Viral reactivation and outcomes in drug reaction with eosinophilia and systemic symptoms (DRESS)

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September 17, 2020

Abstract

Abstract Background Drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe cutaneous adverse drug reaction associated with human herpesvirus reactivation. However, the risk factors for viral reactivation and their impact on outcomes remain unclear.We aimed to explore the impact of viral reactivation on DRESS outcomes and potential risk factors for reactivation. Methods This was a retrospective cohort study in an academic medical center. Cases were validated in-hospital cases of DRESS from 2009 to 2017. Results Overall, 100 patients fulfilled the case criteria. Ninety-three patients had at least one viral marker tested. HHV6, EBV and CMV reactivation occurred in 24 out of 85 cases (28%), 15 out of 87 (17%) cases, and 18 out of 89 (20%) cases respectively. Viral reactivation cases were associated with higher 1-year mortality, dialysis initiation, recurrent flares of disease, and longer hospital stay (all $p<0.05$). Risk of inpatient mortality (OR, 5.8; 95% CI, 1.7-20.7; $p<0.01$) and 1-year mortality (OR, 10.0, 95% CI, 2.9-34.9; $p<0.01$) increased with multiple viral reactivations. Viral reactivation was independent of demographics, comorbidities, treatment or causative drug. Conclusion Human herpesviridae viral reactivation in DRESS, particularly multiple viral reactivations, is associated with poorer clinical outcomes.

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This was a retrospective cohort study in an academic medical center. Cases were validated in-hospital cases of DRESS from 2009 to 2017.

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Conclusion

Human herpesviridae viral reactivation in DRESS, particularly multiple viral reactivations, is associated with poorer clinical outcomes.

(205 words)

Keywords

DRESS

Drug hypersensitivity

Drug reaction with eosinophilia and systemic symptoms

Drug induced hypersensitivity syndrome

Severe cutaneous adverse reaction

Viral reactivation

Human herpesviridae

HHV6

EBV

CMV

Abbreviations Used

CMV – Cytomegalovirus

DRESS – Drug reaction with eosinophilia and systemic symptoms

EBV – Epstein-Barr virus

HHV6 – Human herpesvirus 6

ICU – Intensive care unit

IRR – Incidence rate ratio

OR – Odds ratio

RegiSCAR – European Registry of Severe Cutaneous Adverse Reactions (SCAR) to Drugs and Collection of Biological Samples

1. Background

Drug reaction with eosinophilia and systemic symptoms (DRESS) is an uncommon severe cutaneous adverse reaction associated with internal organ involvement, lymphadenopathy, atypical lymphocytosis and eosinophilia. The manifestations are heterogeneous and features of rash and eosinophilia may be occasionally absent, leading to diagnostic difficulties.[1, 2] The disease course is typically prolonged and episodes of flares may occur despite drug cessation. Mortality has been reported to be between 2 to 10 percent,[3-5] and long-term sequelae of autoimmunity has been reported in survivors.[6]

The majority of reactions can be attributed to a number of high-risk medications such as allopurinol, aromatic anti-epileptic agents, anti-microbial sulfonamides, vancomycin and minocycline.[3] The estimated risk following new prescriptions of aromatic antiepileptic agents is 1-4.5 in 10,000.[7] The latency between culprit drug initiation and onset ranges from 2-8 weeks.

Postulated disease mechanism in DRESS include i) pharmacogenetics susceptibility eg. association of HLA-A*3101 in carbamazepine-induced DRESS, HLA-B*5801 in allopurinol-induced DRESS, and HLA-B*1301 in dapsone-induced DRESS.[8-10] ii) activation of drug-specific T cells,[11] (iii) dysregulation of regulatory cells T cells,[12] iv) human herpesvirus reactivation and the subsequent role of anti-viral immune response.[13]

Reactivation of the human herpesvirus is a known phenomenon of DRESS, occurring in up to 75% of patients.[13] HHV6 is the most common agent within the family to be reactivated, occurring between 45-60% depending on detection methodologies.[13, 14] Multiple, sequential reactivation of viruses has been observed in up to 30% of cases with a temporal pattern similar to that of graft-versus-host disease.[15] Reactivation of HHV6 has been associated with disease flares and severity.[14] Fatal DRESS cases have been anecdotally attributed to CMV reactivations.[16]

Despite these observations, the impact of herpes viral reaction on the clinical course remains largely unknown.[17] The primary aim of our study is to examine the impact of viral reactivation on the clinical course and outcomes in a large cohort of DRESS patients and the secondary aim is to explore potential risk factors for viral reactivation.

2. Methods

2.1 Case Inclusions, Data Collection and Validation

Inpatients referred to the Department of Dermatology, Singapore General Hospital between 2009 and 2017 with a diagnosis of DRESS were retrospectively screened. Clinical and epidemiological data including demographics, photographs, investigations, histology, clinical course, treatments, outcomes were summarized from medical records.

These screened cases were re-validated by a team of dermatologists (HYL, YWY, KC) according to the standardised RegiSCAR DRESS scoring system.[18] Ambiguities and differences during case validation were resolved via consensus. Briefly, the RegiSCAR DRESS scoring system is a standardized scoring system based on the clinical features and investigations with a final score that ranges from -4 to 9. Cases were designated as not DRESS if score is <2, possible case if score is 2-3, probable case if score is 4-5, and definite case if final score is >5.[18]Cases of probable or definite cases of DRESS (Final RegiSCAR score of 4 or more) were included for analysis. DRESS flares were defined as skin eruption not attributable to other skin disorders.

2.2 Herpesviridae Testing Methodology

All suspected DRESS patients referred to the dermatology service are typically tested for herpes viral reactivation during the acute phase of the disease. Testing methodology was based on quantitative real-time polymerase chain reaction (PCR) assay. PCR testing was performed routinely during initial presentation and repeated weekly if the patient was still hospitalised.

