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Contents

Thrice Monthly Volume 10 Number 30 October 26, 2022

REVIEW

- 10823** New insights into the interplay between intestinal flora and bile acids in inflammatory bowel disease
Zheng L
- 10840** Role of visfatin in obesity-induced insulin resistance
Abdalla MMI

MINIREVIEWS

- 10852** Hyperthermic intraperitoneal chemotherapy and colorectal cancer: From physiology to surgery
Ammerata G, Filippo R, Laface C, Memeo R, Solaini L, Cavaliere D, Navarra G, Ranieri G, Currò G, Ammendola M
- 10862** New-onset diabetes secondary to acute pancreatitis: An update
Yu XQ, Zhu Q
- 10867** Ketosis-prone diabetes mellitus: A phenotype that hospitalists need to understand
Boike S, Mir M, Rauf I, Jama AB, Sunesara S, Mushtaq H, Khedr A, Nitesh J, Surani S, Khan SA
- 10873** 2022 Monkeypox outbreak: Why is it a public health emergency of international concern? What can we do to control it?
Ren SY, Li J, Gao RD

ORIGINAL ARTICLE

Retrospective Cohort Study

- 10882** Clinical characteristics and prognosis of non-small cell lung cancer patients with liver metastasis: A population-based study
Wang JF, Lu HD, Wang Y, Zhang R, Li X, Wang S

Retrospective Study

- 10896** Prevalence and risk factors for *Candida* esophagitis among human immunodeficiency virus-negative individuals
Chen YH, Jao TM, Shiue YL, Feng IJ, Hsu PI
- 10906** Prognostic impact of number of examined lymph nodes on survival of patients with appendiceal neuroendocrine tumors
Du R, Xiao JW

Observational Study

- 10921** Clinical and epidemiological features of ulcerative colitis patients in Sardinia, Italy: Results from a multicenter study
Magri S, Demurtas M, Onidi MF, Picchio M, Elisei W, Marzo M, Miculan F, Manca R, Dore MP, Quarta Colosso BM, Cicu A, Cugia L, Carta M, Binaghi L, Usai P, Lai M, Chicco F, Fantini MC, Armuzzi A, Mocci G

- 10931** Clinical observation of laparoscopic cholecystectomy combined with endoscopic retrograde cholangiopancreatography or common bile duct lithotripsy

Niu H, Liu F, Tian YB

Prospective Study

- 10939** Patient reported outcome measures in anterior cruciate ligament rupture and reconstruction: The significance of outcome score prediction

Al-Dadah O, Shepstone L, Donell ST

SYSTEMATIC REVIEWS

- 10956** Body mass index and outcomes of patients with cardiogenic shock: A systematic review and meta-analysis

Tao WX, Qian GY, Li HD, Su F, Wang Z

META-ANALYSIS

- 10967** Impact of being underweight on peri-operative and post-operative outcomes of total knee or hip arthroplasty: A meta-analysis

Ma YP, Shen Q

- 10984** Branched-chain amino acids supplementation has beneficial effects on the progression of liver cirrhosis: A meta-analysis

Du JY, Shu L, Zhou YT, Zhang L

CASE REPORT

- 10997** Wells' syndrome possibly caused by hematologic malignancy, influenza vaccination or ibrutinib: A case report

Šajin M, Luzar B, Zver S

- 11004** Giant cutaneous squamous cell carcinoma of the popliteal fossa skin: A case report

Wang K, Li Z, Chao SW, Wu XW

- 11010** Right time to detect urine iodine during papillary thyroid carcinoma diagnosis and treatment: A case report

Zhang SC, Yan CJ, Li YF, Cui T, Shen MP, Zhang JX

- 11016** Two novel mutations in the *VPS33B* gene in a Chinese patient with arthrogryposis, renal dysfunction and cholestasis syndrome 1: A case report

Yang H, Lin SZ, Guan SH, Wang WQ, Li JY, Yang GD, Zhang SL

- 11023** Effect of electroacupuncture for Pisa syndrome in Parkinson's disease: A case report

Lu WJ, Fan JQ, Yan MY, Mukaeda K, Zhuang LX, Wang LL

- 11031** Neonatal Cri du chat syndrome with atypical facial appearance: A case report

