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Tumor-specific Expression of Insulin-like Growth Factor II mRNA-binding Protein 3 Independently Predicts Worse Survival of Patients With Adenocarcinoma of the Ampulla of Vater

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Abstract. *Background/Aim: Insulin-like growth factor II mRNA-binding protein 3 (IMP3) plays an important role in the adhesion, invasion, and metastasis of tumor cells. Although emerging evidence suggests that IMP3 promotes tumor progression in several malignancies, the expression of IMP3 and its prognostic implication in adenocarcinoma of the ampulla of Vater (AVAC) has not been clarified to date. Materials and Methods: The IMP3 expression status in 87 AVAC tissues was examined using immunostaining, and its association with various clinicopathological features and outcome of patients with AVAC was investigated. Results: The vast majority (87.4%) of AVAC cases displayed at least focal cytoplasmic and membranous IMP3 immunoreactivity in tumor cells, whereas IMP3 expression was consistently absent from normal biliary epithelial cells. Tumor-specific IMP3 expression was associated with submucosal and pancreatic invasion, which were not identified in the corresponding hematoxylin and eosin-stained slides. This finding led to up-staging of the pathological tumor stage in two cases of well-differentiated AVAC. In addition, high IMP3 expression was significantly associated with a poorly differentiated histology (p=0.026). Survival analyses revealed that high IMP3 expression independently predicted shorter recurrence-free (p=0.003) and overall (p=0.029) survival. Conclusion: Our study demonstrated tumor-specific IMP3 expression in AVAC, which will be helpful in determining invasion depth and tumor extent in patients with well-differentiated tumors, as well as indicating worse survival of patients with AVAC. Our data highlight IMP3 expression status as a potential diagnostic and prognostic marker for AVAC.*

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Key Words: Ampulla of Vater, carcinoma, insulin-like growth factor II mRNA-binding protein 3, immunohistochemistry, prognosis.

Adenocarcinoma of the ampulla of Vater (AVAC) is the second most common subtype of periampullary adenocarcinoma, following pancreatic ductal adenocarcinoma (PDAC). Approximately 16-50% of pancreaticoduodenectomy specimens are diagnosed as AVAC (1-3). Although AVAC has a higher rate of potentially curative resection than PDAC, with associated 5-year survival of 37-60%, patients with AVAC who experience relapse will ultimately die of tumor progression within approximately 1 year after detection of recurrence (4, 5). Conventional clinicopathological features, including histological grade, nodal metastasis, and stage, have a significant value in predicting the prognosis of patients with AVAC. However, prognostic prediction solely based on these conventional parameters is not accurate for a subset of AVAC cases. Therefore, developing biomarker-based criteria with significant prognostic implications would be helpful for earlier and improved stratification of patients according to their survival probability.

Insulin-like growth factor II mRNA-binding protein 3 (IMP3) is an oncofetal protein expressed in epithelium, muscle, and placenta during the early stages of human embryogenesis (6, 7), and plays an important role in the migration of cells forming the roof plate of the neural tube and in the subsequent migration of neural crest cells (8). IMP3 also promotes the adhesion, invasion, and metastasis of tumor cells (9). Recent studies have demonstrated the clinical value of IMP3 expression status in many different types of tumor and tumor-like lesions. In particular, IMP3 has been found to be highly expressed in several human malignancies, but not in benign tissues, and a high IMP3 expression status has been found to be associated with tumor development and aggressive oncogenic behavior (10-17).

This accumulating evidence regarding the important role of IMP3 in tumor progression motivated us to examine its expression in AVAC. To the best of our knowledge, the expression status of IMP3 and its prognostic implication in AVAC have not been clarified. Therefore, we investigated the expression of IMP3 protein in AVAC tissue samples using immunohistochemical staining, and analyzed its relationship with various clinicopathological parameters and outcomes of patients with AVAC.

