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Research Article

Novel Prognostic Factors in Tumors of the Ampulla of Vater: The Lymph Node Ratio and Hemoglobin Albumin Lymphocyte Platelet (HALP) Score

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Abstract

Objectives: Tumors of the ampulla-of-Vater are rare, and accurate prognosis is essential. We examined the significance of the hemoglobin-albumin-lymphocyte-platelet (HALP) score and lymph-node-ratio (LNR).

Methods: Thirty-four patients in 2003-2018 were examined retrospectively.

Results: Twelve women and 22 men were enrolled. Tumors were ≤2 cm in 11 (32.4%) and >2 cm in 17 (50%). Seven (38.9%) were in the LNR 1 (<0.1) group and 11 (61.1%) in the LNR 2 (≥0.1) group. Fifteen (62.5%) of the 24 operated patients received adjuvant-therapy, with recurrence in 12 (50%). Overall survival (OS) was significantly shorter with carcinoembryonic-antigen (CEA) elevation at diagnosis compared to normal CEA (mean OS 27.1 vs. 89.8 months, p:0.029). OS was longer in stages 1–2 than 3–4 (mean OS 100.5 vs. 46.7 months, p:0.03), but shorter in patients with tumors >2 cm compared to tumors ≤2 cm (mean OS 53.2 vs. 90 months, p:0.059). No significant difference in OS emerged between the LNR 1 and 2 groups (114.8 vs. 82.9 months). No significant difference emerged in OS, disease-free, or progression-free-survival for HALP.

Conclusion: Pre-operative CEA elevation, Stages 3–4, and tumor sizes exceeding 2 cm result in poor prognosis. The LNR and HALP have no effect on prognosis.

Keywords: Tumors of the ampulla of Vater, hemoglobin-albumin-lymphocyte-platelet (HALP) score, lymph node ratio (LNR)

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The ampulla of Vater is the junction between the main pancreatic duct and the distal bile duct and opens onto the duodenum in the form of a papilla. Periampullary tumors are those that develop within 2 cm of the papilla in the duodenum. These originate from the head of the pancreas, the distal common bile duct, the second part of the duodenum, or the ampulla of Vater.[1] Despite being quite rare, according to some studies, tumors of the ampulla of Vater are the second most common periampullary tumors after tumors of the head of the pancreas.[2] The incidence is 0.6 cases in 100,000 individuals.[3] Since they can lead to symptoms such as obstruction-related jaundice and abdominal pain in the early period, prognosis is better than with other periampullary tumors. However, 5-year overall survival (OS) rates between 30% and 70% have been reported after complete resection.[4]

The most important prognostic factors in tumors of the ampulla of Vater are the status of the surgical margins and the

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presence or absence of lymph node metastasis.[5] Five-year OS of 64-80% has been reported in tumors without lymph node metastasis following pancreaticoduodenectomy compared to 17–50% in those with lymph node metastasis.[6] Studies have therefore recommended the development of new staging systems based on lymph node involvement status in ampullary cancers.[3, 5, 7]

Other important prognostic factors apart from lymph node metastasis and surgical margin positivity include the histological subtype, the degree of tumor invasion, the size, presence of obstructive jaundice at the time of diagnosis, the presence of lymphovascular or perineural invasion, and the degree of tumor differentiation.[8-11] In addition, the prognostic importance of the systemic inflammatory response (SIR) markers neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) in several cancers has also been shown in recent years. SIR is an important regulator in tumor growth, angiogenesis, migration, tumor invasion, and metastasis. The prognostic nutritional index (PNI) reflects both nutritional and immunological status, and low PNI values have been linked to poor prognosis, particularly in gastrointestinal system malignancies. Studies have also shown the prognostic importance of SIR markers and PNI in ampullary cancers.[12-14]

A number of studies have shown that pre-operative hemoglobin, albumin, lymphocyte, platelet (HALP) score values, and a composite index calculated by including hemoglobin and albumin among SIR markers are of prognostic importance in some cancers.[15-18] However, the number of studies evaluating the importance of HALP scores in ampullary cancers is limited.