From 2009-2013

For HHV6, in-house PCR used primers and Taqman probe (Applied Biosystems, Foster City, CA, USA) targeted at the U67 gene of HHV6, and the viral load threshold of detection was 233 copies/mL plasma at 95% confidence level. For EBV, in-house quantitative real-time PCR was targeted at the conserved region of EBNA-1 gene of EBV, and the viral load threshold of detection was 715 copies/mL plasma at 95% confidence level. For CMV, In-house quantitative real-time PCR with primers and probe were targeted at glycoprotein B-specific gene of human cytomegalovirus (CMV), and the viral load threshold of detection was 154 copies/mL plasma at 95% confidence level.

From 2014 to 2017

For HHV6, in-house PCR used primers and Taqman probe (Applied Biosystems, Foster City, CA, USA) targeted at the U67 gene of HHV6, and the viral load threshold of detection was 233 copies/mL plasma at 95% confidence level. For EBV, in-house PCR was targeted at the highly conserved, repetitive region of the EBV genome designated the BamHI-W region, and the viral load threshold of detection was 265 copies/mL plasma at 95% confidence level. One copy of EBV DNA is equivalent to 0.26 International Units (IU) based on the 1st WHO International Standard for Human EBV for Nucleic Acid Amplification Techniques (NIBSC 09/260). For CMV, primers and probe targeted at UL54 gene of human cytomegalovirus were used (Roche

COBAS AmpliPrep/COBAS TaqMan CMV Test), and the viral load threshold of detection was 56 IU/mL plasma at 95% confidence level.

2.3 Statistical analysis

Outcome variables including ICU admission, the need for dialysis, in-hospital mortality, the presence of flares, hospital readmission within 1 year and mortality within 1 year were all treated as binary variables while outcome variable length of hospital stay (LOS) was treated as count data i.e. non-negative integer values. Exposers*viral reactivation* and *antiviral treatment* were both treated as binary data with categories "*yes* " or "*no* ". All categorical and continuous outcomes were summarized as frequency with corresponding percentages and mean (standard deviation) or median (interquartile range), whichever appropriate, respectively based on*viral reactivation* and *antiviral treatment* status. Categorical outcome variables were compared using Chi-Square test while continuous variables were compared using two-sample t-test or Mann–Whitney U test, whichever appropriate.

Univariate logistic regression models were fit to find associated risk factors for binary outcomes. Association from logistic regression was expressed as odds ratio (OR) with 95% confidence interval (95% CI). Outcome variable LOS was fit using the Poisson regression model and association between LOS and exposers were expressed as incidence rate ratio (IRR) with 95% CI. Percentage of reactivation from onset date was analyzed for individual herpesviruses. In case of repeat PCR in this analysis, first positive episode was analyzed and the corresponding number of days from onset of rash to the 1st positive test was calculated. A p-value <0.05 was regarded as statistically significant. For statistical analysis, we used the software SAS (version 9.4, Cary, NC, USA).

This study was approved by Singhealth IRB: 2014/2011.

3. Results

109 patients with a discharge diagnosis of DRESS were re-validated. Of these, 3 were excluded, and there were 6 possible, 38 probable, and 62 definite cases of DRESS. Among the 100 cases of probable/definite DRESS, 93 cases had at least one viral marker studied and were analysed for this study (Supp Fig. 1).

3.1 Demographic and clinical characteristics

Of the 93 patients, 41 (44%) were men and 52 (56%) were women with an age range of 17 to 86 (mean (SD): 57 (17)) years (Table 1). The most common co-morbidities were hypertension (63%), hyperlipidemia(51%), and renal disease (32%). Associated systemic features include blood involvement (99%), hepatic involvement (72%), and renal involvement (44%)(Table 1). Slightly more than half of the cohort (54%) had 3 or more organs involved, and 37% of the cohort had 2 organ involvement.

3.2 Viral Reactivation

Thirty-nine (42%) patients were found to have viral reactivation of at least 1 of the human herpesvirus family (Table 2). Of these 39 patients, 12 (13%) patients had 2 viral reactivations and 3 (3%) patients were found to have all 3 viral reactivation on PCR assay testing. Specifically, HHV6 reactivation was the most common, occurring in 24/85 cases tested (28%). EBV reactivation occurred in 14/87 (16%) cases tested and CMV reactivation occurred in 19/89 (21%) cases tested. Twenty-two (24%) patients had more than 1 set of viral PCR tests carried out, and among them, 11 patients who initially tested negative, became positive on serial testing.

3.3 Latency of onset of rash to detection of human herpes viruses

We trended the days from the onset of rash to the first detection of the herpesviruses with a normal distribution as shown in Figure 1. The peak time from onset of disease to viral reactivation was around 11 days for EBV, 16 days for HHV6, and 23 days for CMV.

3.4 Predisposing factors for viral reactivation DRESS patients

To identify potential predisposing factors for viral reactivation, a comparative analysis of baseline characteristics between viral reactivated (n=39) and non-reactivated (n=54) groups was performed.(Supp Table 1) Our results showed that viral reactivation occurred independent of demographics, baseline co-morbidities, culprit drug and treatment. Of note, viral reactivation was observed in 15 out of 41 patients (37%) treated with topical steroids compared to 24 out of 49 (49%) patients treated with systemic corticosteroids (p=0.24).

3.5 Viral reactivation on DRESS phenotype and outcomes

3.5.1 Clinical phenotype

During the acute phase of the disease, patients with viral reactivation were more likely to have kidney involvement 22/39 (56%) as compared to 19/54 (35%) non-reactivators (OR, 2.4; 95% CI, 1.0-5.5; p=0.04) (Table 3). There were no significant differences between fever, blood, liver, lungs, heart or pancreas involvement.

