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ARTICLE

Risk factors for cytomegalovirus gastrointestinal diseases in adult patients with cancer

J.-H. Ko · K. R. Peck · W. J. Lee · K. Huh · J. R. Yoo · K. Kim · S. Y. Cho · Y. E. Ha · C.-I. Kang · D. R. Chung · C. W. Jung · Y.-H. Kim · N. Y. Lee · K.-M. Kim · J.-H. Song

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Abstract Cytomegalovirus (CMV) gastrointestinal (GI) disease has been noticed frequently in cancer patients, causing abdominal pain, diarrhea, and GI bleeding. However, little is known about its actual incidence, clinical presentation, and the risk factors for its development among cancer patients. To answer these questions, we analyzed all cases that occurred during an 18-year period at our center. A case–control study was performed to identify risk factors for CMV GI disease. Electronic medical records were reviewed from individuals who were admitted and diagnosed with CMV GI disease during the period of January 1995 through March 2013 at a tertiary care center. Two CMV disease-free cancer patients were matched as controls. A total of 98 episodes of CMV GI disease were included in this study, and the overall incidence rate was 52.5 per 100,000 cancer patients, with an increasing trend throughout the study period. According to multivariate analysis, male sex, low body mass index, lymphopenia, hematological malignancy, and steroid use and red blood cell transfusion within 1 month prior to the CMV disease were identified to be independent risk factors. Among these factors, RBC transfusion showed the highest odds ratio (OR=5.09). Male sex, low body mass index, lymphopenia, hematological malignancy, steroid use, and red blood cell transfusion within 1 month prior to the CMV disease diagnosis were independent risk factors for the development of CMV GI disease in adult patients with cancer.

J.-H. Ko · K. R. Peck (✉) · W. J. Lee · K. Huh · J. R. Yoo · K. Kim · S. Y. Cho · Y. E. Ha · C.-I. Kang · D. R. Chung · J.-H. Song
Division of Infectious Diseases, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 135-710, Republic of Korea
e-mail: krpeck@skku.edu

C. W. Jung
Division of Hematology-Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

Y.-H. Kim
Division of Gastroenterology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

N. Y. Lee
Department of Laboratory Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

K.-M. Kim
Department of Pathology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

Introduction

Cytomegalovirus (CMV) establishes lifelong latency in a person after acute infection, and long-term immunosuppression can lead to uncontrolled replication and serious disease [1–5]. Recently, it has been noticed that CMV gastrointestinal (GI) disease frequently occurs in cancer patients, causing abdominal pain, diarrhea, and GI bleeding [6, 7]. However, little is known about its actual incidence, clinical presentation, and the risk factors for its development among cancer patients. To answer these questions, we analyzed all cases that occurred during an 18-year period at our center.

Materials and methods

Study design and patient selection

A case–control study was designed to identify risk factors for the development of CMV GI disease in adult patients with cancer. The electronic medical records (EMRs) were reviewed in individuals who were admitted to Samsung Medical Center,

Seoul, Republic of Korea, and diagnosed with CMV GI disease during the period January 1995 to March 2013. Samsung Medical Center is a 1,950-bed tertiary care university hospital and referral center that includes the 650-bed Samsung Comprehensive Cancer Hospital. This study included patients with either solid tumors or hematological malignancy who were older than 16 years at the time of the CMV disease diagnosis. Patients with human immunodeficiency virus (HIV) infection, ulcerative colitis (UC), or a history of solid organ transplantation (SOT) were excluded. Whole pathological reports were electronically screened with the keyword "cytomegalovirus" or "CMV", and every case detected was reviewed by authors. To select a control group, we screened all adult inpatients with cancer. Two patients admitted to the same ward and on the same day as each case patient were matched as controls.

Data collection

We retrospectively collected the following data from EMRs: age, gender, the date of cancer and CMV disease diagnosis, body mass index (BMI), complete blood count with differential, albumin, C-reactive protein, CMV antigenemia and serology, associated symptoms, underlying diseases, comorbid conditions, drug administration history, transfusion history, achievement of complete remission (CR), and 30-day mortality. Laboratory data were collected on the day of CMV disease diagnosis in the case group and on the day of admission in the control group. To analyze overall, annual, and age-specific incidence rates, the number of cancer patients admitted to our center was obtained, except for patients with HIV, UC, or a history of SOT.