The purpose of this study was to achieve a better understanding of rare tumors of the ampulla of Vater, for which powerful and definitive recommendations in the literature are lacking, to determine host prognostic factors, and to investigate whether HALP score and the lymph-node-ratio (LNR) are of prognostic significance.

Methods

The data for 34 patients diagnosed with tumors of the ampulla of Vater at the Karadeniz Technical University Medical Faculty, between 2003 and 2018 were examined in this retrospective study. The LNR was calculated by dividing the number of involved lymph nodes by the number of lymph nodes examined. Patients were divided into two LNR groups, LNR 1 (<0.1) and LNR 2 (≥0.1). The NLR was calculated by dividing neutrophils and lymphocytes, and the PLR by dividing platelets and lymphocytes. The formula 0.005*lymphocyte/mm^3 + 10*albumin (g/dL) was used for PNI and hemoglobin(g/L)*albumin(g/L)*lymphocyte(/L):platelet(/L) for HALP scores. Data analysis was performed on SPSS version 22.0 statistical software. Descriptive statistics were expressed as number and percentage for categorical variables, and as mean plus standard deviation and median for numerical variables. The determination of cutoff points for all patients' NLR, PLR, PNI, and HALP scores was based on the existing literature. The Kaplan–Meier test was applied for survival analysis. Alpha significance was set at $p<0.05$.

Approval for the study was granted by the Karadeniz Technical University Faculty of Medicine Scientific Research Ethics Committee on April 21, 2021 (Document number 24237859-379, Approval number: 2021/139).

Results

Thirty-four patients, 12 (35.3%) women and 22 (64.7%) men, with a median age of 60.5 (min 33, max 82) years, were included in the study. The patients' clinical and pathological characteristics are summarized in Table 1. The patients' median carcinoembryonic antigen (CEA) value was 2.45 mg/L (min 0.6, max 1031), median cancer antigen 19-9 (Ca 19-9) was 47.4 U/ml (min 0.8, max 1288), and the median tumor size was 2.45 cm (min 1 cm, max 5 cm). Lymph node involvement was known in 18 cases (52.9%). Numbers of lymph nodes involved were ≤3 in 8 patients (%23.5) and >3 in three (%8.8), while seven (20.6%) had no lymph node involvement. The median number of lymph nodes involved was 1.5 (min 0, max 8), and the median number of lymph nodes removed was 8.5 (min 0, max 19). The median LNR was 0.12 (min 0, max 0.42). The patients were divided into two groups depending on their lymph node ratios - LNR 1 (<0.1) and LNR 2 (≥0.1), LNR 1 consisting of seven patients (38.9%) and LNR 2 of 11 (61.1%).

Data concerning receipt of adjuvant therapy and recurrence among our patients are summarized in Table 2. Metastasis was present at the time of diagnosis in five patients, and subsequently developed in 12. Metastasis was most frequent to the liver (70.5%), followed by the lung (11.8%). The median follow-up period was 32.5 months (min 1, max 212), median progression-free survival (PFS) was 22 (95% Confidence Intervals [CI], 2.8–41.1) months, median disease-free survival (DFS) was 36 (95% CI, 14.3–57.6) months, and median OS was 38.0 (95% CI, 13.1–62.8) months. The effect on OS of absence of jaundice at time of diagnosis, CEA elevation, Ca 19-9 elevation, tumor size, metastatic lymph node status, LNR, and receipt or non-receipt of adjuvant therapy was investigated. The clinical and pathological characteristics affecting OS are summarized in Table 3. Median OS of 20 (95% CI, 4.5–35.4) months and mean OS of 27.1 (95% CI, 11.3–42.8) months were determined in the

