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Alpha-fetoprotein for Gastric Cancer Staging: An Essential or Redundant Tumor Marker?

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Abstract. *Background/Aim: This study was designed to clarify the value of routine alpha-fetoprotein (AFP) testing for patients with gastric cancer (GC). Patients and Methods: A total of 905 patients with newly diagnosed GC and available pretreatment carcinoembryonic antigen (CEA), cancer-related antigen 19-9 (CA19-9), and AFP data from 2010 to 2016 were collected for comparison of tumor stage and survival. Results: In total, 139 patients (15.4%), 155 patients (17.1%), and 27 patients (3.0%) had elevated CEA, CA19-9, and AFP levels, respectively. The c-index values of elevated AFP levels in predicting stage IV disease and the 1-year mortality rate were 0.564 (95%CI=0.520-0.608) and 0.594 (95%CI=0.553-0.635), respectively, which were significantly lower than those of CEA (0.673 and 0.665) and CA19-9 (0.619 and 0.618). Conclusion: Elevated AFP is rare in patients with newly diagnosed GC. Routine AFP sampling would not provide a higher survival prediction in GC patients than CEA or CA19-9.*

Gastric cancer (GC) is ranked the fourth most commonly diagnosed malignancy globally, accounting for 8.2% of cancer-related death in 2018 (1) and demonstrating a higher geographic prevalence in the Asia-Pacific area (2). Due to its high incidence and mortality rate, a comprehensive workup for GC tumor staging is the initial step toward the optimal treatment modality. Esophagogastroduodenoscopy (EGD) with endoscopic ultrasonography (EUS) and computed tomography (CT) are essential examinations for a complete tumor staging of GC (3). Additionally, carcinoembryonic antigen (CEA) and cancer-related antigen 19-9 (CA19-9) are commonly used tumor markers in GC for determining tumor stage, monitoring recurrent disease, and predicting prognosis (4).

Alpha-fetoprotein (AFP) is produced in the yolk sac and the fetal liver during fetal development, and its function in adults remains unclear (5). AFP is widely used as a tumor marker in hepatocellular carcinoma (HCC) or germ cell tumors, and AFP elevation has also been reported in GC and other tumor types (6-8). A subset of gastric cancer harboring AFP-producing ability (9) is characterized by a poor prognosis because it commonly presents in the advanced stage, with a huge tumor burden and liver metastases (10).

The standard diagnosis of AFP-elevated GC is based on elevated serum AFP levels combined with specific histological findings including higher proliferative activity, less apoptosis, and richer neovascularization than patients with non-elevated AFP (11). AFP-elevated GC is a rare subtype and accounts for 1%-7% of GC (10, 12). Furthermore, the true prevalence of AFP elevation in GC patients is believed to be underestimated because serum AFP is not a routine serologic test in GC patients at the time of tumor staging. Furthermore, the clinical significance of AFP as a tumor marker for tumor staging in patients with GC has not been thoroughly investigated. By acquiring a large cohort, this study aimed to investigate the prognostic and predictive value of elevated AFP in patients with newly diagnosed GC.

Patients and Methods

Patient selection. Tumor markers including CEA, CA19-9, and AFP have been established as routinely measured biomarkers for patients with newly diagnosed GC by the institutional tumor board of Chang Gung Memorial Hospital Linkou branch in

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Key Words: Gastric cancer, cancer staging, AFP, CEA, CA19-9, overall survival.

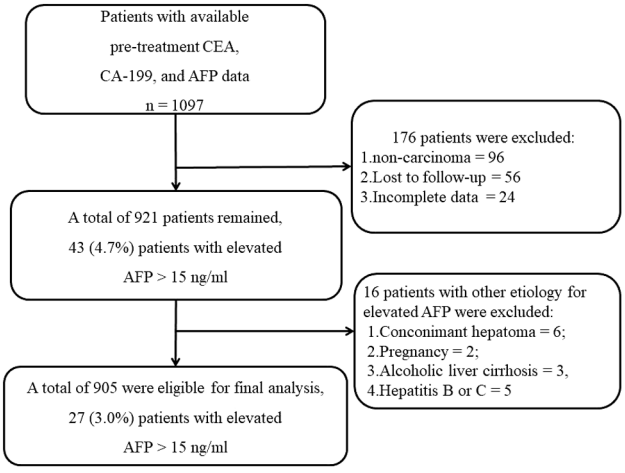

Figure 1. *The algorithm of patient selection.*

Taiwan since 2010. A total of 1097 consecutive patients with newly diagnosed GC confirmed by pathological diagnosis from 2010 to 2016 were included in this study. Patients with histological type other than carcinoma (n=96), were lost to follow up (n=56), or had incomplete tumor markers (n=24) were excluded. Forty-three patients (4.7%) of the remaining 921 patients had elevated AFP levels while 16 of the 43 patients with other etiologies for elevated AFP were further excluded. Finally, 905 patients were included in this study. The selection algorithm is presented in Figure 1.

