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Acute pancreatic injuries: A complication of Stevens-Johnson syndrome/toxic epidermal necrolysis associated with cytotoxic immunocell activation

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Background: Complications involving internal organs are usually present in Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). However, pancreatic complications are rarely reported and studied.

Objective: To summarize clinical characteristics of SJS/TEN-associated acute pancreatic injuries and to investigate underlying inflammatory mechanisms.

Methods: Clinical records of 124 inpatients with SJS/TEN were reviewed. Serum levels of tumor necrosis factor α, interleukin (IL) 6, IL-18, IL-15, IL-12p70, and soluble CD56 were determined in 18 healthy donors and 17 patients with SJS/TEN, including 3 with acute pancreatic injuries.

Results: Acute pancreatic injury was diagnosed in 7.3% of patients (9/124) in the SJS/TEN cohort. Elevation of serum transaminase level and hypoalbuminemia occurred more frequently in patients with acute pancreatic injuries compared with those without pancreatic symptoms (P = .004 and <.001, respectively). Although acute pancreatic injury did not alter mortality rate of SJS/TEN, it was associated with longer hospitalization stays (P = .008). Within the serum cytokines whose levels were elevated in SJS/TEN, only IL-18 was found to be selectively increased in patients with acute pancreatic injuries compared with those without them (P = .03).

Limitations: Cohort was small.

Conclusion: Acute pancreatic injury is a gastrointestinal complication of SJS/TEN in which hepatotoxicity is more likely to occur. Overexpression of IL-18 might be involved in this unique entity. (J Am Acad Dermatol 2021;84:644-53.)

Key words: complication; cytokine storm; interleukin 18; liver dysfunction; pancreatitis; Stevens-Johnson syndrome; toxic epidermal necrolysis.

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INTRODUCTION

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are life-threatening skin diseases that are often triggered by a drug and are characterized by erythema, blisters, epidermal detachment, and mucosal erosions. These 2 diseases are considered to be the same condition that vary in the extent of epidermal detachment.[1] Although the diseases are rare, the mortality rate is less than 10% for SJS but is as high as 45% for TEN.[2] SJS/TEN is fatal not only because of its devastating skin barrier dysfunction but also because of frequent and broad visceral complications. The Toxic Epidermal Necrolysis—Specific Severity-of-Illness Score has listed visceral complications such as kidney dysfunction as risk factors to determine disease mortality.[3]

CAPSULE SUMMARY

- Stevens-Johnson syndrome and toxic epidermal necrolysis are well known to cause visceral complications. Pancreatic injuries are rarely reported.
- Acute pancreatic injures are identified as gastrointestinal complications associated with Stevens-Johnson syndrome and toxic epidermal necrolysis. This entity needs specific screening and monitoring during clinical practice.

So far, documented SJS/TEN-associated complications within internal organs include lungs (pneumonia), heart (myocarditis), kidneys (nephritis), liver (hepatitis), and the esophagus (esophageal stricture).[4] Among them, gastrointestinal involvement has the highest incidence rate and generally presents with transient liver enzyme increases and gastrointestinal tract epithelial necrosis.[5-8] However, pancreatic injuries related to SJS/TEN have been rarely reported.[9,10]

Accumulating evidence has shown that SJS/TEN is mediated by cytotoxic T lymphocytes and, to a lesser extent, natural killer cells.[11] Activation of cytotoxic T lymphocytes and natural killer cells results in release of cytotoxic molecules such as perforin, granzymes, and granulysin, which ultimately lead to widespread epithelial keratinocyte apoptosis and necrosis.[12] Despite advances in understanding skin pathology and immunology, the pathogenesis of damage to internal organs remains unclear. Our previous study has shown that tumor necrosis factor α and interleukin (IL) 6 may promote SJS/TEN-associated interstitial pneumonia[13]; however, the role cytokines play in other visceral involvements has not been fully studied. Given that the pancreas is histologically composed of epithelial cells, which can become targets of cytotoxic T lymphocytes and natural killer cells, we hypothesized that pancreatic injuries would occur in the context of SJS/TEN and cytokines related to cytotoxic T lymphocytes, and natural killer cells may contribute to its development.

