www.jaci-inpractice.org).

Clinical characteristics according to the culprit drugs in SJS/TEN

In SJS/TEN, allopurinol and other drugs were the culprit agents in 51 and 333 subjects, respectively (Table II). Subjects with allopurinol-induced SJS/TEN were significantly older (71 vs 54 years old; $P < .001$) and heavier than the subjects with other drug-induced SCARs. Subjects with allopurinol-induced SJS/TEN had a higher prevalence of underlying comorbidities and were more likely to be smokers or ex-smokers. All the subjects with rheumatologic disease in allopurinol-induced SJS/TEN had gout. Intensive care unit (ICU) admissions were also more likely in allopurinol-induced SJS/TEN than in others. The latent period (19 vs 8 days; $P = .003$), the period after symptoms before hospitalization (5 vs 3 days; $P < .001$), and the disease duration (23 vs 19 days; $P = .014$) were longer in allopurinol-induced SJS/TEN than those induced by other drugs, whereas serum eosinophil counts, baseline and peak creatinine levels, blood urea nitrogen (BUN) levels, and glucose levels were also significantly higher. Allopurinol-induced SJS/TEN led to more death compared with other drug-induced SJS/TEN (17.6% vs 7.6%; $P = .020$).

Clinical characteristics according to the culprit drugs in DRESS

In DRESS, allopurinol and other drugs were the culprit drugs in 55 and 306 subjects, respectively (Table III). Unlike patients with allopurinol-induced SJS/TEN, subjects with allopurinol-induced DRESS were not significantly older than others (56 vs 55 years

TABLE I. List of the culprit drugs in subjects with SCAR

	N (%)
Allopurinol	106
Other drugs	639 (100%)
Anticonvulsants	144 (22.5%)
β -Lactam antibiotics	135 (21.1%)
Nonsteroidal anti-inflammatory drugs	66 (10.3%)
Antituberculosis medication	49 (7.7%)
Glycopeptides	35 (5.5%)
Quinolone	29 (4.5%)
Acetaminophen	23 (3.6%)
Other antibiotics	17 (2.7%)
Dapsone	15 (2.3%)
Antineoplastic agents	14 (2.2%)
Antiglaucoma agents	11 (1.7%)
Macrolide	7 (1.1%)
Others	94 (14.7%)

SCAR, Severe cutaneous adverse reaction.

old; $P = .02$). Hypertension, chronic renal insufficiency, and rheumatologic disease were more prevalent in allopurinol-induced DRESS compared with other drugs. All the subjects with rheumatologic disease in allopurinol-induced DRESS had gout. DRESS developed more frequently during hospitalization for other causes in other drug-induced DRESS than it did in allopurinol-induced DRESS (26.5% vs 5.5%; $P = .002$). The latent period was significantly longer in allopurinol-induced DRESS than that induced by other drugs (29 vs 18 days; $P = .002$), and mucosal involvement was more frequent (35.0% vs 19.2%; $P = .026$). Serum eosinophil counts, creatinine levels, and BUN levels were significantly higher in allopurinol-induced DRESS compared with other drugs. Systemic steroid was prescribed more frequently for allopurinol-induced DRESS than for that induced by other drugs (94.3% vs 73.7%; $P < .001$). However, outcomes were not significantly different between the 2 groups.

Clinical characteristics and outcomes according to SCAR type in allopurinol-induced SCARs

In allopurinol-induced SCARs, subjects with SJS/TEN were significantly older than subjects with DRESS (71 vs 56 years old; $P = .023$) (Table IV), and they had a shorter latent period than subjects with DRESS (19 vs 29 days; $P = .012$). Subjects with SJS/TEN presented with smaller body surface area involvement, more frequent mucosal involvement, less frequent fever, and lower eosinophil counts than subjects with DRESS. SJS/TEN had a higher mortality rate than DRESS (17.6% vs 3.7%; $P = .044$). Among SJS/TEN, we classified them according to the combined DRESS features (Table E2, available in this article's Online Repository at www.jaci-inpractice.org). Subjects who had SJS/TEN with DRESS features had more prevalent chronic renal insufficiency, longer period after symptom until hospitalization, longer disease duration, higher peak eosinophil count, and elevated baseline BUN level, compared with those who had SJS/TEN without DRESS features.

Age distribution according to the culprit drugs and the type of SCAR

SJS/TEN was more common than DRESS in older people with allopurinol-induced SCARs ($P = .025$) (Figure 1, A). In allopurinol-induced SCARs, SJS/TEN was frequently observed in

TABLE II. Clinical characteristics and outcome according to culprit drugs in SJS/TEN

	Other drugs (N = 333)	Allopurinol (N = 51)	P
Age (y)	54.0 [33.0; 69.0]	71.0 [51.0; 77.0]	<.001
Sex (male)	156 (46.8%)	28 (54.9%)	.284
BMI	21.9 [19.5; 24.2]	22.8 [21.8; 25.2]	.010
Smoking (current:ex:never)	11.6%:6.1%:82.3%	14.0%:16.3%:69.8%	.049
Underlying disease			
Diabetes	39 (13.0%)	13 (27.7%)	.009
Hypertension	95 (31.5%)	34 (72.3%)	<.001
Liver disease	11 (3.7%)	5 (11.1%)	.028
Chronic renal insufficiency	15 (5.2%)	14 (31.1%)	<.001
Rheumatologic disease*	16 (5.9%)	9 (23.7%)	<.001
Malignancy	27 (9.2%)	1 (2.4%)	.106
Infection	83 (28.5%)	9 (20.5%)	.264
Allergic disease	35 (11.9%)	8 (19.0%)	.198
SCAR occurring during hospitalization due to other diseases	28 (8.4%)	4 (7.8%)	.526
Latent period (d)	8.0 [2.0; 22.0]	19.0 [3.0; 30.0]	.003
Period after symptom until hospitalization (d)	3.0 [2.0; 6.50]	5.0 [3.0; 15.0]	<.001
Disease duration	19.0 [13.0; 29.0]	23.0 [18.0; 35.0]	.014
ICU care	29 (0.9%)	10 (20.0%)	.018
Duration of ICU care (d)	12.5 [5.3–19.8]	8.0 [6.5–14.0]	.731
Involved skin area (%)	81.0 [41.5; 100.0]	72.0 [50.0; 99.5]	.792
Fever	168 (53.7%)	20 (41.7%)	.121
Highest eosinophil count (/μL)	312.9 [123.6; 835.0]	1012.3 [303.4; 1337.3]	<.001
Lowest platelet count (k/μL)	148.5 [96.5; 212.8]	131.0 [71.8; 205.3]	.383
Baseline creatinine (mg/dL)	0.7 [0.6; 1.0]	1.2 [0.9; 1.5]	<.001
Highest creatinine (mg/dL)	0.9 [0.7; 1.7]	2.1 [1.4; 3.3]	<.001
Creatinine increase > 30%	84 (46.7%)	27 (67.5%)	.017
Baseline ALT (IU/L)	23.0 [14.0; 40.0]	32.5 [18.0; 41.0]	.127
Highest ALT (IU/L)	82.0 [42.0; 163.3]	104.0 [56.5; 263.0]	.130
Heart rate at admission day (/min)	90.0 [77.0; 107.0]	89.0 [80.0; 99.0]	.647
Serum BUN at admission day (mg/dL)	14.7 [10.6; 21.8]	40.1 [23.0; 68.0]	<.001
Serum glucose at admission day (mg/dL)	120.0 [100.0; 146.0]	143.5 [107.5; 178.5]	.016
Treatment			
Intravenous immunoglobulin	85 (26.3%)	10 (19.8%)	.306
Systemic steroid	304 (93.3%)	50 (98.0%)	.154
Other immunosuppressant	15 (4.9%)	5 (10.9%)	.100
Outcome			
Death	25 (7.6%)	9 (17.6%)	.020

