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Can endoscopists differentiate cytomegalovirus esophagitis from herpes simplex virus esophagitis based on gross endoscopic findings?

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Abstract

Differential diagnosis between herpes simplex virus (HSV) esophagitis and cytomegalovirus (CMV) esophagitis is challenging because there are many similarities and overlaps between their endoscopic features. The aims of this study were to investigate the implications of the endoscopic findings for the diagnosis of HSV and CMV esophagitis, and to develop a predictive model for differentiating CMV esophagitis from HSV esophagitis.

Patients who underwent endoscopic examination and had pathologically-confirmed HSV or CMV esophagitis were eligible. Clinical characteristics and endoscopic features were retrospectively reviewed and categorized. A predictive model was developed based on parameters identified by logistic regression analysis.

During the 8-year study period, HSV and CMV esophagitis were diagnosed in 85 and 63 patients, respectively. The endoscopic features of esophagitis were categorized and scored as follows: category 1 (−3 points): discrete ulcers or ulcers with vesicles, bullae, or pseudomembranes, category 2 (−2 points): coalescent or geographic ulcers, category 3 (1 points): ulcers with an uneven base, friability, or with a circumferential distribution, category 4 (2 points): punched-out, serpiginous, or healing ulcers with yellowish exudates. And previous history of transplantation (2 point) was included in the model as a discriminating clinical feature. The optimal cutoff point of the prediction model was 0 (area under receiver operating characteristic curve: 0.967), with positive scores favoring CMV esophagitis. Sensitivity, specificity, accuracy, positive predictive value, and negative predictive value were 96.8%, 89.4%, 92.6%, 87.3%, and 97.5%, respectively.

The predictive model based on endoscopic and clinical findings appears to be accurate and useful in differentiating CMV esophagitis from HSV esophagitis.

Abbreviations: AI = artificial intelligence, CMV = Cytomegalovirus, DNA = deoxyribonucleic acid, H&E = hematoxylin and eosin, HSV = herpes simplex virus, IHC = immunohistochemistry, PCR = polymerase chain reaction.

Keywords: cytomegalovirus, endoscopy, esophagitis, herpes simplex virus

1. Introduction

Herpes simplex virus (HSV) and cytomegalovirus (CMV) esophagitis occur predominantly in immunocompromised hosts but can occasionally be found in immunocompetent individuals.[1–4] Viral esophagitis can be life-threatening, particularly in immunocompromised hosts, such as patients who are under immunosuppressive treatment after solid organ or bone marrow transplantation, and those with human immunodeficiency virus infection.[5–7] Therefore, clinical suspicion and precise diagnosis

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are crucial in the management of patients with symptoms such as dysphagia or odynophagia.

The definitive diagnosis of HSV or CMV esophagitis relies on endoscopy with histopathological evaluation, along with viral culture or deoxyribonucleic acid (DNA) polymerase chain reaction (PCR) of tissue specimens. However, tissue-based diagnosis requires several days, and a presumptive diagnosis based on the endoscopic findings usually guides empirical antiviral therapy. Several endoscopic findings, such as the morphology and distribution of lesions, are useful in differential diagnosis of HSV and CMV esophagitis. HSV esophagitis usually involves the mid-to-lower esophagus and presents with multiple shallow ulcers with vesicles. The ulcers are discrete and the intervening mucosa appears normal.[1,8,9] In contrast, the ulcers in CMV esophagitis tend to be deep or punched-out, with a longitudinal appearance.[10] However, many of the endoscopic features are confusingly similar and overlapping, making differential diagnosis challenging. We therefore investigated the diagnostic implications of the endoscopic features of HSV and CMV esophagitis, and developed a predictive model for differentiating between them.

