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Gamma-Glutamyl Transferase/Albumin Ratio and Alkaline Phosphatase/Albumin Ratio as Novel Prognostic Markers for Metastatic Pancreatic Cancer

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ABSTRACT Objective: Metastatic pancreatic cancer is a common condition and highly lethal condition, emphasizing the urgent need for novel prognostic markers. This study investigated the effect of the gamma-glutamyl transferase/albumin ratio (GAR) and alkaline phosphatase/albumin ratio (APAR) on prognosis. **Material and Methods:** We conducted a retrospective examination 287 patients diagnosed with metastatic pancreatic cancer between January 2008 2019. **Results:** The median age was 65 years, and obstructive jaundice was present in 58 (20.2%). Median overall-surviva (OS) was significantly longer in patients without jaundice (6.0 vs. 3.0 months, p=0.005). Furthermore, median OS and progression-free survival (PFS) were extended in the low-GAR-group (6.0 vs. 4.0 months, p=0.001; 5.0 vs. 3.0 months, p<0.01, respectively). Similarly, patients in the low APAR group exhibited longer median OS and PFS (6.0 vs. 3.0 months, p<0.01; 5.0 vs. 3.0 months, p<0.01, respectively). The low neutrophil-to-lymphocyte-ratio (NLR) group demonstrated prolonged median OS and PFS (8.0 vs. 3.0 months, p<0.01; 6.0 vs. 3.0 months, p<0.01, respectively). Additionally, patients in the high prognostic-nutritional-index (PNI) group experienced extended median OS and PFS (6.0 vs. 3.0 months, p<0.01; 5.0 vs. 2.0 months, p=0.02, respectively). Furthermore, members of the low-GAR-group were significantly more prevalent in the low-NLR and low platelet-to-lymphocyte-ratio-groups (79.4% vs. 20.6%, p=0.02 and 75.9% vs. 24.1%, p=0.04, respectively). By contrast, the low-APAR-group had significantly more members than the high-PNI-group (90% vs. 10%, p<0.01). **Conclusion:** In metastatic pancreatic cancer, both OS and PFS significantly extend in the low-GAR, APAR, and NLR groups, while the high-PNI-group also exhibits enhanced OS and PFS. These findings must be supported by further studies .

Keywords: Metastatic pancreatic cancer; gamma-glutamyl transferase/albumin ratio; alkaline phosphatase/albumin ratio; neutrophil-to-lymphocyte ratio; platelet-to-lymphocyte ratio; prognostic nutritional index

Cancer poses a significant global health challenge and ranks as the second leading cause of mortality in the United States of America (USA). Annually, approximately 62,210 individuals in the USA are diagnosed with exocrine pancreatic cancer, making it the fourth most common cause of cancer-related deaths in the country.[1] The 5-year overall survival (OS) rate for all stages of pancreatic cancer stands at a mere 8%.[2]

In resectable pancreatic cancer, lymph node status emerges as the most crucial prognostic factor. Even with R0 resection, the five-year OS is only 30% for node-negative cases and drops to 10% for node-positive disease.[3] Additional prognostic factors in resectable pancreatic cancer encompass the status of surgical margins, tumor differentiation, the presence of lymphovascular invasion, and preoperative-postoperative serum cancer antibody 19-9 (CA 19-9) levels.[4,5] Nevertheless, as approximately 15% of the general population lacks the CA 19-9 secretion phenotype, relying on this parameter for prognosis can be misleading.[6] Obstructive jaundice constitutes another vital prognostic factor, as it can lead to alterations in hepatic functions, coagulation and fibrinolysis impairments, cholangitis, hepatic insufficiency, increased surgery-related complications, and, consequently, a poorer prognosis.[7]

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In recent years, the association between oxidative stress, inflammation, and cancer has become increasingly evident.[8] Several studies have established a prognostic link between various cancers and laboratory indicators of body inflammation, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), C-reactive protein-to-albumin ratio, and prognostic nutritional index (PNI).[9-12] Gamma-glutamyl transferase (GGT), an enzyme found on the luminal surfaces of hepatocytes and cholangiocytes, plays a crucial role in metabolizing the major intracellular antioxidant glutathione. Elevated GGT levels are considered an early indicator of oxidative stress in the body and have been associated with a poor prognosis in several cancers due to inflammation and oxidative stress.[13-17]