ALT, Alanine aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; ICU, intensive care unit; SCAR, severe cutaneous adverse reaction; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

Bold indicates statistical significance ($P < .05$).

All the values are presented as mean $\pm$ SD or n (%).

*Rheumatologic disease includes gout, systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis and other rheumatologic diseases.

subjects 70 to 79 years of age (31.4%); however, DRESS was frequently observed in subjects 50 to 59 years of age (29.1%). The age distribution was not significantly different between allopurinol-induced DRESS and other drug-induced DRESS (Figure 1, B). However, allopurinol-induced SJS/TEN was more prevalent in older people than that induced by other drugs (Figure 1, C).

Prognosis according to the SCAR type, sex, and age in allopurinol-induced SCARs

Allopurinol-induced SJS/TEN had a higher mortality rate compared with allopurinol-induced DRESS (17.6% vs 3.7%; $P = .004$) (Figure 2, A). In SJS/TEN, subjects with TEN (57.1%) and overlap syndrome (33.3%) had worse outcomes

than subjects with SJS (7.9%; $P = .020$) (Figure 2, B). There was no significant difference in mortality rates according to sex and age group (Figure 2, C and D).

Kaplan-Meier survival curve according to the culprit drugs and SCAR type

Survival probability was not significantly different between allopurinol-induced SCARs and SCARs induced by other drugs (Figure 3, A). However, allopurinol-induced SJS/TEN showed a significantly poorer survival rate compared with other drug-induced SJS/TEN ($P = .0165$) (Figure 3, B). However, survival rates were not significantly different in DRESS (Figure 3, C). TEN and overlap syndrome showed poorer survival compared with

TABLE III. Clinical characteristics and outcome according to culprit drugs in DRESS

	Other drugs (N = 306)	Allopurinol (N = 55)	P
Age (y)	55.0 [40.8; 68.0]	56.0 [48.0; 68.0]	.202
Sex (male)	147 (48.0%)	34 (61.8%)	.060
BMI	22.7 [20.5; 24.7]	23.9 [21.5; 25.7]	.041
Smoking (current:ex:never)	11.6%:11.6%:76.7%	19.1%:12.8%:68.1%	.333
Underlying disease			
Diabetes	48 (17.5%)	14 (26.4%)	.130
Hypertension	85 (30.6%)	36 (67.9%)	<.001
Liver disease	17 (6.3%)	3 (6.3%)	.990
Chronic renal insufficiency	15 (5.7%)	16 (32.7%)	<.001
Rheumatologic disease	13 (5.3%)	9 (20.5%)	<.001
Malignancy	32 (12.4%)	3 (6.3%)	.222
Infection	76 (28.7%)	10 (20.0%)	.206
Allergic disease	32 (11.9%)	3 (5.9%)	.210
SCAR occurring during hospitalization due to other diseases	81 (26.5%)	3 (5.5%)	.002
Latent period (d)	18.0[9.0; 32.5]	29.0 [19.0; 36.0]	.002
Period after symptom until hospitalization (d)	5.0 [2.0; 10.0]	7.0 [3.0; 13.0]	.087
Disease duration	20.0 [14.0; 30.0]	23.0 [16.5; 33.5]	.066
ICU care	17 (6.3%)	3 (6.1%)	.626
Duration of ICU care (d)	7.0 [4.0; 24.0]	10.0 [8.0; 12.0]	.616
Involved skin area (%)	99.0 [72.0; 99.0]	95.8 [85.5; 100.0]	.901
Mucosal involvement	41 (19.2%)	14 (35.0%)	.026
Fever	205 (68.3%)	32 (64.0%)	.544
Highest eosinophil count (/μL)	1117.0 [318.7; 2918.5]	1925.0 [690.0; 3725.0]	.030
Lowest platelet count (k/μL)	133.0 [82.0; 210.0]	136.0 [84.3; 207.3]	.327
Baseline creatinine (mg/dL)	0.8 [0.6; 1.0]	1.4 [0.9; 2.1]	<.001
Highest creatinine (mg/dL)	1.1 [0.8; 1.9]	2.9 [1.5; 4.9]	<.001
Creatinine increase > 30%	115 (62.2%)	37 (77.1%)	.053
Baseline ALT (IU/L)	25.0 [16.0; 40.0]	31.0 [22.0; 42.0]	.078
Highest ALT (IU/L)	151.0 [64.3; 350.0]	150.0 [71.0; 356.0]	.784
Heart rate at admission day (/min)	90.0 [80.0; 104.0]	88.0 [78.0; 100.0]	.287
Serum BUN at admission day (mg/mL)	13.7 [9.7; 21.0]	36.3 [22.0; 55.0]	<.001
Serum glucose at admission day (mg/mL)	117.0 [100.0; 140.0]	126.0 [98.0; 157.8]	.398
Treatment			
Intravenous immunoglobulin	23 (8.4%)	3 (5.9%)	.392
Systemic steroid	219 (73.7%)	50 (94.3%)	<.001
Other immunosuppressant	5 (1.8%)	2 (3.9%)	.283
Outcome			
Death	13 (4.3%)	2 (3.7%)	.602

DRESS, Drug reaction with eosinophilia and systemic symptoms; ALT, alanine aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; ICU, intensive care unit; SCAR, severe cutaneous adverse reaction.

