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The clinical significance of esophagogastric varices in patients with advanced pancreatic cancer

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Abstract

Background: The prevalence of esophagogastric varices (EGV) in patients with advanced pancreatic cancer is not rare. However, its clinical significance has never been investigated. This study was aimed to explore the clinical implication and outcomes of these patients.

Methods: A retrospective analysis comprising 224 patients with advanced pancreatic cancer managed from October 2012 to December 2019 at a tertiary medical center identified 35 patients who had presented with EGV. Clinical characteristics and outcomes were analyzed with special emphasis on comparison between patients with early-onset and late-onset EGV.

Results: Patients with EGV had lower platelet count and a higher proportion of splenomegaly but no difference in overall survival in comparison to those without EGV. Patients with early-onset EGV had a poorer bleeding survival (hazard ratio, 8.347; CI, 2.509-27.772; $p = 0.001$) in comparison to those with late-onset EGV. On multivariate analysis, initial serum bilirubin, γ-Glutamyltransferase, lactate dehydrogenase, cancer stage, and the response to cancer treatment determine the patient's survival. Patients with tumor invasion to superior mesenteric and portal vein are more likely to have esophageal varices (EV) (EV: 13/15 vs gastric varices [GV]: 4/20; $p < 0.001$); those with splenic vein invasion are more likely to have GV (EV: 4/15 vs GV: 20/20; $p < 0.001$).

Conclusion: Patients with advanced pancreatic cancer and early-onset EGV had poorer bleeding-free survival than those with late-onset EGV. Further studies are needed to clarify the benefits of the prophylactic intervention.

Keywords: Advanced pancreatic cancer; Esophagogastric varices; Portal hypertension

1. INTRODUCTION

Pancreatic cancer is one of the most deadly malignancies in the world.[1] Several prognostic factors are related to its survival, which include the tumor stage, surgical margin, perineural invasion, performance status, liver metastasis, treatment response of cancer, serum level of bilirubin, and carbohydrate antigen 19-9 (CA 19-9).[2–6] The incidence of esophagogastric varices (EGV) in patients with pancreatic cancer is not rare (16%-26%),[7,8] but little is known about the clinical significance of EGV in these patients. Variceal bleeding has been reported as the initial presentation of pancreatic tumors such as lymphoma or carcinoma,[9–11] but the risk factors of variceal bleeding and its impact on these patients are unknown and have never been systemically evaluated.

Formation of EGV is due to an increase of portal venous pressure (portal hypertension). Portal hypertension in liver cirrhosis is caused by sinusoidal resistance and hyperdynamic mesenteric blood flow.[12] In contrast, pancreatic cancer can lead to a hypercoagulable status and thus cause thromboembolic disease, resulting in splanchnic vascular thrombosis.[13] Other than hypercoagulable thrombosis, direct tumor invasion of vessels such as the splenic vein, portal vein, or superior mesenteric vein may also cause locoregional portal hypertension and EGV.[14] Furthermore, general portal hypertension can also be caused by pancreatic cancer with liver metastasis as well.

When pancreatic cancer further advances, theoretically, general and locoregional portal hypertension should become worse. However, the evolution of EGV and its impact on patients is still largely unknown. Thus, the aim of this study is to delineate the clinical significance of EGV in patients with advanced pancreatic cancer.

2. METHODS

2.1. Patients

From October 2012 to December 2019, we retrospectively reviewed 399 patients aged 20–80 years old with advanced pancreatic cancer in terms of vascular invasion with or without distant metastasis. Two-hundred fifty-seven patients received esophagogastroduodenoscopy (EGD), endoscopic retrograde cholangiopancreatography (ERCP), or endoscopic ultrasound (EUS) for either staging, treatment, or surveillance for pancreatic cancer within 3 months of initial cancer diagnosis were enrolled.