Bai MM, Li W, Meng L, Sang YF, Cui YJ, Feng HY, Zong ZT, Zhang HB

- 11037** Complete colonic duplication presenting as hip fistula in an adult with pelvic malformation: A case report

Cai X, Bi JT, Zheng ZX, Liu YQ

- 11044** Autoimmune encephalitis with posterior reversible encephalopathy syndrome: A case report
Dai SJ, Yu QJ, Zhu XY, Shang QZ, Qu JB, Ai QL
- 11049** Hypophysitis induced by anti-programmed cell death protein 1 immunotherapy in non-small cell lung cancer: Three case reports
Zheng Y, Zhu CY, Lin J, Chen WS, Wang YJ, Fu HY, Zhao Q
- 11059** Different intraoperative decisions for undiagnosed paraganglioma: Two case reports
Kang D, Kim BE, Hong M, Kim J, Jeong S, Lee S
- 11066** Hepatic steatosis with mass effect: A case report
Hu N, Su SJ, Li JY, Zhao H, Liu SF, Wang LS, Gong RZ, Li CT
- 11074** Bone marrow metastatic neuroendocrine carcinoma with unknown primary site: A case report and review of the literature
Shi XB, Deng WX, Jin FX
- 11082** Child with adenylosuccinate lyase deficiency caused by a novel complex heterozygous mutation in the ADSL gene: A case report
Wang XC, Wang T, Liu RH, Jiang Y, Chen DD, Wang XY, Kong QX
- 11090** Recovery of brachial plexus injury after bronchopleural fistula closure surgery based on electrodiagnostic study: A case report and review of literature
Go YI, Kim DS, Kim GW, Won YH, Park SH, Ko MH, Seo JH
- 11101** Severe *Klebsiella pneumoniae* pneumonia complicated by acute intra-abdominal multiple arterial thrombosis and bacterial embolism: A case report
Bao XL, Tang N, Wang YZ
- 11111** Spontaneous bilateral femur neck fracture secondary to grand mal seizure: A case report
Senocak E
- 11116** Favorable response after radiation therapy for intraductal papillary mucinous neoplasms manifesting as acute recurrent pancreatitis: A case report
Harigai A, Kume K, Takahashi N, Omata S, Umezawa R, Jingu K, Masamune A
- 11122** Acute respiratory distress syndrome following multiple wasp stings treated with extracorporeal membrane oxygenation: A case report
Cai ZY, Xu BP, Zhang WH, Peng HW, Xu Q, Yu HB, Chu QG, Zhou SS
- 11128** Morphological and electrophysiological changes of retina after different light damage in three patients: Three case reports
Zhang X, Luo T, Mou YR, Jiang W, Wu Y, Liu H, Ren YM, Long P, Han F
- 11139** Perirectal epidermoid cyst in a patient with sacroccygeal scoliosis and anal sinus: A case report
Ji ZX, Yan S, Gao XC, Lin LF, Li Q, Yao Q, Wang D

- 11146** Synchronous gastric cancer complicated with chronic myeloid leukemia (multiple primary cancers): A case report
Zhao YX, Yang Z, Ma LB, Dang JY, Wang HY
- 11155** Giant struma ovarii with pseudo-Meigs's syndrome and raised cancer antigen-125 levels: A case report
Liu Y, Tang GY, Liu L, Sun HM, Zhu HY
- 11162** Longest survival with primary intracranial malignant melanoma: A case report and literature review
Wong TF, Chen YS, Zhang XH, Hu WM, Zhang XS, Lv YC, Huang DC, Deng ML, Chen ZP
- 11172** Spontaneous remission of hepatic myelopathy in a patient with alcoholic cirrhosis: A case report
Chang CY, Liu C, Duan FF, Zhai H, Song SS, Yang S
- 11178** Cauda equina syndrome caused by the application of DuraSeal™ in a microlaminectomy surgery: A case report
Yeh KL, Wu SH, Fuh CS, Huang YH, Chen CS, Wu SS
- 11185** Bioceramics utilization for the repair of internal resorption of the root: A case report
Riyahi AM
- 11190** Fibrous hamartoma of infancy with bone destruction of the tibia: A case report
Qiao YJ, Yang WB, Chang YF, Zhang HQ, Yu XY, Zhou SH, Yang YY, Zhang LD
- 11198** Accidental esophageal intubation *via* a large type C congenital tracheoesophageal fistula: A case report
Hwang SM, Kim MJ, Kim S, Kim S
- 11204** Ventral hernia after high-intensity focused ultrasound ablation for uterine fibroids treatment: A case report
Park JW, Choi HY