Study definitions

In this study, patients were defined to have CMV GI disease if they met both of the following criteria:

1. Clinical symptoms and signs compatible with esophagitis, gastritis, enteritis, or proctocolitis
2. The tissue involvement of CMV was confirmed pathologically

Lymphopenia was defined as an absolute lymphocyte count (ALC) of <1,000 cells/mm^3.

Pathological confirmation of CMV infections

Pathological specimens were obtained by endoscopic biopsy or surgery. Pathological diagnosis of CMV infection was confirmed either by immunohistochemistry (IHC) or by polymerase chain reaction, combined with characteristic histopathological findings. IHC staining was performed with monoclonal primary antibodies directed against CMV immediate-early nuclear protein and early nuclear protein (Clones CCH2 + DDG9; Dako, Glostrup, Denmark).

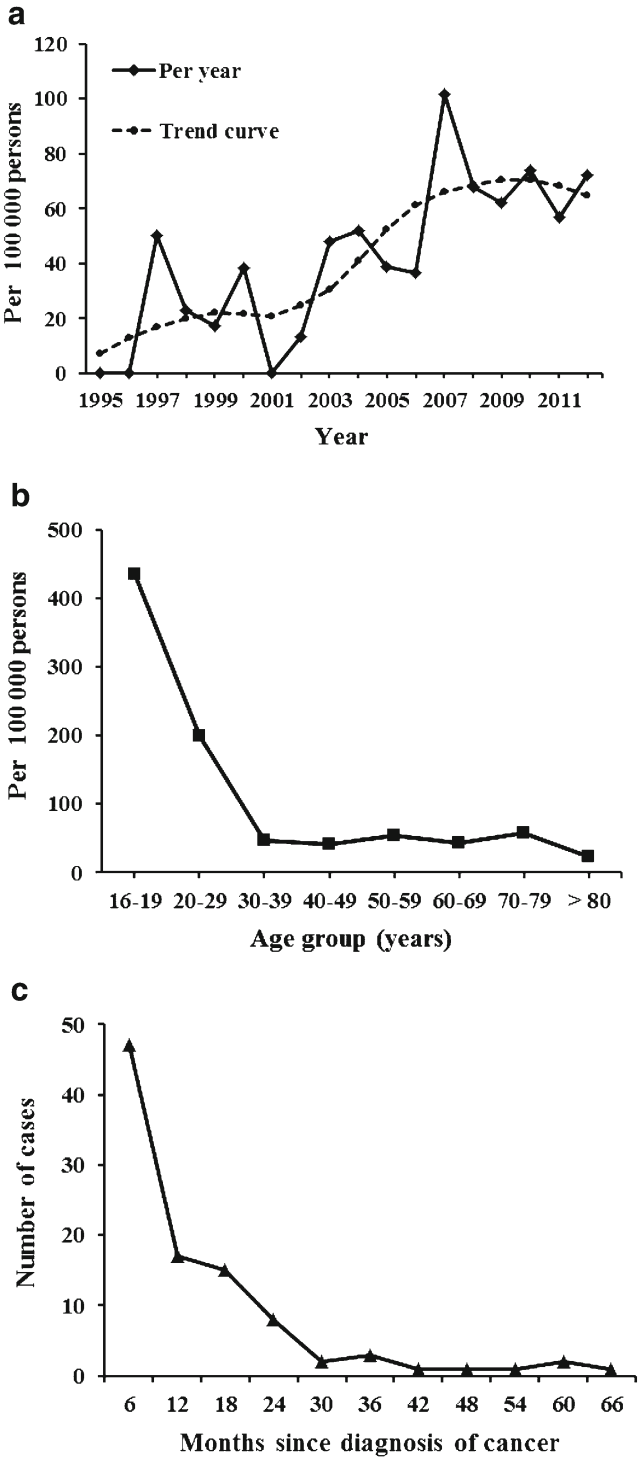

Fig. 1 Incidence rate of cytomegalovirus gastrointestinal (CMV GI) disease from 1995 to 2012. **a** Incidence trends over time for the overall study population. **b** Age-specific incidence rates in the study population. **c** Time interval from diagnosis of cancer to development of CMV GI disease

Table 1 Clinical presentation and prognosis of cytomegalovirus gastrointestinal (CMV GI) diseases