Alkaline phosphatase (ALP), a hydrolase protein predominantly found in the bile duct and kidney, exhibits increased serum levels in cases of obstructive jaundice and primary or metastatic hepatic cancers. Some studies suggest that ALP may serve as a marker of oxidative stress and that its elevation correlates with unfavorable prognostic outcomes in various cancer types.[18-20]

Albumin, a negative acute-phase protein secreted by the liver, contributes to plasma colloid osmotic pressure. Its levels decrease in the presence of inflammation, providing insights into the host's nutritional status and inflammation levels. Albumin has been linked to cancer prognosis, either independently or through albumin-based scoring systems like PNI or other ratios, in several studies.[9,10,21,22]

It is of utmost importance to predict the clinical course of pancreatic cancer, especially in pandemic conditions, given its frequent occurrence, high mortality rate, and tendency to be diagnosed at an advanced stage. Routine laboratory tests, including GGT, ALP, and albumin, are used for patient evaluation and to assess liver functions. Building upon existing literature, our present study investigates whether the GGT/albumin ratio (GAR), ALP/albumin ratio (APAR), NLR, PLR, and PNI have any predictive value in terms of OS and progression-free survival (PFS) in metastatic pancreatic adenocarcinoma, with the aim of enhancing our approach to this disease.

MATERIAL AND METHODS

In this retrospective study, we included 287 patients diagnosed with metastatic pancreatic adenocarcinoma at our hospital between January 2008 and January 2019. All patients diagnosed with metastatic pancreatic cancer in our center between the specified dates were included in this study. To calculate GAR, GGT values (U/L) were divided by albumin values (g/dL). The APAR was computed by dividing ALP values (IU/L) by albumin (g/dL). NLR was determined by dividing neutrophil values (/mm^3) by lymphocyte values (/mm^3), and PLR was calculated by dividing platelet values (/mm^3) by lymphocyte values (/mm^3). The PNI values were derived using the formula 0.005*total lymphocyte count/mm^3+10*albumin (g/dL). Data analysis was conducted using the IBM SPSS Statistics Version 22 program (SPSS Inc., Chicago, IL, USA) statistical software, with categorical variables presented as numbers and percentages and numerical variables represented as medians, minimum, and maximum values. The chi-square test was applied to compare qualitative data. Cutoff values for the ratios were determined using the x-tile method. Survival analysis employed the Kaplan-Meier test, with p-values <0.05 were regarded as representing alpha significance.

The study was performed in strict compliance with the rules concerning research involving human beings applicable under the principles of the 2008 Declaration of Helsinki. Approval for the study was issued by the Karadeniz Technical University Faculty of Medicine Scientific Research Ethics Committee on July 24, 2020 (no: 2020/185).

RESULTS

The median age of the patients in this study was 65 years (range: 35-100 years). Table 1 summarizes the clinical and pathological characteristics of the patients. Median OS was significantly longer in patients without obstructive jaundice, at 6 months [95% confidence interval (CI), 4.9-7.0], compared to those with obstructive jaundice, at 3 months (95% CI, 1.7-4.2, p=0.005). There was no discernible difference in OS between patients with Ca 19-9 levels >1,000 U/mL and <1,000 (6.0 vs. 6.0 months, p=0.12). Like-

TABLE 1: Our patients' clinical and pathological features.

	n (%)
Gender	
Male	192 (66.9)
Female	95 (33.1)
Histological subtype	
Ductal adenocarcinoma	287 (100)
Metastasis	
At time of diagnosis	221 (77)
Later	66 (23)
Site of metastasis	
Hepatic	176 (61.3)
Extrahepatic	70 (24.4)
Hepatic+extrahepatic	41 (14.3)
Obstructive jaundice	
Positive	58 (20.2)
Negative	226 (78.8)
Unknown	3 (1)
Ca 19-9 values	
>1,000 U/mL	110 (38.3)
<1,000 U/mL	120 (41.8)
Unknown	57 (19.9)

wise, no disparity in OS or PFS was observed between women and men (p=0.42 and p=0.39, respectively). Median OS was 6 months in women (95% CI, 3.8-8.1) and men (95% CI, 4.7-7.2), while median PFS was 5 months in women (95% CI, 3.4-6.5) and 4 months in men (95% CI, 3.1-4.8). Table 2 provides an overview of the effects of GAR, APAR, NLR, PLR, and PNI on OS and PFS.