LETTER TO THE EDITOR

- 11210** C-Reactive protein role in assessing COVID-19 deceased geriatrics and survivors of severe and critical illness
Nori W

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Retrospective Study

Prevalence and risk factors for *Candida* esophagitis among human immunodeficiency virus-negative individuals

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Abstract

BACKGROUND

Candida esophagitis (CE) is among the commonest esophageal infections and is known as an opportunistic fungal infection mostly affecting people living with the human immunodeficiency virus (HIV). However, some medical conditions might predispose HIV-negative individuals to esophageal candidiasis. The epidemiology and associated endoscopic findings of CE among people without HIV have rarely been reported.

AIM

To investigate the prevalence of CE among HIV-negative persons, and determine risk factors predicting CE.

METHODS

Between January 2015 and December 2018, all consecutive outpatients who under-

went routine esophagogastroduodenoscopy as part of health check-ups at their own expense at the Health Check-up Center of the Kaohsiung Veterans General Hospital, Taiwan, were recruited in this study. Those with positive HIV serology results were excluded. Sociodemographic and clinical characteristics including age, gender, economic status, smoking history, alcohol consumption, tea and coffee consumption, underlying diseases, body fat percentage, body mass index, endoscopic findings, and *Helicobacter pylori* infection status were carefully reviewed. CE was confirmed by endoscopic biopsy and pathological assessment with hematoxylin and eosin and periodic acid-Schiff staining. To evaluate independent factors predicting the development of CE, we conducted a univariate analysis of clinical characteristics. The variables found to be significant *via* univariate analysis were subsequently included in a multivariable analysis of potential risk factors for CE development.

RESULTS

A total of 11802 participants were included in this study. Forty-seven (0.4%) were confirmed as having CE by pathological examination. Univariate analysis identified older age, the presence of chronic kidney disease, alcohol consumption, and steroid use ($P = 0.023$, < 0.001 , 0.033 , and 0.004 , respectively) as significantly associated with CE. Multivariable analysis revealed older age [adjusted odds ratio (OR) = 1.027; 95%CI: 1.001-1.053; $P = 0.045$], chronic kidney disease (adjusted OR = 13.470; 95%CI: 4.574-39.673; $P < 0.001$), alcohol consumption (adjusted OR = 2.103; 95%CI: 1.151-3.844; $P = 0.016$), and steroid use (adjusted OR = 24.255; 95%CI: 5.343-110.115; $P < 0.001$) as independent risk factors for CE development. The presence of dysphagia was associated with severe CE ($P = 0.021$).

CONCLUSION

The prevalence of CE among HIV-negative persons was 0.4% in Taiwan. Independent risk factors for CE were older age, chronic kidney disease, alcohol consumption, and steroid use.

Key Words: *Candida* esophagitis; Prevalence; Risk factors; Human immunodeficiency virus

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Core Tip: *Candida* esophagitis (CE) is not only an opportunistic fungal infection affecting people living with the human immunodeficiency virus (HIV) but has also been identified in HIV-negative individuals. The prevalence of CE in Taiwan has reached 0.4% in general population, higher than previous reports. Significant risk factors include older age, chronic kidney disease, alcohol consumption, and steroid use. It is among the etiologies causing dysphagia in the general population, and esophagogastroduodenoscopy combined with histopathological examination are essential for accurate diagnosis.

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INTRODUCTION

Candida esophagitis (CE) is a fungal infection of the esophagus caused by *Candida* species. It is one of the most common esophageal infections and is known as an opportunistic infection associated with human immunodeficiency virus (HIV) infection[1-5]. *Candida albicans* is the causative agent in most cases. Infections caused by other species such as *C. glabrata*, *C. dubliniensis*, *C. tropicalis*, *C. stellatoidea* and *C. krusei* have been reported[6,7]. In HIV-negative individuals, the prevalence of CE ranges from 0.3%-10.5%[8-11].