Table 1. Our patients' clinical and pathological features

	n (%)		n (%)
Gender		Negative	11 (32.4)
Male	22 (64.7)	Unknown	19 (55.9)
Female	12 (35.3)	Lymph node ratio	
Operation status		LNR 1 (<0.1)	7 (38.9)
Operated	24 (70.6)	LNR 2 (≥0.1)	11 (61.1)
Not operated	10 (29.4)	Metastatic lymph node	
Histological subtype		≤3	8 (23.5)
Mixt type adenocarcinoma	26 (76.5)	>3	3 (8.8)
Pancreatobiliary type adenocarcinoma	7 (20.6)	None	7 (20.6)
Intestinal type adenocarcinoma	1 (2.9)	Unknown	16 (47.1)
T stage		TNM stage	
T1	1 (2.9)	Stage 1A	-
T2	10 (29.4)	Stage 1B	5 (14.7)
T3	6 (17.6)	Stage 2A	3 (8.8)
T4	4 (11.8)	Stage 2B	-
Unknown	13 (38.2)	Stage 3A	14 (41.2)
Tumor size		Stage 3B	6 (17.7)
≤2 cm	58 (45)	Stage 4	5 (14.7)
>2 cm	57 (44.2)	Unknown	1 (2.9)
Unknown	6 (17.6)	Jaundice at time of diagnosis	
Differentiation		Positive	20 (58.8)
Grade 1	9 (26.5)	Negative	12 (35.3)
Grade 2	7 (20.6)	Unknown	2 (5.9)
Grade 3	3 (8.8)	CEA values time of diagnosis	
Unknown	15 (44.1)	Elevated	10 (29.4)
Lymphovascular invasion		Low	20 (58.8)
Positive	9 (26.5)	Unknown	4 (11.8)
Negative	6 (17.6)	Ca 19-9 values at time of diagnosis	
Unknown	19 (55.9)	Elevated	19 (55.9)
Perineural invasion		Low	12 (35.3)
Positive	4 (11.8)	Unknown	3 (8.8)

Table 2. Our patients' adjuvant treatment and recurrence characteristics

	n (%)
Adjuvant treatment: (n=24)	
Received	15 (62.5)
Not received	9 (37.5)
Adjuvant chemotherapy: (n=15)	
Gemcitabine	7 (46.6)
XELOX	3 (20)
FUFA	3 (20)
Gemcitabine + capecitabine	1 (6.7)
Cisplatin + 5-FU	1 (6.7)
Adjuvant chemotherapy cycle: (n=15)	
>3	13 (86.7)
≤3	2 (13.3)
Recurrence status: (n=24)	
Positive	12 (50)
Negative	12 (50)

patients with CEA elevation at the time of diagnosis, while mean OS in those without CEA elevation was 89.8 (95% CI, 56.0–123.6) months (p=0.029) (Fig. 1). The difference was statistically significant. When our patients were classified according to the eighth American Joint Committee on Cancer (AJCC) TNM staging system, mean OS in the stage 1 and 2 patients was 100.5 (95% CI, 61.2–139.9) months, while mean OS in the stage 3 and 4 patients was 46.7 (95% CI, 23.8–69.7) months, and median OS was 20 (95% CI, 11.8–28.1) months (p=0.03). The difference was statistically significant. Median OS in the patients with tumor sizes >2 cm was 20 (95% CI, 13.2–26.7) months and mean OS was 53.2 (95% CI, 21.6–84.9) months, while mean OS in the patients with tumors ≤2 cm in size was 90.0 (95% CI, 56.6–123.5) months (p=0.059) (Fig. 2). In the LNR 1 group, mean OS was 114.8±17.1 (95% CI, 81.1–148.4). In the LNR 2 group, mean OS was 82.9 (95% CI, 41.6–124.2) months, and median OS was 43 (95% CI, 8.1–77.8) months (p=0.10). The

Table 3. Clinical and pathological features affecting overall survival in patients with tumors of the ampulla of Vater

