

Prognostic factors for survival in patients with gastric adenocarcinoma

Piyakorn Poonyam¹ | Natsuda Aumpan¹ | Ratha-Korn Vilaichone^{1,2,3} 

¹Gastroenterology Unit, Thammasat University Hospital, Pathumthani, Thailand

²Department of Medicine, Chulabhorn International College of Medicine (CICM), Thammasat University, Pathumthani, Thailand

³Digestive Diseases Research Center (DRC), Thammasat University, Pathumthani, Thailand

Correspondence

Ratha-Korn Vilaichone, GI Unit, Department of Medicine, Thammasat University Hospital, Pathumthani 12120, Thailand.
Email: vilaichone@hotmail.co.th

Abstract

Background: Gastric cancer ranks as a leading cause of cancer deaths worldwide. Information of prognostic factors related to gastric cancer are limited.

Aim: This study aimed to gather clinical data and prevalence of prognostic factors related to gastric adenocarcinoma in Thailand.

Methods and results: This retrospective cohort study was conducted at Thammasat University Hospital, Thailand between January 2010 and July 2018. Gastric adenocarcinoma patients were enrolled and followed up for at least 5 years. Total of 210 gastric tumor patients were enrolled. One hundred patients were diagnosed with gastric adenocarcinomas (57 men and 43 women, mean age = 61.1 years). The leading presenting symptoms were weight loss (65%), followed by dyspepsia (54%) and UGI bleeding. Common clinical manifestations were thrombocytosis (26%), followed by syndrome of inappropriate antidiuretic hormone (SIADH; 15%). Eosinophilia was present in early cancer (25.0% vs 6.5%, $P = .123$), while SIADH and thrombocytosis were more common in advanced stages (16.3% vs 0%, $P = .602$, and 28.3% vs 0%, $P = .108$, respectively). SIADH was significantly related to reduced 1-year survival rate compared to normal serum sodium levels (21.4% vs 71.4%, OR 0.109, 95% CI 0.024-0.497, $P = .004$). Five-year survival rates were worse in patients with SIADH, but better in patients with eosinophilia compared to patients without these conditions (0% vs 27.8%, $P = .058$ and 20.0% vs 7.8%, $P = .375$, respectively).

Conclusion: Thrombocytosis and SIADH were common in gastric cancer. SIADH was significantly correlated with poor 1-year survival. These clinical manifestations might be useful for predicting gastric cancer prognosis.

KEYWORDS

gastric cancer, prognostic factors

1 | INTRODUCTION

Gastric cancer is one of the most common cancers leading to cancer-related deaths worldwide. The GLOBOCAN database 2018 noted that more than 1 million people per year were newly diagnosed with

gastric cancer. Most patients present at an advanced unresectable stage resulting in high mortality rate second only to lung cancer.¹ Gastric cancer incidence varied among geographic regions. East Asian countries including the Republic of Korea and Japan have the highest incidence, whereas the rates are low in North America and Africa.¹

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Thailand is the second largest country in mainland Southeast Asia with approximately 69 million people. The age-standardized incidence rate of gastric cancer in Thailand was relatively low (3.1 per 100 000) compared to other Asian countries (14.3 per 100 000).² However, gastric cancer ranked ninth in cancer mortality due to its grave prognosis especially in younger patients.³ The majority of gastric cancers are adenocarcinomas.⁴

Helicobacter pylori, a gram-negative rod-shaped bacterium, has been recognized as the most important factor associated with gastric cancer.⁵⁻⁷ *H. pylori* infection causes persistent gastric mucosal inflammation producing oxidative stress and DNA damage. Gastric glands subsequently undergo precancerous differentiation and eventually become malignant cells.⁸ *H. pylori* eradication is considered the most effective strategy to reduce the incidence of gastric cancer.^{9,10} Apart from bacterial factors, host genetic polymorphisms promoting an inflammatory response and environmental factors such as high dietary salt intake are linked to an increased risk of gastric cancer.^{11,12} In addition to avoiding modifiable risk factors, recognition of symptoms and signs is also important for cancer diagnosis. More than half of gastric cancer patients have predominant symptoms of weight loss (61.6%) and abdominal pain (51.6%).¹³ Some signs and symptoms may occur as a result from the immune response against malignant cells. Previous studies reported atypical clinical features such as abrupt onset of numerous seborrheic keratoses (Leser-Trélat sign), and acanthosis nigricans in gastric cancer patients.^{14,15}