In this study, we systemically reviewed records of 124 inpatients with SJS/TEN from January 2000 to June 2019 and found 9 patients with a diagnosis of acute pancreatic injuries. Herein, we present characteristics of this unique entity by analyzing data with respect to demography, clinical manifestations, laboratory features, and outcomes. Furthermore, we compared serum levels of multiple cytokines between patients with acute pancreatic injuries and nonpancreatitis patients. We found that the cytotoxic T lymphocyte—activating and natural killer cell—activating cytokine IL-18 underwent a significant increase in the setting of acute pancreatic injuries and thus might be a biomarker for this entity.

MATERIALS AND METHODS

Patients and diagnosis criteria

A total of 124 patients with SJS/TEN who were admitted to the First Affiliated Hospital, Sun Yat-sen University from January 2000 to June 2019 were identified according to the diagnostic criteria described by Bastuji-Garin et al,[14] in which SJS/TEN subtypes were mainly classified by the extent of epidermal detachment in addition to skin lesions (widespread erythematous or purpuric macules and flat atypical targets) and involvement of mucous membranes. SJS and SJS/TEN overlap were respectively defined as detachment of the body surface area below 10% and between 10% and 30%, whereas TEN was defined as detachment greater than 30% of body surface area.[14] All enrolled patients had clear medical records of drug administration before skin symptoms. We retrospectively documented their disease history, clinical manifestations, laboratory test results (including complete blood cell count), compressive metabolic panel, serum lipase and amylase activity, autoantibody levels, and imaging examination results, including transabdominal ultrasonography and abdominal computed tomographic scan.

For diagnosis of acute pancreatic injuries, the Atlanta classification standard was used.[15] The diagnosis of acute pancreatitis was made when at least 2 of the following 3 features were met: typical abdominal pain, biochemical evidence consistent with pancreatitis (serum level of lipase activity or amylase

Abbreviations used:

IL: interleukin
SJS: Stevens-Johnson syndrome
TEN: toxic epidermal necrolysis

activity 3-fold greater than the upper limit of normal), and characteristic findings of acute pancreatitis suggested by imaging tomography. Pancreatic hyperenzymemia was defined as an increase in pancreatic enzyme levels more than 3 times the upper limit of normal in the absence of symptoms and abdominal computed tomographic imaging of pancreatic diseases.[16]

Cytokine evaluation

In January 2017, we started a series of SJS/TEN-related scientific studies, which were approved by the ethics committee of the hospital. For cytokine tests, 17 patients with SJS/TEN, 3 with acute pancreatic injuries, were enrolled from December 2017 to June 2019 after consent was obtained from each individual. Simultaneously, 18 sex- and age-matched healthy controls were recruited (Supplemental Table I; available at https://data.mendeley.com/datasets/6vycp9yvnp/draft?a=00db49dc-1212-47e3-9596-dd5ac2e136d4). Peripheral blood (5 mL) was obtained from each of 17 patients during the acute stage before treatment, as well as from 18 controls. Serum specimens were suspended from clotted blood centrifuged at 4°C and 2,500 rpm for 10 minutes and then stored at −80°C until tested.

Serum samples were tested for 6 cytokines; namely, tumor necrosis factor α, IL-6, IL-18, IL-15, IL-12p70, and soluble CD56. Multiplex cytokine analysis kits were obtained from R&D Systems, and data were collected with Luminex 100 (Luminex, Austin, TX). Data analysis was performed with MILLIPLEX Analyst (version 5.1, EMD Millipore Corporation, Billerica, MA).

Statistical analysis

Data with normal distributions were described as mean ± standard deviation. For data not following a normal distribution, median (interquartile range) was used. Differences of incidence rate between every 2 groups were compared by Fisher's exact test. Differences of cytokine levels were assessed with the 2-tailed unpaired Student *t* test when they were normally distributed. For data that were not normally distributed, the Mann-Whitney-Wilcoxon nonparametric test was performed to detect significant differences. All tests were performed with GraphPad Prism (version 8.0, GraphPad Software, Inc). $P < .05$ was considered to indicate a statistically significant difference.