Materials and Methods

Patients and tissue samples. We searched for AVAC cases in the surgical pathology database of Kyung Hee University Hospital (Seoul, Republic of Korea) using a combination of the key words "carcinoma", "ampullary", and "ampulla of Vater". Data from 87 patients who underwent surgical resection for AVAC between 1985 and 2008 were collected. We reviewed all available hematoxylin and eosin-stained slides and selected the most representative slide for immunohistochemical staining for each patient. The medical records and pathology reports were also reviewed to extract data on various clinicopathological features, including age at diagnosis, sex, histological grade, tumor size, pathological tumor stage (pT) and nodal stage (pN), and stage group. The histological grade was determined according to the fourth edition of the World Health Organization Classification of Tumours of the Digestive System (18). pT, pN, and stage group were determined according to the eighth edition of the Cancer Staging Manual developed by the American Joint Committee on Cancer (19). This study was reviewed and approved by the Institutional Review Board of Kyung Hee University Hospital (2019-05-029).

The demographic and basic clinical characteristics of the patients are summarized in Table I. The age of the patients ranged from 30 to 76 years (median=60 years). Forty-three (49.4%) patients were men. None of the patients underwent neoadjuvant chemotherapy or neoadjuvant concurrent chemoradiation therapy. Follow-up data after surgery was available for 76 (87.4%) patients. Local recurrence and distant metastases were revealed based on imaging analyses, including computed tomography and magnetic resonance imaging. In order to analyze recurrence-free survival (RFS), the primary end point was defined as the time of local recurrence or distant metastasis, whichever occurred first.

Immunohistochemistry. IMP3 expression was assessed by immunohistochemical staining using Bond Polymer Intense Detection System (Vision Biosystems, Mount Waverly, Victoria, Australia) according to the manufacturer's instructions with minor modifications (20-27). In brief, 4-μm-thick sections of formalin-fixed, paraffin-embedded tissue were deparaffinized with Bond Dewax Solution (Vision Biosystems). Antigen retrieval was performed using Bond ER2 Solution (Vision Biosystems) for 30 min at 100˚C, and endogenous peroxidases were quenched by incubation with hydrogen peroxide for 5 min. The sections were then incubated for 15 min at ambient temperature with anti-rabbit monoclonal antibody against IMP3 (1:50; Cell Marque, Rocklin, CA, USA) using a biotin-free polymeric horseradish peroxidase-linker antibody conjugate system. Nuclei were counterstained with hematoxylin. An appropriate positive control (normal palatine tonsil sample) was concurrently stained to validate the staining method. A negative control sample was prepared by substituting a non-immune serum for the primary antibody, which resulted in no detectable staining.

The degree of immunohistochemical expression of IMP3 was semiquantitatively determined based on the assessment of the proportion of positively stained cancer cells and the staining intensity. The optimal cutoff value for high and no/low IMP3 expression level was chosen based on the distribution of the staining results as well as the extent of heterogeneity as determined using the log-rank test with respect to overall survival (OS). All slides were examined and scored by two Board-certified pathologists who were blinded to the clinicopathological data and patient identities. Disagreements between the two pathologists were resolved by consensus.

Statistical analysis. The chi-squared test or Fisher's exact test was used to determine the statistical significance of the association between IMP3 expression status and clinicopathological features. Univariate survival analysis was performed to examine the prognostic significance of IMP3 expression status and clinicopathological features with respect to RFS and OS. Multivariate survival analysis was performed for parameters that had a p-value of less than 0.1 in the univariate analysis, using the Cox proportional hazards model (95% confidence interval) with the backward-stepwise elimination method. All statistical analyses were performed using SPSS for Windows, Version 18.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was defined as $p<0.05$.

Results

IMP3 expression in AVAC. The majority (76/87; 87.4%) of the AVAC cases displayed at least focal cytoplasmic and membranous IMP3 immunoreactivity in the tumor cells. Based on the staining proportion and intensity, uniform and strong IMP3 expression was observed in 10 (11.5%) cases (Figure 1A) and heterogeneous expression was observed in 66 (75.9%) cases (Figure 1B). Normal biliary epithelial cells were present in 85 (97.7%) cases, which were all negative for IMP3 expression (Figure 1C).