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Followed abdomen cross-sectional study, include computer tomography and magnetic resonance imaging were also review for occurrence of EGV. Eleven patients with liver cirrhosis, 14 patients lost to follow-up, four patients with unknown primary tumors, and four patients with more than one malignancy were excluded. The remained 224 patients were finally analyzed (Supplementary Fig. 1, http://links.lww.com/JCMA/A92).

Tumor location at the head, neck, or tail and vascular invasion or thrombosis of the portal vein, superior mesenteric vein, or splenic vein were reviewed and coded according to computer tomography or magnetic resonance imaging. Of the 224 remained patients, 35 patients had EGV according to a precise review of their endoscopic images. The presence of EGV, their size, and the red color signs were determined after reaching a consensus between two gastroenterologists. If esophageal varices (EV) and gastric varices (GV) were present simultaneously, the predominant type was coded. None of these patients received prophylactic treatment for EGV, such as nonselective beta-blocker or endoscopic treatment.

The other patient characteristics analyzed included age, sex, tumor stage, blood cell count, liver enzyme, biliary enzyme, fibrosis-4 (FIB-4) score, initial serum level of CA 19-9, and the initial serum level of total bilirubin. The cancer treatment was adherent to the National Comprehensive Cancer Network guidelines of pancreatic cancer and included radiotherapy and chemotherapy.[15–18] The disease control status was defined as stable or regressive changes of tumor status according to image studies at 2–3 months after the first-line cancer treatment.

Early-onset EGV was defined by endoscopic evidence of EGV within 3 months of the pancreatic cancer diagnosis. EGV found after 3 months were defined as late-onset EGV. The size of varices was classified according to the Beppu classification as F_1 (tortured), F_2 (nodular), or F_3 (tumor-like). Large varices were defined by endoscopic evidence of F_2 or F_3 varices.

Variceal bleeding was defined by active bleeding, white nipple sign, and large varices without other potential bleeders. Admission due to gastrointestinal (GI) bleeding was defined by a major presentation of melena or hematemesis. Blood transfusion before and after endoscopic treatment was recorded during each variceal bleeding episode. Rebleeding of varices was defined according to the Baveno V consensus[19] by the presence of hematemesis or melena, which needs hospital admission, blood transfusion, or a drop in hemoglobulin by more than 3 g/dL if no transfusion is given. Bleeding-free survival was calculated from the initial date of endoscopic evidence of EGV to the date of bleeding or death.

2.2. Statistical methods

The primary endpoints were variceal bleeding and overall survival. Subgroup analyses were also performed to find the differences between early-onset and late-onset EGV. Fisher exact test or a chi-square test with Yates' correction was performed to compare the categorical variables as appropriate. Continuous variables with normal distributions were expressed as the mean ± SD and analyzed with two-sample Student *t* tests.

Continuous variables without normal distributions were expressed as the median (minimum-maximum) and analyzed with the Mann-Whitney nonparametric test. The cumulative overall survival rates were estimated using the Kaplan-Meier method and compared using Cox's proportional hazards model. In addition, we confirmed the assumption of proportional hazards by the log-minus-log plot of survival in a Cox regression analysis.

The variables with statistical significance ($p < 0.05$) or approximate significance ($p < 0.1$) according to the univariate analysis were subjected to a multivariate analysis using a forward stepwise logistic regression model. A two-tailed value of $p < 0.05$ was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA).

This study was approved by Taipei Veterans General Hospital Institutional Review Board (protocol number 2020-03-002AC) on April 20, 2020.

3. RESULTS

3.1. Patients' baseline characteristics

During a median follow-up of 7.7 months, 35 of 224 (15.6%) patients had EGV, 19 of them had already existing EGV when pancreatic cancer was diagnosed, and 16 of them developed EGV after 3 months of the cancer diagnosis. There were no differences between patients with and without EGV regardless of age, sex, white blood cell count, hemoglobulin, liver enzyme, biliary enzyme, FIB-4, hepatitis B or C infection, radiotherapy, serum CA 19-9 level, regimen of chemotherapy, TNM stage, and disease control rate. The median survival was not different between patients with EGV and those without them (Table 1). However, serum platelet count was lower in patients with EGV (Table 1). Patients with EGV were more likely to have splenomegaly and to be hospitalized due to GI bleeding (Table 1).