RESULTS

Description of patients

In the entire cohort, SJS, SJS/TEN overlap, and TEN were diagnosed in 91, 4, and 29 patients, respectively. Acute pancreatic injury was documented in 9 of these patients. Among them, 8 patients met the diagnosis of acute pancreatitis, whereas the other patient received a diagnosis of hyperamylasemia. Therefore, the morbidity rate of acute pancreatic injuries was 7.3%. Among the patients with acute pancreatic injuries, there were 3 with SJS, 1 with SJS/TEN overlap, and 5 with TEN (Fig 1, *A*). Accordingly, the acute pancreatic injury incidence rate was 3.3% (3/91) in SJS, 25.0% (1/4) in SJS/TEN overlap, and 17.2% (5/29) in TEN. The acute pancreatic injury morbidity rate in TEN was much higher compared with that in SJS ($P = .02$) (Fig 1, *B*).

Demography

The acute pancreatic injuries cohort consisted of 5 female patients and 4 male patients aged 12 to 69 years (median 31 years [interquartile range 19-56 years]). In the other 115 patients without pancreatic symptoms, the sex ratio of female:male was 1:1.05, and the ages ranged from 5 to 93 years (median 46 years [interquartile range 26-60 years]). The statistical analyses of sex distribution and age revealed no significant difference between the 2 groups ($P = .74$ and .15, respectively).

Clinical manifestations

Similar to classic acute pancreatitis, abdominal pain occurred in 7 patients (7/9; 77.8%) in the initial stage (from day 0 to 8) of SJS/TEN (Table I). However, common triggers in classic acute pancreatitis appear dispensable for SJS/TEN-associated acute pancreatic injuries because gallstone history and alcohol abuse were found in only 1 patient each (Table I). Neither of the incidence rates showed significant difference between acute pancreatic injuries and nonpancreatitis groups ($P = .20$ and .26, respectively) (Fig 2, *A* and *B*).

Accessory examinations

Liver dysfunction is reflected by increased serum transaminase levels and decreased albumin levels.[17] Transaminase level elevation and hypoalbuminemia were found in 77.8% (7/9) and 100% (9/9) of patients, respectively, with acute pancreatic injuries. Both were significantly higher than those in nonpancreatitis patients (31/115, 27.0%, $P = .004$ for

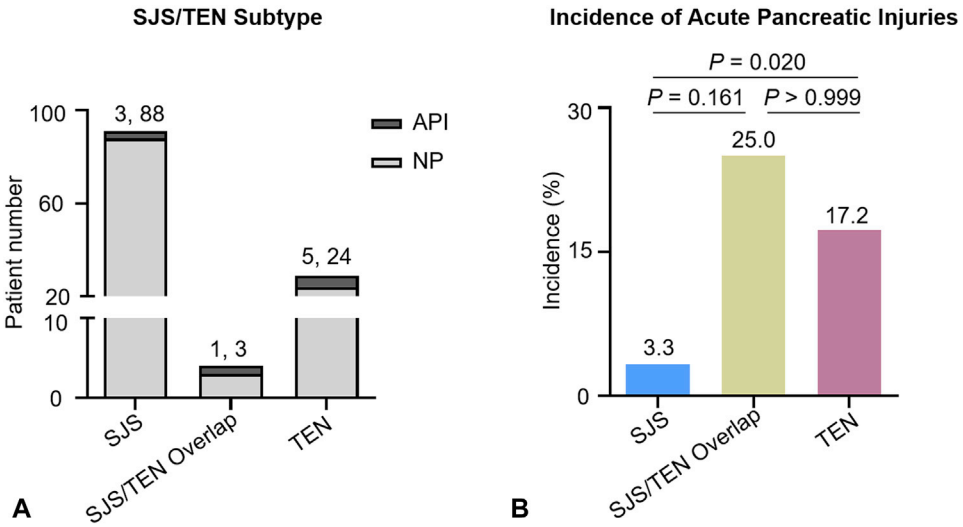

Fig 1. Incidence rate and distribution of acute pancreatic injuries in patients with Stevens-Johnson syndrome/toxic epidermal necrolysis. **A,** Acute pancreatic injuries and nonpancreatitis in the subtypes of Stevens-Johnson syndrome. Patient numbers are shown at the top of the bar. **B,** Incidence of acute pancreatic injuries in Stevens-Johnson syndrome patients, patients with Stevens-Johnson syndrome/toxic epidermal necrolysis overlap, and in the toxic epidermal necrolysis cohort. *P* values are determined by Fisher's exact test. *API*, Acute pancreatic injury; *NP*, nonpancreatitis; *SJS*, Stevens-Johnson syndrome; *TEN*, toxic epidermal necrolysis.