Significantly, patients in the low GAR group were more prominently represented in the low NLR and low PLR groups (79.4% vs. 20.6%, p=0.02 and 75.9% vs. 24.1%, p=0.04, respectively). However, no significant difference was observed between the rates of being in the low or high GAR group and being in the low or high PNI group (p=0.27). Patients in the low APAR group were markedly more prevalent in the high PNI group (90% vs. 10%, p<0.01). By contrast, no significant disparity was noted between the rates of being in the low or high APAR group and being in the low or high NLR and PLR groups (p=0.35 and p=0.18, respectively; Table 3).

DISCUSSION

The enzyme GGT is universally present on cell surfaces and plays a pivotal role in the metabolism of glutathione, a critical antioxidant. It ensures the adequate presence of amino acids, notably cysteine, which is essential for glutathione synthesis, within the cell. Conditions that elevate GGT levels, such as chronic and excessive alcohol consumption and ob-

TABLE 2: The effect of GAR, APAR, NLR, PLR, and PNI scores on survival in patients with metastatic pancreatic adenocarcinoma.

	Median OS (months)		Median PFS (months)	
GAR				
<65.35	6 (95% CI, 4.6-7.3)	**p: 0.001**	5 (95% CI, 4.1-5.8)	**p: 0.00**
>65.35	4 (95% CI, 2.9-5.0)		3 (95% CI, 2.2-3.7)	
APAR				
<115.3	6 (95% CI, 4.7-7.2)	**p: 0.00**	5 (95% CI, 4.7-5.7)	**p: 0.00**
>115.3	3 (95% CI, 1.7-4.2)		3 (95% CI, 2-4)	
NLR				
<3.4	8 (95% CI, 6.4-9.5),	**p: 0.00**	6 (95% CI, 5.0-6.9)	**p: 0.00**
>3.4	3 (95% CI, 1.9-4.0)		3 (95% CI, 2.3-3.6)	
PLR				
<304	6 (95% CI, 4.8-7.1)	**p: 0.145**	4 (95% CI, 3.1-4.8)	**p: 0.267**
>304	5 (95% CI, 2.7-7.2)		4 (95% CI, 2.1-5.8)	
PNI				
<38.5	3 (95% CI, 0.2-5.7)	**p: 0.00**	2 (95% CI, 0.1-3.8)	**p: 0.02**
>38.5	6 (95% CI, 4.8-7.1)		5 (95% CI, 4.2-5.7)	

GAR: Gamma-glutamyl-transferase/albumin ratio; APAR: Alkaline-phosphatase/albumin ratio; NLR: Neutrophil lymphocyte ratio; PLR: Platelet lymphocyte ratio; PNI: Prognostic nutritional index; OS: Overall survival; PFS: Progression-free survival; CI: Confidence interval.

TABLE 3: Ratios of patients in GAR and APAR low and high groups to those in NLR, PLR and PNI low and high groups.

	NLR			PLR			PNI		
	<3.4: n (%)	**>3.4: n (%)**		**<304: n (%)**	**>304: n (%)**		**<38.5: n (%)**	**>38.5: n (%)**	
GAR:									
<65.35:	123 (79.4)	88 (67.2)	p: **0.02**	192 (75.9)	19 (57.6)	p: **0.04**	29 (65.9)	182 (75.2)	p:0.27
>65.35:	32 (20.6)	43 (32.8)		61 (24.1)	14 (42.4)		15 (34.1)	60 (24.8)	
APAR:									
<115.3:	135 (88.2)	108 (83.7)	p: 0.35	217 (87.1)	26 (78.8)	p: 0.18	28 (65.1)	215 (90)	p:**<0.01**
>115.3:	18 (11.8)	21 (16.3)		32 (12.9)	7 (21.2)		15 (34.9)	24 (10)	

structive jaundice, lead to an increase in free radical production and a decrease in glutathione levels. Simultaneously, products resulting from GGT reactions further amplify free radical production, particularly in the presence of environmental iron.[12] Studies have demonstrated that due to these pro-oxidant effects, individuals with high serum GGT levels are more susceptible to coronary artery diseases, metabolic syndrome, cerebrovascular diseases, and increased fatality rates.[23-25]

Inflammation plays a central role in the development and progression of cancer, and oxidative stress within the tumor microenvironment can transform healthy cells into tumor cells by activating various transcription factors.[8] GGT is instrumental in safeguarding cells against oxidative stress by maintaining sufficient intracellular glutathione levels. Elevated GGT levels serve as a well-established marker of pathological oxidative stress.[12]