Table 1

Clinical characteristics of patients with and without esophagogastric varices

Characteristics	Patients with EGV (n = 35)	Patients without EGV (n = 189)	*p*
Age, y	61.9 ± 6.9	63.9 ± 9.6	0.251
Male/female	20/15	103/86	0.729
White blood cell ($\times 10^9$/L)	7.0 ± 1.9	8.3 ± 5.3	0.198
Hemoglobulin (g/dL)	12.7 ± 1.5	12.5 ± 1.7	0.514
Platelet ($\times 10^9$/L)	190.2 ± 79.3	246.7 ± 92.5	0.001
Prothrombin time (s)	11.5 (10.0-32.4)	11.1 (9.4-61.5)	0.031
Activated partial thromboplastin time (s)	27.8 (23.2-40.4)	28.2 (22.5-66.3)	0.303
Total bilirubin (mg/dL)	1.06 (0.47-27.69)	1.39 (0.1-35.37)	0.597
Albumin (g/dL)	3.9 (3.4-4.8)	3.9 (2.3-4.9)	0.261
Creatinine (mg/dL)	0.80 (0.3-1.36)	0.83 (0.29-13.84)	0.553
Alkaline phosphatase (IU/L)	136 (53-729)	113 (35-1542)	0.226
γ-Glutamyltransferase (IU/L)	95 (12-896)	85 (6-2109)	0.731
Alanine aminotransferase (IU/L)	39 (6-461)	30 (4-795)	0.940
Aspartate aminotransferase (IU/L)	36 (13-389)	32 (8-641)	0.869
Lactate dehydrogenase (IU/L)	202 (100-726)	217 (11-2056)	0.844
FIB-4	2.13 (0.70-10.51)	1.71 (0.41-26.86)	0.041
HBsAg positive (%)	3 (8.6)	18 (9.5)	0.859
Anti-HCV positive (%)	5 (16.7)	10 (5.3)	0.065
CA 19-9 (U/mL)	2292 (7.6-2 186 300)	1748.6 (1.04-3 627 000)	0.612
Splenomegaly (%)	17 (48.6)	36 (19)	0.001
Radiotherapy (%)	10 (28.6)	57 (30.1)	0.851
Chemotherapy (gemcitabine-based/5-FU-based)	30/5	179/10	0.065
Disease control rate (%)	15 (42.8)	71 (37.6)	0.554
Stage 3/4	4/31	26/163	0.710
Admission due to GI bleeding, times	1 (0-4)	0 (0-3)	0.001
Median survival, d	262 (38-1129)	231 (29-1558)	0.161

Variables with normal distribution are expressed as mean ± SD and analyzed with two-sample Student *t* tests. Variables with non-normal distribution are expressed as median (minimum-maximum) and analyzed with the Mann-Whitney nonparametric test.

anti-HCV = hepatitis C virus antibody; CA 19-9 = carbohydrate antigen 19-9; EGV = esophagogastric varices; FIB-4 = fibrosis-4; FU = fluorouracil; GI = gastrointestinal; HBsAg = hepatitis B surface antigen; IU = international unit.

In comparison to the patients with late-onset EGV, a higher proportion of patients with early-onset EGV had longer prothrombin time, higher serum creatinine level, higher EGV bleeding rate. More patients with late-onset EGV had a better disease control rate (Table 2).