Until now, there have been few modern era reports about prognostic factors related to survival rate of gastric cancer patients. This study aimed to gather clinical data and prevalence of each prognostic factors related to gastric cancer in Thailand.

2 | METHODS

2.1 | Study design

This retrospective cohort study was conducted at Thammasat University Hospital between January 2010 and July 2018. Patients underwent upper gastrointestinal endoscopy as indicated by Gastroenterology Association of Thailand (GAT). Gastric biopsies from a lesion suspicious for gastric cancer were then performed by gastroenterologists. The inclusion criteria were patients aged more than 18 years old with gastric adenocarcinoma diagnosed by histopathological results of gastric biopsies. Patients with incomplete medical records were excluded from the study. Demographic data, underlying diseases, clinical information, laboratory profiles such as complete blood count, tumor markers (CEA, CA 19-9), endoscopic features, histopathological results, current *H. pylori* infection status, complications, and treatment outcomes were extracted from medical records and retrospectively reviewed. Cancer staging was defined by TNM classification at the time of diagnosis. Long-term follow-up data of patients were monitored for at least 5 years after cancer diagnosis.

2.2 | Definitions

H. pylori infection was defined as positive results of rapid urease test, or presence of *H. pylori* in histopathology of gastric biopsy.

Early stage cancer was defined as primary gastric tumor with the depth of invasion no more than submucosa regardless of lymph node involvement. By TNM classification, early stage gastric cancer comprised T1 and any N.

Leukocytosis was defined as white blood cell count more than 11 000/ μ L without causes of infection, inflammation, myeloproliferative neoplasms, or medications such as glucocorticoids.

Eosinophilia was defined as eosinophil count more than 500/ μ L without causes of allergic disorders, parasitic infection, or hematologic malignancies.

Thrombocytosis was defined as platelet count more than 400 000/ μ L without causes of infection, inflammation, or iron deficiency anemia.

Syndrome of inappropriate antidiuretic hormone secretion (SIADH) was defined as hyponatremia (plasma sodium <135 mEq/L) in euvolemic patients. The plasma osmolality is less than 280 mOsm/kg, while urine osmolality is more than 100 mOsm/kg. The urine sodium is more than 40 mEq/L. Others etiologies of SIADH such as central nervous system disorders, infection, or medications were excluded.

Hypercalcemia was defined as corrected calcium of more than 10.5 mg/dL.

Cancer cachexia was defined as >5% weight loss in the past 6 months without starvation or body mass index (BMI) <20 kg/m² and ongoing weight loss of >2%.¹⁶

2.3 | Statistical analysis

The statistical analysis was performed by using SPSS version 22 (SPSS Inc, Chicago, Illinois). The demographic data were analysed by Fisher's exact test, or Chi-square test where appropriate. *P*-value of less than .05 was defined as statistical significance. The study protocol was approved by the Human Research Ethics Committee of Thammasat University, Thailand and was conducted according to the good clinical practice guideline, as well as the Declaration of Helsinki.

3 | RESULTS

A total of 210 gastric tumor patients were enrolled. One hundred patients were diagnosed with gastric adenocarcinomas (57 men and 43 women, mean age of 61.1 years). The most frequent comorbidities were hypertension (28%), followed by dyslipidemia (18%). The most common presenting symptoms of gastric adenocarcinomas were weight loss (65%), dyspepsia (54%), and upper gastrointestinal bleeding (males vs females: 22.8% vs 7.0%, OR 3.94, 95% CI 1.05-14.84, *P* = .033); the least common symptom was dysphagia (13%). Smoking was more common in men (32.6% vs 2.9%, OR 16.41, 95% CI 2.03-132.49, *P* = .009). The overall rate of active *H. pylori* infection in

gastric cancer patients was 46%. There was no patient with family history of gastric cancer. Intestinal-type gastric cancer was more predominant than diffuse type in both genders (68.4% in men and 53.5% in women). The overall 1-year survival rate was 48.9%. The 1-year survival rate was slightly higher in men than women (51.0% vs 46.2%). Demographic data including gender, age, comorbidities, type of cancer, cancer staging, and 1-year survival rate are shown in Table 1.