3.5.2 Clinical Outcomes

Viral reactivation was shown to be significantly associated with higher risk of outcomes of mortality in 1 year (OR, 3.9; 95% CI, 1.2-12.2; p=0.02), dialysis initiation (OR, 3.4; 95% CI, 1.1-10.9; p=0.04), increased length of hospital stay (IRR, 2.2; 95% CI, 1.4-3.3; p<0.01), and recurrent flares in 1 year among DRESS patients (OR, 3.1; 95% CI, 1.2-8.2; p=0.02) (Table 4). On sub-analysis with respect to individual viruses, the association with mortality, ICU stay, need for dialysis and length of stay (LOS) was significantly associated with CMV reactivation. Similarly, when there were 2 or more viral reactivations detected, the risk of inpatient mortality (OR, 5.8; 95% CI, 1.7-20.7; p<0.01) as well as 1 year mortality was significantly higher. (OR, 10.0, 95% CI, 2.9-34.9; p<0.01).

3.6 Impact of Anti-viral treatment in patients with viral reactivation.

To explore the role of antiviral treatment in DRESS, a preliminary comparative analysis was performed. Among the 39 patients with reactivation, 13 received anti-viral therapy: 11 had serological positive viral PCR, whereas 2 others had additional evidence of pathology-proven clinical disease (CMV pneumonitis, CMV hepatitis). Antivirals included ganciclovir (n=7,54%), acyclovir (n=5, 38%) and valganciclovir (n=1,8%). Treatment decisions were made by the primary physicians. There were no significant differences in outcomes (Mortality, ICU, need for dialysis, LOS) between both groups

4. Discussion

This current study examines the impact of viral reactivation in a large cohort of patients with DRESS syndrome. There were a few unique observations. Firstly, herpes viral reactivation is a common but non-universal phenomenon, occurring in 42% of patients. Secondly, viral reactivation may not be detected at the onset of the rash (Figure 1) and 28% of patients with reactivation were detected on serial testing. Thirdly, there were no baseline clinical, causative drug or treatment factors that predicted reactivation. Lastly, our study suggests the association of viral reactivation with a certain clinical phenotype – such patients were more likely to have renal involvement as well as poorer outcomes, namely recurrent flares, need for dialysis, length of stay and death.

Identification of predictors of severe, life-threatening DRESS remains a research gap. In a series of 15 patients with ICU stay and death[19], HHV6 reactivation was present in 6/7 tested (No other herpes viruses were tested). Similarly, CMV reactivation has been anecdotally reported with severe outcomes. Our current

study further clarifies this association. HHV6 in itself was not associated with ICU stay or death. However, when it is associated with multiple viral reactivation and / or CMV reactivation, poorer prognosis exists.

There were other significant negative findings that are of note. Firstly, there were no baseline factors which predicted viral reactivation. This proved that reactivation occurred independent of systemic steroid treatment, type of culprit drug or baseline factors. Nevertheless, valproic acid has been reported to increase replications of HHV6,[20] and CMV.[21] Secondly, in our exploratory analysis of antiviral treatment in a small cohort of viral-reactivated DRESS cases, there does not appear to be significant difference in outcomes. This warrants further evaluation in a systematic and controlled protocol.

The pathophysiology of DRESS and the role that herpes viruses play remains poorly defined. Although viral reactivation is associated with poorer outcomes, the cause versus effect conundrum remains unresolved. A few possibilities exist: 1) Viral reactivation exist as a bystander effect due to immunodysregulation – not dissimilar to an immune reconstitution phenomenon in graft versus host disease or in critically ill/immunosuppressed subjects. 2) Viral reactivation results in the initiation of the drug allergy. 3) Direct reactivation of viruses from drug / drug metabolites. 4) A combination of the above – with a primary drug-specific immune response as the initiating event, then viral reactivation in certain individuals with an associated secondary anti-viral/self-response. The lack of universal reactivation in all DRESS patients and reactivation occurring after the onset of DRESS symptoms argues against it being the initial trigger or a necessity for DRESS to occur. Furthermore, in-vitro and in-vivo evidence such as the identification of drug-specific T cells in Allopurinol SCARs and positivity on patch testing to the culprit drug in DRESS patients supports the argument for a primary drug-mediated response.[11]

There were various limitations in our study. These included the retrospective design with its inherent flaws. Although viral studies were performed in the acute phase of the disease, the timing of these studies depended on various factors including time to hospital admission and/or dermatological referral. This may have impacted on the proportion of reactivation as well as the latency between onset of symptoms and viral reactivation. This was partially ameliorated by repeated sampling which was performed in 24% of our patients. In our cohort of 93 patients, 28% had HHV6 reactivation and these results are comparable to other validated DRESS cohorts utilizing quantitative PCR viral studies. In those cohorts, HHV6 reactivation varies between 39%-45%.[13, 24] Moreover, the latency between symptoms and reactivation in our cohort is similar to published series.[13, 23] Although we showed univariate analysis for each outcome e.g. mortality, dialysis etc, these results may be limited by the small sample size. A multivariable model for any outcome was not possible due to the small sample and missing values. Our analysis on anti-viral treatment, though novel, is not conclusive due to the non-controlled nature, small cohort and risk of treatment bias. Nevertheless, these preliminary data warrants further evaluation.

There were certain strengths in this study. This was a large cohort of DRESS patients that was validated against standardized criteria. Dermatological care was provided by the same clinical team within the same care setting. This would reduce the bias introduced by care variability and the "centre" effect.

In conclusion, our study suggests that herpes viral reactivation, when present identifies patients at risk of poorer outcomes. Our work is unable to prove a causal or pathogenic association and further work is needed to understand the role of virus reactivation in DRESS disease mechanism, identify patients at risk of reactivation as well as potential impact of anti-viral treatment.

Acknowledgements

Author contributions: Dr Chan and Dr Lee had full access to all of the data in the

study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Chan, Lee, Sultana.