Some medical conditions and treatments, including the presence of malignancies, diabetes mellitus, steroids, radiation therapy, antimicrobial therapy, liver cirrhosis, acid suppression therapy, and dentures, have been associated with CE development[9,12,13]. Upper endoscopy is a sensitive and reliable method for diagnosing CE[14]. The typical endoscopic findings of CE are elevated white plaques coating the esophageal mucosa with either a nodular, linear, or confluent pattern. An endoscopic severity grading for CE has been proposed by Kodsi *et al*[15], Asayama *et al*[16] and Takahashi *et al*[17].

Currently, the prevalence of CE among HIV-negative individuals remains unknown in Taiwan. We aimed to investigate the prevalence of CE among HIV-negative individuals in Taiwan and determine independent risk factors for CE development in the general population.

MATERIALS AND METHODS

Patients

Between January 2015 and December 2018, all consecutive outpatients who underwent routine esophagogastroduodenoscopy (EGD) as part of health check-ups at their own expense at the Health Check-up Center of the Kaohsiung Veterans General Hospital, Taiwan, were recruited in this study. Most of these individuals were physically healthy without medical illness or signs of immunodeficiency and underwent health check-ups to rule out physical disorders, particularly malignancy. Other participants either had routine physical check-ups arranged by their employers or sought medical consultations to evaluate physical symptoms. An HIV serologic test was performed in 81% of the population. The exclusion criteria were: (1) Age < 20 years; (2) Refused biopsy for suspicious gastrointestinal tract lesions; and (3) A positive HIV serology result.

Questionnaire

As a routine practice at our physical examination center, every outpatient was instructed to fill out a questionnaire detailing their personal history, demographic data, medical history, as well as their history of smoking, alcohol consumption, and coffee and tea consumption. The questionnaire was designed with a mainly dichotomous manner, and the questions were divided in detail according to different functional systems of the human body. The questionnaire also captured self-reported gastrointestinal discomfort or symptoms, including acid reflux symptoms, epigastric pain, dysphagia,odynophagia, and dyspepsia.

Study design

Clinical data including personal information from the questionnaire, laboratory data, body weight, body mass index (BMI), body fat percentage, endoscopic findings, and histopathologic findings were collected by retrospective chart review. The endoscopy devices used for examinations from January 2015 through August 2015 were the GIF-XP260N, GIF-XQ260, GIF-Q260, and GIF-H260Z systems (Tokyo, Japan). New endoscopy systems, the GIF-H290Z and GIF-HQ290, were introduced to our department and used for endoscopic examinations from September 2015 onward. All endoscopic examinations throughout the entire study period were performed by five experienced endoscopists. Most of the endoscopic procedures were performed under conscious sedation with the administration of intravenous sedative agents by anesthesiologists. Some patients did not undergo conscious sedation because of advanced age, high risk of anesthesia complications due to underlying medical conditions, or personal reasons. If a participant underwent more than one endoscopic examination during the study period, only the results of the first examination were included in the analysis. CE was suspected when we endoscopically identified white plaques coating the esophageal mucosa that could not be washed away[18]. The endoscopic CE severity was graded according to the classification proposed by Kodsi *et al* [15]. The diagnosis was confirmed by endoscopic biopsy for histopathologic assessment with hematoxylin and eosin and periodic acid-Schiff staining.

Statistical analysis

The primary endpoint was the presence of histopathologically-confirmed CE. To identify risk factors for CE, we conducted univariate analysis with the chi-square test or Fisher's exact test for categorical variables and two sample t test for continuous variables, to individually investigate the associations between 29 clinical variables and the presence of CE. These variables included age; gender; smoking history; alcohol consumption history; coffee, tea, and betel nuts use; underlying disease status; surgical history; systemic steroid use; *Helicobacter pylori* infection status; waist circumference (normal: < 90 cm for males and < 80 cm for females; obese: ≥ 90 cm for males and ≥ 80 cm for females); body fat percentage (normal: < 25% for males and < 30% for females; obese: $\geq 25\%$ for males and $\geq 30\%$ for females); BMI (normal: < 24; overweight: $24 \leq \text{BMI} < 27$; obese: ≥ 27); and endoscopic findings. The variables found to be statistically significant in the univariate analysis were subsequently assessed by multivariable logistic regression analysis to identify independent factors predicting CE. All statistical analyses were performed using the SPSS for Windows, version 12.0 (SPSS Inc., Chicago, IL, United States). *P*-values less than 0.05 were considered statistically significant. The statistical methods in this study were reviewed by Dr. I-Jung Feng, Associate Professor of Biostatistics in National Sun Yat-sen University, Kaohsiung City, Taiwan.