The most common clinical manifestations related to gastric cancer were cancer cachexia (62%), followed by thrombocytosis (26%), SIADH (15%), and eosinophilia (8%) as demonstrated in Table 2. Hematologic manifestations were present in 37 patients including

thrombocytosis, eosinophilia, leukocytosis, and venous thromboembolisms in 26 (70.2%), 8 (21.6%), 8 (21.6%), and 3 (8.1%) patients, respectively. Patients with other causes of reactive thrombocytosis such as infection, or iron deficiency anemia were excluded from paraneoplastic thrombocytosis. In the same way, leukocytosis and eosinophilia from other causes such as parasitic infection, or medication were excluded. Paraneoplastic thrombocytosis, hypercoagulability, and leukocytosis were present only in advanced-stage patients (28.3% vs 0%, $P = .108$, 3.3% vs 0%, $P = 1.000$, and 8.7% vs 0%, $P = 1.000$, respectively), while eosinophilia was more prevalent in early stage disease (25.0% vs 6.5%, $P = .123$). Massive leukocytosis was a rare

TABLE 1 Demographic data of gastric cancer patients classified by genders

Characteristics	Male (N = 57)	Female (N = 43)	P value
Age (years \pm SD)	63.1 \pm 15.2	58.4 \pm 14.8	.128
BMI (kg/m ² \pm SD)	19.1 \pm 3.1	19.5 \pm 4.6	.705
Comorbidities			
None	28 (49.1%)	29 (67.4%)	.067
Diabetes mellitus	8 (14.0%)	7 (16.3%)	.756
Hypertension	20 (35.1%)	8 (18.6%)	.069
Dyslipidemia	12 (21.1%)	6 (14.0%)	.360
Chronic kidney disease	4 (7.0%)	1 (2.3%)	.387
Ischemic heart disease	3 (5.3%)	1 (2.3%)	.632
Cerebrovascular accident	5 (8.8%)	1 (2.3%)	.233
Chronic obstructive pulmonary disease	2 (3.5%)	0 (0%)	.505
Cirrhosis	8 (14.0%)	5 (11.6%)	.723
Clinical presentation			
Weight loss	36 (63.2%)	29 (67.4%)	.657
Dyspepsia	27 (47.4%)	27 (62.8%)	.126
Anorexia	18 (31.6%)	20 (46.5%)	.128
Nausea and vomiting	15 (26.3%)	10 (23.3%)	.726
Anemic symptoms	15 (26.3%)	12 (27.9%)	.859
GI bleeding	13 (22.8%)	3 (7.0%)	.033
Dysphagia	5 (8.8%)	8 (18.6%)	.148
<i>H. pylori</i> infection	25 (43.9%)	21 (48.8%)	.621
Family history of GI cancer	5 (8.8%)	3 (7.0%)	1.000
Smoking	14 (32.6%)	1 (2.9%)	.009
Cancer type			
Intestinal type	39 (68.4%)	23 (53.5%)	.128
Diffuse type	18 (31.6%)	20 (46.5%)	.128
Cancer TNM staging			
Stage I	2 (3.5%)	1 (2.3%)	1.000
Stage II	3 (5.3%)	3 (7.0%)	1.000
Stage III	17 (29.8%)	18 (41.9%)	.212
Stage IV	35 (61.4%)	21 (48.8%)	.210
Cancer staging			
Early stage	5 (8.8%)	3 (7.0%)	1.000
Advanced stage	52 (91.2%)	40 (93.0%)	1.000
1-year survival rate	26/51 (51.0%)	18/39 (46.2%)	.650