Data collection. The patients' demographic data, clinicopathological variables, and tumor markers were recorded by the primary care physicians using a prospectively designed electronic data form (13). Data higher than the cut-off values of CEA (<5 ng/dl), CA 19-9 (<37 ng/dl), and AFP (<15 mg/dl) were considered to indicate elevation of tumor markers. Tumor staging for GC was stratified according to the 7th edition of the American Joint Committee on Cancer (AJCC) (14). Overall survival (OS) was calculated from the time of cancer diagnosis to the date of death from any cause. All the included patients were followed until death or December 31, 2017. All the dates of death were obtained from the Institutional Cancer Registry or the National Registry of Death in Taiwan. This study was approved by the institutional review board of Chang Gung Memorial Hospital on 22 November 2018 (ethic code: 20180164BOC101) and has been conducted in compliance with the Helsinki Declaration (1996).

Statistical analysis. The basic demographic data were summarized as n (%) for categorical variables and median with range for continuous variables. The c-index, (15) sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were calculated for each tumor marker in prediction of stage IV disease and the 1-year mortality rate, separately. The OS was calculated using the Kaplan–Meier method. Patients were allocated into groups according to the tumor stage and the levels of tumor markers for survival comparison. Log-rank tests were used to determine the significance of differences among survival curves.

Table I. *Patient characteristics (n=905).*

Variable	n (%)
Median age (range)	64 (18-94)
Gender	
Male	570 (63.0)
Female	335 (37.0)
Median BMI (range), kg/m^2	23.0 (13.0-41.2)
Smoking	
No	705 (77.9)
Yes	200 (22.1)
Drinking	
No	681 (75.1)
Yes	224 (24.8)
Tumor site	
Cardia or fundus	111 (12.3)
Body	300 (33.1)
Antrum/pyloric	350 (38.7)
Overlapping	144 (15.9)
Clinical T-classification	
1	125 13.8)
2	157 (17.3)
3	302 (33.4)
4	321 (35.5)
Clinical N-classification	
0	316 (34.9)
1	120 (13.3)
2	230 (25.4)
3	239 (26.4)
Clinical M-classification	
0	662 (73.1)
1	243 (26.9)
AJCC staging	
1	220 (24.3)
2	167 (18.5)
3	275 (30.4)
4	243 (26.9)
Histological grade	
Well/moderate	291 (32.2)
Poorly	464 (51.3)
Unclassified	150 (16.6)
Helicobacter pylori infection	
No	601 (66.4)
Yes	304 (33.6)
CEA, ng/ml	
≤5	766 (84.6)
>5	139 (15.4)
CA19-9, U/ml	
≤37	750 (82.9
>37	155 (17.1)
AFP, ng/ml	
≤15	878 (97.0)
>15	27 (3.0)

BMI: Body mass index; AJCC: American Joint Committee on Cancer; CEA: carcinoembryonic antigen; CA19-9: carbohydrate Antigen 19-9; AFP: alpha fetoprotein.

SPSS version 17.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. All statistical assessments were two-sided, and a *p*-value less than 0.05 was considered statistically significant.