Bold indicates statistical significance ($P < .05$).

All the values are presented as mean $\pm$ SD or n (%).

SJS and DRESS in allopurinol-induced SCARs ($P < .001$) (Figure 3, D).

Clinical characteristics according to death in allopurinol-induced SCARs

Significant risk factors for death in SJS/TEN were chronic renal insufficiency, ICU admission, low platelet counts, high creatinine levels, low baseline alanine aminotransferase (ALT) levels, and high baseline serum BUN levels (Table V). Even though there were only 2 deceased cases in DRESS, ICU care and high serum glucose levels were noted to be significant risk factors for death. Treatment was not a significant factor for death in either group.

Risk factors for death in allopurinol-induced SCARs

We sought significant risk factors and cutoff values using ROC curves to predict death in allopurinol-induced SCARs. Compared with DRESS, SJS/TEN is a significant risk factor for death (OR, 5.571; 95% CI, 1.142-27.190; $P = .034$) (Table E3, available in this article's Online Repository at www.jaci-inpractice.org). In SJS/TEN, TEN was a significant and important factor for death compared with overlap syndrome and SJS (OR, 10.400; 95% CI, 1.784-60.622; $P = .013$). ICU care (OR, 10.400) and chronic renal insufficiency (OR, 8.056) were also important risk factors for death. Significant risk factors for death in allopurinol-induced SJS/TEN included increased baseline serum BUN levels (>49 mg/dL) at day 1, increased peak eosinophil counts ($>1135/\mu\text{L}$), decreased

TABLE IV. Clinical characteristics and outcome according to SCAR type in allopurinol-induced SCARs

	SJS/TEN (N = 51)	DRESS (N = 55)	P
Age (y)	71.0 [51.0; 77.0]	56.0 [48.0; 68.0]	.023
Sex (male)	28 (54.9%)	34 (61.8%)	.600
BMI	22.8 [21.8; 25.2]	23.9 [21.6; 25.7]	.646
Latent period (d)	19.0 [3.0; 19.0]	29.0 [19.0; 36.0]	.012
Period after symptom until hospitalization (d)	5.0 [3.0; 15.0]	7.0 [3.0; 13.0]	.902
Disease duration	23.0 [18.0; 35.0]	23.0 [16.5; 33.5]	.935
ICU care	10 (20.0%)	3 (6.1%)	.081
Duration of ICU care (d)	7.5 [5.75; 14]	10 [8; 12]	.287
Involved skin area (%) [*]	72.0 [50.5; 99.0]	95.0 [85.5; 100.0]	.013
Mucosal involvement	38 (90.5%)	14 (35.0%)	<.001
Fever	20 (41.7%)	32 (64.0%)	.044
Lowest WBC count (/μL)	4500.0 [2670.0; 6740.0]	6070.0 [3990.0; 8490.0]	.061
Highest eosinophil count (/μL)	1012.5 [310.0; 1210.0]	1925.0 [741.0; 3371.0]	.019
Lowest platelet count (k/μL)	131.0 [74.0; 204.0]	136.0 [90.5; 202.5]	.672
Baseline creatinine (mg/dL)	1.2 [0.2; 1.4]	1.4 [0.9; 2.1]	.178
Highest creatinine (mg/dL)	2.1 [1.4; 3.3]	2.9 [1.5; 4.8]	.104
Creatinine increase > 30%	27 (67.5%)	37 (77.1%)	.444
Baseline ALT (IU/L)	32.5 [18.0; 41.0]	31.0 [22.0; 42.0]	.684
Highest ALT (IU/L)	104.0 [57.0; 246.0]	150.0 [72.5; 353.5]	.139
Heart rate at admission day (/min)	89.0 [80.00; 99.0]	88.0 [78.0; 100.0]	.814
Serum BUN at admission day (mg/mL)	40.0 [24.0; 65.0]	36.0 [22.0; 55.0]	.468
Serum glucose at admission day	143.5 [108.0; 178.0]	126.0 [98.0; 157.5]	.169
Treatment (mg/mL)			
Intravenous Immunoglobulin	10 (19.6%)	3 (5.9%)	.075
Systemic steroid	50 (98.0%)	50 (94.3%)	.638
Other immunosuppressant	5 (10.9%)	2 (3.9%)	.354
Outcome			
Death	9 (17.6%)	2 (3.7%)	.044

DRESS, Drug reaction with eosinophilia and systemic symptoms; ALT, alanine aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; ICU, intensive care unit; SCAR, severe cutaneous adverse reaction; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; WBC, white blood cell.

Bold indicates statistical significance ($P < .05$).

All the values are presented as mean $\pm$ SD or n (%).

^{*}The involved skin area (%) reflects the extent of skin detachment in SJS/TEN. As DRESS patients did not have skin detachment, it reflects the extent of the rash.

lowest platelet counts ($<113\text{k}/\mu\text{L}$), increased baseline creatinine levels ($>1.86\text{ mg/dL}$), increased peak creatinine levels ($>3.19\text{ mg/dL}$), low baseline ALT levels ($<25\text{ IU/L}$), and high peak ALT levels ($>280\text{ IU/L}$). In DRESS, 2 deceased patients were admitted to the ICU and had elevated serum BUN levels ($>62\text{ mg/dL}$) and elevated serum glucose levels ($>232\text{ mg/dL}$) on day 1 ($P = .003$, .040, and .001, respectively, in Fisher's exact test). However, none of the parameters included in the SCORTEN scale could predict death significantly (Table E4, available in this article's Online Repository at www.jaci-inpractice.org). We also found that the reliability of SCORTEN in predicting death was not significantly different between SJS/TEN with or without DRESS features (data not shown).

DISCUSSION

This is the first research study to reveal the unique clinical characteristics and prognosis of allopurinol-induced SCARs compared with other drug-induced SCARs, where the main strength of this study lies in the relatively high number of subjects enrolled from national multicenters. Patients with allopurinol-induced SCARs were older and had other underlying diseases. In addition, they presented with more deranged

laboratory findings and increased disease severity. This might be due to the prescription of allopurinol in gout and hyperuricemia, which frequently coexist with diabetes, hypertension, renal insufficiency, and rheumatologic disease in older subjects.^{19,20} We speculate that these distinct characteristics of allopurinol-induced SCARs (old age and high comorbidities) lead to poorer lab findings, higher disease scores, and worse clinical outcomes leading to death.

