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Clinical Characteristics and Manifestation of Herpes Esophagitis

One Single-center Experience in Taiwan

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Abstract: We aimed to investigate the clinical characteristics of patients with herpes esophagitis (HE) based on endoscopic typing.

Herpes simplex virus infection in the gastrointestinal tract primarily affects the esophagus. However, little is known about the presentation, endoscopic findings, and outcomes of HE.

From 2003 to 2013, 47 patients with HE were identified histologically from among 1843 patients with esophageal ulcers. Personal data, underlying disease, esophagogastroduodenoscopy indication, endoscopic characteristics, pathological findings, laboratory data, and outcomes were collected. Endoscopic findings were classified into 3 types based on gross appearance and were correlated with clinical presentation.

The mean age of patients was 62.04 ± 14.76 years, and most patients were men (39/47, 83%). The most common symptoms were odynophagia/dysphagia (20/47, 42.6%). Whereas 25 patients (53.2%) were diagnosed with malignancy, it was related to human immunodeficiency virus in only 1 patient (2.1%). HE was classified into 3 types based on endoscopic images: type I (n = 19), type II (n = 10), and type III (n = 18). The majority of patients with HE type III had sepsis (72%) and obvious leukocytosis than the other 2 types ($P = 0.03$). The overall mortality rate was 6.4% (3/47), and most of the patients who died (66.7% [2/3]) belonged to the endoscopic classification type III group. Clinical parameters were analyzed for the risk of poor outcome. Postchemotherapy and/or radiotherapy were associated with 30-day mortality after appearance of HE ($P < 0.05$).

Herpes esophagitis primarily affects men and patients with malignancy or sepsis. However, the disease is usually self-limiting, and HE-related mortality is low. Relationship between severity of endoscopic findings and patients' outcome remains questionable. Further prospective study is needed.

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Abbreviations: CCRT = concurrent chemoradiotherapy, COPD = chronic obstructive pulmonary disease, ESRD = end-stage renal disease, HE = herpes esophagitis, HIV = human immunodeficiency virus, HSV = herpes simplex virus, WBC = white blood cell.

INTRODUCTION

Esophageal infections are rare in immunocompetent individuals, but common in immunosuppressed patients, particularly in patients with end-stage renal disease (ESRD), malignancy, transplanted organs, and human immunodeficiency virus (HIV), and in those undergoing steroid or immunosuppressive therapy.[1–6] Herpes simplex virus (HSV) infection is one of the common opportunistic infections among immunocompromised patients. The most commonly affected part of the alimentary tract is the esophagus, with an incidence of 0.5% to 2% based on an autopsy series.[3,7–9] Dysphagia and odynophagia are the typical symptoms of herpes esophagitis (HE). Endoscopic findings reveal erosions or ulcers, typically involving the lower third of the esophagus. The correlations of clinical manifestations in patients with HE with endoscopic typing of HE has not been widely described. Therefore, in the present study, we aimed to investigate the clinical characteristics of HE in patients based on endoscopic typing.

METHODS

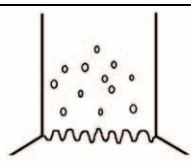
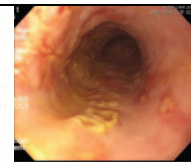
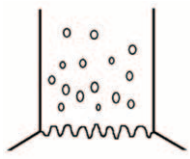
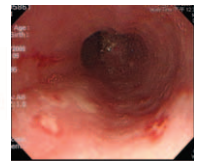
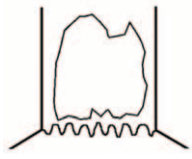
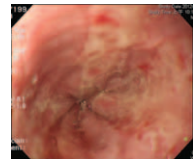
Patient Selection

A total of 47 patients with histologically proven HSV infections were identified from among 1843 patients with esophageal ulcers, who presented at the Chang Gung Memorial Hospital (CGMH) Medical Center in Linkou between January 2003 and December 2013. We retrospectively reviewed these patients' pathological reports. Patients' personal data collected from medical records for further analysis included age, sex, smoking habits, alcohol consumption, and the presence of underlying systemic diseases, such as diabetes mellitus, ESRD, chronic obstructive pulmonary disease (COPD), HIV infection and malignancy, and history of organ transplantation. This study was carried out with preapproval from the Linkou CGMH Institutional Review Board (104–2794B), and patient consent was waived.