RESULTS

Participant characteristics and endoscopic findings

During the study period, a total of 11805 participants were enrolled. Most of these individuals ($n = 7968$, 67.5%) were physically healthy and underwent their health check-ups to rule out physical disorders, particularly malignancies. The remaining individuals either underwent employment-related check-ups ($n = 2691$, 22.8%) or had sought medical consultations to evaluate physical symptoms ($n = 1146$, 9.7%). Of these, we excluded two participants who refused biopsy sample collection and one with a positive HIV serology result. Finally, the data of 11802 individuals (mean age, 51.29 ± 11.58 years; 55.7% male) were included in the analyses.

Endoscopically suspected CE was observed in 71 (0.6%) individuals, and 47 participants were confirmed to have CE *via* biopsy examination. Therefore, the overall prevalence of CE was 0.4%. The histopathologic diagnoses of the remaining 24 participants were normal esophageal mucosa ($n = 3$), chronic esophagitis ($n = 18$), and glycogenic acanthosis ($n = 3$). No dysplasia or adenocarcinoma was detected. Among the included 11802 individuals, a total of 9560 participants received HIV serology testing, and the results were negative. The prevalence of CE in the participants with negative results of HIV serology was 0.5%.

Univariate analysis of clinical characteristics associated with CE

Table 1 shows the clinical characteristics of the subjects with and without CE. The mean age was significantly higher among individuals with CE than among those without CE. Alcohol consumption, chronic kidney disease (CKD), and steroid use were more common among participants with CE. Although men and obese individuals (defined by a high body fat percentage) were more likely to have CE than women and participants with normal body fat percentages, respectively, these differences were not statistically significant.

Multivariable analysis of independent factors predicting the development of CE

Multivariable analysis revealed older age [adjusted odds ratio (OR) = 1.027; 95%CI: 1.001-1.053; $P = 0.045$], CKD (adjusted OR = 13.470; 95%CI: 4.574-39.673; $P < 0.001$), steroid use (adjusted OR = 24.255; 95%CI: 5.343-110.115; $P < 0.001$), and alcohol consumption (adjusted OR = 2.103; 95%CI: 1.151-3.844; $P = 0.016$) as significant risk factors for CE development (Table 2).

Clinical symptoms predicting endoscopic severity

The endoscopic appearance of CE was classified as grade I to grade IV according to the Kodsi system [15]. Table 3 summarizes the association between the endoscopic severity of CE and clinical symptoms. Most of the participants were classified as grade II ($n = 29$). Of the 47 participants with histopathologically-confirmed CE, seven had chest pain, three had abdominal pain, and one had dysphagia. None of the patients complained of globus, acid reflux, or odynophagia. The presence of dysphagia was associated with severe CE ($P = 0.021$).

DISCUSSION

CE is the most common opportunistic gastrointestinal disorder among people living with HIV, and a low CD4+ cell count (< 200 cells/mL) is one of the most important risk factors for CE in this population [19]. However, in the HIV-negative population, CE is occasionally identified accidentally during EGD for other indications. In this study, 47 otherwise healthy subjects undergoing routine health check-ups in Taiwan were confirmed to have CE, reflecting an overall prevalence of 0.4%. Our study also demonstrated older age, CKD, steroid use, and alcohol consumption as independent risk factors predicting the presence of CE.