The latent period, the period between the onset of symptoms and hospitalization, and the disease duration were longer in allopurinol-induced SCARs compared with other drug-induced SCARs in this study. Shorter latent periods were also observed with antibiotics and analgesics compared with those observed with allopurinol in previous studies.^{21,22} Subjects may have been exposed to antibiotics and analgesics multiple times before the event, shortening the latent period for inducing T-cell activation and the development of hypersensitivity reactions. This speculation should be addressed through *in vitro* and *in vivo* studies. Because of the longer latent period in allopurinol-induced SCARs, unsuspecting clinicians may have taken longer to diagnose SCARs and stop administrations of allopurinol, resulting in a longer period between the onset of symptoms and hospitalization. Alternatively, as allopurinol-induced SCARs were less

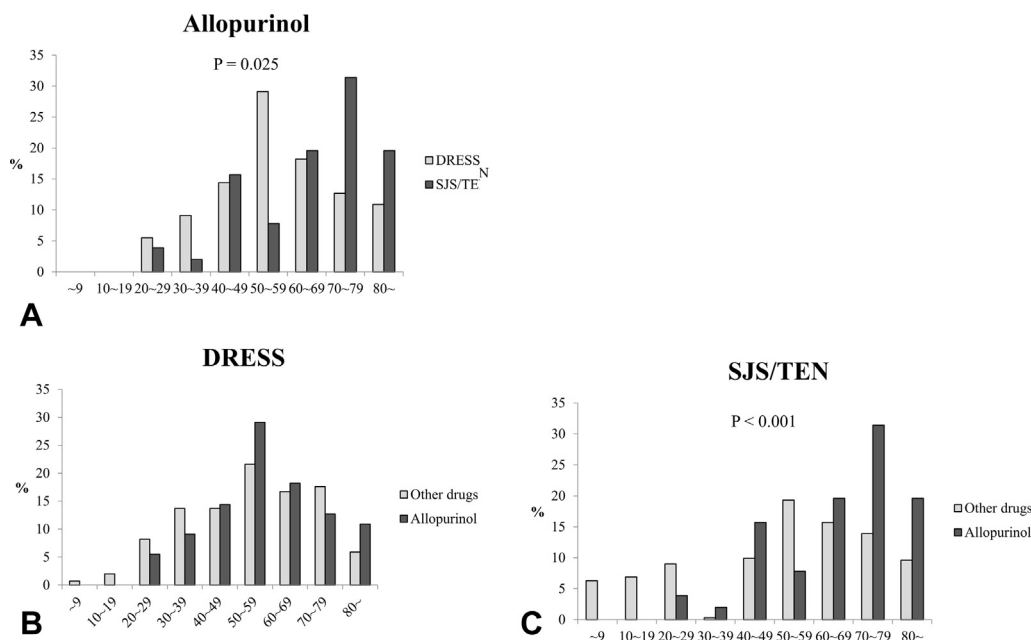


FIGURE 1. Age distribution according to the culprit drug and the type of SCAR. **A**, Prevalence of SJS/TEN and DRESS according to age in allopurinol-induced SCARs. **B**, Prevalence of allopurinol-induced and other drug-induced DRESS according to age. **C**, Prevalence of allopurinol-induced and other drug-induced SJS/TEN according to age. *DRESS*, Drug reaction with eosinophilia and systemic symptoms; *SCAR*, severe cutaneous adverse reaction; *SJS*, Stevens-Johnson syndrome; *TEN*, toxic epidermal necrolysis.

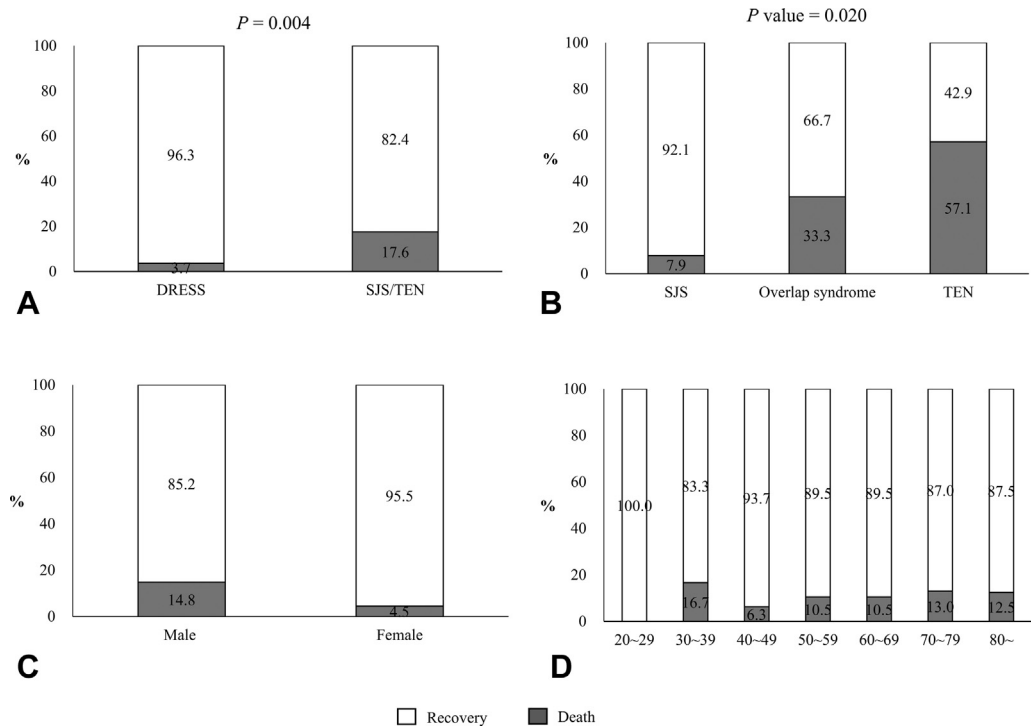


FIGURE 2. Prognosis in allopurinol-induced SCARs according to the SCAR type (**A**, **B**), sex (**C**), and age (**D**). *DRESS*, Drug reaction with eosinophilia and systemic symptoms; *SCAR*, severe cutaneous adverse reaction; *SJS*, Stevens-Johnson syndrome; *TEN*, toxic epidermal necrolysis.

common in hospitalized settings, it could have taken longer for patients to seek prompt medical attention and stop the drug. In either case, this relatively prolonged use of allopurinol without prompt withdrawal might be an important contributing factor to

the poor prognosis.²³ Finally, the age and general condition of subjects might affect the disease duration, as older subjects with higher comorbidities were likely to take longer to recover from the SCARs.