Endoscopic Manifestations and Histological Diagnosis of HSV Infection

We recorded the indications of esophagogastroduodenoscopy (EGD) from the medical reports, including odynophagia/dysphagia, heartburn sensation, nausea/vomiting, gastrointestinal bleeding, epigastric pain, chest pain, and so on, and endoscopic manifestations (friable mucosa, ulcers, polyploid/

TABLE 1. Classifications of Herpes Esophagitis (Gross Appearance Vs Endoscopic Images)

Type	Typical gross appearance†	Histology†	Endoscopic image	Description and location
I				**Description:** small, punched-out lesions with raised margins; a slightly yellowish color and fibrin exudation at the centers of lesions **Location:** the middle and lower thirds of the esophagus
II				**Description:** small, punched-out lesions without raised margins; no color and no exudation **Location:** the middle and lower thirds of the esophagus
III				**Description:** multiple ulcers become confluent, like a map **Location:** the extended esophageal lesions

†Typical gross appearance and histology pictures were modified from schematic figures of herpes simplex esophagitis.[7]

nodular pattern, and site of involvement). Serological findings, such as anti-HSV immunoglobulin (Ig)M and anti-HSV IgG, were also collected. All endoscopic images of HE were reviewed by experienced endoscopists at our department of gastroenterology and classified into 3 typical types according to Itoh typing by gross appearance (Table 1).[7]

Histological identification of HSV infection includes multinucleated giant cells, with nuclear molding and margination of chromatin or the classic Cowdry A inclusion bodies on routine hematoxylin and eosin-stained sections of formalin-fixed, paraffin-embedded materials and/or immunohistochemical staining (Figure 1).

Statistical Analysis

For the potential risks of HE, several factors, including age, sex, underlying diseases, smoking, alcohol, and white blood cell count (WBC) (/mm^3), were analyzed by the chi-square test for categorical variables and *t* tests for continuous variables. For the clinical outcome of HE, Kaplan–Meier estimate was used to evaluate importance of clinical risk factors (eg, underlying diseases, WBC, treatment, and endoscopic typing). A 2-sided *P* value <0.05 was considered statistically significant. All statistical analyses were performed by using IBM SPSS Statistics, Version 20.0 (IBM Corp., Armonk, NY).

RESULTS

Patient Characteristics and Clinical Manifestations of HE

In the database of 1843 patients with esophageal ulcers, 47 patients (2.6%) were diagnosed as having HE. The mean age of the patients was 62.04 ± 14.76 years (range 13–87 years), and the male-to-female ratio was 4.9:1. Odynophagia/dysphagia (20/47 patients, 42.6%) and gastrointestinal bleeding (15/47 patients, 31.9%) were common symptoms (Table 2). Twenty-one patients were smokers, and 14 were alcohol consumers.

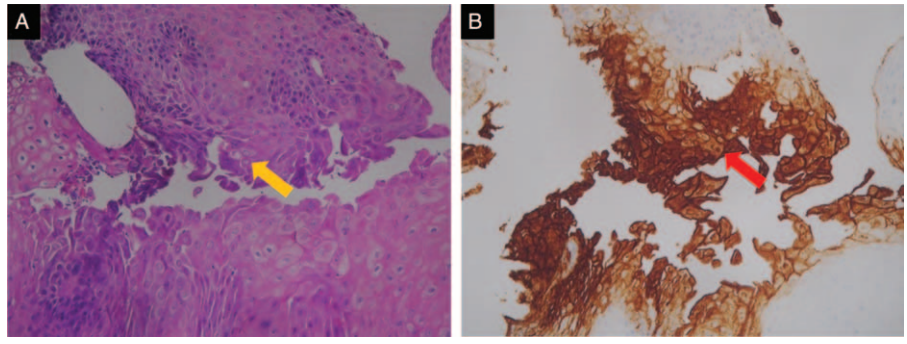


FIGURE 1. Histologic findings for herpes esophagitis. A, Hematoxylin and eosin (×400) staining shows typical multinucleated epithelial cells with ground-glass nuclei and margination of the chromatin (yellow arrow). These cells are positive for herpes simplex virus infection. B, Inclusion bodies (red arrow) can be observed in the ulcerative esophageal epithelial cells with specific antibodies (in brown) against herpes simplex virus 1 (immunohistochemical stain ×400).