IMP3 expression in the periampullary lymph nodes was observed in 10 (11.5%) cases. Strong IMP3 expression was observed in most lymphocytes of the germinal center and in a few non-germinal center lymphocytes (Figure 1D). When

Table I. *Clinicopathological features of patients with adenocarcinoma of the ampulla of Vater.*

Feature		Number of cases (%)	RFS (months)		OS (months)	
			Median (95% CI)	*p*-Value	Median (95% CI)	*p*-Value
Age	≤60 Years	44 (50.6)	134 (15-252)	0.281	216 (NA)	0.372
	>60 Years	43 (49.4)	75 (47-102)		90 (52-127)	
Gender	Male	43 (49.4)	80 (0-186)	0.824	180 (9-350)	0.971
	Female	44 (50.6)	104 (79-128)		113 (16-209)	
Histological grade	WD/MD	76 (87.4)	113 (40-185)	**0.002**	180 (51-308)	**0.003**
	PD	11 (12.6)	27 (2-51)		27 (2-51)	
Tumor size	≤2 cm	33 (37.9)	90 (58-121)	0.454	96 (55-136)	0.704
	>2 cm	54 (62.1)	104 (0-241)		180 (39-320)	
Pathological tumor stage (pT)	pT1-2	44 (50.6)	134 (29-238)	0.068	113 (NA)	**0.020**
	pT3	43 (49.4)	58 (26-89)		70 (40-99)	
Pathological nodal stage (pN)	pN0	65 (74.7)	134 (40-227)	**0.004**	113 (NA)	**0.002**
	pN1-2	22 (25.3)	35 (0-70)		66 (11-120)	
Stage	I-II	65 (74.7)	134 (40-227)	**0.004**	113 (NA)	**0.002**
	III	22 (25.3)	35 (0-70)		66 (11-120)	

CI: Confidence interval, MD: moderately differentiated, NA: not applicable, OS: overall survival, PD: poorly differentiated, RFS: recurrence-free survival, WD: well-differentiated. Statistically significant results are shown in bold.

the tumor cells were associated with heavy lymphocytic infiltration, IMP3-positive lymphocytes mimicked the pattern of tumor cells. Thus, it was difficult to distinguish between reactive lymphocytes and tumor cells in poorly differentiated AVACs, in which the IMP3-positive tumor cells were singly scattered or clustered within the lymphoid tissue. In contrast to tumor cells, the IMP3-positive lymphocytes did not form any glandular or clustered architecture, but were instead scattered individually (Figure 1E). Furthermore, some vascular endothelial cells weakly expressed IMP3 in their cytoplasm (Figure 1F). Irregular-shaped vascular lumina lined by IMP3-positive endothelial cells mimicked those of infiltrating tumorous glands. In such cases, a low nuclear-cytoplasmic ratio and the lack of nuclear atypia in the vascular endothelial cells, as well as a stronger IMP3 staining intensity in the tumor cells, were helpful in discriminating endothelial cells from tumor cells.

Revision of pT staging based on IMP3 immunostaining results. Based on the observation of the tumor-specific expression of IMP3, we re-evaluated the pT stage using the IMP3-immunostained slides. Two out of the 21 (9.5%) well-differentiated AVACs showed submucosal invasion and pancreatic extension, which were not detected in the corresponding hematoxylin and eosin-stained slides. Consequently, we revised the pT stage for these cases [pT1a to pT1b for submucosal invasion (Figure 1G) and T2 to T3a for pancreatic extension (Figure 1H), respectively]. The tumorous glands identified by IMP3 immunostaining were few in number and possessed low-grade nuclei, thus appearing to be benign glands.

Clinicopathological significance of IMP3 expression in AVAC. The cases were divided into two groups according to the proportion of IMP3-positive tumor cells among total tumor cells: No/low IMP3 expression (≤50%) and high IMP3 expression (>50%). The majority of cases (84/87; 96.6%) were easily classified into the two groups because the staining proportion was either over 70% or under 30%. The remaining three (3.4%) equivocal cases had a staining proportion close to 50% and were therefore re-reviewed using a computer-aided interpretation system for calculating the immunoreactivity index. Two out of the three cases were ultimately classified into the high-expression group, and the remaining case was classified into the low-expression group.