	OS (months)		
	Mean	**Median**	**p**
Jaundice at time of diagnosis			
Positive	50.8	20	0.19
Negative	125.9	?	
CEA values time of diagnosis			
Elevated	27.1	20	0.029
Low	89.8	?	
Ca 19-9 values at time of diagnosis			
Elevated	34.8	22	0.13
Low	89.9	49	
Tumor size			
≤2cm	90	?	0.059
>2 cm	53.2	20	
Metastatic lymph nodes			
≤3	89.5	22	0.21
>3	34.3	43	
0	114.8	?	
Stage			
1-2	100.5	?	0.03
3-4	46.7	20	
Lymph node ratio			
LNR 1 (<0.1)	114.8	?	0.10
LNR 2 (≥0.1)	82.9	43	
Adjuvant treatment			
Received	76.6	43	0.68
Not received	89.5	36	

effects of SIR markers (NLR, PLR, and PNI) and HALP scores on overall, disease-free, and PFS are summarized in Table 4. No statistically significant difference was observed in terms of survival in patients above and below the cutoff values for these ratios.

Discussion

It is very important to determine the prognoses of tumors of the ampulla of Vater since even the National Comprehensive Cancer Network and European Society for Medical Oncology guidelines, frequently employed for the treatment of all cancers, contain no strong recommendations for the treatment of these cancers.

One of the most important factors determining the prognosis of tumors of the ampulla of Vater is lymph node involvement. One study of 313 patients reported a significant association between lymph node involvement and perineural invasion, lymphovascular invasion, tumor size, and surgical margin positivity. OS was also significantly longer among patients without lymph node involvement (107.5 vs. 32 months, p<0.001). The authors argued that methods

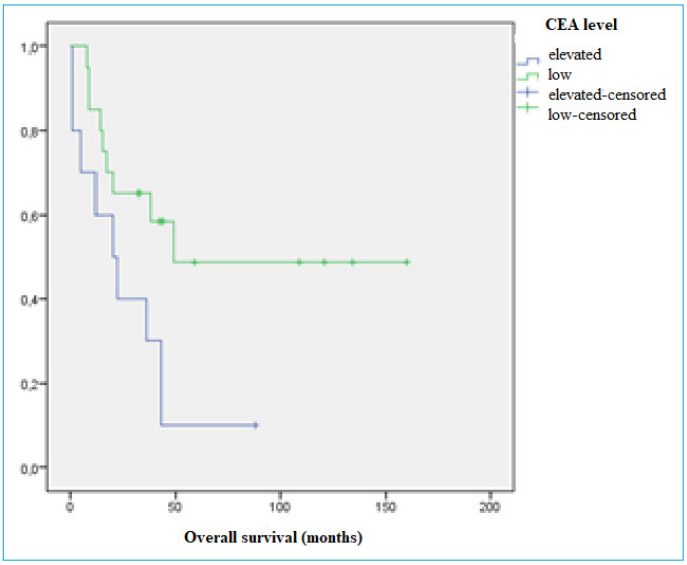

Figure 1. The relationship between elevated CEA at diagnosis and survival in the patients with tumors of the ampulla of Vater.

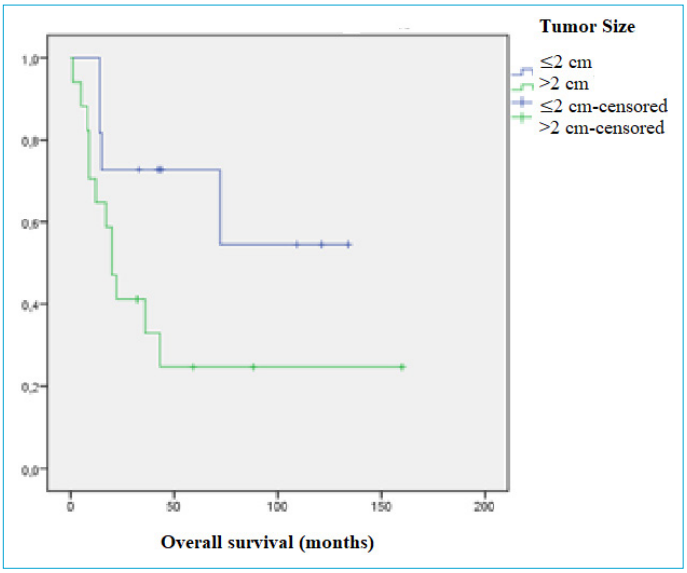

Figure 2. The relationship between tumor size and survival in the patients with tumors of the ampulla of Vater.