TABLE 2. Clinical Data and Endoscopic Patterns of Patients With Herpes Esophagitis

No.	Age/Sex	Underlying Disease	Gastrointestinal Symptom	Endoscopic Features				Serum HSV Marker
				Friable Mucosa	Ulcer	Polyploid/ Nodular Pattern	Location at Esophagus	
Endoscopic type I								
1	70/F	ESRD, DM	GI bleeding	P	N	N	Entire	HSV-1 IgG, HSV-2 IgG
2	66/M	Malignancy	Odynophagia/dysphagia	N	Few	P	Distal	NA
3	63/M	Malignancy	Odynophagia/dysphagia	P	Numerous	N	Distal	NA
4	39/M	ESRD	Odynophagia/dysphagia	P	N	N	Entire	NA
5	77/M	Malignancy, ESRD	GI bleeding	N	N	P	Mid	NA
6	68/M	Malignancy, COPD	Epigastric pain	P	N	N	Mid-distal	NA
7	57/M	Malignancy	Epigastric pain	P	N	N	Entire	NA
8	58/M	Malignancy, COPD	Odynophagia/dysphagia	P	N	N	Mid-distal	NA
9	57/F	Malignancy	Odynophagia/dysphagia	P	Numerous	N	Upper	NA
10	74/F	Malignancy, DM	Odynophagia/dysphagia	N	Few	N	Mid-distal	NA
11	56/F	ESRD, DM	Epigastric pain	N	Few	N	Upper	NA
12	72/M	Malignancy	Odynophagia/dysphagia	P	Numerous	N	Mid-distal	NA
13	66/M	Malignancy, DM, LC	Epigastric pain	P	N	N	Mid	NA
14	65/M	Malignancy	Substernal chest pain	N	N	P	Mid-distal	NA
15	76/M	Malignancy, ESRD, DM	GI bleeding	N	Numerous	N	Mid	NA
16	13/M	Malignancy	Epigastric pain	P	Numerous	N	Mid-distal	NA
17	53/M	NA	GI bleeding	N	Few	N	Distal	NA
18	76/M	ESRD, COPD	Nausea/vomiting	N	Numerous	N	Mid	NA
19	78/M	Malignancy	Nausea/vomiting	N	Few	N	Mid	NA
Endoscopic type II								
1	63/M	ESRD	GI bleeding	N	Numerous	N	Mid-distal	NA
2	50/M	DM	GI bleeding	N	Few	N	Mid-distal	NA
3	47/M	NA	Odynophagia/dysphagia	P	N	N	Mid-distal	NA
4	63/M	COPD	GI bleeding	P	Numerous	N	Mid-distal	NA
5	74/M	NA	Odynophagia/dysphagia	N	Numerous	N	Distal	NA
6	47/M	Malignancy	Odynophagia/dysphagia	P	N	N	Mid	NA
7	57/M	Malignancy, LC	GI bleeding	N	Numerous	N	Mid-distal	NA
8	58/M	Malignancy	Odynophagia/dysphagia	P	N	N	Mid-distal	NA
9	24/M	HIV	Odynophagia/dysphagia	N	Numerous	N	Distal	NA
10	68/F	DM	Odynophagia/dysphagia	P	N	N	Mid	HSV-1 IgG
Endoscopic type III								
1	53/M	NA	Epigastric pain	P	N	N	Mid-distal	NA
2	87/F	Malignancy, ESRD	GI bleeding	P	N	N	Entire	NA
3	48/M	NA	Odynophagia/dysphagia	P	Numerous	P	Distal	NA
4	75/M	Malignancy, DM	Odynophagia/dysphagia	N	Numerous	N	Mid-distal	NA
5	59/M	Malignancy	GI bleeding	N	Numerous	N	Mid-distal	NA
6	77/M	COPD	GI bleeding	N	Numerous	N	Entire	NA