Variable	Esophagitis, *n*=26 (%)	Gastritis, *n*=14 (%)	Enteritis, *n*=16 (%)	Proctocolitis, *n*=58 (%)	Total, *n*=98 (%)
Underlying cancer					
Acute leukemia	2 (7.7)	5 (35.7)	7 (43.8)	20 (36.4)	29 (29.6)
Lymphoma	4 (15.4)	2 (14.3)	3 (18.8)	6 (10.9)	14 (14.3)
Lung cancer	7 (26.9)	1 (7.1)	0 (0.0)	4 (7.3)	12 (12.2)
Colon cancer	2 (7.7)	0 (0.0)	1 (6.3)	6 (10.9)	8 (8.2)
Fever	1 (3.8)	1 (7.1)	2 (12.5)	4 (7.3)	7 (7.1)
Symptoms					
Dysphagia	9 (34.6)	2 (14.3)	0 (0.0)	0 (0.0)	11 (11.2)
Heartburn	5 (19.2)	0 (0.0)	0 (0.0)	0 (0.0)	5 (5.1)
Dyspepsia	2 (7.7)	5 (35.7)	0 (0.0)	0 (0.0)	7 (7.1)
Nausea/vomiting	2 (7.7)	4 (28.6)	1 (6.3)	2 (3.6)	7 (7.1)
Abdominal pain	7 (26.9)	5 (35.7)	9 (56.3)	13 (23.6)	30 (30.6)
Diarrhea	0 (0.0)	1 (7.1)	7 (43.8)	34 (61.8)	35 (35.7)
Hematochezia	0 (0.0)	3 (21.4)	2 (12.5)	23 (41.8)	24 (24.5)
Melena	8 (30.8)	2 (14.3)	1 (6.3)	3 (5.5)	12 (12.2)
Ganciclovir treatment	15 (57.7)	12 (85.7)	12 (75)	45 (81.8)	72 (73.5)
30-day mortality	2 (7.7)	1 (7.1)	2 (12.5)	6 (10.3)	9 (9.2)
Attributable mortality	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	1 (1.0)

Data are number (%) of patients

Statistical analysis

To analyze the incidence rates of CMV GI disease, the number of cases was divided by the total number of cancer patients admitted, and it was converted to rate per 100,000 persons. To analyze the overall trend and statistical significance, we applied a locally weighted scatterplot smoothing (LOESS) curve and linear regression.

To evaluate risk factors, Student's *t* test and the Mann–Whitney test were used to compare continuous variables, and the Chi-squared test and Fisher's exact test were used to compare categorical variables. We used a logistic regression model to control confounding variables. All *P* values were two-tailed, and *P* values<0.05 were considered to be statistically significant. SPSS for Windows, PASW version 20.0, was used for the analysis.

Results

Incidence, clinical presentation, and prognosis of CMV GI disease

During the study period, we identified 98 episodes of CMV GI disease in 96 patients. The overall incidence of CMV GI disease in the study population was 52.5 per 100,000 cancer patients with an increasing trend throughout the study period (Fig. 1a). This incremental trend was statistically significant by linear regression ($P<0.001$). Compared with the older age group, the age-specific incidence was higher in the 16- to 19- and the 20- to 29-year age groups at 435.4 and 200.1 per 100,000 persons (Fig. 1b). CMV GI disease was also more common in patients with hematological malignancies compared with those with solid tumors (710.3 vs 23.7). It took an average of 202 days for CMV GI disease to develop after the diagnosis of the underlying cancer, and most cases developed within 2 years (Fig. 1c).

The clinical presentation and prognosis of CMV GI disease are presented in Table 1. Among 98 episodes, the colorectum was the most frequently involved site, followed by the esophagus, small intestine, and stomach. Fourteen episodes of CMV GI disease involved multiples sites. Dysphagia was the most frequently observed symptoms in CMV esophagitis, while dyspepsia and abdominal pain were most common in CMV gastritis. Patients with CMV enteritis usually presented with abdominal pain, and those with CMV proctocolitis with diarrhea. CMV antigenemia was positive only in 58 % of the patients tested (median 3, IQR 0–12 /200,000 WBCs). Seventy-two patients with CMV GI disease received ganciclovir treatment. Thirty-day mortality was 9.2 %, and only 1 patient died directly of CMV GI disease (colon perforation). To assess the impact of CMV GI disease on the course of malignancies, we performed sub-group analysis in patients with acute leukemia and lymphoma, which can attain CR by chemotherapy or hematopoietic stem cell transplantation (HSCT). However, CMV GI disease had no statistical relationship with achievement of CR or mortality in either of the populations.