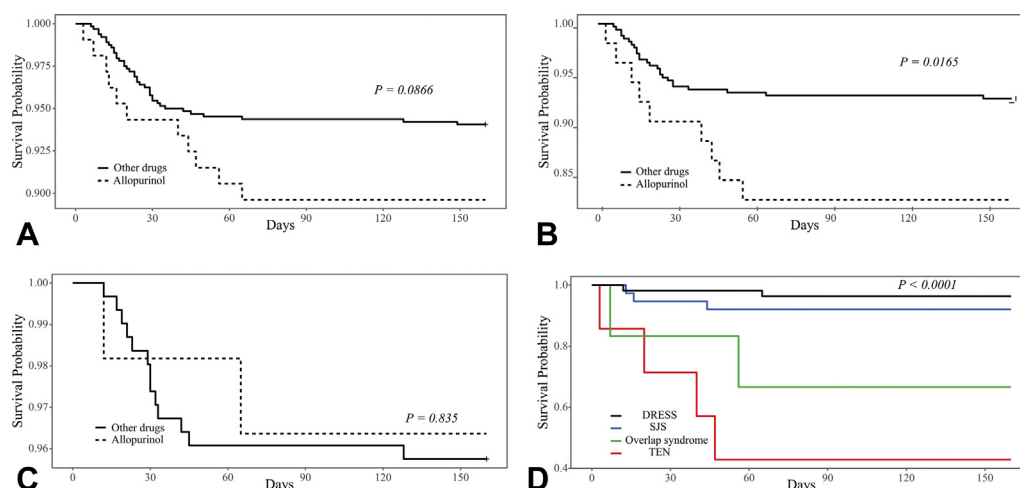


FIGURE 3. Kaplan-Meier survival curve according to the culprit drug in SCARs (A), SJS/TEN (B), DRESS (C), and SCAR type (D) in allopurinol-induced SCARs. DRESS, Drug reaction with eosinophilia and systemic symptoms; SCAR, severe cutaneous adverse reaction; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

SJS/TEN was more prevalent in the older age group compared with DRESS in this study. SJS/TEN and DRESS are both major forms of SCAR, but the underlying mechanisms are quite different.²⁴ In SJS/TEN, allopurinol interacts with the HLA-B*58:01 protein on keratinocytes and activates drug-specific CD8⁺ cytotoxic T cells.^{25,26} This results in accumulation of CD8⁺ T cells within the epidermis and the release of cytotoxic mediators.^{27,28} SJS/TEN then manifests as a painful, blistering skin rash leading to epidermal necrosis and detachment. In DRESS, CD8⁺ and CD4⁺ T cells are the key mediators, and these induce lymphatic infiltration of T cells into the dermis and the release of tumor necrosis factor- α and interferon- γ to systemic circulation.^{29,30} DRESS then presents rash, fever, internal organ involvement, and eosinophilia. Aging leads to loss of T-cell diversity and induces a predominant presence of CD8⁺ T cells, resulting in a reduction of the CD4:CD8 ratio.³¹ In addition, aging disrupts epidermal barrier function.³² Therefore, we suspect that older subjects can be more susceptible to SJS/TEN compared with DRESS, though further studies are needed to address this hypothesis.

This study shows that allopurinol-induced SJS/TEN present a higher peak eosinophil level compared with other drug-induced SJS/TEN. Among subjects with allopurinol-induced SJS/TEN, 47% had accompanying DRESS features. SJS/TEN with DRESS features have unique characteristics compared with others; however, severity and prognosis were not significantly different possibly due to the small number of subjects. In addition, allopurinol-induced DRESS accompanied mucosal involvement more frequently compared with other drug-induced DRESS. Nonetheless, these peculiar findings are interesting given that confirmed overlap cases are rare.^{33,34} On the other hand, HLA-B*58:01 is unique in that it is associated with both allopurinol-induced SJS/TEN and DRESS, whereas most other HLA-associated drug hypersensitivity reactions are limited to either SJS/TEN or DRESS, but not both. Therefore, we speculate that this unique association of HLA-B*58:01 with both allopurinol-induced SJS/TEN and DRESS explains the overlapping features.

We found important predictive factors of death in allopurinol-induced SCARs in this study. Chronic renal insufficiency was a

significant factor for death in allopurinol-induced SJS/TEN. Oxypurinol, the main metabolite of allopurinol, is excreted by the kidney, and renal impairment can cause a reduction in renal clearance of this metabolite.³⁵ An increased level of oxypurinol can enhance its concentration-related antigenic property that induces cytotoxic T-cell response and leads to poor prognosis of SJS/TEN.³⁶ Because of this interactive relationship, allopurinol is frequently used to treat hyperuricemia in renal impairment subjects but with the increased risk of SJS/TEN. Conversely, given the higher incidence of pre-existing renal impairment, these patients require unique modified cutoff values in creatinine and bicarbonate to predict death more accurately.

The SCORTEN scale is widely used to predict clinical prognosis of SJS/TEN, regardless of the culprit drugs. Many previous studies have shown good accuracy of SCORTEN in predicting the mortality rate in SJS/TEN.^{37,38} In addition, the accuracy is increased with serial analysis of SCORTEN.^{39,40} It contains multiple variables including age, malignancy, heart rate, BUN, detached BSA, serum bicarbonate, and serum glucose level.¹⁸ However, in this study, there was no significant predictive factor included in the SCORTEN scale for death in allopurinol-induced SJS/TEN. As SCORTEN is not known to predict mortality rate in DRESS, we speculated that the higher incidence of DRESS-like systemic features in allopurinol-induced SJS/TEN diminishes the predictive power of the SCORTEN scale. However, validity of SCORTEN was not significantly different in both SJS/TEN with DRESS features and SJS/TEN without DRESS in this study, but this could have been due to the small sample size. Suggested cutoff levels of parameters to predict death in allopurinol-induced SJS/TEN using ROC curves were quite different from the SCORTEN scale (as described below).