Research suggests that elevated GGT levels may contribute to tumor formation and progression. A 2008 population-based cohort study involving 92,843 women followed up prospectively for a median period of 13 years identified 4,884 cancer cases, revealing an increased cancer risk associated with elevated GGT levels compared with low-normal GGT levels ($p<0.0001$). The study found that GGT elevation significantly increases the risk of gastrointestinal, lung, breast, gynecological, and hematological malignancies in cancer site-specific models ($p<0.006$).[26] A similar study involving men reported analogous results, linking elevated GGT levels to increased cancer risk, especially in men aged ≤65 years ($p<0.001$).[27] Furthermore, several studies have associated GGT elevation with poor prognosis in various malignancies, including pancreatic, cervical, prostate, and renal cancers.[13-17] In line with existing literature, our study demonstrates that OS and PFS were longer in the low GAR group (median OS 6.0 vs. 4.0 months, $p=0.001$, and median PFS 5.0 vs. 3.0 months, $p<0.01$).

ALP is a hydrolase enzyme abundantly present in the liver, bile duct, and kidney. Studies have indicated that its levels rise in response to inflammation, making it an essential marker of oxidative stress and a predictor of poor prognosis in several cancers.[18-20,28,29] Consistent with previous literature, our study reveals that OS and PFS were longer in the low APAR group (median OS 6.0 vs. 3.0 months, $p<0.01$, and median PFS 5.0 vs. 3.0 months, $p<0.01$).

In the study conducted by Doğan et al., involving 146 patients with metastatic pancreatic adenocarcinoma, it was concluded that age >60 years, an Eastern Cooperative Oncology Group performance score >2, and the presence of obstructive jaundice were associated with poor prognosis. Additionally, the study suggested that these parameters alone might not suffice for managing metastatic pancreatic adenocarcinoma, prompting the consideration of systemic inflammatory response parameters for identifying poor prognosis groups. The study found that the NLR was significantly linked to prognosis, although no statistically significant conclusions were drawn regarding the low PLR and high PNI groups.[21,30] Similarly, in our present study, OS was longer among individuals with metastatic pancreatic

cancer without obstructive jaundice (median OS 6.0 vs. 3.0 months, p=0.005). Our investigation into the effect of systemic inflammatory response markers on prognosis in metastatic pancreatic adenocarcinoma aligns with the reference study. We found that OS and PFS were longer in the low NLR group (median OS 8.0 vs. 3.0 months, p<0.01, and median PFS 6.0 vs. 3.0 months, p<0.01). While no significant findings emerged in the low PLR group, both OS and PFS were extended in the high PNI group (median OS 6.0 vs. 3.0 months, p<0.01, and median PFS 5.0 vs. 2.0 months, p=0.02). Furthermore, in line with our study's hypothesis that GAR and APAR could serve as novel parameters indicating inflammation-related prognosis in metastatic pancreatic cancer, the low GAR group exhibited a significantly higher proportion of individuals in the low NLR and low PLR groups (79.4% vs. 20.6%, p=0.02 and 75.9% vs. 24.1%, p=0.04, respectively). Additionally, the low APAR group contained a significantly higher proportion of individuals in the high PNI group (90% vs. 10%, p<0.01). The congruence of our results with previous literature underscores the reliability of our study.

Given the high mortality rate associated with metastatic pancreatic cancer, the need for novel prognostic markers is paramount. The ratios explored in this study are easily accessible laboratory parameters applicable to nearly all patients in oncology clinics. We anticipate that our findings will enhance the overall approach to patients with metastatic pancreatic cancer.

CONCLUSION

Similar to other cancer types, inflammation negatively impacts prognosis in metastatic pancreatic cancer. The GAR and APAR may serve as novel markers of oxidative stress and inflammation in metastatic pancreatic cancer. OS and PFS are significantly extended in the low GAR, low APAR, low NLR, and high PNI groups. OS is notably prolonged in cases without obstructive jaundice. These results warrant further validation through more extensive studies.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Elif Yüce;* ***Design:*** *Elif Yüce;* ***Control/Supervision:*** *Evren Fidan;* ***Data Collection and/or Processing:*** *Elif Yüce;* ***Analysis and/or Interpretation:*** *Elif Yüce;* ***Literature Review:*** *Evren Fidan;* ***Writing the Article:*** *Elif Yüce;* ***Critical Review:*** *Evren Fidan;* ***References and Fundings:*** *Elif Yüce;* ***Materials:*** *Elif Yüce.*

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