TABLE 2 Clinical manifestations classified by gender and stage of cancer

Factors	Total (N = 100)	Male (N = 57)	Female (N = 43)	P-value	Early (N = 8)	Advanced (N = 92)	P-value
Cachexia	62	36 (63.2%)	26 (60.5%)	.784	1 (12.5%)	61 (66.3%)	.016
Hematologic system	37	20 (35.1%)	17 (39.5%)	.648	2 (25.0%)	35 (38.0%)	.469
Thrombocytosis	26	13 (22.8%)	13 (30.2%)	.402	0	26 (28.3%)	.108
Hypercoagulability	3	1 (1.8%)	2 (4.7%)	.576	0	3 (3.3%)	1.000
Leukocytosis	8	2 (3.5%)	6 (14.0%)	.072	0	8 (8.7%)	1.000
Eosinophilia	8	5 (8.8%)	3 (7.0%)	1.000	2 (25.0%)	6 (6.5%)	.123
Endocrine system	16	6 (10.5%)	10 (23.3%)	.086	0	16 (17.4%)	.348
SIADH	15	6 (10.5%)	9 (20.9%)	.149	0	15 (16.3%)	.602
Hypercalcemia	2	1 (1.8%)	1 (2.3%)	1.000	0	2 (2.2%)	1.000

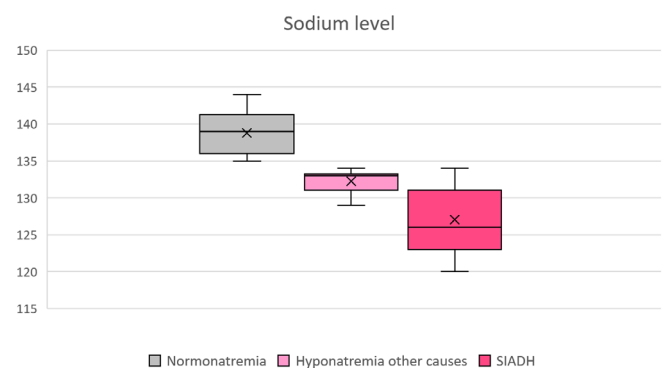
Abbreviation: SIADH, syndrome of inappropriate antidiuretic hormone.

manifestation present in only one patient (ie, a 35-year-old man with stage IV gastric adenocarcinoma and an absolute neutrophil count of 70 800 per mm³). Three patients had malignant thrombosis according to hypercoagulable stage related to gastric cancer. One patient presented with bilateral pulmonary embolism and inferior mesenteric vein thrombosis. The second one had inferior vena cava thrombosis extending downwards to right common iliac vein. Another had deep vein thrombosis of left leg.

Hyponatremia from SIADH was present in 15% of patients. The mean plasma sodium level at initial presentation of patients with SIADH was lower than that of hyponatremia from other causes as demonstrated in Figure 1 (126.2 ± 2.7 vs 132.5 ± 1.3, $P < .001$). All patients with SIADH had advanced cancer. Hypercalcemia was also present in only advanced disease. Two patients with hypercalcemia died within 1 year (3 and 9 months) after diagnosis.

Disease outcomes within the first year after diagnosis could be evaluated in 90 patients as 10 (10%) were lost to follow-up. Risk factors associated with mortality rate within 1 year are shown in Table 3. Mortality rate within 1 year after diagnosis was higher in advanced cancer than early disease (54.2% vs 14.3%, OR 7.11, 95% CI 0.82-61.65, $P = .075$). Gender, age, and comorbidities did not exhibit significant associations with one-year mortality rate. Anorexia was significantly associated with higher mortality rate within 1 year. (67.6% vs 39.6%, OR 3.42, 95% CI 1.32-8.86, $P = .011$). SIADH was the only manifestation significantly related to lower 1-year survival rate compared to normal serum sodium levels (21.4% vs 71.4%, OR 0.109, 95% CI 0.109-0.497, $P = .004$) as demonstrated in Figure 2. The median survival time of gastric cancer patients with SIADH was 145 days (IQR 91-315).