other than the number of involved lymph nodes should be determined in terms of establishing the prognosis of tumors of the ampulla of Vater.[5] Another study favoring that suggestion, involving 199 patients and published in 2022, calculated LNR values by determining the proportion of numbers of lymph nodes involved to numbers of lymph nodes examined and obtained a cutoff value of 0.1. Patients were divided into high and low LNR groups and a new staging system was produced using the degree of tumor invasion and LNR. Although no difference was determined in OS in the high and low LNR groups alone, the new staging system created using these groups yielded more information in terms of survival than the eighth AJCC TNM staging

Table 4. The effect of NLR, PLR, PNI and HALP scores on survival in patients with tumors of the ampulla of Vater

	OS (months)			DFS (months)			PFS (months)		
	Mean	Median	p	Mean	Median	p	Mean	Median	p
NLR									
<3	71.1	38	0.73	76.4	37	0.92	65.8	20	0.62
≥3	83.5	36		95.6	26		73.2	22	
PLR:									
<212	60.7	38	0.48	62.6	36	0.34	56.4	20	0.57
≥212	112.2	43		124.5	?		98.6	31	
PNI									
<38	46.8	36	0.84	48	36	0.94	41.1	31	0.91
≥38	88.1	43		106.4	26		82.2	20	
HALP									
≤26.5	63	36	0.94	70.6	36	0.63	57	31	0.84
>26.5	66	43		71.1	17		59.6	20	

DFS: Disease-free survival, HALP: Hemoglobin albumin lymphocyte platelet, NLR: Neutrophil lymphocyte ratio, OS: Overall survival, PLR: Platelet lymphocyte ratio, PFS: Progression-free survival, PNI: Prognostic nutritional index.

system.[3] On the basis of these studies, we investigated the prognostic significance of the LNR in tumors of the ampulla of Vater. No statistically significant difference in survival was determined between the LNR 1 (<0.1) and LNR 2 (≥0.1) groups. We then restaged our patients based on Zhang et al.'s study. We knew the LNR values of 18 patients, and therefore performed a repeat general survival analysis for these patients, and also compared them with one another, using both the staging system in the reference study and the eighth AJCC TNM system. No significant difference in terms of survival was found between the two staging systems (mean OS was 114.8 months for stages 1–2 and 82.9 months for stages 3–4 in Zhang et al., p=0.10) (while under the eighth AJCC TNM staging system, mean OS was 114.8 for Stages 1–2 and 82.9 months for Stages 3–4, p=0.10). We attributed this result to the lack of sufficient patients to reflect the difference between the two staging systems. In addition, survival analysis of the entire patient group according to the eighth AJCC TNM staging system revealed significantly longer OS in Stages 1 and 2 cancers (mean OS 100.5 months for Stages 1–2 vs. 46.7 months for Stages 3–4, p:0.03). This confirms the reliability of the current eighth AJCC TNM staging system. Studies with larger patient numbers are now needed to understand the advantages of the new staging system created using LNR.

Another prognostic factor in tumors of the ampulla of Vater is the histological subtype. One study of 170 patients showed that the best prognosis was in the intestinal type, followed by the mixed type and pancreatobiliary type (mean OS 115 months, 94.7 months, and 52.5 months, respectively, p<0.001).[10] Since distribution was not homogeneous in the subtypes in the present study, the effect of this characteristic on survival could not be investigated. The previous studies have confirmed that high Ca 19–9 levels, jaundice at the time of diagnosis, tumor size >2 cm, and poor differentiation result in poorer prognosis.[8, 9] Although high Ca 19–9 levels and the presence of jaundice at the time of diagnosis exhibited no significant effect on survival in the present study, the mean OS of 90 months in patients with tumors ≤2 cm in size and of 53.2 months in those with tumor sizes >2 cm emphasizes the prognostic importance of tumor dimensions (p=0.059). This study also revealed shorter survival in patients with high pre-operative CEA levels (mean OS 27.1 vs. 89.8 months, p=0.029). Our results confirm the prognostic significance of CEA levels, in agreement with the previous literature.[19]