Table 2 Baseline characteristics of patients with CMV GI diseases

Variable	Case group (n=98)	Control group (n=196)	P value
Age, year (mean ± SD)	53.8±16.0	58.0±15.0	0.030
Male	69 (70.4 %)	108 (55.1 %)	0.011
BMI (kg/m^2, mean ± SD)	20.8±3.5	22.4±3.3	<0.001
Laboratory tests			
WBC/mm^3 (median, IQR)	5,470 (3,145–9,075)	5,585 (3,910–8,093)	0.956
Hemoglobin (mg/dL, median, IQR)	10.4 (9.0–11.4)	11.4 (9.8–13.0)	<0.001
Platelet×10^3/mm^3 (median, IQR)	88 (47–159)	182 (129–248)	<0.001
ANC/mm^3 (median, IQR)	4,084 (2,155–6,900)	3,421 (2,049–5,764)	0.214
ALC/mm^3 (median, IQR)	601 (396–1,273)	1,176 (725–1,710)	<0.001
Albumin (g/dL, median, IQR)	2.8 (2.4–3.2)	3.9 (3.4–4.1)	<0.001
CRP (mg/dL, median, IQR)	3.44 (0.9–7.9)	0.9 (0.1–5.1)	<0.001
Lymphopenia	63 (64.3 %)	77 (39.3 %)	<0.001
Underlying disease, n (%)			
Cardiovascular disease	4 (4.1)	14 (7.1)	0.440
Pulmonary disease	4 (4.1)	3 (1.5)	0.227
Liver disease	5 (5.1)	16 (8.2)	0.472
Renal disease	11 (11.2)	9 (4.6)	0.047
Neurological disease	7 (7.1)	6 (3.1)	0.134
DM	14 (14.3)	23 (11.7)	0.577
HT	14 (14.3)	29 (14.8)	1.000
Hematological malignancy	58 (59.2)	53 (27.0)	<0.001
Leukemia	32 (32.7)	20 (10.2)	<0.001
Lymphoma	19 (19.4)	26 (13.3)	0.174
Gastric DLBCL	3 (2.8)	0 (0.0)	0.014

Data are number (%) of patients, unless indicated otherwise

SD standard deviation, *BMI* body mass index, *WBC* white blood cell, *IQR* interquartile range, *ANC* absolute neutrophil count, *ALC* absolute lymphocyte count, *CRP* C-reactive protein, *DM* diabetes mellitus, *HT* hypertension, *DLBCL* diffuse large B cell lymphoma

Baseline characteristics of patients with CMV GI disease

The 98 episodes of CMV GI disease were compared with 196 control cancer patients without CMV disease. The most common type of underlying malignancy in the case group was acute leukemia (29.6 %), followed by lymphoma (14.3 %), lung cancer (12.2 %), and colorectal cancer (8.2 %). The control group showed more evenly distributed underlying malignancies; Lung cancer (11.7 %) was the most common disease, followed by colorectal cancer (11.2 %), acute leukemia (9.6 %), and lymphoma (9.6 %). Baseline characteristics of patients with CMV GI disease are presented in Table 2. Patients with CMV GI disease were younger (P=0.030), tended to be male (P=0.011), had lower BMIs (P<0.001), and tended to be more lymphopenic (P<0.001) compared to the control group. Compared to the control group, more patients in the CMV GI disease group had renal disease (P=0.047) and hematologic malignancies (P<0.001).