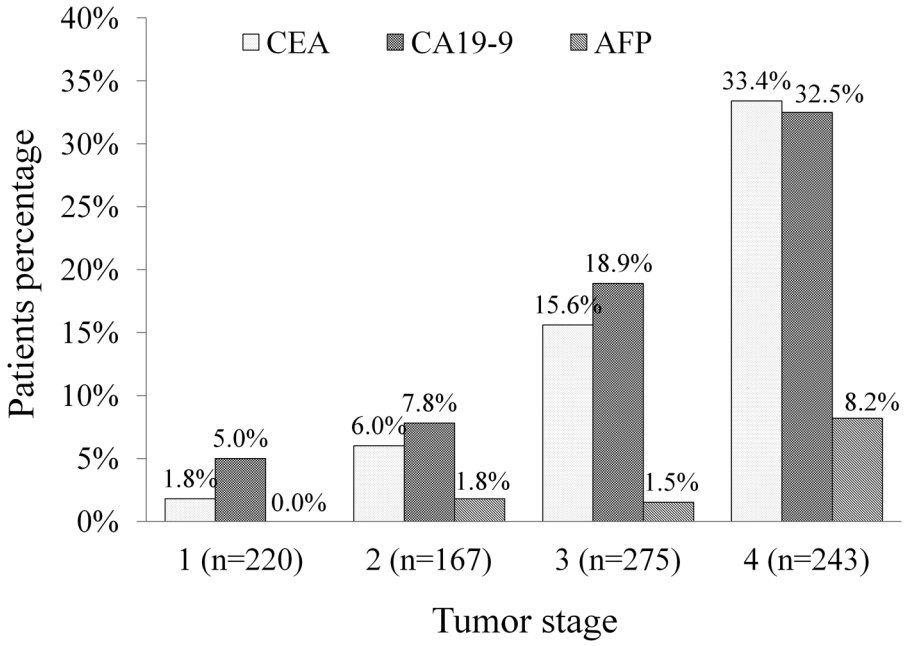

Figure 2. *The distribution of elevated tumor markers among each tumor stage.*

Results

Basic patient characteristics. The patient characteristics are summarized in Table I. The median age of the 905 patients was 66 years (range=18-94 years), and 63% were male. The distributions of patients in stage I, II, III, and IV disease were 24.3%, 18.5%, 30.4%, and 26.9% of the cohort, respectively. The most common elevated tumor marker of the cohort was CA19-9 (155 patients, 17.1%), followed by CEA (139 patients, 15.4%), and AFP (27 patients, 3.0%).

Distribution of abnormal tumor markers according to the tumor stage. Figure 2 shows the percentage of abnormal tumor makers stratified by tumor stage. The percentage of patients with elevated CEA among patients with stage I to stage IV diseases increased from 1.8% to 33.4%, while that of patients with elevated CA19-9 and elevated AFP increased from 5.0% to 32.5% and 0% to 8.2%, respectively. Among the 27 patients presented with elevated AFP, 3 (11.1%), 4 (14.8%), and 20 patients (74.1%) presented with stage II, III, and IV disease, respectively. The median AFP levels were 44 ng/ml (range=31-259 ng/ml), 141 ng/ml (range=26-308 ng/ml), and 142 ng/ml (range=16-54337 ng/ml) for stage II, III, and IV disease, respectively (Figure 3). Additionally, no significant difference in AFP levels was found among the different tumor stages (p=0.55).

The accuracy of elevated tumor markers in the prediction of stage IV disease is presented in Table II. The accuracies

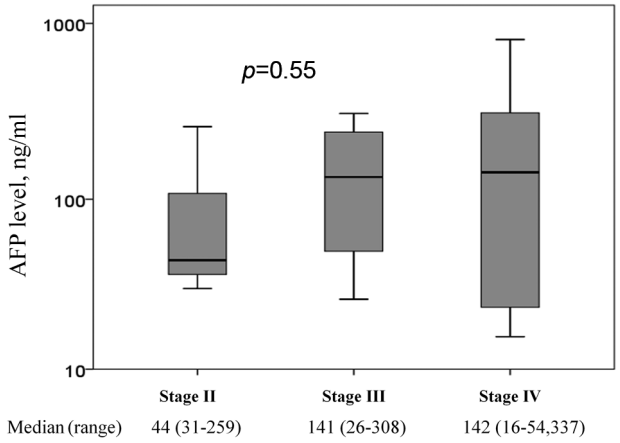

Figure 3. *The levels of abnormal AFP in each cancer stage.*

to predict stage IV disease were 75.9%, 73.5%, and 78.1% for those with elevated CEA, CA19-9, and AFP, respectively. The c-index values to predict stage IV disease were 0.673 (95%CI=0.630-0.717), 0.619 (95%CI=0.571-0.666), and 0.564 (95%CI=0.520-0.608) for those with elevated CEA, CA19-9, and AFP, respectively. The c-index value of CEA in the prediction of stage IV disease was significantly higher than that of AFP (p<0.001). No difference in the c-index value was evident between CA19-9 and AFP (p=0.10).