Table II summarizes the association of IMP3 expression with clinicopathological features of patients with AVAC. There was a statistically significant difference in IMP3 expression between well-to-moderately and poorly differentiated AVACs (p=0.026). Most (9/11; 81.8%) of the poorly differentiated tumors were classified in the group with high expression, whereas fewer than half (34/76; 44.8%) of the well-to-moderately differentiated tumors exhibited high IMP3 expression. Other clinicopathological features were not significantly associated with IMP3 expression status.

Prognostic implication of IMP3 expression in AVAC. Ten (11.5%) patients ultimately developed recurrence. Thirty-seven (48.7%) out of the 76 patients whose follow-up data were available died; the median follow-up time was 82 months (range=11-260 months). As shown in Table I, univariate analysis revealed that poorly differentiated histology, nodal metastasis, and advanced stage were

Table II. *Association of insulin-like growth factor II mRNA-binding protein 3 (IMP3) expression status with clinicopathological features of patients with adenocarcinoma of the ampulla of Vater.*

Feature	IMP3 expression status, n (%)		*p*-Value
	No/low (≤50%)	High (>50%)	
Age (years)			
≤60 Years	26 (59.0)	18 (40.9)	0.082
>60 Years	18 (41.9)	25 (58.1)	
Gender			
Male	22 (51.2)	21 (48.8)	0.542
Female	22 (50.0)	22 (50.0)	
Histological grade			
WD/MD	42 (82.4)	9 (17.6)	**0.026**
PD	2 (5.6)	34 (94.4)	
Tumor size (cm)			
≤2 cm	15 (45.5)	18 (54.5)	0.300
>2 cm	29 (53.7)	25 (46.3)	
Pathological tumor stage (pT)			
pT1-2	23 (52.3)	21 (47.7)	0.458
pT3	21 (48.8)	22 (51.2)	
Pathological nodal stage (pN)			
pN0	34 (52.3)	31 (47.7)	0.379
pN1-2	10 (45.5)	12 (54.5)	
Stage			
I-II	34 (52.3)	31 (47.7)	0.379
III	10 (45.5)	12 (54.5)	

MD: Moderately differentiated, PD: poorly differentiated, WD: well-differentiated. Statistically significant results are shown in bold.

significantly associated with a shorter RFS and OS. Patients with pT3 AVAC had a shorter OS compared with those who had pT1-2 tumors. None of the other clinicopathological features were significant predictors of shorter RFS or OS (Table I).

The median RFS for patients with tumors with high IMP3 expression (56 months) was significantly shorter than that of patients harboring tumors with low/no IMP3 expression (216 months; p=0.006). The median OS for patients with IMP3-high AVAC (88 months) was also significantly shorter than that of patients with no/low IMP3-expressing tumors (216 months; p=0.004). Kaplan–Meier curves showed a decrease in OS and RFS for patients with high IMP3-expressing tumors (Figure 2). At the multivariate level (Table III), the factors independently associated with shorter RFS and OS were advanced stage (p=0.004 and p=0.003, respectively) and high IMP3 expression (p=0.003 and p=0.029, respectively). These analyses demonstrated that high IMP3 expression in patients with AVAC was independently associated with prognosis [significant hazard ratios (HR) of 2.555 and 2.135 for RFS and OS, respectively], which was comparable to the effects of stage group (HR=2.603 and 2.873, respectively) but had greater predictive power than histological grade (HR=2.109 and 2.031, respectively).

Discussion

We observed focal IMP3 expression in the vast majority of AVAC samples diagnosed from pancreaticoduodenectomy specimens, but not in any of the normal biliary-type epithelium tissues, suggesting that IMP3 immunostaining has a potential value as a diagnostic marker for AVAC. This finding is consistent with that of previous studies showing the diagnostic value of IMP3 immunostaining in pancreatobiliary biopsy and fine-needle aspiration specimens (28-33). However, our results also highlight that IMP3 expression status should be used with caution as a diagnostic marker for AVAC in clinical practice, especially for tumors with negative staining, because approximately 10% of the AVACs in this study showed no IMP3 expression. In addition, since patchy IMP3 expression with a variable staining intensity was found in approximately 70% of cases, the absence of IMP3 expression in a small-sized specimen might be misleading and reflect intratumoral heterogeneity.