Table 3 Comorbid conditions of patients with CMV GI disease

Variables	Case group, n=98 (%)	Control group, n=196 (%)	P value
HSCT	28 (28.6)	4 (2.0)	<0.001
GVHD	24 (24.5)	1 (0.5)	<0.001
ICU care	11 (11.2)	3 (1.5)	<0.001
Chemotherapy within 3 month	53 (54.1)	74 (37.8)	0.008
Concomitant CDAD	4 (4.1)	0 (0.0)	0.004
Concomitant ischemic colitis	2 (2.0)	0 (0.0)	0.110
Charlson's WIC (median, IQR)	2 (2–4)	3 (2–6)	0.024
Steroid use within 1 month	69 (70.4)	50 (25.5)	<0.001
RBC transfusion within 1 month	68 (69.4)	39 (19.9)	<0.001
PLT transfusion within 1 month	44 (44.9)	21 (10.7)	<0.001
FFP/cryo transfusion within 1 month	21 (21.4)	4 (2.1)	<0.001

Data are number (%) of patients, unless indicated otherwise

HSCT hematopoietic stem cell transplantation, *GVHD* graft versus host disease, *ICU* intensive care unit, *CDAD Clostridium difficile*-associated diarrhea, *WIC* weighted index of comorbidity, *RBC* red blood cell, *PLT* platelet, *FFP* fresh frozen plasma, *cryo* cryoprecipitate

Table 4 Independent risk factors for the development of CMV GI disease

	Unadjusted analysis		Adjusted analysis	
	OR (95 % CI)	*P* value	OR (95 % CI)	*P* value
Age	0.98 (0.97–1.00)	0.031	1.00 (0.98–1.02)	0.807
Male	1.94 (1.16–3.25)	0.012	2.01 (1.04–3.91)	0.039
BMI	0.85 (0.80–0.93)	<0.001	0.89 (0.81–0.99)	0.024
Lymphopenia	2.78 (1.68–4.60)	<0.001	2.01 (1.04–3.86)	0.037
Renal disease	2.63 (1.05–6.57)	0.039	3.26 (0.85–12.50)	0.085
Hematological malignancy	3.91 (2.35–6.53)	<0.001	2.09 (1.01–4.32)	0.046
ICU care	8.13 (2.21–29.89)	0.002	1.67 (0.36–7.87)	0.516
Chemotherapy within 3 months	1.94 (1.19–3.17)	0.008	1.09 (0.57–2.09)	0.800
Steroid use within 1 month	6.95 (4.10–11.92)	<0.001	4.07 (2.11–7.86)	<0.001
RBC transfusion within 1 month	9.13 (5.24–15.89)	<0.001	5.09 (2.58–10.04)	<0.001

Comorbid conditions of patients with CMV GI disease

Variables related to comorbid conditions of CMV GI disease were analyzed and presented in Table 3. Compared with patients in the control group, patients with CMV GI disease were more likely to have received HSCT, and most of them had graft versus host disease (both *P'* values <0.001). More patients in the CMV group were admitted to the intensive care unit (ICU) ($P<0.001$), received chemotherapy within 3 months prior to CMV disease diagnosis ($P=0.008$), and experienced *Clostridium difficile*-associated diarrhea than the control group ($P=0.004$).

Around 70 % of patients with CMV GI disease had a history of steroid use and RBC transfusions within 1 month prior to the CMV disease, which is a significantly higher proportion than in the control group (both *P* values<0.001). Transfusions of platelet concentrate, fresh frozen plasma, and cryoprecipitate were also more frequent in the CMV group (all *P* values<0.001).

Risk factors for the development of CMV GI disease

Univariate analysis showed CMV GI disease to be significantly associated with younger age, male sex, low BMI, lymphopenia, underlying renal disease, and hematologic malignancy, ICU care, chemotherapy within 3 months, and steroid use, and RBC transfusion within 1 month prior to CMV disease diagnosis (all *P* values <0.05; Table 4). According to multivariate analysis, male sex, low BMI, lymphopenia, hematological malignancy, steroid use, and RBC transfusion within 1 month were identified to be independent risk factors for the development of CMV GI disease in adult patients with cancer (all *P* values<0.05). Among these independent risk factors, RBC transfusion showed the highest odds ratio (OR=5.09).

Discussion

Cytomegalovirus gastrointestinal disease among adult cancer patients has been reported since the late 1980s [8, 9], and more than 40 case reports have described the severe morbidity of CMV GI disease [6, 7]. Most patients with CMV GI disease in our center also suffered from dysphagia, abdominal pain, diarrhea or GI bleeding. Eleven patients (11.2 %) underwent surgical resection due to perforation, uncontrolled bleeding, or obstruction, and 1 patient died.