The previously reported prevalence of CE in HIV-negative populations ranges from 0.3%-10.5%; these rates have tended to increase over time [17]. However, the prevalence of CE in the general population is rarely discussed. Choi *et al* [8] conducted a retrospective study from July 2005 through April 2011 to evaluate the prevalence of incidentally identified CE among healthy individuals in Korea, diagnosed endoscopically or histologically; they found a prevalence of 0.32%. Another retrospective study conducted in Korea by Kim *et al* [9] revealed a 0.35% prevalence of histology proven CE in a health check-up population. Recently, Ou *et al* [13] determined a prevalence of 0.39% among patients undergoing EGD for various medical conditions in Taipei, Taiwan. However, most of their patients with CE were diagnosed by endoscopic findings and not confirmed histopathologically. In our study, all CE diagnoses were confirmed by histopathologic examination. The results estimate the prevalence of CE in the Taiwanese general population to be 0.40%. We also identified older age, steroid use, alcohol consumption, and CKD as independent risk factors for CE development.

Candida albicans commonly colonizes the human gastrointestinal tract, with a variety of adhesins facilitating attachment to epithelial and endothelial surfaces [20]. Whether or not mucocutaneous

Table 1 Univariate analysis of clinical characteristics associated with *Candida* esophagitis

Characteristics	<i>Candida</i> esophagitis (%)		P value
	Yes (n = 47)	No (n = 11755)	
Age (yr) (mean \pm SD)	55.13 \pm 11.73	51.27 \pm 11.58	0.023
Male gender	32 (68.1)	6541 (55.6)	0.087
Smoking	9 (19.1)	1979 (16.8)	0.672
Consumption of alcohol	30 (63.8)	5674 (48.3)	0.033
Consumption of betel nuts	3 (6.4)	400 (3.4)	0.216
Underlying disease			
Cardiovascular disease	5 (10.6)	1520 (12.9)	0.640
Pulmonary disease	3 (6.4)	542 (4.6)	0.478
Diabetes mellitus	4 (8.5)	845 (7.2)	0.579
Hepatitis	6 (12.8)	975 (8.3)	0.281
Malignancy	0 (0)	224 (1.9)	1.000
Hyperlipidemia	6 (12.8)	1376 (11.7)	0.821
Chronic kidney disease	4 (8.5)	70 (0.6)	< 0.001
Steroid use	2 (4.3)	21 (0.2)	0.004
Previous gastric surgery	0 (0)	3 (< 0.1)	1.000
Symptoms			
Acid reflux	0 (0)	344 (2.9)	0.648
Chest pain	7 (14.9)	1549 (13.2)	0.729
Nausea/vomiting	0 (0)	200 (1.7)	1.000
Abdominal pain	3 (6.4)	1264 (10.8)	0.334
Dysphagia	1 (2.1)	134 (1.1)	0.525
Odynophagia	0 (0)	7 (0.1)	0.867
Globus	0 (0)	25 (0.2)	1.000
Waist			0.182
Normal (< 90 cm for males, < 80 cm for females)	26 (55.3)	7600 (64.7)	
Obese (\geq 90 cm for males, \geq 80 cm for females)	21 (44.7)	4155 (35.3)	
Body fat percentage			0.081
Normal (< 25% for males, < 30% for females)	28 (59.6)	8347 (71.1)	
Obese (\geq 25% for males, \geq 30% for females)	19 (40.4)	3387 (28.9)	
BMI			0.463
Normal (BMI < 24)	22 (46.8)	6523 (55.5)	
Overweight (24 \leq BMI < 27)	15 (31.9)	3293 (28.0)	
Obese (27 \geq BMI)	10 (21.3)	1939 (16.5)	
<i>Helicobacter pylori</i> infection	9 (19.1)	2047 (17.4)	0.754
Endoscopic findings			
Reflux esophagitis	7 (14.9)	2940 (25.0)	0.110
Hiatal hernia	20 (42.6)	5302 (45.1)	0.726
Gastric ulcer	23 (48.9)	4896 (41.7)	0.312
Duodenal ulcer	2 (4.3)	850 (7.2)	0.580
Gastric and duodenal ulcer	23 (48.9)	5179 (44.1)	0.501

ESEM	5 (10.6)	1277 (10.9)	0.961
Barrett's esophagus	1 (2.1)	283 (2.4)	1.000

BMI: Body mass index; ESEM: Endoscopically suspected esophageal metaplasia.