Based on the IMP3 immunostaining results, we revised the pT stage of two (9.5%) well-differentiated AVACs. IMP3-positive tumorous glands, which were not observed in hematoxylin and eosin-stained slides but only in the IMP3-immunostained slides, were located in the submucosa and pancreatic parenchyma, resulting in up-staging from pT1a to pT1b and from pT2 to pT3a, respectively. The complicated microanatomy of the AV, along with the presence of normal submucosal glands and small branches of pancreatic ducts pose a challenge for pathologists in accurately determining pT in well-differentiated AVACs. Accordingly, IMP3 immunostaining in AVACs is expected to improve the

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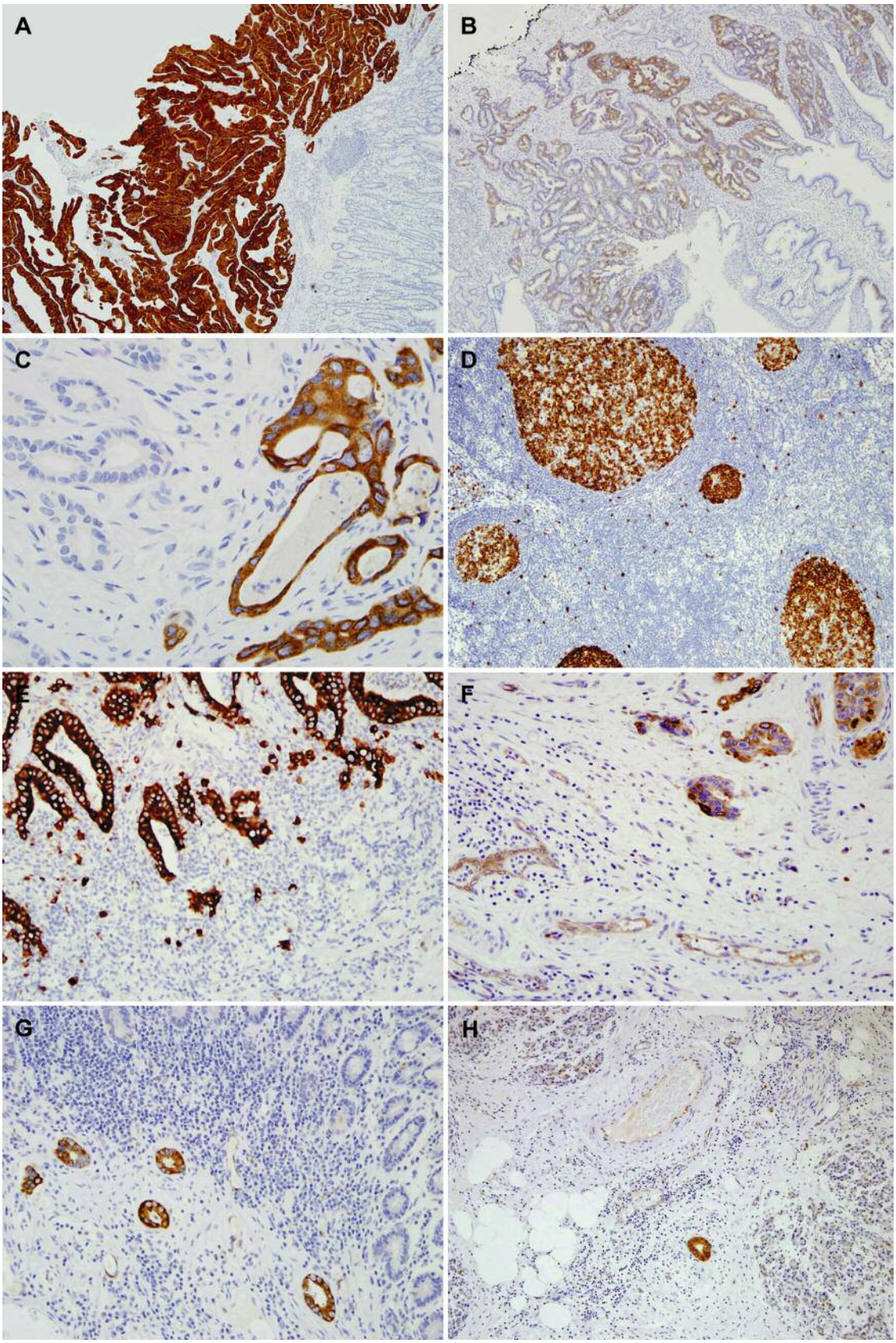
Figure 1. *Insulin-like growth factor II mRNA-binding protein 3 (IMP3) expression in adenocarcinoma of the ampulla of Vater. A: Uniform and strong IMP3 immunoreactivity in the tumor