No.	Age/Sex	Underlying Disease	Gastrointestinal Symptom	Endoscopic Features				Serum HSV Marker
				Friable Mucosa	Ulcer	Polyploid/ Nodular Pattern	Location at Esophagus	
7	67/M	ESRD, DM	Epigastric pain	N	Numerous	N	Mid-distal	NA
8	77/M	Malignancy, ESRD, COPD	GI bleeding	N	Numerous	N	Entire	NA
9	75/M	Malignancy	Odynophagia/dysphagia	P	N	N	Entire	NA
10	58/M	COPD	Odynophagia/dysphagia	P	N	N	Mid-distal	NA
11	43/F	ESRD	Epigastric pain	N	Numerous	N	Distal	NA
12	62/M	Malignancy	Odynophagia/dysphagia	P	Numerous	N	Entire	NA
13	77/F	COPD	GI bleeding	P	Numerous	N	Entire	NA
14	79/M	DM, COPD	GI bleeding	N	Numerous	N	Mid-distal	NA
15	80/M	COPD	Odynophagia/dysphagia	P	Numerous	N	Mid-distal	NA
16	42/M	DM, LC, transplant	Odynophagia/dysphagia	N	Numerous	N	Mid-distal	NA
17	56/M	Malignancy	GI bleeding	N	Numerous	N	Entire	NA
18	66/M	Malignancy, DM	Nausea/vomiting	P	Numerous	N	Distal	NA

COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus, ESRD = end-stage renal disease, F = female, GI = gastrointestinal, HIV = human immunodeficiency virus, LC = liver cirrhosis, M = male, N = negative, NA = not applicable, P = positive.

Among the 47 patients, 11 had ESRD and were on regular hemodialysis, 3 had liver cirrhosis, 10 had been diagnosed with COPD, 12 had diabetes mellitus, and 1 had undergone organ transplantation. One patient (1/47 patients, 2.1%) was infected with HIV. Twenty-five of 47 patients (53.2%) were diagnosed with malignancy, including lung cancer (7 patients), esophageal cancer (3 patients), gastric cancer (3 patients), colon cancer (3 patients), head and neck cancer (3 patients), lymphoma (2 patients), breast cancer (1 patient), bladder cancer (1 patient), hepatocellular carcinoma (1 patient), and pancreatic cancer (1 patient). Patients with malignancy had undergone chemotherapy (24%), radiotherapy (12%), and concurrent chemoradiotherapy (CCRT) (28%).

Endoscopic Findings of HE

The EGD images were assessed by experienced endoscopists. Friable mucosa (51.1%; 24/47), ulcers (66%; 31/47), and polypoid/nodular patterns (8.5%; 4/47) were recorded on endoscopic reports. Regarding esophagitis location, 21.3% (10/47) of patients had HE over the entire esophagus, and 4.3% (2/47) had it in the upper third of the esophagus. In most patients (74.5%; 35/47), HSV-related ulcers were located at the middle to distal esophagus (Table 2).

Analysis of Clinical Factors in Patients With HE

In a previously published report on HE, macroscopic features were described and classified into 3 types (Table 1).[7] Type I was characterized by small, punched-out lesions with raised margins usually coated with yellowish exudate, whereas type II was characterized by small, punched-out lesions, but no raised margins or exudate. Type I and type II were primarily located in the middle to lower third of the esophagus. Type III HE was characterized by multiple ulcers, with a map-like, confluent appearance over the entire esophagus.

Endoscopic images of the 47 cases of HE were reviewed and classified into these 3 types, including type I (n = 19), type II (n = 10), and type III (n = 18). The locations for types I and II HE were recorded primarily at the mid-to-distal third of the esophagus (73.7% and 100%, respectively). Type III seemed more extensive than were the other types.

The clinical characteristics and risk factors of the patients with HE were reviewed and analyzed between different endoscopic typing. No significantly different factor was found, except for the WBC (Table 3), which differed significantly among HSV endoscopic typing ($P = 0.03$). Among patients with HE type III, 72% suffered sepsis, whereas less than 50% patients with HE type I or II had sepsis (type I: 47% and type II: 40%). Two patients belonging to the endoscopic type III group died—1 of pneumonia with respiratory failure and 1 of intra-abdominal infection with septic shock. Clinical risk factors (eg, WBC, HE endoscopic typing, underlying diseases, and treatment) were also analyzed to correlate the clinical outcome of HE. Only the factor of receiving chemotherapy and/or radiotherapy for clinical outcome revealed significant difference ($P < 0.05$) (Figure 2).