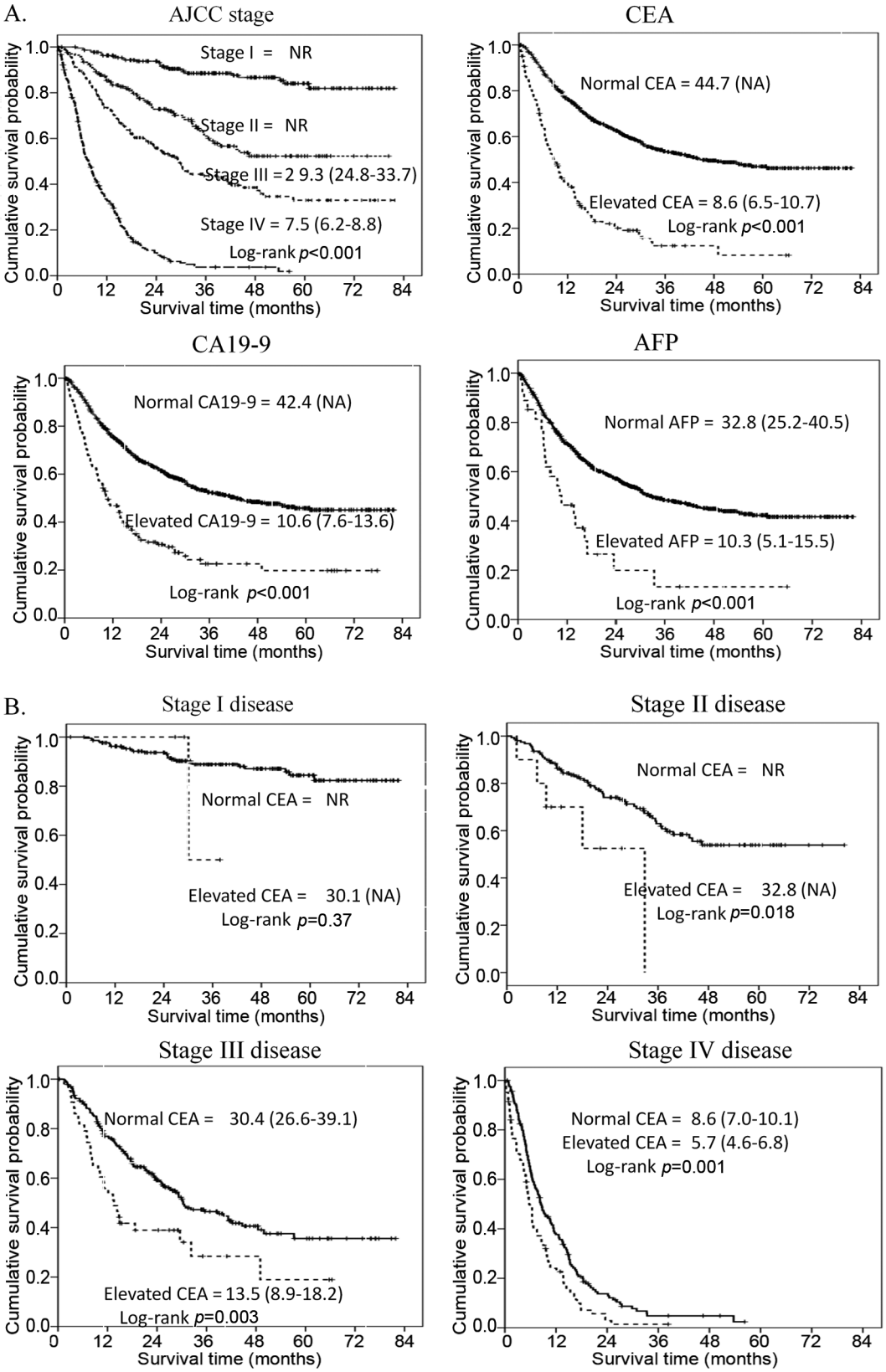

Figure 4. *Continued*

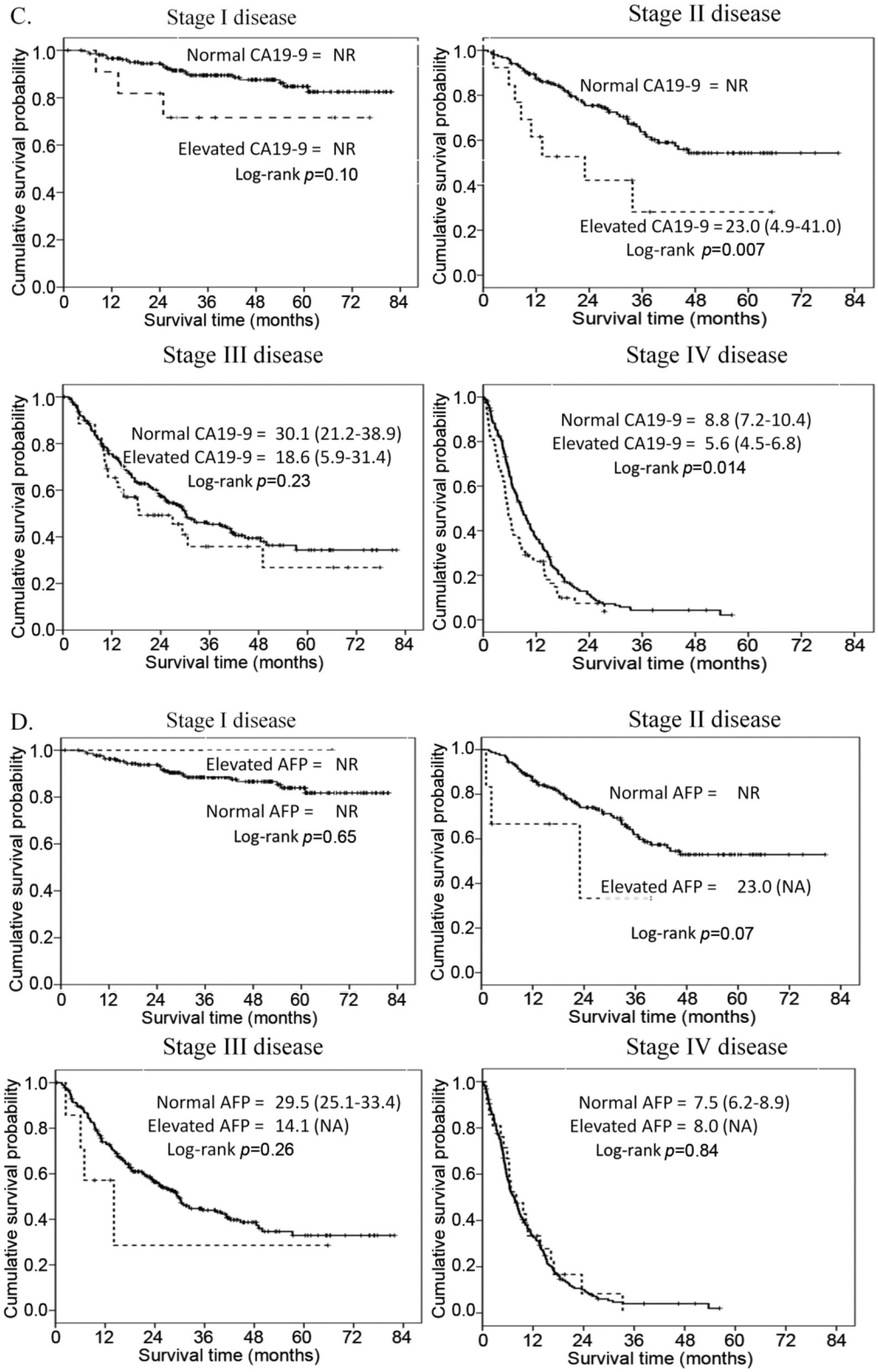

Figure 4. *The Kaplan–Meier survival curves. (A) According to AJCC cancer staging system and elevated CEA, CA 19-9, and AFP. (B) According to patients with elevated CEA or normal CEA in different cancer stages. (C) According to patients with elevated CA 19-9 or normal CA 19-9 in different cancer stages. (D) According to patients with elevated AFP or normal AFP in different cancer stages. NR: Not reached; NA: not available.*

Table II. *Performance of tumor markers in prediction stage IV disease and 1-year mortality probability.*

