Drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms severity score: A useful tool for assessing disease severity and predicting fatal cytomegalovirus disease

Yoshiko Mizukawa, MD, PhD,[a] Kazuhisa Hirahara, MD, PhD,[a,b] Yoko Kano, MD, PhD,[a] and Tetsuo Shiohara, MD, PhD[a]
Tokyo and Saitama, Japan

Background: The prognosis of drug-induced hypersensitivity syndrome (DiHS)/drug reaction with eosinophilia and systemic symptoms (DRESS) is highly unpredictable. Severe complications, either related or unrelated to cytomegalovirus (CMV) reactivation, are a highly probable cause of death.

Objectives: The aim was to establish a scoring system for DiHS/DRESS that can be used to monitor severity, predict prognosis, and stratify the risk of developing CMV disease and complications.

Methods: A retrospective analysis of 55 patients with DiHS/DRESS was performed. A composite score was created using clinical data. DiHS/DRESS patients were also stratified into 3 groups based on the scores to predict the risk of CMV reactivation and complications.

Results: This scoring system made it possible to predict CMV disease and complications. Scores ≥4 were associated with the later development of CMV disease and complications, while no patients with scores <4 developed complications.

Limitations: This was a single-institution study with a relatively small patient cohort that lacked a validation cohort.

Conclusions: Our scoring system may be useful for predicting CMV-related complications, and early intervention with anti-CMV agents should be considered in patients with scores ≥4 or with evidence of CMV reactivation. (J Am Acad Dermatol 2019;80:670-8.)

Key words: CMV reactivation; disease severity; drug-induced hypersensitivity syndrome (DiHS)/drug reaction with eosinophilia and systemic symptoms (DRESS); prognosis; scoring system.

Patients with drug-induced hypersensitivity syndrome (DiHS)/drug reaction with eosinophilia and systemic symptoms (DRESS) may experience repeated exacerbations beyond the point where the causative drug would be expected to be eliminated from the body,[1-4] reflecting sequential reactivations of herpesviruses. In particular, cytomegalovirus (CMV) reactivation occurring 3 to

From the Departments of Dermatology at Kyorin University School of Medicine,[a] Shinkawa, Mitaka, Tokyo, and Saitama Medical University,[b] Saitama Medical Center, Kawagoe, Saitama, Japan.
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Reprint requests: Yoshiko Mizukawa, MD, Department of Dermatology, Kyorin University School of Medicine, Shinkawa, 6-20-2, Mitaka, Tokyo 181-8611, Japan. E-mail: ymizu@ks.kyorin-u.ac.jp.
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7 weeks after the onset of DiHS/DRESS may result in uncontrolled viral replication that can lead to fatal disease, including pneumonia, hepatitis, and gastroenteritis[5]; CMV disease could be regarded as the most important factor for the prognosis of these patients. In addition, complications such as myocarditis are more common than are generally realized.[6] Therefore, the severity of clinical symptoms at onset provides only a guide to prognosis. Various clinical symptoms and fatal complications that have traditionally been regarded as being either related or unrelated to severe drug eruptions or CMV reactivation may develop at various time points after onset, indicating difficulties to predict its prognosis.[1-3,6] Because these complications have been underrecognized and are often fatal if not promptly treated,[5-15] there is a clear need to identify effective parameters for assessing disease severity and predicting prognosis of the disease in the early stage.

CAPSULE SUMMARY

- The clinical course of drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms is unpredictable.
- We developed a scoring system to predict development of cytomegalovirus disease and complications. Using this scoring system, cytomegalovirus disease and complications could be preventable by prompt treatment with anticytomegalovirus agents.

Unfortunately, no previous studies have established a scoring system by which severity and treatment efficacy can be assessed and complications can be predicted at any time. Our aim in this study was to establish a scoring system for DiHS/DRESS that would be useful for monitoring severity and predicting patient prognosis, especially fatal complications. We hypothesized that DiHS/DRESS patients who later go on to develop fatal complications differ from those who can overcome these complications.