DISCUSSION

Herpes esophagitis was first reported by Johnson in 1940 and is commonly seen in immunocompromised hosts, such as those with malignancy, HIV infection, and organ transplantation, and in those undergoing systemic corticosteroid or other immunosuppressive therapy.[1,3,5,10–12] Male

TABLE 3. Clinical Characteristics of Patients With Herpes Esophagitis by Endoscopic Typing

	Total (N = 47)	Type I (n = 19)	Type II (n = 10)	Type III (n = 18)	*P*
Age ≥60 years	27 (57%)	12 (63%)	4 (40%)	11 (61%)	0.45
Male sex	39 (83%)	15 (79%)	9 (90%)	15 (83%)	0.75
Smoking	21 (45%)	8 (42%)	3 (30%)	10 (56%)	0.41
Alcohol	14 (30%)	5 (26%)	3 (30%)	6 (33%)	0.89
Underlying disease					
ESRD	11 (23%)	6 (32%)	1 (10%)	4 (22%)	0.42
Type 2 DM	12 (26%)	5 (26%)	2 (20%)	5 (28%)	0.89
Liver cirrhosis	3 (6.4%)	1 (5.3%)	1 (10%)	1 (5.6%)	0.87
COPD	10 (21%)	3 (16%)	1 (10%)	6 (33%)	0.26
HIV infection	1 (2.1%)	0 (0%)	1 (10%)	0 (0%)	0.15
Malignancy	25 (53%)	14 (74%)	3 (30%)	8 (44%)	0.05
Status of infection	26 (55%)	9 (47%)	4 (40%)	13 (72%)	0.17
Sepsis	23 (49%)	8 (42%)	4 (40%)	11 (61%)	0.42
Sepsis with shock	3 (6.4%)	1 (5.3%)	0 (0%)	2 (11%)	0.49
Other factors					
WBC (/mm^3, mean ± SD)	9914 ± 9949	7137 ± 4854	5057 ± 1604	14,272 ± 13195	0.03
Steroids	15 (32%)	7 (37%)	2 (20%)	6 (33%)	0.64
Mortality	3 (6.4%)	1 (5.3%)	0 (0%)	2 (11%)	0.49

COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus, ESRD = end-stage renal disease, HIV = human immunodeficiency virus, SD = standard deviation, WBC = white blood cell.

sex is predominant (M/F: 2.3–4.7) in patients with HE (Table 4).[7,10,13–16] Most patients undergo endoscopic examination due to such symptoms as odynophagia, dysphagia, chest pain, and gastrointestinal bleeding. A comparison of HE between immunocompetent and immunocompromised hosts showed that, though clinical symptoms are similar, for immunocompromised hosts, the endoscopic appearances are usually more severe and the recovery time is much longer. Immunocompetent hosts are typically diagnosed at a younger average age than are immunocompromised hosts. Previously published reports of HE are summarized in Table 4. In our study, male was also predominant (M/F: 4.8) and 57% patients were older than 60 years. Immunocompromised status was recorded, including malignancy (53%), HIV (2.1%), organ transplantation (2.1%), or other immunosuppressed therapy.