Acquisition, analysis, and interpretation of data: Chan, Lee, Sultana.

Drafting of the manuscript: Chan, Lee, Sultana.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Sultana, Chan, Lee.

Administrative, technical, or material support: Choo, Yeo.

Study supervision: Lee.

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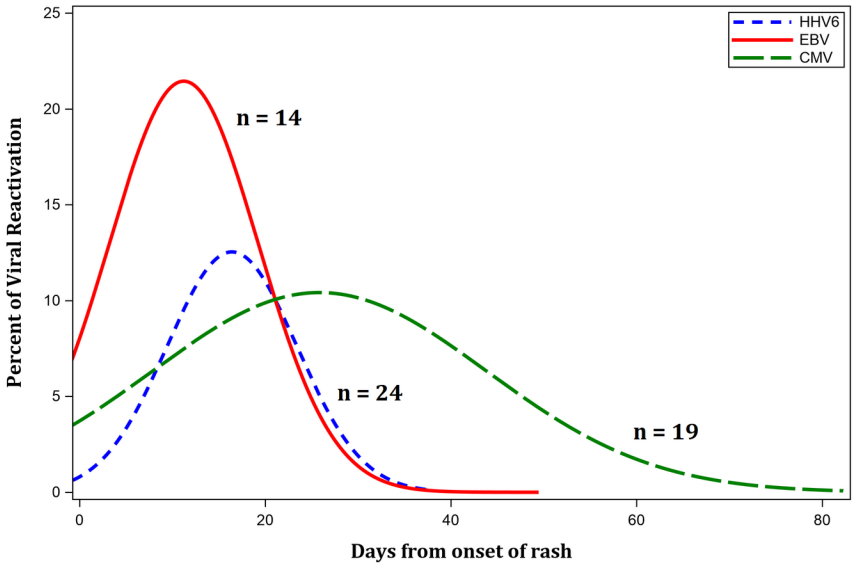
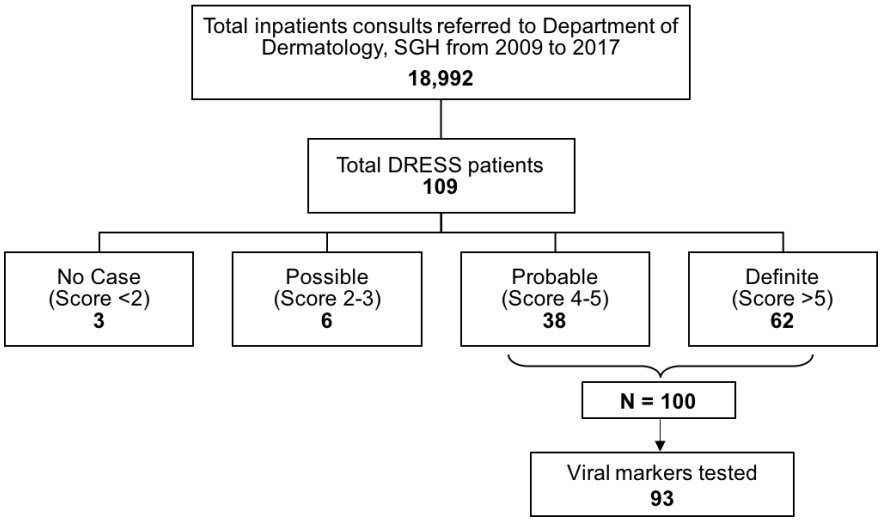
Figures

Figure 1. Latency between onset of rash to detection of human herpes viruses. The peak time from onset of disease to viral reactivation was around 16 days for HHV6 (blue line) 11 days for EBV (red line), and 23 days for CMV (green line).



Supplementary Figure 1. Flowchart of patients included in study



Tables

Table 1. Demographics, co-morbidities, and clinical characteristics of DRESS patients

Clinical Characteristics
Gender (Male : Female)
Age (years), Mean ± SD
Ethnicity
Chinese
Malay
Indian
Others

Table 1. Demographics, co-morbidities, and clinical characteristics of DRESS patients

Comorbidities	
Malignancy	
HIV	
Infection	
Liver disease	
Renal disease	
Heart Disease	
Hypertension	
Hyperlipidemia	
Diabetes	
Autoimmune	
Fever $>$ 38.5 °C	
Lymphadenopathy	
Blood involvement*	
Eosinophilia	
Atypical Lymphocytes	
Organ Involvement	
1 organ involved	
2 organs involved	
3 organs involved	
$>$ 3 organs involved	
Liver	
Kidney	
Lung	
Heart	
Pancreas	
Gastrointestinal	
Thyroid	
Others	

Note: Infections include tuberculosis (4), sepsis (4), urinary tract infection (2), wound infection (1) ** Includes patients wit
[?] Note: Other organ involvements include (patients): central nervous system (8), gallbladder (3), aorta (1), spleen (1)

Table 2. Viral reactivation of DRESS patients

Viral Reactivation	**Summary, n**	**(%)**
Viral Reactivation (N=93)	39	42
HHV6 (N=85)	24	28
CMV (N=89)	19	21
EBV (N=87)	14	16
1 herpesvirus reactivation	24	26
2 herpesvirus reactivations	12	13
3 herpesvirus reactivations	3	3
More than 1 set of PCR tested	22	24