3.2. Bleeding and survival outcomes of patients with EGV and without EGV

There was no difference of overall survival between patients with or without EGV (Fig. 1). Variceal bleeding occurred in eight of the 35 (22.9%) patients with EGV, but there was none in the non-EGV group. Risk of variceal bleeding was higher in early-onset EGV group (7/19, 36.8%), in contrast to the late-onset group (1/16, 6.3%; $p = 0.047$) (Table 2). The amount of blood transfusion with pack red blood cell was 6.5 ± 2.3 units during each variceal bleeding episode. Of the eight patients with variceal bleeding, seven of them received endoscopic treatment and achieved successful hemostasis, but the other one patient refused endoscopic treatment and experienced rebleeding of GV. The bleeding-free survival was lower in patients with early-onset EGV than late-onset EGV

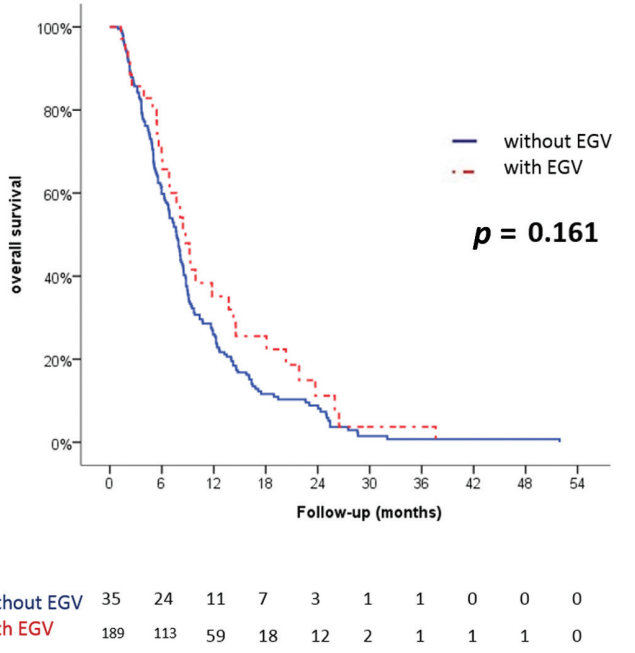

Fig. 1 Overall survival of patients with or without EGV. EGV = esophagogastric varices.

Table 2

Clinical characteristics of patients with early-onset or late-onset EGV

Characteristics	Patients with early-onset EGV (n = 19)	Patients with late-onset EGV (n = 16)	*p*
Age (y)	61.9 ± 6.9	60.8 ± 6.8	0.528
Male/female	14/5	6/10	0.031
White blood cell (×10^9/L)	7.1 ± 2.1	6.9 ± 1.8	0.756
Hemoglobulin (g/dL)	12.4 ± 1.2	13.0 ± 1.0	0.331
Platelet (×10^9/L)	192.4 ± 71.2	187.6 ± 90.4	0.545
Prothrombin time (s)	11.9 (10.3-32.4)	11.05 (10-12)	0.008
Activated partial thromboplastin time (s)	27.9 (24.7-40.4)	27.15 (23.2-30.9)	0.091
Total bilirubin (mg/dL)	1.57 (0.55-27.69)	0.78 (0.47-16.95)	0.043
Albumin (g/dL)	3.9 (3.4-4.8)	4.15 (3.4-1.5)	0.237
Creatinine (mg/dL)	0.87 (0.75-1.36)	0.75 (0.3-1.21)	0.027
Alkaline phosphatase (IU/L)	203 (57-728)	125 (53-729)	0.301
γ-Glutamyltransferase (IU/L)	110 (15-896)	67.5 (12-766)	0.151
Alanine aminotransferase (IU/L)	39 (11-461)	32 (6-443)	0.545
Aspartate aminotransferase (IU/L)	48 (15-389)	35 (13-257)	0.301
Lactate dehydrogenase (IU/L)	213 (122-726)	198.5 (100-489)	0.659
FIB-4	2.21 (0.91-10.51)	2.13 (0.70-4.80)	0.508
HBsAg positive (%)	0	3 (18.7)	0.086
Anti-HCV positive (%)	2 (10.5)	3 (18.7)	0.642
CA 19-9 (U/mL)	4776.5 (14.9-1 198 800)	434.7 (7.6-2 186 300)	0.151
Liver metastasis (%)	15 (78.9)	10 (62.5)	0.454
EGV bleeding (%)	7 (36.8)	1 (6.3)	0.047
Admission times due to GI bleeding	1 (0-4)	1 (0-3)	0.336
Radiotherapy (%)	3 (15.8)	7 (43.7)	0.132
Chemotherapy (gemcitabine-based/5-FU-based)	16/3	14/2	1.000
Disease control rate (%)	5 (26.3)	10 (62.5)	0.031
Bleeding-free survival, d	80 (0-524)	255.5 (33-1093)	0.008
Survival, d	169 (38-566)	297 (179-1129)	0.001