Studies have shown that that SIR indicators are among the host factors determining prognosis in many cancers. One 87-patient study investigating this in tumors of the ampulla of Vater reported shorter OS and DFS in groups with high pre-operative NLR compared to low NLR groups. High NLR was also found to be associated with a high Eastern Cooperative Oncology Group performance score.[13] Another study with a similar number of patients reported worse OS times in a group with high pre-operative PLR values than in a low PLR group.[20] A larger study involving 169 patients supported the idea of a link between high NLR and PLR and low OS times.[21] No statistically significant difference was observed in the present study between the high and low NLR and PLR groups in terms of OS, DFS, or PFS. We think that this may be due to the lower number of patients in the present research compared to those studies.

Pre-operative PNI elevation has been associated with good prognosis in several gastrointestinal system malignancies

and has also been studied in tumors of the ampulla of Vater.[22-24] One study of 82 patients reported better OS durations in a high PNI group and concluded that, similarly to other gastrointestinal malignancies, PNI was also an independent prognostic factor in ampullary cancers.[12] Although we obtained no statistically significant results regarding the prognostic significance of PNI in the present research, we think that this may attributable to the study limitations.

The novel inflammatory marker HALP score has been shown to be of prognostic importance in several cancers. One study of 820 locally advanced colorectal cancer cases determined that a low pre-operative HALP score increased the risk of cancer-related mortality.[15] Since, to the best of our knowledge, no previous research has investigated the relationship between this score and prognosis in tumors of the ampulla of Vater, we examined the association between our patients' general survival and HALP scores. No significant difference was observed in OS survival between patients with high and low HALP scores. In addition to the general limitations of this study, we attributed this to the lack of studies investigating the HALP score in tumors of the ampulla of Vater and our use of the above colorectal cancer study as a reference for the cutoff value.

Although all patients diagnosed with tumors of the ampulla of Vater in our center between 2003 and 2018 were included in the study, due to the rarity of these, only 34 patients were enrolled. At the same time, since the standards in the surgical and pathological evaluation of these tumors have become established over the course of time, we were unable to obtain the same data in all our patients. For these reasons, we were unable to provide median values for some groups in the survival analyses. Furthermore, ROC analysis failed to yield significant results due to our low patient number, and we therefore relied on the existing literature for NLR, PLR, PNI, and HALP score cutoff points. In particular, since we encountered no studies investigating the prognostic importance of HALP scores in tumors of the ampulla of Vater, we were obliged to employ the cutoff point given in the colorectal cancer study. These represent the principal limitations of the present study. These may have made resulted in an inability to provide statistical evidence the importance of SIR markers and HALP score in the prognosis of tumors of the ampulla of Vater. Further multicenter studies with larger patient numbers may be useful in yielding a better understanding of these rare tumors.

Conclusion

This study confirms the prognostic importance of pre-operative CEA values, 8th AJCC TNM staging, and tumor size in tumors of the ampulla of Vater. Further, more extensive studies are now needed to demonstrate the prognostic significance of the LNR, systemic inflammatory markers, and HALP scores.

Disclosures

Ethics Committee Approval: Approval for the study was granted by the Karadeniz Technical University Faculty of Medicine Scientific Research Ethics Committee on 21.04.2021 (Document number 24237859-379, Approval number: 2021/139).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – E.Y.; Design – E.Y.; Supervision – E.F.; Materials – E.Y.; Data collection &/or processing – E.Y.; Analysis and/or interpretation – E.Y.; Literature search – E.Y.; Writing – E.Y.; Critical review – E.F.

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