comparison of transaminase elevation; 42/115, 36.5%, $P < .001$ for hypoalbuminemia) (Fig 2, *C*). In contrast to liver dysfunction, no difference in the incidence of kidney dysfunction was observed ($P = .65$) (Fig 2, *D*). Results of autoantibody tests were available for 7 patients with acute pancreatic injuries and 56 in the nonpancreatitis cohort. The percentage of positive autoantibody results was 3 of 9 (33.3%) in patients with acute pancreatic injuries, whereas 15 patients (15/115; 13.0%) without pancreatic injuries exhibited positive serum autoantibody levels. The difference between the 2 groups was not statistically significant ($P = .12$) (Fig 2, *E*). According to the imaging examinations, pancreas abnormality presenting as diffuse enlargement of the pancreas was found in 4 patients (4/9; 44.4%). Detailed auxiliary test results are listed in Table II.

Treatment and prognosis

To control SJS/TEN, a combination of systemic corticosteroids and intravenous immunoglobulin therapy was administered. To treat pancreatic injuries, 7 patients with abdominal pain were given a short period of fasting, whereas the other 2 patients received a low-fat solid diet. Simultaneously, all 9 patients were given intravenous injection of proton-pump inhibitors and antisecretory agents. The therapeutics were effective and the survival rate for acute pancreatic injuries cohort was 100%. Although 3 of the 115 patients without pancreatic symptoms died because of SJS/TEN, no significant difference in mortality rate was found between the 2 groups ($P > .99$) (Fig 2, *F*). However, the hospitalization stay of patients with acute pancreatic injuries ranged from 9 to 53 days (average 26.3 ± 13.9 days), which was significantly longer than that of nonpancreatitis patients (average 14.9 ± 4.9 days) ($P = .008$) (Fig 2, *G*).

Cytokine profile

In patients who had serum cytokine tests, the SJS/TEN group exhibited elevated serum levels of tumor necrosis factor α, IL-6, IL-18, IL-15, and IL-12p70 compared with healthy controls (Supplemental Table II; available at https://data.mendeley.com/datasets/4jwjfc5gzv/draft?a=d83ff42c-96b1-45d1-ba85-cb801da61fda). Conversely, soluble CD56 levels were significantly lower in SJS/TEN group than those in heathy controls (Supplemental Table II). In the SJS/TEN cohort, we compared cytokine results between groups classified by the existence of pancreatic injuries (Supplemental Table I). IL-18 levels were significantly increased in the acute pancreatic injuries group (average $1.35 \pm 0.12 \times 10^3$ pg/mL) compared with the nonpancreatitis individuals (median 0.86×10^3 pg/mL [interquartile range $0.63\text{-}1.15 \times 10^3$ pg/mL], $P = .03$) (Fig 3, *C*). None of the other cytokines was significantly different between the 2 groups (Fig 3, *A*, *B*, *D*, and *F*).

Table I. Demographic and clinical details of patients with acute pancreatic injuries in the context of Stevens-Johnson syndrome/toxic epidermal necrolysis

Case	Diagnosis	Sex/age, years	Culprit drug	Biliary history	Alcohol abuse	Abdominal pain/interval* (days)	API	Hospitalization stay (days)	Treatment	Outcome
1†	SJS/TEN overlap	F/33	Nimesulide/ sulfonamides	No	No	No/NA	AP	17	Low-fat liquid diet, octreotide acetate, steroids and etanercept	Cured
2†	TEN	F/22	TCM	No	No	No/NA	Hyperamylasemia	40	Low-fat liquid diet, octreotide acetate, steroids, IVIG	Cured
3†	TEN	F/17	Uncertain	No	No	Yes/0	AP	53	Fasting, octreotide acetate, steroids, IVIG	Cured
4	TEN	M/52	Aminopyrine/ Cefoperazone	No	No	Yes/0	AP	18	Fasting, somatostatin, steroids	Cured
5	TEN	M/69	Allopurinol	Yes	No	Yes/8	AP	25	Fasting, somatostatin, steroids	Cured
6	TEN	F/59	Carbamazepine	No	No	Yes/7	AP	14	Fasting, octreotide acetate, steroids, IVIG	Cured
7	SJS	F/20	Cephalosporin	No	No	Yes/6	AP	31	Fasting, somatostatin, steroids	Cured
8	SJS	M/12	Acetaminophen/ kitasamycin	No	No	Yes/1	AP	30	Fasting, somatostatin, antibiotics, steroids	Chronic hyperamylasemia
9	SJS	M/31	Acetaminophen/ sulfonamides	No	Yes	Yes/1	AP	9	Fasting, octreotide acetate, steroids, IVIG	Cured