Variables with normal distribution were expressed as mean ± SD and analyzed with two-sample Student *t* tests. Variables with non-normal distribution median (minimum-maximum) and analyzed with the Mann-Whitney nonparametric test.

anti-HCV = hepatitis C virus antibody; CA 19-9 = carbohydrate antigen 19-9; EGV = esophagogastric varices; FIB-4 = fibrosis-4; FU = fluorouracil; GI = gastrointestinal; HBsAg = hepatitis B surface antigen; IU = international unit.

(median: 80 vs 255.5 days; $p = 0.008$) (Fig. 2A). On multivariate analysis, γ-Glutamyltransferase ≥ 50 international unit (IU)/L, splenomegaly, TNM stage 4, early-onset EGV, high-risk varices, and uncontrolled disease under first-line treatment were unfavorable factors for variceal bleeding-free survival (Table 3).

The median survival was lower in patients with early-onset EGV (median survival: 169 vs 297 days; $p < 0.001$) (Table 2 and Fig. 2B). On multivariate analysis, γ-Glutamyltransferase ≥ 50 IU/L, lactate dehydrogenase ≥200 IU/L, total bilirubin ≥1 mg/dL, TNM stage 4, uncontrolled disease under first-line treatment were unfavorable factors for overall survival (Table 4). Overall survival and disease control rate were not different between patients with early-onset EGV and patients without EGV.

3.3. Tumor location and EGV

Of the 35 patients with varices, 15 (42.8%) of them had EVs, and 20 (57.2%) of them had GVs. The median survival was not different between patients with EVs and GVs (253 vs 243.5 days; $p = 0.633$). EVs were more frequently found in patients with pancreatic head tumors. On the other hand, GVs were more frequently found in patients with pancreatic tail tumors. Portal vein and superior mesenteric vein invasion were more frequently found in patients with EVs (13/15) than patients with GVs (4/20). In contrast, splenic vein invasion was more frequently found in the GV group (20/20) than EV group (4/15) (Table 5).

4. DISCUSSION

This study is the largest series to describe the natural history of EGV in patients with advanced pancreatic cancer. We found patients with EGV are vulnerable to bleeding, particularly those with early-onset EGV. This suggests possible benefits of routine endoscopic screening to assess the presence of EGV and appropriate intervention to prevent EGV bleeding. We also delineated the association of EGV with the location of tumors and vascular invasion.

During 7.7 months of follow-up, 15.6% of patients with advanced pancreatic cancer had EGV, which is compatible with previous reports.[7,8] Patients with EGV were likely to have