Table 2 Multivariable analysis of risk factors predicting *Candida* esophagitis

Clinical factor	Coefficient	Standard error	Odds ratio (95%CI)	P value
Age	0.026	0.013	1.027 (1.001-1.053)	0.045
Chronic kidney disease	2.600	0.551	13.470 (4.574-39.673)	< 0.001
Steroid use	3.189	0.772	24.255 (5.343-110.115)	< 0.001
Alcohol consumption	0.743	0.308	2.103 (1.151-3.844)	0.016

Table 3 The relationship between endoscopic severity of *Candida* esophagitis and clinical symptoms

Symptoms	Severity (%)				P value
	Grade 1 (n = 11)	Grade 2 (n = 29)	Grade 3 (n = 6)	Grade 4 (n = 1)	
Chest pain	3 (27.3)	4 (13.8)	0 (0)	0 (0)	0.564
Abdominal pain	1 (9.1)	2 (6.9)	0 (0)	0 (0)	1.000
Dysphagia	0 (0)	0 (0)	0 (0)	1 (100)	0.021
Globus	0 (0)	0 (0)	0 (0)	0 (0)	N/A
Acid reflux	0 (0)	0 (0)	0 (0)	0 (0)	N/A
Odynophagia	0 (0)	0 (0)	0 (0)	0 (0)	N/A

N/A: Not applicable.

invasion or systemic infection occurs depends on host and fungal factors[21]. Oral or aerosolized corticotherapy is a well-known risk factor associated with CE[22-24]. The prevalence of CE among inhaled corticosteroid users has been reported to be as high as 37%[25].

We are not the first to report alcohol consumption as an independent risk factor for CE development. Choi *et al*[8] and Zillesen *et al*[26] also identified alcohol consumption as a significant predisposing factor for CE. Recently, a retrospective study conducted at the endoscopy unit of a tertiary hospital in Mwanza, Tanzania, by Mushi *et al*[27] also identified that individuals with a history of alcohol consumption were at high risk of developing CE. According to previous reports, the amount of gastric acid output may be influenced by different alcohol concentrations; beverages with low ethanol content, such as beer and wine, are stimulants of gastric acid secretion, while beverages with higher ethanol concentrations, such as spirits, do not stimulate and even may decrease gastric acid secretion[28,29]. Moreover, the stomach's adaptive capacity may change its response to alcohol in association with chronic alcoholism. Atrophic gastritis and superficial gastritis, with or without associated hyposecretion of gastric acid or achlorhydria, are more often associated with chronic alcoholism[28]. In addition, the parietal cells, which are responsible for acid secretion, decrease in number with increasing alcohol exposure[29]. Given that acid suppression therapy probably facilitating colonization of the esophagus by oral bacteria and yeast due to elevated gastric pH may contribute to the development of CE, heavy alcohol consumption may also increase the risk of CE *via* the same mechanism[28,30-32].

In the present study, older age was another independent risk factor associated with CE development. This finding was consistent with previous findings by Takahashi *et al*[17], who demonstrated advanced age as a risk factor for CE among HIV-negative patients[20]. Indeed, the aging process may attenuate the host's ability to mount a robust or effective immune response. The underlying mechanism of impaired immunity may be associated with defects in hematopoietic bone marrow and peripheral lymphocyte migration, maturation, and function[33].

The present study also revealed CKD as an independent risk factor for CE development. This important finding has rarely been reported. Thorman *et al*[34] reported that oral fungal infection was significantly more prevalent among patients with end-stage renal disease (ESRD). In addition, lymphocyte numbers and the CD4/CD8 ratio are diminished in patients with ESRD. In fact, both the quantity and quality of T-cell activation are impaired in the context of chronic renal failure[35].

Furthermore, cellular mechanisms are essential in host responses to fungal infections and candidiasis at the gastrointestinal surface. Dysfunction of T-lymphocytes and a reduction in their number are typically observed in patients with mycotic diseases. Reductions in T-lymphocyte number and in the ratio of T-helper to T-suppressor cells are of critical importance for explaining diminished IgA production and enhanced adhesion of fungal cells to the surface of host cells, as well as for facilitating the intrusion of fungi throughout the skin and mucous membranes[20]. Therefore, it is reasonable to expect CKD as a risk factor for CE.