We suggested a higher cutoff value of BUN than that suggested by the SCORTEN scale. Fouchard et al¹⁸ developed the SCORTEN score using 165 subjects with a mortality rate of 26.5%. However, recent studies including a sufficient number of subjects, including this study, have shown a better prognosis (approximately 10%) because of improved insights on early diagnosis and treatment of SJS/TEN.^{41,42} Early detection of SJS/

TABLE V. Clinical characteristics according to death in allopurinol-induced SCARs

	SJS/TEN			DRESS		
	Recovery (N = 42)	Death (N = 9)	P	Recovery (N = 52)	Death (N = 2)	P
Age (y)	70.0 [51.0; 77.0]	71.0 [68.0; 79.0]	.630	56.0 [48.0; 70.0]	58.5 [58.0; 58.5]	.942
Sex (male)	21 (50.0%)	7 (77.8%)	.250	31 (59.6%)	2 (100.0%)	.369
BMI	23.0 [27.8; 25.2]	15.8 [11.1; 21.7]	.884	23.9 [21.4; 25.8]	23.2 [21.8; 24.6]	.804
Underlying disease						
Hypertension	27 (71.1%)	7 (77.8%)	1.000	34 (68.0%)	1 (50.0%)	1.000
Diabetes	13 (33.3%)	0 (0%)	.137	13 (26.0%)	1 (50.0%)	1.000
Chronic renal insufficiency	9 (23.7%)	5 (71.4%)	.039	16 (34.0%)	0 (0%)	.814
Allergic disease	7 (19.4%)	1 (16.7%)	1.000	3 (6.1%)	0 (0%)	.895
Latent period (d)	18.0 [3.0; 26.0]	30.0 [28.0; 31.0]	.094	28.5 [18.5; 35.0]	36.0 [35.0; 37.0]	.225
ICU care	5 (12.2%)	5 (55.6%)	.013	1 (2.2%)	2 (100.0%)	<.001
Duration of ICU care	9.0 [6.5; 14.0]	7.0 [3.5; 23.5]	.421	10.0 [10.0; 10.0]	12 [8; 12]	1.000
Involved skin area (%)	72.0 [49.5; 99.0]	90.0 [60.8; 99.5]	.472	94.5 [85.5; 100.0]	100.0 [100.0; 100.0]	.127
Fever	14 (35.0%)	6 (75.0%)	.089	31 (66.0%)	0 (0.0%)	.252
Lowest WBC count (/μL)	4600.0 [2850.0; 8020.0]	3015.0 [2260.0; 5225.0]	.137	6070.0 [4007.5; 8445.0]	8990.0 [1940.0; 8990.0]	.782
Highest eosinophil count (/μL)	900.0 [370.0; 1119.5]	1200.0 [740.0; 3038.0]	.239	1925.0 [690.0; 3725.0]	1633.5 [946.0; 2321.0]	.854
Lowest platelet count (k/μL)	162.0 [96.0; 209.0]	56.0 [22.5; 103.5]	.004	138.0 [96.8; 212.3]	64.0 [13.0; 64.0]	.131
Creatinine increase > 30%	21 (65.6%)	6 (75.0%)	.933	35 (76.1%)	2 (100.0%)	1.000
Baseline creatinine (mg/dL)	1.1 [0.9; 1.4]	2.0 [0.8; 3.1]	.155	1.4 [1.0; 2.1]	1.1 [0.9; 1.2]	.390
Highest creatinine (mg/dL)	1.8 [1.3; 2.3]	4.4 [3.4; 5.7]	<.001	2.9 [1.5; 4.7]	7.8 [4.8; 10.8]	.094
Baseline ALT (IU/L)	33.0 [21.0; 42.0]	14.0 [8.0; 21.5]	.006	31.0 [22.0; 42.0]	37.0 [30.0; 44.0]	.470
Highest ALT (IU/L)	82.5 [53.0; 186.0]	299.0 [116.5; 538.5]	.054	150.0 [74.0; 351.0]	432.0 [58.0; 806.0]	.895
Heart rate at admission day (/min)	90.0 [80.0; 101.5]	82.5 [75.0; 92.0]	.368	88.0 [77.5; 105.5]	81.0 [78.0; 81.0]	.445
Serum BUN at admission day (mg/mL)	35.0 [22.0; 51.5]	74.0 [54.0; 87.5]	.004	34.0 [22.0; 53.0]	83.0 [72.0; 94.0]	.065
Serum glucose at admission day (mg/mL)	6 (16.7%)	1 (16.7%)	1.000	122.0 [98.0; 150.0]	328.0 [245.0; 411.0]	.035
Treatment						
Intravenous immunoglobulin	7 (16.7%)	3 (33.3%)	.496	3 (6.2%)	0 (0%)	1.000
Systemic steroid	41 (97.6%)	9 (100%)	1.000	47 (94.0%)	2 (100%)	1.000
Other immunosuppressant	5 (13.2%)	0 (0%)	.644	2 (4.1%)	0 (0%)	1.000

DRESS, Drug reaction with eosinophilia and systemic symptoms; ALT, alanine aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; ICU, intensive care unit; SCAR, severe cutaneous adverse reaction; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; WBC, white blood cell.

Bold indicates statistical significance ($P < .05$).

All the values are presented as mean $\pm$ SD or n (%).

TEN, sufficient hydration, renal protective management, and early use of proper therapeutic agents might improve the clinical prognosis of SJS/TEN. In light of the recent therapeutic advances, we needed to permit higher BUN cutoff values to predict clinical outcomes of allopurinol-induced SJS/TEN. We recommend doubling previous BUN cutoff values to provide more powerful predictions of clinical outcomes, especially mortality, in allopurinol-induced SJS/TEN.

We also suggest additional important prognostic factors for allopurinol-induced SJS/TEN, which are not included in the SCORTEN scale. First, increased eosinophil levels were a significant prognostic factor for death. Eosinophilia does not frequently accompany SJS/TEN, so an increased eosinophil level may suggest combined drug-induced eosinophilia or DRESS-like features. This combined disease might lead to a poor prognosis. Second, increased baseline and peak creatinine levels were associated with increased mortality. Creatinine is one of the important markers reflecting kidney function, and an elevated creatinine level means renal insufficiency, which is a well-known

risk factor for death in allopurinol-induced SJS/TEN.⁴³ Third, a low baseline ALT level (<25 IU/L) was also a significant predictive factor for death. Decreased baseline ALT levels likely reflect decreased muscular mass or sarcopenia, and it has been shown to be associated with higher mortality for other conditions.⁴⁴ Sarcopenia might lead to reduced general conditions overcome SJS/TEN. Decreased platelet levels and increased peak ALT levels were additional prognostic factors, representing multiorgan failure. Decreased platelet levels can be due to either an infection or widespread inflammatory response from SJS/TEN resulting in platelet consumption or marrow suppression. In this context, decreased platelet levels likely reflect the severity of SJS/TEN or its complications. Increases in peak ALT levels mean hepatotoxicity, decreased function of the liver in detoxifying therapeutic drugs, initiation of multiorgan failure, and finally poor clinical prognosis including mortality.⁴⁵ All of these were significant factors in predicting mortality in allopurinol-induced SJS/TEN, though DRESS has fewer predictive factors for death.