Table 2. Viral reactivation of DRESS patients

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Table 3. Clinical phenotypes of viral reactivation among DRESS patients	**Table 3.** Clinical phenotypes of viral reactivation among DRESS patients	**Table 3.** Clinical phenotypes of viral reactivation among DRESS patients	**Table 3.** Clinical phenotypes of viral reactivation among DRESS patients	**Table 3.** Clinical phenotypes of viral reactivation among DRESS patients	**Table 3.** Clinical phenotypes of viral reactivation among DRESS patients
Phenotypes	**Viral Reactivation No (N=54)**	**Viral Reactivation Yes (N=39)**	**Total (N=93)**	**Univariate Analysis Unadjusted OR* (95% CI)**	**Univariate Analysis p-value**
Fever > 38.5 °C, n(%)	34 (63.0)	28 (71.8)	62 (66.7)	1.5 (0.6 to 3.7)	0.37
Lymphadenopathy, n(%)	17 (31.5)	7 (17.9)	24 (25.8)	0.5 (0.2 to 1.3)	0.15
Blood involvement, n(%)	53 (98.1)	39 (100)	92 (98.9)	NE	0.99
Eosinophilia	46 (85.2)	35 (89.7)	81 (87.1)	1.5 (0.4 to 5.5) 0.52	1.5 (0.4 to 5.5) 0.52
Atypical Lymphocytes	46 (85.2)	36 (92.3)	82 (88.2)	2.1 (0.5 to 8.4)	0.30
Organ Involvement, n(%)					
1 organ involved	23 (48.9)	11 (29.7)	34 (40.5)	Reference	
2 organs involved	12 (27.7)	12 (32.4)	25 (29.8)	1.9 (0.7 to 5.6)	
3 organs involved	6 (12.8)	4 (10.8)	10 (11.9)	1.4 (0.3 to 6.0)	0.16+
> 3 organs involved	5 (10.6)	10 (27.0)	15 (17.9)	4.2 (1.2 to 15.2)	
Liver	39 (72.2)	28 (71.8)	67 (72.0)	1.0 (0.4 to 2.5)	0.96
Kidney	19 (35.2)	22 (56.4)	41 (44.1)	2.4 (1.0 to 5.5)	0.04
Lungs	05 (9.3)	06 (15.4)	11 (11.8)	1.8 (0.5 to 6.3)	0.37
Heart	07 (13.0)	10 (25.6)	17 (18.3)	2.3 (0.8 to 6.8)	0.13
Pancreas	03 (5.6)	03 (7.7)	06 (6.5)	1.4 (0.3 to 7.4)	0.68
Gastrointestinal	07 (13.0)	07 (17.9)	14 (15.1)	1.5 (0.5 to 4.6)	0.51
Thyroid	8 (14.8)	10 (25.6)	18 (19.4)	2.0 (0.7 to 5.6)	0.20
Others*	5 (9.3)	08 (20.5)	13 (14.0)	2.5 (0.8 to 8.4)	0.13

Table 3. Clinical phenotypes of viral reactivation among DRESS patients	**Table 3.** Clinical phenotypes of viral reactivation among DRESS patients	**Table 3.** Clinical phenotypes of viral reactivation among DRESS patients	**Table 3.** Clinical phenotypes of viral reactivation among DRESS patients	**Table 3.** Clinical phenotypes of viral reactivation among DRESS patients	**Table 3.** Clinical phenotypes of viral reactivation among DRESS patients
NE: Not estimable * Note: Other organ involvements include (patients): central nervous system (8), gallbladder (3), aorta (1), spleen (1)	NE: Not estimable * Note: Other organ involvements include (patients): central nervous system (8), gallbladder (3), aorta (1), spleen (1)	NE: Not estimable * Note: Other organ involvements include (patients): central nervous system (8), gallbladder (3), aorta (1), spleen (1)	NE: Not estimable * Note: Other organ involvements include (patients): central nervous system (8), gallbladder (3), aorta (1), spleen (1)	NE: Not estimable * Note: Other organ involvements include (patients): central nervous system (8), gallbladder (3), aorta (1), spleen (1)	NE: Not estimable * Note: Other organ involvements include (patients): central nervous system (8), gallbladder (3), aorta (1), spleen (1)

Table 4. Clinical outcomes of viral reactivation in DRESS patients	**Table 4.** Clinical outcomes of viral reactivation in DRESS patients	**Table 4.** Clinical outcomes of viral reactivation in DRESS patients	**Table 4.** Clinical outcomes of viral reactivation in DRESS patients	**Table 4.** Clinical outcomes of viral reactivation in DRESS patients	**Table 4.** Clinical outcomes of viral reactivation in DRESS patients	**Table 4.** Clinical outcomes of viral reactivation in DRESS patients	**Table 4.** Clinical outcomes of viral reactivation in DRESS patients	**Table 4.** Clinical outcomes of viral reactivation in DRESS patients	**Table 4.** Clinical outcomes of viral reactivation in DRESS patients	**Table 4.** Clinical outcomes of viral reactivation in DRESS patients	**Table 4.** Clinical outcomes of viral reactivation in DRESS patients	
	Inpatient mortality, n(%)	**Mortality in 1 year, n(%)**	**ICU, n(%)**	**Dialysis, n(%)**	**Dialysis, n(%)**	**Length of hospital stay**, Mean (SD)**	**Length of hospital stay**, Mean (SD)**	**Length of hospital stay**, Mean (SD)**	**Flares in 1 year, n(%)**	**Flares in 1 year, n(%)**	**Readmiss in 1 year, n(%)**	**i y n**
Viral Reactivation												
No (N=54)	5 (9.3)	5 (9.3)	6 (11.1)	5 (9.3)	5 (9.3)	14.4 (16.3)	14.4 (16.3)	14.4 (16.3)	9 (16.7)	9 (16.7)	13 (24.1)	1 (
Yes (N=39)	9 (23.1)	11 (28.2)	9 (23.1)	10 (25.6)	10 (25.6)	31.3 (47.5)	31.3 (47.5)	31.3 (47.5)	15 (38.5)	15 (38.5)	19 (48.7)	1 (
Total (N=93)	14 (15.1)	16 (17.2)	15 (16.1)	15 (16.1)	15 (16.1)	21.5 (34.0)	21.5 (34.0)	21.5 (34.0)	24 (25.8)	24 (25.8)	32 (34.4)	3 (