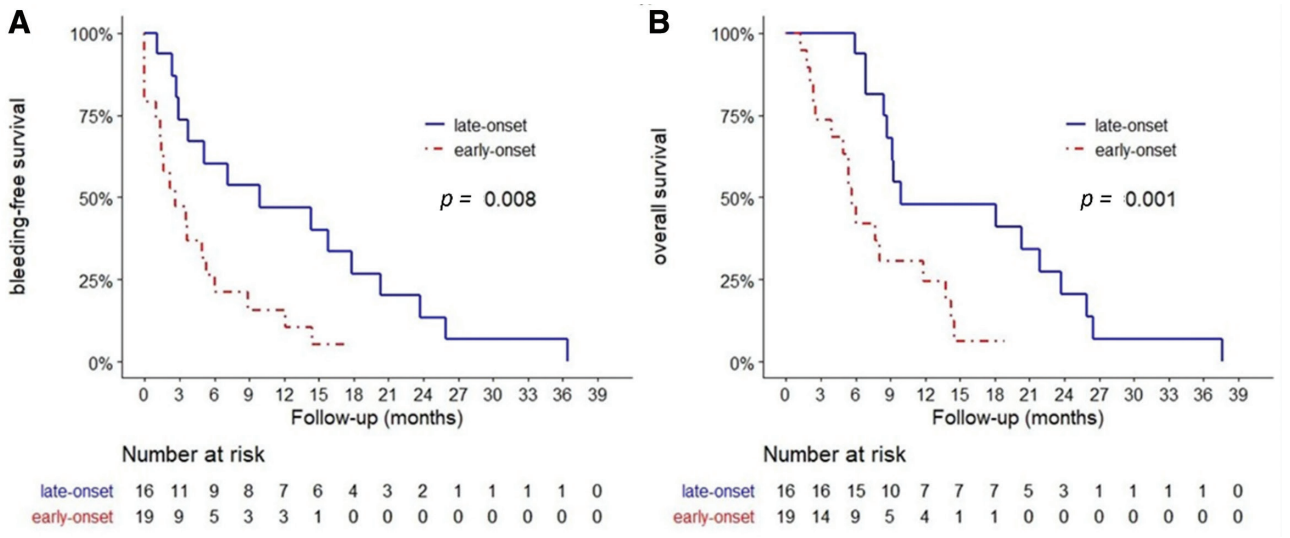

Fig. 2 Bleeding-free survival and overall survival of patients with or without early-onset EGV. Compare to late-onset EGV, bleeding-free survival are shorter in patients with early-onset EGV (A), and overall survival are also shorter in patients with early-onset EGV (B). EGV = esophagogastric varices.

lower platelet count and splenomegaly, which may indicate progression of portal hypertension. It is also not surprising to find patients with EGV was more likely to admission due to GI bleeding. Actually, we found the risk of variceal bleeding was around 22.9% (8/35) for patients with pancreatic cancer and EGV, which is higher than the annual bleeding rate of 11%-16% for patients with liver cirrhosis.[20] Furthermore, we found a higher proportion of patients with early-onset EGV had lower disease control rate, jaundice, and higher creatinine level, which indicated a more advanced stage of pancreatic cancer.[2–6] The reason why patients with early-onset EGV had lower disease control rate might be related to the more advanced disease status, leading to shorter survival. On multivariate analysis, patients with high-risk EGV were more likely to experience variceal bleeding, which was compatible to previous study.[20] On the other hand, patients with early-onset EGV not only had poorer bleeding-free survival (median: 80 vs 255 days) but also had poorer overall survival than those with late-onset EGV (median: 169 vs 297 days). It is probable that more advanced pancreatic cancer and response to cancer treatment are the most critical factors in determining survival, which is in consistence with our multivariate analysis. Though the survival advantage in patients with late-onset EGV was associated with better disease control rate, the causal relationship could not be established.