METHODS

Patients

Of patients admitted to our hospital for DiHS/DRESS between 1998 and 2016, 55 patients (22 men, 33 women) were selected if information sufficient for retrospective analyses was available from the medical records (ethics approval number 125-01). The mean age was 54.5 ± 20.0 years (range 14-88 years). Clinical symptoms of DiHS/DRESS developed 44.0 ± 6.9 days (range 10 days to 1 year) after starting the culprit drugs, and these drugs were withdrawn 6.8 ± 1.4 days (range 1-60 days) after the onset of clinical symptoms. Most patients were followed longitudinally for ≥1 year after clinical resolution. The diagnosis of DiHS/DRESS was made according to the criteria for DiHS (including atypical DiHS[16]) and DRESS (including probable and definite DRESS[17,18]) on clinical grounds. Inclusion criteria were as follows: age >12 years and only patients with no symptoms suggestive of DiHS/DRESS before drug exposure in the medical record.

Composite score

A composite score was created using demographic data, medical history, and clinical variables (Table I); this scoring was constructed based on previously published and unpublished data, including our own,[5,6,18-23] particularly on the effect of age and clinical variables on the development of CMV disease and complications.[5,24-29] A score of 1 was given whenever allopurinol was given, because allopurinol has been regarded as one of the factors involved in disease severity and renal insufficiency.[19,23] The severity score was determined routinely on at least 2 occasions, at the early stage (days 0-3 after the initial presentation, early score) and at a later stage (2-4 weeks after the initial presentation, late score).

Various other parameters, as shown in Table I, were graded from −1 to 3 to measure disease severity. The scores obtained at any time were compared with the early score to assess whether patients had progressive disease or were resolving.

All patients analyzed were CMV immunoglobulin G−positive. CMV reactivation was defined as ≥20 genome copies in 10^6 peripheral leukocytes or the detection of CMV-C10/11 antigenemia.[30] CMV disease was defined as having symptoms consistent with an infection and an inflammatory condition, temporally related to CMV reactivation, as previously described.[27] In contrast, complications were defined as severe clinical symptoms, such as pneumonia, peritonitis, and intestinal bleeding, either temporally or clinically related or unrelated to CMV reactivation. Complications were divided into 2 types, as previously indicated: early-onset (≤2 weeks after the initial presentation) and late-onset (>2 weeks after the initial presentation).[6] Most early-onset complications were regarded as comorbidities; most late-onset complications included myocarditis, gastrointestinal bleeding, and pneumonia, which could have generally been related to treatment.

The composite scores obtained were compared between CMV^+ cases and CMV^- cases with the

Table I. Composite scores for evaluating the severity of drug-induced hypersensitivity syndrome and drug reaction with eosinophilia and systemic symptoms and predicting the disease outcomes

Parameters	Grade/extent	Score
Fixed		
Age, y	≤40/41-74/≥75	−1/0/2
Duration of drug exposure after onset, days	0-6/≥7	0/1
Allopurinol exposure	Yes	1
Variable		
Pulsed prednisone*	Yes	2
Skin involvement		
Erythema, % BSA	<70/≥70/erythroderma	0/1/2
Erosion, % BSA	<10/10-29/≥30	0/1/3
Fever ≥38.5°C, days duration	0 or 1/2-6/≥7	0/1/2
Appetite loss (≤70% of regular food intake), days	0-4/≥5	0/1
Renal dysfunction (creatinine), mg/dL	<1.0/1.0-2.0/≥2.1 or HD	0/1/3
Liver dysfunction (ALT), IU/L	<400/400-1000/>1000	0/1/2
C-reactive protein, mg/dL	≤2/<2-<10/≥10-<15/≥15	−1/0/1/2

Each variable parameter was determined at early (days 0-3 after the initial presentation) and later times (2-4 weeks after the initial presentation), and on an as-needed basis.
ALT, Alanine aminotransferase; *BSA*, body surface area; *HD*, hemodialysis.
*Intravenous methylprednisone use ≥500 mg/day for 3 days.

Mann-Whitney U test (Table II). Receiver operator characteristic curves were used to test the performance of the composite score to predict CMV reactivation in DiHS/DRESS cases.