AP, Acute pancreatitis; *API*, acute pancreatic injuries; *F*, female patient; *IVIG*, intravenous immunoglobulin; *M*, male patient; *NA*, not available; *SJS*, Stevens-Johnson syndrome; *TCM*, traditional Chinese medicine; *TEN*, toxic epidermal necrolysis.

*Interval from rash to abdominal pain.

†Subjects underwent serum cytokine examination.

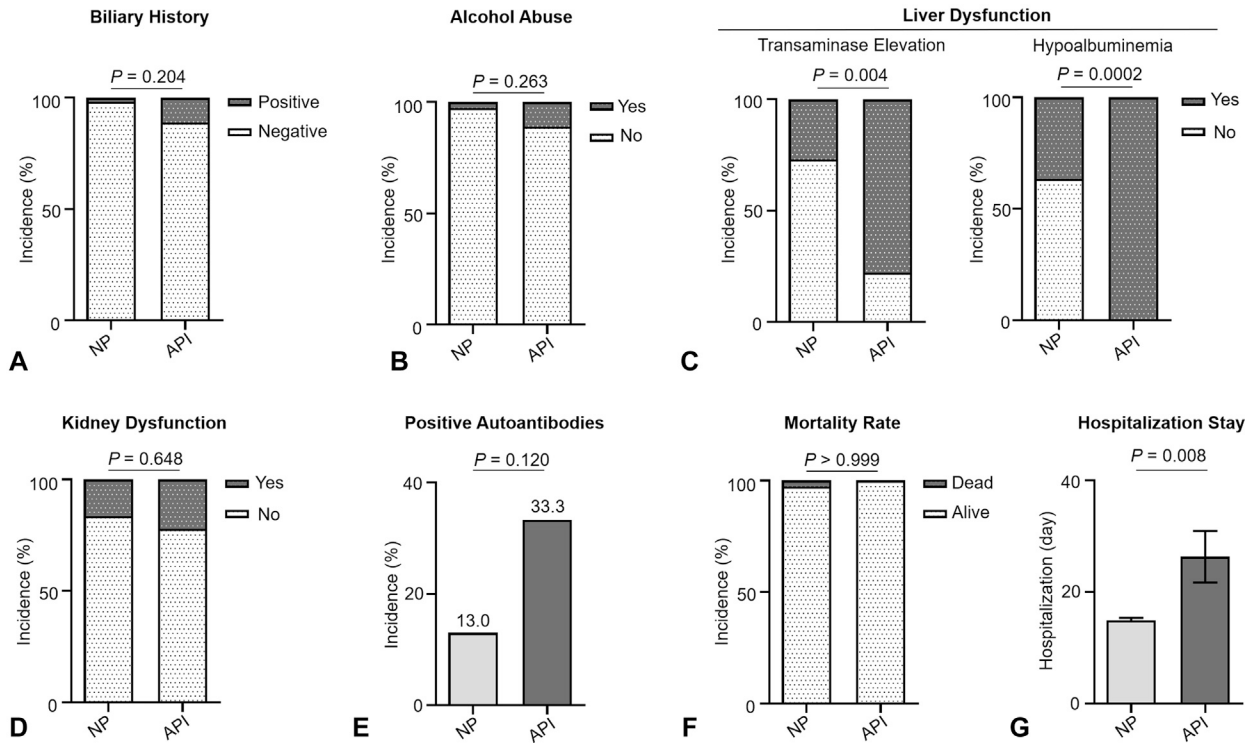

Fig 2. Comparison of disease triggers, laboratory test results, and prognosis between the acute pancreatic injuries group and nonpancreatitis group in the context of Stevens-Johnson syndrome/toxic epidermal necrolysis. No significant difference was revealed in biliary history **(A),** alcohol abuse **(B),** kidney dysfunction **(D),** positive autoantibody results **(E),** and mortality rate **(F)** between the 2 groups. **C,** A higher incidence rate of liver dysfunction was shown in patients with acute pancreatic injuries than in the nonpancreatitis cohort. **G,** The average hospitalization stay was much greater when patients developed acute pancreatic injuries. Fisher's exact test was applied for comparison **(A-F)**; the *P* value was determined by Student *t* test **(G).** *API*, Acute pancreatic injury; *NP*, nonpancreatitis.

DISCUSSION

To date, there are only a few publications that have reported SJS/TEN-associated acute pancreatic injuries. Dylewski et al[9] reported 4 pediatric patients with TEN who developed asymptomatic hyperamylasemia and hyperlipasemia among a cohort of 10 patients. A study conducted by Chatproedprai et al[18] disclosed 1 pancreatitis patient with SJS/TEN overlap in a reviewed database of 36 patients. Two other reports each described a single patient with pancreatic damage in the process of SJS/TEN.[19,20] In the current study, we found 9 patients with acute pancreatic injuries in a cohort of 124 individuals. These epidemiologic data indicate that acute pancreatic injuries should be identified as a complication of SJS/TEN, although the incidence rate may be variable among studies.