2. Material and methods

2.1. Patients

Data were retrospectively retrieved from the medical records of 169 patients with a presumed diagnosis of HSV or CMV esophagitis on the basis of endoscopic examination between April 2008 and December 2016 at Asan Medical Center, Seoul, Republic of Korea, a 2700-bed tertiary care teaching hospital. Only patients with confirmed HSV or CMV esophagitis which met upper GI symptoms and macroscopic mucosal lesions with histopathologic documentation or immunohistochemistry (IHC) were enrolled. We therefore performed a retrospective cohort study to investigate the diagnostic implications. One experienced endoscopist (DHK) reviewed and categorized all the endoscopic findings. The study protocol was approved by the institutional review board of Asan Medical Center (IRB number 2018–1017), which confirmed that it accorded with the ethical principles of the Declaration of Helsinki.

We investigated whether the extent of clinical experience affected the diagnostic accuracy of HSV and CMV esophagitis. Experienced endoscopists were arbitrarily defined as having 15 years or more of experience in performing gastrointestinal endoscopy. Endoscopic pictures of 19 randomly selected cases (9 HSV and 10 CMV esophagitis) were presented to eight experienced and five less-experienced endoscopists blindly asked to identify them as: HSV esophagitis, CMV esophagitis, or indeterminate. To avoid random decisions between HSV and CMV esophagitis, indeterminate answers were considered to be wrong. The average diagnostic accuracies were evaluated and compared.

2.2. Statistical analysis

Categorical variables were compared using the chi-square or Fisher exact test, and continuous variables using Student's *t* test and the Mann-Whitney *U* test, as appropriate. All tests of significance were two-tailed and a *P* value of less than .05 was considered to indicate statistical significance. Calculations were performed using SPSS for Windows software package, version 21.0 (SPSS Inc., Chicago, IL).

To develop the predictive model, distinguishing features of HSV or CMV esophagitis were identified and listed, and classified into four categories using average linkage clustering (Supplemental Digital Figure 3, http://links.lww.com/MD/D15). Logistic regression analysis was used to identify candidate variables for differentiating CMV esophagitis from HSV esophagitis. Each β-coefficient was rounded off and converted to an integer, and integrated into the score. Receiver operating characteristic (ROC) analysis was performed, and areas under ROC curves were calculated to assess the ability to discriminate CMV esophagitis from HSV esophagitis and to determine the optimal cutoff value for predictive diagnosis. In addition, the calibration of the model was assessed using the Hosmer-Lemeshow test (Supplemental Fig. 4, http://links.lww.com/MD/D15). Data were analyzed with R software package version (3.4.3) and the *PredictABEL* package was used to build up the final model and to assess its performance.

3. Results

3.1. Demographic and clinical features

A total of 169 patients were initially screened. Of these, 21 were excluded from the analysis for the following reasons: 6 for recurrent infections, 11 for co-infection with HSV and CMV, 3 for missing endoscopic findings, and 1 for diagnosis other than esophagitis. Ultimately, 148 patients with histopathologically-confirmed HSV (n = 85) or CMV (n = 63) esophagitis were included in the analysis (Fig. 1). The baseline characteristics of the study patients are summarized in Table 1. The median age was 59.3 years (interquartile range [IQR], 51.8–70.0 years) and 118 patients (79.7%) were immunocompromised. CMV esophagitis was more common in solid organ transplant recipients than HSV esophagitis (36.5% and 12.9%, $P = .001$). The median interval between transplantation and the development of esophagitis showed a trend toward being shorter in CMV esophagitis (4 months; IQR, 1–7 months) than in HSV esophagitis (20 months; IQR, 2–12 months) ($P = .084$). From October 2011, IHC was performed to diagnose HSV esophagitis, and all the patients (n = 37) who underwent IHC tested positive. For CMV esophagitis, 60 (95.2%) of the 63 patients ultimately diagnose with CMV esophagitis gave positive results for IHC. Of 63 patients with confirmed CMV esophagitis, 45 (71%) underwent CMV antigenemia tests. Of these 45 patients, 34 (76%) showed positive CMV antigenemia. Of 63 patients with confirmed CMV esophagitis, 46 (73%) and 12 (19%) underwent tissue CMV PCR tests and blood CMV PCR tests, respectively. Of the 46 patients who underwent tissue CMV PCR tests, 41 (91%) revealed positive tissue CMV PCR results. Of the 12 patients who underwent tissue CMV PCR tests, 11 (92%) revealed positive blood CMV PCR results. Before definitive diagnosis, 6 patients (7.1%) ultimately diagnosed with HSV esophagitis and 37 (58.7%) with CMV esophagitis received empirical antiviral therapy, and the remaining patients were treated conservatively. After the pathological diagnosis, 47.1% of the patients ultimately diagnosed with HSV esophagitis received acyclovir, and 81.0% of those with CMV esophagitis received ganciclovir.