cells and absence of IMP3 expression in normal biliary epithelial cells (lower right corner). B: Heterogeneous IMP3 expression with variable staining intensity in the tumor cells. C: Cytoplasmic and membranous IMP3 expression in tumorous glands (right) and no immunoreactivity in benign glands (left). D: Strong IMP3 expression in the germinal centers and in a few scattered non-germinal center lymphocytes. E: IMP3 expression in individually scattered peritumoral lymphocytes, displaying similar staining intensity to that of the tumorous glands. F: Weak cytoplasmic IMP3 expression in vascular endothelial cells (lower half). G: Some well-differentiated submucosal tumorous glands highlighted by IMP3 immunostaining. H: IMP3-positive tumorous gland infiltrating the pancreatic parenchyma. Original magnification, A, B, D, G, H, 40×; E, F, 100×; C, 200×.*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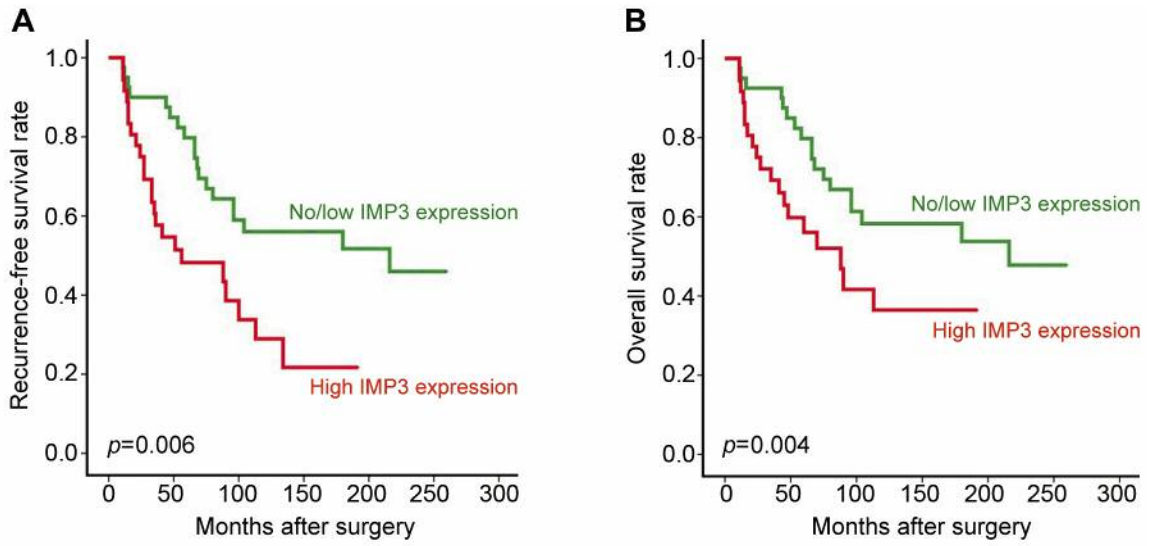