RESULTS

Early and late scores

Early scores usually represented the severity of the disease before treatment. In contrast, because approximately half of the patients received systemic corticosteroids, late scores represented the severity of the disease after starting corticosteroid and non-corticosteroid treatment.

Of the 55 patients investigated for the presence of CMV in sequential blood samples by polymerase chain reaction (PCR) or antigenemia assay, 44 remained quantitatively CMV^- throughout the period of surveillance. In CMV^+ cases, CMV DNA or antigenemia was initially detected at 27.2 days (range 16-45 days) after the initial presentation. CMV^+ DiHS/DRESS cases were significantly older and had more complications associated with a fatal course (Table II). CMV^+ cases were found to run a more severe and protracted course, as evidenced by longer periods of hospitalization; CMV^+ cases had a longer average hospital length of stay (56.9 ± 6.1 vs 25.3 ± 1.9 days, $P < .01$). There was no significant difference in the DRESS score[18] between them (data not shown). Among variable laboratory parameters, C-reactive protein levels at the initial presentation were significantly linked to later development of CMV reactivation (Supplemental Table I; available at http://www.jaad.org). Total doses of corticosteroids used until 8 weeks after initial presentation were higher in CMV^+ than CMV^- cases (Table II), although there was no significant difference. Most importantly, either early or late scores were significantly higher in CMV^+ than CMV^- cases (Table II), even when an elderly population ≥60 years of age and corticosteroid-treated cases after initial presentation were analyzed (data not shown).

CMV-related and -unrelated complications

Five of 11 CMV^+ patients who were quantitatively CMV PCR- or antigenemia-positive developed CMV disease or complications, while the remaining 6 patients, who were quantitatively CMV PCR- or antigenemia-positive, had no evidence of CMV disease and complications at any time (Table III). None of the 44 CMV^- patients developed any late-onset complications. CMV disease such as enterocolitis or complications developed immediately after the detection of CMV reactivation (mean 33.2 ± 6.2 days after the initial presentation) in all cases, usually 2 to 28 days after the detection of CMV reactivation (mean 10.0 ± 4.8 days). CMV viral loads were usually determined once every 2 weeks before, during ganciclovir (GCV) or valganciclovir (VGCV) therapy, and after cessation of anti-CMV therapy. Anti-CMV therapy was initiated after positive PCR or antigenemia results were obtained and was continued until negative PCR or antigenemia results were obtained. Treatment delay defined as an interval of ≥3 days from the first positive PCR or

Table II. Demographic and clinical characteristics of patients with CMV^+ and CMV^- drug-induced hypersensitivity syndrome and drug reaction with eosinophilia and systemic symptoms

	CMV^+ (n = 11)	CMV^- (n = 44)
Age, y, mean ± SEM	73.3 ± 3.4*	49.8 ± 2.9
Gender, M:F	7:4	16:28
Underlying disease (n)	Arrhythmia (1), brain tumor (2), bullous disease (1), cerebrovascular disease (1), dementia (1), epilepsy (2), Guillain–Barre syndrome (1), and hyperuricemia (3)	Brain tumor (1), cerebrovascular disease (2), epilepsy (12), fibromyalgia (1), hyperuricemia (7), neuralgia (3), psychological illness (17), and restless legs syndrome (1)
Causative drug (n)	Allopurinol (2), carbamazepine (5), dapsone (1), mexiletine (1), phenytoin (1), and trimethoprim/sulfamethoxazole (1)	Allopurinol (5), carbamazepine (27), lamotrigine (9), and phenytoin (3)
Early score, median (IQR)	6 (4-7)*	2 (1-4)
Late score, median (IQR)	3 (1-5)*	−1 (−2 to 0)
Duration of causative drug exposure before onset, mean ± SEM	42.9 ± 8.1 days	44.3 ± 8.1 days
Hospitalization period, mean ± SEM (range)	56.9 ± 6.1 days* (28-81 days)	25.3 ± 1.9 days (6-54 days)
Total doses of systemic corticosteroids before initial presentation, mean ± SEM (range) [n]†‡	673.3 ± 600.8 mg (75-1875 mg) [3]	120.3 ± 64.5 mg (7.5-690 mg) [10]
Starting doses of systemic corticosteroids after initial presentation, mean ± SEM (range) [n]‡	54.3 ± 4.8 mg (40-80 mg) [9]*	45.5 ± 5.1 mg (10-70 mg) [11]
Total doses of systemic corticosteroids until 8 weeks after initial presentation, mean ± SEM (range) [n]‡§	1928.9 ± 127.0 mg (1290-2470 mg) [9]*	1729.1 ± 232.1 mg (260-3200 mg) [11]
No. of cases with CMV disease/complications‡	5*	0
Mortality rate (no. of deaths)‡	27.3% (3)*	0% (0)