In the present acute pancreatic injuries cohort, we found that more patients developed liver dysfunction compared with those without pancreatic symptoms. Thus, we suspect that acute pancreatic injury is a gastrointestinal complication analogous to injuries in other gastrointestinal organs. Patients with acute pancreatic injuries did not show more evidence of kidney toxicity or positive autoantibody results, suggesting that SJS/TEN may have preference and subtypes regarding toxicity in diverse internal organs. Moreover, we found that patients with acute pancreatic injuries on average had longer hospitalization stays, implying increased financial and medical burdens. Therefore, screening and early monitoring for acute pancreatic injuries are required via abdominal symptom inquiry, physical examination of the abdomen, and routine laboratory tests for lipase and amylase activity.

It has been well recognized that classic acute pancreatitis is usually triggered by gallstones or alcohol abuse.[21] Occasionally, drugs such as acetaminophen and valproic acid also contribute to the etiology.[22] In the present cohort, neither biliary disorders nor alcohol abuse was present as a trigger for SJS/TEN-associated acute pancreatic injuries.

Table II. Auxiliary examination results of patients with Stevens-Johnson syndrome/toxic epidermal necrolysis accompanied by acute pancreatic injuries

	Pancreas function		Liver function				Kidney function	Autoantibody		
Case	Lipase (N = 23–300 U/L)	Amylase (N = 30–110 U/L)	ALT (N = 1–40 U/L)	AST (N = 1–37 U/L)	ALP (N = 0–110 U/L)	ALB (N = 35–50 g/L)	Cr (N = 56–115 μmol/L)	ANA	Anti-Ro/SSA antibodies	Abdominal CT or ultrasonographic scan
1	1429↑	503↑	725↑	730↑	403↑	31↓	58	(+)	(+)	Diffuse enlargement of the pancreas
2	2684↑	1386↑	148↑	73↑	191↑	27↓	40↓	(−)	(−)	NA
3	1930↑	400↑	1042↑	2503↑	503↑	24.2↓	56	(+)	(−)	NA
4	397↑	436↑	140↑	108↑	84	28↓	56	NA	NA	Unclear border of the pancreas, pancreatic duct dilatation
5	958↑	1028↑	58↑	38↑	65	23↓	446↑	NA	NA	Gallstones in the gallbladder
6	1294↑	235↑	94↑	83↑	503↑	29.6↓	53↓	(+)	(−)	No evidence of pancreatic disease
7	525↑	814↑	13	20	42	34↓	56	(−)	(−)	Diffuse enlargement of the pancreas, haziness in the peripancreatic fat
8	2098↑	533↑	87↑	52	182↑	23↓	112	(−)	NA	Diffuse enlargement of the pancreas
9	4603↑	630↑	89↑	140↑	120↑	31↓	973↑	(−)	(−)	No evidence of pancreatic disease

ALB, Albumin; *ALP*, alkaline phosphatase; *ALT*, alanine aminotransferase; *ANA*, antinuclear antibodies; *AST*, aspartate aminotransferase; *Cr*, creatinine; *CT*, computed tomography; *N*, normal range; *NA*, not available; +, positive; −, negative.