Table 3

Factors associated with poorer bleeding-free survival in patients with EGV and advanced pancreatic cancer

	Univariable		Multivariable	
Factors	**Hazard ratio (95% CI)**	***p***	**Hazard ratio (95% CI)**	***p***
Age (y/o) >65/≤65	0.315 (0.071-1.396)	0.128		
Gender (male/female)	0.622 (0.173-2.232)	0.467		
HBsAg (yes/no)	13.496 (0.725-251.275)	0.081		
Anti-HCV (yes/no)	3.608 (0.490-26.571)	0.208		
Albumin (g/dL) ≥3.5/<3.5	1.184 (0.296-4.744)	0.811		
Alkaline phosphatase (IU/L) ≥100/<100	1.033 (0.096-11.091)	0.979		
γ-Glutamyltransferase (IU/L) ≥50/<50	4.087 (1.021-16.365)	0.047	2.833 (1.197-6.707)	0.018
ALT (U/L) ≥40/<40	1.183 (0.302-4.632)	0.809		
AST (U/L) ≥40/<40	1.535 (0.292-8.062)	0.612		
Lactate dehydrogenase (IU/L) ≥200/<200	2.251 (0.484-10.464)	0.301		
Total bilirubin (mg/dL) ≥1/<1	4.371 (0.878-21.754)	0.072		
CA 19-9 (U/mL) ≥1000/<1000	4.001 (0.852-18.783)	0.079		
FIB-4 ≥3.25/<3.25	0.209 (0.037-1.201)	0.079		
Splenomegaly (yes/no)	9.760 (1.259-75.670)	0.029	2.527 (1.091-5.854)	0.030
TNM stage 4/3	27.489 (1.828-413.450)	0.017	6.837 (1.044-44.758)	0.044
Chemotherapy gemcitabine-based/5-FU-based	1.682 (0.345-7.062)	0.537		
Radiotherapy (yes/no)	1.025 (0.270-3.893)	0.971		
Early-onset varices (yes/no)	33.651 (1.335-848.233)	0.033	8.347 (2.509-27.772)	0.001
High-risk varices (yes/no)	12.328 (1.616-94.038)	0.015	6.311 (1.993-19.989)	0.002
Disease uncontrolled under first-line treatment (yes/no)	8.856 (2.047-38.308)	0.004	5.551 (1.505-29.353)	0.045

ALT = alanine transaminase; Anti-HCV = hepatitis C virus antibody; AST = aspartate aminotransferase; CA 19-9 = carbohydrate antigen 19-9; EGV = esophagogastric varices; FIB-4 = fibrosis-4; FU = fluorouracil; HBsAg = hepatitis B surface antigen; IU = international unit; y/o = years old.

Table 4

Factors associated with poor overall survival in patients with advanced pancreatic cancer

Factors	Univariable		Multivariable	
	Hazard ratio (95% CI)	*p*	Hazard ratio (95% CI)	*p*
Age (y/o) >65/≤65	1.312 (0.957-1.798)	0.092		
Gender (male/female)	0.892 (0.657-1.213)	0.467		
HBsAg (yes/no)	1.589 (0.972-2.597)	0.065		
Anti-HCV (yes/no)	1.160 (0.660-2.038)	0.606		
Albumin (g/dL) ≥3.5/<3.5	1.043 (0.698-1.556)	0.838		
Alkaline phosphatase (IU/L) ≥100/<100	1.145 (0.679-1.932)	0.611		
γ-Glutamyltransferase (IU/L) ≥50/<50	1.676 (1.002-2.802)	0.049	1.594 (1.076-2.359)	0.020
ALT (U/L) ≥40/<40	1.503 (0.889-2.543)	0.129		
AST (U/L) ≥40/<40	0.879 (0.509-1.519)	0.644		
Lactate dehydrogenase (IU/L) ≥200/<200	1.416 (1.045-1.920)	0.025	1.459 (1.093-1.947)	0.010
Total bilirubin (mg/dL) ≥1/<1	1.445 (1.021-2.045)	0.038	1.421 (10.26-1.969)	0.035
CA 19-9 (U/mL) ≥1000/<1000	0.952 (0.681-1.333)	0.776		
FIB-4 ≥3.25/<3.25	1.019 (0.665-1.561)	0.933		
Splenomegaly (yes/no)	3.875 (1.134-5.454)	0.031	2.223 (1.112-4.854)	0.020
TNM stage 4/3	1.856 (1.131-3.046)	0.014	1.841 (1.145-2.959)	0.012
Chemotherapy gemcitabine-based/5-FU-based	1.382 (0.269-6.089)	0.475		
Radiotherapy (yes/no)	0.707 (0.492-1.015)	0.06		
Early-onset varices (yes/no)	2.589 (1.081-6.547)	0.042		
High-risk varices (yes/no)	3.691 (1.113-7.456)	0.039		
Disease uncontrolled under first-line treatment (yes/no)	5.781 (4.070-8.211)	<0.001	5.670 (4.009-8.017)	<0.001