Herpes simplex virus infects the epithelial cells of the esophagus. Thus, histologic findings based on staining with hematoxylin and eosin show large, red intranuclear inclusion bodies (Cowdry A inclusion bodies) and/or multinucleated giant cells with ground-glass nuclei in epithelial cells. Immunohistochemical stains are another useful method for diagnosing HSV.[13] Diagnosis of HE depends on pathology for suspicious area of esophageal erosion or ulcer, and the preferred location of endoscopic biopsy should be taken from the margin of ulcer. Based on the literature, there have been many endoscopic descriptions of HE,[7,10,13–16] but there has been less discussion of the connection between clinical characteristics and endoscopic findings. Itoh et al described and classified the macroscopic characteristics of HE.[7] The 3 main types of HE are classified and described as follows: small, punched-out lesions with and without raised margins are type I and type II, respectively; multiple confluent ulcers with a map-like appearance is type III. In our study, we stratified patients into 3 different types based on this classification and tried to analyze their clinical characteristics. Between the 3 different endoscopic typing, no significant factor was found except the level of WBC (Table 3). We found the majority of patients with HE type III had sepsis (72%) and obvious leukocytosis than the other 2 types ($P = 0.03$). The previous study revealed when suffering from sepsis, 2 stages would be observed, including a hyperinflammatory state and the secondary occurrence of immunosuppression. Dendritic cells during sepsis stimulate cytokine secretion and cause T-cell dysfunction.[17,18] We assume the severity of immunosuppression correlates well with mortality and impaired cellular immunity is also contributed for the development of HE. However, presented endoscopic classification could not be clinically relevant with reference to clinical outcome by Kaplan–Meir estimate ($P = 0.520$) (Figure 2). We consider the reason might be due to low HE-related mortality (6.4% [3/47]), though most of the patients who died (66.7% [2/3]) belonged to the endoscopic classification type III group. For other clinical risk factors, postchemotherapy and/or radiotherapy showed significant difference for clinical outcome ($P < 0.05$) (Figure 2). Thus, patients with malignancy who are receiving chemotherapy and/or radiotherapy are at increased risk of death within 30 days (17.6% [3/17]) after appearance of herpes esophagitis compared with patients without immunosuppressive therapy.

Antiviral therapy, including acyclovir, famciclovir, and valacyclovir, is used to treat HE in immunocompromised hosts.[19,20] However, the benefit of antiviral therapy for HE is controversial in immunocompetent patients because of reported rare complications, regardless of the specific antiviral therapy.[14,15,21] Canalejo Castrillero et al[16] demonstrated that the average healing time in patients receiving antiviral therapy was shorter than that for patients receiving symptomatic therapy alone (7.2 ± 4.8 and 8.8 ± 5.9 days, respectively). Therefore, antiviral therapy might speed recovery time and