CMV, Cytomegalovirus; *CRF*, chronic renal failure.
*$P < .01$.
†No. of cases treated with corticosteroid before presentation.
‡Fisher's exact test used.
§No. of cases undergoing corticosteroid therapy at 8 weeks.

antigenemia result until the initiation of antiviral therapy was associated with the development of CMV disease or complications. The interval was longer in patients with complications than in those without complications (10.3 ± 6.1 vs 2.2 ± −0.2 days, $P = .08$). In case 5, CMV disease or complications developed 2 days after cessation of anti-CMV therapy. In cases 2 and 4, VGCV or GCV was started after the development of complications. All but case 1 received GCV or VGCV 2 to 28 days after the detection of CMV reactivation. Fatal outcomes were found exclusively in CMV^+ cases, especially those in whom GCV was initiated ≥3 days after the detection of CMV reactivation, while most cases in whom GCV or VGCV was started within 2 days after detection recovered fully, indicating a great need for starting GCV or VGCV immediately. Importantly, all cases who later developed serious complications, such as pneumonia and intestinal bleeding, had CMV reactivation 10.0 ± 4.8 days before onset of the complications.

We next asked whether we could identify patients who were at a greater risk of developing CMV disease and complications by using the composite score. Early or late scores ≥4 were associated with the later development of CMV disease and complications (Table III). Receiver operator characteristic curves confirmed that this composite score had the

Table III. Demographic and clinical characteristics of cytomegalovirus DNA$^+$ cases with or without complications

Case no., age, y/sex	Causative drug	Underlying disease(s)	Score early	Score late	CMV, C10/11* or DNA†	Time to CMV reactivation (factors thought to be the trigger)	Complications (day of detection)/outcome	Time to initiation of anti-CMV therapy after detection of CMV	Duration of anti-CMV therapy (anti-CMV agents)
1, 88/F	Allopurinol	Hyperuricemia	4	3	ND, 4.4 × 10	28 days (unknown)	Pneumonia (day 32)/death	N/A	N/A
2, 79/M	Carbamazepine/ allopurinol	Guillain—Barre syndrome/ hyperuricemia	11	6	5/4, ND	29 days (2 days after tapering systemic corticosteroids)	Peritonitis (day 31)/death	3 days	8 days (VGCV)
3, 81/M	Allopurinol	Hyperuricemia	8	5	4/2, ND	24 days (1 day after discontinuation of IVIG)	Intestinal bleeding (day 28)/recovery	8 days	24 days (GCV)
4, 74/M	Mexiletine	Arrhythmia	4	3	149/112, 3.7 × 10	16 days (3 days after tapering systemic corticosteroids)	Intestinal bleeding (day 44)/death	28 days	22 days (GCV + IVIG)
5, 48/M	TMP/SMX	Brain tumor	6	1	17/18, ND	19 days/31 days (2 days after tapering systemic corticosteroids/2 days after discontinuation of VGCV)‡	Intestinal bleeding (day 31)/recovery	2 days/2 days	8 + 15 days‡ (VGCV)
6, 67/F	Carbamazepine	Epilepsy	1	6	7/3, ND	45 days (10 days after tapering systemic corticosteroids)	No/recovery	2 days	15 days (VGCV)
7, 83/F	Carbamazepine	Dementia	6	3	1/2, ND	26 days (10 days after tapering systemic corticosteroids)	No/recovery	2 days	8 days (VGCV)
8, 80/F	Phenytoin	Epilepsy	7	1	0/1, 2.0 × 10	25 days (1 day after tapering systemic corticosteroids)	No/recovery	2 days	21 days (VGCV)
9,§ 63/M	Carbamazepine	Brain tumor	4	5	ND, 9.0 × 10	25 days (7 days after tapering systemic corticosteroids)	No/recovery	N/A	N/A
10, 73/M	Carbamazepine	Cerebrovascular disease	7	0	2/1, ND	35 days (15 days after tapering systemic corticosteroids)	No/recovery	3 days	8 days (VGCV)
11, 70/M	Dapsone	Bullous disease	5	0	4/2, ND	27 days (6 days after tapering systemic corticosteroids)	No/recovery	2 days	18 days (VGCV)