ALT = alanine transaminase; Anti-HCV = hepatitis C virus antibody; AST = aspartate aminotransferase; CA 19-9 = carbohydrate antigen 19-9; FIB-4 = fibrosis-4; FU = fluorouracil; HBsAg = hepatitis B surface antigen; IU = international unit; y/o = years old.

It is noteworthy that there was no difference in survival between patients with and without variceal bleeding. It may be due to variceal bleeding actually can be controlled effectively by current treatments, including vasoactive agents, early antibiotics, and endoscopic intervention, which have already substantially improved bleeding mortality.[21–23] However, it cannot be over emphasized that EGV bleeding may delay cancer treatment and increase the hospitalization burden of these patients.

Not surprisingly, EVs are likely to develop in patients with portal vein or superior mesenteric vein thrombosis, in contrast to GVs in patients with splenic vein thrombosis because of the relation for the anatomical territory of vascular drainage. Moreover, cases with primary tumors located at the pancreatic head tend to develop EVs, in contrast to those located at the pancreatic tail and the development of gastric varices.

Table 5

Characteristics of patients with esophageal varices or gastric varices

Characteristics	Patient with EVs (n = 15)	Patient with GVs (n = 20)	*p*
Age (y/o) >65/≤65	62 ± 1.4	62.4 ± 1.4	0.966
Gender (male/female)	8/7	10/8	0.935
Total bilirubin (mg/dL) ≥1/<1	10 (66.7%)	8 (40%)	0.450
CA 19-9 (U/mL) ≥1000/<1000	8 (53.3%)	14 (70%)	0.320
Tumor location (head/body/tail)	8/5/2	1/6/13	0.005
Vessel invasion			
SMV/PV	13 (86.7%)	4 (20%)	<0.001
SPV	4 (26.7%)	20 (100%)	<0.001
FIB-4 ≥3.25/<3.25	6 (40%)	3 (15%)	0.129
Survival, d	253 (38-779)	243.5 (54-712)	0.633

Variables with normal distribution were expressed as mean ± SD and analyzed with two-sample Student *t* tests. Variables with non-normal distribution median (minimum-maximum) and analyzed with the Mann-Whitney nonparametric test.

CA 19-9 = carbohydrate antigen 19-9; EV = esophageal varices; FIB-4 = fibrosis-4; GV = gastric varices; PV = portal vein; SMV = superior mesenteric vein; SPV = splenic vein; y/o = years old.

There are several limitations to this study. First, the sample size of patients with varices was not big enough to delineate the whole scope of the natural history of EGV. However, it is still the largest series at present. Second, not all but only two-thirds (257/399) of patients undergoing surveillance endoscopy. Although selected bias cannot be prevented, however, endoscopy is essential to exactly document the presence of EGV and most (224/257, 87%) of patients undergoing endoscopy were included. Finally, the efficacy of prophylactic treatment for EGV could not be determined due to the inherent nature of a retrospective study. Prospective randomized trials are required to clarify the best strategy for prophylactic treatment.

We have described the natural history of EGV in patients with advanced pancreatic cancer. The presence of EGV at the diagnosis of pancreatic cancer indicates poor outcomes in terms of bleeding and survival. A well-controlled trial is required to determine whether active screening of EGV and prophylactic intervention can improve the outcomes of these patients.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://doi.org/10.1097/JCMA.0000000000000264.

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