There were 69 patients included for estimating the 5-year survival rate. Six patients were alive after diagnosis for 5 years. Patients with early cancer had superior 5-year survival rate to advanced cancer (66.7% vs 6.1%, OR 31.0, 95% CI 2.29-419.35, $P = .01$). Five-year survival rates were worse in patients with SIADH, but better in patients with eosinophilia compared to patients without these conditions (0% vs 27.8%, $P = .058$ and 20.0% vs 7.8%, $P = .375$, respectively). One-year and five-year survival rates classified by sodium level and prognostic factors were demonstrated in Figures 2 and 3, respectively.

**FIGURE 1** The box plot of plasma sodium level

4 | DISCUSSION

Gastric cancer has ranked as the second leading cause of global cancer mortality for more than 30 years. The global database revealed over 1 million new cases and approximately 783 000 deaths attributed to stomach cancer annually.¹ Although the incidence and mortality rate remain high, there has been a decline in cancer mortality over the past 90 years.¹⁷ Reduction in gastric cancer mortality are explained in part by the discovery and eradication of *H. pylori* which is a significant risk factor for development of gastric cancer.¹⁸ In addition, the invention of electric refrigerators in the mid-19th century improved quality of food storage by decreasing salt-based food preservation and bacterial contamination.¹⁹ Thailand is the Southeast Asian country with low gastric cancer incidence (2.3%), but high *H. pylori* infection and its mortality rate is still high positioning in the ninth place of national cancer death statistics.²⁰ Patients with gastric adenocarcinomas in this study demonstrated the usual male to female predominance with the ratio of 1.33 to 1 although the ratio was slightly lower than the previous study in Thailand and other countries.^{17,21} Although previous studies observed protective effects of estrogen on gastric cancer, there was no difference in 1-year survival rate between genders in this study.^{22,23} Considering risk factors for gastric cancer, our study demonstrated no difference of *H. pylori* infection between gender and significantly higher history of smoking in males. Overall prevalence of

TABLE 3 Univariate and multivariate analyses for risk factors associated with mortality rate within 1 year of gastric cancer patients

Variables	Univariate analysis			Multivariate analysis		
	OR	(95% CI)	P-value	OR	(95% CI)	P-value
Male gender	0.82	(0.36-1.90)	.650			
Age >60 years	1.09	(0.48-2.49)	.837			
Comorbidities	1.01	(0.44-2.33)	.977			
FH of GI cancer	1.67	(0.37-7.44)	.503			
Clinical presentation						
Weight loss	1.18	(0.50-2.82)	.708			
Dyspepsia	1.56	(0.67-3.61)	.302			
Anorexia	3.18	(1.32-7.66)	.010	3.42	(1.32-8.86)	.011
Nausea and vomiting	1.37	(0.51-3.67)	.529			
Anemic symptoms	0.75	(0.29-1.91)	.546			
GI bleeding	0.68	(0.21-2.13)	.503			
Dysphagia	0.50	(0.14-1.86)	.303			
Cancer type						
Intestinal type	1					
Diffuse type	0.96	(0.40-2.30)	.927			
Cancer staging						
Advanced stage	7.11	(0.82-61.65)	.075			
Cachexia	1.07	(0.46-2.52)	.869			
Hematological lab values						
Leukocytosis (>11 000/ μ L)	1.30	(0.27-6.18)	.740			
Eosinophilia (>500/ μ L)	0.36	(0.07-1.93)	.231			
Thrombocytosis (>400 000/ μ L)	1.31	(0.52-3.32)	.565			
Plasma sodium level						
Normonatremia (\geq 135 mEq/L)	1			1		
Hyponatremia from other causes	3.21	(1.18-8.73)	.022	3.56	(1.24-10.19)	.018
SIADH	9.17	(2.01-41.80)	.004	9.65	(1.99-46.67)	.005

Abbreviation: SIADH, syndrome of inappropriate antidiuretic hormone.