The seroprevalence in Korean populations is reported to be 96–98 % in pregnant women [10, 11], and 98–100 % in SOT recipients [12, 13]. Considering the mean age of the study population, most cases of CMV disease in the present study should be understood in the context of reactivation of CMV rather than primary infection. Although it is not clear whether the increment of incidence is a real reflection of the rising incidence or if it is due to improved clinical suspicion and diagnosis, there has been a statistically significant, increasing trend in the incidence rate of CMV GI disease since 1995. Also, the incidence was much higher amongst the younger age group (16–29 years) in our study population, probably because of the higher proportion (21.3 %) of hematological malignancy in this age group compared with the older age group (4.45 %).

In our data, male sex predominance was noticed in the multivariate analysis (OR 2.01, CI 1.04–3.91). As previous studies described different sexual predominance depending on the underlying immunosuppressive conditions [9, 14, 15], we think that data regarding sexual predominance in CMV disease should be interpreted carefully in the context of the underlying disease and site of infection. Also, patients with CMV GI disease had significantly lower BMIs than patients in the control group (OR 0.89, CI 0.81–0.99). Theoretically, cachexia in cancer patients may affect immunity [16], and the correlation between malnutrition and vulnerability to CMV infection was previously noticed in animal and human

studies [17–19]. In addition, lymphopenia had a statistically significant relationship with CMV GI disease development (OR 2.01, CI 1.04–3.86), which correlates rationally well with previous findings in HSCT and HIV patients [20, 21]. However, since lymphocyte count was assessed at the time of CMV disease diagnosis, it is not certain whether this relationship can be interpreted as a risk factor or as a phenomenon of CMV reactivation.

Including HSCT recipients, leukemia and lymphoma were the most frequently noted underlying malignancies of CMV GI disease, according to a PubMed search [22, 23]. Consistent with this review of the literature, our results suggest hematological malignancy to be an independent risk factor for the development of CMV GI disease (OR 2.09, CI 1.04–3.86). When classifying CMV GI disease specifically by the site involved, acute leukemia and lymphoma were the most frequently observed and the second most frequently observed underlying malignancy of CMV gastritis, enteritis, and colitis. On the contrary, lung cancer (26.9 %) was the most frequently observed host condition of CMV esophagitis, followed by lymphoma (15.4 %).

Of all the significant independent risk factors identified in this study, a history of steroid use (OR 4.07, CI 2.11–7.86), or an RBC transfusion (OR 5.09, CI 2.58–10.04) within 1 month prior to the CMV disease diagnosis were the independent risk factors with the highest ORs. Long-term use of systemic steroids may increase the risk of viral infections [24, 25], and recent retrospective studies suggest that systemic steroid use might be a risk factor for CMV disease among patients with SOT, hematological malignancies, and rheumatological diseases [26–30]. As noted above, most cases in the present study should be understood in the context of reactivation of CMV owing to a high seropositivity rate. There have been some animal and clinical data suggesting that allogeneic blood transfusions might trigger reactivation of CMV infections [31, 32]. However, since most studies on transfusion-related CMV infection among seropositive recipients were designed to find evidence of viral replication in the blood, whether transfusion might result in CMV end-organ diseases had not been evaluated. The present data will be good clinical evidence of the relationship between transfusion and CMV end-organ disease.

As a retrospective study, there may be a bias in collecting medical information reviewing an 18-year period. However, all the records of laboratory results and medications were fully computerized from the opening of Samsung Medical Center, which minimized possible information bias. In addition, the control group was selected based on the admission date, and no clinical variables were matched to the case patients. Although this may result in selection bias, we chose this non-specific matching method in order to search every potential risk factor because there have been no reported data about risk factors for the development of CMV GI disease in cancer patients. Last, this study may not provide representative data to the general cancer population because it was conducted in a single tertiary care center. Despite these limitations, the present study is to our knowledge the first to report the incidence rate and risk factors of CMV GI disease among adult cancer patients and the findings in this investigation may provide useful information to clinicians treating these patients.

In conclusion, this study identified male sex, low BMI, lymphopenia, hematological malignancy, steroid use, and RBC transfusion within 1 month prior to the CMV disease diagnosis to be independent risk factors for the development of CMV GI disease in adult cancer patients. The overall incidence rate was 52.5 per 100,000 persons, with an increasing trend throughout the study period.

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