Additionally, the culprit drug spectrum is broader than the one that is regularly related to acute pancreatitis. Thus, we hypothesize that acute pancreatic injury in the context of SJS/TEN is more likely to be mediated by systemic inflammation than by common mechanical obstruction or dysfunction in pancreatic ducts.

Among the cytokines that we examined, IL-6 is commonly used in classic acute pancreatitis as an early marker to predict disease severity.[23] Some studies have shown that the assessment of serum IL-6 increases the accuracy of systemic inflammatory response syndrome in severe acute pancreatitis.[24-26] In an acute pancreatitis rat model, an increase of serum IL-6 precedes severe pancreatic edema and necrosis.[27] However, in our present study, the level of IL-6 did not show significant elevation in SJS/TEN patients with acute pancreatic injuries. This negative finding indicates that acute pancreatic injuries related to SJS/TEN may have a cytokine profile distinct from those in classic acute pancreatitis.

Previously, only 1 study reported that serum IL-18 levels were elevated in patients with classic acute pancreatitis and might aggravate liver injuries.[28] In an obese murine model, injection of IL-18 combined with IL-12 was sufficient to cause pancreatic necrolysis.[29] In another pancreatitis murine model, tumor necrosis factor α directly mediated protease activation and subsequent necrosis of pancreatic acinar cells.[30] In the present acute pancreatic injuries cohort, in addition to the significant elevation of serum IL-18 level, that of IL-12p70 and tumor necrosis factor α also exhibited an increasing trend. These results indicate that cytotoxic cytokine dysregulation might be a cause for acute pancreatic injuries in the setting of SJS/TEN. However, because of the small cohort size and the lack of pancreas histopathology, the precise role cytokines play in acute pancreatic injury mechanisms and whether they have distinct function in mediating other internal organ toxicities associated with SJS/TEN will be an interesting area of further inquiry.

Consistent with previous studies,[12,13,31,32] we found a universal elevation of levels of multiple cytokines in SJS/TEN. In addition to tumor necrosis factor α, IL-6, IL-15, IL-18, and IL-12, other cytokines we previously found had elevated levels in SJS/TEN included IL-10, interferon gamma, and interferon gamma–inducible chemokines CXCL9 and CXCL10.[33,34] Such phenomena led us to speculate that drug-induced SJS/TEN could be another form of "cytokine storm" syndrome,[35] the condition that is triggered by a wide variety of infections such as COVID-19[36,37] or noninfectious diseases such as graft-versus-host disease.[38] In contrast to the broad