3.2. Clinical experience of endoscopy and diagnostic accuracy

Eight experienced endoscopists and 5 less-experienced ones were asked to make a set of diagnoses of esophagitis based on

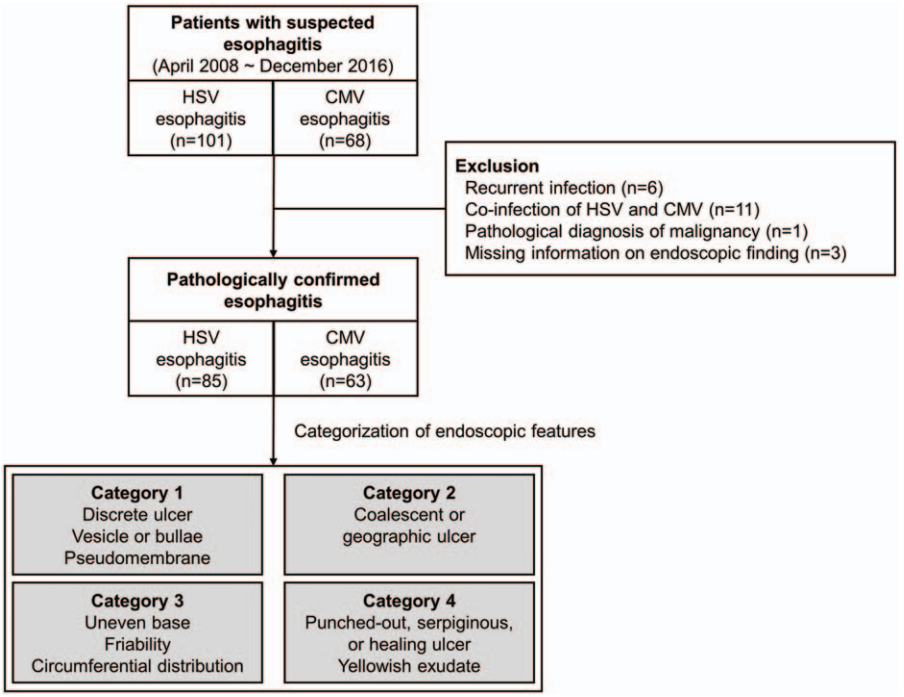

Figure 1. Flowchart of the study.

Table 1

Demographic and clinical characteristics of patients with viral esophagitis.