Table 4. Clinical outcomes of viral reactivation in DRESS patients	**Table 4.** Clinical outcomes of viral reactivation in DRESS patients	**Table 4.** Clinical outcomes of viral reactivation in DRESS patients	**Table 4.** Clinical outcomes of viral reactivation in DRESS patients	**Table 4.** Clinical outcomes of viral reactivation in DRESS patients	**Table 4.** Clinical outcomes of viral reactivation in DRESS patients	**Table 4.** Clinical outcomes of viral reactivation in DRESS patients	**Table 4.** Clinical outcomes of viral reactivation in DRESS patients	**Table 4.** Clinical outcomes of viral reactivation in DRESS patients	**Table 4.** Clinical outcomes of viral reactivation in DRESS patients	**Table 4.** Clinical outcomes of viral reactivation in DRESS patients	**Table 4.** Clinical outcomes of viral reactivation in DRESS patients	
Unadjusted OR/IRR (95% CI)*	2.9 (0.9 to 9.6)	3.9 (1.2 to 12.2)	2.4 (0.8 to 7.4)	3.4 (1.1 to 10.9)	3.4 (1.1 to 10.9)	2.2 (1.4, 3.3)	2.2 (1.4, 3.3)	2.2 (1.4, 3.3)	3.1 (1.2 to 8.2)	3.1 (1.2 to 8.2)	1.3 (0.7 to 2.3)	1 (t 2
p-value	0.07	0.02	0.13	0.04	0.04	<0.01	<0.01	<0.01	0.02	0.02	0.41	0
HHV6 Reactivation												
No (N=61)	07 (11.5)	08 (13.1)	09 (14.8)	08 (13.1)	08 (13.1)	11.0 (15.0)	11.0 (15.0)	11.0 (15.0)	14 (23.0)	14 (23.0)	22 (36.1)	2 (
Yes (N=24)	6 (25.0)	7 (29.2)	6 (25.0)	6 (25.0)	6 (25.0)	18.0 (22.5)	18.0 (22.5)	18.0 (22.5)	10 (41.7)	10 (41.7)	10 (41.7)	1 (
Total (N=85)	13 (15.3)	15 (17.6)	15 (17.6)	14 (16.5)	14 (16.5)	12.0 (14.0)	12.0 (14.0)	12.0 (14.0)	24 (28.2)	24 (28.2)	32 (37.6)	3 (
Unadjusted OR/IRR (95% CI)[?]	2.6 (0.8 to 8.7)	2.7 (0.9 to 8.6)	1.9 (0.6 to 6.2)	2.2 (0.7 to 7.2)	2.2 (0.7 to 7.2)	1.1 (0.7, 1.8)	1.1 (0.7, 1.8)	1.1 (0.7, 1.8)	2.4 (0.9 to 6.6)	2.4 (0.9 to 6.6)	1.2 (0.5 to 3.1)	1 (t 3
p-value	0.13	0.09	0.27	0.19	0.19	0.68	0.68	0.68	0.09	0.09	0.74	0
CMV Reactivation												
No (N=70)	7 (10.0)	8 (11.4)	8 (11.4)	8 (11.4)	8 (11.4)	10.5 (12.0)	10.5 (12.0)	10.5 (12.0)	18 (25.7)	18 (25.7)	23 (32.9)	2 (
Yes (N=19)	6 (13.6)	7 (36.8)	6 (31.6)	6 (31.6)	6 (31.6)	24.0 (30.0)	24.0 (30.0)	24.0 (30.0)	6 (31.6)	6 (31.6)	9 (47.4)	9 (
Total (N=89)	13 (14.6)	15 (16.9)	14 (15.7)	14 (15.7)	14 (15.7)	13.0 (14.0)	13.0 (14.0)	13.0 (14.0)	24 (27.0)	24 (27.0)	32 (36.0)	3 (
Unadjusted OR/IRR (95% CI)[?]	4.2 (1.2 to 14.4)	4.5 (1.4 to 14.8)	3.6 (1.1 to 12.1)	3.6 (1.1 to 12.1)	3.6 (1.1 to 12.1)	2.6 (1.8, 4.0)	2.6 (1.8, 4.0)	2.6 (1.8, 4.0)	1.3 (0.4 to 4.0)	1.3 (0.4 to 4.0)	1.7 (0.6 to 4.8)	1 (t 4
p-value	0.03	0.01	0.04	0.04	0.04	<0.01	<0.01	<0.01	0.61	0.61	0.30	0
EBV Reactivation												