Cases 1-5 indicate those with complications, either CMV-related or CMV-unrelated drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms.
CMV, Cytomegalovirus; *F*, female; *GCV*, ganciclovir; *IVIG*, intravenous immunoglobulin; *M*, male; *N/A*, not applicable; *ND*, not done; *TMP/SMX*, trimethoprim/sulfamethoxazole; *VGCV*, valganciclovir.
*Data on the first positive of antigenemia (no. of CMV$^+$ cells/slide).
†Data on the first positive polymerase chain reaction study (≥20 genome copies in 10^6 peripheral leukocytes).
‡VGCV was administered from day 21 to day 28 (for 8 days) 2 days after detection of CMV reactivation, and from day 33 to day 47 (for 15 days), 2 days after intestinal bleeding, respectively.
§Pulsed prednisone used before the initial presentation.

Table IV. Risk stratification of drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms cases based on the early score

	Mild (1>) (n = 5)	Moderate (1-3) (n = 23)	Severe (4≤) (n = 27)
No. of CMV^+ cases[§]	0	1*	10 *
Late score, median (IQR)	−2 (−2 to −1.5)	−1 (−1 to 0)	1 (0-5)[†]
No. of cases with CMV disease/complications[§]	0	0	5[†]
Mortality rate (no. of dead patients)[§]	0% (0)	0% (0)	11.5% (3)
Hospitalization period, days, mean ± SEM (range)	16.2 ± 3.7 (9-27)	23.2 ± 2.4 (6-65)	41.7 ± 3.8[†] (14-81)
Total doses of systemic corticosteroids until 8 weeks after initial presentation, mean ± SEM (range) [no. of cases][§‖]	0 mg (0 mg) [0]	1459.2 ± 247.8 mg* (260-2170 mg) [6]	1973.2 ± 154.6 mg* (620-3200 mg) [14]
WBC (cells/μL), mean ± SEM	5740.0 ± 1059.1	8708.7 ± 1521.8	10,388.9 ± 972.0
Plt (μL), mean ± SEM	21.8 ± 2.0	19.9 ± 1.6	29.8 ± 7.8
ALT (IU/L), mean ± SEM	115.0 ± 32.2	201.9 ± 48.9	80.4 ± 15.2
CRP (mg/dL), mean ± SEM	0.8 ± 0.2	2.9 ± 0.5	7.4 ± 1.1*
Early NLR, mean ± SEM	1.6 ± 0.6	4.3 ± 0.6	6.5 ± 1.3
Late NLR, mean ± SEM	1.4 ± 0.2	2.1 ± 0.3	3.2 ± 0.4

ALT, Alanine aminotransferase; *CMV*, cytomegalovirus; *CRP*, C-reactive protein; *DiHS/DRESS*, drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms; *IQR*, interquartile range; *NLR*, neutrophil/lymphocyte ratio; *WBC*, white blood cell count.
*$P < .05$ (mild vs moderate, severe).
†$P < .05$.
§Fisher's exact test.
‖No. of cases undergoing corticosteroid therapy at 8 weeks.

potential to identify CMV disease and complications in patients with DiHS/DRESS (Supplemental Fig 1).