Although SCARs have extremely low incidences, we were able to include a relatively high number of subjects with allopurinol-induced and other drug-induced SCARs from 34 national multicenters. However, the study has some limitations. First, this is a retrospective, uncontrolled, and unmatched cross-sectional registry study with potential selection bias and confounders. To minimize these, we included only those variables that did not exceed 30% of the missing values. In addition, given the low incidence of SCARs, it will be extremely difficult to perform prospective studies comparing allopurinol-induced SCARs with other drug-induced SCARs with comparable number of subjects. Secondly, data were missing for some subjects due to the retrospective design of the study. To account for this, we excluded variables missing more than 30% of the total values, such as dose of allopurinol, sequelae of the disease, detached, and compromised body surface area, and serum bicarbonate levels. Thirdly, we did not perform drug skin tests and/or challenges to confirm causality in all the cases. Drug challenges to confirm the culprit drug is contraindicated in SCARs, and intradermal tests are also considered to be relatively contraindicated although a recent study has highlighted that they may be safe in some cases.⁴⁶ Patch tests may be safely performed, but they generally have poor sensitivity, especially in allopurinol-induced SCAR, and have limited predictive power for searching culprit drug.⁴⁷ Instead, we used the World Health Organization-Uppsala Monitoring Center causality assessment system to define culprit drug with minimizing errors. Finally, it would be interesting to classify other drug-induced SCARs according to the culprit drugs in order to reveal other unique characteristics compared with allopurinol-induced SCARs. Further studies detailing the unique drug specific features of these SCARs should be performed.

In this retrospective, cross-sectional multicenter registry study, subjects with allopurinol-induced SCARs are older and have more comorbidities compared with other drug-induced SCARs. These subjects also present a longer latent period and disease duration, poorer lab findings, increased disease severity, and poorer clinical outcomes leading to death than other drug-induced SCARs. We confirmed that some parameters in SCORTEN have unique cutoff values to predict mortality in allopurinol-induced SCARs. In addition, we also revealed some important non-SCORTEN predictors of mortality specifically for allopurinol-induced SCARs, such as eosinophilia, baseline, and peak creatinine levels, low baseline ALT level (<25 IU/L), increased peak ALT level, and decreased platelet level. Clinicians should recognize the above unique characteristics of allopurinol-induced SCARs compared with other drug-induced SCARs. We suggest that the new cutoff values of SCORTEN predictors and the new non-SCORTEN predictors should be used to identify allopurinol-induced SCAR patients with poor prognosis, so that early intensive treatment can be implemented to prevent death.

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HJP analyzed and interpreted the data, drafted and revised the article, and approved the final version of the article for publication. H-RK generated and analyzed the data, contributed to the draft, revised the article, and approved the final version of the article for publication. J-WJ provided constructive criticism on the concept and design of this study as a corresponding author, interpreted the data, drafted and revised the article, and approved the final version of the article for publication.

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TABLE E1. Clinical characteristics according to culprit drugs

	Other drugs (N = 639)	Allopurinol (N = 106)	P
Age (y)	54.0 [37.0; 68.0]	62.0 [49.0; 76.0]	<.001
Sex (male)	303 (47.4%)	62 (58.5%)	.045
BMI (kg/m ²)	22.1 [19.9; 24.4]	23.3 [21.7; 25.3]	.001
Smoking (current:ex:never)	11.6%:8.8%:79.6%	16.7%:14.4%:68.9%	.070
Underlying disease			
Diabetes	87 (15.2%)	27 (27.0%)	.006
Hypertension	180 (31.0%)	70 (70.0%)	<.001
Liver disease	28 (4.9%)	8 (8.6%)	.232
Chronic renal insufficiency	30 (5.5%)	30 (31.9%)	<.001
Rheumatologic disease	29 (5.6%)	18 (22.0%)	<.001
Malignancy	59 (10.7%)	4 (4.4%)	.097
Infection	159 (28.6%)	19 (20.2%)	.119
Allergic disease	67 (11.9%)	11 (11.8%)	1.000
SCAR occurring during hospitalization due to other diseases	109 (17.1%)	7 (6.6%)	.009
Latent period (d)	13.0 [3.0; 28.0]	24.0 [13.0; 33.0]	<.001
Period after symptom until hospitalization (d)	4.0 [2.0; 8.0]	6.0 [3.0; 13.0]	<.001
Disease duration	20.0 [14.0; 30.0]	23.0 [17.25; 34.0]	.002
SCAR type			.437
SJS	229 (35.8%)	38 (35.8%)	
Overlap syndrome	75 (11.7%)	7 (6.6%)	
TEN	29 (4.5%)	6 (5.7%)	
DRESS	306 (47.9%)	55 (51.9%)	
ICU care	46 (7.8%)	13 (13.1%)	.117
Duration of ICU care (d)	10.0 [1.0; 109.0]	8.0 [1.0; 40.0]	.695
Outcome			
Death	38 (6.0%)	11 (10.5%)	.089

DRESS, Drug reaction with eosinophilia and systemic symptoms; ICU, intensive care unit; SCAR, severe cutaneous adverse reaction; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

Bold indicates statistical significance ($P < .05$).

All the values are presented as mean $\pm$ SD or n (%).