Variable	HSV (n = 85)	CMV (n = 63)	*P* value
Age, years, median (IQR)	58 (42–72)	61 (57–68)	.222
Male gender	60 (70.6)	40 (63.5)	.560
Comorbidity			
Solid tumor	27 (31.8)	19 (30.2)	.834
Diabetes	14 (16.5)	17 (27.0)	.125
Transplantation	13 (15.3)	24 (38.1)	.001
Solid organ	11 (12.9)	23 (36.5)	.001
Hematopoietic stem cell	2 (2.4)	1 (1.6)	.999
Hematologic malignancy	6 (7.1)	3 (4.8)	.733
Rheumatologic disease	6 (7.1)	2 (3.2)	.467
Chronic kidney disease	4 (4.7)	3 (4.8)	.999
Liver cirrhosis	1 (1.2)	2 (3.2)	.575
HIV infection	0	2 (3.2)	.179
Steroid user*	2 (2.4)	0	.507
No underlying illness	4 (4.7)	0	.136
Time of onset after transplantation			
Months (IQR)	20 (2–12)	4 (1–7)	.084
Duration of symptoms, days, media (IQR)	4.81 ± 3.53	7.5 ± 5.65	.036
Treatment before pathological diagnosis			
Ganciclovir	3 (3.5)	35 (55.6)	<.001
Acyclovir	3 (3.5)	2 (3.2)	.999
Conservative management	79 (92.9)	26 (41.3)	<.001
Treatment after pathological diagnosis			
Ganciclovir	4 (4.7)	51 (81.0)	<.001
Valganciclovir	2 (2.4)	1 (1.6)	<.001
Acyclovir	40 (47.1)		.136
Famciclovir	4 (4.7)		.999
Conservative management	35 (41.2)	11 (17.5)	.002

Data are presented as number of patients (%) or median (interquartile range).
CMV = cytomegalovirus, HIV = human immunodeficiency virus, HSV = herpes simplex virus.
* Patients treated with steroid for asthma or interstitial lung disease.

endoscopic pictures. Their average diagnostic accuracy was 74.7% for the experienced endoscopists, and 74.3% for the less-experienced endoscopists (Table 2). Thus, the accuracy of diagnosis of viral esophagitis did not differ between the experienced and less-experienced endoscopists ($P = .935$) (Table 2).

3.3. Endoscopic features of esophagitis

The typical endoscopic findings for HSV esophagitis and CMV esophagitis are shown in Figures 2 and 3, respectively. Endoscopic findings of discrete ulcers, bullae or vesicles, pseudomembranes, and shouldered margins were significantly more common in patients ultimately diagnosed with HSV esophagitis than in those ultimately diagnosed with CMV esophagitis (Table 3). In addition, coalescent features and geographic ulcers were more frequent in HSV esophagitis. In contrast, deep or punched-out ulcers, serpiginous ulcers, healing ulcers, ulcers with an uneven base or yellowish exudate, and with circumferential involvement, were significantly more common in CMV esophagitis than in HSV esophagitis.

3.4. Development of predictive models for differentiating between HSV and CMV esophagitis

To develop a predictive model, candidate scoring components were selected from the list of variables differentiating CMV esophagitis from HSV esophagitis identified by logistic regression analysis. In addition, the endoscopic features were classified into four categories as follows: category 1, discrete ulcers or ulcers with vesicles, bullae, or pseudomembranes, category 2, coalescent or geographic ulcers, category 3, ulcers with an uneven base, friability, or a circumferential

Table 2

Average percentages of correct answers in randomly-selected cases of esophagitis.

	HSV (n = 9)	CMV (n = 10)	Total
Experienced endoscopists (n = 8)	70.8% (54.6–90.9%)	77.5% (61.1–88.9%)	74.3% (63.4–84.4%)
Less experienced endoscopists (n = 5)	69.0% (55.0–86.9%)	80.0% (63.6–91.4%)	74.7% (63.8–84.8%)
Total	70.1% (62.5~77.7%)	78.5% (72.7–84.3%)	74.3% (69.3–79.2%)

Data are presented as average percentages (95% confidence interval).
CMV = cytomegalovirus, HSV = herpes simplex virus.

distribution, category 4, punched-out, serpiginous, or healing ulcers with yellowish exudates. In addition, previous history of transplantation was included in the model as a discriminating clinical feature. Using the above categories and the single clinical variable, β-coefficients were calculated by logistic regression analysis, and each component of the predictive model was scored from −3 to +2 (Supplemental Table 1, http://links.lww.com/MD/D15).