Risk stratification of CMV reactivation

We next stratified disease severity into 3 groups based on early scores to predict the risk of CMV reactivation or CMV disease and complications (Table IV). Mild disease was defined as scores <1 (n = 5), moderate disease as scores 1 to 3 (n = 23), and severe disease as scores ≥4 (n = 27). CMV reactivation including CMV disease and complications occurred most frequently in the severe group: CMV disease and complications developed exclusively in the severe group. Median CRP levels were significantly different among the 3 categories, with the severe group having the highest. The average hospital length of stay was also the longest in the severe group. Mild and moderate disease groups had no evidence of progression to overt CMV disease or severe complications after 12 months of follow-up. Adjusted analyses of variance across the 3 disease severity groups showed that disease severity from mild to moderate to severe was associated with increasing periods of hospitalization and increasing white blood cell counts and CRP levels. A diagnostic and prognostic algorithm based on early and late scores is proposed in Fig 1.

DISCUSSION

Complications occurring during DiHS/DRESS have been extensively described in previous studies[5-14] and have received attention as the cause of mortality in DiHS/DRESS. These complications include myocarditis, *Pneumocystis jirovecii* pneumonia, sepsis, and gastrointestinal bleeding,[5-14] most of which lead to significant morbidity and mortality if unrecognized and untreated.[5-7,10,12,13] Therefore, the establishment of a scoring system using routinely obtained parameters by which disease severity and treatment efficacy can be assessed at any time and disease progression to more aggressive stage can be predicted is urgently needed for the successful management of DiHS/DRESS. By comparing the composite score in the early phase (days 0-3) with that at any time after starting therapy, the composite score can provide clinicians with clues for optimizing therapeutic efficacy and preventing treatment-related relapse. Not only worsening of clinical symptoms but also lack of improvement can be also evaluated by comparing these scores on different occasions. This scoring system might be useful in predicting beneficial treatment results in DiHS/DRESS (Table III). In addition to the utility of the scoring system for monitoring the extent of disease severity, this report supports the potential