TABLE E2. Clinical characteristics and outcome according to SJS/TEN with or without DRESS features in allopurinol-induced SJS/TEN

	SJS/TEN without DRESS features (N = 27)	SJS/TEN with DRESS features (N = 24)	P
Age (y)	64.0 [43.0; 77.0]	72.5 [62.5; 77.8]	.157
Sex (male)	16 (59.3%)	12 (50.0%)	.352
BMI	22.5 [21.7; 24.2]	24.0 [22.0; 25.2]	.322
Smoking (current:ex:never)	16.7%:12.5%:70.8%	10.5%:21.1%:68.4%	.680
Underlying disease			
Diabetes	8 (33.3%)	5 (21.7%)	.374
Hypertension	16 (64.0%)	18 (81.8%)	.173
Liver disease	2 (8.3%)	3 (14.3%)	.435
Chronic renal insufficiency	4 (17.4%)	10 (45.5%)	.043
Rheumatologic disease*	5 (20.5%)	4 (22.2%)	.573
Malignancy	0 (0%)	1 (5.0%)	.476
Infection	4 (17.4%)	5 (23.8%)	.438
Allergic disease	3 (13.6%)	5 (25.0%)	.349
SCAR occurring during hospitalization due to other diseases	1 (3.7%)	3 (12.5%)	.261
Latent period (d)	18.0 [3.0; 24.5]	24.0 [5.3; 33.8]	.281
Period after symptom until hospitalization (d)	4.0 [2.8; 6.0]	15.0 [5.5; 26.5]	.001
Disease duration	20.0 [16.0; 23.0]	34.0 [24.0; 48.0]	<.001
ICU care	3 (11.1%)	7 (30.4%)	.089
Duration of ICU care (d)	0.0 [0.0; 0.0]	0.0 [0.0; 5.5]	.102
Involved skin area (%)	90.0 [51.0; 100.0]	72.0 [49.5; 95.5]	.322
Fever	9 (37.5%)	11 (45.8%)	.558
Highest eosinophil count (/μL)	178.0 [79.9; 326.7]	1119.5 [927.5; 2780.25]	<.001
Lowest platelet count (k/μL)	204.0 [55.5; 284.0]	111.0 [80.5; 172.0]	.129
Baseline creatinine (mg/dL)	1.0 [0.7; 1.3]	2.3 [1.5; 4.1]	.073
Highest creatinine (mg/dL)	1.9 [1.2; 2.3]	2.3 [1.5; 4.1]	.120
Creatinine increase >30%	12 (70.6%)	15 (65.2%)	.720
Baseline ALT (IU/L)	31.5 p[18.0; 41.0]	33.5 [15.3; 45.5]	.573
Highest ALT (IU/L)	67.5 [39.8; 245.5]	105.0 [58.0; 299.0]	.446
Heart rate at admission day (/min)	89.0 [80.0; 100.8]	87.0 [76.3; 101.0]	.950
Serum BUN at admission day (mg/dL)	35.3 [20.7; 46.2]	55.9 [29.8; 85.5]	.014
Serum glucose at admission day (mg/dL)	142.0 [108.0; 167.0]	147.0 [104.0; 180.0]	.899
Treatment			
Intravenous immunoglobulin	3 (11.1%)	7 (29.2%)	.102
Systemic steroid	26 (96.3%)	24 (100.0%)	.529
Other immunosuppressant	1 (4.0%)	4 (19.0%)	.124
Outcome			
Death	3 (11.1%)	6 (25.0%)	.176

ALT, Alanine aminotransferase; BUN, blood urea nitrogen; DRESS, drug reaction with eosinophilia and systemic symptoms; SCAR, severe cutaneous adverse reaction; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

Bold indicates statistical significance ($P < .05$).

All the values are presented as mean $\pm$ SD or n (%).

*Rheumatologic disease includes gout, systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis and other rheumatologic diseases.

TABLE E3. Risk factor for death using cutoff values through the ROC curve in allopurinol-induced SCARs

	Recovery	Death	<i>P</i>	OR	95% CI
In SCARs					
SJS/TEN vs DRESS	42 (44.7%)	9 (81.8%)	.034	5.571	1.142-27.190
In SJS/TEN					
TEN vs overlap and SJS	3 (7.1%)	4 (44.4%)	.013	10.400	1.784-60.622
ICU care	5 (12.2%)	5 (55.6%)	.010	9.000	1.793-45.187
Chronic renal insufficiency	9 (23.7%)	5 (71.4%)	.023	8.056	1.329-48.846
Serum BUN > 49 mg/dL at admission day	10 (25.6%)	7 (87.5%)	.008	20.300	2.216-186.00
Highest eosinophil count > 1135/ μ L	6 (22.2%)	5 (71.4%)	.023	8.750	1.343-57.005
Lowest platelet count < 113k/ μ L	9 (34.6%)	7 (87.5%)	.024	13.222	1.400-124.9007
Baseline creatinine > 1.86 mg/dL	1 (3.4%)	5 (62.5%)	.002	46.667	4.000-543.545
Highest creatinine > 3.19 mg/dL	3 (9.4%)	7 (87.5%)	.001	67.667	6.084-752631
Baseline ALT < 25 IU/L	11 (35.5%)	6 (85.7%)	.027	12.600	1.332-119.181
Highest ALT > 280 IU/L	5 (14.7%)	4 (57.1%)	.024	7.733	1.314-45.513
DRESS					
ICU care	1 (2.2%)	2 (100.0%)	.003	—	—
Serum BUN > 62 mg/dL at admission day	9 (17.6%)	2 (100.0%)	.040	—	—
Serum glucose > 232 mg/dL at admission day	3 (7.1%)	2 (100.0%)	.011	—	—

ALT, Alanine aminotransferase; BUN, blood urea nitrogen; CI, confidence interval; DRESS, drug reaction with eosinophilia and systemic symptoms; OR, odds ratio; ROC, receiver operation characteristic; SCAR, severe cutaneous adverse reaction; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

TABLE E4. SCORTEN scale on day 1 according to death in allopurinol-induced SJS/TEN

	Recovery (N = 42)	Death (N = 9)	<i>P</i>	OR	95% CI	<i>P</i>
Age $\geq$ 40	40 (95.2%)	8 (88.9%)	.449	1.190	0.138-10.299	.476
Associated malignancy	1 (2.8%)	0 (0%)	.857	—	—	1.000
Heart rate > 120/min	3 (7.5%)	1 (12.5%)	.530	1.593	0.172-14.746	.644
Serum BUN > 27 mg/dL	26 (66.7%)	8 (100%)	.058	—	—	.999
Serum glucose > 250 mg/dL	6 (16.7%)	1 (11.1%)	.743	2.556	0.447-14.626	1.000

Items of detached or compromised body surface area and serum bicarbonate were not expressed because of missing data.

BUN, Blood urea nitrogen; CI, confidence interval; OR, odds ratio; SCORTEN, A severity-of-illness score for toxic epidermal necrolysis; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.