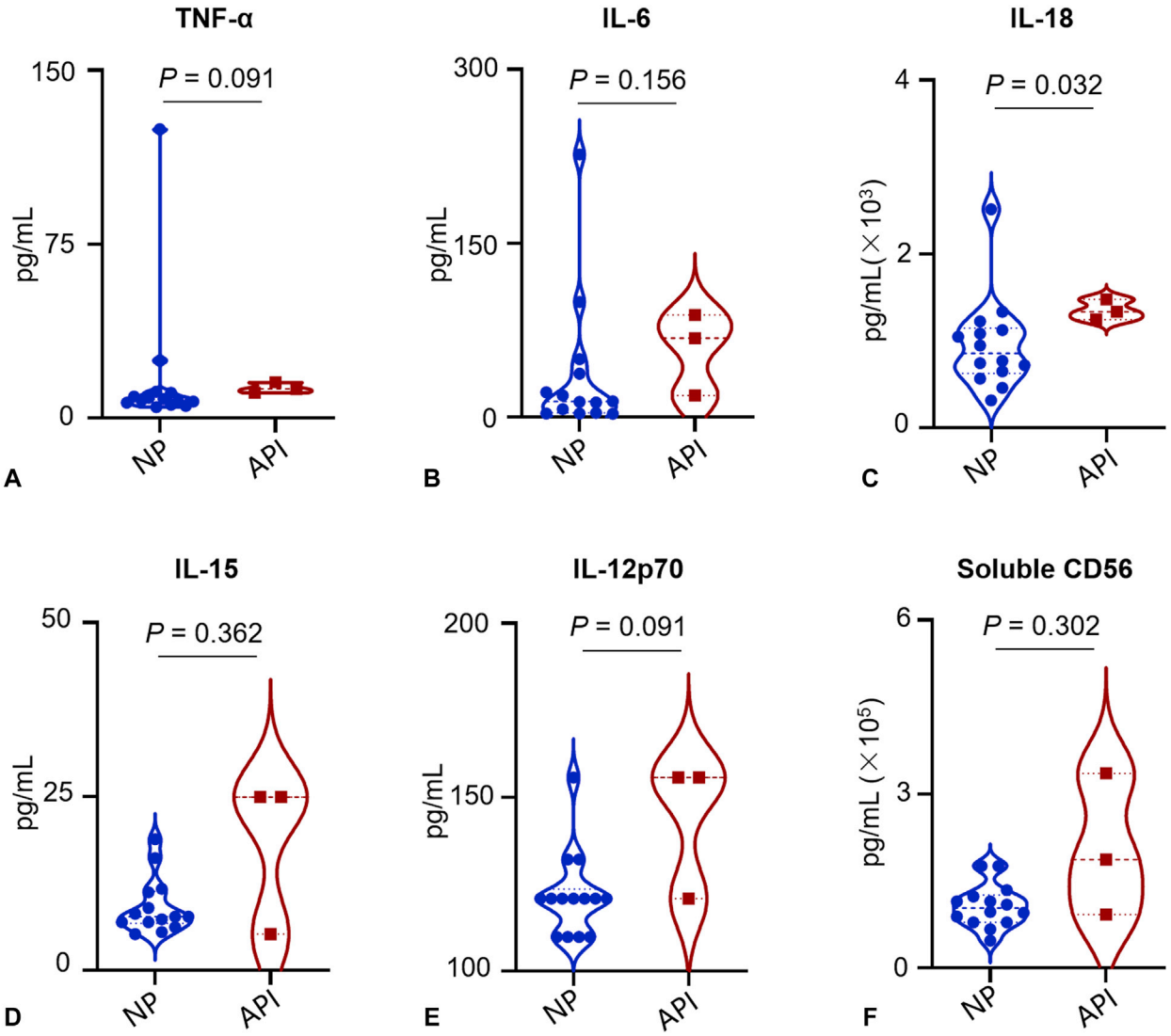

Fig 3. Comparison of serum cytokine levels. None of cytokines, including tumor necrosis factor α **(A),** IL-6 **(B),** IL-15 **(D),** IL-12p70 **(E),** and soluble CD56 **(F),** has significantly different levels between the nonpancreatitis group (n = 14) and acute pancreatic injuries group (n = 3). IL-18 levels were significantly increased in the acute pancreatic injuries group compared with those in nonpancreatitis patients **(C).** Symbols represent individuals. *P* values were determined by Mann-Whitney-Wilcoxon test. *API*, Acute pancreatic injury; *IL*, interleukin; *NP*, nonpancreatitis; *TNF*, tumor necrosis factor.

cytokine-level elevation, we found a significant decrease of serum-soluble CD56 in SJS/TEN. CD56 (also called neural cell adhesion molecule 1) is expressed on the surface of natural killer cells and some innate lymphoid cells and is a well-known phenotypic marker for natural killer cells.[39,40] Soluble CD56 can be released from membrane-bound CD56 by enzymatic cleavage of the extracellular domain.[41] A decreased expression of soluble CD56 in SJS/TEN serum may indicate more peripheral natural killer cells have migrated to skin lesions, which is consistent with the histopathologic findings from skin bulla.[11] Notwithstanding this, future studies will be required to clearly define cytokine diversity and their specific function in promoting the SJS/TEN process.

CONCLUSIONS

In conclusion, acute pancreatic injury is identified as a visceral complication associated with SJS/TEN. The specific monitoring may help reduce medical burdens. Given that more symptoms in internal organs are identified in SJS/TEN, specific subclassification will be needed. The precise role cytokines

play in internal organ injuries related to SJS/TEN is an outstanding question for further studies.

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