Table 4. Clinical outcomes of viral reactivation in DRESS patients	**Table 4.** Clinical outcomes of viral reactivation in DRESS patients	**Table 4.** Clinical outcomes of viral reactivation in DRESS patients	**Table 4.** Clinical outcomes of viral reactivation in DRESS patients	**Table 4.** Clinical outcomes of viral reactivation in DRESS patients	**Table 4.** Clinical outcomes of viral reactivation in DRESS patients	**Table 4.** Clinical outcomes of viral reactivation in DRESS patients	**Table 4.** Clinical outcomes of viral reactivation in DRESS patients	**Table 4.** Clinical outcomes of viral reactivation in DRESS patients	**Table 4.** Clinical outcomes of viral reactivation in DRESS patients	**Table 4.** Clinical outcomes of viral reactivation in DRESS patients	**Table 4.** Clinical outcomes of viral reactivation in DRESS patients	
No (N=73)	8 (11.0)	8 (11.0)	10 (13.7)	9 (12.3)	9 (12.3)	11.0 (12.0)	11.0 (12.0)	11.0 (12.0)	20 (27.4)	20 (27.4)	23 (31.5)	2 (
Yes (N=14)	4 (28.6)	6 (42.9)	3 (21.4)	4 (28.6)	4 (28.6)	22.0 (22.0)	22.0 (22.0)	22.0 (22.0)	4 (28.6)	4 (28.6)	9 (64.3)	9 (
Total (N=87)	12 (13.8)	14 (16.1)	13 (14.9)	13 (14.9)	13 (14.9)	12.0 (15.0)	12.0 (15.0)	12.0 (15.0)	24 (27.6)	24 (27.6)	32 (36.8)	3 (
Unadjusted OR/IRR (95% CI)[?]	3.3 (0.8 to 12.8)	6.1 (1.7 to 22.1)	1.7 (0.4 to 7.3)	2.8 (0.7 to 11.0)	2.8 (0.7 to 11.0)	1.2 (0.7, 2.1)	1.2 (0.7, 2.1)	1.2 (0.7, 2.1)	1.1 (0.3 to 3.8)	1.1 (0.3 to 3.8)	3.7 (1.1 to 12.2)	3 (t 1
p-value	0.09	<0.01	0.46	0.13	0.13	0.53	0.53	0.53	0.93	0.93	0.03	0
Number of Herpesvirus reactivations	Number of Herpesvirus reactivations	Number of Herpesvirus reactivations	Number of Herpesvirus reactivations	Number of Herpesvirus reactivations								
< 2 (N=78)	8 (10.3)	8 (10.3)	10 (12.8)	10 (12.8)	10 (12.8)	20.0 (36.0)	20.0 (36.0)	19 (24.4)	19 (24.4)	19 (24.4)	25 (32.1)	2 (
[?] 2 (N=15)	6 (40.0)	8 (53.3)	5 (33.3)	5 (33.3)	5 (33.3)	29.1 (19.0)	29.1 (19.0)	5 (33.3)	5 (33.3)	5 (33.3)	8 (53.3)	8 (
Total (N=93)	14 (15.1)	16 (17.2)	15 (16.1)	15 (16.1)	15 (16.1)	21.5 (34.0)	21.5 (34.0)	24 (25.8)	24 (25.8)	24 (25.8)	33 (35.5)	3 (
Unadjusted OR/IRR (95% CI)	5.8 (1.7 to 20.7)	10.0 (2.9 to 34.9)	3.4 (1.0 to 12.0)	3.4 (1.0 to 12.0)	3.4 (1.0 to 12.0)	1.5 (0.9, 2.5)	1.5 (0.9, 2.5)	1.6 (0.5 to 5.1)	1.6 (0.5 to 5.1)	1.6 (0.5 to 5.1)	2.4 (0.8 to 7.4)	2 (t 7
p-value	<0.01	<0.01	0.06	0.06	0.06	0.16	0.16	0.47	0.47	0.47	0.12	0

Table 4. Clinical outcomes of viral reactivation in DRESS patients	**Table 4.** Clinical outcomes of viral reactivation in DRESS patients	**Table 4.** Clinical outcomes of viral reactivation in DRESS patients	**Table 4.** Clinical outcomes of viral reactivation in DRESS patients	**Table 4.** Clinical outcomes of viral reactivation in DRESS patients	**Table 4.** Clinical outcomes of viral reactivation in DRESS patients	**Table 4.** Clinical outcomes of viral reactivation in DRESS patients	**Table 4.** Clinical outcomes of viral reactivation in DRESS patients	**Table 4.** Clinical outcomes of viral reactivation in DRESS patients	**Table 4.** Clinical outcomes of viral reactivation in DRESS patients	**Table 4.** Clinical outcomes of viral reactivation in DRESS patients	**Table 4.** Clinical outcomes of viral reactivation in DRESS patients
Note: **Poisson regression model was fit and associated risk is expressed as incidence rate ratio (IRR) with corresponding 95%CI. *Unadjusted OR is calculated with respect to “no viral reactivation”, [?]Unadjusted	Note: **Poisson regression model was fit and associated risk is expressed as incidence rate ratio (IRR) with corresponding 95%CI. *Unadjusted OR is calculated with respect to “no viral reactivation”, [?]Unadjusted	Note: **Poisson regression model was fit and associated risk is expressed as incidence rate ratio (IRR) with corresponding 95%CI. *Unadjusted OR is calculated with respect to “no viral reactivation”, [?]Unadjusted	Note: **Poisson regression model was fit and associated risk is expressed as incidence rate ratio (IRR) with corresponding 95%CI. *Unadjusted OR is calculated with respect to “no viral reactivation”, [?]Unadjusted	Note: **Poisson regression model was fit and associated risk is expressed as incidence rate ratio (IRR) with corresponding 95%CI. *Unadjusted OR is calculated with respect to “no viral reactivation”, [?]Unadjusted	Note: **Poisson regression model was fit and associated risk is expressed as incidence rate ratio (IRR) with corresponding 95%CI. *Unadjusted OR is calculated with respect to “no viral reactivation”, [?]Unadjusted	Note: **Poisson regression model was fit and associated risk is expressed as incidence rate ratio (IRR) with corresponding 95%CI. *Unadjusted OR is calculated with respect to “no viral reactivation”, [?]Unadjusted	Note: **Poisson regression model was fit and associated risk is expressed as incidence rate ratio (IRR) with corresponding 95%CI. *Unadjusted OR is calculated with respect to “no viral reactivation”, [?]Unadjusted	Note: **Poisson regression model was fit and associated risk is expressed as incidence rate ratio (IRR) with corresponding 95%CI. *Unadjusted OR is calculated with respect to “no viral reactivation”, [?]Unadjusted	Note: **Poisson regression model was fit and associated risk is expressed as incidence rate ratio (IRR) with corresponding 95%CI. *Unadjusted OR is calculated with respect to “no viral reactivation”, [?]Unadjusted	Note: **Poisson regression model was fit and associated risk is expressed as incidence rate ratio (IRR) with corresponding 95%CI. *Unadjusted OR is calculated with respect to “no viral reactivation”, [?]Unadjusted	Note: **Poisson regression model was fit and associated risk is expressed as incidence rate ratio (IRR) with corresponding 95%CI. *Unadjusted OR is calculated with respect to “no viral reactivation”, [?]Unadjusted