When the sum of the five scores was used, the optimal cutoff score was −0.5, where a positive score favors CMV esophagitis (Supplemental Figure 1, http://links.lww.com/MD/D15). However, we chose a cut-off of 0 for clinical convenience because it is more intuitive and easy for distinguishing HSV esophagitis from CMV esophagitis without sacrificing sensitivity. A ROC analysis of the scoring system revealed good discriminatory power, with an area under the ROC curve of 0.967 (Supplemental Fig. 2,

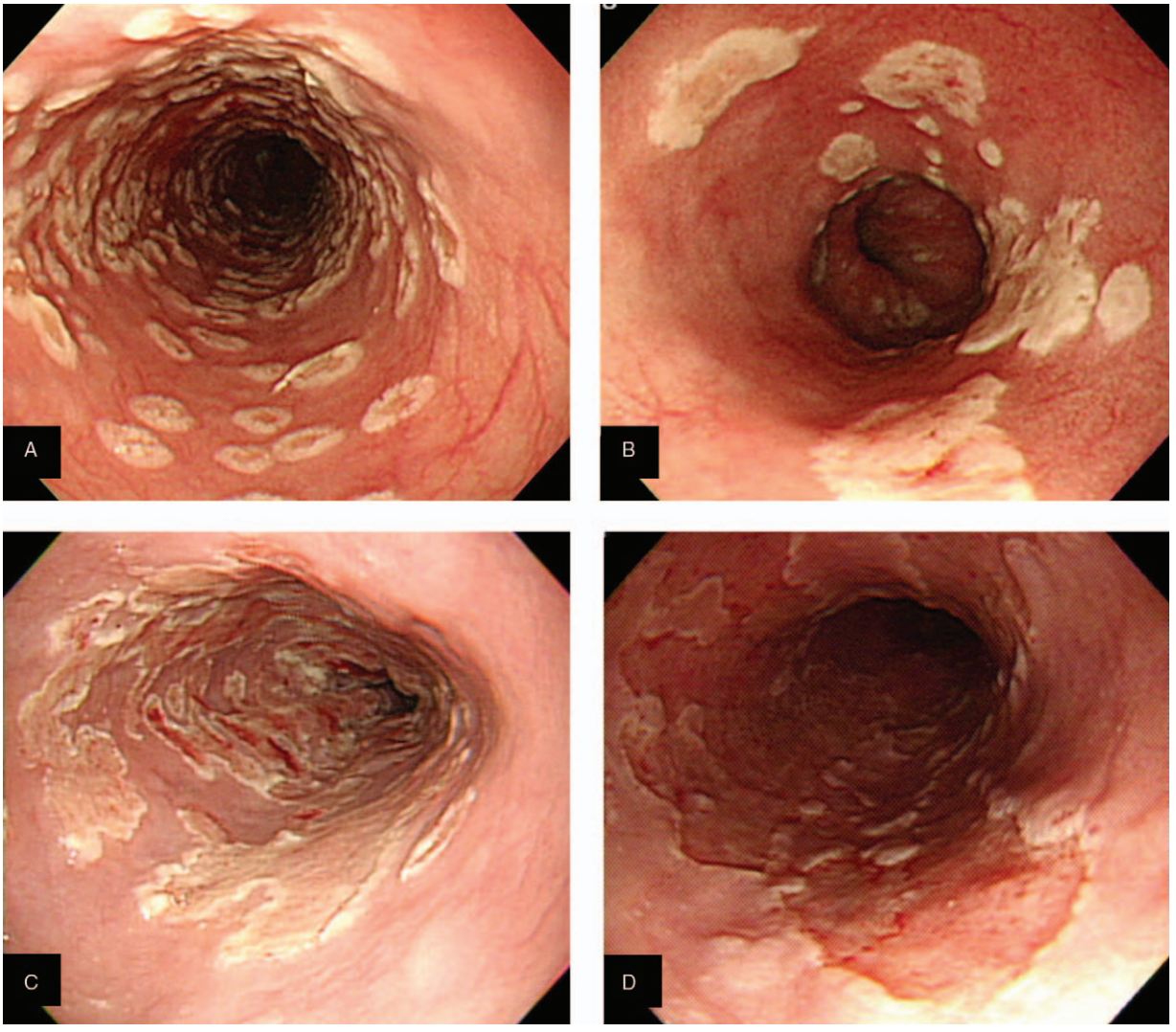

Figure 2. Endoscopic features of herpes simplex virus esophagitis. (A) Diffusely distributed white or yellowish lesions with vesicles. The lesions are demarcated, and the intervening mucosa appears normal. (B) Shallow ulcers with pseudomembranes. (C) Multiple small shallow ulcers formed by coalescence of precursor vesicles. (D) Well-demarcated shallow ulcers with a circumferential distribution.