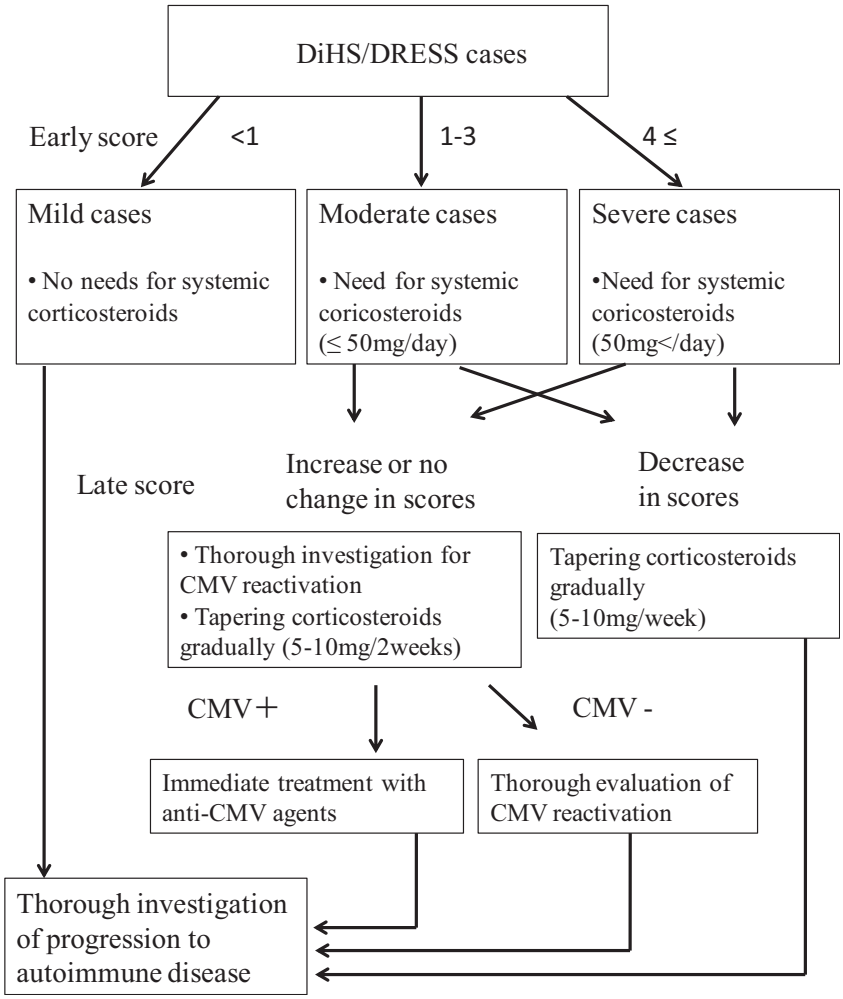

Fig 1. Proposed flow diagram for the diagnosis and outcome prediction of drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms based on early and late scores. *CMV*, Cytomegalovirus; *DiHS/DRESS*, drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms.

use of this scoring system for identifying individuals with a likelihood of CMV reactivation and complications, either CMV-related or CMV-unrelated, with fatal outcomes. Indeed, the present data show that patients with an early or late score ≥4 were significantly more likely to later develop CMV disease and complications; 5 of 26 patients with scores ≥4 developed CMV disease and complications, while no patients with a score <4 developed severe complications.

The immunosuppressive effects of corticosteroids are more pronounced in elderly patients, resulting in an increased risk of CMV reactivation. Indeed, there was a positive relationship between age of DiHS/DRESS onset and the score ($P < .01$). Indeed, in these patients, especially those treated with systemic corticosteroids and elderly patients ≥60 years of age, frequent relapses and worsening of clinical symptoms were observed with reduction of the corticosteroid dose. In this regard, previously reported cases suggest that the use of pulsed prednisone may be related to later development of CMV reactivation.[24,31] It is probable that a large reduction of prednisone doses needed immediately after pulsed prednisone may paradoxically induce a rapid recovery of immune responses that could in turn contribute to the development of CMV reactivation as a manifestation of immune reconstitution inflammatory syndrome.[32] To prevent a rapid immune recovery, we recommend that systemic corticosteroids be initiated at a sufficient dose of 40 to 60 mg per day prednisone equivalent in DiHS/DRESS and be followed by a gradual dose reduction of prednisone at least over >8 weeks (Fig 1). Tapering more gradually

over a prolonged period is recommended to achieve the optimum therapeutic result in patients with DiHS/DRESS.[1,3]

As pointed out by Bourgeois et al,[6] the present data also show that late-onset complications, such as myocarditis, which occur months after the rash and laboratory abnormalities have resolved and long after withdrawal of the causative drug, are more likely associated with fatal outcomes than early-onset complications. In view of our finding that CMV reactivation occurred 27.2 ± 2.3 days after onset while complications developed 33.2 ± 6.2 days after onset in CMV^+ cases, most late-onset complications would be caused by CMV reactivation. Because previous studies indicated that CMV reactivation could be the cause of several complications, such as gastrointestinal bleeding,[5,14] renal dysfunction,[7] myocarditis,[10] and sepsis,[12,13] it is likely that fatal complications occurring in the late stage of DiHS/DRESS could be preventable with anti-CMV therapy. In support of this possibility, a delay in initiating anti-CMV therapy after the first detection of CMV reactivation was likely to reduce efficacy; cessation of anti-CMV therapy was temporarily associated with the development of CMV disease or complications, as shown in case 5. Therefore, no development of CMV disease and complications during anti-CMV therapy and its transient resurgence soon after cessation of anti-CMV therapy suggest that anti-CMV therapy is effective in preventing the development of not only overt CMV disease but also complications that are generally regarded as being CMV-unrelated. Because CMV is thought to affect the other herpesviruses, such as Epstein—Barr virus,[33,34] the present data concur with previous observations that anti-CMV therapy may have been also effective at curtailing the risk of other herpesvirus-related complications; anti-CMV therapy has been reported to exert beneficial anti-Epstein—Barr virus or human herpesvirus-6 effects,[34,35] although the efficacy of anti-CMV therapy against other members of the herpesvirus family, either directly or indirectly, has not been compared. Given that mortality in DiHS/DRESS is estimated to be 10% among patients in previous studies,[22] the mortality rate of 5% in the present cohort appeared to be the lowest, to the best of our knowledge, reflecting a clear benefit of the prompt recognition of CMV disease and appropriate management.