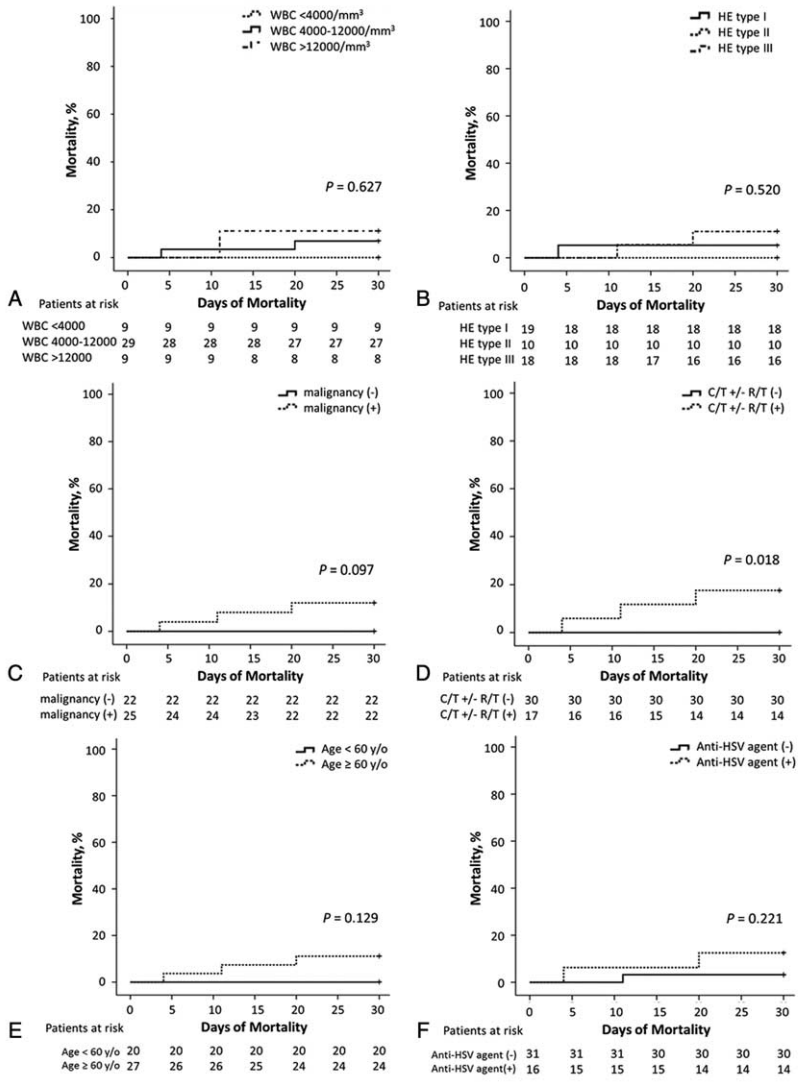


FIGURE 2. Kaplan–Meier estimates of 30-day mortality rate after appearance of herpes esophagitis (HE) stratified by: A, white blood cell count (WBC) (/mm^3) ($P = 0.627$); B, endoscopic typing of HE ($P = 0.520$); C, malignancy ($P = 0.097$); D, chemotherapy and/or radiotherapy ($P = 0.018$); E, age $\geq$60 years ($P = 0.129$); and F, anti-HSV agent ($P = 0.221$). HSV = herpes simplex virus.

relieve HE-related discomfort earlier, although further prospective studies are needed to evaluate the benefits and cost-effectiveness of antiviral therapy in immunocompetent patients.[22] In our retrospective study, 1/3 patients (16/47) received antivirus therapy, and their symptoms, especially dysphagia, were improved obviously within 3 to 5 days as medical chart recording. Early endoscopic diagnosis and classification of HE could help clinicians evaluate the severity of HE and provide prompt treatment.[23]

The present retrospective study has some limitations. First, laboratory data about immune status such as CD4 count were not checked on all HE patients. Second, typically endoscopic typing includes type I, type II, and type III of HE. However, variations were shown to exist while reviewing endoscopic image because there were other combined types of HE.[7] Third, all HE cases were diagnosed by pathologists, and biopsy bias, which involved factors like the performance and location of biopsy, depended on the experience of the endoscopists. Fourth, no appropriate objective could be compared with the population of HE because of some shortage of clinical information for 1843 patients with esophageal ulcers from 10-year pathological database.

In conclusion, HE primarily affects men and patients with malignancy or sepsis. Patients with malignancy, especially receiving chemotherapy and/or radiotherapy, are at increased risk of death within 30 days after appearance of HE compared with other HE patients. However, the disease is usually self-limiting, and HE-related mortality is low. Relationship between severity of endoscopic findings and patients' outcome remains questionable. Further prospective study is needed.

TABLE 4. Clinical Characteristics of Patients With Herpes Esophagitis

Authors/Year of Publication	No. Patients	Patient Demographics*	Clinical Symptoms	Underlying Diseases	Endoscopic Findings
McBane and Gross/1991[13]	23	ND	Odynophagia and chest pain (50%); GI bleeding (30%)	Immunocompromised (22/23)	Nonspecific finding; discrete ulcers; coalescent ulcers; pseudomembranous
Généreau et al/1996[10]	34	M/F: 4.7; mean age: 38 years (27–65)	Odynophagia and/or chest pain (82%)	AIDS (34/34)	Erythema; vesicles; ulcers (or volcano ulcers); pseudomembranous
Ramanathan et al/2000[14]	38	M/F: 3.2; mean age: 28.5 years (1–76)	Odynophagia (76%), heartburn (50%), fever (45%)	Immunocompetent (38/38)	Friable mucosa; numerous ulcers; whitish-exudates
Itoh et al/2003[7]	24	M/F: 3; mean age: 63.1 years (31–81)	ND	Immunocompromised (23/24); malignancy (18/24)	Punched-out lesions with/without raised margins; multiple ulcers with geographic appearance
Kato et al/2005[15]	52	M/F: 3.7; mean age: 29 years (0.9–75)	Odynophagia/ dysphagia (71%), fever (46%); dysphagia (27%)	Immunocompetent (52/52)	Redness; vesicle; ulcer; exudate
Canalejo Castrillero et al/2010[16]	56	M/F: 2.3; mean age: 35 years (14–82)	Odynophagia (61%), fever (52%), chest pain (46%)	Immunocompetent (56/56)	Ulcers: small, discrete or coalescent, superficial or punched-out

AIDS = acquired immune deficiency syndrome, F = female, M = male, ND = no data, No. = number.
* Patient demographics: M/F: male/female; mean age (range).

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