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Supplementary table 1 Table 1. Predisposing risk factors for viral reactivation among DRESS patients	**Supplementary table 1 Table 1.** Predisposing risk factors for viral reactivation among DRESS patients	**Supplementary table 1 Table 1.** Predisposing risk factors for viral reactivation among DRESS patients	**Supplementary table 1 Table 1.** Predisposing risk factors for viral reactivation among DRESS patients	**Supplementary table 1 Table 1.** Predisposing risk factors for viral reactivation among DRESS patients	**Supplementary table 1 Table 1.** Predisposing risk factors for viral reactivation among DRESS patients
Characteristics	**Viral Reactivation No (N=54)**	**Viral Reactivation Yes (N=39)**	**Total (N=93)**	**Univariate Analysis Unadjusted OR* (95% CI)**	**Univariate Analysis p-value**
Age (years), Mean (SD)	54 (18)	61 (15)	57 (17)	1.0 (1.0 to 1.1)	0.06
Gender, n(%)					
Female	30 (55.6)	22 (56.4)	52 (55.9)	1.0 (0.5 to 2.4)	0.94
Male	24 (44.4)	17 (43.6)	41 (44.1)	Reference	Reference
Ethnicity, n(%)					
Chinese	32 (59.3)	30 (76.9)	62 (66.7)	Reference	Reference
Malay	10 (18.5)	04 (10.3)	14 (15.1)	0.4 (0.1 to 1.5)	
Indian	05 (9.3)	05 (12.8)	10 (10.8)	1.1 (0.3 to 4.1)	0.61+
Others	07 (13.0)	00	07 (7.5)	NE	
Comorbidities, n(%)					
Malignancy	06 (11.1)	04 (10.3)	10 (10.8)	0.9 (0.2 to 3.5)	0.90
HIV	00	01 (2.6)	01 (1.1)	NE	0.99
Infection	05 (9.3)	05 (12.8)	10 (10.8)	1.4 (0.4 to 5.4)	0.59
Liver disease	06 (11.1)	02 (5.1)	08 (8.6)	0.4 (0.1 to 2.3)	0.32
Renal disease	17 (31.5)	13 (33.3)	30 (32.3)	1.1 (0.5 to 2.6)	0.85
Heart disease	10 (18.5)	09 (23.1)	19 (20.4)	1.3 (0.5 to 3.6)	0.59
Hypertension	32 (59.3)	27 (69.2)	59 (63.4)	1.6 (0.7 to 3.7)	0.33
Hyperlipidemia	25 (46.3)	22 (56.4)	47 (50.5)	1.5 (0.7 to 3.4)	0.34
Diabetes	17 (31.5)	09 (23.1)	26 (28.0)	0.7 (0.3 to 1.7)	0.37

Supplementary table 1 Table 1. Predisposing risk factors for viral reactivation among DRESS patients	**Supplementary table 1 Table 1.** Predisposing risk factors for viral reactivation among DRESS patients	**Supplementary table 1 Table 1.** Predisposing risk factors for viral reactivation among DRESS patients	**Supplementary table 1 Table 1.** Predisposing risk factors for viral reactivation among DRESS patients	**Supplementary table 1 Table 1.** Predisposing risk factors for viral reactivation among DRESS patients	**Supplementary table 1 Table 1.** Predisposing risk factors for viral reactivation among DRESS patients
Autoimmune Treatment, n(%)**	06 (11.3)	01 (2.6)	07 (7.6)	0.2 (0 to 1.8)	0.15
Topical Steroids	26 (51.0)	15 (38.5)	41 (45.6)	Reference	
Systemic Steroids	25 (49.0)	24 (61.5)	49 (54.4)	1.7 (0.7 to 3.9)	0.24
Causative Drug, n(%)					
Anti-epileptic drugs	08 (14.8)	01 (2.6)	09 (9.7)	0.2 (0 to 1.3)	0.08
Allopurinol	19 (35.2)	17 (43.6)	36 (38.7)	1.4 (0.6 to 3.3)	0.41
Bactrim	08 (14.8)	04 (10.3)	12 (12.9)	0.7 (0.2 to 2.4)	0.52
Sulfasalazine	06 (11.1)	03 (7.7)	09 (9.7)	0.7 (0.2 to 2.9)	0.58
NE: Not estimable *	NE: Not estimable *	NE: Not estimable *	NE: Not estimable *	NE: Not estimable *	NE: Not estimable *
Note: Odds ratio (OR) of viral reactivation, liver, kidney, lungs, heart, pancreas, gastrointestinal and others (e.g. thyroid) involvement are based on presence of condition **	Note: Odds ratio (OR) of viral reactivation, liver, kidney, lungs, heart, pancreas, gastrointestinal and others (e.g. thyroid) involvement are based on presence of condition **	Note: Odds ratio (OR) of viral reactivation, liver, kidney, lungs, heart, pancreas, gastrointestinal and others (e.g. thyroid) involvement are based on presence of condition **	Note: Odds ratio (OR) of viral reactivation, liver, kidney, lungs, heart, pancreas, gastrointestinal and others (e.g. thyroid) involvement are based on presence of condition **	Note: Odds ratio (OR) of viral reactivation, liver, kidney, lungs, heart, pancreas, gastrointestinal and others (e.g. thyroid) involvement are based on presence of condition **	Note: Odds ratio (OR) of viral reactivation, liver, kidney, lungs, heart, pancreas, gastrointestinal and others (e.g. thyroid) involvement are based on presence of condition **
No treatment (3)	No treatment (3)	No treatment (3)	No treatment (3)	No treatment (3)	No treatment (3)