Figure 2. *Kaplan–Meier plots for recurrence-free (A) and overall (B) survival of patients with adenocarcinoma of the ampulla of Vater according to insulin-like growth factor II mRNA-binding protein 3 (IMP3) expression. Recurrence-free and overall survival rates were significantly lower in patients with tumors with a high IMP3 expression than in those with no/low IMP3 expression.*

Table III. *Multivariate analysis of survival for patients with ampulla of Vater adenocarcinoma.*

Feature		RFS (months)		OS (months)	
		HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Histological grade	PD	2.109 (0.889-5.002)	0.106	2.031 (0.814-5.067)	0.147
Pathological tumor stage (pT)	pT3	1.591 (0.810-3.127)	0.176	1.870 (0.897-3.899)	0.142
Stage	III	2.603 (1.387-4.884)	**0.004**	2.873 (1.480-5.577)	**0.003**
IMP3 expression	High	2.555 (1.345-4.855)	**0.003**	2.135 (1.085-4.204)	**0.029**

CI: Confidence interval, HR: hazard ratio, IMP3: insulin-like growth factor II mRNA-binding protein 3, OS: overall survival, PD: poorly differentiated, RFS: recurrence-free survival. Statistically significant results are shown in bold.

accuracy of pT staging based on the observation of tumor-specific IMP3 expression. In line with our expectation, recent studies have shown that IMP3 immunostaining is helpful in searching for invasive foci of lung adenocarcinoma and papillary brain tumors (34, 35).

In addition to tumor cells, we detected IMP3 expression in some normal lymphocytes and vascular endothelial cells. The presence of IMP3-positive lymphocytes or endothelial cells can result in misinterpretation of the tumor extent if these cells are located in the vicinity of the tumor. To avoid this problem, IMP3 expression should be interpreted in the context of cytomorphological correlations and staining patterns. IMP3 is usually expressed in only a few scattered lymphocytes located within clusters of IMP3-negative lymphocytes, whereas IMP3-positive tumor cells form glands or clusters. The tumor cells are homogeneously and uniformly stained with IMP3, whereas endothelial cells display a patchy staining pattern with weak intensity along the vascular lumina.

We found that the number of poorly differentiated AVAC cases was significantly higher among those with tumors with high IMP3 expression compared to those with no or low IMP3 expression. Previous studies using cell lines retrieved from carcinomas of the pancreas, colorectum, and breast demonstrated that IMP3 plays an important role in the epithelial–mesenchymal transition (36-38). This finding is in agreement with our observation given that loss of epithelial differentiation in carcinoma is a marker of the epithelial–mesenchymal transition. A significant relationship between high IMP3 expression and a higher histological grade has also been described in hepatocellular carcinoma (39).

There were significant differences in OS and RFS between patients with AVACs with high and those with no or low IMP3 expression. The statistical significance of high IMP3 expression status for both OS and RFS was maintained at the multivariate level, indicating that IMP3 expression is an independent prognostic marker for OS and RFS of patients with AVAC. Association of increased IMP3 expression with poor prognosis have been documented in many different types of malignancies (9, 15, 32, 35, 39-44), although the scoring systems differed among these studies. We used a 50% staining proportion as the cut-off level for high expression, and most cases were unequivocally classified into the high or no/low expression groups. We consider that our use of whole tissue sections for immunostaining and the relatively long follow-up period strengthen the reliability of our findings. Nevertheless, a larger population-based study would be valuable in confirming the diagnostic value and prognostic implication of IMP3 expression in AVACs.

In conclusion, we demonstrated a tumor-specific IMP3 expression pattern in AVACs, which will be helpful in determining the invasion depth or tumor extent, especially in those with well-differentiated tumors. Importantly, a high IMP3 expression status in AVAC was significantly associated with poorly differentiated histology, and emerged as an independent factor for predicting a shorter RFS and OS in patients with AVAC. Overall, our data suggest IMP3 expression status as a candidate diagnostic and prognostic marker for AVAC, that can improve the early detection of recurrence and patient outcome.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors' Contributions

All Authors made substantial contributions to the conception and design of the study, acquisition of data, analysis and interpretation of the data, as well as drafting the manuscript, revising the article critically for important intellectual content, and providing final approval of the version to be published.

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