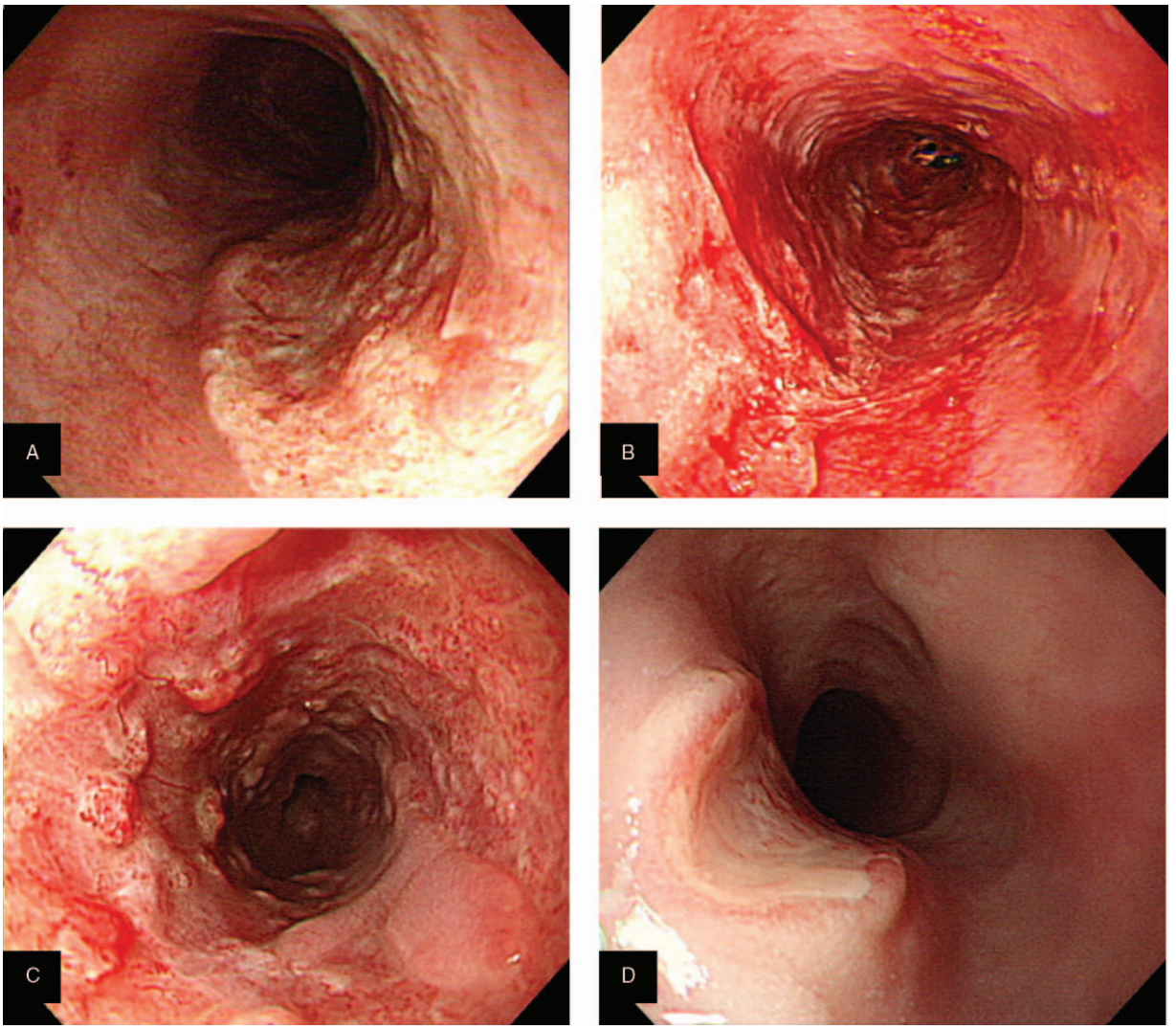

Figure 3. Endoscopic features of cytomegalovirus esophagitis. (A) Longitudinal ulcer with uneven base. (B) Ill-defined, circumferential ulcer with friability. (C) Geographic, healing ulcer. (D) Deep, punch-out ulcer with shouldered margin.

Table 3

Endoscopic features of HSV and CMV esophagitis.

Variable	HSV (n = 85)	CMV (n = 63)	*P* value
Discrete ulcers	56 (65.9)	1 (1.6)	<.001
Bullae or vesicles	45 (52.9)	0	<.001
Pseudomembranes	60 (70.6)	2 (3.2)	<.001
Coalescent features	37 (43.5)	0	<.001
Geographic ulcers	34 (40.0)	9 (14.3)	.001
Friability	8 (9.4)	13 (20.6)	.090
Uneven bases	0	22 (34.9)	<.001
Deep or punched-out ulcers	4 (4.7)	23 (36.5)	<.001
Healing ulcers	0	38 (60.3)	<.001
Serpiginous ulcers	2 (2.4)	13 (20.6)	.001
Yellowish exudate	7 (8.2)	46 (73.0)	<.001
Shouldered margin	68 (80.0)	9 (14.3)	<.001
Circumferential involvement	12 (14.1)	24 (38.1)	.002
Distribution			
Upper esophagus	4 (4.7)	4 (6.3)	.723
Middle esophagus	10 (11.8)	12 (19.0)	.218
Lower esophagus	25 (29.4)	13 (20.6)	.270
Two or more segments	46 (54.1)	25 (39.6)	.083

CMV = cytomegalovirus, HSV = herpes simplex virus.

http://links.lww.com/MD/D15). Sensitivity, specificity, accuracy, positive predictive value, and negative predictive value were 96.8%, 89.4%, 92.6%, 87.3%, and 97.5% respectively (Supplemental Table 2, http://links.lww.com/MD/D15).

4. Discussion

Clinical suspicion and precise diagnosis of esophagitis are important for the correct timing of treatment and for avoiding administering an inappropriate antiviral agent. However, making a presumptive diagnosis of CMV vs HSV esophagitis based on the endoscopic findings alone is challenging because many of their endoscopic features overlap. In fact, we found that about a quarter of the patients who were presumptively diagnosed as HSV or CMV esophagitis based on the endoscopic findings were incorrectly assigned regardless of the endoscopists' expertise. It means that diagnosis of CMV or HSV esophagitis on the endoscopic findings alone might be insufficient because underlying disease is substantially overlapping between two

diseases and some findings are can be seen both HSV esophagitis and CMV esophagitis. To help endoscopists' tentative gross findings and guide appropriate empirical antiviral therapy until definitive diagnostic results are available, the clinical characteristics and endoscopic features of esophagitis were analyzed, and a predictive model for differentiating CMV esophagitis from HSV esophagitis was developed. The predictive model consists of endoscopic features divided into 4 categories plus clinical factor. The model had good powers of discrimination, suggesting that it is useful for differential diagnosis of esophagitis.