Tumor markers	Sensitivity	Specificity	PPV	NPV	Accuracy	c-index
In prediction of stage IV disease						
CEA	33.7%	91.4%	59.0%	79.0%	75.9%	0.673 (0.630-0.717)*
CA19-9	32.5%	88.5%	51.0%	78.1%	73.5%	0.619 (0.571-0.666)
AFP	8.2%	98.9%	74.1%	74.6%	78.1%	0.564 (0.520-0.608)*
In prediction of 1-year mortality						
CEA	31.4%	91.1%	59.0%	76.6%	73.9%	0.665 (0.625-0.706)*
CA19-9	31.4%	88.7%	52.9%	76.1%	72.2%	0.618 (0.572-0.663)
AFP	5.4%	98.0%	51.9%	71.9%	71.3%	0.594 (0.553-0.635)*

PPV: Positive predictive value; NPV: negative predictive value; CEA: carcinoembryonic antigen; CA19-9: carbohydrate Antigen 19-9; AFP: alpha fetoprotein. *Significant difference between groups ($p<0.05$).

Survival outcome and performance of tumor markers in survival prediction. The median duration of follow up was 31 months (95%CI=24.5-37.6), and 451 (49.8%) of the patients died at the end of the study. The median survival among patients with stage I and II GC was not reached at the time of survival analysis, whereas that of stage III GC was 29.3 months (95%CI=24.8-33.8) and that of stage IV GC was 7.5 months (95%CI=6.2-8.8) (Figure 3A). Patients with elevated CEA levels had a significantly poorer median OS than those with normal CEA levels (8.6 *versus* 44.7 months, respectively; $p<0.001$) (Figure 4A). Patients with elevated CA19-9 levels had a significantly poorer median OS than those with values within the normal range (10.6 *versus* 42.4 months, respectively; $p<0.001$) (Figure 4A). Similarly, patients with elevated AFP levels presented with a significantly poorer median OS than those with levels within the normal range (10.3 *versus* 32.8 months, respectively; $p<0.001$) (Figure 4A).

All the patients were categorized based on normal or elevated tumor makers in each AJCC-defined tumor stage for survival comparison. Patients with elevated CEA had a significantly poorer survival than those with a normal CEA levels in stage II, III, and IV disease (Figure 4B). Patients with elevated CA19-9 had a significantly poorer survival than those with normal CA19-9 levels in stage II and IV disease (Figure 4C). However, patients with elevated AFP levels were not associated with a significantly poorer survival outcome compared to those with normal AFP levels in each tumor stage (Figure 4D).

The median survival times were 8.6 months, 10.6 months, and 10.8 months for patients with elevated CEA, CA19-9, and AFP, respectively. Owing to the median survival time of less than one year for patients with elevated biomarkers, we used the 1-year mortality rate as the time frame to evaluate the prognostic performance of each tumor marker in survival prediction. The accuracies to predict stage IV disease were 73.9%, 72.2%, and 71.3%, for those with elevated CEA, CA19-9, and AFP, respectively. The c-index values to predict the 1-year mortality rate were 0.665 (95%CI=0.625-0.706), 0.618 (95%CI=0.572-0.663), and 0.594 (95%CI=0.553-0.635) for elevated CEA, CA19-9, and AFP, respectively. Again, the c-index value of CEA in the prediction of the 1-year mortality was significantly higher than that of AFP ($p=0.009$). No difference in the c-index value was evident between CA19-9 and AFP ($p=0.45$).

Discussion

Gastric cancer is one of the most common malignant tumors worldwide. Except for endemic countries that have applied regular endoscopic screening, most gastric cancer cases are diagnosed at advanced stages (16). The survival outcomes of advanced gastric cancers are devastating compared with those of early-stage ones. Through a prospectively designed data collection, our study showed that only 3% of GC patients had elevated AFP following cancer diagnosis. Although the prevalence of elevated AFP positively correlated with advanced tumor stage, the c-index of elevated AFP in prediction of stage IV disease and 1-year mortality was inferior to that of CEA but similar to that of CA19-9, indicating that we can not rely on AFP as a single tumor marker as CEA or CA19-9 is more reliable in the prediction of advanced GC.