Our study is limited by its retrospective nature, single-institution assessment, the lack of a validation cohort, and the limited follow-up time, although it is the largest longitudinal retrospective cohort study to date in patients with DiHS/DRESS. Studies with large numbers of patients with DiHS/DRESS pooled from multiple centers and long-term follow-up would be of further significant value in assessing outcomes associated with CMV reactivation.

In conclusion, our scoring system offers the possibility of screening high-risk patients before the development of CMV reactivation followed by CMV-related or CMV-unrelated complications; this scoring system can guide treatment options and help predict outcomes. Patients with scores ≥4 at any time are candidates for a more thorough clinical evaluation of CMV reactivation.

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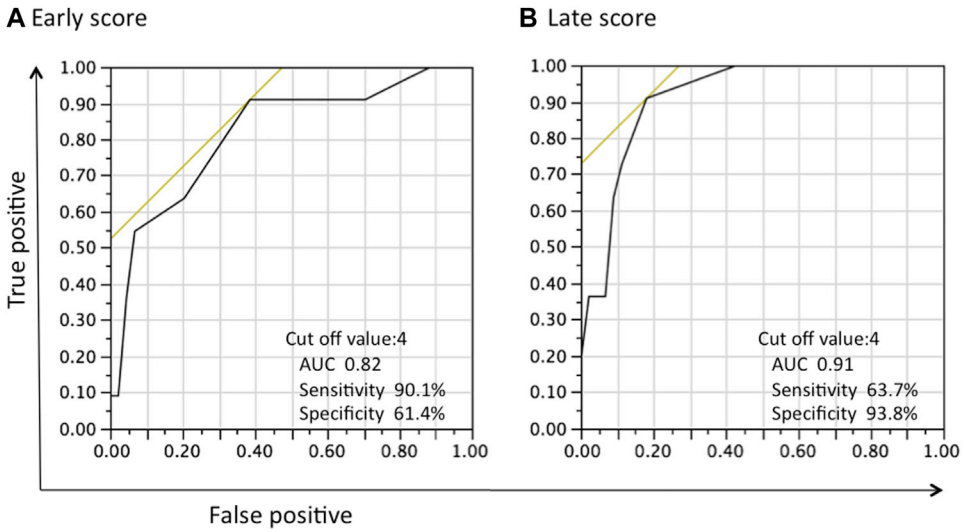

Supplemental Fig 1. Receiver operating characteristic curves and diagnostic performance of the predicted probability for detection of the later development of CMV disease and complications based on early and late scores.

Supplemental Table I. Laboratory findings of CMV^+ and CMV^- cases at the initial presentation

	CMV^+ (n = 11)	CMV^- (n = 44)
WBC (cells/μL), mean ± SEM	9418 ± 952	9225 ± 992
Lymphocytes (μL)	1170 ± 166	1482 ± 185
Eosinophils (μL)	1205 ± 503	1454 ± 359
Plt (μL), mean ± SEM	37.8 ± 18.5	21.4 ± 1.2
Cr (mg/dL), mean ± SEM	1.4 ± 0.5	1.0 ± 0.2
ALT (IU/L), mean ± SEM	80.5 ± 19.9	147.8 ± 40.1
CRP (mg/dL), mean ± SEM	8.5 ± 2.1*	3.9 ± 0.6
NLR, mean ± SEM	5.8 ± 0.9	4.9 ± 0.9

ALT, Alanine aminotransferase; *CMV*, cytomegalovirus; *Cr*, creatinine; *CRP*, C-reactive protein; *NLR*, neutrophil/lymphocyte ratio; *WBC*, white blood cell count.
*$P < .05$.