A diagnosis of HSV or CMV esophagitis is made on the basis of endoscopic findings and histopathological examination of the lesions. A diagnosis of HSV infection is generally based on the Tzank smear test, tissue culture, or IHC using tissue specimens.[11] For CMV esophagitis, hematoxylin and eosin (H&E) staining reveals hypertrophic cells containing large eosinophilic cytoplasmic inclusions surrounded by a clear halo, described as an "owl's eye".[12,13] IHC increases the diagnostic sensitivity to 93% with specificity approaching 100%.[14] However, histological evaluation or PCR may take several days, thus delaying confirmation of the diagnosis and the initiation of antiviral therapy. As misdiagnosis and inappropriate management may expose patients to unnecessary drug toxicity and increase medical costs, differential diagnosis of HSV and CMV esophagitis based on the endoscopic features is crucial in clinical practice. However, we found in the present study that about one quarter of presumptive diagnoses of esophagitis were incorrect, regardless of the expertise of the endoscopist.

Certain endoscopic and clinical features are known to be helpful in discriminating CMV esophagitis from HSV esophagitis. Endoscopic findings of discrete ulcers, presence of vesicles or bullae, shouldered margins, and coalescent or geographic ulcers were more frequent in patients with HSV esophagitis, whereas punch-out ulcers, serpiginous ulcers, ulcers with an uneven base, friability, and with a circumferential distribution were more frequent in CMV esophagitis in this study. These findings are consistent with previous observations.[15,16] To generate a prediction model, we divided the endoscopic findings into four categories, and a previous history of transplantation was added as a clinical factor for discriminating CMV esophagitis from HSV esophagitis. The sensitivity, specificity, and accuracy of the diagnosis of CMV esophagitis were 96.8%, 89.4%, and 92.6%, respectively. Our endoscopic classification and its incorporation into an objective prediction model may improve diagnostic accuracy in patients with esophagitis.

Recently, artificial intelligence (AI) with deep learning of digital imaging has yielded promising results for diagnosing diabetic retinopathy[17] and detecting lymph node metastasis in breast cancer.[18] It has also been demonstrated that convolutional neural network-aided diagnosis using upper gastrointestinal endoscopy images is useful for identifying *H. pylori* infection.[19] In this context, our prediction model based mainly on endoscopic images may be useful for developing AI-aided diagnosis of viral esophagitis. Further studies are needed in this area.

Our study has several limitations. As it was a retrospective study of patients who visited a tertiary-care hospital with a high volume of transplantation, the prevalence of HSV and CMV esophagitis may not reflect those in the general population. Another limitation is that we could not perform internal or external validation because of the small number of cases. Further studies are warranted to validate this prediction model. Third, patient population in this study was not homogenous in terms of underlying diseases. Underlying disease or immunosuppression may affect the endoscopic findings as well as the incidence of HSV or CMV esophagitis. So, further studies are needed about the effect of immunosuppression on the endoscopic findings in HSV or CMV esophagitis. Finally, the specificity of 89% for our clinical prediction model is still suboptimal for clinical use in real clinical practice to confirm HSV or CMV esophagitis. So, further diagnostic tests such as immunohistochemical staining or molecular tests are needed to confirm the diagnosis. However, it takes a few days. Therefore, our predictive model may help to reduce inappropriate use of acyclovir or unnecessary exposure to ganciclovir toxicity until these confirmative test results are available. It is worth to note that the "possible" category of CMV GI disease including blood by nuclear acid test (e.g., PCR) or antigenemia or CMV documented by PCR from tissue biopsies according to the recent IDSA guidelines[20] may open a new way to suspect GI CMV disease and/or decide empirical antiviral agent. So, further studies are needed on the clinical usefulness of our clinical prediction model or new diagnostic category for the early management in patients with suspected HSV or CMV esophagitis.

In conclusion, the endoscopic findings were helpful in the differential diagnosis of CMV and HSV esophagitis. A prediction model based on the endoscopic findings and a clinical factor seems to be reliable for differentiating CMV esophagitis from HSV esophagitis, and may be useful for guiding empirical antiviral therapy until a definitive diagnosis can be made.

Author contributions

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Do Hoon Kim: study concept and design; data acquisition; critical revision of the manuscript for important intellectual content, study supervision
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