Common symptoms associated with CE include dysphagia, odynophagia, retrosternal chest pain, epigastric pain, and acid reflux symptoms[16,22]. A cross-sectional study conducted by Takahashi *et al* [10] found dysphagia and odynophagia as the only two symptoms predicting CE among individuals without HIV. In our study, the presenting symptoms among participants with CE were chest pain ($n = 7$, 14.9%), abdominal pain ($n = 3$, 6.4%) and dysphagia ($n = 1$, 2.1%), similar to the findings mentioned above. However, none of these symptoms were significantly associated with CE according to the multivariable analysis.

The association between clinical symptoms and the endoscopic severity of CE graded by Kodsí's classification has been investigated before. Asayama *et al*[16] reported that the presence of odynophagia was significantly associated with grade III and grade IV CE. In our study, none of the participants with CE presented with odynophagia. Although none of the patients with grade I to grade III CE presented with dysphagia, dysphagia was a presenting complaint in the one patient with grade IV CE.

This study has several limitations. First, its retrospective observational design means that it was subject to confounding by unmeasured variables. Second, in real-world clinical practice, some situational factors can influence the CE detection rate, such as the foregoing of endoscopic biopsy examination because of overlooked low-grade CE or misdiagnoses of CE as foreign body reactions or glycogenic acanthosis. Third, there were relatively few CE cases, making it difficult to definitively confirm associations between clinical symptoms and the endoscopic severity of CE.

CONCLUSION

In conclusion, the prevalence of CE among HIV-negative participants in this single-center cohort in Taiwan was 0.4% from 2015 through 2018. Older age, CKD, alcohol consumption, and steroid use were independent risk factors for CE development.

ARTICLE HIGHLIGHTS

Research background

Candida esophagitis (CE) is an opportunistic esophageal fungal infection mostly affecting human immunodeficiency virus (HIV)-positive people. However, some HIV-negative individuals are prone to esophageal candidiasis under certain medical conditions.

Research motivation

The definite diagnosis of CE relies on both endoscopic and histopathological findings. However, the epidemiology of CE diagnosed with strict histopathological confirmation among the general population without HIV in Taiwan has rarely been reported.

Research objectives

To update the prevalence of CE among HIV-negative persons, and identify independent risk factors predicting CE in Taiwan.

Research methods

HIV-negative outpatients who underwent routine esophagogastroduodenoscopy at the Health Check-up Center of the Kaohsiung Veterans General Hospital, Taiwan, between January 2015 and December 2018 were recruited. Sociodemographic status, clinical characteristics, and endoscopic findings were carefully reviewed. CE was confirmed by endoscopic biopsy and pathological assessment. A univariate analysis of clinical characteristics was conducted to evaluate independent factors predicting CE. Significant variables found *via* univariate analysis were subsequently included in a multivariable analysis of potential risk factors for CE development.

Research results

A total of 11802 participants were included in this study. The prevalence of CE confirmed by pathological examination was 0.4%. Multivariable analysis revealed older age [adjusted odds ratio (OR) = 1.027; 95%CI: 1.001-1.053; $P = 0.045$], chronic kidney disease (adjusted OR = 13.470; 95%CI: 4.574-

39.673; $P < 0.001$), alcohol consumption (adjusted OR = 2.103; 95%CI: 1.151-3.844; $P = 0.016$), and steroid use (adjusted OR = 24.255; 95%CI: 5.343-110.115; $P < 0.001$) as independent risk factors for CE development.

Research conclusions

The prevalence of CE among HIV-negative population in Taiwan has reached 0.4%. Older age, chronic kidney disease, alcohol consumption, and steroid use were independent risk factors for CE.

Research perspectives

CE is not an uncommon esophageal disease among the HIV-negative population in Taiwan. Chronic kidney disease was an independent risk factor for the development of CE, which was a unique finding in our study.

FOOTNOTES

Author contributions: All authors helped to perform the research; Chen YH and Hsu PI designed the study and drafted the manuscript; Chen YH, Jao TM, Shiue YL and Feng IJ collected the data; Chen YH, Jao TM, Shiue YL and Feng IJ performed statistical analyses; Chen YH, Jao TM, Shiue YL, Feng IJ and Hsu PI revised the manuscript critically for important intellectual content. All authors have read and approved the final manuscript.

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