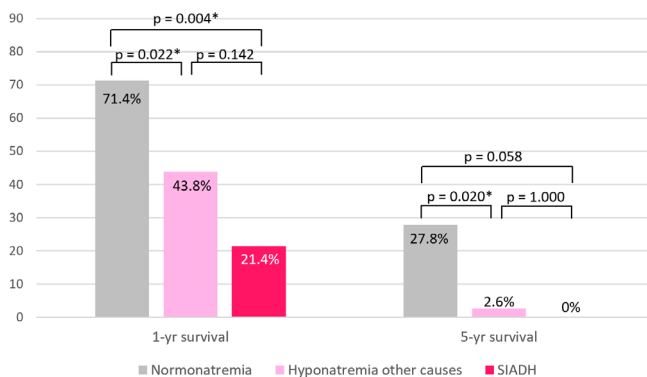


FIGURE 2 The 1-year and 5-year survival rates between groups according to sodium level

current *H. pylori* infection in gastric cancer patients was 46% which was comparable to the previous study.²⁴ The earlier study conducted in 10 European countries with low incidence of gastric cancer

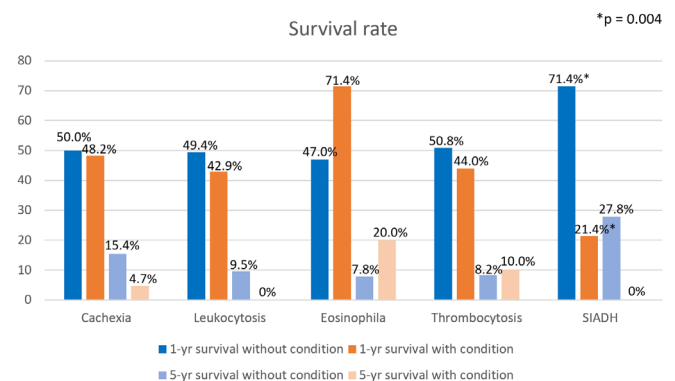


FIGURE 3 One-year and five-year survival rates classified by prognostic factors

demonstrated that both current and former smokers were at higher risk of development of gastric cancer.²⁵ The two most common presenting symptoms were weight loss (65%) and dyspepsia (54%) same



as the prior report.²¹ In our study, 16% of patients presented with upper gastrointestinal bleeding which was comparable to the previous report.¹³ However, the previous study did not mention patients presenting symptoms classified by gender. Furthermore, this study indicated that upper gastrointestinal bleeding as a clinical presentation in men significantly higher than women (22.8% vs 7.0%, OR 3.94, 95% CI 1.05-14.84, $P = .033$). Apart from presenting symptoms, the important findings of this study highlighted common manifestations in gastric cancer patients and might have an impact on patient's prognosis.

This study documented possible manifestations of various organ systems which developed in patients with gastric cancer. The most common clinical manifestation was cancer cachexia which was comparable to the previous study.²⁶ Almost half of cancer patients presenting with cachexia had poor outcomes.²⁶ The pathogenesis of cancer cachexia involves in tumor-secreted cytokines stimulating hypothalamic response and subsequently leading to anorexia. Moreover, cytokines can potentiate catabolic state resulting in increased energy consumption along with protein breakdown and eventually cause reduced muscle mass.²⁷

Thrombocytosis was the most frequent hematologic manifestation (26%) which was higher than prior studies in East Asian countries (6.4%-11.4%).^{28,29} This might be explained by greater number of advanced-stage patients in this study than other countries.^{28,29} The mechanisms of paraneoplastic thrombocytosis occurred by production of several cytokines such as interleukin-1 (IL-1), IL-6, and IL-11 in malignant solid tumors.³⁰ IL-6 overproduced by gastric cancer mediated the induction of hepatic thrombopoietin (TPO) mRNA expression resulting in rising of TPO level and consequently increasing a platelet count.^{31,32} Elevation of platelet count found only in patients with advanced gastric cancer could be correlated to poor prognosis.³³ However, there was no significant difference of survival rates between groups having thrombocytosis and normal platelet numbers. Apart from thrombocytosis, a hypercoagulable state can be caused by several mechanisms including procoagulant activity expressed by both normal human cells and cancer procoagulant itself. Venous thromboembolism (VTE) was established from hypercoagulable state associated with gastric cancer. All three patients having VTE were diagnosed with advanced-stage gastric cancer. Two of them survived more than 1 year after diagnosis. The previous study revealed overall survival within VTE group of approximately 12 months and also stated that advanced disease with VTE contributed to almost three times higher mortality rates than early cancer without VTE.³⁴