Previous studies have indicated that GC patients with elevated AFP are frequently associated with lymphatic or vascular microinvasion and synchronous liver metastasis at diagnosis, thus having a worse outcome than those with normal-AFP GC (10, 17). Our conjecture is that measurement of AFP levels during initial diagnosis for GC might provide information regarding prognosis. However, these studies did not stratify the outcome of patients with elevated AFP compared with those with normal-AFP GC according to different tumor stage. Consistent with previous studies, our results showed that elevated levels of CEA, CA19-9, and AFP were associated with a poor survival outcome compared to those with normal levels of each tumor marker. However, our results also showed that while CEA and CA199 remained eligible for survival discrimination,

AFP could not demonstrate a survival difference among GC patients within each AJCC defined tumor stage. To the best of our knowledge, this is the first study to demonstrate the insignificance of AFP in survival prediction of GC patients with the same tumor stage. Our study indicated that tumor stage, but not elevated AFP, is a prognostic factor for GC patients. Therefore, AFP does not have prognostic value within the standardized practice of the AJCC staging system.

CEA and CA19-9 are the two most utilized tumor markers for surveillance, staging, and follow up for GC (18, 19). By stratification, the elevation of CEA and CA 19-9 for stage I GC in our cohort was 1.8% and 5.0%, respectively. The results are compatible with those of other series indicating that the positive rate of CEA and CA 19-9 is low for early GC (20, 21). Our cohort also demonstrated that the incidence of elevated AFP in stage I GC was 0%. Furthermore, the analysis of survival between elevated and normal tumor markers for stage I GC did not yield statistical difference (Figure 4). Based on the above findings, we hypothesize that these tumor markers do not play significant roles in prediction of prognosis for stage I (early) GC. On the contrary, our study reaffirmed the prognostic role of CEA and CA19-9 for more advanced stages of GC, and revealed the low prevalence of AFP elevation in GC, which was similar to that in previous studies (22).

Gastric hepatoid adenocarcinoma (GHA), first described by Ishikura et al, (23) is represented as an extrahepatic tumor morphologically identical to hepatoma. GHA is stratified as one of the four subtypes of AFP-elevated GC (hepatoid type, fetal gastrointestinal type, yolk sac tumor-like type, and mixed type) with an even worse prognosis (24, 25). The largest series comparing GHA with AFP-elevated GC was proposed by Liu et al. (26) and concluded that the prognosis of GHA was poorer than that of AFP-elevated GC. However, we did not further analyze the outcome of GHA from our cohort because we mainly focused on the predictive and prognostic power of AFP in GC patients. Although previous studies have demonstrated GHA as a worse prognostic subtype of AFP-elevated GC, histological review needs to identify the GHA morphological pattern in GC patients with elevated AFP.

This study has some limitations. First, the cut-off value of AFP for diagnosing AFP-elevated GC in our study differed from that in previous series (12, 26, 27), defined as positive when serologic AFP was >15 ng/dl as the cut-off value of the normal range at our institute. Second, we excluded 16 patients from this study based on their underlying diseases that might present with an elevated AFP level. This selection might have excluded patients with concomitant diseases but bearing AFP-elevated GC. Therefore, the true incidence of AFP-elevated GC in our cohort might be underestimated. Finally, only 27 patients with AFP-elevated GC were included in our study. The small patient number might limit the power of statistical analysis for survival outcome. Nevertheless, the incidence of AFP-elevated GC was universal between our cohort and other reported series. The comparison of OS between APF-elevated GC and normal-AFP GC remained at a univariate level because we did not adjust for other confounding factors that might exist, such as between-group differences in clinical characteristics. Further study to understand the prognostic value of these markers and identify novel markers for diagnosis of gastric cancer is warranted.

Conclusion

This prospective study with a large number of patients reaffirmed the prognostic role of CEA and CA199 in advanced GC and revealed the low prevalence of AFP elevation in all stages of GC. Although elevated AFP has been previously shown to be a poor prognostic factor in GC, our study revealed that AFP cannot replace CEA and CA 19-9 as a definitive marker in prognosis prediction under the current standardized AJCC system. Inclusion of AFP during initial staging for GC patients would not provide additional clinical information compared with the current practice of measuring CEA or CA 19-9.

Conflicts of Interest

The Authors declare that no competing interests exist regarding this study.

Authors' Contributions

Conception/design: CYT, and CTC, WCC; Provision of study material or patients: SWH and CYH; Collection and/or assembly of data: CYT, WCC, and YSH; Data analysis and interpretation: CYT, NMT, and JTH; Manuscript writing: CYT, WCC, and KHL; Final approval of manuscript: CYT, KHL, CTC, SWH, CYH, JTH, NMT, YSH, and WCC.

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