The second most common hematologic abnormalities were eosinophilia and leukocytosis. The prevalence of eosinophilia in this study was 8%. Patients experiencing eosinophilia were more likely to have early-stage than advanced cancer. Moreover, both 1-year and 5-year survival rates of patients with eosinophilia were higher than patients with normal eosinophil count. This might be explained by anti-tumorigenic factors, for example, TNF- α , granzyme, and cationic proteins generated from eosinophils.³⁵ The study in 1986 observed that eosinophilic infiltration in gastric tumors significantly corresponding to blood eosinophilia was a good prognostic marker for prolonged survival rate of patients with gastric cancer. In addition, the reappearance

of eosinophilia was noted in patients with recurrent gastric cancer.³⁶ On the contrary, there were a few case reports describing massive eosinophilia in advanced gastric cancers contributing to poor prognosis.^{37,38} Leukocytosis was another hematologic manifestation presented in eight patients after excluding causes of infection, inflammation, medications, or myeloproliferative neoplasms. Some studies exhibited hyperleukocytosis as an uncommon paraneoplastic syndrome in advanced pancreatic adenocarcinoma and soft tissue sarcoma. These rare events were caused by excessive secretion of serum granulocyte colony-stimulating factor and associated with poor prognosis.^{39,40} However, there was no previous report of this condition in gastric cancer patients.

Electrolyte abnormalities caused by endocrine disorders were present in gastric cancer patients. Hyponatremia from SIADH was evidently demonstrated only in advanced disease. This study demonstrated significantly lower 1-year survival rate in patients with SIADH. No patients with SIADH survived after 5 years of diagnosis. The median survival time was less than 1 year in SIADH group designating poor prognosis possibly related to this condition. Until now, there has been no report about prevalence and prognosis of SIADH in gastric cancer patients. Two case reports demonstrated patients presenting with symptomatic hyponatremia with the initial plasma sodium level of less than 130 mEq/L.^{41,42} The prior study indicated that terminal cancer was associated with hyponatremia and also mentioned that the lower the sodium level was, the shorter survival time the patient had left.⁴³ Our study reported two patients with hypercalcemia diagnosed with advanced stage gastric cancer and subsequently died within 1 year after diagnosis. Hypercalcemia in gastric cancer might be a grave prognostic factor in this particular disease.^{44,45}

5 | CONCLUSION

Gastric cancer is an important cause of cancer mortality worldwide. Smoking and upper GI bleeding were significantly common among men with gastric cancer. Thrombocytosis and SIADH were common in gastric cancer. SIADH was significantly correlated with poor 1-year survival. These clinical manifestations might be useful for predicting gastric cancer prognosis.

ETHICS STATEMENT

The study received ethical approval by the Human Research Ethics Committee of Thammasat University, Thailand and was conducted according to the good clinical practice guideline, as well as the Declaration of Helsinki. The project number of ethical approval was MTU-EC-IM-2-160/61. All data had been fully anonymized before they were accessed. The Ethics Committee waived the requirement for informed consent because of no greater than minimal risk for participants.

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AUTHOR CONTRIBUTIONS

Piyakorn Poonyam: Data curation; formal analysis; resources; writing-original draft. **Natsuda Aumpan:** Formal analysis; writing-original draft; writing-review and editing.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Ratha-Korn Vilaichone  <https://orcid.org/0000-0003-4298-9331>

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